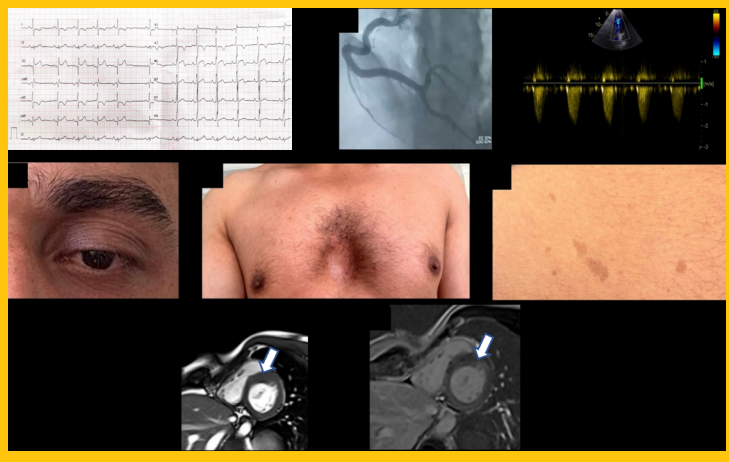
TURKISH SOCIETY OF CARDIOLOGY

April 2026
Volume 54, Number 3

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

ORIGINAL ARTICLES



KARE MEDYA

ISSN - 1016 - 5169 eISSN 1308 - 4488
www.archivestsc.com

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Sahibi/Owner

Türk Kardiyoloji Derneği adına
On behalf of the Turkish Society of Cardiology
Dr. Ertuğrul Okuyan

Yazı İşleri Müdürü / Publishing Manager

Dr. Dilek Ural

Yayın Sekreteri / Publication Secretary

Ebru Boz Sandıkçı

Yayın Koordinatörü / Publication Coordinator

Zeynep Sena Pekşen

Yönetim Yeri Adresi / Corresponding Address

Turkish Society of Cardiology
Nish İstanbul A Blok Kat: 8
No: 47-48, Çobançeşme
Sanayi Cad. 11, Yenibosna,
Bahçelievler, İstanbul
Phone: +90 212 221 1730 - 221 17 38
Fax: +90 212 221 17 54
E-Mail: tkd@tkd.org.tr
URL: http://www.tkd.org.tr

Yayıncı / Publisher

Kare Yayıncılık
www.karepb.com
Circulation: 12

Indexed in PubMed, Europe PMC, Index Medicus, Web of Science, Emerging Sources Citation Index (ESCI), SCOPUS, EMBASE (the Excerpta Medica database), EBSCO, DOAJ, CNKI (China National Knowledge Infrastructure), GENAMICS, Research4Life, Hinari, SCILIT, OUCI, Turkish Medical Index and Turkiye Citation Index./PubMed, Europe PMC, Index Medicus, Web of Science, Emerging Sources Citation Index (ESCI), SCOPUS, EMBASE (Excerpta Medica), EBSCO, DOAJ, CNKI (China National Knowledge Infrastructure), GENAMICS, Research4Life, Hinari, SCILIT, OUCI, TÜBİTAK ULAKBİM Türk Tıp Dizini ve Türkiye Atıf Dizini'nde yer almaktadır.

Issued by the Turkish Society of Cardiology. / Türk Kardiyoloji Derneği'nin yayın organıdır.

Commercial activites are carried out by Turkish Society of Cardiology Economic Enterprise. / Ticari faaliyeti TKD İktisadi İşletmesi'nce yürütülmektedir.

Published eight issues a year. / Yılda sekiz sayı yayınlanır.

Publication Type: Periodical Publication / Yayın Türü: Yaygın Süreli.

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Volume: 54 / Issue: 3 / Year: 2026

CONTENTS/İÇİNDEKİLER

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Türk Hipertansiyon Uzlaşı Raporu 2025

The Turkish Hypertension Consensus Report 2025

Bülent Özin[1a], Bülent Altun[2b], Mustafa Cesur[3c], Cüneyt Ardıç[4d], Mustafa Arıcı[2e], Sinan Aydoğdu[5f], Sevgi Aras[6g], Kerim Güler[7a], Serpil Müge Değer[8b], Alper Sönmez[3c], Güzin Zeren Öztürk[9d], Gülsüm Özkan[10e], Hülya Çiçekçioğlu[5f], Gülistan Bahat[11g], Tufan Tükek[7a], Ülver Derici[12b], İbrahim Şahin[13,14c], Şükrü Ulusoy[15e], Mehmet Akif Düzenli[16f]

[1]İç Hastalıkları Anabilim Dalı, Kardiyoloji Bilim Dalı, Başkent Üniversitesi Tıp Fakültesi, Ankara, Türkiye; [2]İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, Hacettepe Üniversitesi Tıp Fakültesi, Ankara, Türkiye; [3]Endokrinoloji ve Metabolizma Hastalıkları Kliniği, Ankara Güven Hastanesi, Ankara, Türkiye; [4]Aile Hekimliği Anabilim Dalı, Recep Tayyip Erdoğan Üniversitesi Tıp Fakültesi, Rize, Türkiye; [5]Kardiyoloji Kliniği, Ankara Bilkent Şehir Hastanesi, Ankara, Türkiye; [6]İç Hastalıkları Anabilim Dalı, Geriatri Bilim Dalı, İstanbul Medipol Üniversitesi Tıp Fakültesi, İstanbul, Türkiye; [7]İç Hastalıkları Anabilim Dalı, İstanbul Üniversitesi İstanbul Tıp Fakültesi, İstanbul, Türkiye; [8]İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, Dokuz Eylül Üniversitesi Tıp Fakültesi, İzmir, Türkiye; [9]Aile Hekimliği Anabilim Dalı, Sağlık Bilimleri Üniversitesi İstanbul Şişli Hamidiye Etfal Sağlık Uygulama ve Araştırma Merkezi, Türkiye; [10]İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, Tekirdağ Namık Kemal Üniversitesi Tıp Fakültesi, Tekirdağ, Türkiye; [11]İç Hastalıkları Anabilim Dalı, Geriatri Bilim Dalı, İstanbul Üniversitesi İstanbul Tıp Fakültesi, İstanbul, Türkiye; [12]İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, Gazi Üniversitesi Tıp Fakültesi, Ankara, Türkiye; [13]Endokrinoloji ve Metabolizma Hastalıkları Kliniği, Memorial Şişli Hastanesi, İstanbul, Türkiye; [14]İç Hastalıkları Anabilim Dalı, Endokrinoloji ve Metabolizma Bilim Dalı, Haliç Üniversitesi Tıp Fakültesi Türkiye; [15]İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, Karadeniz Teknik Üniversitesi Tıp Fakültesi, Trabzon, Türkiye; [16]Kardiyoloji Anabilim Dalı, Necmettin Erbakan Üniversitesi Tıp Fakültesi, Konya, Türkiye

[a]Türk İç Hastalıkları Uzmanlık Derneği (TİHUD), [b]Türk Hipertansiyon ve Böbrek Hastalıkları Derneği (THBHD), [c]Türkiye Endokrinoloji ve Metabolizma Derneği (TEMD), [d]Türkiye Aile Hekimleri Uzmanlık Derneği (TAHUD), [e]Türk Nefroloji Derneği (TND), [f]Türk Kardiyoloji Derneği (TKD), [g]Akademik Geriatri Derneği (AGD)

ÖZET

Türk Hipertansiyon Uzlaşı Raporu (THUR), dünyada çok önemli bir sağlık sorunu olan hipertansiyonun tanı ve tedavisindeki gelişmeleri ülkemiz gerçekleri perspektifinden değerlendirerek, Türkiye'de hipertansiyon hastaları ile ilgilenen hekimlere temel bir başvuru kaynağı olabilecek pratik bir metin oluşturmak amacıyla ilk kez 2015 yılında yayımlanmış ve 2019'da güncellenmiştir. Son yıllarda hipertansiyon tanımı ve evrelemesinde önemli değişiklikler olmuş ve çeşitli kuruluşlar kılavuzlarında farklı sınırlar ile kardiyovasküler risk belirleme için farklı skorlama sistemleri önermişlerdir. Bu veriler ışığında Türk Hipertansiyon Uzlaşı Raporu'nun güncellenmesi zorunlu hâle gelmiştir. THUR'da daha önce yer alan beş derneğe ek olarak, birinci basamağın hipertansiyon tanı ve tedavisindeki kritik rolü nedeniyle Türkiye Aile Hekimleri Uzmanlık Derneği; toplumun giderek yaşlanması ve yaşlılarda hipertansiyon tanı ve tedavisinin daha özellikli hâle gelmesi nedeniyle ise Akademik Geriatri Derneği raporun 2025 güncellemesine katılmıştır. Güncellenen 2025 raporunda "normal kan basıncı", poliklinik şartlarında ölçülen sistolik kan basıncının (SKB) 120 mmHg'nin altında ve diyastolik kan basıncının (DKB) 80 mmHg'nin altında olması şeklinde tanımlandı. Kan basınçlarının sistolik 120–139 mmHg arasında ya da diyastolik 80–89 mmHg arasında olması "artmış kan basıncı" olarak değerlendirilirken; kan basınçlarının sistolik 140 mmHg ve üzerinde ya da diyastolik 90 mmHg ve üzerinde olması "hipertansiyon" olarak tanımlandı. Hipertansiyon, Evre 1 (SKB: 140–159 mmHg veya DKB: 90–99 mmHg) ve Evre 2 (SKB ≥160 mmHg veya DKB ≥100 mmHg) olarak kategorize edildi. Hipertansiyon tanısında klinik kan basıncı ölçümlerinin yanı sıra ev kan basıncı ölçümleri ve ambulatuvar kan basıncı değerlerinin de kullanılması vurgulandı. Laboratuvar tetkikleri başlangıçta istenecekler ve hipertansif hastalarda hedef organ hasarını saptamak için istenebilecek ek tetkikler olarak detaylandırılarak sekonder hipertansiyon araştırma kriterleri güncellendi. Yaş ve kırılganlık durumuna göre ilaç tedavisi için eşik ve hedef kan basıncı düzeyleri, komorbiditeden bağımsız olarak üç alt grup için belirlendi: 18–79 yaş (eşik ≥140/90 mmHg, hedef 120–130/70–80 mmHg), ≥80 yaş (eşik ≥140 mmHg, hedef 130–140 mmHg) ve kırılgan hastalar (eşik ≥160 mmHg, hedef 140–150 mmHg). İlaç tedavisine SKB/DKB ≥140/90 mmHg olan hastalarda (Evre 1 ve Evre 2) hemen ve tüm hastalarda kombinasyon tedavisi ile başlanması önerildi. Artmış kan basıncı tedavi alt grubunda (SKB: 130–139 mmHg, DKB: 80–89 mmHg), üç ay yaşam tarzı değişikliğine rağmen değerlerin düzelmediği durumlarda diabetes mellitus (40 yaş üzeri, 10 yıldan uzun süredir diyabeti olan, komplikasyonu bulunan ve obezite, sigara kullanımı gibi diğer risk faktörlerine sahip hastalarda), kronik böbrek hastalığı (albüminüri >30 mg/gün veya spot idrarda albümin/kreatinin oranı >30 mg/g varlığında), kardiyovasküler hastalık (koroner arter hastalığı, periferik arter hastalığı, kalp yetersizliği), inme ve SCORE2 kardiyovasküler risk >%15 ile SCORE2 OP kardiyovasküler risk >%20 varlığında antihipertansif tedavinin başlanması önerildi. Bu raporda ACEİ (anjiyotensin dönüştürücü enzim inhibitörü), ARB (anjiyotensin reseptör blokeri), KKB (kalsiyum kanal blokeri), tiyazid veya tiyazid benzeri diüretik ve MRA (mineralokortikoid reseptör antagonisti) tedavileri temel alınarak kombinasyon tedavi algoritması; ilk adımda düşük veya tam doz başlanan ikili tedavi ("ACEİ veya ARB + KKB" veya "ACEİ veya ARB + diüretik"), ikinci adımda ikili tedavinin tam dozuna (düşük doz başlananlarda) veya düşük ya da tam doz üçlü tedaviye (ACEİ/ARB + KKB + diüretik) geçiş, üçüncü adımda üçlü tedavinin tam dozuna (düşük doz başlananlarda) geçiş ve dördüncü adımda ACEİ veya ARB + KKB + diüretik + MRA dörtlü tedavisinin kullanımı şeklinde basamaklandırıldı. Monoterapinin öncelikle tercih edilebileceği özel durumlar ise 80 yaş üstü, kırılgan hasta, artmış kan basıncı ve ortostatik hipotansiyon olarak belirlendi. 2025 raporuna, önceki raporda yer almayan yedi yeni bölüm (Hipertansiyonda kırılganlık değerlendirmesi, dirençli hipertansiyon, izole sistolik hipertansiyon, izole diyastolik hipertansiyon, ortostatik hipotansiyon, hipertansif acil durumlar ve antihipertansif ilaç kullanan hastalarda ek kardiyovasküler ve renal koruma tedavileri) eklendi. Ayrıca manuel aneroid ve ambulatuvar kan basıncı ölçümü sırasında hasta ve hekimin dikkat etmesi gerekenler, kan basıncını artırabilecek ilaçlar ve diğer maddeler, kırılgan–dinç tanımı ile antihipertansif tedavi özelinde kırılganlık ve antihipertansif tedavi altında kan basıncını ideal düzeylerin altına düşürebilen kardiyovasküler olmayan ilaçlar başlıkları altında dört ek dosya sunuldu. Bu raporda sunulan kanıta dayalı öneriler poliklinik şartlarında tedavi edilen çoğu hipertansif hasta için geçerli olmakla birlikte, tedaviden sorumlu hekimin klinik değerlendirmesine göre vereceği karar, hastaya özgü bireyselleştirilmiş tedavinin sunulabilmesinde kritik öneme sahiptir.

Anahtar Kelimeler: Hipertansiyon, kılavuz, tanı, tedavi

Corresponding author: Bülent Özin / ✉ bozin1@gmail.com **Received:** December 12, 2025, **Accepted:** January 26, 2026 / **DOI:** 10.5543/tkda.2026.23791

Cite this article as: Özin B, Altun B, Cesur M, et al. The Turkish Hypertension Consensus Report 2025. *Turk Kardiyol Dern Ars.* 2026;54(3):207–226.

ABSTRACT

The Turkish Hypertension Consensus Report (THCR) was first published in 2015 and subsequently updated in 2019 to provide practical guidance for clinicians involved in the diagnosis and management of hypertension in outpatient clinical settings. The report was prepared as a joint initiative of the Turkish Society of Cardiology, the Turkish Society of Internal Medicine, the Turkish Society of Endocrinology and Metabolism, the Turkish Society of Nephrology, and the Turkish Society of Hypertension and Renal Diseases. In recent years, substantial changes have occurred in the definition and staging of hypertension, and various professional organizations have proposed different blood pressure thresholds and cardiovascular risk scoring systems in their guidelines. These developments necessitated a further update of the consensus report. In addition to the original five societies, the Turkish Academic Geriatrics Society and the Turkish Association of Family Physicians contributed to the preparation of the 2025 update of the THCR. In the updated 2025 report, "normal blood pressure" was defined as systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg, based on measurements obtained in outpatient clinical settings. SBP values of 120–139 mmHg or DBP values of 80–89 mmHg were classified as "elevated blood pressure," whereas SBP ≥140 mmHg or DBP ≥90 mmHg was defined as "hypertension." Hypertension was categorized as Stage 1 (SBP 140–159 mmHg or DBP 90–99 mmHg) and Stage 2 (SBP ≥160 mmHg or DBP ≥100 mmHg). In addition to office blood pressure measurements, the use of home and ambulatory blood pressure monitoring in the diagnosis of hypertension was emphasized. Laboratory investigations were updated and categorized into baseline tests and additional tests aimed at detecting target organ damage in hypertensive patients, and the diagnostic criteria for secondary hypertension were revised. Age- and frailty-based treatment thresholds and blood pressure targets were defined independently of comorbidities for three subgroups: patients aged 18–79 years (treatment threshold ≥140/90 mmHg; target 120–130/70–80 mmHg), patients aged ≥80 years (threshold ≥140 mmHg; target 130–140 mmHg), and frail patients (threshold ≥160 mmHg; target 140–150 mmHg). Immediate initiation of combination antihypertensive therapy was recommended for all patients with SBP/DBP ≥140/90 mmHg (Stage 1 and Stage 2 hypertension). In the elevated blood pressure treatment subgroup (SBP 130–139 mmHg, DBP 80–89 mmHg), antihypertensive therapy was recommended if blood pressure remained uncontrolled despite three months of lifestyle modification in the presence of diabetes mellitus (age >40 years, diabetes duration >10 years, diabetes-related complications, or additional risk factors such as obesity or active smoking), chronic kidney disease (albuminuria >30 mg/day or spot urine albumin-to-creatinine ratio >30 mg/g), established cardiovascular disease (coronary artery disease, peripheral artery disease, heart failure), stroke, or increased cardiovascular risk as assessed by SCORE2 (>15%) or SCORE2-OP (>20%). A stepwise combination treatment algorithm was provided based on angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide or thiazide-like diuretics, and mineralocorticoid receptor antagonists (MRAs). The algorithm includes initiation with low- or full-dose dual therapy ("ACEI or ARB + CCB" or "ACEI or ARB + diuretic") as the first step; escalation to full-dose dual therapy (for those started on low doses) or to low- or full-dose triple therapy (ACEI or ARB + CCB + diuretic) as the second step; escalation to full-dose triple therapy as the third step; and use of quadruple therapy (ACEI or ARB + CCB + diuretic + MRA) as the fourth step. Monotherapy was recommended primarily in selected clinical situations, including patients aged >80 years, frail patients, those with elevated blood pressure, and patients with orthostatic hypotension. Overall, seven new sections were added to the 2025 report: frailty assessment in hypertension, resistant hypertension, isolated systolic hypertension, isolated diastolic hypertension, orthostatic hypotension, hypertensive emergencies, and recommendations addition, four supplementary files were provided, addressing key considerations for patients and physicians during manual aneroid and ambulatory blood pressure measurements, medications and substances that may increase blood pressure, definitions of frailty and fitness and their implications for antihypertensive therapy, and non-cardiovascular drugs that may lower blood pressure below target levels during antihypertensive treatment. Although the evidence-based recommendations presented in this report are applicable to most hypertensive outpatients, clinical decision-making by the treating physician remains essential for the delivery of individualized, patient-centered care.

Keywords: Hypertension, guideline, diagnosis, treatment

KISALTMALAR

ACC	Amerikan Kardiyoloji Koleji
ACEİ	Anjiyotensin Dönüştürücü Enzim İnhibitörleri
AHA	Amerikan Kalp Derneği
AKBM	Ambulatuar Kan Basıncı Monitorizasyonu
AKBÖ	Ambulatuar Kan Basıncı Ölçümü
ALT	Alanin Aminotransferaz
ARB	Anjiyotensin Reseptör Blokerleri
ARNİ	Anjiyotensin Reseptör Neprisilin İnhibitörü
AST	Aspartat Aminotransferaz
AST	Aspartat Aminotransferaz
BRAF	B-raf geni
BT	Bilgisayarlı Tomografi
CFS	Klinik Kırılganlık Skalası
DEF-KY	Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliği
DH	Dirençli Hipertansiyon
DKB	Diyastolik Kan Basıncı
DM	Diabetes Mellitus
eGFR	Tahmini Glomerüler Filtrasyon Hızı
EKBÖ	Ev Kan Basıncı Ölçümleri
ESC	Avrupa Kalp Derneği
ESH	Avrupa Hipertansiyon Derneği
GFR	Glomerüler Filtrasyon Hızı
GHB	Gebeliğin Hipertansif Bozuklukları
GIP	Glikoz bağımlı insülinotropik polipeptit
GLP-1 RA	Glukagon Benzeri Peptid-1 Reseptör Agonisti
HT	Hipertansiyon
İDH	İzole Diyastolik Hipertansiyon
İSH	İzole Sistolik Hipertansiyon
KAH	Koroner Arter Hastalığı
KB	Kan Basıncı
KBH	Kronik Böbrek Hastalığı
KEF-KY	Korunmuş Ejeksiyon Fraksiyonlu Kalp Yetersizliği
KKB	Kalsiyum Kanal Blokeri
KV	Kardiyovasküler
KVH	Kardiyovasküler hastalık
LDH	Laktat Dehidrogenaz
MEK	Mitojenle etkinleşen hücre-dışı sinyal düzenlemeli kinaz
MR	Manyetik Rezonans
MRA	Mineralokortikoid Reseptör Antagonisti
mTOR	Memeli Rapamisin Hedefi
NT – proBNP	N-terminal pro-B tipi natriüretik peptit
OAB	Ortalama Arter Basıncı
ODPKBH	Otozomal Dominant Polikistik Böbrek Hastalığı
PARP Poli	ADP Riboz Polimeraz
PRA	Plazma Renin Aktivitesi
PTH	Parathormon
RAAS	Renin Anjiyotensin Aldosteron Sistemi
RET	Transfeksiyon sırasında yeniden düzenlenen
SALTURK	Türk Toplumunda Tuz Tüketimi ve Kan Basıncı Çalışması
SCORE2	Sistematik Koroner Risk Değerlendirmesi (40–69 yaş grubu)
SCORE2-OP	Sistematik Koroner Risk Değerlendirmesi (ileri yaş grubu 70–89 yaş)
$SGLT_2i$	Sodyum-Glukoz Kotransporter-2 inhibitörü
SKB	Sistolik Kan Basıncı
SNRI	Serotonin-Norepinefrin Geri Alım İnhibitörleri
TSH	Tiroid Stimülan Hormon
USG	Ultrasonografi
VEGF	Vasküler Endotelyal Büyüme Faktörü
VKİ	Vücut Kitle İndeksi

Hipertansiyon, en sık görülen kronik hastalıklardan biridir ve küresel bir halk sağlığı sorunudur. Dünyada kardiyovasküler hastalıkların en önemli nedeni hipertansiyondur ve prevalansı giderek artmaktadır. 2019 yılında, dünya genelinde 30–79 yaş arası bireylerde yaşa göre standardize edilmiş hipertansiyon prevalansı kadınlarda %32, erkeklerde ise %34 olarak rapor edilmiştir.[1] Prevalans, yaş arttıkça artmaktadır ve 80 yaş ve üzeri bireylerin neredeyse %80'ini etkilemektedir. Hipertansiyon; kalp hastalıkları, inme, böbrek hastalığı, erken ölüm ve yeti yitimi gibi durumlarla ilişkili olup sağlık ve ekonomi alanında önemli bir yük oluşturmaktadır. Bununla birlikte, hipertansiyon önlenebilir ve tedavi edilebilir bir hastalıktır. Hipertansiyon tanı ve tedavisi konusunda ülkemizdeki uygulamalar için bir rehber olması amaçlanan "Türk Hipertansiyon Uzlaşı Raporu", Türk Kardiyoloji Derneği, Türk İç Hastalıkları Uzmanlık Derneği, Türkiye Endokrinoloji ve Metabolizma Derneği, Türk Nefroloji Derneği ve Türk Hipertansiyon ve Böbrek Hastalıkları Derneği tarafından ilk kez 2015 yılında yayınlanmış ve 2019'da güncellenmiştir.[2,3]

Son yıllarda, hipertansiyon tanım ve evrelemesinde çok önemli değişiklikler olmuş ve çeşitli dernekler bu konuda farklı sınırlar önermişlerdir. 2017 yılında ACC/AHA tarafından ortaklaşa hazırlanan hipertansiyon kılavuzunda eşik değerleri, sistolik kan basıncı için 130 mmHg, diyastolik kan basıncı için 80 mmHg olarak belirlenmiştir.[4] 2018 yılında ESC ve ESH'nın ortaklaşa yayınladığı hipertansiyon kılavuzunda eşik değerleri, eskiden olduğu gibi sistolik kan basıncı için 140 mmHg, diyastolik kan basıncı için 90 mmHg olarak sabit bırakılmıştır.[5] Bu iki dernek arasında, bu kılavuzdan sonra görüş ayrılığı ortaya çıkmıştır. ESH, 2023 yılında yayınlanan kılavuzunda hipertansiyon eşik sınırları için herhangi bir değişiklik yapmazken; ESC, 2024 yılında yayınladığı kılavuzda sistolik 120–139 mmHg ve/veya diyastolik 70–89 mmHg arasındaki değerler için artmış kan basıncı terimini kullanmıştır.[6,7] 2025 yılında geniş bir katılımla güncellenen AHA/ACC kılavuzunda da sistolik kan basıncı 130–139 mmHg veya diyastolik kan basıncı 80–89 mmHg aralığının Evre 1 hipertansiyon olduğu yeniden vurgulanmıştır.[8] Bu kılavuzların tümünde, kardiyovasküler risklerin hesaplanması ve tedavinin bu riskler temelinde belirlenmesi ortak nokta olarak vurgulanmış; ancak kardiyovasküler risk belirleme için farklı skorlama sistemleri kullanılmıştır. Bu veriler ışığında, en son 2019 yılında kaleme alınan Türk Hipertansiyon Uzlaşı Raporu'nun güncellenmesi gerekmektedir. Bu kılavuzun güncellenmesine daha önce katkıda bulunan dernekler yanında, birinci basamağın hipertansiyon tanı ve tedavisindeki önemi nedeniyle Türkiye Aile Hekimleri Uzmanlık Derneği ve toplumumuzun giderek yaşlanması ve yaşlılarda hipertansiyon tanı ve tedavisinin çok daha özellikli hâle gelmesi nedeniyle Akademik Geriatri Derneği de katılmışlardır. Kılavuzun yazımında birinci basamakta hipertansiyon tanım ve tedavisindeki sorulara net yanıtlar verilmeye çalışılmıştır. İlaç tedavisi için "eşik" ve "hedef" kan basıncı düzeyleri, komorbiditeden bağımsız olarak yaş ve kırılganlık durumuna göre belirlenmiş ve hipertansiyon sınıflamasına (evre 1, evre 2, artmış kan basıncı) göre tedavi algoritması, tedavi başlama kriterleri ve ilaç seçimi bazında değerlendirilmiştir. Toplumumuzun giderek yaşlanması nedeniyle, yaşlı popülasyonda hipertansiyon yönetimi çok önem kazanmıştır. Bu kılavuzda, ileri yaşlarda hipertansiyonlu hastaların değerlendirilmesi ve tedavisi, önceki rapordan çok daha detaylı bir şekilde incelenerek günümüz ihtiyaçlarına cevap verilmiştir (Ek A).

Uzlaşı raporunun 2025 güncellemesinde; hipertansiyonda kırılganlık değerlendirmesi, dirençli hipertansiyon, izole sistolik hipertansiyon, ortostatik hipotansiyon, hipertansif acil durumlar ve antihipertansif ilaç kullanan hastalarda ek kardiyovasküler ve renal koruma tedavileri gibi yeni bölümlerin yanı sıra, diğer kılavuzlarda da yeni olan izole diyastolik hipertansiyon konusu da yerini almıştır (Ek A).

Bu uzlaşı raporu, tüm yazarlar tarafından ortak olarak kaleme alındı. Bu amaçla 5 kez yüz yüze, 7 kez çevrim içi toplantı yapıldı. Taslak olarak 2019 Hipertansiyon Uzlaşı Raporu kullanıldı. Rapor hazırlanırken, ağırlıklı olarak Avrupa Kardiyoloji Derneği, Avrupa Hipertansiyon Derneği ve Amerikan Kalp Derneği ile Amerikan Kardiyoloji Koleji tarafından hazırlanan kılavuzlar göz önünde bulundurulduk.[6-8] Bu kılavuzların ilgili bölümleri; Türk İç Hastalıkları Uzmanlık Derneği, Türk Hipertansiyon ve Böbrek Hastalıkları Derneği, Türkiye Endokrinoloji ve Metabolizma Derneği, Türkiye Aile Hekimleri Uzmanlık Derneği, Türk Nefroloji Derneği, Türk Kardiyoloji Derneği ile Akademik Geriatri Derneği temsilcileri arasında paylaştırılıp derlendi. Daha sonra bu bölümler, toplantılarda tüm yazarlar tarafından değerlendirilerek metne son şekli verildi.

TANIM VE SINIFLANDIRMA

Poliklinik ölçümü (birkaç kez)
Kan Basıncı
≥ 140/90 mmHg: Hipertansiyon

Bu uzlaşı raporunda, 18 yaş üzerindeki erişkinlerde hekim tarafından yapılan, standardize edilmiş, tekrarlanan poliklinik ölçümleri ile sistolik kan basıncının ≥140 mmHg ve/veya diyastolik kan basıncının ≥90 mmHg olması, hipertansiyon olarak tanımlanır.

Genel popülasyonda, poliklinik kan basıncı düzeylerine göre sınıflandırma Tablo 1'de gösterilmiştir.

TANI

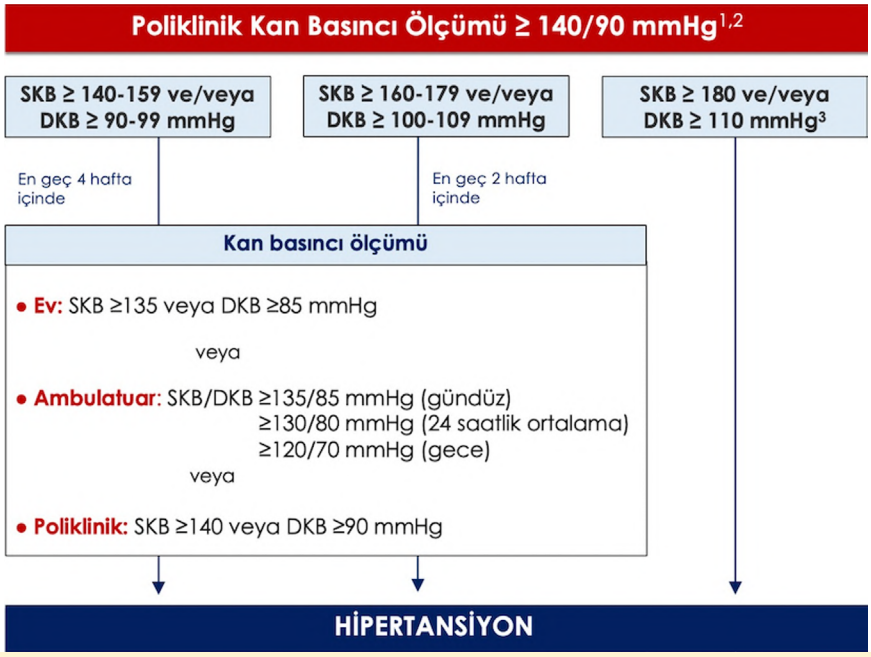
Erişkinlerde her muayenede kan basıncı mutlaka ölçülmeli ve 30 saniyeden daha kısa süre olmamak koşuluyla nabız sayılmalıdır. Bunun yanı sıra, hastanın risk faktörlerini belirlemek ve sekonder hipertansiyon nedenlerini sorgulamak amacıyla ayrıntılı tıbbi öykü alınmalı, sistemik fizik muayene ve gerekli laboratuvar incelemeleri yapılmalıdır.

1. Tıbbi Öykü

Hipertansiyonu olan hastalarda; önceki kan basıncı ölçümleri, geçirilmiş ve/veya eşlik eden hastalıklar, kardiyovasküler hastalık

Tablo 1. Standart poliklinik kan basıncı düzeylerine göre kan basıncı sınıflandırması

Kategori	Sistolik kan basıncı (mmHg)		Diyastolik kan basıncı (mmHg)
Normal kan basıncı	<120	ve	<80
Artmış kan basıncı	120–139	veya	80–89
Hipertansiyon	≥140	veya	≥90
Evre 1 hipertansiyon	140–159	veya	90–99
Evre 2 hipertansiyon	≥160	veya	≥100



Şekil 1. Hipertansiyon tanısı için akış şeması. [1]Kan basıncı ölçümü ilk muayenede iki koldan ayrı ayrı yapılmalı ve takiplerde yüksek ölçülen kol kullanılmalıdır. En az iki ölçüm yaparak hastanın kan basıncı (KB) ortalamasına göre tanı akışı kullanılmalıdır. İki ölçüm arasında 10 mmHg dan daha fazla fark varsa üçüncü ölçüm de yapılmalıdır. Ortostatik hipotansiyon dışlanmalıdır. [2]Bu ölçümler sırasında öykü, fizik muayene ve temel laboratuvar incelemelerinin yapılması önerilir. Ev kan basıncı veya ambulatuar KB ölçümü imkanı olmayan hastalarda, laboratuvar sonuçlarını getirdikleri zaman yeniden ölçüm yapılarak tanı konulması önerilir. [3]Hastanın kan basıncı bu değerlerde ise bir iki kez daha ölçülmelidir. Bu değerler devam ediyorsa, hastaya hipertansiyon tanısı hemen konulmalıdır.

DKB, Diyastolik kan basıncı; SKB, Sistolik kan basıncı.

risk faktörleri, ailede kalp ve damar hastalığı öyküsü, hipertansiyon tedavisi için kullanılmış veya kullanılmakta olan ilaçlar, düzenli kullanılmakta olan diğer ilaçlar/ilaç dışı ürünler ile sekonder hipertansiyon nedenlerine ve organ hasarına yönelik belirtiler sorgulanmalıdır.

2. Poliklinik Kan Basıncı Ölçümlerine Göre Hipertansiyon Tanısı

Poliklinik kan basıncı ölçümlerine göre hipertansiyon tanısı Şekil 1'de özetlenmiştir.

- İlk değerlendirmede, tekrarlanan ölçümler sonucu sistolik kan basıncı 180 mmHg veya diyastolik kan basıncı 110 mmHg üzerinde olan hastalarda hipertansiyon tanısı hemen konulur.
- Ancak, kan basıncı 140/90 mmHg ile 180/110 mmHg arasında olan hastalar, hipertansiyon tanısının doğrulanması için mümkünse evde kan basıncı ölçümleri (EKBÖ) veya ambulatuar kan basıncı ölçümleri (AKBÖ) ile mutlaka ikinci kez muayeneye çağrılmalıdır.
- Tanının kesinleştirilmesi için sistolik kan basıncı 140–159 mmHg veya diyastolik kan basıncı 90–99 mmHg olan hastalarda en geç 4 hafta içinde; sistolik kan basıncı 160–179 mmHg veya diyastolik kan basıncı 100–109 mmHg olan hastalarda en geç 2 hafta içinde, en az 5 gün sabah ve akşam otomatik ölçüm cihazı ile EKBÖ yapılması önerilir. Ortalama sistolik kan basıncının 135 mmHg veya diyastolik kan basıncının 85 mmHg üzerinde olması durumunda tanı konulur.
- Evde kan basıncı takibi olanağı yoksa, bir sağlık çalışanı tarafından tercihen otomatik osilometrik ölçüm cihazları ile kan basıncı ölçümü yaptırmaları önerilmelidir.
- Tanıyı doğrulamak için imkân olan durumlarda AKBÖ yapılmalıdır. Ambulatuar kan basıncının 24 saatlik ortalaması ≥130/80 mmHg, gündüz ortalaması ≥135/85 mmHg veya gece ortalaması ≥120/70 mmHg ise hipertansiyon tanısı konulur.
- Evde kan basıncı takibi veya AKBÖ imkânı yoksa, kontrol muayenesi sırasında tekrarlanan ölçümlerle tanı konulur.

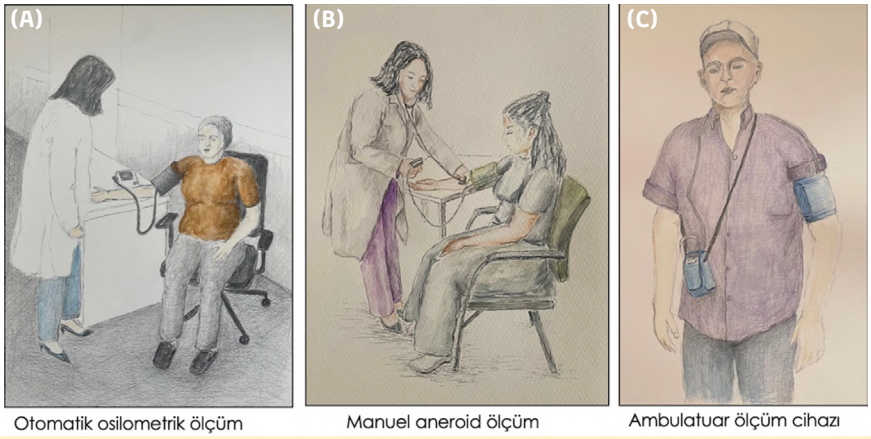
Ölçüm yöntemlerine göre hipertansiyon tanısı için eşik değerler Tablo 2'de gösterilmiştir.

Tablo 2. Kan basıncı ölçüm yöntemlerine göre hipertansiyon tanısı için eşik değerler

Ölçüm yöntemi	Sistolik kan basıncı (mmHg)		Diyastolik kan basıncı (mmHg)
Poliklinik	≥140	ve/veya	≥90
Ev	≥135	ve/veya	≥85
Ambulatuar kan basıncı			
24 saatlik ortalama	≥130	ve/veya	≥80
Gündüz ortalaması	≥135	ve/veya	≥85
Gece ortalaması	≥120	ve/veya	≥70

Şekil 2. İlk değerlendirmede kan basıncı <140/90 mmHg olan hastalarda kan basıncı takibi önerileri.

DKB, Diyastolik kan basıncı; KB, Kan basıncı; SKB, Sistolik kan basıncı.



Şekil 3. Kan basıncı ölçüm yöntemleri.

İlk değerlendirmede hipertansiyon tanısı almamış olgularda izlem önerileri Şekil 2'de özetlenmiştir.

İlk değerlendirmede hipertansiyonu olmayan olgularda:

- Kan basıncı normal aralıkta olanlarda (<120/80 mmHg) yılda bir,
- Sistolik kan basıncı 120–139 mmHg veya diyastolik kan basıncı 80–89 mmHg olanlarda 3-6 ayda bir tekrar kan basıncı ölçümü önerilir.

3. Kan Basıncı Ölçüm Teknikleri

• Standart kan basıncı ölçümü

Hekim tarafından, üst koldan ve geçerliliği onaylanmış otomatik osilometrik kan basıncı ölçüm cihazıyla (https://www.stridebp.org/office-hospital-pdf/), böyle bir cihaz yoksa manuel aneroid tansiyon ölçüm aletleri kullanılarak ölçüm yapılmalıdır (Şekil 3A, B).

İlk muayenede hastanın iki kolundan da ölçüm yapılmalıdır. İki koldan yapılan kan basıncı ölçümleri arasında >10 mmHg fark varsa, ölçümler tekrarlanmalı; tekrarlanan ölçümlerde sistolik kan basıncı farkı >20 mmHg ise nedeni araştırılmalı; her durumda, sonraki ölçümler kan basıncının yüksek olduğu koldan yapılmalıdır.

Ölçüm öncesi hastanın oturur durumda en az 5 dakika dinlenmesine izin verilmeli, uygun koşullarda, avuç açık, kol kalp seviyesinde desteklenerek ölçüm yapılmalıdır. Bir seferde en az iki ölçüm (1-2 dakika ara ile), iki ölçüm arasında 10 mmHg'den daha fazla fark varsa ardışık ölçümler yapılarak son iki ölçümün ortalaması kaydedilmelidir.

Hastada aritmi varsa, otomatik cihazlarla kan basıncı ölçümü hatalı sonuç verebilir. Bu nedenle, mutlaka her ölçümden önce palpasyonla nabız en az 30 sn değerlendirilmeli ve düzensizlik varsa stetoskop kullanılarak kan basıncı klasik yöntemle ölçülmelidir.

• Evde kan basıncı ölçümü (EKBÖ)

Evde kan basıncı ölçümünde, kol için uygun manşonlu ve onaylı otomatik osilometrik tansiyon ölçüm aleti kullanılmalıdır (https://www.stridebp.org/home-pdf/; http://www.turkhipertansiyon.org/pdf/Onayli_Aletler_2017.pdf).

Evde ölçümler en az 5 gün yapılmalıdır. Kan basıncı, sabah ve akşam saatlerinde ve her seferinde en az ikişer kez ölçülmelidir. Evde kan basıncı ölçümü, en az 5 dakika dinlendikten sonra yapılmalı ve ölçümden önceki 30 dakika içinde sigara veya kahve içilmemeli, egzersiz yapılmamalıdır.

Tablo 3. Ev kan basıncı ölçümü ve ambulatuar kan basıncı ölçümü: Klinik kullanım, endikasyon, eşik değerler ve ölçüm sıklığı

	EKBÖ Onaylı cihaz, standart teknik	AKBÖ Onaylı cihaz, standart teknik
Klinik kullanım		
HT tanısını doğrulama	++	+++
Maskeli ve beyaz önlük HT tanısı	+++	+++
Nokturnal KB yüksekliği	-	+++
Sabah KB yüksekliği	++	+++
Gerçek dirençli HT tanısı	++	+++
Gebelikte HT	+	+++
Postural hipotansiyon	+	+++
24 saatlik KB kontrolü	+	+++
Kan basıncı değişkenliği	++	+++
Uzun dönem takip	+++	+
Ana endikasyon	Tedavi altındaki hastalarda uzun dönem takip	HT tanısı
HT tanısı için eşik değerler	● ≥135/85 mmHg	● ≥135/85 mmHg (gündüz) ● ≥130/80 mmHg (24 saatlik ortalama) ● ≥120/70 mmHg (gece)
Ölçüm sıklığı	● 5 gün sabah akşam 1-2 dk ara ile en az 2'şer ölçüm ● Uzun dönem takipte ayda 1 hafta	● Gündüz 15-30 dk'da bir, gece 30-60 dk da bir ölçüm ● Gündüz 20, gece 7 geçerli ölçüm veya 24 saatte %70 geçerli ölçüm

AKBÖ, Ambulatuar kan basıncı ölçümü; EKBÖ, Ev Kan Basıncı Ölçümü; HT, Hipertansiyon; KB, Kan basıncı.

Tablo 4. Hipertansif hastada önerilen başlangıç incelemeleri

Başlangıç tetkikleri
Tam kan sayımı
Tam idrar tetkiki
Açlık plazma glukozu ve/veya HbA1c
Kreatinin ve eGFR
Sodyum, potasyum ve ürik asit
Lipid profili
Elektrokardiyografi
AST/ALT
Kalsiyum
TSH
Spot idrar albümin kreatinin oranı
Aldosteron/Plazma Renin Aktivitesi*

*Evre 2 hipertansiyonda (imkan varsa). ALT, Alanin aminotransferaz; AST, Aspartat aminotransferaz; eGFR, Tahmini glomerüler filtrasyon hızı; TSH, Tiroid stimülan hormon.

Tablo 5. Değerlendirmede istenilebilecek ek tetkikler

Hedef organ hasarını saptamaya yönelik ek tetkikler
Ekokardiyografi
Karotis Ultrasonografisi (USG)
Fundoskopi
Abdominal USG
Ayak bileği kol indeksi

Bir dakika arayla iki ölçüm alınarak, bu iki ölçümün ortalaması kaydedilmelidir. Kan basıncı ölçümünde kullanılacak otomatik tansiyon ölçüm cihazının koldan ölçüm yapan cihaz olması önemlidir. Bilekten ölçüm yapan cihazlar genellikle tercih edilmemekle birlikte, kol ölçümünü çeşitli nedenlerle yapamayan kişilerde geçerliliği bildirilmiş bilekten ölçüm yapan cihazlar evde kan basıncı takibinde kullanılabilir. Hastalara, evde kan basıncı ölçümünün nasıl yapılacağına dair eğitim verilmelidir. Beyaz önlük etkisi veya maskeli hipertansiyon şüphesi varsa, ev ölçümleri özellikle istenmelidir.

● Ambulatuar kan basıncı ölçümü (AKBÖ)

Özel bir cihazın hasta üzerinde 24 saat süreyle taşınarak günlük aktivite ve uyku sırasında kan basıncı kayıtlarının alınması ile yapılan AKBÖ, hipertansiyonun tanısında ve takibinde ideal bir yöntemdir ve imkân olan her durumda kullanılmalıdır (Şekil 3C).

Manuel aneroid sfigmomanometre ile ölçüm ilkeleri ve AKBÖ cihazının hastaya takılması, ölçüm aralıklarının ayarlanması ve raporun değerlendirilmesiyle ilgili detaylı bilgi Ek B'de verilmiştir.

Ev kan basıncı ölçümü ve ambulatuar ölçüm için klinik kullanım, ana endikasyon, eşik değerler ve ölçüm sıklığı Tablo 3'te karşılaştırmalı olarak belirtilmiştir.

4. Başlangıçta Yapılması Gereken İncelemeler

Kardiyovasküler riski, hedef organ hasarını ve sekonder hipertansiyonu araştırmak ve değerlendirmek amacıyla, her hastada bazı laboratuvar tetkiklerinin yapılması gereklidir. Başlangıçta istenilmesi gereken tetkikler Tablo 4'te gösterilmiştir. Hipertansif hastalarda, hedef organ hasarını saptamak için istenilebilecek ek tetkikler Tablo 5'te gösterilmiştir.

Tablo 6. Sekonder hipertansiyon düşünülen hastalarda öncelikli tetkikler[7,9,10]

Klinik veya laboratuvar belirti/bulgular	Öncelikli tetkikler
Renovasküler hastalık	
● RAAS blokeri başlandıktan sonra kreatinin düzeyinin akut olarak %30'dan fazla yükselmesi ve sebat etmesi ● Diffüz aterosklerozu olan hastada hipertansiyon, tek taraflı küçük böbrek veya her iki böbrek boyutu arasında nedeni açıklanamayan 1.5 cm'den fazla fark ● Tekrarlayan akut pulmoner ödem atakları ● Renal arter trasesinde üfürüm	● Renal arter Doppler USG ● BT/MR anjiyografi
Renal parankim hastalığı	
● Serum kreatinin yüksekliği ● Anormal idrar sedimenti ● Proteinüri	● Serum kreatinin düzeyi, eGFR ● Renal USG ● Tam idrar tetkiki ● Spot idrar albümin kreatinin oranı
Primer aldosteronizm	
● Açıklanamayan hipokalemi (olguların yarısında görülmeyebilir) ● Metabolik alkaloz ● Adrenal insidentaloma ● Evre 2 hipertansiyon ● Dirençli hipertansiyon	● Aldosteron /PRA oranı
Cushing sendromu	
● Santral obezite, cushingoid yüz, proksimal kas güçsüzlüğü ve ekimozlar ● Glukokortikoid kullanım öyküsü olabilir	● Düşük doz deksametazon süpresyon testi ● 24 saatlik idrar kortizolü
Hipotiroidi/hipertiroidi	
● Kilo alma/Kilo verme ● Bradikardi/Taşikardi ● Soğuk/sıcak intoleransı ● Diyare/konstipasyon ● Adet düzensizliği, menoraji, amenore	● TSH, Serbest T4
Feokromasitoma	
● Kan basıncında paroksismal yükselme ● Zonklayıcı baş ağrısı, çarpıntı, terleme ● Al basması (flushing) ve ani solukluk	● Plazma veya 24 saatlik idrar metanefrin ve normetanefrin düzeyleri
Obstruktif uyku apne sendromu	
● Dirençli hipertansiyonu olan, fazla kilolu veya obeziteli bireyler ● Horlama ve apne epizodları ● Gün içinde uykululuk, yorgunluk	● Polisomnografi
Aort koarktasyonu	
● Kol ve bacak SKB farkı (>20 mmHg) ● Femoral nabızların gecikmesi veya alınamaması	● Ekokardiyografi ● MR/BT anjiyografi
Primer hiperparatiroidi	
● Böbrek taşı öyküsü ● Hiperkalsemi ● Peptik ülser öyküsü	● PTH, Kalsiyum, Fosfor

BT, Bilgisayarlı tomografi; eGFR, Tahmini glomerüler filtrasyon hızı; MR, Manyetik rezonans; PRA, Plazma renin aktivitesi; PTH, Paratiroid hormonu; RAAS, Renin anjiyotensin aldosteron sistemi; SKB, Sistolik kan basıncı; TSH, Tiroid stimülan hormon; USG, Ultrasonografi.

SEKONDER HİPERTANSİYON

Hipertansiyon, bilinen bir etiyolojik nedene bağlı ise sekonder hipertansiyon olarak kabul edilmektedir. Sekonder hipertansiyon, tüm hipertansiyon olgularının yaklaşık %10'unu oluşturur.

Hipertansiyon hastalarının hepsinin sekonder hipertansiyon açısından değerlendirilmesi hem zaman hem de maliyet açısından uygun olmayacağından, poliklinikte elde edilen ipuçlarıyla kimlerin araştırılacağına karar verilmesi daha uygundur. Bununla birlikte, kanıta dayalı çalışmalar, hipertansiyonu olan ve primer hipertansiyon tanısı almış hastalarda primer hiperaldosteronizm prevalansının oldukça fazla olduğunu göstermektedir. Bu nedenle, evre 2 hipertansiyonu olan bireylerde imkân varsa aldosteron ve plazma renin aktivitesi ölçümü ile primer hiperaldosteronizm için tarama yapılması uygundur.

Sekonder hipertansiyonun araştırılması gereken durumlar aşağıda özetlenmiş; sekonder hipertansiyon düşünülen hastada istenilecek tetkikler ise Tablo 6'da gösterilmiştir.[7,9,10]

Kimlerde sekonder hipertansiyon araştırılmalıdır?

1. Anamnezde sekonder hipertansiyonu düşündürecek durumlar:

a. Ailede böbrek hastalığı öyküsü

b. İlaç kullanımı: Nonsteroid antiinflamatuarlar, dekonjestanlar, glukokortikoidler, oral kontraseptifler, serotonin-norepinefrin geri alım inhibitörleri (SNRI) grubu antidepresanlar (özellikle venlafaksin), meyan kökü şurubu, kokain, amfetamin, mirabegron, modafinil, eritropoietin, siklosporin, anti-kanser ilaçlar (vasküler endotelyal büyüme faktörü [VEGF] inhibitörleri, platin bazlı ilaçlar, alkilleyici ajanlar, kalsinörin inhibitörleri, proteazom inhibitörleri, B-raf geni/mitojenle etkinleşen hücre dışı sinyal düzenlemeli kinaz [BRAF/MEK] inhibitörleri, transfeksiyon sırasında yeniden düzenlenen [RET] geni kinaz inhibitörleri, poli ADP riboz polimeraz [PARP] inhibitörleri, memeli rapamisin hedefi [mTOR] inhibitörleri, androjen sentez inhibitörleri), alkol ve bitkisel ürünler (sarı kantaron, ginseng vb.) sekonder hipertansiyon ve/veya dirençli hipertansiyon sebebi olabilirler (Ek C).

c. Kas güçsüzlüğü

d. Horlama, uyku apnesi

e. Terleme atakları, baş ağrısı, anksiyete, çarpıntı

2. Dirençli hipertansiyonu olan hastalar:

Farklı sınıf (biri diüretikler olmak üzere) üç adet, yeterli dozda antihipertansif kullanımına rağmen kan basıncı kontrolde olmayan hastalar

3. Antihipertansif tedavi altındayken kan basıncı kontrolü aniden bozulan hastalar
4. 30 yaşından önce başlayan veya 60 yaş üzerinde ani başlayan evre 2 hipertansiyon
5. Kan basıncı düzeyine göre beklenenden daha ağır hedef organ hasarı gelişmiş hastalar
6. ACEİ (Anjiyotensin dönüştürücü enzim inhibitörleri) veya ARB (Anjiyotensin reseptör blokerleri) kullanımı sonrası kreatinin değerlerinde ciddi yükselme (kısa sürede %30 üzerinde) olan hastalar
7. Rutin laboratuvar incelemelerinde hipokalemi tespit edilen hastalar
8. Endokrin hipertansiyonu düşündüren klinik veya biyokimyasal bulgular (Tablo 6)
9. Aterosklerotik renovasküler hastalık veya fibromüsküler displazi lehine klinik bulgular (Tablo 6)

HİPERTANSİYONDA KIRILGANLIK DEĞERLENDİRMESİ

Kırılganlık, stres faktörlerine karşı adaptasyon yeteneğinde azalma ve dolayısıyla sağlıkla ilişkili olumsuz sonuçlara (örneğin yeti kaybı/engellilik ve mortalite) karşı artmış duyarlılık hâlidir. Kırılganlık, "biyolojik yaşlılık"ı ifade eder. Takvim yaşı (kronolojik yaş), biyolojik yaş için kaba bir öngörü sağlasa da tedavi planlamasında tek başına yeterli değildir (Ek D).

Kırılgan bireyler, genellikle yavaş yürüyen, fiziksel aktivite düzeyi azalmış, son aylarda kilo kaybı ve/veya iştahsızlık yaşayan, güçsüzlük, yorgunluk ve bitkinlik yakınmaları olan kişilerdir. Bu belirtiler, klinik gözlemle ya da hasta/hasta yakınıyla görüşerek kolayca fark edilebilir. Klinisyen, bu alanlardaki gözlemleri ve sorgulamalar ile kırılganlığın varlığı ve düzeyi hakkında fikir sahibi olmalıdır. Bu süreçte, Klinik Kırılganlık Skalası gibi görsel araçlar da değerlendirmeye yardımcı olabilir.[11-14]

Grup 5 ve üzeri için kırılganlık söz konusudur. Grup 1-3 (çok dinç-dinç-iyi idare eden), Grup 4-5 (çok hafif kırılgan/hafif kırılgan), Grup 6-9 (orta, ileri, çok ileri kırılgan ve terminal dönem) olarak nitelendirilir (Şekil 4).

Yaşlı bireylerde, antihipertansif tedaviye başlamadan önce, ayrıca yılda en az bir kez ya da genel sağlık durumunda belirgin bir değişiklik olduğunda kırılganlık durumu tekrar değerlendirilmelidir. Bu değerlendirme, tedavi hedeflerinin ve ilaç seçimlerinin yeniden gözden geçirilmesi açısından önemlidir.

Demans, kırılganlık için önemli bir belirleyicidir ve sınıflamayı da etkiler. Kırılganlık derecesi, genellikle demans derecesiyle paralellik gösterir. Bu nedenle, tüm yaşlı hipertansif hastalar – özellikle 80 yaş ve üzerindekiler – bilişsel bozukluk açısından taranmalı ya da uygun bir uzmana yönlendirilmelidir.

TEDAVİ

1. Yaşam Tarzı Değişiklikleri

Toplum sağlığı açısından, erişkin bireyin kan basıncı hangi düzeyde olursa olsun uygun yaşam tarzı değişiklikleri önerilmelidir. Bu değişikliklerin hayata geçirilmesi için tüm sağlık profesyonellerinin katkısı sağlanmalı ve hastanın her vizitinde önerilere uyum durumu sorgulanmalıdır. Yaşam tarzı değişiklik önerileri şunlardır:

- **İdeal vücut ağırlığı:** Türkiye Sağlık Araştırması 2022 verilerine göre, 15 yaş ve üzeri popülasyonda obezite prevalansı %20,2'dir (kadınlarda %23,6, erkeklerde %16,8).[15] Fazla kilolu ve obeziteli bireylerde en az %5-10 düzeyinde ağırlık kaybı sağlanması ve kilo kontrolünün sürdürülmesi önerilmektedir. Ancak, yaşlı bireylerde durum farklıdır; bu grupta ölüm riski ve/veya işlevsel bağımlılık, genellikle fazla kilolu kategorisinde en düşük seviyede görülmektedir. Bu nedenle, fazla kilolu yaşlılarda kilo kaybı genellikle önerilmez. Obeziteli yaşlı bireylerde ise, eğer genel sağlık durumu iyi ve fiziksel olarak "dinç"lerse, dikkatli ve yavaş bir kilo kaybı sağlanması risk-yarar dengesi göz önünde bulundurularak değerlendirilebilir.[6,16,17]

- **Tuz kısıtlaması:** Günlük sodyum alımı 2–2,4 g (5–6 g tuz) ile sınırlandırılmalıdır.[18,19] SALTURK çalışmaları, Türkiye'de ortalama tuz tüketiminin önerilenin yaklaşık 3 kat üzerinde olduğunu göstermiştir (14–15 g/gün).[20,21] Bu nedenle, ülkemizde sodyum alımının mutlaka azaltılması önerilmelidir. Sodyumu kısıtlamada güçlük yaşayan hastalarda, sodyumu azaltılmış tuzların kullanılması önerilebilir. Ancak, ciddi böbrek fonksiyon bozukluğu veya potasyum tutucu diüretik kullanan olgularda dikkat edilmelidir. Malnütrisyon riski yüksek olan ve/veya kırılgan hastalarda sıkı tuz kısıtlamasından kaçınılmalıdır.[6,17,22,23]

- **Sağlıklı beslenme:** Hipertansiyon hastalarının beslenmesinde ağırlıklı olarak sebze ve meyve, az yağlı besinler, tam tahıl, sebze kaynaklı protein ve haftada en az iki kez balık yer almalıdır. Çabuk tüketilen, işlenmiş ve aşırı yağ, rafine şeker ve tuz içeren yiyecekler ile enerji içeceklerinden kaçınılmalıdır. Yaşlı bireylerin yeterli protein alması sağlanmalıdır. Bu, hem genel sağlığın

Şekil 4. Klinik Kırılganlık Skalası. Demansı olan hastalarda kırılganlık derecesi ve demans dereceleri benzerdir. Hafif demans: Yakın zamanlı olayın kendisini hatırlasa da detaylan unutma, aynı sorulan/hikayeyi tekrarlama, sosyal geri çekilme. Orta evre demans: Eski olaylar hatırlansa da yakın dönem hafıza ciddi olarak bozulmuştur. Destekleme ile kişisel bakim yapabilirler. İleri evre demans: Kişisel bakım desteksiz yapılamaz.

Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489-495. [CrossRef]
Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. *Can Geriatr J*. 2020;23(3):210-215. [CrossRef]
Özsürekci C, Balcı C, Kızılarslanoğlu MC, et al. An important problem in an aging country: identifying the frailty via 9 Point Clinical Frailty Scale. *Acta Clin Belg*. 2020;75(3):200-204. [CrossRef]
Aşık Z, Kılınç Ş, Kurşun Ö, Özen M. Validation of the Clinical Frailty Scale version 2.0 in Turkish older patients. *Geriatr Gerontol Int*. 2022;22(9):730-735. [CrossRef]

korunması hem de kilo kontrolü hedeflenen durumlarda kas kaybını önlemek için özellikle önemlidir.

- **Sigaranın bırakılması:** Hipertansif hastaların sigara veya elektronik sigara kullanmaması, kullanıyor ise mutlaka bırakması tavsiye ve teşvik edilmelidir. Sigara bırakma, kardiyovasküler riski azaltmada en etkili faktörlerden biridir. Her bir sigara, 30 dk süreyle kan basıncını yükseltebilir.

- **Alkolün bırakılması:** Hipertansif hastaların alkol kullanması önerilmez. Eskiden, belli bir düzeydeki alkol alımının zararsız olduğu düşüncesi hâkimken, son zamanlarda alkolün hiçbir dozunun kardiyovasküler açıdan koruyucu özellik içermediği belirlenmiştir.

- **Fiziksel aktivite:** Hastalara, yaşına ve fiziksel durumuna uygun şekilde düzenli fiziksel aktivite/egzersiz yapması tavsiye edilmelidir. Genel olarak, haftada en az 5 kez 30 dakikadan az olmayan aerobik aktivite; ilave olarak kas güçlendirici egzersizler, denge ve germe egzersizleri de önerilmelidir. Buna ek olarak, gün boyunca hareketli bir yaşam tavsiye edilmelidir. Yaşlı bireylerde hem genel sağlık için hem de özellikle ılımlı kilo kaybı hedeflendiğinde, kas kaybını önlemek amacıyla kas güçlendirme (direnç) egzersizlerine ayrıca önem verilmelidir.

- **Stres yönetimi:** Stresi azaltmaya yönelik nefes ve gevşeme egzersizleri, meditasyon, yoga ve tai chi gibi zihin-beden uygulamaları; stres ve duygu durumu üzerine olumlu etkilerinin yanı sıra, sistolik ve diyastolik kan basıncını da düşürmekte ve bu açıdan hipertansiyon hastalarında önerilebilecek stres azaltıcı teknikler arasında kabul edilmektedir.

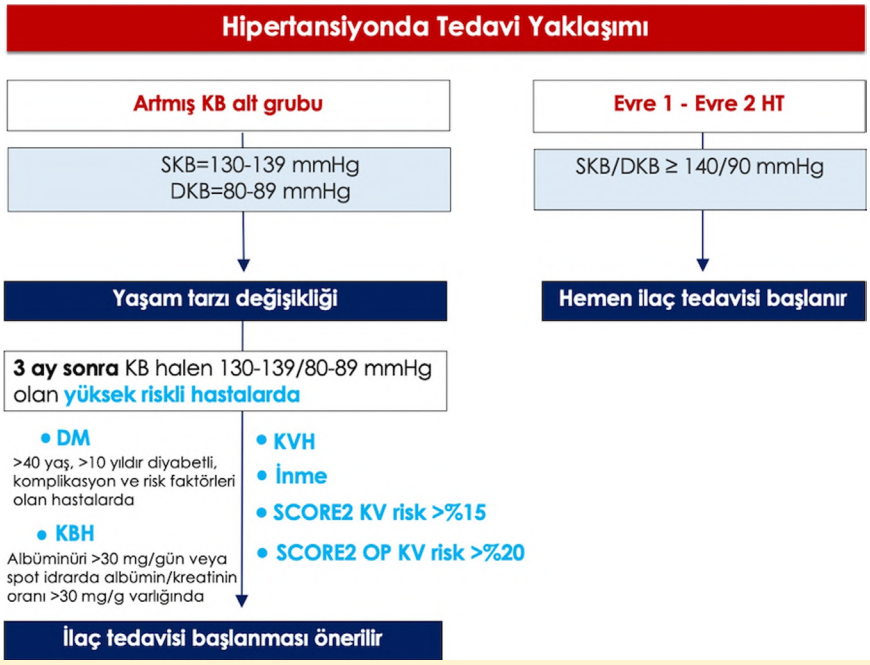
- **Uyku hijyeni:** Hipertansiyon hastalarının uyku kalitesinin yükseltilmesi gereklidir. Her akşam aynı saatte uyunması, yatak odasında televizyon, bilgisayar vb. ekranların olmaması, günlük uyku süresinin ortalama 7–9 saat olması, yatak odasının havalandırılmasının yeterli olması ve ses ile gürültü kirliliğinden arındırılması gerekir.

- **Hava ve gürültü kirliliği:** Kardiyovasküler sağlığı olumsuz etkileyen bu durumlardan, açık hava aktivitelerinin zaman, yer ve tipi uygun şekilde ayarlanarak ve ev içi ortamda maruziyet mümkün olduğunca azaltılarak kaçınılması önerilir.

2. İlaç Tedavisi

İlaç tedavisi için Eşik KB:
- **18-79 yaş: SKB/DKB ≥ 140/90 mmHg**
- **≥ 80 yaş (dinç): SKB ≥ 140 mmHg**
- **Kırılgan hasta: SKB ≥ 160 mmHg**

Antihipertansif ilaç tedavisine başlamak için, kan basıncı değeri ile birlikte risk faktörleri, eşlik eden hastalıklar ve kırılganlık durumu dikkate alınmalıdır.



Şekil 5. Hipertansiyonda tedavi yaklaşımı.

DKB, Diyastolik kan basıncı; DM, Diabetes mellitus; HT, Hipertansiyon; KB, Kan basıncı; KBH, Kronik böbrek hastalığı; KV, Kardiyovasküler; KVH, Kardiyovasküler hastalık (Koroner arter hastalığı, periferik arter hastalığı, kalp yetersizliği); SKB, Sistolik kan basıncı.

a) Yaş ve kırılganlık durumuna göre eşik ve hedef kan basıncı düzeyleri:

● 18–79 yaş arasındaki dinç hastalarda, tedaviye başlamak için eşik poliklinik sistolik kan basıncı değeri ≥140 mmHg veya diyastolik kan basıncı değeri ≥90 mmHg iken, ≥80 yaş veya kırılgan hastalarda eşik poliklinik sistolik kan basıncı değeri ≥160 mmHg'dir. Dinç ≥80 yaş bireylerde, sistolik kan basıncı ≥140 mmHg değerinde tedavi başlanması düşünülebilir (Tablo 7).

● 18–79 yaş arasındaki dinç hastalarda, hedef kan basıncı düzeyi 120–130/70–80 mmHg iken, yaşı ≥80 olan hastalarda hedef sistolik kan basıncı düzeyi 140–150 mmHg'dir. Dinç ≥80 yaş bireylerde, 130–140 mmHg hedeflenmesi düşünülebilir (Tablo 7).

b) Evre 1- Evre 2 hipertansiyon ilaç tedavisi yaklaşımı: Evre 1 ve Evre 2 hipertansiyonda (SKB/DKB ≥140/90 mmHg), ilaç tedavisine hemen başlanır (Şekil 5, Şekil 6).

SKB/DKB ≥140/90 mmHg: İlaç tedavisine hemen başlanır

c) Artmış kan basıncına ilaç tedavisi yaklaşımı: En az 3 ay yaşam tarzı değişikliği uygulamasına rağmen artmış kan basıncı olan hastalarda, aşağıdaki durumlardan herhangi birinin varlığında antihipertansif tedavi (tercihen monoterapi) önerilir (Şekil 5, Şekil 6):

- Diyabetes mellitus (DM: 40 yaş üzeri, 10 yıldan uzun süredir diyabetli, komplikasyonu ve obezite, sigara kullanımı gibi diğer risk faktörleri olan hastalarda)
- Kronik böbrek hastalığı (KBH: Albüminüri >30 mg/gün veya spot idrarda albümin/kreatinin oranı >30 mg/g varlığında)

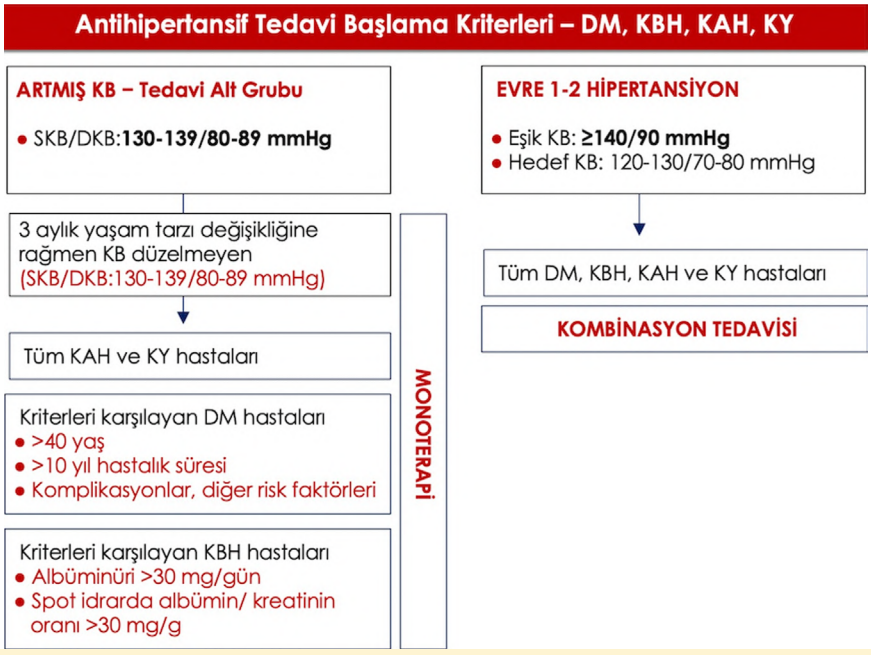
Tablo 7. Hipertansiyonu olan hastalarda yaş ve kırılganlık durumuna göre ilaç tedavisi için eşik ve hedef kan basıncı düzeyleri

Yaş grubu/kırılganlık	Eşik kan basıncı (mmHg)	Hedef kan basıncı (mmHg)
18–79 yaş[1]	≥140/90	120–130/70–80
≥80 yaş (dinç)[2]	≥140	130-140
Kırılgan hastalar[3]	≥160	140-150

[1]Komorbiditeden bağımsız (Diyabetes mellitus, koroner arter hastalığı, kronik böbrek hastalığı, kalp yetersizliği). [2]80 yaş öncesi başlanmış tedaviyi tolere ediyorsa, sadece yaş nedeniyle antihipertansif tedavi azaltılmamalı; fakat yakın takip edilmelidir. [3]Çoklu komorbiditesi, fonksiyonel kısıtlaması olan kırılgan bireylerde yaştan bağımsız bu hedefler geçerlidir. Organ hipoperfüzyonu açısından dikkatli takip gereklidir ve buna göre tedavi bireyselleştirilmelidir.

- Kardiyovasküler hastalık (KVH: Koroner arter hastalığı, periferik arter hastalığı, kalp yetersizliği)
- İnme
- SCORE2 kardiyovasküler (KV) risk >%15 (40–79 yaş arası); SCORE2-OP KV risk >%20 (yaşlı hastalar)

Farklı kılavuzlarda, risk belirlemek için değişik skorlar ve eşik değerleri kullanılmaktadır. Artmış kan basıncına yönelik antihipertansif tedavinin, kardiyovasküler koruma açısından sadece yüksek ve çok yüksek kardiyovasküler riski olan hastalarda etkili olduğu; düşük veya orta dereceli kardiyovasküler riski olan hastaların bu anlamda tedaviden fayda görmediğini gösteren meta-analiz verilerinden de hareketle,[24] ülkemiz için bu şekilde bir risk eşiği belirlemenin uygun olduğu düşünüldü.



Şekil 6. Özel hasta gruplarında antihipertansif tedavi başlama kriterleri – DM, KBH, KAH, KY.

DKB, Diyastolik kan basıncı; DM, Diabetes mellitus; HT, Hipertansiyon; KAH, Koroner arter hastalığı; KB, Kan basıncı; KBH, Kronik böbrek hastalığı; KY, Kalp yetersizliği; SKB, Sistolik kan basıncı.

Tablo 8. Antihipertansif ilaçların kontrendikasyonları

İlaç	Mutlak kontrendikasyon	Göreceli kontrendikasyon
Diüretikler (tiyazid veya tiyazid benzerleri)	Tiyazide bağlı hiponatremi öyküsü	Glukoz intoleransı, gebelik, hiperkalsemi, hipokalemi, gut
Kalsiyum kanal blokerleri (dihidropiridinler)	Yok	Kalp yetersizliği, ayak bileği ödemi öyküsü
Kalsiyum kanal blokerleri (verapamil, diltiazem)	AV blok (2. veya 3. derece ile trifasiküler blok), ciddi sol ventrikül sistolik disfonksiyonu	Yok
ACEİ	Gebelik, gebelik planı olan kadınlar, anjionörotik ödem, hiperkalemi, bilateral renal arter stenozu	Yok
ARB	Gebelik, gebelik planı olan kadınlar, hiperkalemi, bilateral renal arter stenozu	Yok
Beta blokerler	Aktif astım, AV blok (2. veya 3. derece)	Glukoz intoleransı, sporcu veya aktif kişiler, astım öyküsü

ACEİ, Anjiyotensin dönüştürücü enzim inhibitörleri; ARB, Anjiyotensin reseptör blokerleri; AV, Atriyoventriküler.

3. İlaç Seçimi

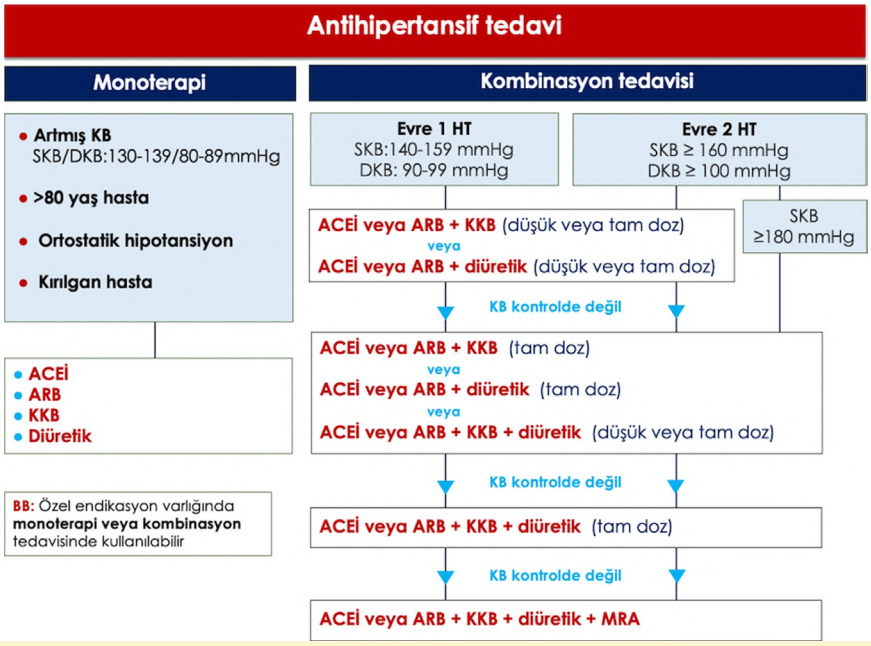
Ek bir hastalığı olmayan tüm hipertansif bireylerde, birinci basamak ilaç tedavisinde tercih edilecek ilaç grupları; anjiyotensin dönüştürücü enzim inhibitörleri (ACEİ), anjiyotensin reseptör blokerleri (ARB), tiyazid ve tiyazid-benzeri diüretikler ve kalsiyum kanal blokerleri (KKB) olarak sayılmaktadır. Beta blokerler; atriyal fibrilasyon, kalp yetersizliği, koroner arter hastalığı ve gebelikteki hipertansif durumlar gibi başlıca endikasyonları dışında, özellikli endikasyonlarında da hipertansiyon tedavisi için ilk seçenek olarak kullanılabilir ya da tedavinin herhangi bir basamağına eklenebilir.

Bu dört ana grup ilacın, Evre 1–Evre 2 hipertansiyonda aşağıda önerilen algoritma ile kombinasyon tedavisi şeklinde başlanması önerilir. Ancak, özel durumlarda (80 yaş üstü, kırılgan, artmış kan basıncı, ortostatik hipotansiyon) monoterapi tercih edilebilir.

Kombinasyon tedavisi – Algoritma: Evre 1 hipertansiyon ve SKB'nin <180 mmHg olduğu Evre 2 hipertansiyonda, tedaviye ilk basamakta "ACEİ veya ARB + KKB" veya "ACEİ veya ARB + diüretik" düşük veya tam doz ikili kombinasyonu ile başlanılması tercih edilir.

İkili kombinasyon tedavisi başlandığı takdirde, hedef kan basıncına ulaşılamadığında mevcut düşük doz kombinasyonun maksimum dozuna çıkılabileceği gibi, düşük veya tam doz "ACEİ veya ARB + KKB + diüretik" üçlü kombinasyonuna da geçilebilir.

Maksimal tolere edilebilen dozda kullanılan üçlü kombinasyonla (biri diüretik olmak kaydıyla) kan basıncı kontrol altında değilse, bu durum dirençli hipertansiyon olarak kabul edilip tedaviye mineralokortikoid reseptör antagonistinin (MRA) eklenmesi düşünülmelidir.



Şekil 7. Hipertansiyon tedavisinde ilaç seçimi akış şeması.

ACEİ, Anjiyotensin dönüştürücü enzim inhibitörleri; ARB, Anjiyotensin reseptör blokerleri; BB, Beta blokerler; DKB, Diyastolik kan basıncı; HT, Hipertansiyon; KB, Kan basıncı; KKB, Kalsiyum kanal blokerleri; MRA, Mineralokortikoid reseptör antagonisti; SKB, Sistolik kan basıncı.

SKB'nin ≥180 mmHg olduğu Evre 2 hipertansiyon olgularında ise tedaviye doğrudan 2. basamaktan (tam doz ikili kombinasyon veya düşük ya da tam doz üçlü kombinasyon) başlanabilir (Şekil 7).

Hasta uyumu açısından, tek tablette kombinasyon tedavisi tercih edilmelidir. Tedavide birden fazla tablet kullanılıyorsa, en az birinin akşam saatlerinden sonra verilmesi önerilir.

İlaç seçiminde, ilaç kontrendikasyonları, hasta cevabı ve tolere edilebilirlik dikkate alınmalıdır. İlaçların mutlak ve göreceli kontrendikasyonları Tablo 8'de gösterilmiştir.[18]

DİRENÇLİ HİPERTANSİYON

Uygun yaşam tarzı önlemleri ve optimal veya maksimum dozlarda en az üç veya daha fazla ilaç (tiyazid/tiyazid benzeri diüretik, RAAS blokeri ve KKB) kullanılmasına rağmen, poliklinik KB değerinin <140/90 mmHg'ye düşürülememesi dirençli hipertansiyon olarak tanımlanmaktadır. Poliklinik kan basıncı ölçümlerini doğrulamak ve beyaz önlük etkisini dışlamak için; 24 saatlik AKBÖ (SKB ≥130 mmHg veya DKB ≥80 mmHg) yapılmalıdır.

Dirençli hipertansiyon tanısı koymak için, yalancı dirençli hipertansiyon mutlaka dışlanmalıdır. Bu amaçla, yalancı dirençli hipertansiyonun en sık sebebi olan yaşam tarzı değişiklikleri de dâhil olmak üzere, hastanın tedaviye uyumu doğrulanmalıdır. Hastanın kan basıncı yüksekliğine sebep olan ilaç alımı ve gıda tüketimi ile diğer yalancı dirençli hipertansiyon sebepleri araştırılmalıdır (Ek C). Hastanın, sekonder hipertansiyon sebeplerinin araştırılması ve daha ileri tetkik için üçüncü basamak ya da bir hipertansiyon merkezine sevk edilmesi, bu aşamada uygun bir yaklaşım olabilir (Şekil 8).

Dirençli hipertansiyonun en sık rastlanan sekonder sebeplerinden birisi primer aldosteronizmdir. Bu nedenle, bu hastalarda serum potasyum değerinden bağımsız olarak mutlaka serum/plazma aldosteron konsantrasyonu ve plazma renin (konsantrasyon veya aktivitesi) ile primer aldosteronizm taraması yapılmalıdır.[25] Ayrıca, semptomlarla uyumsuz olarak kan basıncı ısrarlı biçimde yüksek bulunanlarda psödohipertansiyon araştırılmalıdır.

Gerçek dirençli hipertansiyona yaklaşım; yaşam tarzı değişikliklerinin (özellikle sodyumun ve alkol alımının azaltılması, düzenli fiziksel aktivite uygulanması, obeziteli hastalarda kilo kaybı) sıkı şekilde uygulanması ve mevcut üçlü tedaviye antihipertansif ilaçların eklenmesini içermektedir.

İlaçlar, tolere edilebilen maksimum dozlarda kullanılmalı; tablet yükünü azaltmak ve tedaviye uyumu artırmak için tek tablet kombinasyonları tercih edilmelidir.

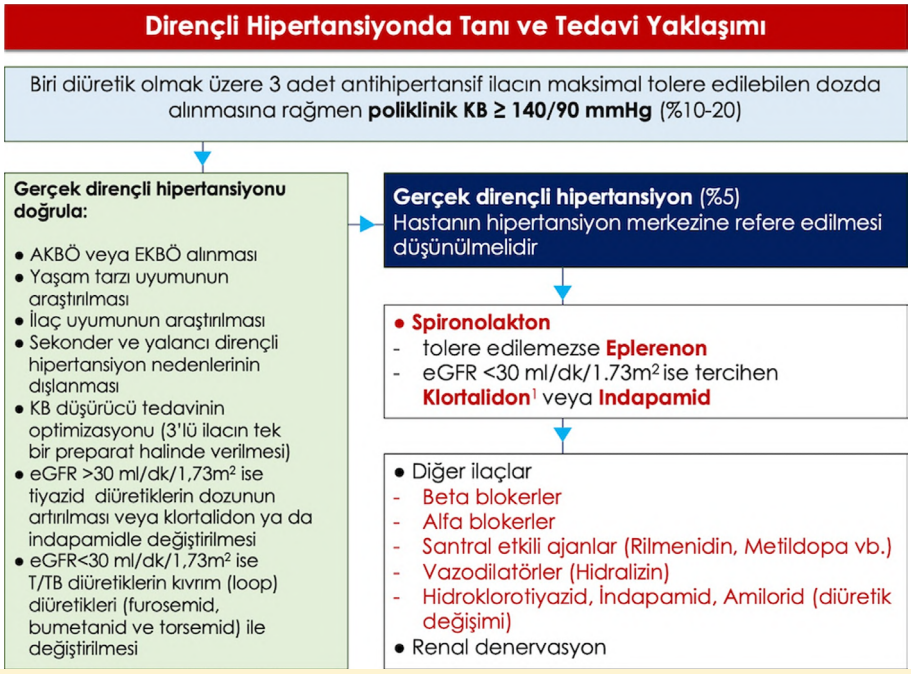
Tahmini glomerüler filtrasyon hızı (eGFR) ≥30 ml/dk/1,73 m² ise tiyazid diüretiğin dozu artırılarak veya daha güçlü ve daha uzun etkili indapamid ya da klortalidon gibi tiyazid benzeri diüretiklerle değiştirilerek KB kontrolü sağlanabilir.

eGFR <30 ml/dk/1,73 m² ise tiyazid/tiyazid benzeri diüretiklerin yerine kıvrım (loop) diüretikleri (furosemid, bumetanid ve torsemid) tercih edilmelidir (Şekil 8).

Bu tedaviler sonrasında kan basıncı hâlâ kontrol altına alınamıyorsa, dördüncü basamak tedavide öncelikle MRA olan spironolakton eklenir; tolere edemeyen hastalarda eplerenon 50–100 mg dozlarında kullanılabilir.

eGFR <30 ml/dk/1,73 m² olan hastalarda hiperkalemi riski nedeniyle klortalidon da tercih edilebilir.

Bunların yanı sıra; beta blokerler, alfa blokerler ve santral etkili antihipertansifler (rilmenidin, metildopa vb.), potasyum tutucu diüretikler (amilorid) ve vazodilatörler (ülkemizde mevcut olmayan hidralazin) gibi diğer ajanlar, alternatif olarak tedaviye eklenebilir.



Şekil 8. Dirençli hipertansiyonda tanı ve tedavi yaklaşımı.

AKBÖ, Ambulatuar kan basıncı ölçümü; eGFR, Tahmini glomerüler filtrasyon hızı; EKBÖ, Ev kan basıncı ölçümü; KB, Kan basıncı; T/TB, Tiyazid/Tiyazid benzeri.
[1]Türkiye'de izole preparat olarak bulunmamaktadır.

Dirençli hipertansiyon tedavisinde tüm farmakolojik tedaviler yetersiz kaldığında, seçilmiş hastalarda renal denervasyon akla getirilebilir. Bu son aşamada, sekonder hipertansiyonu ve renal fonksiyonları korunmuş hastalarda renal denervasyon seçeneğinin değerlendirilmesi açısından hastanın daha ileri merkezlere yönlendirilmesi düşünülebilir (Şekil 8).

Dirençli hipertansiyon tedavisi için yeni ilaç grupları (aldosteron sentaz inhibitörleri gibi) geliştirilmektedir ve yakın gelecekte kullanıma girmeleri beklenmektedir.

İZOLE SİSTOLİK HİPERTANSİYON

İzole sistolik hipertansiyon (İSH), tipik olarak sistolik kan basıncının ≥140 mmHg ve diyastolik kan basıncının <90 mmHg olması olarak tanımlanır.

İSH, genç hastalarda nadir görülürken yaşlı hastalarda en sık görülen hipertansiyon türüdür. Yaşlılarda İSH'nın yönetimi, genç yetişkinlerde görülen kombine sistolik-diyastolik hipertansiyonla genel olarak benzerdir.

Diyastolik kan basıncı hâlihazırda <70 mmHg olan olgularda tedavi verilir; ancak dikkatli olunmalıdır. Antihipertansif tedavi altında diyastolik kan basıncının <60 mmHg olmasından kaçınılması uygundur.

Terapötik hedeflerde, yaşlı bireyin kırılganlık özelliklerine dikkat edilerek dihidropiridin kalsiyum kanal blokerleri, tiyazid ve tiyazid benzeri diüretikler, ACEİ/ARB öncelikle tercih edilecek ilaç gruplarıdır.

Beta bloker kullanımından, İSH tanısı olan veya daha genel olarak arteriyel sertliği olan yaşlılarda diyastolik basınç ve strok volümü daha da azaltacağından, tercihen kaçınılmalıdır.

İZOLE DİYASTOLİK HİPERTANSİYON

Sistolik kan basıncının <140 mmHg, diyastolik kan basıncının >90 mmHg olması, izole diyastolik hipertansiyon (İDH) olarak tanımlanır.

Prevalansı %2,8–7,5 arasında değişmektedir. Gençlerde ve erkeklerde daha sık görülen İDH'nın prevalansı, 60'lı yaşlardan sonra azalır.

Farkındalığı ve tedavi oranları düşüktür. Yüksek vücut kitle indeksi (VKİ), sigara kullanımı, alkol kullanımı, hipotiroidi ve DM, İDH için risk faktörü olarak bildirilmiştir.

Öte yandan, bu fenotipin yıllar içinde sistolik kan basıncı yüksekliği geliştirme riski yüksek bulunmuştur.

Tedavide, risk faktörleri göz önüne alınarak yaşam tarzı değişiklikleri tüm hastalarda öncelenmelidir.

İDH tanısı olan hastalarda ilaç tedavisi ile ilgili kanıtlar yok denecek kadar azdır.

İDH'nın, özellikle 50 yaşın altındaki bireylerde KV riski belirgin olarak artırdığı göz önüne alınarak, bu yaş grubunda KV risk değerlendirmesi yapılmaksızın ilaç tedavisi başlanmalıdır.

50 yaşın üzerinde ise yüksek KV riski olan hastalarda ilaç tedavisi başlanabilir.

Diyastolik kan basıncı için ilaç tedavisine başlama değeri >90 mmHg, tedavi hedefi ise 70–79 mmHg olmalıdır.

İlaç tercihlerinde genel prensipler izlenir.

ORTOSTATİK HİPOTANSİYON

Ortostatik hipotansiyon, tipik olarak ayakta dururken veya dik bir duruş alındığında kan basıncında gözlenen önemli bir azalma

Tablo 9. Hipertansif acil durumlarda yapılması gereken tetkikler

İlk basamakta
EKG
Tam kan sayımı, periferik yayma
Kreatinin, sodyum, potasyum, eGFR, LDH
İdrar tetkiki ve idrar mikroskopisi
Gebelik testi
Fundoskopi
Klinik duruma göre
Troponin, NT-proBNP
Akciğer grafisi
Ekokardiyografi
Toraks ve abdomen bilgisayarlı tomografi
Kranial BT ya da MR
Üriner sistem ultrasonografisi
Haptoglobin

BT, Bilgisayarlı tomografi; eGFR, Tahmini glomerüler filtrasyon hızı; LDH, Laktat dehidrogenaz; MR, Manyetik rezonans; NT-proBNP, N-terminal pro-B tipi natriüretik peptit.

ile tanımlanan bir durumdur. Asemptomatik veya semptomatik olabilir ve bozulmuş otonomik reflekslere veya intravasküler volüm azalmasına bağlı olabilir.

Böbrek ve kalp yetmezliği, hipofiz ve adrenal hipofonksiyonu, dehidratasyon, uzun süreli uzanma, kondisyon kaybı, anti-hipertansif ve diüretik kullanımı gibi durumlar ortostatik hipotansiyona yatkınlığı artırır. Ortostatik hipotansiyon, otonomik disfonksiyona eğilim yaratan DM ve Parkinson hastalığı ile ilişkili durumları olanlarda daha sık görülür.

Semptomlar; baş dönmesi, senkop, boyun ve omuzlarda kas ağrısı ve hatta anjinayı içerebilir.

Ortostatik hipotansiyon tanısı, ayağa kalktıktan sonraki 3 dakika içinde sistolik kan basıncında 20 mmHg ve/veya diyastolik kan basıncında 10 mmHg düşüş olması ve/veya serebral hipoperfüzyon semptomları ile konulur.[17,26]

Ortostatik hipotansiyon sıklığı ve ilişkili kötü klinik sonuçlar göz önüne alındığında, özellikle riskli bireylerde kurallara uygun şekilde yatarak ölçüm yapıldıktan sonra, kontrollü bir şekilde ayağa kalktıktan sonraki 1. ve/veya 3. dakikada ölçümler yapılmalıdır.

Ortostatik hipotansiyon tespit edildiğinde, özellikle yüksek kırılganlık ve/veya fonksiyonel otonomik bozukluğu olan hastalarda ilişkili olan durumların tespit ve tetkikleri yapılırken; semptomlardan bağımsız olarak antihipertansif tedavinin kademeli olarak azaltılması düşünülmelidir.

Beyaz önlük etkisi veya hipotansif ataklardan şüpheleniliyorsa AKBÖ yapılmalıdır.

Ortostatik hipotansiyon yönetiminde, hipotansiyon riskini artırabilen diüretik, alfa bloker ve doğrudan etkili vazodilatör grubu ilaçlardan kaçınılmalı; kısa etkili ve düşük doz antihipertansifler tercih edilmelidir.

Yavaşça ayağa kalkmak, alt ekstremite direnç egzersizleri, varisler için çorap giymek, yeterli sıvı alımı, alkolden kaçınmak, daha az ve sık yemek yemek, yeterli tuz alımı, sıcak havalarda yoğun egzersizden kaçınmak, yatağın başını 30 ila 45 derece yüksekte tutmak gibi önlemler uygulanmalıdır.

Ortostatik hipotansiyon için hastalar sersemlik hissi, dengesizlik ve düşme açısından sorgulanmalı; böbrek fonksiyonları, elektrolitler, dehidratasyon ve anemi açısından düzenli takip edilmelidir.

HİPERTANSİF ACİL DURUMLAR

Kan basıncının 180/110 mmHg ya da daha üzerinde olduğu ve eşlik eden akut veya ilerleyici hedef organ hasarı varlığı, hipertansif acil durum olarak tanımlanır.

Organ hasarının gelişim hızı göz önüne alınarak, kan basıncı değeri dikkate alınmaksızın tüm hipertansif acil durumlarda tedavi uygulanmalıdır.

Bu hastalarda, neredeyse her zaman etkilenen organa göre baş ağrısı, görme bozuklukları, göğüs ağrısı, nefes darlığı, sersemlik hissi veya bazı nörolojik bulgular eşlik eder.

Hipertansif acil durumlar yaşamı tehdit eder ve bu hastalar mutlaka hastaneye yatırılarak izlenmelidir.[7]

Hipertansif acil durumlar sıklıkla akut inme (iskemik ya da hemorajik), aort anevrizması, aort diseksiyonu, akut dekompanze kalp yetersizliği, akut koroner sendrom ya da akut böbrek yetmezliği ile karşımıza çıkar.

Feokromositoma ya da sempatomimetik ajanların kullanımı (kokain ya da metamfetamin) da hipertansif acil durumlara yol açabilir.

Preeklampsi ve eklampsi de hipertansif acil durum nedenlerindendir. Gebelikte kan basıncının 160/110 mmHg ya da daha üzerinde olduğu durumlarda hasta yatırılarak izlenmelidir.[7]

Hipertansif acil durumlarda, hasta yatırıldıktan sonra hedef organ hasarını belirlemek amacıyla inceleme yapılmalıdır. Bu hastalarda istenmesi gereken tetkikler Tablo 9'da belirtilmiştir.[5,27]

Tedavide; hedef organ tutulumuna göre kan basıncını düşürme dışında yapılacak girişimler, kan basıncındaki ani yükselmeyi etkileyen faktörlerin tedavisi ve hastanın kliniğine göre kan basıncını düşürmenin hangi hızda ve ne düzeyde yapılması gerektiği değerlendirilmelidir.

Hipertansif acillerde, intravenöz tedavi ile kan basıncının kontrollü düşürülmesi hedeflenmelidir. Kan basıncının hızlı ve kontrolsüz düşürülmesinden kaçınılmalıdır.[28]

Hedef organ tutulumuna göre kan basıncı hedefleri ve bu hedefleri gerçekleştirmek için öngörülen süre farklıdır.

Bu hastalar için tedavi hedefleri, kullanılacak ilaçlar ve dozları aşağıda verilmiştir (Tablo 10).

Kan basıncının 180/110 mmHg ya da daha üzerinde olduğu ve eşlik eden hedef organ hasarı olmayan hastalarda, şiddetli hipertansiyondan bahsedilir. Bu hastaların hastaneye yatırılmalarına gerek yoktur. Genellikle, kan basıncının (kısa sürede etkili olan dilaltı formları ile değil) orta etkili oral tedavi ile 24–48 saat içinde düşürülmesi hedeflenmelidir. Burada tedavi, hastanın kullanmakta olduğu ilaçların yeniden düzenlenmesi ya da yeni bir

Tablo 10. İntravenöz ilaç tedavisi ile hemen kan basıncının düşürülmesi gereken hipertansif acil durumlarda tedavi

Klinik prezantasyon	Zamanlama ve KB hedefi	İlk sıra tedavi	Alternatif tedavi
Akut böbrek yetmezliğinin eşlik ettiği malign HT	Birkaç saat OAB %20-25 düşürülür	Nikardipin Labetalol*	Nitroprussid Urapidil
Hipertansif ensefalopati	Hemen OAB %20-25 düşürülür	Labetalol* Nikardipin	Nitroprussid
Akut koroner olay	KB hemen SKB<140 mmHg olacak şekilde düşürülür	Nitrogliserin Labetalol*	Urapidil
Akut kardiyojenik pulmoner ödem	KB hemen SKB<140 mmHg olacak şekilde düşürülür	Nitroprussid ya da nitrogliserin (Kıvrım diüretiği ile birlikte)	Urapidil (Kıvrım diüretiği ile birlikte)
Akut aort diseksiyonu	KB hemen SKB<120 mmHg ve nabız <60/dk olacak şekilde düşürülür	Esmolol ve nitroprussid ya da Nitrogliserin ve nikardipin	Labetalol* ya da metoprolol
Eklampsi ve ağır preeklampsi (HELLP sendromu)	KB hemen SKB<160 mmHg ve DKB <105 mm Hg olacak şekilde düşürülür	Labetalol* ya da nikardipin ve magnezyum sülfat	Doğumu değerlendir
Akut hemorajik inme	-İlk 6 saatte: KB <140/90 mmHg olacak şekilde düşürülür -6 saati geçmişse: SKB≥220 mmHg ise SKB<180 mmHg, SKB<220 mmHg ise SKB 140/90 mmHg olacak şekilde düşürülür.**	Nikardipin ya da Labetolol	Nitroprussid
Akut iskemik inme	-Reperfüzyon tedavisi uygulanacaksa (trombolitik veya endovasküler***) işlem esnasında ve sonrası 24 saat boyunca KB <180/105 mmHg olacak şekilde düşürülür. -Reperfüzyon tedavisi uygulanamayan ve KB >220/120 mmHg olan hastalarda ilk 24 saatte KB'yi %15 oranında düşürmek uygun olabilir.	Nikardipin ya da Labetolol	Nitroprussid

DKB, Diyastolik kan basıncı; HT, Hipertansiyon; KB, Kan basıncı; OAB, Ortalama arter basıncı; SKB, Sistolik kan basıncı. *Ülkemizde bulunmamaktadır. **SKB 130 mmHg altına düşürülmemelidir. ***Endovasküler girişimle büyük bir damar perfüze edilmişse ilk 24-72 saat boyunca SKB140 mmHg altına düşürülmemelidir.

ilacın eklenmesi şeklinde yapılabilir. Yeni ilaç eklenmesi gerektiği durumlarda, dihidropiridin türevi kalsiyum kanal blokerleri – yan etkilerinin az olması ve sekonder hipertansiyon tanısal testlerinin sonuçlarını etkilememeleri nedeniyle – sıklıkla tercih edilir. Dilaltı kısa etkili nifedipin kullanımından kaçınılmalıdır[27,28] Yaşam tarzı değişikliğinin önemi vurgulanmalı ve hastalar ilgili branş doktorlarına yönlendirilmelidir.

Acil servislerde ölçülen asemptomatik kan basıncı yükseklikleri için bu uzlaşı raporunda yer alan tedavi hedef ve önerileri geçerli değildir. Hastanın acil sorununun giderilmesi ya da stresinin ortadan kaldırılması, sıklıkla kan basınçlarının düşmesi için yeterli olacaktır.

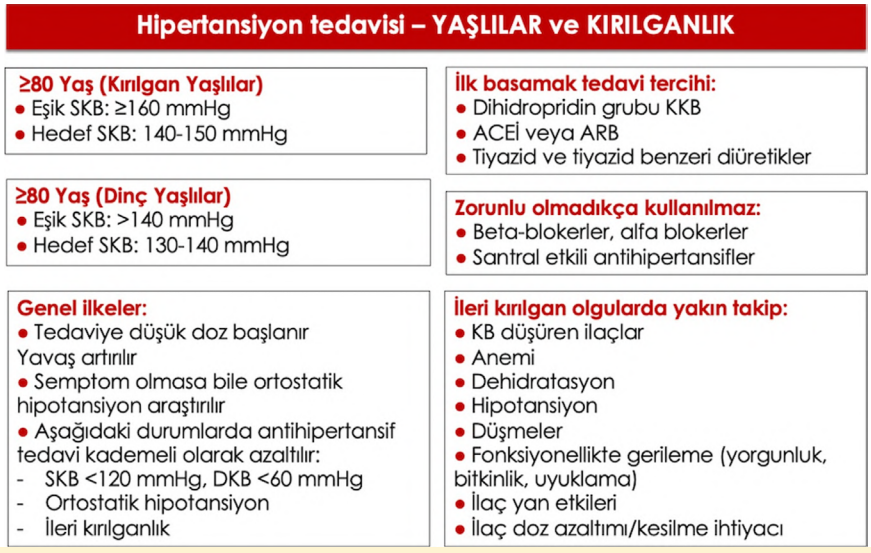
ÖZEL HASTA GRUPLARINDA HİPERTANSİYON TEDAVİSİ

1. Yaşlılar ve Kırılganlık: Yaşlılarda özgün endikasyonları yok ise beta-blokerler ilk basamakta tercih edilmemelidir (izole sistolik hipertansiyonda sınırlı etkinlik, yorgunluk, depresyon, uyku problemleri, ileti blokları, metoprolol ile deliryum, demans tedavisiyle (kolinesteraz inhibitörleri) kullanımda ileti bozukluğu riskleri vb. yan etkileri nedeniyle). KKB'ler arasında dihidropiridinler, bilişsel düşüşe karşı koruyucu etkileri, ileti bozukluğu/konstipasyon yan etkilerinin olmaması ve demanslı olgulardaki kolinesteraz inhibitörü tedavisiyle olumsuz etkileşimlerinin bulunmaması nedeniyle tercih edilebilir. Yaşlılar alfa blokerler ve santral etkili antihipertansiflerin düşmeler, yorgunluk, depresyon ve ortostatik hipotansiyon yan etkilerine özellikle duyarlıdır ve zorunlu olmadıkça bu ilaçlar kullanılmamalıdır (Şekil 9).

80 yaş ve üzeri hipertansiyon tedavisinde genel ilke, tedaviye düşük dozla başlanması ve doz artışlarının yavaş yapılmasıdır (düşük başla, yavaş artır). Semptom olmasa bile ortostatik hipotansiyon araştırması standart olarak yapılmalıdır. Hiçbir olguda terapötik olarak sistolik kan basıncı <120 mmHg, diastolik kan basıncı <70 mmHg hedeflenmez. Sistolik kan basıncının <120 mmHg olması veya diastolik kan basıncının <60 mmHg olması ya da ortostatik hipotansiyon varlığı veya ileri kırılganlık durumunda antihipertansif tedavinin azaltılması düşünülmelidir. Özellikle grup 6–9 (orta–çok ileri kırılgan, terminal hastalık) hastalarda antihipertansif verilenler, ortostatik hipotansiyon, düşmeler, fonksiyonellikte gerileme (yorgunluk, bitkinlik, uyuklama), ilaç yan etkileri ve ilaç doz azaltımı/kesilme ihtiyacı açısından çok yakın takip edilmelidir (Şekil 9).

İleri kırılgan olgularda tedavi verildiğinde kan basıncı sistolik 140–150 mmHg düzeylerinde hedeflenerek, kan basıncını düşüren ilaçlar (Ek C), anemi ve dehidratasyon gözden geçirilerek hipotansiyondan kaçınılacak şekilde düzenleme yapılmalıdır.[17] Hipotansiyon nedeniyle antihipertansif azaltılması gereken olgularda azaltım ani değil, kademeli yapılmalı, kan basıncı ve klinik yakın takip edilmelidir (Şekil 9). Yaşlı bireylerde tedavide ilk basamakta tercih edilebilecek ilaç grupları; KKB, ACEİ veya ARB ve tiyazid ile tiyazid benzeri diüretiklerdir.

2. Diyabet: Kan basıncı ≥140/90 mmHg ise ilaç tedavisine hemen ve kombinasyonla başlanmalıdır. Artmış KB (SKB 130–139 mmHg, DKB 80–89 mmHg) olan hastalarda 3 aylık nonfarmakolojik tedaviye rağmen artmış kan basıncı devam ediyorsa; 40 yaş



Şekil 9. Özel hasta gruplarında HT tedavisi – Yaşlılar ve Kırılganlık.

ACEİ, Anjiyotensin dönüştürücü enzim inhibitörleri; ARB, Anjiyotensin reseptör blokerleri; DKB, Diyastolik kan basıncı; KB, Kan basıncı; SKB, Sistolik kan basıncı.

üzeri, 10 yıldan uzun süredir diyabeti olan, komplikasyonu ve diğer risk faktörleri (sigara kullanımı, obezite) bulunan hastalarda antihipertansif tedavi başlanabilir (Şekil 6). Yaş gruplarına özgü eşik ve hedef KB değerleri Tablo 7'de verilmiştir. Diyabetlilerde tedaviye tek ilaçla başlanacaksa ACE inhibitörü veya ARB grubu ilaçlardan birinin seçilmesi önerilir.

3. Koroner Arter Hastaları: Koroner arter hastalığı olan bireylerde kan basıncı 140/90 mmHg üzerinde ise ilaç tedavisine hemen ve kombinasyonla başlanmalıdır. Artmış KB (SKB 130–139 mmHg, DKB 80–89 mmHg) olan ve 3 aylık nonfarmakolojik tedaviye rağmen düzelmeyen hastalarda antihipertansif tedavi başlanmalıdır (Şekil 6). Yaş gruplarına özgü eşik ve hedef KB değerleri Tablo 7'de verilmiştir. Koroner arter hastalığı olan bireylerde tedavide tercih edilecek ilaç grupları beta-bloker, ACE inhibitörü, ARB veya KKB'dir.

4. Kronik Böbrek Hastaları: Kronik böbrek hastalarında artmış KB (SKB 130–139 mmHg, DKB 80–89 mmHg) olan ve 3 aylık nonfarmakolojik tedaviye rağmen düzelmeyen albüminürik KBH hastalarının (albüminüri >30 mg/gün veya spot idrarda albümin/kreatinin oranı >30 mg/g varlığında) tümüne antihipertansif tedavi (monoterapi: ACEİ veya ARB) başlanmalıdır. Kan basıncı 140/90mmHg üzerinde ise ilaç tedavisine hemen ve kombinasyonla başlanmalıdır (Şekil 6, Şekil 10). Tedavi hedefi SKB/DKB 120–130/70–80 mmHg olup, >1g proteinüri ve otozomal dominant polikistik böbrek hastalığı (ODPKBH) gibi özellikli KBH gruplarında hedef kan basıncı ilgili kılavuz önerilerine göre belirlenir.[29]

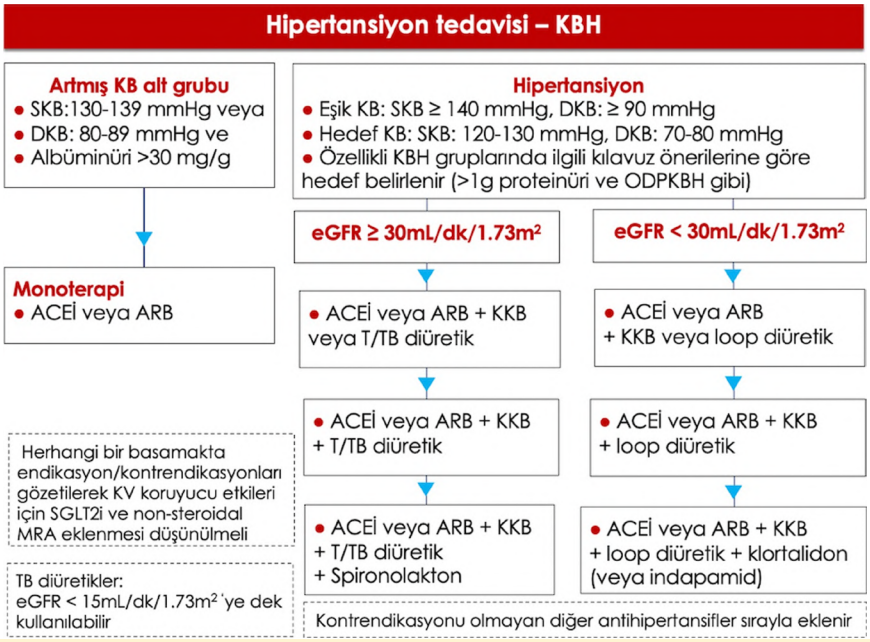
- eGFR ≥30 mL/dk/1.73m² olan hastalarda kombinasyon tedavisi: (1) ACEİ veya ARB + KKB veya tiyazid/tiyazid benzeri diüretik, (2) ACEİ veya ARB + KKB + tiyazid/tiyazid benzeri diüretik ve (3) ACEİ veya ARB + KKB + tiyazid/tiyazid benzeri diüretik + spironolakton algoritması ile uygulanır.
- eGFR <30 mL/dk/1.73m² olan hastalarda kombinasyon tedavisi: (1) ACEİ veya ARB + KKB veya loop diüretik, (2) ACEİ veya ARB + KKB + loop diüretik ve (3) ACEİ veya ARB + KKB + loop diüretik + klortalidon (veya indapamid) algoritması ile uygulanır.

Herhangi bir basamakta endikasyon/kontrendikasyonlar gözetilerek KV koruyucu etkileri için sodyum-glukoz kotransporter-2 inhibitörü (SGLT2i) ve nonsteroidal MRA eklenmesi ve KB kontrolüne ek katkılarından faydalanılması önerilir (Şekil 10).

Hastanın yaşı, eşlik eden DM ve/veya kardiyovasküler hastalık varlığı ve diyaliz durumu göz önünde bulundurularak tedavi bireyselleştirilmelidir.[25] Yaş gruplarına özgü eşik ve hedef KB değerleri Tablo 7'de verilmiştir. Proteinürisi olanlarda hastanın tolere edebildiği en düşük sistolik kan basıncı hedeflenmelidir.

5. Kalp Yetersizliği: Düşük ejeksiyon fraksiyonlu kalp yetersizliğinde (DEF-KY) ACE inhibitörleri, ARB, beta-bloker, ARNİ (anjiyotensin reseptör-neprilisin inhibitörü), MRA ve SGLT2 inhibitörleri gibi ilaçların mortalite ve morbiditeyi azalttığı gösterilmiştir. ACEİ (eğer tolere edilemiyorsa ARB'ler) veya ARNİ, beta-blokerler, MRA'lar ve SGLT2i kullanmasına rağmen halen KB yüksekse sıvı dengesini yönetmek için ek diüretik tedavisi ve dihidropiridin grubu KKB kullanılabilir. Korunmuş ejeksiyon fraksiyonlu kalp yetersizliğinde (KEF-KY) eşlik eden hastalıklara ve hasta özelliklerine göre antihipertansif tedavi verilir. Ayrıca bu hastalarda KV koruma için kullanılan SGLT2 inhibitörlerinin KB düşüşüne de etkisi vardır. Kalp yetersizliğinde (DEF-KY veya KEF-KY) KB >140/90 mmHg ise nonfarmakolojik tedavi ve ilaç tedavisine birlikte başlanır. Artmış KB (SKB 130–139 mmHg, DKB 80–89 mmHg) olan ve 3 aylık nonfarmakolojik tedaviye rağmen düzelmeyen hastalarda antihipertansif tedavi başlanmalıdır (Şekil 6). Yaş gruplarına özgü eşik ve hedef KB değerleri Tablo 7'de verilmiştir.

6. Gebelik: Gebeliğin hipertansif bozukluklarının (GHB) tanı ve tedavi eşik değerleri ile gebelik ve laktasyonda antihipertansif tercihi uzun yıllardır tartışma konusudur. Tartışmanın nedeni, KB'yi düşürürken sağlanacak maternal kazanım ile oluşturacağı plasental perfüzyon bozulmasına bağlı fetal etkilenimler arasında ince bir denge bulunmasıdır. Ancak son yıllarda gebelikte sıkı KB kontrolünün değerlendirildiği randomize kontrollü çalışmalara dayanarak GHB'da 140/90 mmHg üzerinde tedavi başlanabileceği



Şekil 10. KBH tanılı hipertansif hastalarda hipertansiyon tedavisi.

ACEİ, Anjiyotensin dönüştürücü enzim inhibitörleri; ARB, Anjiyotensin reseptör blokerleri; DKB, Diyastolik kan basıncı; eGFR, Tahmini glomerüler filtrasyon hızı; KB, Kan basıncı; KKB, Kalsiyum kanal blokerleri; ODPKBH, Otozomal dominant polikistik böbrek hastalığı; SGLT2i, Sodyum-glukoz kotransporter-2 inhibitörü; SKB, Sistolik kan basıncı; T/TB, Tiyazid/Tiyazid-benzeri.

ve hedef sistolik kan basıncının <140 mmHg, hedef diastolik kan basıncının 80–90 mmHg arası olabileceği düşünülmektedir.[6,30,31]

HT tanısı koyulurken özellikle 24 saatlik AKBÖ kullanımı önerilmekte, ancak gerek ev gerekse AKBÖ ile HT tanısı koymada gebeliğe özgü bir eşik KB değeri olmadığı için normal popülasyon değerlerinin kullanılması tavsiye edilmektedir.

Gebelikte HT'de uzun yıllardır ilk tercih olarak başlanan antihipertansifler alfa metildopa, beta-blokerler ve dihidropiridin KKB'lerdir. Beta-blokerlerden labetalol ve metoprolol güvenle kullanılabilirken atenolol, fetal büyüme-gelişme geriliği yaptığı için gebelikte önerilmemektedir. Nifedipin ilk tercih olmak üzere diğer dihidropiridin KKB'leri güvenle kullanılabilmektedir. Şu ana kadar olan metaanalizler ışığında bir antihipertansifin diğerine tercih edilmesi yönünde bir kanıt bulunmamaktadır. Gebelikte kullanımı fetüse olan yan etkileri ve teratojenik etkileri nedeniyle sakıncalı olan antihipertansifler ise ACEİ, ARB, renin inhibitörleri, MRA ve sodyum nitroprussit olarak sayılabilir. Ayrıca diüretiklerin amniyotik sıvı volümünü azaltması ve beta-blokerlerin fetal bradikardi yapıcı etkisi endişesiyle dikkatli kullanımı önerilir (Şekil 11).[6,30,32,33]

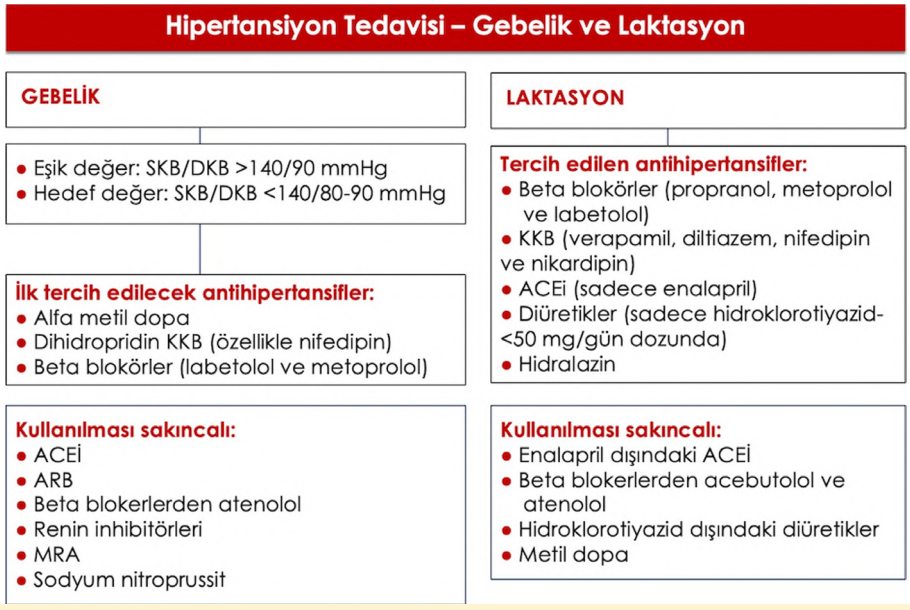
7. Laktasyon: Beta-blokerler ve kalsiyum kanal blokerleri süte geçmesine rağmen fetüste yan etkiye yol açmamakta, bu nedenle laktasyonda tercih edilen antihipertansif grupları arasında yer almaktadır. Beta-blokerlerden propranolol, metoprolol ve labetalolün süte geçişi daha az olduğu için tercih edilebilirken atenolol ve asetabutolol yoğun süte geçişleri ve bu nedenle fetal yan etkiler oluşturabilmeleri nedeniyle tercih edilmemelidir. Kalsiyum kanal blokerlerinden verapamil, diltiazem, nifedipin ve nikardipin laktasyonda güvenle kullanılabilmektedir. ARB'lerin laktasyonda kullanımı ile ilgili yeterli kanıt yokken enalapril dışında ACEİ'lerin fetal hemodinamik yan etki endişesi nedeniyle kullanımı önerilmemektedir. Diüretiklerin süt volümünü azaltabileceği endişesiyle kullanımı önerilmemekle birlikte <50 mg/gün hidroklorotiyazid laktasyonda güvenle kullanılabilmektedir. Ayrıca hidralazin laktasyonda güvenle kullanılabilmektedir; ancak metildopa'nın postpartum psikoz yapıcı etkisi nedeniyle laktasyonda kullanımı tavsiye edilmemektedir (Şekil 11).[34]

ANTİHİPERTANSİF İLAÇ KULLANAN HASTALARDA EK KARDİYOVASKÜLER VE RENAL KORUMA TEDAVİLERİ

Antihipertansif ilaç tedavisinin temelinde, hastaların kardiyovasküler ve renal olay geçirme olasılıklarını azaltma prensibi bulunmaktadır. Bu nedenle antihipertansif ilaç tedavisi kullanan hastaların ek kardiyovasküler ve renal koruma tedavilerine olan ihtiyacı mutlaka göz önünde bulundurulmalı ve uygun hastalarda bu ilaçlar antihipertansif tedavi planı içinde yer almalıdır.

1. Asetilsalisilik Asit: Hipertansiyonda asetilsalisilik asit (aspirin) tedavisini önerme kararı, normotansif hastalarda olduğu gibi bireyin kardiyovasküler riskine ve kanama riskine göre verilmelidir. İkincil önleme amacıyla, kalp damar hastalığı yerleşik olan hastalarda düşük doz asetilsalisilik asit kullanımı, gastrointestinal sistemden kaynaklanan kanama riskini artırmasına rağmen majör kardiyovasküler olayların klinik olarak anlamlı düzeyde azalmasıyla ilişkilidir. Bu nedenle ikincil koruma gereksinimi olan tüm hipertansif hastalara düşük doz asetilsalisilik asit kullanımı önerilmelidir. Hipertansif hastalarda kardiyovasküler hastalıklarda birincil korunmada asetilsalisilik asit tedavisinin yeri için yeterli kanıt bulunmamaktadır.

2. Statin: Hipertansiyon ile dislipidemi birlikteliği oldukça sıktır. Bu birliktelik, hipertansif hastaların kardiyovasküler riskini daha da artırmaktadır. Bu nedenle hipertansif hastalarda kardiyovasküler



Şekil 11. Gebelik ve laktasyonda hipertansiyon tedavisi.

ACEİ, Anjiyotensin dönüştürücü enzim inhibitörleri; ARB, Anjiyotensin reseptör blokerleri; DKB, Diyastolik kan basıncı; KKB, Kalsiyum kanal blokerleri; MRA, Mineralokortikoid reseptör antagonisti; SKB, Sistolik kan basıncı.

riski değerlendiren risk skorları kullanılarak, lipid kılavuzlarının önerileri de dikkate alınarak statin tedavisi planlanmalıdır. Çok sayıda randomize çalışma ve meta-analiz, statin tedavisinin LDL kolesterol azalmasına orantılı olarak kardiyovasküler sonuçları iyileştirdiğini kanıtlamıştır. Düşük kardiyovasküler riskli hipertansif hastalarda yaşam tarzı önerilerine ek olarak statin tedavisine genellikle gereksinim yoktur. Primer korunmada, bilinen kardiyovasküler hastalığı, diyabetes mellitusu ya da kronik böbrek hastalığı olmayan ve kardiyovasküler riski düşük–orta olan bireylerde LDL kolesterol düzeyi <100 mg/dL, yüksek riskli hastalarda <70 mg/dL ve çok yüksek riskli hastalarda <55 mg/dL olarak hedeflenmelidir.

3. SGLT2 İnhibitörleri: Kronik böbrek hastalığı, diyabetes mellitus ve kalp yetersizliği, hipertansiyonla birlikte sık görülen durumlardır. SGLT2 inhibitörleri ile son 10 yılda yapılan çalışmalar, bu ilaç grubunun tip 2 DM hastalarında, diyabetli veya diyabeti olmayan kronik böbrek hastalarında ve kalp yetersizliği hastalarında kardiyovasküler ve renal olay riskini anlamlı düzeyde azalttığını göstermiştir. Bunun yanında SGLT2 inhibitörlerinin hafif düzeyde kan basıncı düşürücü etkileri de bulunmaktadır. Bu nedenle hipertansiyonla birlikte tip 2 DM, kronik böbrek hastalığı ve kalp yetersizliği bulunan hastalarda antihipertansif tedaviye ek olarak SGLT2 inhibitörü kullanımı, ilgili kılavuzlar da dikkate alınarak planlanmalıdır.

4. Glukagon benzeri peptid-1 reseptör agonistleri (GLP-1 RA) ve glikoz bağımlı insülinotropik polipeptit (GIP) kombinasyonları: GLP-1 RA ve GLP-1 RA/GIP kombinasyonları, tip 2 DM ve obezite tedavisinde kullanılan ilaçlardır. Hipertansiyon hastalarında obezite sık görülmektedir. Bu hastalarda %5 ve üzerindeki kilo kaybı ile kan basıncı kontrolünde anlamlı iyileşme sağlanabilmektedir. GLP-1 RA ve GLP-1 RA/GIP kombinasyonlarının, tip 2 DM, fazla kilolu veya obezitesi olan hipertansiyon hastalarında kullanılması önerilmelidir. Bu ilaçların aterosklerotik kardiyovasküler hastalık, kronik böbrek hastalığı veya kalp yetersizliği bulunan hastalarda mortalite ve morbiditeyi azalttığı gösterilmiştir. Bu nedenle aterosklerotik kardiyovasküler hastalığı, kronik böbrek hastalığı veya kalp yetersizliği olan bireylerde ve aterosklerotik kardiyovasküler hastalık açısından yüksek riskli hipertansiyon hastalarında tercih edilmeleri önerilebilir.

ANTİHİPERTANSİF İLAÇ KULLANAN HASTALARIN TAKİBİ

Bir antihipertansif ilaçtan beklenen etkinin önemli bir kısmı 3–4 hafta içinde ortaya çıkar. Bu nedenle antihipertansif ilaç tedavisi başlanan veya tedavi rejiminde değişiklik yapılan hastalarda kan basıncı kontrolünün sağlanıp sağlanmadığı 3–4 hafta sonraki kontrolde değerlendirilmelidir. Hastalar, olanak varsa ev kan basıncı ölçümlerini yaparak kontrole çağrılmalıdır. Kontrolde, kan basıncının yeterli kontrolünün yanı sıra hedeflenenin ötesinde kan basıncı düşüşü olup olmadığı da özellikle yaşlı ve/veya kırılgan olgularda değerlendirilmelidir. Bu bağlamda kontrollerde hastanın kullandığı tüm ilaçlar; yan etkileri, ilaç–ilaç etkileşimleri ve hipertansiyon yönetimine olası etkileri (kan basıncında artış veya azalma) açısından mutlaka değerlendirilmelidir (Ek E).

İLAÇ UYUMU VE KAN BASINCI KONTROLÜNÜN İYİLEŞTİRİLMESİ

Hipertansiyon tedavisinde başarılı olabilmenin temel koşulları; hastaların zamanında ve doğru tanı almasını sağlamak, yaşam tarzı değişikliklerini etkin biçimde uygulamak, ilaç tedavisine zamanında başlamak ve ilaç uyumunu mutlaka sağlamaktır. Bunun için dikkat edilmesi gereken hususlar:

- Hastanın hastalığını anlamasına yardımcı olunmalı ve bilgilendirme için gerekirse yazılı kaynaklar sağlanmalıdır.
- Yaşam tarzı önerilerinin ilaç tedavisi kadar önemli olduğu anlatılmalıdır.
- Hastalığın kronik olduğu, ilaçların sürekli alınması ve düzenli kontrollere gelinmesi gerektiği vurgulanmalıdır.
- Kan basıncı kontrolünün en geç 3 ay içinde sağlanmasına çalışılmalıdır. Kan basıncı kontrolünün sürdürülmesi için hem

hekimin hem de hastanın çaba göstermesi gerekmektedir.

- Kan basıncı kontrol altında olan hastalarda tıbbi başka bir gerekçe olmadıkça antihipertansif ilaç değişikliği yapılmamalıdır. Gereksiz ilaç değişiklikleri tedavi uyumunu bozmaktadır.
- Kan basıncı kontrol altında olmayan hastaların tedavisine, gerektiğinde ilaç eklemekten kaçınılmamalıdır.
- Özellikle kırılgan bireylerde düşmeler veya ortostatik hipotansiyon gelişmesi, antihipertansif tedavi altında bilişsel ve fonksiyonel gerileme (örneğin gün içinde uyuklama, yorgunluk, bitkinlik) ortaya çıkması ve planlanan kan basıncı değerlerinin altına inilmesi durumlarında ilaç azaltımı gerekebileceği ve antihipertansif ilaçların dikkatle izlenmesi gerektiği göz önünde bulundurulmalıdır. Hedeflenenin ötesinde kan basıncı düşüşü olan kırılgan olgularda kullanılan tüm ilaçlar, dehidratasyon ve anemi dâhil olmak üzere hipotansiyona katkıda bulunabilecek tüm faktörler açısından gözden geçirilmeli ve tedavi buna göre düzenlenmelidir.
- İlaç azaltımı planlanıyorsa ani değil, yakın takip altında ve kademeli olarak yapılmalıdır.
- Hastaya yeterli zaman ayrılmalı, hastanın kendini ifade etmesine izin verilmeli ve hasta ile etkili bir iletişim kurulmalıdır.
- Gelişen teknolojiyle birlikte "teletıp" uygulamalarının kan basıncı kontrolü ve ilaç uyumunun artırılması amacıyla kullanılmaya başlanması önerilir.

Çıkar Çatışması: Yazarlar, bu makalenin içeriğiyle ilişkili olarak açıklayacakları herhangi bir bağlantıları olmadığını bildirmiştir.

Finansal Destek: Uzlaşı raporu hazırlık toplantıları derneklerin öz kaynakları ile yapılmıştır.

Yazma Yardımı için Yapay Zeka Kullanımı: Yazarlar bu uzlaşı raporunun hazırlanmasında, Büyük Dil Modelleri (LLM), chatbot veya görüntü oluşturucular gibi yapay zeka (AI)-destekli teknolojileri kullanmadıklarını beyan ederler.

Yazar Katkıları: Konsept – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Tasarım – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Denetim – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Veri Toplama ve/veya İşleme – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Analiz ve/veya Yorumlama – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Literatür Taraması – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Yazan – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Eleştirel Değerlendirme – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.

Teşekkür: Bu Uzlaşı Raporu'nda yer alan görseller için Tekirdağ Namık Kemal Üniversitesi Resim Bölümü öğretim üyesi Prof. Dr. Dalila Özbay'a şükranlarımızı sunarız. Ayrıca bu Uzlaşı Raporunun hazırlık toplantı tutanaklarının tutulmasında ve alınan notların makaleye konulmasında Kappa Eğitim Danışmanlık ve Araştırma Ltd. Şti.'den destek alınmıştır. Anılan şirkete ve özellikle tüm süreçte bize destek olan Dr. Çağla Ayhan'a teşekkürlerimizi sunarız.

Hakem Değerlendirmesi: Dış bağımsız.

Conflict of Interest: The authors declare that they have no affiliations to disclose in relation to the content of this article.

Funding: The meetings for preparing the consensus report were funded by the associations' own resources.

Use of AI for Writing Assistance: The authors declare that they did not use artificial intelligence (AI)-assisted technologies such as Large Language Models (LLMs), chatbots, or image generators in the preparation of this consensus report.

Author Contributions: Concept – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Design – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Supervision – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Data Collection and/or Processing – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Analysis and/or Interpretation – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Literature Review – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Writing – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.; Critical Review – B.Ö., B.A., M.C., C.A., M.A., S.Aydoğdu, S.Aras, K.G., S.M.D., A.S., G.Z.Ö., G.Ö., H.Ç., G.B., T.T., Ü.D., İ.Ş., Ş.U., M.A.D.

Acknowledgments: We would like to express our gratitude to Prof. Dr. Dalila Özbay, faculty member of the Department of Painting at Tekirdağ Namık Kemal University, for the images included in this Conciliation Report. We would also like to thank Kappa Education Consulting and Research Ltd. for their support in preparing the minutes of the meetings for this Conciliation Report and for including the notes taken in the article. We would like to express our gratitude to the aforementioned company and especially to Dr. Çağla Ayhan for her support throughout the entire process.

Peer-review: Externally peer-reviewed.

Kaynaklar

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021;398(10304):957-980. Erratum in: *Lancet*. 2022;399(10324):520.
2. Arıcı M, Birdane A, Güler K, et al. Turkish hypertension consensus report. *Turk Kardiyol Dern Ars*. 2015;43(4):402-409. Turkish.
3. Aydoğdu S, Güler K, Bayram F, et al. 2019 Turkish Hypertension Consensus Report. *Turk Kardiyol Dern Ars*. 2019;47(6):535-546. Turkish. [CrossRef]
4. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127-e248. Erratum in: *J Am Coll Cardiol*. 2018;71(19):2275-2279. [CrossRef]
5. Williams B, Mancia G, Spiering W, et al.; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. Erratum in: *Eur Heart J*. 2019;40(5):475. [CrossRef]
6. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension

(ISH) and the European Renal Association (ERA). *J Hypertens*. 2023;41(12):1874–2071. Erratum in: *J Hypertens*. 2024;42(1):194. [CrossRef]
7. McEvoy JW, McCarthy CP, Bruno RM, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45(38):3912–4018. Erratum in: *Eur Heart J*. 2025;46(14):1300. Erratum in: *Eur Heart J*. 2025;46(45):4949. [CrossRef]
8. Jones DW, Ferdinand KC, Taler SJ, et al.; Peer Review Committee Members. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2025;86(18):1567–1678. Erratum in: *J Am Coll Cardiol*. 2025;86(18):1679.
9. Charles L, Triscott J, Dobbs B. Secondary Hypertension: Discovering the Underlying Cause. *Am Fam Physician*. 2017;96(7):453–461.
10. Fay KS, Cohen DL. Resistant Hypertension in People With CKD: A Review. *Am J Kidney Dis*. 2021;77(1):110–121. [CrossRef]
11. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–495. [CrossRef]
12. Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. *Can Geriatr J*. 2020;23(3):210–215. [CrossRef]
13. Özsürekci C, Balcı C, Kızılarslanoğlu MC, et al. An important problem in an aging country: identifying the frailty via 9 Point Clinical Frailty Scale. *Acta Clin Belg*. 2020;75(3):200–204. [CrossRef]
14. Aşık Z, Kılınç Ş, Kurşun Ö, Özen M. Validation of the Clinical Frailty Scale version 2.0 in Turkish older patients. *Geriatr Gerontol Int*. 2022;22(9):730–735. [CrossRef]
15. Turkish Statistical Institute. Türkiye Health Survey, 2022. Turkish. Accessed September 12, 2025. https://data.tuik.gov.tr/Bulten/Index?p=Turkiye-Saglik-Arastirmasi-2022-49747
16. Volkert D, Beck AM, Cederholm T, et al. ESPEN practical guideline: Clinical nutrition and hydration in geriatrics. *Clin Nutr*. 2022;41(4):958–989. [CrossRef]
17. Bahat G, Ribeiro H, Sheppard JP, et al.; ESH Working Group on Hypertension in older adults. Twelve hot questions in the management of hypertension in patients aged 80+ years and their answers with the help of the 2023 European Society of Hypertension Guidelines. *J Hypertens*. 2024;42(11):1837–1847. [CrossRef]
18. Williams B, Mancia G, Spiering W, et al.; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021–3104. Erratum in: *Eur Heart J*. 2019;40(5):475. [CrossRef]
19. Nerenberg KA, Zarnke KB, Leung AA, et al.; Hypertension Canada. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J Cardiol*. 2018;34(5):506–525.
20. Erdem Y, Arici M, Altun B, et al. The relationship between hypertension and salt intake in Turkish population: SALTURK study. *Blood Press*. 2010;19(5):313–318. [CrossRef]
21. Erdem Y, Akpolat T, Derici Ü, et al. Dietary Sources of High Sodium Intake in Turkey: SALTURK II. *Nutrients*. 2017;9(9):933. [CrossRef]
22. Zeanandin G, Molato O, Le Duff F, Guérin O, Hébuterne X, Schneider SM. Impact of restrictive diets on the risk of undernutrition in a free-living elderly population. *Clin Nutr*. 2012;31(1):69–73. [CrossRef]
23. Jefferson K, Ahmed M, Choleva M, et al. Effect of a Sodium-Restricted Diet on Intake of Other Nutrients in Heart Failure: Implications for Research and Clinical Practice. *J Card Fail*. 2015;21(12):959–962. [CrossRef]
24. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. *J Hypertens*. 2017;35(11):2150–2160. [CrossRef]
25. Adler GK, Stowasser M, Correa RR, et al. Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2025;110(9):2453–2495. Erratum in: *J Clin Endocrinol Metab*. 2025;110(11):e3933–e3934. [CrossRef]
26. Egan BM. Treatment of hypertension in older adults, particularly isolated systolic hypertension. UpToDate; 2023. Accessed November 18, 2025. https://www.uptodate.com/contents/treatment-of-hypertension-in-older-adults-particularly-isolated-systolic-hypertension
27. van den Born BH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother*. 2019;5(1):37–46. Erratum in: *Eur Heart J Cardiovasc Pharmacother*. 2019;5(1):46. [CrossRef]
28. Williams B, Mancia G, Spiering W, et al.; Authors/Task Force Members:. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018;36(10):1953–2041. Erratum in: *J Hypertens*. 2019;37(1):226. [CrossRef]
29. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int*. 2021;99(3S):S1–S87. [CrossRef]
30. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. *Obstet Gynecol*. 2019;133(1):e26–e50. [CrossRef]
31. Tita AT, Szychowski JM, Boggess K, et al.; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for Mild Chronic Hypertension during Pregnancy. *N Engl J Med*. 2022;386(19):1781–1792. [CrossRef]
32. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: diagnosis and management. NICE guideline (NG133). Accessed October 20, 2025. https://www.nice.org.uk/guidance/ng133
33. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *Can J Cardiol*. 2020;36(5):596–624. [CrossRef]
34. Schimmel MS, Eidelman AI, Wilschanski MA, Shaw D Jr, Ogilvie RJ, Koren G. Toxic effects of atenolol consumed during breast feeding. *J Pediatr*. 1989;114(3):476–478. Erratum in: *J Pediatr*. 1990;116(1):158. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Clinical Outcomes of Using Drug-Coated Balloons During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Patients – Insights from High-Risk Groups: A Single-Center Experience

ST Yükselmeli Miyokard Enfarktüsü Hastalarında Primer Perkütan Koroner Girişim Sırasında İlaç Kaplı Balonların Kullanımının Klinik Sonuçları – Yüksek Risk Gruplarından Elde Edilen Bulgular: Tek Merkez Deneyimi

ABSTRACT

Objective: ST-elevation myocardial infarction (STEMI) is one of the leading causes of mortality worldwide. Current guidelines recommend primary percutaneous coronary intervention (PPCI) using drug-eluting stents as the standard management for these patients. Stent-free percutaneous coronary intervention (PCI) using drug-coated balloons (DCB) has been suggested as a novel approach to avoid stent-related complications. This study aimed to assess the efficacy and safety of using DCB in STEMI patients.

Method: We compared STEMI patients who presented during the period between 2019 and 2023 and underwent primary PCI using DCB to those treated with drug-eluting stents (DES) in terms of in-hospital and six-month major adverse cardiac events (MACE).

Results: A total of 128 STEMI patients who underwent primary PCI using DCB were compared to 128 matched patients managed using DES. Small-vessel culprit lesions (< 3 mm) and distal lesions were significantly more frequent in the DCB group compared to the DES group. DCBs were used in major epicardial vessels in around 55% of patients and in side branches in almost 45% of cases. Regarding MACE, either in-hospital or within six months, there was no significant difference between the two groups. Moreover, at six-month follow-up, MACE, reinfarction, and repeat revascularization were numerically lower but statistically non-significant in the DCB group. Subgroup analysis showed that in-hospital MACE and reinfarction rates were statistically significantly higher when DCBs were applied to large vessels (> 3 mm) and in cases of in-stent thrombosis (P = 0.014 and 0.001, respectively).

Conclusion: Drug-coated balloons appear non-inferior to DES during primary PCI in terms of MACE, including mortality and reinfarction, even in major epicardial coronaries. However, it should be used cautiously in certain lesion subsets, especially large vessels (> 3 mm) and in-stent thrombosis.

Keywords: Drug-coated balloons, drug-eluting stents, primary percutaneous coronary intervention, ST-elevation myocardial infarction

ÖZET

Amaç: ST yükselmeli miyokard enfarktüsü (STEMI), dünya çapında önde gelen ölüm nedenlerinden biridir. Mevcut kılavuzlar, bu hastalar için standart tedavi olarak ilaç salımlı stentler kullanılarak yapılan primer perkütan koroner girişim (PPCI) önermektedir. İlaç kaplı balonlar (DCB) kullanılarak yapılan stent içermeyen PCI, stentle ilişkili komplikasyonları önlemek için yeni bir yaklaşım olarak önerilmektedir. Bu çalışma, STEMI hastalarında DCB kullanımının etkinliğini ve güvenliğini değerlendirmek amacıyla yapılmıştır.

Yöntem: 2019-2023 yılları arasında başvuran ve DCB kullanılarak primer PCI uygulanan STEMI hastalarını, DES ile tedavi edilen hastalarla hastane içi ve 6 aylık Majör Kardiyak Olaylar (MACE) açısından karşılaştırdık.

Bulgular: Toplam 128 STEMI hastası, DCB kullanılarak primer PCI uygulandı ve DES kullanılarak tedavi edilen 128 eşleştirilmiş hastayla karşılaştırıldı. 3 mm'den küçük damarlar ve distal lezyonlar, DES'e kıyasla DCB'de önemli ölçüde daha yüksekti. DCB, hastaların yaklaşık %55'inde

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

Ahmed Darwish[1,2]
Saleh M. Khouj[1]
Abdallah Alzoobiy[1]
Abdullah Ghabashi[1]
Ismail Alghamdi[1]
Saad Alhassani[1]
Ibrahim Elsawah[1]
Ghada Shalaby[1,2]
Abdulaziz Alshamrani[1]
Sheeren Khaled[1,3]

[1]*Cardiac Centre, King Abdullah Medical City, Makkah, Saudi Arabia*
[2]*Department of Cardiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt*
[3]*Department of Cardiology, Faculty of Medicine, Benha University, Banha, Egypt*

Corresponding author:
Ahmed Darwish
✉ ahmeddarwish9@gmail.com

Received: September 03, 2025
Accepted: December 29, 2025

Cite this article as: Darwish A, Khouj SM, Alzoobiy A, et al. Clinical Outcomes of Using Drug-Coated Balloons During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Patients – Insights from High-Risk Groups: A Single-Center Experience. *Turk Kardiyol Dern Ars.* 2026;54(3):227-235.

DOI: 10.5543/tkda.2025.17824

majör epikardiyal damarlarda ve vakaların neredeyse %45'inde yan dallarda kullanıldı. Hastane içinde veya 6 ay içinde MACE açısından iki grup arasında anlamlı bir fark yoktu. Ayrıca, 6 aylık takipte, MACE, reinfarktüs ve tekrar revaskülarizasyon DCB grubunda sayısal olarak daha düşüktü, ancak istatistiksel olarak anlamlı değildi. Alt grup analizi, DCB'nin 3 mm'den büyük damarlara uygulandığı durumlarda ve stent içi trombozda hastane içi MACE ve reinfarktüs oranlarının istatistiksel olarak anlamlı şekilde daha yüksek olduğunu gösterdi (P değeri sırasıyla 0,014 ve 0,001).

Sonuç: DCB, mortalite ve reinfarktüs dahil MACE açısından, majör epikardiyal koroner arterlerde bile primer PCI sırasında DES'e göre daha düşük performans göstermiyor gibi görünmektedir. Ancak, belirli lezyon alt gruplarında, özellikle 3 mm'den büyük damarlarda ve stent içi trombozda dikkatli kullanılmalıdır.

Anahtar Kelimeler: İlaç kaplı balonlar, ilaç salınımlı stentler, primer perkütan koroner girişim, ST yükselmeli miyokard enfarktüsü

ST-elevation myocardial infarction (STEMI) is one of the leading causes of mortality worldwide.[1] Currently, guidelines recommend primary percutaneous coronary intervention (PCI) using drug-eluting stents (DES) as the standard management for these patients.[2] DES have been shown to perform better compared to bare-metal stents (BMS) and percutaneous transluminal coronary angioplasty (PTCA) over the last decade. DES are made of a scaffold coated with an antiproliferative drug that reduces cell proliferation inside the stent and prevents early in-stent restenosis.[3]

On the other hand, several complications of DES, such as stent thrombosis, in-stent restenosis, stent fracture, and the need for long-term dual antiplatelet therapy, still exist.[4] Moreover, the no-reflow phenomenon, which is a nightmare for interventional cardiologists inside the catheterization laboratory, commonly occurs after stent deployment, unfortunately leading to a greater area of myocardial scarring and reduced myocardial salvage.[5]

Accordingly, the stent-free PCI era started to emerge with bioresorbable vascular scaffolds (BVS), which were first proposed by Tamai in 1999.[6] Initially, BVS showed favorable outcomes in early clinical trials for selected coronary lesions, comparable to second-generation DES.[7] Later on, randomized trials involving larger numbers of patients revealed inferior long-term outcomes for BVS compared to DES, with higher rates of thrombotic events and myocardial infarction.[8,9] As a consequence, Abbott withdrew the Absorb BVS from the market in 2017.[10] Hence, drug-coated balloons (DCB) have been suggested as a novel approach to avoid stent-related complications and currently stand alone as the concept of metal-free PCI. Drug-coated balloons are semi-compliant angioplasty balloons covered with antiproliferative drugs, which are released immediately at the site of balloon inflation and diffuse into the subintimal space.[11]

Drug-coated balloons stand for the concept of "leaving nothing behind," in which no permanent stent struts or vascular implants are left in the vessel wall. Hence, DCBs are expected to minimize stent-related complications such as in-stent restenosis and stent thrombosis. In addition, native vessels preserve normal vasomotion due to the lack of chronic inflammation caused by metallic struts and polymers.[12]

Currently, DCBs have been studied in clinical trials for various indications, but they have only been validated in the guidelines for the treatment of in-stent restenosis (ISR).[13] However, there is a paucity of data in the literature discussing the effects of DCBs on the entire acute coronary syndrome (ACS) population. This study aimed to assess the clinical outcomes of using DCBs in STEMI patients undergoing primary PCI.

ABBREVIATIONS

ACS	Acute coronary syndrome
BMS	Bare-metal stents
BVS	Bioresorbable vascular scaffolds
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CVA	Cerebrovascular accident
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloons
DES	Drug-eluting stents
DM	Diabetes mellitus
ECG	Electrocardiography
ECHO	Echocardiography
GP	Glycoprotein
HTN	Hypertension
IHD	Ischemic heart disease
ISR	In-stent restenosis
IV	Intravenous
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCX	Left circumflex artery
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
NC	Non-complaint
PPCI	Primary percutaneous coronary intervention
PVD	Peripheral vascular disease
RCA	Right coronary artery
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
TLF	Target lesion failure
TLR	Target lesion revascularization
VIF	Variance inflation factor

Materials and Methods

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethics Committee

of King Abdullah Medical City (Approval Number: 24-1237, Date: 19.05.2024).

Study Design, Setting, and Duration

This was a single-center, retrospective cohort observational study conducted in the catheterization laboratory of the Cardiology Department during the period from February 2019 to December 2023. Written informed consent was obtained from every patient to review their medical records after an explanation of the medical research and publication process.

Study Population

The study included STEMI patients with diffuse long culprit segments (> 20 mm) who underwent primary PCI to the culprit lesion using either drug-eluting stents or a paclitaxel drug-coated balloon-only strategy, without the need to use a drug-eluting stent.

We excluded patients who developed significant flow-limiting dissection (type C-F) after using DCBs that necessitated crossover to DES, those who were non-compliant with or stopped dual antiplatelet therapy (DAPT) due to any medical issues, and patients with insufficient follow-up data.

Study Variables and Clinical Assessment

Baseline demographic and clinical data were obtained from all patients. Risk factors for coronary artery disease, including diabetes mellitus (DM), hypertension (HTN), smoking, dyslipidemia, previous cerebrovascular accident (CVA), peripheral vascular disease (PVD), ischemic heart disease (IHD), and previous PCI or coronary artery bypass grafting (CABG) due to coronary artery disease (CAD), were reviewed. Electrocardiography (ECG) was evaluated to confirm the diagnosis of STEMI and identify the expected culprit lesion. All patients were loaded before transfer to the catheterization laboratory with aspirin 300 mg, ticagrelor 180 mg or clopidogrel 600 mg, atorvastatin 80 mg, and unfractionated heparin (70–100 IU/kg intravenous (IV) bolus when glycoprotein IIb/IIIa inhibitors were not planned to be used, and 50–70 IU/kg when glycoprotein (GP) IIb/IIIa inhibitors were planned).

A total of 256 STEMI cases underwent primary PCI to the culprit lesion and were stratified into a DCB-only strategy group consisting of 128 patients and a matched DES group consisting of 128 patients.

All cases were subjected to a conventional PPCI procedure, where a workhorse wire was used to cross the distal lesion, with or without aspiration thrombectomy according to the operator's decision. For the DCB group, balloon dilatation of the culprit lesion was performed using semi-compliant, non-compliant, cutting, or scoring balloons according to operator choice. If residual stenosis was less than 30% and dissection was less than type C, the DCB was inflated at nominal pressure (6-8 atm) at the lesion site for one minute. SeQuent Please Neo (B. Braun) and Prevail (Medtronic) were the only two DCB brands used in this study.

On the other hand, the DES group was managed by deploying a DES at the culprit lesion, with or without pre-stenting balloon dilatation according to the operator's choice.

Coronary angiographic findings were recorded, including access site, culprit vessel, native or in-stent culprit lesion, use of regular balloons, non-complaint balloons (NC), cutting or scoring balloons, use of aspiration catheters, and tirofiban. Size, length, presence of calcification, bifurcation lesions, and the site of the treated culprit lesion (proximal, mid, or distal) were also recorded. Small-caliber vessels were defined as vessels less than 3 mm in diameter. Thrombolysis in myocardial infarction (TIMI) flow before and after the intervention was evaluated by two blinded interventional cardiologists.

During index hospitalization, bedside echocardiography (ECHO) was performed, with left ventricular ejection fraction (LVEF) measured using the Simpson method immediately after the procedure. All patients were followed in-hospital for major adverse cardiac events, including acute heart failure, stroke, reinfarction, repeat revascularization, and cardiac arrest.

Follow-up was performed by reviewing patients' medical records. Routinely in our center, patients are scheduled for a follow-up visit one month after discharge and then every three to six months as outpatient visits, according to clinical evaluation. Echocardiographic assessment is routinely performed three to six months after primary PCI and in the case of any new events.

At six-month follow-up, all patients were assessed for left ventricular systolic function and MACE, including hospitalization for heart failure, reinfarction, repeat revascularization, stroke, and cardiac arrest. During follow-up, compliance with DAPT for one year was reviewed for all patients, as non-compliance was one of the exclusion criteria.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 23.0) software produced by IBM (Chicago, Illinois, USA). Patients were classified into two groups: DCB and DES. Qualitative data were presented as numbers and percentages and compared using the chi-square test. Quantitative data were presented as mean ± standard deviation and compared using the independent t-test. A p value < 0.05 was considered statistically significant. Regarding regression analysis, multicollinearity was assessed using variance inflation factors (VIFs). All variables included in the multivariable model had VIF values below the commonly accepted threshold (VIF < 5), indicating no significant multicollinearity. Furthermore, variables were first screened in univariable analyses, and those with $P < 0.05$ were considered candidates for inclusion in the multivariate analysis.

Results

Characteristics of the Study Population

This retrospective observational study included STEMI patients who underwent primary PCI using a drug-coated balloon at our institution between February 2019 and December 2023. A total of 128 patients met the inclusion criteria and were included in the DCB group. The sample size was determined by the total number of eligible cases available during the study period. A control group of 128 matched patients who underwent primary PCI with drug-eluting stents was selected based on key clinical and angiographic variables (e.g., age, gender, diabetes status, and lesion characteristics) to minimize selection bias. The matched design allowed for a balanced comparison of major adverse cardiac events between the two groups.

Table 1. Clinical profile of both study groups

Variables	DCB (n = 128) (%)	DES (n = 128) (%)	*P*
Diabetes	82 (64)	100 (78.1)	0.08
Hypertension	78 (61)	94 (73.4)	0.13
Smoking	52 (41)	48 (37.5)	0.71
Obesity	40 (31)	54 (42.2)	0.22
Dyslipidemia	38 (29.7)	46 (35.9)	0.48
Previous revascularization	30 (23)	44 (34.4)	0.17
Previous CVA	12 (9.4)	16 (12.5)	0.57
Killip class I	84 (65.6)	78 (61)	0.72
Killip class II	36 (28)	31 (24.2)	0.84
Killip class III	8 (6)	18 (14)	0.09
Killip class IV	0 (0)	1 (0.8)	0.96

DCB, Drug-coated balloons; DES, Drug-eluting stents; CVA, Cerebrovascular accident.

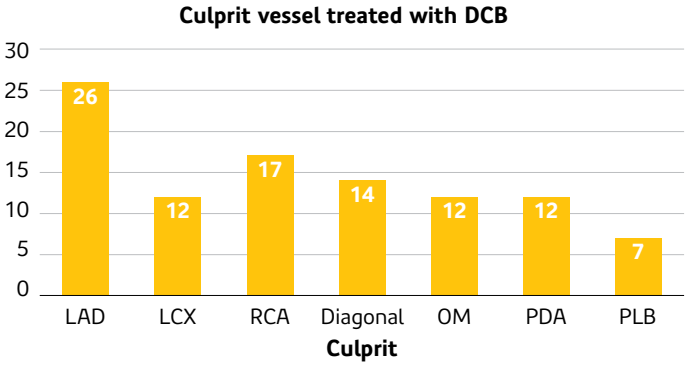


Figure 1. Culprit vessels treated with drug-coated balloons (DCB).

Included patients were followed for major adverse cardiac events both in-hospital and for six months after the procedure.

Regarding demographic and clinical characteristics, there was no significant difference between the two groups in terms of age, diabetes, hypertension, smoking, previous revascularization, and Killip class at presentation (Table 1).

Several nationalities were identified in the study population, including patients from 13 countries. Around 62% were Saudi, 7% were Egyptian, 6% were from Bangladesh, and the remaining 25% represented ten other countries.

Regarding angiographic analysis, small-vessel culprit lesions (< 3 mm) and distal lesions were statistically significantly higher in the DCB group compared to the DES group. On the other hand, there was no significant difference between the two groups in terms of culprit vessel, native or in-stent culprit, lesion size and length, presence of calcification, bifurcation lesions, and TIMI flow before and after intervention. Furthermore, a high thrombus burden (≥ grade 4) was observed in 42.2% of the DCB groups versus 32.8% of the DES group, without a statistically significant difference (P = 0.27) (Table 2).

Table 2. Angiographic analysis of lesions treated with DCB versus DES

Variables	DCB (n = 128) (%)	DES (n = 128) (%)	*P*
LAD	34 (26.6)	48 (37.5)	0.19
LCX	16 (12.5)	30 (23.4)	0.11
RCA	22 (17.2)	28 (21.9)	0.5
Diagonal	18 (14.1)	12 (9.4)	0.41
Obtuse marginal (OM)	16 (12.5)	14 (10.9)	0.78
Posterior descending artery (PDA)	16 (12.5)	8 (6.3)	0.23
Posterolateral branch (PLB)	10 (7.8)	1 (1.6)	0.09
Native culprit lesion	104 (81.2)	108 (84.4)	0.63
In-stent culprit lesion	24 (18.8)	20 (15.6)	0.64
Proximal lesion	72 (56.3)	78 (60.9)	0.59
Mid lesion	18 (14.1)	34 (26.6)	0.08
Distal lesion	38 (29.7)	16 (12.5)	**0.02**
Small-caliber vessel (< 3 mm)	94 (73.4)	70 (54.7)	**0.03**
Large-caliber vessel (> 3 mm)	34 (26.6)	62 (48.4)	**0.01**
Regular balloon predilatation	86 (67.2)	94 (73.4)	0.44
NC balloon predilatation	36 (28.1)	46 (35.9)	0.33
Cutting balloon predilatation	6 (4.7)	8 (6.3)	0.69
Calcification	42 (33.3)	38 (29.7)	0.66
Bifurcation lesion	22 (17.2)	14 (10.9)	0.31
High thrombus burden	54 (42.2)	42 (32.8)	0.27
Aspiration catheter use	36 (28.1)	26 (20.3)	0.3
Tirofiban use	30 (23.4)	14 (10.9)	0.06
TIMI flow before intervention			
TIMI 0	102 (79.7)	95 (74.2)	0.29
TIMI I	16 (12.9)	21 (16.4)	0.43
TIMI II	7 (5.5)	8 (6.3)	0.79
TIMI III	3 (1.9)	4 (3.1)	0.53
TIMI flow after intervention			
TIMI I	4 (3.1)	9 (7)	0.15
TIMI II	13 (10.2)	17 (13.3)	0.44
TIMI III	111 (86.7)	102 (79.7)	0.13

DCB, Drug-coated balloons; DES, Drug-eluting stents; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; NC, Non-complaint; TIMI, Thrombolysis in myocardial infarction.

Drug-coated balloons were used in both major epicardial vessels and side branches. They were used in 55% of cases in major epicardial coronaries, including the left anterior descending artery (26%), right coronary artery (17%), and left circumflex artery (12%). The remaining 45% were side branches, such as diagonal branches (14%), obtuse marginal branches (12%), posterior descending artery (12%), and posterolateral branches (7%) (Figure 1).

Drug-coated balloons were used to treat in-stent culprit lesions in 19% of patients and native coronary lesions in 81% of the study group. They were applied to proximal lesions in 56% of cases and to distal lesions in 30%. Regarding the treated culprit

Table 3. Comparison of MACE between STEMI patients treated with DCB and DES

Variables	DCB (%)	DES (%)	*P*
In-hospital MACE	12 (9.4)	6 (4.7)	0.30
Reinfarction	10 (7.8)	4 (3.1)	0.24
Repeat revascularization	10 (7.8)	4 (3.1)	0.24
Acute heart failure	4 (3.1)	2 (1.6)	0.56
Cardiac arrest	6 (4.7)	2 (1.6)	0.32
Stroke	0 (0)	2 (1.6)	0.83
Six-Month MACE	16 (12.5)	18 (14.1)	0.79
Reinfarction	4 (3.4)	6 (4.8)	0.7
Repeat revascularization	6 (5.1)	8 (6.3)	0.76
Hospitalization for heart failure	6 (5.1)	12 (9.5)	0.3
Cardiac arrest	4 (3.1)	2 (1.6)	0.56
Stroke	5 (3.9)	2 (1.6)	0.77

MACE, Major adverse cardiac events; STEMI, ST-elevation myocardial infarction; DCB, Drug-coated balloons; DES, Drug-eluting stents.

vessels where DCBs were used, 73% were small-caliber vessels (< 3 mm) (Figure 2). Most lesions were modified using regular balloons in around 67% of cases, while non-compliant balloons were used in 28%. Cutting and scoring balloons were used in a minority of cases, accounting for only 5% (Table 2).

All patients were followed during their hospital stay and for six months after discharge for major adverse cardiac events, including reinfarction, repeat revascularization, stroke, heart failure, and cardiac arrest. There was no significant difference in MACE either in-hospital or within six months between patients treated with DCB and those treated with DES during primary PCI. Moreover, at six-month follow-up, MACE, reinfarction, and repeat revascularization were numerically lower but statistically non-significant in the DCB group. Kaplan-Meier curves showed no significant difference between DCB and DES regarding cumulative MACE hazard and MACE-free survival during the six months following primary PCI (P = 0.77) (Figure 3).

Among patients treated with a DCB-only strategy, MACE was observed in 9.4% during index hospitalization and in 12.4% during the six-month follow-up after discharge. Regarding in-hospital MACE, reinfarction and repeat revascularization occurred in 7.8% of patients, and 4.7% developed cardiac arrest. During the six months after discharge, the reinfarction rate was approximately 3.4%, repeat revascularization occurred in 5.1%, and cardiac arrest occurred in 3.1% of patients (Table 3, Figure 4).

Subgroup analysis of clinical outcomes was performed among different interventional strategies in which DCBs were used and showed that in-hospital MACE and reinfarction were statistically significantly higher when DCBs were used to treat large vessels (> 3 mm) (P = 0.014 and 0.005, respectively) and in cases of in-stent thrombosis (P = 0.001 and <0.001, respectively). Regarding lesion preparation, in-hospital MACE and reinfarction were numerically higher but statistically non-significant when regular balloon dilatation was used compared to specialized balloons (NC and cutting balloons) before DCB application (Table 4).

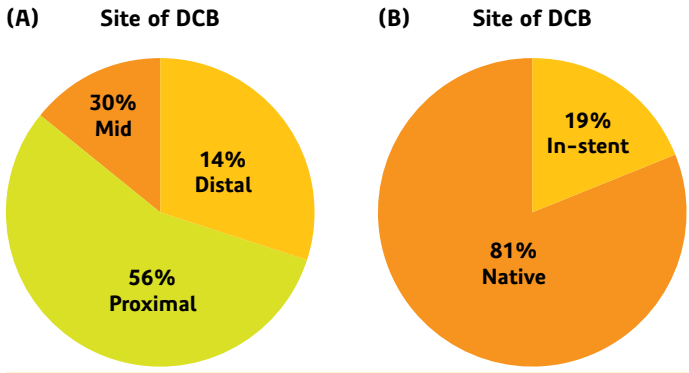


Figure 2. Coronary lesion sites where drug-coated balloons (DCB) were used. (A) Site where DCBs were used, either proximal, mid, or distal. (B) Site where DCBs were used, either in native lesions or in-stent.

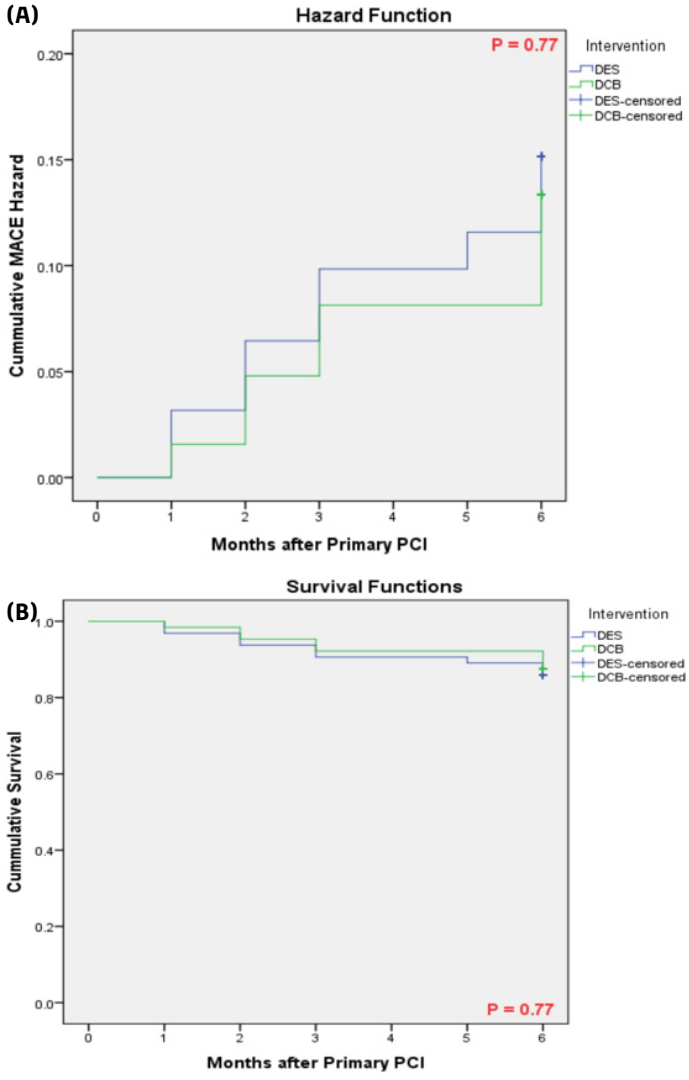


Figure 3. Kaplan-Meier curves comparing drug-coated balloons (DCB) versus drug-eluting stents (DES). (A) Cumulative major adverse cardiac event (MACE) hazard within six months after primary percutaneous coronary intervention (PCI). (B) MACE-free survival over six months after primary PCI.

Table 4. Subgroup analysis of clinical outcomes among different angiographic interventional strategies in patients treated with DCB

Variables	Small vessel (n = 94)	Large vessel (n = 34)	*P*	Native culprit (n = 104)	In-stent culprit (n = 24)	*P*	Regular balloons (n = 100)	Specialized balloons (n = 28)	*P*
In-hospital outcomes, %									
MACE	6 (6.4)	10 (29.4)	**0.014***	6 (5.8)	10 (41.7)	**0.001***	12 (12)	4 (4.3)	0.82
Reinfarction	2 (2.1)	8 (23.5)	**0.005***	2 (1.9)	8 (33.3)	**<0.001***	8 (8)	2 (7.1)	0.92
Repeat revascularization	2 (2.1)	8 (23.5)	**0.005***	2 (1.9)	8 (33.3)	**<0.001***	8 (8)	2 (7.1)	0.92
Cardiogenic shock	2 (2.1)	2 (5.9)	0.45	2 (1.9)	2 (8.3)	0.25	4 (4)	0 (0)	0.447
Cardiac arrest	4 (4.3)	2 (5.9)	0.79	4 (3.8)	2 (8.3)	0.51	4 (4)	2 (7.1)	0.62
Six-month outcomes, %									
MACE	12 (35.3)	10 (10.6)	0.12	12 (11.5)	10 (41.7)	0.16	16 (16)	6 (21.4)	0.964
Reinfarction	4 (4.7)	0 (0)	0.38	4 (4.2)	0 (0)	0.49	4 (4.4)	0 (0)	0.42
Repeat revascularization	4 (4.7)	2 (3.6)	0.8	4 (4.2)	2 (9.1)	0.5	4 (4.4)	2 (7.1)	0.69
Hospitalization for heart failure	0 (0)	6 (18.8)	**<0.05***	0 (0)	6 (27.3)	**<0.001***	5 (5)	2 (7.1)	0.83
Cardiac arrest	4 (4.8)	2 (6.3)	0.82	4 (3.8)	2 (8.3)	0.51	4 (4.4)	2 (7.1)	0.69

*Statistically significant. DCB, Drug-coated balloons; MACE, Major adverse cardiac events.

Multivariate binary logistic regression analysis showed that treating in-stent culprit lesion was an independent predictor of in-hospital MACE in PPCI cases managed using DCBs (odds ratio [OR] = 1.22, P = 0.041) (Table 5).

Regarding left ventricular ejection fraction at follow-up, there was no statistically significant difference between the two groups six months after the procedure (21.4% ± 23.2 vs. 28.3% ± 24.4; P = 0.48).

Discussion

In the present observational study, we evaluated the use of a drug-coated balloon-only strategy during primary PCI for ST-elevation myocardial infarction in a diverse and clinically complex patient population. Our results demonstrate that this approach is technically feasible and associated with acceptable short-term outcomes. The in-hospital MACE rate was 9.4%, increasing to 12.4% at six months, while reinfarction occurred in 7.8% of patients during the index hospitalization and in 3.4% during follow-up. DCBs were used not only in small coronary vessels but also in large epicardial arteries and proximal segments—55% and 56% of cases, respectively. In addition, vessel diameter > 3 mm and in-stent restenosis as the culprit lesion emerged as key angiographic predictors of adverse in-hospital outcomes. To our knowledge, our study represents one of the largest real-world assessments of a DCB-only PPCI strategy in a multinational cohort, offering new insights into clinical and procedural factors that may influence outcomes.

Moreover, this study aimed to identify high-risk groups and angiographic criteria that are more susceptible to complications and adverse events following the use of DCBs during PPCI.

In 2001, the basic concept of a drug-coated balloon providing a short-lasting application was proposed, and the first experimental studies were performed.[14,15] Scheller et al.[15] suggested delivering anti-cell proliferation drugs to the target diseased blood vessel through balloon expansion, thereby inhibiting intimal proliferative inflammation.[16]

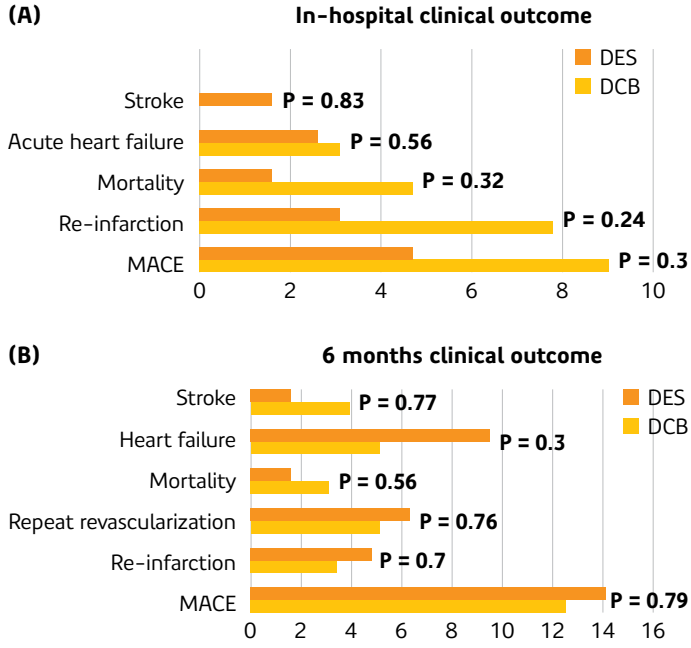


Figure 4. Comparison of clinical outcomes between drug-coated balloons (DCB) and drug-eluting stent (DES) groups. (A) In-hospital clinical outcomes. (B) Six-month clinical outcomes.

Several advantages and disadvantages have been proposed for using a DCB-only strategy during PPCI. On the one hand, it may overcome stent undersizing that occurs due to spastic condition during acute myocardial infarction. In addition, it may simplify complex lesions, especially in critically ill patients, and avoid the strict need for long-term antiplatelet therapy.[13,17] On the other hand, in cases with a high thrombus burden, large thrombi may hinder adequate drug delivery to the vessel wall.[13,18] Moreover, to achieve maximum benefit, DCBs require adequate and aggressive lesion preparation, which may result in significant coronary dissection.

Table 5. Independent predictors of in-hospital MACE in the DCB group

Variables	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Diabetes	0.29	0.7–1.16	0.08			
Killip class	1.62	1.11–2.37	**0.013***	1.14	0.9–1.43	0.27
In-stent culprit	1.85	1.07–2.45	**0.02***	1.22	1.01–1.48	**0.041***
Regular balloon use	1.21	1.03–1.51	0.96			
Large vessel	1.42	1.16–1.81	**0.003***	1.03	0.92–1.15	0.62
Proximal lesion	1.34	0.86–1.67	0.74			
Distal lesion	0.31	0.18–1.19	0.28			

*Statistically significant. MACE, Major adverse cardiac events; DCB, Drug-coated balloon; OR, Odd ratios; CI, Confidence interval.

To our knowledge, this is the first study to evaluate the use of DCBs during PPCI in a heterogeneous patient population, including up to 13 nationalities. This was facilitated by the unique location and role of our institute in treating Hajj and Umrah patients while they are performing their religious activities in Makkah.

Despite the general concept that DCBs are mainly designed for treating small vessels and side branches, they were used in major epicardial coronaries, including the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA), in up to 55% of cases in the present study. In addition, DCBs were applied to proximal lesions in 56% of cases during PPCI.

The present study showed that in-hospital MACE was 9.4%, increasing to 12.4% at six-month follow-up. These results are concordant with Hao et al.,[16] who reported that in PPCI cases treated with DCBs, MACE at one year was observed in 11% of cases, with no significant difference compared to the DES group.[19]

In addition, the REVELATION trial (Randomized Evaluation of paclitaxEL-coated balloon Versus drug-eLuting stent In Acute ST-elevation myocardial infarction), published in 2017, evaluated the use of DCB versus DES during primary PCI in STEMI patients. At two-year follow-up, MACE was observed in only four out of 60 patients in the DCB arm, with no significant difference compared to the DES arm.[20] The higher MACE rate observed in our study may be explained by differences in the demographic data of the study groups and by different definitions of MACE between the two studies. In the present study, 64% of patients in the DCB arm were diabetic and 30% had dyslipidemia, compared to 13% and 17%, respectively, in the REVELATION trial. In addition, hospitalization due to heart failure was included as a component of MACE in the present study, which may have influenced the results.

More recently, Merinopoulos et al.[21] published a large study conducted on 1,139 patients over four years, of whom 452 cases were managed using DCBs during PPCI. According to their results, all-cause mortality was observed in 10.8% of the DCB arm versus 9% in the DES group, without a statistically significant difference.

On the other hand, the present study showed that reinfarction in PPCI cases treated with DCB was observed in ten cases, with rates of 7.8% in-hospital and 3.4% at six-month follow-up. In this regard, the study by Gobić et al.[22] reported a reinfarction rate in the DCB arm during PPCI of 5.3% at one-month follow-up and 0% during the subsequent six months. This relatively different result could be attributed to the smaller sample size of their study, as they included 38 patients in the DCB group, whereas the present study analyzed 128 patients treated with DCB.

Discordant with the present study, the REVELATION trial showed a zero reinfarction rate and a 3% target lesion revascularization (TLR) rate at nine-month follow-up, and rates of 1.8% and 5.4%, respectively, at two-year follow-up.[23] The higher reinfarction rate observed in our study may be explained by differences in lesion modification methods used prior to DCB application. In the present study, 67% of lesions were predilated using semi-compliant balloons, 28% using NC balloons, and 5% using cutting or scoring balloons. Previous studies have shown that modified balloons (specifically cutting and scoring balloons) were associated with significantly lower rates of major dissection and a reduced need for crossover to DES compared to conventional balloons in small-vessel lesions.[24,25]

A few months ago, Sanz-Sánchez et al.[26] published an observational study evaluating the use of DCB-only therapy during PPCI and demonstrated low rates of target lesion failure (TLF) (3.4%). A target lesion revascularization rate of 1.8% was observed, with no reported cases of target vessel myocardial infarction. This discrepancy between their results and ours may be related to differences in patient population, as diabetic patients constituted 67% of our study group compared to only 32% in their study. In addition, stent thrombosis accounted for approximately 28% of patients treated with DCB in their study versus 19% in our cohort. Furthermore, only two DCB brands were used in the present study, whereas six different DCBs were used in the study by Sanz-Sánchez et al.,[27] which may have influenced the results. These promising findings by Sanz-Sánchez et al.[27] prompted the initiation of the COPERNICAN trial (Comparison Of Paclitaxel-Eluting Balloon versus Drug-Eluting Stent in ST-Elevation Myocardial Infarction), a randomized study comparing clinical outcomes of DCB versus DES in STEMI patients, with results anticipated soon.

Finally, subgroup analysis of the present study showed that in-hospital MACE and reinfarction rates were significantly higher in large vessels (> 3 mm) and in patients with in-stent culprit. Moreover, treatment of an in-stent culprit was identified as an independent predictor of in-hospital MACE following DCB use during PPCI. This finding may be explained by the higher thrombus burden in primary PCI cases, which could hinder adequate drug delivery to the vessel wall. In addition, semi-compliant balloons were used in more than 60% of our patients, which may have resulted in inadequate vessel preparation. Emerging published

evidence has shown that TLR rates are significantly higher in the semi-compliant balloon group compared to scoring and non-compliant balloons used prior to DCB therapy.[28]

Theoretically, the routine use of scoring or cutting balloons before DCB deployment has been proposed to create cracks and dissections in the vessel wall, thereby facilitating drug transfer and penetration into the vessel wall and potentially enhancing the anti-restenosis efficacy of DCBs.[29] In this regard, the randomized NATURE trial (Non-compliant or cUtting balloon for lesion pReparaTion bEfore drug-coated balloon angioplasty) is currently ongoing to evaluate the safety and efficacy of cutting balloons compared to standard balloons (semi-compliant or non-compliant balloons) for lesion preparation prior to DCB treatment in normal-sized vessels.[30]

Overall, our study provides one of the most detailed assessments to date of angiographic subgroups and procedural characteristics associated with outcomes following DCB-only PPCI in STEMI patients. The results underscore the importance of careful lesion assessment, meticulous vessel preparation, and individualized procedural planning.

In summary, DCB-only PPCI represents a viable alternative to DES in selected STEMI cases—particularly when long-term DAPT is undesirable, vessel dimensions are uncertain, or a metal-free PCI is preferred.[31] However, heightened caution is warranted in lesions with a high thrombus burden, inadequate preparation, large-caliber vessels, or in-stent restenosis, where the risk of adverse events is increased. Optimal balloon preparation—preferably using scoring or cutting devices—and thoughtful angiographic evaluation remain central to the successful implementation of this strategy. As evidence from ongoing randomized trials becomes available, the role of DCBs in acute STEMI management is expected to become more clearly defined.

Limitation

The present study is a retrospective observational study and, consequently, is subject to multiple confounding factors. Therefore, large randomized, double-blinded clinical trials are recommended to compare DCB and DES during primary PCI. Although the relatively large sample size improves sensitivity compared to smaller cohorts, this study was powered only to detect relatively large absolute differences. Smaller but potentially clinically meaningful differences—particularly subgroup effects—may not have been detected. Accordingly, subgroup analyses should be considered exploratory and interpreted with caution. We also recommend greater use of intravascular ultrasound (IVUS) during the index procedure to adequately evaluate for and exclude major dissection after lesion preparation. Moreover, IVUS-guided angiographic follow-up is recommended to measure minimal lumen area and assess late lumen enlargement.

Conclusion

Drug-coated balloons appear to be non-inferior to DES during primary PCI in terms of MACE, including mortality, reinfarction, and repeat revascularization, even in major epicardial coronary arteries. However, DCB use should be approached cautiously in certain lesion subsets, particularly large vessels (> 3 mm) and cases of in-stent thrombosis. These findings are still exploratory and should be interpreted with caution until confirmed by large, IVUS-guided, randomized double-blinded clinical trials.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of King Abdullah Medical City (Approval Number: 24-1237, Date: 19.05.2024).

Informed Consent: Written informed consent was obtained from every patient to review their medical records.

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: The authors did not use AI-assisted technologies in the writing of this manuscript.

Author Contributions: Concept – A.D., S.M.K., A.Alzoobiy, A.G., I.A., S.A., I.E., G.S., A.Alshamrani, S.K.; Design – A.D., S.M.K., S.K.; Supervision – A.Alzoobiy, A.G., S.A., I.E.; Resource – A.D., S.M.K., A.G., I.A., A.Alshamrani, S.K.; Materials – A.D., S.M.K., A.G., S.A., I.E.; Data Collection and/or Processing – A.D., I.E., G.S., A.Alshamrani; Analysis and/or Interpretation – A.D., G.S.; Literature Review – A.D., S.K.; Writing – A.D.; Critical Review –S.M.K., A.Alzoobiy, A.G., I.A., S.A.

Peer-review: Externally peer-reviewed.

References

1. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med*. 2016;4(13):256. [CrossRef]
2. Byrne RA, Rossello X, Coughlan JJ, et al.; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44(38):3720-3826. Erratum in: *Eur Heart J*. 2024;45(13):1145. [CrossRef]
3. Krackhardt F, Rosli MA, Leschke M, et al. Propensity score matched all comers population treated with ultra-thin strut bare metal and sirolimus-probucol coated drug-eluting stents of identical stent architecture. *Catheter Cardiovasc Interv*. 2018;91(7):1221-1228. [CrossRef]
4. Khan SU, Singh M, Valavoor S, et al. Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents: A Systematic Review and Network Meta-Analysis. *Circulation*. 2020;142(15):1425-1436. [CrossRef]
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)]. *G Ital Cardiol (Rome)*. 2019;20(7-8 Suppl 1):1S-61S. Italian.
6. Lafont A, Mennuni MG. What Happened to the Bioresorbable Scaffold Concept: Black Tide or Chernobyl? *Circ Cardiovasc Interv*. 2018;11(1):e006283. [CrossRef]
7. Serruys PW, Chevalier B, Sotomi Y, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet*. 2016;388(10059):2479-2491. Erratum in: *Lancet*. 2017;389(10071):804. [CrossRef]
8. Kereiakes DJ, Ellis SG, Metzger C, et al.; ABSORB III Investigators. 3-Year Clinical Outcomes With Everolimus-Eluting Bioresorbable Coronary Scaffolds: The ABSORB III Trial. *J Am Coll Cardiol*. 2017;70(23):2852-2862. [CrossRef]
9. Waksman R. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. *N Engl J Med*. 2017;377(18):1790-1791. [CrossRef]
10. Joner M, Klosterman G, Byrne RA. Novel bioresorbable scaffolds and lessons from recent history. *EuroIntervention*. 2023;19(3):193-195.
11. Claessen BE, Henriques JPS, Vendrik J, et al. Paclitaxel-eluting balloon versus everolimus-eluting stent in patients with diabetes mellitus and in-stent restenosis: Insights from the randomized DARE trial. *Catheter Cardiovasc Interv*. 2019;93(2):216-221. [CrossRef]

12. Zhang YB, Liu HD, Xing JH, et al. Safety and Efficacy of Drug-Coated Balloons in Patients with Acute Coronary Syndromes and Vulnerable Plaque. *Clin Appl Thromb Hemost*. 2022;28:10760296221130063. [CrossRef]
13. Giacoppo D, Saucedo J, Scheller B. Coronary Drug-Coated Balloons for De Novo and In-Stent Restenosis Indications. *J Soc Cardiovasc Angiogr Interv*. 2023;2(3):100625. [CrossRef]
14. Alfonso F, Scheller B. State of the art: balloon catheter technologies - drug-coated balloon. *EuroIntervention*. 2017;13(6):680-695. [CrossRef]
15. Scheller B, Cremers B, Schmitmeier S, Schnorr B, Clever Y, Speck U. Drug-coated Balloons - History and Peripheral Vascular Opportunities. *Interv Cardiol*. 2010;5(1):70-73. [CrossRef]
16. Hao X, Huang D, Wang Z, Zhang J, Liu H, Lu Y. Study on the safety and effectiveness of drug-coated balloons in patients with acute myocardial infarction. *J Cardiothorac Surg*. 2021;16(1):178. Erratum in: *J Cardiothorac Surg*. 2021;16(1):247. [CrossRef]
17. Naganawa H, Ito A, Saiki S, et al. The Efficacy of Drug-Coated Balloon for Acute Coronary Syndrome. *Cardiol Res Pract*. 2023;2023:4594818. [CrossRef]
18. Scheller B, Eccleshall S. Drug-coated balloons for acute coronary syndromes. *EuroIntervention*. 2024;20(13):e791-e792. [CrossRef]
19. Belkacemi A, Agostoni P, Nathoe HM, et al. First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation myocardial infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. *J Am Coll Cardiol*. 2012;59(25):2327-2337. [CrossRef]
20. Niehe SR, Vos NS, Van Der Schaaf RJ, et al. Two-Year Clinical Outcomes of the REVELATION Study: Sustained Safety and Feasibility of Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction. *J Invasive Cardiol*. 2022;34(1):E39-E42. [CrossRef]
21. Merinopoulos I, Gunawardena T, Corballis N, et al. Assessment of Paclitaxel Drug-Coated Balloon Only Angioplasty in STEMI. *JACC Cardiovasc Interv*. 2023;16(7):771-779. [CrossRef]
22. Gobić D, Tomulić V, Lulić D, et al. Drug-Coated Balloon Versus Drug-Eluting Stent in Primary Percutaneous Coronary Intervention: A Feasibility Study. *Am J Med Sci*. 2017;354(6):553-560. [CrossRef]
23. Vos NS, Fagel ND, Amoroso G, et al. Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction: The REVELATION Randomized Trial. *JACC Cardiovasc Interv*. 2019;12(17):1691-1699. [CrossRef]
24. Funatsu A, Nakamura S, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon with plain balloon angioplasty in patients with small vessel disease. *Clin Res Cardiol*. 2017;106(10):824-832. [CrossRef]
25. Her AY, Shin ES, Bang LH, et al. Drug-coated balloon treatment in coronary artery disease: Recommendations from an Asia-Pacific Consensus Group. *Cardiol J*. 2021;28(1):136-149. [CrossRef]
26. Sanz-Sánchez J, Teira Calderón A, Neves D, et al. Culprit-Lesion Drug-Coated-Balloon Percutaneous Coronary Intervention in Patients Presenting with ST-Elevation Myocardial Infarction (STEMI). *J Clin Med*. 2025;14(3):869. [CrossRef]
27. Sanz-Sánchez J, Santos Martínez S, Rumiz González E, et al. Reduced stent strategy versus conventional percutaneous coronary revascularization in patients presenting with STEMI: the COPERNICAN trial. *Rev Esp Cardiol (Engl Ed)*. 2025:S1885-5857(25)00150-1. English, Spanish. [CrossRef]
28. Basavarajaiah S, Sharma V, Agip-Fustamante D, et al. Which predilatation balloons provide the best lesion preparation prior to use of drug coated balloons in de-novo lesions? Results from the PREPARE study. *Minerva Cardiol Angiol*. 2023;71(2):182-188. [CrossRef]
29. Adriaenssens T, Bennett J. Aggressive predilatation seeking medial dissection: a prerequisite for a drug-coated balloon-only strategy in de novo coronary lesions? *EuroIntervention*. 2024;20(13):e789-e790. [CrossRef]
30. Ono M, Asano T, Noguchi M, et al.; NATURE trial investigators. Cutting balloon versus standard balloon for lesion preparation of drug-coated balloon treatment in de-novo coronary artery lesions: Rationale and design of the randomized NATURE trial. *Cardiovasc Revasc Med*. 2025;81:48-56. [CrossRef]
31. Vrints C, Andreotti F, Koskinas KC, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45(36):3415-3537. Erratum in: *Eur Heart J*. 2025;46(16):1565. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Assessing the Predictive Value of Kolmogorov–Arnold Networks for the No-Reflow Phenomenon in ST-Segment Elevation Myocardial Infarction: A Comparative Machine Learning Study

ST Segment Yükselmeli Miyokard Enfarktüsünde No-Reflow Fenomeni için Kolmogorov–Arnold Ağlarının Öngörü Değerinin Değerlendirilmesi: Karşılaştırmalı Makine Öğrenimi Çalışması

ABSTRACT

Objective: The no-reflow phenomenon in ST-segment elevation myocardial infarction (STEMI) is a significant clinical issue associated with poor cardiovascular outcomes. This study aimed to develop and compare multiple supervised machine learning algorithms, including the recently introduced Kolmogorov–Arnold Network (KAN), to predict the occurrence of the no-reflow phenomenon in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

Method: This prospective, single-center study included 890 consecutive STEMI patients undergoing primary PCI. The Synthetic Minority Over-sampling Technique (SMOTE) was utilized to address class imbalance during training. Feature selection using analysis of variance (ANOVA) F-statistics and validation of feature independence (Variance Inflation Factor [VIF] < 5) identified ejection fraction (EF), baseline troponin level, stent length, B-type natriuretic peptide (BNP) level, and total ischemic time as the most influential predictors.

Results: The KAN and Extreme Gradient Boosting (XGBoost) models achieved the highest predictive accuracy (area under the curve > 0.98, F1 > 0.95), outperforming traditional models such as logistic regression and decision tree classifiers (DeLong test, $P < 0.001$). Feature selection improved efficiency and reduced runtime by 20–40%, while Shapley Additive exPlanations-based (SHAP-based) explainability confirmed that the predictions were physiologically consistent: higher EF and lower BNP reduced the probability of no-reflow, whereas longer stent length and ischemic time increased it. The superior performance of KAN and XGBoost underscores the importance of modeling nonlinear relationships and multidimensional interactions among clinical, laboratory, and procedural variables.

Conclusion: These findings suggest that KAN may serve as a reliable analytical framework for exploring complex cardiovascular outcomes. However, further multicenter and externally validated studies are needed to confirm its generalizability and potential role in clinical risk assessment.

Keywords: Extreme Gradient Boosting, Kolmogorov–Arnold network, machine learning, no-reflow phenomenon, Shapley Additive exPlanations explainability, ST-segment elevation myocardial infarction

ÖZET

Amaç: ST-segment yükselmeli miyokard enfarktüsünde (STEMI) görülen no-reflow fenomeni, kötü kardiyovasküler sonuçlarla ilişkilendirilen önemli bir klinik sorundur. Bu çalışma, primer perkütan koroner girişim (PKG) uygulanan STEMI hastalarında no-reflow fenomeninin görülmesini öngörmek amacıyla, yakın zamanda tanıtılan Kolmogorov–Arnold Ağı (KAN) da dâhil olmak üzere birden fazla denetimli makine öğrenimi algoritmasını geliştirmeyi ve karşılaştırmayı amaçlamıştır.

Yöntem: Bu ileriye dönük, tek merkezli çalışma, primer PKG uygulanan ardışık 890 STEMI hastasını kapsamıştır. Eğitim sırasında sınıf dengesizliğini gidermek amacıyla Sentetik Azınlık Aşırı Örnekleme Tekniği (SMOTE) kullanılmıştır. ANOVA F-istatistikleri kullanılarak yapılan özellik seçimi ve özellik bağımsızlığının doğrulanması (VIF < 5); ejeksiyon fraksiyonu (EF), bazal troponin seviyesi, stent uzunluğu, BNP seviyesi ve toplam iskemik süreyi en etkili öngörücüler olarak belirlemiştir.

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

Hakan Taşolar[1]
Adil Bayramoğlu[1]
Mehmet Akif Günen[2]
Sümeyye Levent[3]
Yunus Güral[3]
Nurhan Halisdemir[3]

[1]Department of Cardiology, İnönü University, Faculty of Medicine, Malatya, Türkiye
[2]Department of Geomatics Engineering, Gümüşhane University, Faculty of Engineering and Natural Sciences, Gümüşhane, Türkiye
[3]Department of Statistics, Fırat University, Faculty of Arts and Sciences, Elazığ, Türkiye

Corresponding author:
Hakan Taşolar
✉ hakantasolar@gmail.com

Received: October 16, 2025
Accepted: January 05, 2026

Cite this article as: Taşolar H, Bayramoğlu A, Günen MA, Levent S, Güral Y, Halisdemir N. Assessing the Predictive Value of Kolmogorov–Arnold Networks for the No-Reflow Phenomenon in ST-Segment Elevation Myocardial Infarction: A Comparative Machine Learning Study. *Turk Kardiyol Dern Ars.* 2026;54(3):236–244.

DOI: 10.5543/tkda.2026.02730

Bulgular: KAN ve XGBoost modelleri, en yüksek tahmin doğruluğuna ulaşarak (AUC > 0,98, F1 > 0,95), lojistik regresyon ve karar ağacı sınıflandırıcıları gibi geleneksel modelleri istatistiksel olarak anlamlı düzeyde geride bırakmıştır (P < 0,001). Özellik seçimi, verimliliği artırmış ve çalışma süresini %20–40 oranında azaltmıştır; SHAP tabanlı açıklanabilirlik ise tahminlerin fizyolojik olarak tutarlı olduğunu doğrulamıştır. Daha yüksek EF ve daha düşük BNP, no-reflow olasılığını azaltırken; daha uzun stent uzunluğu ve iskemik süre bu olasılığı artırmıştır. KAN ve XGBoost'un üstün performansı, klinik, laboratuvar ve prosedürel değişkenler arasındaki doğrusal olmayan ilişkilerin ve çok boyutlu etkileşimlerin modellenmesinin önemini vurgulamaktadır.

Sonuç: Bu bulgular, KAN'ın karmaşık kardiyovasküler sonuçların incelenmesinde güvenilir bir analitik çerçeve olarak hizmet edebileceğini göstermektedir. Ancak, genellenebilirliğinin ve klinik risk değerlendirmesindeki potansiyel rolünün doğrulanması için çok merkezli ve harici olarak doğrulanmış ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Aşırı Gradyan Güçlendirme, Kolmogorov–Arnold ağı, makine öğrenimi, no-reflow fenomeni, Shapley Additive exPlanations açıklanabilirlik, ST-segment yükselmeli miyokard enfarktüsü

The no-reflow phenomenon in ST-segment elevation myocardial infarction (STEMI) is a significant clinical issue that can hinder recovery, even after successful primary percutaneous coronary intervention (PCI). It is characterized by inadequate myocardial tissue perfusion despite reopening of the infarct-related coronary artery. Various studies have explored the mechanisms, predictors, and consequences of this phenomenon, as well as how machine learning (ML) can aid in its prediction and management. The no-reflow phenomenon is associated with poor cardiovascular outcomes in patients with STEMI and may present as an in-hospital complication, including arrhythmias and cardiogenic shock.[1,2] The pathophysiology involves multiple factors, including endothelial dysfunction, microvascular spasm, distal embolization, and reperfusion injury.[1]

The pathophysiology of the no-reflow phenomenon is complex and multifactorial, primarily involving ischemic injury followed by reperfusion injury. This process leads to oxidative stress, intracellular calcium overload, and an intense inflammatory response.[1,2] Key mechanisms contributing to microvascular obstruction include distal embolization of atherosclerotic debris or thrombus, endothelial swelling, and accumulation of neutrophils and platelets that physically obstruct the microcirculation. These pathological changes prevent effective myocardial perfusion at the tissue level, even when the epicardial coronary artery is successfully recanalized.[2]

In recent years, several biochemical and hematological indices have been proposed to improve risk stratification for the no-reflow phenomenon in patients with STEMI. These indices integrate inflammatory, lipid-related, and metabolic parameters, offering a more comprehensive assessment compared to conventional clinical predictors.[3–6]

In the context of predicting the no-reflow phenomenon, ML models have been increasingly applied across various fields owing to their predictive accuracy and ability to analyze large datasets. Although the specific application of ML models to the no-reflow phenomenon, commonly associated with coronary interventions, has not been directly addressed in the retrieved literature, several related ML approaches are commonly used in medical predictive tasks and can be extrapolated to no-reflow prediction.

ABBREVIATIONS

ANN	Artificial Neural Networks
ANOVA	Analysis of variance
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass grafting
CK-MB	Creatine kinase-myocardial band
EF	Ejection fraction
KAN	Kolmogorov–Arnold Network
MBG	Myocardial Blush Grade
ML	Machine learning
PCI	Percutaneous coronary intervention
RF	Random Forest
SMOTE	Synthetic Minority Over-sampling Technique
STEMI	ST-segment elevation myocardial infarction
SVM	Support Vector Machines
SYNTAX	Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery
TIMI	Thrombolysis in Myocardial Infarction
VIF	Variance Inflation Factor

In cardiovascular and medical applications, ML models such as Support Vector Machines (SVM), Artificial Neural Networks (ANN), and ensemble methods, including Random Forest (RF) and Gradient Boosting, have been frequently employed owing to their proficiency in classification and prediction tasks.[7,8] These models are known for their ability to handle complex interactions within data, making them suitable for predicting clinical outcomes such as no-reflow, which involves multifactorial influences.

This study aimed to develop and compare multiple supervised machine learning algorithms, including the recently introduced Kolmogorov–Arnold Network (KAN), to predict the occurrence of the no-reflow phenomenon in patients with STEMI undergoing primary PCI. By integrating comprehensive clinical, laboratory, and angiographic parameters, this study sought to evaluate the predictive performance, interpretability, and computational efficiency of KAN in comparison with conventional models such as Extreme Gradient Boosting (XGBoost), Multilayer Perceptron (MLP), and logistic regression, and to determine whether feature selection and model explainability could enhance risk stratification and clinical interpretability in real-world STEMI cohorts.

Materials and Methods

Patient Selection and Data Source

This prospective, single-center investigation included 890 consecutive patients who presented to our institution's emergency department between 2022 and 2024 with a confirmed diagnosis of STEMI. Each patient underwent primary PCI within 15 hours of the onset of chest pain. The criteria for diagnosing STEMI included chest pain or an angina equivalent lasting more than 30 minutes, ST-segment elevation of at least 1 mm in two or more contiguous leads, and a subsequent increase in creatine kinase (CK), creatine kinase-myocardial band (CK-MB), or troponin levels following PCI. The study was approved by the İnönü University Scientific Research and Publication Ethics Committee (Approval Number: 2022/3133, Date: 08.03.2022), and adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants before inclusion in the study.

The detailed clinical, echocardiographic, and angiographic definitions—including criteria for Thrombolysis in Myocardial Infarction (TIMI) flow grading, thrombus burden, Killip class, and SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) score assessment—were previously described in our earlier publication.[9] Specifically, the no-reflow phenomenon was defined angiographically as a TIMI flow grade < 3, or a TIMI flow grade of 3 with a Myocardial Blush Grade (MBG) < 2 in the absence of mechanical obstruction, dissection, or distal macroembolism immediately following the procedure. In the current study, the same inclusion and exclusion criteria were applied, and all definitions of demographic and procedural variables were kept consistent with the prior methodology to ensure data comparability.

Data Collection and Variable Description

A total of 37 demographic, clinical, laboratory, and angiographic features were initially included in the dataset. These variables included left ventricular ejection fraction (EF), stent length and diameter, total ischemic time, TIMI thrombus score, SYNTAX score, cardiac biomarkers (troponin, brain natriuretic peptide (BNP), and C-reactive protein [CRP]), and baseline hemodynamic and metabolic parameters such as blood pressure, hemoglobin, lipid profile, and inflammatory indices.

To identify the most informative predictors, feature importance ranking was conducted using one-way analysis of variance (ANOVA) F-statistics. These parameters were prioritized for subsequent modeling analyses. To ensure the absence of multicollinearity, a Variance Inflation Factor (VIF) analysis was performed. All VIF values were < 5, indicating acceptable feature independence.

Prior to model training, a comprehensive data quality check was performed. The distributions of the 37 baseline demographic, clinical, and angiographic variables are presented in Table 1. Missing data were handled using K-Nearest Neighbors (KNN) imputation, which estimates missing values based on the similarity of multidimensional feature vectors, thereby preserving dataset integrity without sample loss. Subsequently, to address class imbalance within this cohort (lower incidence of no-reflow), the Synthetic Minority Over-sampling Technique (SMOTE) was applied exclusively to the training folds during the cross-validation process.

Table 1. Baseline demographic, clinical, and angiographic characteristics

Variables	n = 890
Demographic data	
Age	58.1 ± 12.2
Male sex	737 (82.8%)
Smoking	502 (56.4%)
Diabetes mellitus	201 (22.6%)
Hypertension	403 (45.3%)
Dyslipidemia	371 (41.7%)
Family history	193 (21.7%)
Clinical data	
History of MI	84 (9.4%)
History of PCI	89 (10.0%)
History of CABG	22 (2.5%)
Hemodialysis	0 (0.0%)
ASA	101 (11.3%)
Beta-blocker use	118 (13.3%)
Statin use	182 (20.4%)
Killip class	
I	818 (91.9%)
II	60 (6.7%)
III	4 (0.4%)
IV	8 (0.9%)
Pre-angina score	210 (23.6%)
Angiographic and procedural data	
Tirofiban (bolus)	430 (48.3%)
SYNTAX score	15.2 ± 7.0
CTO	28 (3.1%)
Lesion localization	
Proximal	470 (52.8%)
Mid	376 (42.2%)
Distal	44 (4.9%)
Infarct-related artery	
LAD	469 (52.7%)
CX	134 (15.1%)
RCA	269 (30.2%)
Saphenous graft	4 (0.4%)
Other	14 (1.6%)
Number of diseased vessels	
One-vessel disease	569 (63.9%)
Two-vessel disease	209 (23.5%)
Three-vessel disease	112 (12.6%)
TIMI thrombus score	4.4 ± 0.9
Stent length	21.3 ± 8.8
Stent diameter	3.1 ± 0.3
Direct stenting	258 (29.0%)
Total ischemic time	200.6 ± 108.4
Door-to-balloon time	29.7 ± 5.8
Corrected TFC	24.1 ± 14.1

ASA, Acetylsalicylic acid; CABG, Coronary artery bypass grafting; CTO, Chronic total occlusion; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; TFC, TIMI frame count; TIMI, Thrombolysis in myocardial infarction.

Feature Selection Strategy

The feature selection process was designed to enhance model efficiency and generalizability by identifying the most informative predictors among all candidate variables. The workflow consisted of two sequential stages. Initially, a full-feature modeling approach was employed, incorporating all 37 demographic, laboratory, and angiographic variables to establish a baseline reference model. In the subsequent stage, a reduced-feature modeling approach was implemented, retaining only the top-ranked variables as determined by ANOVA F-statistics and verified for low multicollinearity through VIF analysis. This two-step strategy facilitates assessment of whether dimensionality reduction enhances model stability, mitigates the risk of overfitting, and improves the generalizability of machine learning algorithms without compromising predictive accuracy.

Machine Learning Framework

To predict the occurrence of the no-reflow phenomenon, six supervised machine-learning algorithms with distinct architectures were developed and evaluated. The Decision Tree (C4.5) algorithm was used as a rule-based classifier to segment data into homogeneous groups through recursive partitioning.[10] The K-Nearest Neighbors algorithm classified patients based on feature similarity using distance metrics in multidimensional space. Logistic Regression (LR) provided a benchmark linear model for estimating event probability from weighted predictors.[11] The XGBoost algorithm, a tree-based ensemble learning method, was employed to capture nonlinear feature interactions using gradient-based optimization and regularization.[12] The MLP, a feedforward neural network trained by backpropagation, was applied to model complex nonlinear relationships between clinical and angiographic data.[13] Finally, the KAN, a recent spline-based deep learning framework, was implemented according to its original formulation.[14]

These algorithms were selected to reflect the complex and multifaceted clinical structure of the no-reflow phenomenon. This diversity aimed to identify the most suitable strategy for predicting no-reflow by enabling a comprehensive comparison of both model architectures and learning paradigms. In this study, machine learning models were evaluated using Python. For model implementation, the scikit-learn library (Decision Tree, KNN, Logistic Regression), XGBoost library (XGBoost), PyTorch frameworks, MLP, and pykan library (KAN) were used.

Performance Evaluation

Model performance was assessed using a set of standard classification metrics to ensure a comprehensive evaluation of predictive ability. The following measures were calculated for each model: accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (AUC). These metrics collectively quantify the discrimination capacity of the models, the balance between sensitivity and specificity, and overall classification consistency.

In addition, runtime (s) was recorded for each algorithm to evaluate computational efficiency. Receiver operating characteristic (ROC) curves were generated to visualize model discrimination before and after feature selection.

The dataset was split into 70% training and 30% test sets using a stratified hold-out method to objectively evaluate model generalization performance. Five-fold cross-validation was applied to the training data for hyperparameter optimization (Grid Search) and for internal performance assessment of the models. During this process, cross-validation was performed exclusively on the training set. For model selection and evaluation, external validity and the risk of overfitting were minimized using an independent 30% test dataset that the model had never seen before. The reported performance metrics were obtained from the test set to reflect predictive ability of the model under real-world conditions. Performance evaluation and cross-validation procedures were performed using libraries such as Python scikit-learn and imbalanced-learn.

Explainability Analysis

To enhance model transparency and interpretability, SHapley Additive exPlanations (SHAP) analysis was applied to the final trained models. This approach decomposes individual predictions into additive feature contributions, enabling both global and local interpretation of model outputs. SHAP summary plots were generated to illustrate the overall importance and directionality of each variable's influence on prediction outcomes, while SHAP waterfall plots were used to visualize case-specific feature impacts and cumulative contribution patterns.[15,16] Global and local explainability analyses were conducted to enhance model interpretability using the Python SHAP library. The matplotlib and seaborn libraries were used for visualization.

Statistical Analysis and Software

Continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test or the Mann–Whitney U test, depending on data distribution. Categorical variables were presented as percentages and analyzed using the chi-square test or Fisher's exact test, where appropriate. A p-value < 0.05 was considered statistically significant.

All machine learning models were developed and executed in Python (v3.12). Hyperparameter optimization was performed using grid search with algorithm-specific tuning of learning rate, network depth, and regularization parameters. Model training was designed to maximize the F1-score and AUC while minimizing computational runtime to achieve optimal performance. Model interpretability was assessed using the SHAP library integrated into Python, ensuring consistent post hoc explainability across all algorithms. Descriptive and inferential statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA), whereas visualization and performance metrics were generated using the matplotlib and SHAP packages in Python.

Results

Baseline Demographic, Clinical, and Angiographic Characteristics

This study included 890 patients diagnosed with STEMI. The average age of these individuals was 58.1 ± 12.2 years. There was a significant prevalence of traditional cardiovascular risk factors among participants, with smoking (56.4%), hypertension (45.3%), dyslipidemia (41.7%), and diabetes mellitus (22.6%) being the most common. Additionally, 21.7% of patients had a family history of coronary artery disease. In terms of pre-admission medical therapy, 11.3% of patients were administered

Figure 1. Variance Inflation Factor (VIF) analysis of selected features. This radar chart visualizes the VIF values for the candidate predictor variables. The radial axes represent individual clinical and angiographic features, while the concentric circles indicate VIF thresholds. The purple shaded area demonstrates that all variables have VIF values well below the critical threshold of 5, confirming the absence of significant multicollinearity and ensuring the independence of the features used in the modeling process.

acetylsalicylic acid, 13.3% were prescribed beta-blockers, and 20.4% received statin therapy. Prior cardiovascular interventions were relatively infrequent, with 9.4% of patients having a history of myocardial infarction, 10.0% having undergone PCI, and 2.5% having undergone coronary artery bypass grafting (CABG). None of the patients underwent chronic hemodialysis.

Angiographic and procedural parameters showed a mean SYNTAX score of 15.2 ± 7.0 and a mean TIMI thrombus score of 4.4 ± 0.9. Chronic total occlusion was observed in 3.1% of cases, whereas direct stenting was performed in 29.0% of cases. The mean stent length was 21.3 ± 8.8 mm, with an average stent diameter of 3.1 ± 0.3 mm. The mean total ischemic time was 200.6 ± 108.4 minutes, and the mean door-to-balloon time was 29.7 ± 5.8 minutes, indicating prompt revascularization. The corrected TIMI frame count (TFC) was 24.1 ± 14.1, consistent with the angiographic findings presented in Table 1.

Feature Selection and Model Performance

Feature importance analysis using ANOVA F-statistics identified variables associated with ventricular function, ischemic duration, and angiographic complexity as the most discriminative predictors of the no-reflow phenomenon (Table 2). The highest-ranking features included EF, baseline troponin level, stent length, BNP level, and total ischemic time, reflecting the combined influence of myocardial function and procedural parameters.

To evaluate potential interdependence among the selected predictors, a VIF analysis was performed. As shown in Figure 1, all variables demonstrated VIF values below 5, confirming the absence of multicollinearity. This finding indicates that each feature contributes unique information to the model without redundancy, thereby supporting the stability and interpretability of the final predictive framework.

Table 2. Feature importance scores based on ANOVA F-statistics

Ejection fraction	39.6127
Baseline troponin	33.3236
Stent length	32.9244
BNP	28.9555
Total ischemic time	22.2068
CTO	20.575
SYNTAX score	15.0598
CRP	13.9356
Age	11.7462
Direct stenting	10.3063
Stent diameter	9.1559
Statin use	8.2875
Killip class	7.6746
Lesion localization	7.3628
TIMI thrombus score	6.7071
Hgb	5.466
WBC	5.1448
Smoking	4.0696
Number of diseased vessels	3.6549
Diabetes mellitus	3.3704
Tirofiban (bolus)	2.2916
Sex	1.7781
Beta-blocker use	1.7555
History of MI	1.5564
Dyslipidemia	1.4562
Triglycerides	1.2415
History of PCI	1.1027
HDL cholesterol	1.0034
Pre-angina score	0.7585
History of CABG	0.6592
ASA use	0.5223
Infarct-related artery	0.3551
Hypertension	0.1003
Door-to-balloon time	0.0785
LDL cholesterol	0.0575
Heart rate	0.0491
Systolic blood pressure	0.0069
Hemodialysis	0

ASA, Acetylsalicylic acid; BNP, B-type natriuretic peptide; CABG, Coronary artery bypass grafting; CRP, C-reactive protein; CTO, Chronic total occlusion; HDL, High-density lipoprotein; Hgb, Hemoglobin; LDL, Low-density lipoprotein; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; SYNTAX, Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; TFC, TIMI frame count; TIMI, Thrombolysis in myocardial infarction; WBC, White blood cell count.

Table 3. Performance comparison of models before and after feature selection

Model	Accuracy	Precision	Recall	F1-Score	ROC AUC	Runtime (s)
Decision tree	90.82/91.22	91.02/90.12	90.65/92.68	90.84/91.38	90.82/91.22	0.041/0.026
KNN	89.39/80	84.64/72.56	96.34/96.75	90.11/82.93	97.53/94.72	0.052/0.050
Logistic regression	83.47/84.9	84.23/85.83	82.52/83.74	83.37/84.77	91.67/92.57	0.021/0.022
XGBoost	94.49/95.1	95.06/95.49	93.9/94.72	94.48/95.1	98.28/98.37	0.052/0.043
MLP	85.31/81.84	85.08/79.62	85.77/85.77	85.43/82.58	90.9/89.02	0.170/0.174
KAN	92.04/94.49	94.87/96.27	90.24/94.31	92.5/95.28	98.46/98.19	22.22/20.81

KAN, Kolmogorov–Arnold Network; KNN, K-Nearest Neighbors; MLP, Multilayer Perceptron; ROC AUC, Receiver Operating Characteristic – Area Under the Curve; XGBoost, Extreme Gradient Boosting.

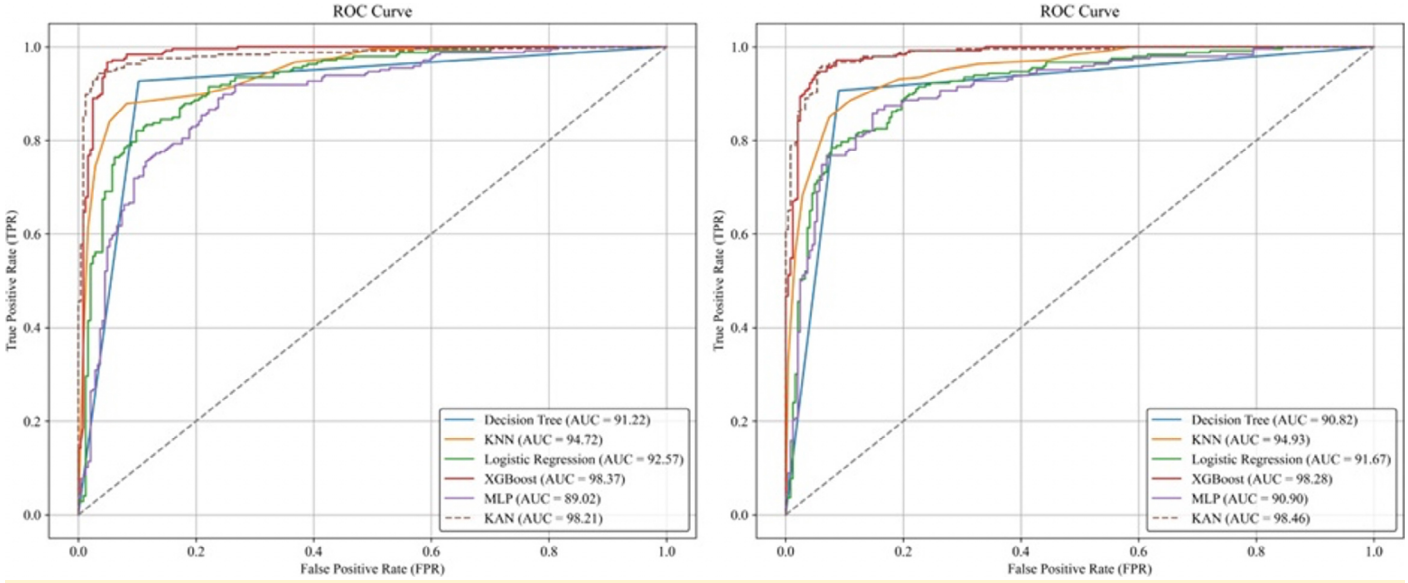


Figure 2. Receiver Operating Characteristic (ROC) curve comparison before and after feature selection. The panels display the ROC curves for the six machine learning algorithms evaluated. The left panel illustrates model performance using the full set of variables, whereas the right panel shows performance after applying feature selection. The x-axis represents the False Positive Rate (1 - specificity) and the y-axis represents the True Positive Rate (sensitivity). The Kolmogorov–Arnold Network (KAN) model (dashed brown line) and Extreme Gradient Boosting (XGBoost) model (red line) exhibit the largest Area Under the Curve (AUC), indicating superior discriminative ability in predicting the no-reflow phenomenon compared to traditional models such as logistic regression and decision trees.

After applying feature selection, the performance of all machine learning models was re-evaluated. As shown in Table 3, dimensionality reduction improved overall model stability and computational efficiency. Among the algorithms, XGBoost and KAN demonstrated the highest predictive performance, achieving AUC values above 0.98 and F1-scores exceeding 0.95. These models effectively captured nonlinear and hierarchical relationships within the dataset, outperforming traditional classifiers such as logistic regression and decision tree models.

The results also indicated that feature selection enhanced accuracy and reduced runtime by approximately 20–40% across all algorithms, suggesting that eliminating redundant or low-impact variables improved both computational feasibility and generalizability. Although the KAN model required longer processing time owing to its spline-based nonlinear structure, it provided superior interpretability and a balanced trade-off between precision and efficiency.

Overall, the combination of feature selection and advanced learning architectures such as KAN and XGBoost yielded the most reliable and clinically meaningful predictions of the no-reflow phenomenon in patients with STEMI.

Receiver Operating Characteristic Analysis

Figure 2 illustrates the ROC curves of all machine learning models before and after feature selection. The overall shape of the post-selection ROC curves shifted toward the upper-left corner of the plot, indicating a clear improvement in discriminative performance. The AUC increased across all algorithms, demonstrating that the elimination of redundant variables enhanced the ability of the models to distinguish between patients with and without no-reflow.

The ROC profiles also became smoother after dimensionality reduction, suggesting greater model stability and reduced variability across cross-validation folds. Among the algorithms, ensemble and neural models, particularly XGBoost and KAN,

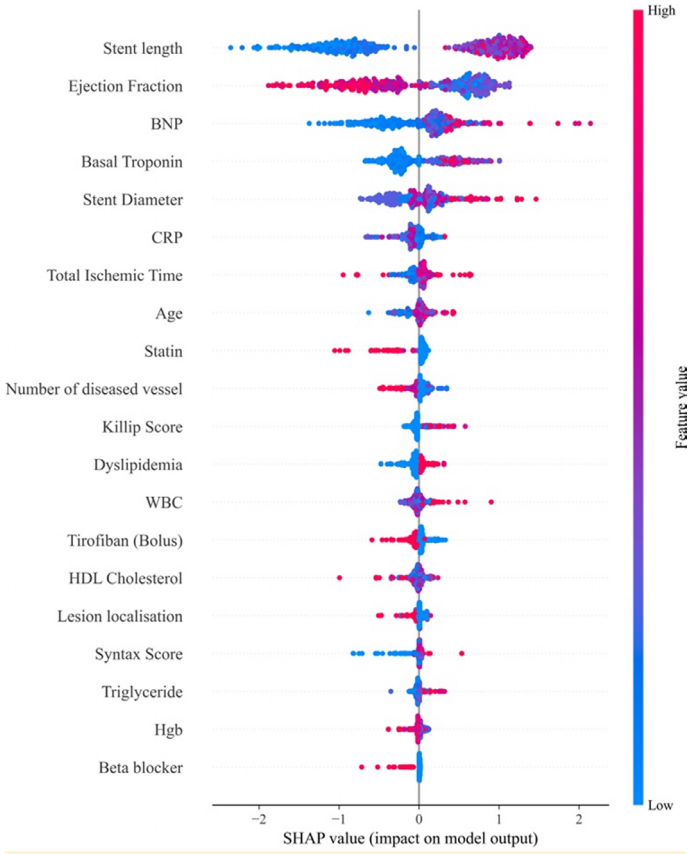


Figure 3. Shapley Additive exPlanations (SHAP) summary plot for selected features. This plot illustrates the global importance and impact of clinical features on the prediction of the no-reflow phenomenon using the model. Features are ranked on the y-axis in descending order of importance, with stent length and ejection fraction being the most influential. Each dot represents an individual patient. Color indicates the feature value (red = high value, blue = low value). The position on the x-axis (SHAP value) reflects the direction of impact: points to the right (positive values) increase the probability of no-reflow, whereas points to the left (negative values) decrease it. For example, higher stent length (red dots) is associated with positive SHAP values, indicating increased risk.

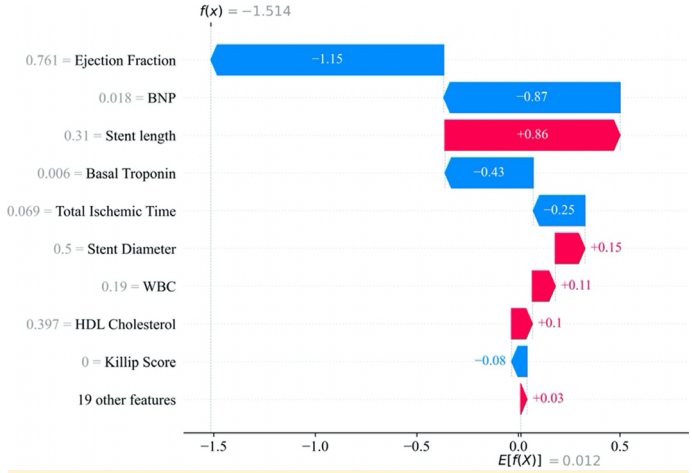


Figure 4. Shapley Additive exPlanations (SHAP) waterfall plot for a representative case. This plot illustrates the contribution of individual features to the prediction score (f(x)) for a specific patient. The base value (E[f(X)]) represents the average model output across the dataset. Red bars indicate features that push the prediction toward the no-reflow outcome (increasing risk), such as stent length, while blue bars indicate features that push the prediction toward normal flow (decreasing risk), such as higher ejection fraction. In this example, the strong protective effect of functional parameters (blue bars) outweighs procedural risk factors, resulting in a negative final score (f(x) = -1.514), corresponding to a low probability of no-reflow.

displayed the steepest initial ascent and largest enclosed area, confirming their superior classification performance compared to conventional methods.

To verify the statistical significance of these performance differences, DeLong's test was applied to the ROC curves. The analysis revealed that while the performance difference between KAN and XGBoost was not statistically significant ($P > 0.05$), both KAN and XGBoost demonstrated statistically significant improvements in discriminative ability compared to logistic regression and decision tree classifiers ($P < 0.001$), confirming the superiority of nonlinear modeling approaches.

Explainability and Feature Contribution Analysis

To enhance the clinical interpretability of the predictive models, SHAP analysis was used to identify how each variable influenced the model's decisions. Rather than focusing on mathematical details, SHAP outputs were interpreted in a clinically meaningful manner.

The SHAP summary plot demonstrates that variables reflecting myocardial function (ejection fraction and BNP), ischemic burden (total ischemic time and baseline troponin), and procedural complexity (stent length) were the dominant contributors to prediction of the no-reflow phenomenon. Higher ejection fraction and lower BNP levels consistently decreased the predicted risk of no-reflow, whereas longer stent length and prolonged ischemic time increased the predicted risk (Figure 3).

The SHAP waterfall plot enabled patient-level interpretation by illustrating how individual clinical factors shifted the prediction toward higher or lower risk. In the representative case, preserved ejection fraction and low BNP exerted a strong protective effect, whereas longer stent length increased risk. These findings demonstrate that the model's predictions rely on clinically established pathophysiological mechanisms rather than spurious correlations (Figure 4).

Accordingly, SHAP analysis was used as a transparent clinical explanation tool rather than a purely technical mathematical framework.

Discussion

In this study, multiple machine learning algorithms were compared to predict the no-reflow phenomenon in patients with STEMI undergoing primary PCI. After feature selection using ANOVA F-statistics and validation of feature independence (VIF < 5), the most influential predictors were EF, baseline troponin level, stent length, BNP level, and total ischemic time. Model comparison revealed that KAN and XGBoost achieved the highest

predictive accuracy (AUC > 0.98, F1 > 0.95), outperforming traditional models such as logistic regression and decision tree classifiers. Feature selection improved efficiency and reduced runtime by 20–40%, while SHAP-based explainability confirmed that the predictions were physiologically consistent: higher EF and lower BNP reduced the probability of no-reflow, whereas longer stent length and ischemic time increased it.

Coronary no-reflow is characterized by inadequate myocardial reperfusion after reopening the infarct-related artery during primary percutaneous coronary intervention and accounts for up to 40% of cases with incomplete myocardial reperfusion despite restored artery patency. The pathophysiology involves microvascular obstruction and is associated with increased mortality, arrhythmias, and heart failure. Diagnostic approaches include angiographic scoring and advanced imaging techniques such as myocardial contrast echocardiography and cardiac magnetic resonance imaging. Prevention and treatment strategies incorporate both pharmacological therapies and device-based interventions.[1] ML has been applied in cardiology, including coronary artery disease and cardiac imaging, with promising results. ML algorithms can analyze large datasets to enable earlier diagnosis, improved risk stratification, and individualized therapy. In coronary artery disease, ML supports cardiac imaging through score computation, phenotypic differentiation, heart function quantification, and segmentation, thereby enhancing anomaly detection and cardiovascular risk prediction.[17] While direct studies on coronary no-reflow prediction using ML algorithms are limited, clinical predictors—such as admission hyperglycemia, reperfusion delay, thrombus burden, and blood biomarkers—serve as crucial input features for ML models aimed at risk stratification in acute coronary syndromes (ACS), where no-reflow commonly manifests.[18-20]

Supervised machine learning algorithms have shown promise in predicting coronary events, including the no-reflow phenomenon. For cardiovascular prediction tasks, LR, SVM, Naïve Bayes, KNN, RF, and XGBoost are among the most widely evaluated models14. Logistic regression and gradient boosting techniques, particularly XGBoost, have demonstrated superior performance in clinical outcome prediction, achieving acceptable to high AUC values in cardiac surgery mortality and cardiovascular endpoints.[21,22] Khalaji et al.[21] evaluated multiple ML algorithms for mortality prediction after coronary artery bypass grafting and demonstrated the superiority of ensemble learning models over conventional approaches. Our study showed that XGBoost and KAN significantly outperformed logistic regression and decision tree models. Kendale et al.[22] reported that gradient-based learning models provide high predictive accuracy for post-induction hypotension in cardiovascular patients, supporting the use of boosting-based methods in acute care settings. The high performance of XGBoost in our study directly parallels these observations.

Deng et al.[23] reported moderate success using a random forest model to predict no-reflow and mortality in STEMI patients undergoing primary PCI. In contrast, our KAN and XGBoost models performed better, demonstrating the superiority of advanced learning methods in understanding microvascular reperfusion failure. While Celik et al.[24] found the red cell distribution width-to-platelet ratio to be a predictor of no-reflow, our model identified heart function and procedural complexity as more significant predictors. Similarly, Wang et al.[20] identified inflammatory and biochemical parameters as predictors of the no-reflow phenomenon. Our model confirmed baseline troponin and BNP as strong predictors of the no-reflow condition. Dong-Bao et al.[19] linked prolonged ischemic time and thrombus burden to slow/no-reflow, and in our study, total ischemic time and stent length emerged as top predictors. While Celik et al.[3] emphasized blood count parameters, our cohort demonstrated functional and procedural factors such as ejection fraction, BNP, and stent length were dominant, suggesting that mechanical factors outweigh inflammation. Although Kurtul et al.[25] and Toprak et al.[26] highlighted inflammatory markers, our findings indicate that physical and blood flow-related factors play a more significant role.

The study also identified that higher ejection fraction and lower levels of B-type natriuretic peptide were associated with a reduced risk of the no-reflow phenomenon, indicating that optimal cardiac function facilitates effective blood circulation. Conversely, the use of longer stents may increase the risk of no-reflow due to potential damage to smaller blood vessels. Additionally, prolonged ischemic duration was associated with increased risk, underscoring the detrimental effects of interrupted blood flow. These findings are consistent with established etiologies of the no-reflow phenomenon. Stent length and the time without blood flow highlight the need to address blockage in small blood vessels. Low EF and elevated BNP levels illustrate how impaired blood flow affects small vessels. This helps identify high-risk patients early, especially those needing long stents or experiencing long periods without blood flow, suggesting that additional treatments might be needed. Our model uses different factors to predict no-reflow in patients with STEMI. Unlike past studies that focused on single markers or simple models, our research includes heart function, blood markers, stent length, and time without blood flow in a detailed deep learning model. This improves the prediction of no-reflow and shows how artificial intelligence can help manage STEMI cases.

There are concerns that the high AUC and F1-scores might indicate that the model is overfitting. To address this, a careful method was used. The model was trained on 70% of the data, and its settings were fine-tuned using five-fold cross-validation only on this portion. This prevented any data from leaking into the test phase. The final results came from the remaining 30% of the data, which the model had not seen before. The high accuracy likely reflects a strong link between the key features—EF, BNP, and total ischemic time—and the no-reflow phenomenon rather than overfitting. However, we acknowledge that the lack of external validation and a full calibration analysis is a limitation, meaning that the high scores should be interpreted with caution.

This study was conducted using a single-center prospective design, which inherently limits the generalizability of our findings to a broader patient population. The absence of external validation restricts the confidence with which these results can be extrapolated to other institutions with different demographic profiles or procedural protocols. Consequently, while the KAN model demonstrates high internal validity, rigorous testing in diverse multicenter cohorts is essential to confirm its robustness and ensure that the reported predictive accuracy is reproducible in real-world clinical settings.

Conclusion

This study demonstrates that Kolmogorov–Arnold Networks provide highly accurate prediction of the no-reflow phenomenon in patients with STEMI. However, the model requires external multicenter validation before any clinical implementation. At present, KAN should be considered a promising research tool rather than a ready-to-use clinical decision support system.

Ethics Committee Approval: Ethics committee approval was obtained from İnönü University Scientific Research and Publication Ethics Committee (Approval Number: 2022/3133, Date: 08.03.2022).

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

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

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

Use of AI for Writing Assistance: No artificial intelligence (AI)–assisted technologies, including large language models (LLMs), chatbots, or image generators, were used in the writing, data analysis, figure preparation, or any other aspect of the production of this manuscript.

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

Peer-review: Externally peer-reviewed.

References

1. Yılmaz C, Üngan İ, Arslan E, et al. The HALP Score's Prognostic Value for the Elderly Patients (≥ 75 years) Patients Following Percutaneous Coronary Intervention for Acute Myocardial Infarction. *Turk Kardiyol Dern Ars*. 2025;53(6):388-397. [CrossRef]
2. Pantea-Roșan LR, Pantea VA, Bungau S, et al. No-Reflow after PPCI-A Predictor of Short-Term Outcomes in STEMI Patients. *J Clin Med*. 2020;9(9):2956. [CrossRef]
3. Celik T, Balta S, Mikhailidis DP, et al. The Relation Between No-Reflow Phenomenon and Complete Blood Count Parameters. *Angiology*. 2017;68(5):381-388. [CrossRef]
4. Özbay MB, Değirmen S, Güllü A, Nriagu BN, Özen Y, Yayla Ç. Association of the C-Reactive Protein to Albumin Ratio with the No-Reflow Phenomenon After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. *Turk Kardiyol Dern Ars*. 2025;53(6):428-432. [CrossRef]
5. Vatan MB, Çakmak AC, Ağaç S, Eynel E, Erkan H. The Systemic Immune-Inflammation Index Predicts Impaired Myocardial Perfusion and Short-Term Mortality in ST-Segment Elevation Myocardial Infarction Patients. *Angiology*. 2023;74(4):365-373. [CrossRef]
6. Süleymanoğlu M, Rencüzoğulları İ, Karabağ Y, et al. The relationship between atherogenic index of plasma and no-reflow in patients with acute ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention. *Int J Cardiovasc Imaging*. 2020;36(5):789-796. [CrossRef]
7. Cuocolo R, Perillo T, De Rosa E, Ugga L, Petretta M. Current applications of big data and machine learning in cardiology. *J Geriatr Cardiol*. 2019;16(8):601-607.
8. Battineni G, Sagaro GG, Chinatalapudi N, Amenta F. Applications of Machine Learning Predictive Models in the Chronic Disease Diagnosis. *J Pers Med*. 2020;10(2):21. [CrossRef]
9. Bayramoğlu A, Taşolar H, Kaya A, et al. Prediction of no-reflow and major adverse cardiovascular events with a new scoring system in STEMI patients. *J Interv Cardiol*. 2018;31(2):144-149. [CrossRef]
10. Esteva A, Chou K, Yeung S, et al. Deep learning-enabled medical computer vision. *NPJ Digit Med*. 2021;4(1):5. [CrossRef]
11. Rajkomar A, Dean J, Kohane I. Machine Learning in Medicine. *N Engl J Med*. 2019;380(14):1347-1358. [CrossRef]
12. Liu P, Li XJ, Zhang T, Huang YH. Comparison between XGboost model and logistic regression model for predicting sepsis after extremely severe burns. *J Int Med Res*. 2024;52(5):3000605241247696. [CrossRef]
13. Iyer K, Nallamothu BK, Figueroa CA, Nadakuditi RR. A multi-stage neural network approach for coronary 3D reconstruction from uncalibrated X-ray angiography images. *Sci Rep*. 2023;13(1):17603. [CrossRef]
14. Liu Z, Wang Y, Vaidya S, et al. Kan: Kolmogorov-arnold networks. *arXiv preprint*. April 30, 2024. doi: 10.48550/arXiv.2404.19756 [Epub ahead of print].
15. Erkan İ, Günen MA. Comparison of Zn recovery prediction from carbonate ores with machine-learning methods. *Int J Miner Metall Mater*. 2026;33:820-832. [CrossRef]
16. Lundberg SM, Lee SI. A unified approach to interpreting model predictions. *Adv Neural Inf Process Syst*. 2017;30:4765-4774.
17. Lin A, Kolossváry M, Motwani M, et al. Artificial Intelligence in Cardiovascular Imaging for Risk Stratification in Coronary Artery Disease. *Radiol Cardiothorac Imaging*. 2021;3(1):e200512. [CrossRef]
18. Wang H, Zu Q, Chen J, Yang Z, Ahmed MA. Application of Artificial Intelligence in Acute Coronary Syndrome: A Brief Literature Review. *Adv Ther*. 2021;38(10):5078-5086. [CrossRef]
19. Dong-bao L, Qi H, Zhi L, Shan W, Wei-ying J. Predictors and long-term prognosis of angiographic slow/no-reflow phenomenon during emergency percutaneous coronary intervention for ST-elevated acute myocardial infarction. *Clin Cardiol*. 2010;33(12):E7-E12. [CrossRef]
20. Wang L, Huang S, Zhou Q, Dou L, Lin D. The predictive value of laboratory parameters for no-reflow phenomenon in patients with ST-elevation myocardial infarction following primary percutaneous coronary intervention: A meta-analysis. *Clin Cardiol*. 2024;47(2):e24238. [CrossRef]
21. Khalaji A, Behnoush AH, Jameie M, et al. Machine learning algorithms for predicting mortality after coronary artery bypass grafting. *Front Cardiovasc Med*. 2022;9:977747. [CrossRef]
22. Kendale S, Kulkarni P, Rosenberg AD, Wang J. Supervised Machine-learning Predictive Analytics for Prediction of Postinduction Hypotension. *Anesthesiology*. 2018;129(4):675-688. [CrossRef]
23. Deng L, Zhao X, Su X, Zhou M, Huang D, Zeng X. Machine learning to predict no reflow and in-hospital mortality in patients with ST-segment elevation myocardial infarction that underwent primary percutaneous coronary intervention. *BMC Med Inform Decis Mak*. 2022;22(1):109. [CrossRef]
24. Celık T, Balta S, Demır M, et al. Predictive value of admission red cell distribution width-platelet ratio for no-reflow phenomenon in acute ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Cardiol J*. 2016;23(1):84-92. [CrossRef]
25. Kurtul A, Yarlioglues M, Celik IE, et al. Association of lymphocyte-to-monocyte ratio with the no-reflow phenomenon in patients who underwent a primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Coron Artery Dis*. 2015;26(8):706-712. [CrossRef]
26. Toprak K, Toprak İH, Acar O, Ermiş MF. The predictive value of the HALP score for no-reflow phenomenon and short-term mortality in patients with ST-elevation myocardial infarction. *Postgrad Med*. 2024;136(2):169-179. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Atherogenic Index of Plasma as a Novel Marker of Critical Multivessel Disease in Non-ST-Elevation Myocardial Infarction

Non-ST Yükselmeli Miyokard Enfarktüsünde Kritik Çok Damar Hastalığının Yeni Bir Belirteci Olarak Plazma Aterojenik İndeksi

ABSTRACT

Objective: This study aimed to determine whether the atherogenic index of plasma (AIP) can predict critical multivessel coronary artery disease (MVD) in patients presenting with non-ST-segment elevation myocardial infarction (NSTEMI).

Method: In this retrospective analysis, patients diagnosed with NSTEMI who underwent coronary angiography between January and December 2024 were evaluated. Based on angiographic findings, patients were classified according to the number of major epicardial vessels with significant stenosis, and MVD was defined as critical involvement of all three major vessels. The AIP was calculated as log (triglyceride/high-density lipoprotein [HDL]-cholesterol). Multivariable logistic regression analysis was used to identify independent predictors of MVD, and receiver operating characteristic (ROC) curve analysis was performed to assess diagnostic accuracy.

Results: Of the 1,216 patients included in the study, 302 (24.8%) had MVD. Those with critical MVD had significantly higher AIP values than those without MVD (0.74 ± 0.28 vs. 0.59 ± 0.26, P < 0.001). In multivariable analysis, AIP remained an independent determinant of MVD (odds ratio: 3.132, 95% confidence interval: 1.626–6.030, P = 0.001). Diabetes mellitus, higher hemoglobin A1c (HbA1c), and elevated low-density lipoprotein (LDL)-cholesterol levels were also independently associated with MVD. AIP demonstrated moderate discriminative ability for predicting MVD, with an area under the curve (AUC) of 0.689 and sensitivity and specificity of 65.6%.

Conclusion: AIP was independently associated with the presence of critical MVD in patients with NSTEMI. Given its simplicity, affordability, and accessibility, AIP may serve as a practical indicator of atherogenic burden and help identify patients who are more likely to have multivessel coronary involvement.

Keywords: Acute coronary syndrome, atherogenic index of plasma, multivessel coronary artery disease, non-ST-segment elevation myocardial infarction, predictors

ÖZET

Amaç: Bu çalışma, plazma aterojenik indeksi (AIP)'nin, non-ST-segment yükselmeli miyokard enfarktüsü (NSTEMI) tanısı alan hastalarda kritik çok damarlı koroner arter hastalığı (ÇDH) varlığını öngörmede bir belirteç olarak kullanılıp kullanılamayacağını değerlendirmeyi amaçladı.

Yöntem: Bu retrospektif analizde, Ocak 2024 ile Aralık 2024 tarihleri arasında NSTEMI tanısı konulan ve koroner anjiyografi yapılan hastalar incelendi. Anjiyografik bulgulara göre hastalar, anlamlı darlık saptanan majör epikardiyal damar sayısına göre sınıflandırıldı ve ÇDH, üç ana epikardiyal damarın tamamında kritik darlık bulunması olarak tanımlandı. AIP, log (trigliserid/HDL-kolesterol) formülüyle hesaplandı. Çok değişkenli lojistik regresyon analizi, ÇDH'nin bağımsız belirleyicilerini saptamak için uygulandı. Ayrıca ROC eğrisi analizi, tanısal doğruluğu değerlendirmek amacıyla gerçekleştirildi.

Bulgular: Çalışmaya dâhil edilen 1.216 hastanın 302'sinde (%24,8) ÇDH saptandı. Kritik ÇDH'si bulunan hastaların AIP değerleri, ÇDH bulunmayanlara kıyasla anlamlı olarak daha yüksekti (0.74 ± 0.28'e karşı 0.59 ± 0.26, P < 0.001). Çok değişkenli analizde AIP, ÇDH'nin bağımsız bir belirleyicisi olarak kaldı (olasılık oranı: 3.132; %95 güven aralığı: 1.626–6.030; P = 0.001). Diyabetes mellitus, yüksek HbA1c ve artmış LDL kolesterol düzeyleri de ÇDH ile bağımsız olarak ilişkili bulundu. AIP, ÇDH'yi öngörmede orta düzeyde ayırt edici bir yetenek göstermiş olup, AUC değeri 0.689 ve duyarlılık ile özgüllük oranları %65.6 olarak bulundu.

Sonuç: AIP, NSTEMI hastalarında kritik ÇDH varlığıyla bağımsız olarak ilişkili bulunmuştur. Basit, ekonomik ve kolay erişilebilir bir parametre olması nedeniyle AIP, aterojenik yükü yansıtan ve ÇDH olasılığı yüksek hastaların belirlenmesine yardımcı olabilecek pratik bir gösterge niteliği taşıyabilir.

Anahtar Kelimeler: Akut koroner sendrom, plazma aterojenik indeksi, çok damar koroner arter hastalığı, ST elevasyonsuz miyokard enfarktüsü, öngördürücüler

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

Vedat Hekimsoy[1]
Veysel Ozan Tanık[1]
Kürşat Akbuğa[1]
Alperen Taş[2]
Ali Sezgin[1]
Çağatay Tunca[1]
Erhan Saraçoğlu[1]
Bülent Özlek[3]

[1]Department of Cardiology, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Department of Cardiology, Kırşehir Training and Research Hospital, Kırşehir, Türkiye
[3]Department of Cardiology, Muğla Sıtkı Koçman University, Faculty of Medicine, Muğla, Türkiye

Corresponding author:
Bülent Özlek
✉ bulent_ozlek@hotmail.com

Received: October 17, 2025
Accepted: November 24, 2025

Cite this article as: Hekimsoy V, Tanık VO, Akbuğa K, et al. The Atherogenic Index of Plasma as a Novel Marker of Critical Multivessel Disease in Non-ST-Elevation Myocardial Infarction. *Turk Kardiyol Dern Ars.* 2026;54(3):245–252.

DOI: 10.5543/tkda.2025.41820

Acute coronary syndromes (ACS) remain a major global cause of mortality.[1] Recent epidemiological observations indicate a shift in ACS presentation patterns, with an increasing proportion of patients now being diagnosed with non–ST-segment elevation myocardial infarction (NSTEMI) rather than ST-segment elevation myocardial infarction (STEMI).[2-4] Individuals with NSTEMI are typically older, have multiple comorbidities, and more frequently present with severe multivessel coronary artery disease (MVD)—a condition linked to poorer prognoses and a greater likelihood of recurrent ischemic events.[5] Therefore, early identification of NSTEMI patients who are more likely to have MVD is clinically relevant, as the presence of MVD reflects a higher anatomical disease burden.[6] Despite advances in diagnostic modalities, accurately estimating coronary artery disease (CAD) severity in NSTEMI remains challenging in routine practice. Consequently, identifying simple, economical, and easily measurable biomarkers that can assist in estimating atherosclerotic burden and the likelihood of MVD has become an area of increasing clinical interest.

The atherogenic index of plasma (AIP), calculated as the logarithm of the ratio of triglycerides (TG) to high-density lipoprotein (HDL) cholesterol, is a key indicator of lipid metabolism.[7] Beyond conventional lipid parameters, AIP is increasingly regarded as a biomarker reflecting plasma atherogenicity, owing to its association with cholesterol esterification, lipoprotein particle size, and the presence of remnant lipoproteins.[8] Recent evidence suggests that AIP may outperform traditional single-lipid measures in predicting CAD risk.[9] Prior studies have also demonstrated a relationship between AIP and several cardiovascular risk factors, including obesity, metabolic syndrome, and diabetes mellitus (DM).[10–12] Moreover, elevated AIP levels have been correlated with greater CAD burden among patients with stable disease.[13] However, although the association between AIP, cardiovascular risk factors, and CAD extent has been widely explored in stable CAD populations, limited evidence exists regarding its relationship with critical MVD specifically in NSTEMI patients. Therefore, this study aimed to determine whether AIP could predict MVD in individuals with NSTEMI.

Materials and Methods

Study Population

This single-center retrospective study included patients hospitalized with a diagnosis of NSTEMI who underwent coronary angiography (CAG) between January 2024 and December 2024. The diagnosis of NSTEMI was established in accordance with the latest European Society of Cardiology recommendations and the Fourth Universal Definition of Myocardial Infarction.[14,15]

Patients were excluded if they met any of the following criteria: medically managed ACS, previous percutaneous coronary intervention (PCI), ongoing lipid-lowering therapy at admission, left ventricular ejection fraction (LVEF) < 50%, prior coronary artery bypass grafting, thyroid dysfunction (hypo- or hyperthyroidism) confirmed clinically or biochemically, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, antibiotic administration during the hospitalization in which CAG was performed, a history of malignancy, evidence of severe hepatic dysfunction, or absence of complete lipid profile data.

ABBREVIATIONS

AIP	Atherogenic index of plasma
NSTEMI	Non–ST-segment elevation myocardial infarction
MVD	Multivessel
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
HbA1c	Hemoglobin A1c
ACS	Acute coronary syndromes
CAD	Coronary artery disease
TG	Tiglycerides
DM	Diabetes mellitus
CAG	Coronary angiography
PCI	Percutaneous coronary intervention
LVEF	Left ventricular ejection fraction
eGFR	Estimated glomerular filtration rate
LMCA	Left main coronary artery
LAD	Left anterior descending
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
GRACE	Global Registry of Acute Coronary Events
TIMI	Thrombolysis in Myocardial Infarction
CCS	Chronic coronary syndrome
SYNTAX scores	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery

The study protocol received institutional Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (Approval Number: AEŞH-BADEK-2025-0319, Date: 09.04.2025) and was conducted in accordance with the Declaration of Helsinki. Owing to its retrospective design, the committee waived the requirement for informed consent.

Demographic, clinical, and laboratory information were extracted from the hospital's electronic medical record system. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive agents. DM was defined as fasting plasma glucose ≥ 126 mg/dL, hemoglobin A1c ≥ 6.5%, or treatment with glucose-lowering medications. Current smoking status was defined as regular daily cigarette use.

Laboratory Measurements

Blood samples were collected from the antecubital vein in the early morning after a minimum fasting period of 12 hours, prior to the initiation of any lipid-lowering therapy. Total cholesterol and TG concentrations were determined using enzymatic assays, while HDL and low-density lipoprotein (LDL) cholesterol levels were measured using direct homogeneous methods. Complete blood counts, standard biochemical markers, and cardiac enzyme levels were analyzed using validated automated systems in the hospital's central laboratory.

The atherogenic index of plasma was calculated as the logarithm of the ratio of TG to HDL cholesterol: AIP = log (TG / HDL - cholesterol).

Coronary Angiography

Conventional CAG was performed using the standard Judkins technique via either the radial or femoral approach, with at least four projections of the left coronary artery and two of the right

coronary artery. Nitroglycerin was administered when coronary spasm was suspected. Quantitative angiographic assessment was conducted according to a standardized protocol, evaluating maximal luminal narrowing from two orthogonal views.

All angiograms were independently reviewed by two experienced interventional cardiologists who were blinded to the patients' laboratory data. Critical CAD was defined as ≥ 70% luminal diameter stenosis in at least one major epicardial vessel, or ≥ 50% stenosis in the left main coronary artery (LMCA) or the proximal segment of the left anterior descending artery (LAD). The number of diseased vessels was determined by counting significant (≥ 70%) stenoses in major arteries (LAD, left circumflex [LCx], and right coronary artery [RCA]) and their large branches (e.g., diagonal branch) with a reference diameter ≥ 2.0 mm. In the present study, we intentionally focused on a stricter angiographic definition of MVD, requiring critical stenosis in all three major epicardial coronary arteries. This approach is conceptually consistent with previous reports that have specifically examined LMCA and/or three-vessel disease, or triple-vessel CAD, as representing the most advanced spectrum of MVD in ACS/NSTEMI populations.[16,17] When LMCA stenosis was present, it was classified as two-vessel disease regardless of concurrent LAD or LCx lesions.

Any discrepancies between the two cardiologists were resolved by consensus with a senior investigator. Based on angiographic findings, patients were categorized into single-vessel, two-vessel, or three-vessel disease groups.

Statistical Analysis

All statistical analyses were performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Variables with a normal distribution were expressed as mean ± standard deviation and compared using the Student t-test, whereas those not following a normal distribution were reported as median (interquartile range) and evaluated with the Mann–Whitney U test. Categorical variables were described as frequencies and percentages, and intergroup differences were analyzed using the chi-square or Fisher's exact test, as appropriate. To determine the independent association of MVD, univariable analyses were first conducted, followed by multivariable logistic regression. Parameters with p-values below 0.05 in the multivariable model were considered independent predictors. The diagnostic and discriminative performance of AIP and other relevant variables for identifying MVD was further examined using receiver operating characteristic (ROC) curve analysis. To explore potential non-linear associations between AIP and the probability of MVD, AIP was modeled as a restricted cubic spline (RCS) with four knots placed at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles of its distribution. Spline terms were incorporated into a multivariable logistic regression model, and non-linearity was assessed using a likelihood ratio test comparing the spline model to a model including a single linear AIP term. Statistical significance was defined as a two-tailed p-value of less than 0.05 for all tests. A post hoc power analysis was performed for the primary comparison of AIP values between patients with and without MVD. Using the observed group means, sample sizes, and a two-sided alpha level of 0.05, the standardized effect size (Cohen's d) was calculated as 0.57, corresponding to an estimated statistical power > 0.99 for detecting this difference.

Results

A total of 1,216 patients diagnosed with NSTEMI were included in the study, of whom 302 (24.8%) were found to have critical MVD. Among the remaining 914 patients without MVD, 610 (66.7%) had single-vessel disease, while 304 (33.3%) had two-vessel disease. The baseline demographic and clinical characteristics of patients with and without MVD are summarized in Table 1.

Patients in the MVD group had a significantly higher prevalence of hypertension and DM compared to those without MVD ($P < 0.05$ for both). No significant differences were observed between groups for age, sex, or smoking status ($P > 0.05$ for all). Regarding laboratory parameters, patients with MVD exhibited higher fasting plasma glucose, HbA1c, LDL cholesterol, triglycerides, and AIP values, along with lower HDL cholesterol levels ($P < 0.05$ for all). Serum creatinine levels were higher, and eGFR values were lower in the MVD group ($P < 0.05$ for both). LVEF did not differ significantly between the groups ($P = 0.191$).

The results of the univariable and multivariable logistic regression analyses for MVD predictors are presented in Table 2. In the univariable analysis, AIP, HbA1c, LDL cholesterol, reduced eGFR, hypertension, and DM were all significantly associated with MVD ($P < 0.05$ for all). In the multivariable analysis, AIP remained an independent predictor of MVD (odds ratio [OR]: 3.132, 95% confidence interval [CI]: 1.626–6.030, $P = 0.001$), together with DM (OR: 3.201, 95% CI: 2.432–3.822, $P = 0.001$), HbA1c (OR: 1.153, 95% CI: 1.038–1.280, $P = 0.008$), and LDL cholesterol (OR: 1.007, 95% CI: 1.003–1.012, $P = 0.002$). Reduced eGFR and the presence of hypertension did not retain statistical significance after adjustment ($P > 0.05$ for both).

The diagnostic performance of AIP, LDL cholesterol, and HbA1c in predicting MVD is summarized in Table 3 and illustrated in Figure 1. Among the three markers, AIP demonstrated the highest discriminatory ability, with an area under the curve (AUC) of 0.689 (95% CI: 0.658–0.720, $P < 0.001$) for identifying patients with MVD. The optimal cut-off value for AIP was 0.648, yielding 65.6% sensitivity and 65.6% specificity. In comparison, LDL cholesterol and HbA1c showed lower predictive capacities, with AUCs of 0.550 and 0.575, respectively.

In RCS analysis, the probability of MVD increased progressively across the AIP spectrum, with a steeper rise at higher values (Figure 2). A likelihood ratio test comparing the spline model with a simple linear term demonstrated a statistically significant deviation from linearity ($P = 0.018$), indicating that the association between AIP and MVD was not strictly linear.

Discussion

To the best of our knowledge, this study is the first to identify AIP as an independent predictor of critical MVD specifically among patients with NSTEMI. In our analysis, NSTEMI patients with MVD demonstrated significantly higher AIP values than those with single- or two-vessel disease. ROC curve analysis revealed that AIP showed better discriminatory performance than LDL cholesterol and HbA1c for detecting MVD. However, the AUC

Table 1. Baseline demographic, clinical, angiographic, and laboratory characteristics of NSTEMI patients with and without multivessel coronary artery disease

Variables	Patients without multivessel disease (n = 914)	Patients with multivessel disease (n = 302)	P
Demographic data			
Age, (years)	63.6 ± 13.5	63.9 ± 11.8	0.745
Male, n (%)	644 (70.5)	198 (65.6)	0.110
Active smoking, n (%)	569 (62.3)	181 (59.9)	0.433
Past medical history, n (%)			
Hypertension	551 (60.3)	205 (67.9)	0.018
Diabetes mellitus	217 (23.7)	124 (41.1)	< 0.001
COPD	77 (8.4)	28 (9.3)	0.671
Vital signs			
SBP, mmHg	150.9 ± 28.5	147.8 ± 28.7	0.180
DBP, mmHg	82.9 ± 16.2	82.7 ± 16.6	0.841
Heart rate, beats/min	86.0 ± 23.3	86.2 ± 23.3	0.928
CAG characteristics, n (%)			< 0.001
One-vessel disease	610 (66.7)	0 (0)	
Two-vessel disease	304 (33.3)	0 (0)	
Three-vessel disease	0 (0)	302 (100)	
Preadmission medications, n (%)			
Aspirin	307 (33.6)	108 (35.8)	0.516
ACEi/ARB	356 (38.9)	120 (39.7)	0.739
Beta-blocker	274 (30)	99 (32.8)	0.360
Laboratory parameters			
Hemoglobin, (g/dL)	13.4 ± 2.1	13.4 ± 2.0	0.856
White blood cells, ($\times 10^9$/L)	9.8 ± 3.4	9.9 ± 3.4	0.794
Platelets, ($\times 10^9$/L)	230.0 ± 67.2	233.9 ± 76.0	0.436
Serum creatinine, (mg/dL)	1.1 ± 0.6	1.2 ± 0.7	< 0.001
Estimated GFR, (mL/min/1.73 m^2)	80.0 ± 25.3	72.7 ± 27.0	< 0.001
ALT, (U/L)	20 (6-71)	21 (6-79)	0.283
AST, (U/L)	23 (5-76)	23 (6-65)	0.249
TSH, (mIU/L)	1.20 (0.63-4.40)	1.23 (0.72-4.70)	0.573
Blood glucose, (mg/dL)	145.1 ± 69.2	158.7 ± 78.9	0.002
HbA1c, (%)	6.7 ± 1.6	7.0 ± 1.8	0.004
Peak troponin T, (ng/mL)	1.145 (0.10-189.6)	1.285 (0.10-179)	0.154
Lipid profiles			
Total cholesterol, (mg/dl)	186.2 ± 48.4	194.1 ± 53.0	0.008
LDL cholesterol, (mg/dl)	119.8 ± 36.1	130.8 ± 41.9	< 0.001
HDL cholesterol, (mg/dl)	36.7 ± 9.3	34.1 ± 9.4	< 0.001
Triglycerides, (mg/dl)	131 (42-860)	179 (60-960)	< 0.001
Atherogenic index of plasma	0.59 ± 0.26	0.74 ± 0.28	< 0.001
Echocardiography			
LVEF, (%)	54.8 ± 4.4	53.8 ± 4.3	0.191

ACEi, Angiotensin-Converting Enzyme Inhibitor; ALT, Alanine Aminotransferase; ARB, Angiotensin II Receptor Blocker; AST, Aspartate Aminotransferase; CAG, Coronary Angiography; COPD, Chronic Obstructive Pulmonary Disease; DBP, Diastolic Blood Pressure; GFR, Glomerular Filtration Rate; HbA1c, Hemoglobin A1c; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein Cholesterol; LVEF, Left Ventricular Ejection Fraction; SBP, Systolic Blood Pressure; TSH, Thyroid-Stimulating Hormone.

Table 2. Univariable and multivariable logistic regression analyses for predictors of multivessel coronary artery disease in patients with NSTEMI

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Hypertension	1.747 (1.595–1.939)	0.013	1.727 (0.994–2.071)	0.107
Diabetes mellitus	3.872 (2.876–4.653)	< 0.001	3.201 (2.432–3.822)	0.001
GFR	0.995 (0.990–0.999)	0.030	1.002 (0.994–1.009)	0.663
HbA1c	1.149 (1.073–1.230)	< 0.001	1.153 (1.038–1.280)	0.008
LDL cholesterol	1.004 (1.001–1.006)	0.010	1.007 (1.003–1.012)	0.002
AIP	5.430 (3.972–8.381)	< 0.001	3.132 (1.626–6.030)	0.001

AIP, Atherogenic Index of Plasma; CI, Confidence Interval; DM, Diabetes Mellitus; GFR, Glomerular Filtration Rate; HbA1c, Hemoglobin A1c; LDL, Low-Density Lipoprotein; LVEF, Left Ventricular Ejection Fraction; OR, Odds Ratio.

Table 3. Receiver operating characteristic curve analysis of atherogenic index of plasma, LDL-C, and HbA1c for predicting multivessel coronary artery disease in patients with NSTEMI

Variables	AUC	P	95% Confidence Interval		Sensitivity (%)	Specificity (%)	Cut-off point
			Lower Bound	Upper Bound			
AIP	0.689	< 0.001	0.658	0.720	65.6	65.6	0.648
LDL-C	0.550	0.004	0.516	0.583	54	53	114.50
HbA1c	0.575	< 0.001	0.542	0.609	58	54	6.05

AIP, Atherogenic Index of Plasma; AUC, Area Under the Curve; HbA1c, Hemoglobin A1c; LDL-C, Low-Density Lipoprotein Cholesterol.

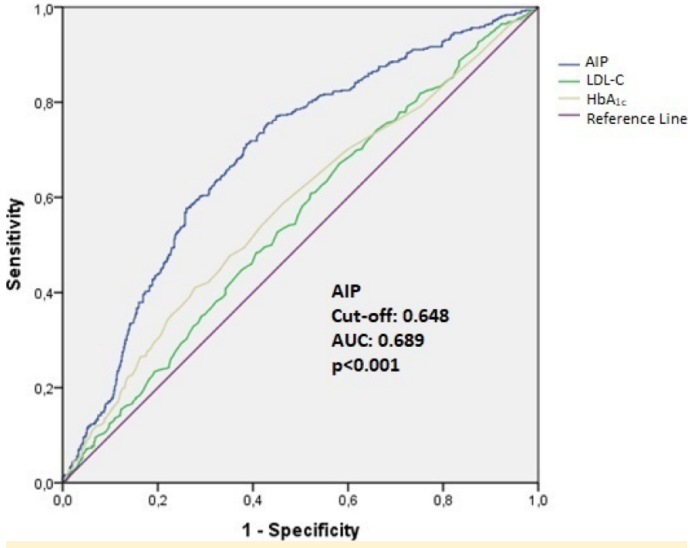


Figure 1. Comparison of receiver operating characteristic (ROC) curves for AIP, LDL-C, and HbA_1c in predicting multivessel coronary artery disease in patients with non-ST-segment elevation myocardial infarction.

AIP, Atherogenic Index of Plasma; AUC, Area under the curve; HbA1c, Hemoglobin A1c; LDL-C, Low-density lipoprotein cholesterol.

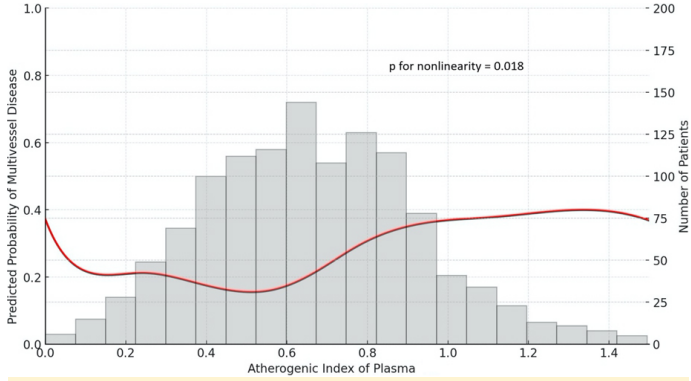


Figure 2. Restricted cubic spline curve illustrating the association between atherogenic index of plasma (AIP) and the predicted probability of multivessel disease. The red line represents the spline-derived predicted probability, and the gray bars depict the distribution of patients across AIP values.

value of 0.689 indicates only moderate discriminative ability. Therefore, the clinical relevance of AIP should be interpreted in the context of stronger prognostic indicators, such as troponin, Global Registry of Acute Coronary Events (GRACE) score, or the Thrombolysis in Myocardial Infarction (TIMI) score,[14] which were not directly compared in our study because their primary roles are risk stratification and prognosis rather than assessment of anatomical disease burden. In this regard, AIP may still provide complementary value as a simple and accessible metabolic marker reflecting atherogenic burden.

The proportion of NSTEMI cases relative to STEMI has been steadily increasing, even though the overall incidence of ACS has declined in many developed countries over recent decades.[18,19] Within the NSTEMI population, the presence of MVD is a marker of adverse prognosis,[20,21] which is particularly relevant given that NSTEMI patients often experience higher long-term mortality after hospital discharge compared with those presenting with STEMI.[22,23] In our cohort, MVD was detected in 24.8% of patients with NSTEMI. Although this rate is somewhat lower than in previous reports, it falls within the wide range observed across the

literature, likely reflecting differences in patient selection criteria, definitions of MVD, and population characteristics. For instance, Baumann et al.[5] reported a prevalence of 42% among NSTEMI patients undergoing CAG in a contemporary registry. Conversely, a Portuguese study observed a lower prevalence of 18%, while other investigations have reported rates ranging from 40% to 60% among NSTEMI patients treated with PCI.[17,24,25] Despite this variability, most studies consistently indicate that the presence of MVD is associated with poorer outcomes.[26] These findings highlight the clinical relevance of identifying MVD in NSTEMI.

AIP is a logarithmic index that reflects the relationship between fasting triglycerides and HDL cholesterol. It was first introduced as a marker of plasma atherogenicity, based on its inverse relationship with LDL particle size.[7] Small dense LDL (sdLDL), an LDL subclass, is more atherogenic due to its smaller particle size, which facilitates penetration and retention within the arterial intima.[27] Furthermore, sdLDL particles are more susceptible to oxidative modification; oxidized LDL is then engulfed by macrophages, forming foam cells that contribute to atheroma development. The mechanisms underlying the enhanced atherogenicity of sdLDL include lipid peroxidation, increased expression of endothelial adhesion molecules, and activation of reactive oxygen species—all of which play integral roles in the progression of CAD.[28] Previous studies have identified sdLDL as a valuable biomarker for predicting atherosclerosis, and its clinical application has been encouraged.[29] However, sdLDL measurement remains limited in routine practice due to methodological complexity and high cost. AIP serves as a convenient and cost-effective surrogate for sdLDL, as elevated AIP values indicate smaller LDL particle size and a higher proportion of sdLDL.[7] These associations reinforce the value of AIP as an accessible marker of atherogenic risk. The current study adds to this body of evidence by demonstrating that AIP correlates with the extent of CAD, thereby supporting its utility as a reliable indicator of atherosclerotic burden.

Several studies have explored the relationship between AIP and CAD severity in patients with chronic coronary syndrome (CCS). Wang et al.[13] reported that AIP was not only an independent risk factor for CAD but also correlated with higher SYNTAX scores (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery), indicating a strong association with both disease occurrence and anatomical complexity. Similarly, Wu et al.[30] demonstrated that AIP independently predicted the severity of newly diagnosed CAD, particularly in individuals with normal glucose metabolism. Zhou et al.[9] also confirmed that AIP is a powerful and independent predictor of CAD in patients with DM, with progressively increasing odds ratios across AIP quartiles. Furthermore, Cai et al.[31] identified AIP as the lipid parameter most strongly associated with CAD among a broad panel of lipid indices in a large Chinese cohort. In addition, Mangalesh et al.[32] found that AIP not only correlated with CAD severity but also predicted major adverse cardiovascular events during a three-year follow-up period, underscoring its prognostic value beyond the initial diagnosis.

The role of AIP has also been examined in patients with ACS. Two recent studies found that elevated AIP levels were significantly associated with both the presence and severity of ACS. Cai et al.[33] reported that AIP was independently associated with ACS occurrence and lesion severity in very young adults (≤ 35 years), demonstrating stronger predictive power than traditional lipid parameters, particularly among men. Jin et al.[34] similarly found that AIP was independently associated with MVD in patients with acute myocardial infarction, especially among those with prediabetes. However, Jin et al.'s[34] cohort included both STEMI and NSTEMI patients, and the analysis did not differentiate between these subtypes. Their investigation mainly focused on the interaction between AIP and glucose metabolism rather than assessing AIP as an independent stratification tool within a specific ACS population. In contrast, our study concentrated exclusively on NSTEMI patients—a group characterized by distinct pathophysiological mechanisms and prognostic outcomes[35]—and evaluated AIP specifically as a predictor of MVD. Moreover, the definition of MVD used in our study required critical stenosis in all three major epicardial coronary arteries. In contrast, Jin et al.[34] defined MVD as the involvement of two or more vessels. This distinction in MVD definitions across studies should be taken into account when comparing our results with previous literature. This stricter criterion may enhance the specificity of our findings and better represent advanced coronary atherosclerosis.

Although several previous studies have demonstrated the predictive value of AIP for assessing CAD severity in CCS or suspected CAD, its relevance in ACS—particularly in NSTEMI—remains insufficiently characterized. Several studies have linked higher AIP values with elevated SYNTAX scores, increased anatomical complexity, and higher odds of CAD in various metabolic contexts.[9,13,30] Furthermore, investigations across diabetic, normoglycemic, and young adult populations have confirmed the consistency of AIP as a risk marker across diverse cardiovascular risk categories.[9,28,33] However, most of these studies were conducted in patients undergoing elective CAG or in broader ACS cohorts without differentiating NSTEMI from other ACS types. This distinction is crucial because NSTEMI represents a unique subset of ACS, characterized by heterogeneous mechanisms, a higher prevalence of comorbidities, and often more extensive coronary involvement.[36] In addition, MVD in NSTEMI has been linked to poorer short- and long-term outcomes, yet reliable tools for early identification are still lacking in clinical practice.[37] Our study directly addresses this knowledge gap by focusing solely on NSTEMI patients and examining AIP's predictive ability for detecting MVD. We found that elevated AIP values were significantly associated with MVD, even after adjustment for HbA1c, LDL cholesterol, renal function, and LVEF. Among the analyzed parameters, AIP showed modest but better discriminative performance in ROC analysis than conventional metabolic indicators. These findings suggest that AIP may reflect atherogenic burden in NSTEMI and could offer additional clinical value when interpreted alongside established risk markers.

Study Limitations

This study is not without limitations, which should be carefully considered. First, because of its single-center, retrospective, and observational nature, a definitive causal relationship between elevated AIP levels and MVD in patients with NSTEMI cannot be established. In addition, the retrospective, single-center design of our study may further limit the external validity and generalizability of the results. Because patient characteristics and clinical practices may differ across centers and regions, caution

is required when extrapolating these findings to broader NSTEMI populations. Second, although the sample size was relatively large, all participants were drawn from a single tertiary hospital, which may have introduced selection bias and reduced generalizability of the findings. Third, the potential effects of unmeasured confounding factors, including lifestyle-related variables such as diet and physical activity, could not be fully excluded. Fourth, AIP values were calculated based on laboratory measurements obtained during a single hospitalization; therefore, longitudinal exposure or temporal changes in AIP levels were not evaluated, and the cumulative impact of sustained AIP elevation on the development of MVD in NSTEMI patients remains uncertain. Fifth, CAD severity in this study was determined by the number of major epicardial vessels with significant stenosis rather than by the SYNTAX score. Although the SYNTAX score provides valuable information regarding anatomical complexity, it does not necessarily reflect the overall extent of vessel involvement, which was the focus of our investigation. Finally, as the study cohort consisted primarily of patients of Turkish descent, the generalizability of our findings to other ethnic and geographic populations may be limited.

Conclusion

In conclusion, our study demonstrates that AIP is significantly associated with the presence of critical MVD in patients with NSTEMI. After adjustment for conventional cardiometabolic risk factors, AIP remained an independent predictor of MVD and showed better discriminative performance than the other evaluated parameters. Owing to its simplicity, affordability, and wide availability, AIP may serve as a practical and accessible indicator of atherogenic burden, helping identify NSTEMI patients who are more likely to have multivessel coronary involvement. Nevertheless, further large-scale, prospective, multicenter randomized studies involving diverse ethnic and demographic populations are warranted to validate and expand upon these findings.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (Approval Number: AEŞH-BADEK-2025-0319, Date: 09.04.2025).

Informed Consent: Informed consent was waived due to the study's retrospective nature.

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: The authors confirm that no artificial intelligence (AI)-assisted technologies were employed in the preparation or analysis of this manuscript, and they take full responsibility for its accuracy and originality.

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

Peer-review: Externally peer-reviewed.

References

1. Martin SS, Aday AW, Allen NB, et al.; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Committee. 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation*. 2025;151(8):e41-e660. Erratum in: *Circulation*. 2025;151(25):e1096.
2. Küçük U, Volina E, Arslan K. Can Glypican-6 Levels Be Used to Determine Right Ventricular Remodeling After Non-ST Segment Elevation Myocardial Infarction? *Turk Kardiyol Dern Ars*. 2024;52(5):307-314. [CrossRef]
3. Pasterkamp G, den Ruijter HM, Libby P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. *Nat Rev Cardiol*. 2017;14(1):21-29. [CrossRef]
4. Köktürk U, Onalan O, Somuncu MU, et al. The Prognostic Value of the Triglyceride-Glucose Index in Forecasting Ten-Year Major Adverse Cardiovascular Events in Non-Diabetic Patients with Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention. *Turk Kardiyol Dern Ars*. 2024;52(4):253-259. [CrossRef]
5. Baumann AAW, Tavella R, Air TM, et al. Prevalence and real-world management of NSTEMI with multivessel disease. *Cardiovasc Diagn Ther*. 2022;12(1):1-11. [CrossRef]
6. He H, Wang J, Wang Y, et al.; CCC-ACS investigators. Predictive factors for multivessel disease in patients with acute coronary syndrome: analysis from the CCC-ACS project in China. *BMC Cardiovasc Disord*. 2024;24(1):617. Erratum in: *BMC Cardiovasc Disord*. 2025;25(1):154. [CrossRef]
7. Dobiásová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). *Clin Biochem*. 2001;34(7):583-538. [CrossRef]
8. Quispe R, Manalac RJ, Faridi KF, et al. Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: The Very Large Database of Lipids-4 (VLDL-4) study. *Atherosclerosis*. 2015;242(1):243-250. [CrossRef]
9. Zhou K, Qin Z, Tian J, Cui K, Yan Y, Lyu S. The Atherogenic Index of Plasma: A Powerful and Reliable Predictor for Coronary Artery Disease in Patients With Type 2 Diabetes. *Angiology*. 2021;72(10):934-941. [CrossRef]
10. Shen SW, Lu Y, Li F, et al. Atherogenic index of plasma is an effective index for estimating abdominal obesity. *Lipids Health Dis*. 2018;17(1):11. [CrossRef]
11. Zhang X, Zhang X, Li X, Feng J, Chen X. Association of metabolic syndrome with atherogenic index of plasma in an urban Chinese population: A 15-year prospective study. *Nutr Metab Cardiovasc Dis*. 2019;29(11):1214-1219. [CrossRef]
12. Zhu XW, Deng FY, Lei SF. Meta-analysis of Atherogenic Index of Plasma and other lipid parameters in relation to risk of type 2 diabetes mellitus. *Prim Care Diabetes*. 2015;9(1):60-67. [CrossRef]
13. Wang L, Chen F, Xiaoqi C, Yujun C, Zijie L. Atherogenic Index of Plasma Is an Independent Risk Factor for Coronary Artery Disease and a Higher SYNTAX Score. *Angiology*. 2021;72(2):181-186. [CrossRef]
14. Byrne RA, Rossello X, Coughlan JJ, et al.; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44(38):3720-3826. Erratum in: *Eur Heart J*. 2024;45(13):1145. [CrossRef]
15. Thygesen K, Alpert JS, Jaffe AS, et al.; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40(3):237-269. [CrossRef]
16. Ahmed F, Khan MS, Ali Shah SD, Jalbani J, Ali Shah A, Shaikh GA. Frequency of Three-Vessel Disease Among Patients With Non-ST Segment Elevation Myocardial Infarction. *Cureus*. 2020;12(11):e11634. [CrossRef]
17. Carvalho JF, Belo A, Congo K, et al.; investigators of the Portuguese Registry on Acute Coronary Syndromes (ProACS). Left main and/or three-vessel disease in patients with non-ST-segment elevation

myocardial infarction and low-risk GRACE score: Prevalence, clinical outcomes and predictors. *Rev Port Cardiol (Engl Ed)*. 2018;37(11):911-919. English, Portuguese. [CrossRef]
18. Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129(14):1483-1492. [CrossRef]
19. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med*. 2016;4(13):256. [CrossRef]
20. Corpus RA, House JA, Marso SP, et al. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. *Am Heart J*. 2004;148(3):493-500. [CrossRef]
21. Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J*. 2007;28(14):1709-1716. [CrossRef]
22. Darling CE, Fisher KA, McManus DD, et al. Survival after hospital discharge for ST-segment elevation and non-ST-segment elevation acute myocardial infarction: a population-based study. *Clin Epidemiol*. 2013;5:229-236. [CrossRef]
23. Nadlacki B, Horton D, Hossain S, et al. Long term survival after acute myocardial infarction in Australia and New Zealand, 2009-2015: a population cohort study. *Med J Aust*. 2021;214(11):519-525. [CrossRef]
24. Thiele H, Rach J, Klein N, et al.; LIPSIA-NSTEMI Trial Group. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J*. 2012;33(16):2035-2043. [CrossRef]
25. Rathod KS, Koganti S, Jain AK, et al. Complete Versus Culprit-Only Lesion Intervention in Patients With Acute Coronary Syndromes. *J Am Coll Cardiol*. 2018;72(17):1989-1999. [CrossRef]
26. Desperak P, Hawranek M, Gąsior P, Desperak A, Lekston A, Gąsior M. Long-term outcomes of patients with multivessel coronary artery disease presenting non-ST-segment elevation acute coronary syndromes. *Cardiol J*. 2019;26(2):157-168. [CrossRef]
27. Galeano NF, Al-Haideri M, Keyserman F, Rumsey SC, Deckelbaum RJ. Small dense low density lipoprotein has increased affinity for LDL receptor-independent cell surface binding sites: a potential mechanism for increased atherogenicity. *J Lipid Res*. 1998;39(6):1263-1273. [CrossRef]
28. Mikhailidis DP, Elisaf M, Rizzo M, et al. "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses: executive summary. *Curr Vasc Pharmacol*. 2011;9(5):531-532. [CrossRef]
29. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421. [CrossRef]
30. Wu X, Qiu W, Yang H, Chen YJ, Liu J, Zhao G. Associations of the triglyceride-glucose index and atherogenic index of plasma with the severity of new-onset coronary artery disease in different glucose metabolic states. *Cardiovasc Diabetol*. 2024;23(1):76. [CrossRef]
31. Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. *Medicine (Baltimore)*. 2017;96(37):e8058. [CrossRef]
32. Mangalesh S, Yadav P, Dudani S, Mahesh NK. Atherogenic index of plasma predicts coronary artery disease severity and major adverse cardiac events in absence of conventional risk factors. *Coron Artery Dis*. 2022;33(7):523-530. [CrossRef]
33. Cai G, Liu W, Lv S, et al. Gender-specific associations between atherogenic index of plasma and the presence and severity of acute coronary syndrome in very young adults: a hospital-based observational study. *Lipids Health Dis*. 2019;18(1):99. [CrossRef]
34. Jin K, Ma Z, Zhao C, et al. The correlation between the atherogenic index of plasma and the severity of coronary artery disease in acute myocardial infarction patients under different glucose metabolic states. *Sci Rep*. 2025;15(1):6128. [CrossRef]
35. Theofilis P, Oikonomou E, Chasikidis C, Tsioufis K, Tousoulis D. Pathophysiology of Acute Coronary Syndromes-Diagnostic and Treatment Considerations. *Life (Basel)*. 2023;13(7):1543. [CrossRef]
36. Baumann AAW, Mishra A, Worthley MI, Nelson AJ, Psaltis PJ. Management of multivessel coronary artery disease in patients with non-ST-elevation myocardial infarction: a complex path to precision medicine. *Ther Adv Chronic Dis*. 2020;11:2040622320938527. [CrossRef]
37. Zimbardo G, Cialdella P, Di Fusco P, et al. Acute coronary syndromes and multivessel coronary artery disease. *Eur Heart J Suppl*. 2023;25(Suppl C):C74-C78. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Evaluation of Soluble ST2 and Galectin-3 Levels in Patients with Heart Failure

Kalp Yetersizliği Olan Hastalarda Çözünür ST2 ve Galektin-3 Düzeylerinin Değerlendirilmesi

ABSTRACT

Objective: Soluble stromelysin-2 (sST2) and galectin-3 have been found to be associated with prognosis in patients with heart failure (HF). However, there is no study evaluating the clinical importance of sST2 and galectin-3 in HF classification according to ejection fraction (EF). In the present study, we aimed to assess the diagnostic value of sST2 and galectin-3 in HF classification based on EF.

Method: Forty-one heart failure patients with reduced ejection fraction (HFrEF), 41 with mildly-reduced EF (HFmrEF), 41 with preserved EF (HFpEF), and 41 healthy controls were included in the study. EF ≤ 40% was defined as HFrEF, 41-49% as HFmrEF, and ≥ 50% as HFpEF. Levels of sST2 and galectin-3 were measured, and comparisons were performed.

Results: There were significant differences among the groups in terms of sST2 (P < 0.001) and galectin-3 (P = 0.007) levels. Post hoc analysis demonstrated that patients with HFmrEF and HFrEF had significantly higher sST2 (P = 0.001 and P = 0.001, respectively) and galectin-3 (P = 0.043 and P = 0.007, respectively) levels compared to the control group, whereas the HFpEF and control groups were similar in terms of sST2 and galectin-3 levels (P = 0.645 and P = 0.436, respectively). In correlation analysis, sST2 and galectin-3 levels were positively correlated with B-type natriuretic peptide (BNP) (r = 0.240, P = 0.002 and r = 0.172, P = 0.028, respectively) and negatively correlated with EF (r = -0.403, P < 0.001 and r = -0.295, P < 0.001, respectively).

Conclusion: sST2 and galectin-3 levels were higher in patients with HFrEF and HFmrEF compared to the control group, and these markers increased as EF decreased. However, these markers did not differ between patients with HFpEF and the control group.

Keywords: Heart failure, stromelysin 2, galectin-3

ÖZET

Amaç: Soluble Stromelysin-2 (sST2) ve galektin-3'ün kalp yetersizliği (KY) hastalarının prognozu ile ilişkili olduğu gösterilmiştir. Ancak, ejeksiyon fraksiyonu (EF) temelinde KY sınıflandırmasında sST2 ve galektin-3'ün klinik önemini değerlendiren hiçbir çalışma bulunmamaktadır. Mevcut çalışmada, EF temelinde KY sınıflandırmasında sST2 ve galektin-3'ün tanısal değerini incelemeyi amaçladık.

Yöntem: EF'si azalmış 41 KY hastası (HFrEF), EF'si hafif azalmış 41 hasta (HFmrEF), EF'si korunmuş 41 hasta (HFpEF) ve 41 sağlıklı kontrol grubu çalışmaya dahil edildi. EF ≤ 40% HFrEF, %41 ile %49 arası HFmrEF ve ≥5 0% HFpEF olarak tanımlandı. Hastaların sST2 ve galektin-3 düzeyleri ölçüldü ve karşılaştırmalar yapıldı.

Bulgular: Gruplar arasında sST2 (P < 0.001) ve galektin-3 (P = 0.007) düzeyleri açısından önemli farklar vardı. Post hoc analiz, HFmrEF ve HFrEF hastalarında sST2 (sırasıyla P = 0.001 ve P = 0.001) ve galektin-3 (sırasıyla P = 0.043 ve P = 0.007) düzeylerinin kontrol grubuna göre anlamlı derecede daha yüksek olduğunu, buna karşılık HFpEF ve kontrol gruplarının sST2 ve galektin-3 düzeyleri açısından benzer olduğunu (sırasıyla P = 0.645 ve P = 0.436) gösterdi. Korelasyon analizinde, sST2 ve galektin-3 düzeyleri BNP ile pozitif korelasyon gösterirken (sırasıyla r = 0.240, P = 0.002 ve r = 0.172, P = 0.028), EF ile negatif korelasyon gösterdi (sırasıyla r = -0.403, P < 0.001 ve r = -0.295, P < 0.001).

Sonuç: sST2 ve galektin-3, kontrol grubuna kıyasla HFrEF ve HFmrEF hastalarında daha yüksekti ve bu belirteçler EF azaldıkça daha da arttı. Ancak, bu belirteçler HFpEF hastaları ile kontrol grubu arasında farklılık göstermedi.

Anahtar Kelimeler: Kalp yetersizliği, stromelysin-2 galektin-3

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

Mustafa Çetin[1]
Zulkif Tanriverdi[2]
Recep Demirbağ[2]
İbrahim Halil Altıparmak[2]
Asuman Biçer Yeşilay[2]
Mustafa Begenc Tascanov[2]
Halil Fedai[2]
Kenan Toprak[2]
İsmail Koyuncu[3]

[1]*Department of Cardiology, Mehmet Akif Inan Training and Research Hospital, Şanlıurfa, Türkiye*
[2]*Department of Cardiology, Harran University Faculty of Medicine, Şanlıurfa, Türkiye*
[3]*Department of Biochemistry, Harran University Faculty of Medicine, Şanlıurfa, Türkiye*

Corresponding author:
Mustafa Çetin
✉ mustafactndr@gmail.com

Received: September 09, 2025
Accepted: December 29, 2025

Cite this article as: Çetin M, Tanriverdi Z, Demirbağ R, et al. Evaluation of Soluble ST2 and Galectin-3 Levels in Patients with Heart Failure. *Turk Kardiyol Dern Ars.* 2026;54(3):253-260.

DOI: 10.5543/tkda.2025.44679

Heart failure (HF) is a clinical syndrome defined as a functional and/or structural abnormality of the heart, resulting in elevated intracardiac pressures and/or inadequate cardiac output.[1] It is still the most important cause of mortality and morbidity worldwide. It places a substantial burden on both patients and society and leads to high healthcare costs.[2] The incidence and prevalence of HF increases with age, and this increase is even more pronounced in individuals over 60 years of age.[3] Because HF is associated with poor prognosis, the underlying pathophysiological mechanisms should be well understood, diagnosed early, and treated effectively.

Biomarkers can assist physicians in the diagnosis of heart failure, risk stratification, and treatment guidance. To date, many biomarkers have been investigated in patients with HF. Current guidelines state that B-natriuretic peptide (BNP or pro-BNP) can be used as an important biomarker for the diagnosis, follow-up, and prognosis of HF.[1] On the other hand, studies investigating additional biomarkers are still ongoing. Soluble suppression of tumorigenicity (sST2) and galectin-3 are biomarkers that have recently begun to be used in clinical practice.[4,5]

Galectin-3 is encoded by the LGALS3 gene, which is located on chromosome 14. This biomarker is a member of the beta-galactosidase-binding protein family and is secreted by macrophages. It is a multifunctional protein that plays a critical role in many pathophysiological processes, including cell growth, differentiation, programmed cell death, cell adhesion, angiogenesis, inflammation, fibrogenesis, and tumor progression.[4] On the other hand, ST2 is a member of the interleukin (IL)-1 receptor family and is synthesized on chromosome 2q12. ST2 exists in two different forms: the transmembrane receptor ST2 ligand (ST2L) and the soluble form (sST2).[5] Interaction between ST2L and IL-33 has been shown to have cardioprotective effects in experimental models, improving myocardial function and reducing myocardial fibrosis, myocyte hypertrophy, and apoptosis. The cardioprotective effect of this interaction is mediated only through the ST2L receptor and not through sST2. sST2 binds to ST2L by competing with IL-33 and inhibits IL-33 binding to ST2L. Thus, the ST2L/IL-33 interaction does not occur, and the cardioprotective effects described above are abolished.[6] Studies have shown that sST2 and galectin-3 levels are significantly elevated in patients with HF, and increased levels of these markers are significantly correlated with the severity of HF.[7-9] In the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for chronic HF, measurement of galectin-3 and sST2 is recommended to determine the risk level of patients with chronic HF.[10]

Although increased levels of sST2 and galectin-3 have been demonstrated in heart failure patients with reduced ejection fraction (HFrEF),[11,12] the clinical significance of these two biomarkers in HF patients with mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) has not been clarified. This study aimed to examine the clinical value of sST2 and galectin-3 levels in ejection fraction (EF)-based heart failure classification.

Materials and Methods

The study was initiated after approval from Harran University Clinical Research Ethics Committee (Approval Number: HRÜ/22.16.12, Date: 22.08.2022).

ABBREVIATIONS

BNP	B-type natriuretic peptide
EF	Ejection fraction
HF	Heart failure
HFmrEF	Heart failure patients with mildly-reduced EF
HFpEF	Heart failure patients with preserved EF
HFrEF	Heart failure patients with reduced ejection fraction
IL	Interleukin
sST2	Soluble stromelysin-2
ST2L	ST2 ligand
TTE	Transthoracic echocardiography

The study population was selected from outpatients admitted to the cardiology outpatient clinic of Harran University Medical Faculty Hospital who were not in acute respiratory distress and who underwent transthoracic echocardiography (TTE). A total of 123 HF patients (41 with HFrEF, 41 with HFmrEF, and 41 with HFpEF) and 41 control subjects (164 participants in total) were included in the study. All authors adhered to the Declaration of Helsinki and conducted the study appropriately. Furthermore, no artificial intelligence-supported applications were used in our study.

The diagnosis of HF and classification of subtypes were made according to the 2021 European Society of Cardiology (ESC) heart failure guideline. HF subtypes were determined based on left ventricular EF. According to these guidelines, HF classification based on EF is as follows: EF ≤ 40% indicates heart failure with reduced EF, EF between 41% and 49% indicates heart failure with mildly reduced EF, and EF ≥ 50% indicates heart failure with preserved EF.1 Patients aged ≥ 18 years who were diagnosed with HF based on medical evaluations were included in the study. Patients aged < 18 years; those with active infection, severe liver or kidney disease; pregnant women; patients diagnosed with acute coronary syndrome within the previous six months; patients with inflammatory or autoimmune diseases, malignancy, sepsis, or thyroid dysfunction; and patients who did not undergo TTE were excluded from the study. Written informed consent was obtained from all participants.

All patients included in the study underwent a detailed echocardiographic examination. All echocardiographic examinations were performed using the Vivid S6 device (GE Healthcare, Wauwatosa, USA). Echocardiographic measurements were obtained in the supine or left decubitus position using appropriate windows, in accordance with the American Society of Echocardiography recommendations. The modified Simpson's method was used for left ventricular EF measurements. End-systolic and end-diastolic diameters of the left ventricle (LVESD and LVEDD, respectively), left atrium (LA), interventricular septum (IVS), and right ventricle (RV), were measured and recorded.[13]

Statistical Analysis

The evaluations were performed using the SPSS (Statistical Package for the Social Sciences) version 22.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the distribution of variables. Continuous data with normal distribution were presented as mean ± standard deviation (SD), whereas continuous data without normal distribution were presented as

Table 1. Comparison of baseline characteristics among heart failure subtypes and control patients

	Control (n = 41)	HFpEF (n = 41)	HFmrEF (n = 41)	HFrEF (n = 41)	*P*
Age (years), (mean±SD)	56.6 ± 8.9	56.6 ± 9.6	56.6 ± 12.6	58.6 ± 14.8	0.831
Gender, female (%)	20 (48.8)	26 (63.4)	10 (24.4)	15 (36.6)	**0.003**
BMI, kg/m²	29.4 ± 4.4	32.2 ± 6.7	28.3 ± 3.7	27.9 ± 4.6	**0.001**
SBP (mmHg)	125.9 ± 23.9	127.3 ± 20.1	123.4 ± 25.0	117.2 ± 20.5	0.192
DBP (mmHg)	69.0 ± 15.3	70.3 ± 12.2	69.8 ± 12.9	68.8 ± 13.3	0.955
HT (%)	17 (41.5)	24 (58.5)	24 (58.5)	18 (43.9)	0.244
DM (%)	12 (29.3)	12 (29.3)	7 (17.1)	8 (19.5)	0.425
HL (%)	7 (17.1)	9 (22)	10 (24.4)	2 (4.9)	0.088
Rhythm (%)					**0.021**
SR	41 (100)	41 (100)	37 (90.2)	36 (87.8)	
AF	0 (0)	0 (0)	4 (9.8)	5 (12.2)	
LBBB (%)	2 (4.9)	1 (2.4)	6 (14.6)	27 (65.9)	**<0.001**

AF, Atrial fibrillation; BMI, Body mass index; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HFmrEF, Heart failure patients with mildly-reduced EF; HFpEF, Heart failure patients with preserved EF; HFrEF, Heart failure patients with reduced ejection fraction; HL, Hyperlipidemia; HT, Hypertension; LBBB, Left bundle branch block; SBP, Systolic blood pressure; SR, Sinus rhythm.

median (25th–75th percentiles). Categorical data were presented as numbers (%). Continuous data with normal distribution were compared using the t-test, while the Mann-Whitney U test was used for data without normal distribution. Comparisons of more than two independent groups were performed using analysis of variance (ANOVA) for normally distributed variables. In the presence of differences between groups, Bonferroni and/or Tukey post hoc tests were applied to determine which groups accounted for the differences. The Kruskal-Wallis test was used to compare more than two independent groups that did not follow a normal distribution. In the presence of a difference between groups, the Mann-Whitney U test with Bonferroni correction was applied to determine the source of the difference. Correlation analyses were performed using Pearson and Spearman correlation coefficients. Receiver operating characteristic (ROC) curve analyses were conducted to determine the area under the curve and cut-off values of soluble ST2 and galectin-3 levels for predicting heart failure subtypes. The predictive validity of sST2 and galectin-3 was quantified using the area under the ROC curve (AUC), and comparisons were performed using MedCalc version 16 statistical software (trial version) with the DeLong test. A post hoc power analysis was performed and indicated that the power of the study was 97% for sST2 and 75% for galectin-3. A p value < 0.05 was considered statistically significant.

Results

A total of 123 HF patients and 41 control subjects were included in the study, with 41 patients each in the HFrEF, HFmrEF, and HFpEF groups. A comparison of baseline characteristics among the groups is presented in Table 1. There were significant differences among the four groups in terms of sex (P = 0.003) and body mass index (BMI) (P = 0.001). Subgroup analyses showed that the frequency of female sex (P < 0.001 and P = 0.015, respectively) and BMI (P = 0.003 and P = 0.001, respectively) were significantly higher in patients with HFpEF compared to those with HFmrEF and HFrEF.

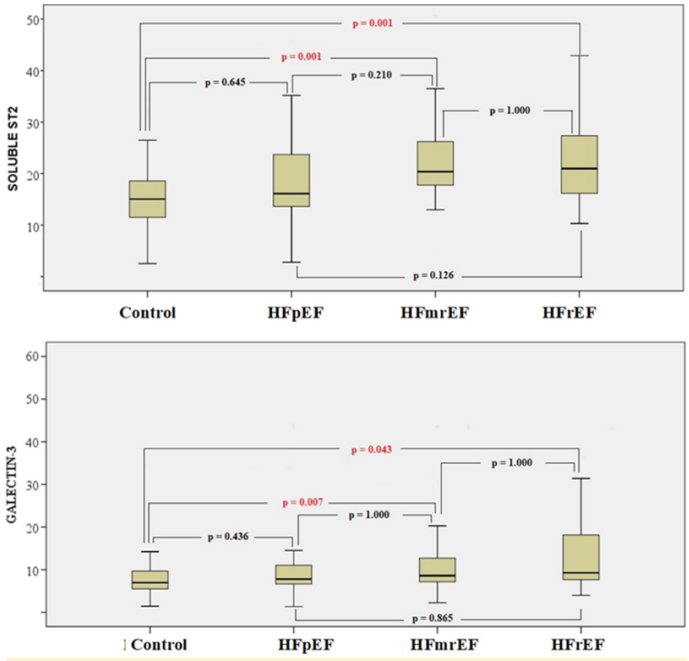


Figure 1. Comparison of sST2 and galectin-3 levels among heart failure subtypes and the control group.

HFmrEF, Heart failure patients with mildly-reduced EF; HFpEF, Heart failure patients with preserved EF; HFrEF, Heart failure patients with reduced ejection fraction.

The comparison of laboratory data between the patient and control groups is shown in Table 2. There were significant differences among the groups in urea (P = 0.014), creatinine (P < 0.001), uric acid (P = 0.007), N-terminal pro–B-type natriuretic peptide (NT-pro BNP) (P < 0.001), sST2 (P < 0.001), and galectin-3 (P = 0.007) (Table 2). Post hoc analyses revealed that sST2 (P = 0.001 and P = 0.001, respectively) and galectin-3 levels (P = 0.043 and P = 0.007, respectively) were significantly higher in the HFmrEF

Table 2. Laboratory characteristics of heart failure subtypes and the control group

	Control (n = 41)	HFpEF (n = 41)	HFmrEF (n = 41)	HFrEF (n = 41)	*P*
Urea (mg/dL) (median [Q1-Q3])	32.1 (24.6-38.5)	29.9 (26.3-38.5)	29.9 (25.6-36.3)	38.5 (29.9-52.4)	**0.014**
Creatinine (mg/dL) (mean±SD)	0.79 ± 0.14	0.8 ± 0.19	0.89 ± 0.19	0.95 ± 0.20	**< 0.001**
Glucose (mg/dL) (median [Q1-Q3])	112 (93.5-135.0)	103 (92.5-130.5)	100 (93.5-125.5)	103 (90.5-130.0)	0.667
Uric acid (mg/dL) (mean±SD)	4.9 ± 1.2	5.3 ± 1.4	5.3 ± 1.4	6.0 ± 1.5	**0.007**
Sodium (mmol/L) (mean±SD)	139.9 ± 3.0	140 ± 2.1	139.9 ± 2.1	140.1 ± 2.0	0.976
Potassium (mmol/L) (mean±SD)	4.3 ± 0.3	4.4 ± 0.3	4.3 ± 0.4	4.3 ± 0.4	0.942
Albumin (g/dL) (mean±SD)	4.4 ± 0.2	4.4 ± 0.2	4.3 ± 0.3	4.3 ± 0.2	0.584
LDL-C (mg/dL) (median [Q1-Q3])	101.8 (83.0-132.2)	103 (81.3-131.3)	91 (72.4-103.8)	105.8 (73.1-123.6)	0.104
TSH (uIU/dL) (median [Q1-Q3])	1.3 (0.9-1.6)	1.3 (0.9-2.2)	1.1 (0.7-1.7)	1.0 (0.7-2.0)	0.255
CRP (mg/dL) (median [Q1-Q3])	0.4 (0.1-0.6)	0.7 (0.2-1.1)	0.3 (0.1-0.8)	0.5 (0.2-1.0)	0.105
Leukocytes (x10³/uL) (median [Q1-Q3])	8.4 (6.7-10.8)	7.6 (6.6-9.2)	7.7 (6.4-9.7)	8.6 (7.4-9.9)	0.188
Hematocrit (%) (mean±SD)	41.9 ± 5.5	42.6 ± 4.1	43.7 ± 3.9	43.2 ± 4.9	0.329
Hemoglobin (g/dL) (mean±SD)	13.4 ± 1.8	14.1 ± 1.5	14.2 ± 1.6	14.1 ± 1.6	0.148
Platelets (x10³/uL) (median [Q1-Q3])	288 (236.0-331.5)	275 (217.0-344.0)	245 (211.5-327.5)	255 (232.0-312.5)	0.254
NT pro-BNP (pg/mL) (median [Q1-Q3])	88.8 (53.2-167.0)	85.8 (50.4-162.5)	138 (105.0-510.0)	769 (321.0-1289.5)	**< 0.001**
Soluble ST2, ng/L (median [Q1-Q3])	15.0 (9.6-20.2)	16.1 (13.5-26.9)	20.3 (17.1-26.6)	20.9 (16.1-28.4)	**< 0.001**
Galectin-3, ng/Ml (median [Q1-Q3])	7.0 (5.4-9.7)	7.8 (6.4-12.4)	8.6 (6.9-13.2)	9.2 (7.5-18.6)	**0.007**

AF, Atrial fibrillation; BMI, Body mass index; CRP, C-reactive protein; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HFmrEF, Heart failure patients with preserved ejection fraction; HFpEF, Heart failure patients with reduced ejection fraction; HL, Hyperlipidemia; HT, Hypertension; HFrEF, Heart failure patients with reduced ejection fraction; LDL-C, Low-density lipoprotein cholesterol; LBBB, Left bundle branch block; NT pro-BNP, N-terminal pro b-type natriuretic peptide; SBP, Systolic blood pressure; SR, Sinus rhythm; TSH, Thyroid-stimulating hormone.

Table 3. Echocardiographic characteristics of heart failure subtypes and control patients

	Control (n = 41)	HFpEF (n = 41)	HFmrEF (n = 41)	HFrEF (n = 41)	*P*
LVEF (%) (mean±SD)	60.0 ± 2.2	57.7 ± 2.7	44.3 ± 1.5	29.2 ± 4.2	**< 0.001**
LVEDD (cm) (mean±SD)	4.8 ± 0.4	5.0 ± 0.5	5.1 ± 0.5	6.2 ± 0.7	**< 0.001**
LVESD (cm) (mean±SD)	3.3 ± 0.2	3.5 ± 0.4	3.9 ± 0.4	5.1 ± 0.6	**< 0.001**
IVS (cm) (mean±SD)	0.9 ±0.1	1.0 ± 0.3	1.0 ± 0.1	0.9 ± 0.2	**0.042**
LA (cm) (mean±SD)	3.4 ± 0.2	3.7 ± 0.3	3.6 ± 0.5	4.1 ± 0.5	**< 0.001**
Ascending Aorta (cm) (mean±SD)	3.4 ± 0.3	3.6 ± 0.4	3.4 ± 0.3	3.6 ± 0.4	0.104
RV (cm) (mean±SD)	3.5 ± 0.2	3.5 ± 0.2	3.6 ± 0.3	3.7 ± 0.5	**0.026**
E/e' (mean±SD)	7.0 ± 0.9	14.6 ± 0.9	12.0 ± 2.1	15.9 ± 1.0	**< 0.001**

HFmrEF, Heart failure patients with mildly-reduced EF; HFpEF, Heart failure patients with preserved EF; HFrEF, Heart failure patients with reduced ejection fraction; IVS, Interventricular septum; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; RV, Right ventricle.

and HFrEF groups than in the control group. On the other hand, sST2 and galectin-3 levels (P = 0.645 and P = 0.436, respectively) were similar between the HFpEF and control groups (Figure 1).

A comparison of echocardiographic parameters among the study groups is shown in Table 3. As expected, there was a significant difference in EF among the groups. Additionally, LVEDD, LVESD, and LA differed significantly among the groups. Post hoc analysis indicated that these differences were mainly between the HFrEF group and the other groups.

Correlation analysis was performed to evaluate the relationships between galectin-3 and sST2 levels and laboratory and echocardiographic variables. We observed that sST2 levels were positively correlated with BNP (r = 0.240, P = 0.002) and negatively correlated with EF (r = -0.403, P < 0.001). Similarly, galectin-3 levels showed a positive correlation with BNP (r = 0.172, P = 0.028) and a negative correlation with EF (r = -0.295, P < 0.001) (Figure 2).

In our study, ROC analysis was performed to determine the AUC, optimal cut-off values, sensitivities, and specificities of galectin-3 and sST2 levels in predicting HFrEF and HFmrEF compared to the control group. ROC curve analyses of sST2 and galectin-3 for predicting HFrEF are shown in Figure 3. An sST2 value ≥ 18.62 predicted HFrEF with 73.2% sensitivity and 75.6% specificity (AUC: 0.751, 95% confidence interval [CI]: 0.646-0.856, P < 0.001). A galectin-3 value ≥ 7.61 predicted HFrEF with 75.6% sensitivity and 61% specificity (AUC: 0.708, 95%

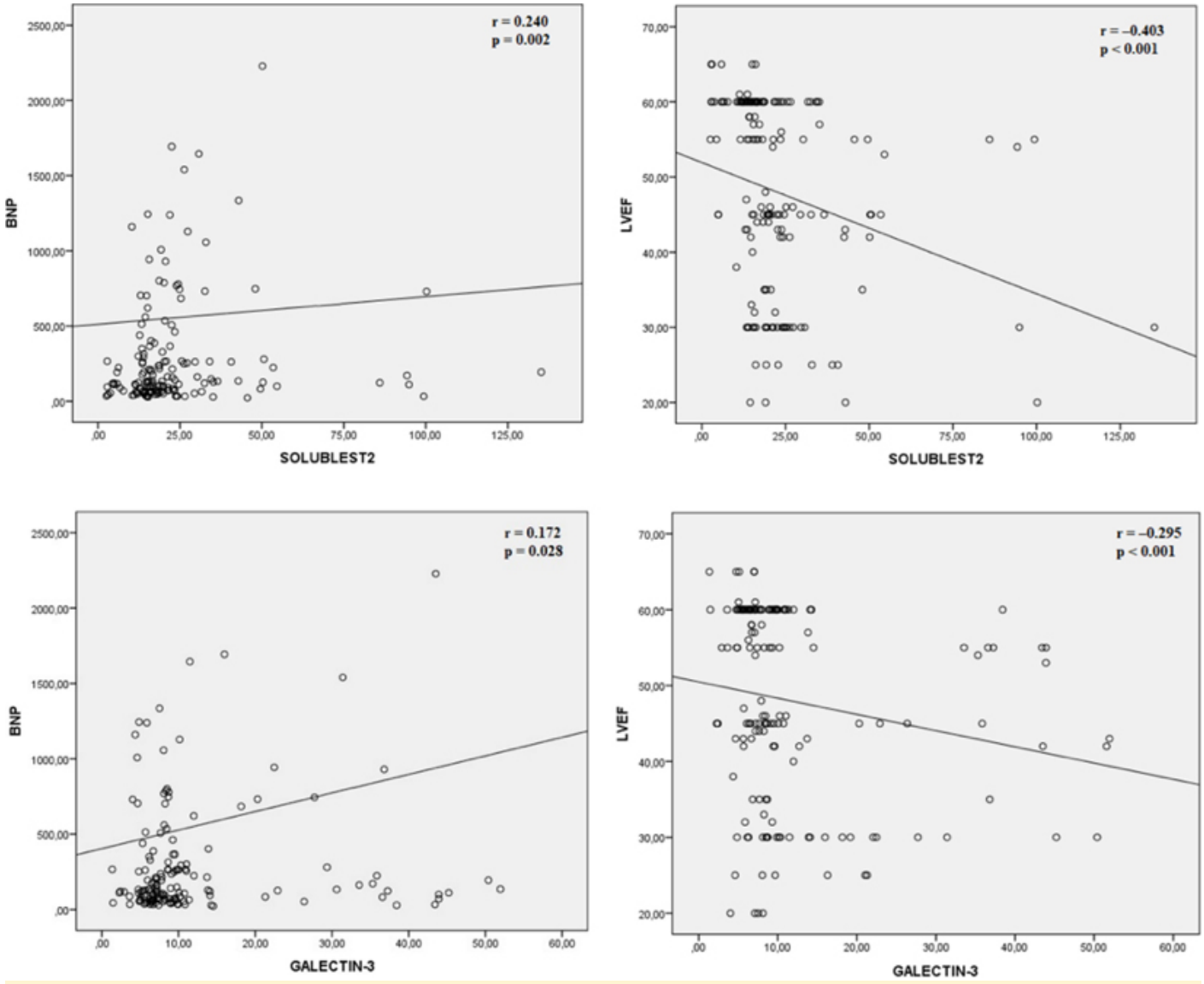


Figure 2. Correlation of sST2 and galectin-3 with BNP levels and left ventricular ejection fraction.

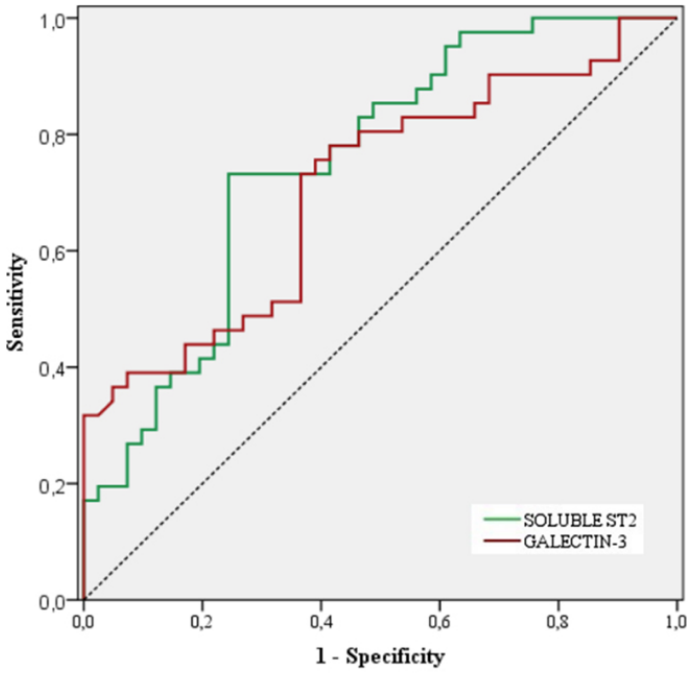
BNP, B-type natriuretic peptide; SOLUBLEST2,Soluble stromelysin-2.

CI: 0.595-0.820, P = 0.001). When we compared the AUC values of sST2 and galectin-3 for predicting HFrEF, we found that the AUCs of sST2 and galectin-3 were comparable (0.751 vs. 0.708, P = 0.455). ROC curve analysis of soluble ST2 and galectin-3 levels for predicting HFmrEF is shown in Figure 4. Accordingly, an ST2 value ≥ 18.78 predicted HFmrEF with 68.3% sensitivity and 75.6% specificity (AUC: 0.740, 95% CI: 0.632-0.848, P < 0.001). A galectin-3 value ≥ 7.17 predicted HFmrEF with 75.6% sensitivity and 58.5% specificity (AUC: 0.672, 95% CI: 0.555-0.789, P = 0.007). When the AUC values of sST2 and galectin-3 were compared for predicting HFmrEF, the AUC of sST2 tended to be higher than that of galectin-3 (0.740 vs. 0.672, P = 0.098).

Discussion

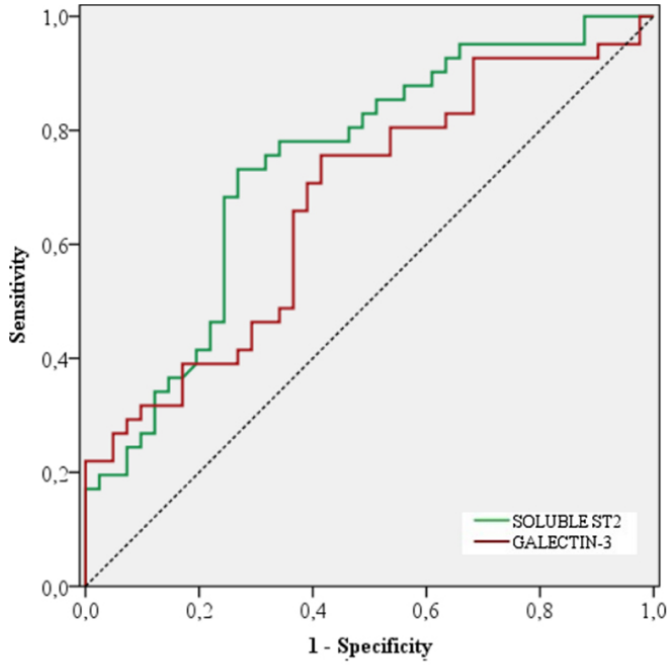
The results of the current study can be summarized as follows: (I) galectin-3 and sST2 levels were significantly increased in HF patients compared to the control group; (II) galectin-3 and sST2 levels were significantly higher in the HFrEF and HFmrEF subgroups compared to the control group, whereas no significant difference was observed between the HFpEF and control groups in terms of these two biomarkers; and (III) galectin-3 and sST2 levels were positively correlated with BNP and negatively correlated with left ventricular ejection fraction (LVEF). EF-based heart failure classification was first defined in the 2016 ESC HF guidelines as HFrEF, HFmrEF, and HFpEF. Although sST2 and galectin-3 have been evaluated separately in these HF subtypes in previous studies, to our knowledge, this study is the first to examine ST2 and galectin-3 across all three HF subtypes simultaneously.

Galectin-3 and sST2 are novel biomarkers of inflammation and fibrosis that have been increasingly used in patients with HF in recent years. Because inflammation and fibrosis play a very important role in the natural history of HF, these biomarkers



	AUC	95 % CI	P
Soluble ST2	0.751	0.646-0.856	<0.001
Galectin-3	0.708	0.595-0.820	0.001

Figure 3. Receiver operating characteristic (ROC) curve analysis of soluble ST2 and galectin-3 levels for predicting heart failure with reduced ejection fraction (HFrEF).



	AUC	95 % CI	P
Soluble ST2	0.740	0.632-0.848	<0.001
Galectin-3	0.672	0.555-0.789	0.007

Figure 4. Receiver operating characteristic (ROC) curve analysis of soluble ST2 and galectin-3 levels for predicting heart failure with mildly reduced ejection fraction (HFmrEF).

provide valuable information in this patient population.[14] However, both biomarkers are influenced by general pathological processes such as fibrosis, programmed cell death, and inflammation in other parts of the body; therefore, they are not specific to the cardiovascular system.[15] While enrolling patients in our study, we excluded individuals with conditions such as acute infection, inflammatory or autoimmune diseases, malignancy, and renal or hepatic insufficiency to eliminate the effects of potential non-cardiac factors that may influence galectin-3 and sST2 levels. Therefore, we suggest that our results were not affected by these confounding factors.

In the 2016 ESC HF guidelines, HFmrEF was defined for the first time, and three HF subtypes were classified according to left ventricular EF: HFrEF, HFmrEF, and HFpEF.[16] There are conflicting results regarding this newly defined HFmrEF subtype. Some studies have shown an overlap between HFmrEF and the other two classes, whereas others have not demonstrated such a relationship.[17] The etiologic factors for HFrEF and HFpEF are well known. It has been reported that comorbid conditions, female sex, and obesity are more frequent in patients with HFpEF.[18] In our study, we also found that female sex and BMI were higher in patients with HFpEF compared to other HF subtypes. In addition, hypertension (HT) and diabetes mellitus (DM) were more common in these patients compared to those with HFrEF, although the difference did not reach statistical significance. These findings obtained in our study support the literature. Although the pathophysiological pathways in the HFrEF and HFpEF subtypes are relatively well understood, the pathophysiology of HFmrEF, a newer classification, has not yet been fully elucidated. Current evidence suggests that HFmrEF may result from progressive deterioration of left ventricular function in patients with HFpEF or, conversely, from improvement in left ventricular systolic function in patients with HFrEF.[17] However, it is also thought that HFmrEF may be a distinct condition from the other two HF subtypes. For these reasons, further studies are needed to better elucidate the pathogenesis of HFmrEF.

Numerous studies have investigated sST2 and galectin-3 levels in patients with HF. Most have shown that sST2 and galectin-3 levels are elevated and associated with poor prognostic outcomes in HF patients.[14,19-23] In addition, increased galectin-3 levels have been independently associated with an increased risk of developing HF in the general population.[24] Moreover, it has been reported that sST2, unlike NT-proBNP, is not affected by age, BMI, renal function, or HF etiology in patients with HFrEF and is superior to NT-proBNP in predicting one-year mortality in patients with HFpEF and HFrEF.[25,26]

Although sST2 and galectin-3 levels have been frequently examined in patients with HFrEF and HFpEF in previous studies, data regarding these parameters in patients with HFmrEF are very limited. Najjar et al.[27] examined sST2 levels in patients with HFrEF, HFpEF, and a control group. They found that sST2 levels were significantly higher in the HFrEF group compared with the HFpEF and control groups; however, they observed no difference between the HFpEF and control groups. In studies evaluating galectin-3, it was reported that galectin-3 levels

were associated with the degree of diastolic dysfunction in patients with HFpEF.[28] In addition, a review by Rabkin et al.[29] examined the importance of growth differentiation factor-15 (GD-15), galectin-3, and sST2 in differentiating HFpEF from HFrEF. They concluded that these three biomarkers alone may not be sufficient for differentiation between HFpEF and HFrEF, but their combined use with BNP may be useful. To date, studies have primarily focused on patients with HFrEF and HFpEF, and HFmrEF patients have not been included in these studies. In our study, a control group was included in addition to all three HF subtypes, allowing for detailed comparisons.

In our study, galectin-3 and sST2 levels were significantly higher in the HFrEF and HFmrEF subgroups compared to the control group, whereas they were similar between the HFpEF and control groups. In a recent study, sST2 and galectin-3 levels were evaluated in HFrEF, HfpEF, and control groups, and similar to our findings, sST2 and galectin-3 levels were significantly higher in the HFrEF group compared to the control group; however, no difference was observed between the HFpEF and control groups in terms of sST2 levels.[30] Unlike our study, that study found a significant difference between the control and HFpEF groups with respect to galectin-3 levels. However, in that study, the number of patients in the control (n = 30) and HFpEF (n = 172) groups were quite different, which may have affected the results. In addition, unlike our study, that study did not include patients with HFmrEF. In another recent study, galectin-3 and sST2 levels were analyzed in patients with atrial fibrillation (AF), HFmrEF, and HFpEF.[22] In the subgroup analysis of that study, unlike our study, HFmrEF (n = 16) and HFpEF (n = 71) patients were compared, and no significant difference was found between the two groups in terms of either biomarker. This may again be due to the insufficient number of patients in the HFmrEF group. The fact that a sufficient number of patients representing all three HF subtypes were examined in our study makes our findings stronger compared to previous studies. Considering that galectin-3 and sST2 reflect myocardial strain and fibrosis, our findings suggest that fibrosis is more prevalent in the HFmrEF and HFrEF groups than in the HFpEF group, and that HFmrEF patients are more similar to those with HFrEF. In addition, the fact that fibrosis was proven to be more common in HFrEF and HFmrEF patients than in HFpEF patients in previous studies also supports our findings.[31-33] Since sST2 and galectin-3 also indicate the risk of future HF development, our results suggest that the HF subgroup (HFmrEF) may potentially be included within the HFrEF group in the future. However, since we have not followed these patients for a long time, studies with longer follow-up periods are needed in this regard.

Another important finding of our study was that sST2 and galectin-3 levels were positively correlated with BNP and negatively correlated with LVEF. Similar to our findings, previous studies have reported positive correlations between these biomarkers and BNP, and negative correlations with LVEF.[27,30] Several mechanisms may explain the relationship between these two biomarkers and BNP and LVEF. BNP is released in response to myocardial tension and is elevated in patients with HF.[34] Given that sST2 and galectin-3 reflect fibrosis, myocardial tension, and stress, our findings are consistent with the literature. In addition, left ventricular EF was negatively correlated with these parameters, indicating that they were more elevated in patients with lower EF and more extensive fibrosis. These findings also partially explain why sST2 and galectin-3 levels may be higher in patients with HFmrEF than in those with HFpEF.

In our study, we also evaluated the areas under the curve of sST2 and galectin-3 levels using ROC analysis to predict HFmrEF. Compared to the control group, sST2 levels tended to have a higher AUC than galectin-3 levels for predicting HFmrEF (P = 0.098). Although this finding suggests that sST2 may be a better biomarker, particularly for predicting HFmrEF, it should be noted that the power of our study for galectin-3 was relatively lower than that for sST2. Further prospective studies with larger patient populations are needed to better elucidate the relationship among HFmrEF, sST2, and galectin-3.

Limitations of the Study

The relatively small number of patients is one of the main limitations of the present study. Second, the lack of long-term follow-up and prognostic assessment is another limitation. Third, performing cardiac magnetic resonance imaging (MRI) to provide visual evidence of fibrosis would have been useful. However, we could not perform cardiac MRI because it is not part of routine clinical evaluation. Assessment with cardiac MRI and analysis of the relationship between fibrosis level and sST2 and galectin-3 would have increased the clinical value of our study. Fourth, the inclusion of echocardiographic strain parameters could have further contributed to our findings. Fifth, we performed a post hoc power analysis. Although the power of our study was quite high for sST2, it was slightly lower for galectin-3. Finally, because only outpatients were analyzed in our study, our results cannot be generalized to patients presenting with acute decompensated heart failure.

Conclusion

sST2 and galectin-3 levels may help guide EF-based HF classification in patients with HF. These biomarkers were significantly higher in patients with HFrEF and HFmrEF, suggesting potential diagnostic value in identifying these subgroups. However, no significant differences were observed between HFpEF patients and the control group. To better establish the diagnostic significance of these biomarkers, validation in a larger patient population is required.

Ethics Committee Approval: Ethics committee approval was obtained from Harran University Clinical Research Ethics Committee (Approval Number: HRÜ/22.16.12, Date: 22.08.2022).

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

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

Funding: Financial support was received from Harran University - Scientific Research Projects unit (Number: 22202).

Use of AI for Writing Assistance: No use of AI-asssisted technologies was declared by the authors.

Author Contributions: Concept – M.Ç., Z.T., R.D.; Design – M.Ç., Z.T., R.D., İ.H.A., A.B.Y.; Supervision – M.Ç., Z.T., R.D., H.F., K.T., İ.K.; Resource – M.Ç., H.F.; Materials – M.Ç., Z.T., R.D., İ.H.A., A.B.Y., H.F; Data Collection and/or Processing – M.Ç., Z.T.; Analysis and/or Interpretation – M.Ç., Z.T., A.B.Y., M.B.T., H.F; Literature Review – M.Ç., Z.T., R.D., İ.H.A., A.B.Y., M.B.T., H.F.; Writing – M.Ç., Z.T., R.D., İ.K.; Critical Review – M.Ç., Z.T., R.D., İ.H.A., A.B.Y., M.B.T., H.F., K.T., İ.K.

Peer-review: Externally peer-reviewed.

References

1. McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. Erratum in: *Eur Heart J*. 2021;42(48):4901.
2. Schocken DD, Benjamin EJ, Fonarow GC, et al.; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation*. 2008;117(19):2544-2565. [CrossRef]
3. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93(9):1137-1146. [CrossRef]
4. Raimond J, Zimonjic DB, Mignon C, et al. Mapping of the galectin-3 gene (LGALS3) to human chromosome 14 at region 14q21-22. *Mamm Genome*. 1997;8(9):706-707. [CrossRef]
5. Iwahana H, Yanagisawa K, Ito-Kosaka A, et al. Different promoter usage and multiple transcription initiation sites of the interleukin-1 receptor-related human ST2 gene in UT-7 and TM12 cells. *Eur J Biochem*. 1999;264(2):397-406. [CrossRef]
6. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*. 2005;23(5):479-490. [CrossRef]
7. McMurray JJ, Adamopoulos S, Anker SD, et al.; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787-1847. Erratum in: *Eur Heart J*. 2013;34(2):158.
8. Crnko S, Printezi MI, Jansen TPJ, et al. Prognostic biomarker soluble ST2 exhibits diurnal variation in chronic heart failure patients. *ESC Heart Fail*. 2020;7(3):1224-1233. [CrossRef]
9. Gül İ, Yücel O, Zararsız A, et al. Prognostic role of soluble suppression of tumorigenicity-2 on cardiovascular mortality in outpatients with heart failure. *Anatol J Cardiol*. 2017;18(3):200-205. [CrossRef]
10. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e161. [CrossRef]
11. Maisel AS, Di Somma S. Do we need another heart failure biomarker: focus on soluble suppression of tumorigenicity 2 (sST2). *Eur Heart J*. 2017;38(30):2325-2333. [CrossRef]
12. Zaborska B, Sygitowicz G, Smarż K, Pilichowska-Paszkiet E, Budaj A. Galectin-3 is related to right ventricular dysfunction in heart failure patients with reduced ejection fraction and may affect exercise capacity. *Sci Rep*. 2020;10(1):16682. [CrossRef]
13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314. [CrossRef]
14. Meijers WC, Bayes-Genis A, Mebazaa A, et al. Circulating heart failure biomarkers beyond natriuretic peptides: review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail*. 2021;23(10):1610-1632. [CrossRef]
15. Mueller T, Dieplinger B. Soluble ST2 and Galectin-3: What We Know and Don't Know Analytically. *EJIFCC*. 2016;27(3):224-237.
16. Ponikowski P, Voors AA, Anker SD, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200. Erratum in: *Eur Heart J*. 2018;39(10):860. [CrossRef]
17. Lakhani I, Leung KSK, Tse G, Lee APW. Novel Mechanisms in Heart Failure With Preserved, Midrange, and Reduced Ejection Fraction. *Front Physiol*. 2019;10:874. [CrossRef]
18. Gajewski P, Zymlinski R, Biegus J. The Critical Role of Comorbidities in Managing Heart Failure with Preserved Ejection Fraction (HFpEF). *ESC Heart Fail*. 2025;12(3):1541-1543. [CrossRef]
19. Bošnjak I, Selthofer-Relatić K, Včev A. Prognostic value of galectin-3 in patients with heart failure. *Dis Markers*. 2015;2015:690205. [CrossRef]
20. Villacorta H, Maisel AS. Soluble ST2 Testing: A Promising Biomarker in the Management of Heart Failure. *Arq Bras Cardiol*. 2016;106(2):145-152. [CrossRef]
21. Binas D, Daniel H, Richter A, et al. The prognostic value of sST2 and galectin-3 considering different aetiologies in non-ischaemic heart failure. *Open Heart*. 2018;5(1):e000750. [CrossRef]
22. Merino-Merino A, Gonzalez-Bernal J, Fernandez-Zoppino D, Saez-Maleta R, Perez-Rivera JA. The Role of Galectin-3 and ST2 in Cardiology: A Short Review. *Biomolecules*. 2021;11(8):1167. [CrossRef]
23. Öncel CR. Soluble suppression of tumorigenicity-2 for risk stratification in outpatients with heart failure. *Anatol J Cardiol*. 2018;19(3):228. [CrossRef]
24. Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol*. 2012;60(14):1249-1256. [CrossRef]
25. Manzano-Fernández S, Mueller T, Pascual-Figal D, Truong QA, Januzzi JL. Usefulness of soluble concentrations of interleukin family member ST2 as predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. *Am J Cardiol*. 2011;107(2):259-267. [CrossRef]
26. Bayes-Genis A, Zamora E, de Antonio M, et al. Soluble ST2 serum concentration and renal function in heart failure. *J Card Fail*. 2013;19(11):768-775. [CrossRef]
27. Najjar E, Faxén UL, Hage C, et al. ST2 in heart failure with preserved and reduced ejection fraction. *Scand Cardiovasc J*. 2019;53(1):21-27. [CrossRef]
28. Beltrami M, Ruocco G, Dastidar AG, et al. Additional value of Galectin-3 to BNP in acute heart failure patients with preserved ejection fraction. *Clin Chim Acta*. 2016;457:99-105. [CrossRef]
29. Rabkin SW, Tang JKK. The utility of growth differentiation factor-15, galectin-3, and sST2 as biomarkers for the diagnosis of heart failure with preserved ejection fraction and compared to heart failure with reduced ejection fraction: a systematic review. *Heart Fail Rev*. 2021;26(4):799-812. [CrossRef]
30. Cui Y, Qi X, Huang A, Li J, Hou W, Liu K. Differential and Predictive Value of Galectin-3 and Soluble Suppression of Tumorigenicity-2 (sST2) in Heart Failure with Preserved Ejection Fraction. *Med Sci Monit*. 2018;24:5139-5146. [CrossRef]
31. Hara A, Niwa M, Noguchi K, et al. Galectin-3 as a Next-Generation Biomarker for Detecting Early Stage of Various Diseases. *Biomolecules*. 2020;10(3):389. [CrossRef]
32. Tromp J, Khan MAF, Mentz RJ, et al. Biomarker Profiles of Acute Heart Failure Patients with a Mid-Range Ejection Fraction. *JACC Heart Fail*. 2017;5(7):507-517. [CrossRef]
33. Solomon SD, Rizkala AR, Lefkowitz MP, et al. Baseline Characteristics of Patients with Heart Failure and Preserved Ejection Fraction in the PARAGON-HF Trial. *Circ Heart Fail*. 2018;11(7):e004962.
34. Goetze JP, Bruneau BG, Ramos HR, Ogawa T, de Bold MK, de Bold AJ. Cardiac natriuretic peptides. *Nat Rev Cardiol*. 2020;17(11):698-717. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Association of QTc Dispersion with Mortality, Intensive Care Unit Admission, Intubation, and Hospital Stay Duration in Acute Methadone Poisoning

Akut Metadon Zehirlenmesinde QTc Dispersiyonunun Mortalite, Yoğun Bakım Ünitesi Kabulü, Entübasyon ve Hastanede Kalış Süresi ile İlişkisi

ABSTRACT

Objective: The objective of this study is to investigate the prognostic significance of QTc dispersion (QTcd) in patients with acute methadone poisoning and its association with critical clinical outcomes, including mortality, Intensive Care Unit (ICU) admission, intubation, and hospital stay duration.

Method: A retrospective cross-sectional analysis was performed using medical records from 311 individuals who presented with acute methadone toxicity to the Emergency Department of Loghman-Hakim Hospital Poison Center, Tehran, Iran between March 20, 2023 and June 1, 2023. Eligibility was based on a confirmed record of methadone ingestion supported by a positive urine drug screen. To calculate QTcd, the longest and shortest corrected QT (QTc) intervals recorded across the 12-lead electrocardiogram (ECG) were identified, and their difference was taken. The final study population included 100 patients, categorized into prolonged QTcd (QTcd > 60 ms, n = 50) and non-prolonged QTcd (QTcd ≤ 60 ms, n = 50) groups.

Results: This retrospective study included 100 consecutive patients with acute methadone poisoning. The mean QTcd was 64.26 ± 24.55 ms, significantly higher than in the normal population (P < 0.001). Comparison of the two groups revealed no meaningful variation in demographic factors, methadone intake, or time elapsed before Emergency Department (ED) admission (all P > 0.05). Pulse rate was notably higher among individuals with prolonged QTcd (P = 0.03), but there were no significant differences in other vital signs. Hospital stay duration, ICU admission (n = 8), need for intubation (n = 6), and mortality (n = 4) were comparable across both groups.

Conclusion: This study indicates that QTcd did not predict major clinical outcomes such as mortality, ICU admission, or intubation.

Keywords: Methadone, outcome, poisoning, prognosis, QT dispersion, QT interval, QTc dispersion

ÖZET

Amaç: Bu çalışmanın amacı, akut metadon zehirlenmesi olan hastalarda QTc dispersiyonunun (QTcd) prognostik önemini ve mortalite, Yoğun Bakım Ünitesi (YBÜ) kabulü, entübasyon ve hastanede kalış süresi gibi kritik klinik sonuçlarla ilişkisini araştırmaktır.

Yöntem: 20 Mart 2023 ile 1 Haziran 2023 tarihleri arasında Loghman-Hakim Hastanesi Poison Center, (Tehran, Iran) Acil Servisi'ne akut metadon toksisitesi ile başvuran 311 kişinin tıbbi kayıtları kullanılarak retrospektif, kesitsel bir analiz gerçekleştirildi. Dahil edilme kriteri, pozitif idrar uyuşturucu taraması ile doğrulanan metadon alımının kayıtlarda bulunmasıydı. QTcd hesaplamak için 12 derivasyonlu elektrokardiyogramda (EKG) kaydedilen en uzun ve en kısa düzeltilmiş QT (QTc) aralıkları belirlenerek aralarındaki fark alındı. Nihai çalışma popülasyonu, QTcd uzamış (QTcd > 60 ms, n = 50) ve QTcd uzamamış (QTcd ≤ 60 ms, n = 50) olarak sınıflandırılan toplam 100 hastadan oluştu.

Bulgular: Bu retrospektif çalışma, akut metadon zehirlenmesi olan ardışık 100 hastayı içermektedir. Ortalama QTcd 64,26 ± 24,55 ms olup normal popülasyona kıyasla anlamlı derecede yüksekti (P < 0.001). İki grup karşılaştırıldığında demografik faktörler, metadon alımı veya acil servise başvuruya kadar geçen süre açısından anlamlı farklılık görülmedi (tüm P > 0.05). Nabız hızı, QTcd uzamış hastalarda belirgin şekilde daha yüksekti (P = 0.03), ancak diğer yaşamsal bulgularda anlamlı fark bulunmadı. Hastanede kalış süresi, YBÜ'ye kabul (n = 8), entübasyon gereksinimi (n = 6) ve mortalite (n = 4) her iki grupta da benzerdi.

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

Amirreza Taherkhani[1]
Houra Yeganegi[2]
Arian Tavasol[3]
Sayed Masoud Hosseini[4]
Maryam Taherkhani[1]

[1]*Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tahran, Iran*
[2]*Clinical Research Development Center of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tahran, Iran*
[3]*School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4]*Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tahran, Iran*

Corresponding author:
Maryam Taherkhani
✉ dr_taherkhani2004@yahoo.com

Received: June 12, 2025
Accepted: November 14, 2025

Cite this article as: Taherkhani A, Yeganegi H, Tavasol A, Hosseini SM, Taherkhani M. Association of QTc Dispersion with Mortality, Intensive Care Unit Admission, Intubation, and Hospital Stay Duration in Acute Methadone Poisoning. *Turk Kardiyol Dern Ars.* 2026;54(3):261–267.

DOI: 10.5543/tkda.2025.69048

Sonuç: Bu çalışma, QTcd'nin mortalite, YBÜ'ye kabul veya entübasyon gibi önemli klinik sonuçları öngörmediğini göstermektedir.

Anahtar Kelimeler: Metadon, sonuç, zehirlenme, prognoz, QT dispersiyonu, QT aralığı, QTc dispersiyonu

Methadone, a synthetic opioid with an extended duration of action, is commonly prescribed for managing chronic pain and assisting in the treatment of opioid addiction.[1] Despite its therapeutic benefits, methadone may contribute to considerable cardiac disturbances, particularly corrected QT interval (QTc) prolongation, predisposing patients to torsades de pointes (TdP), a fatal arrhythmia.[2,3] Acute methadone overdose, whether intentional or accidental, is a significant public health concern in Iran due to the widespread availability of methadone through methadone maintenance therapy (MMT) clinics. The high prevalence of opioid addiction has led to increased access to methadone, contributing to the risk of overdose.[2,4] While QTc prolongation has been extensively studied in opioid maintenance therapy, the role of QTc dispersion (QTcd) as a prognostic indicator in cases of acute methadone overdose remains less explored.[5,6]

QTcd quantifies how unevenly the ventricular muscle returns to its resting state after activation.[1,7] While the normal range of QTcd remains controversial across studies, most reports suggest a range between 30 and 60 milliseconds (ms).[1,8,9] Increased QTcd has been linked to heightened arrhythmic risk and adverse cardiac events in various clinical conditions, including cardiotoxic drug poisoning.[1,5,8,9] Although numerous studies have demonstrated QTcd prolongation in patients undergoing long-term methadone therapy, data on the impact of acute methadone overdose on QTcd remain limited.[1,6,10]

Excessive opioid ingestion can lead to severe cardiac and systemic complications. Methadone toxicity often necessitates admission to the intensive care unit (ICU), respiratory support via mechanical ventilation, and extended hospitalization.[3,11] However, the relationship between QTcd and critical outcomes such as mortality, ICU admission, intubation, and length of hospital stay remains unclear. Understanding this association could aid in identifying high-risk individuals and support appropriate clinical actions.

In this retrospective cross-sectional study, we aim to investigate the prognostic significance of QTcd in patients with acute methadone poisoning. By examining its association with mortality, ICU admission, intubation, and hospital stay duration, this study aims to assess the potential of QTcd as an independent prognostic marker for unfavorable clinical events in patients with acute methadone toxicity.

Materials and Methods

Investigative Approach and Patient Enrollment

This study was conducted using a retrospective cross-sectional design. We reviewed the medical records of patients presenting with acute methadone overdose to the Emergency Department of Loghman-Hakim Hospital Poison Center, Tehran, Iran, one of the busiest poison control centers in the world, between March 20, 2023 and June 1, 2023. Patients were enrolled if they had a history of methadone consumption, either self-reported in conscious individuals or provided by relatives for unconscious patients. Acute methadone overdose was defined as methadone ingestion in non-users or consumption exceeding the usual dose in regular users, leading to a clinical condition that prompted them or their companions to seek medical assistance. Patients who tested negative for methadone in urine analysis or lacked a documented urine toxicology screen were excluded from the study. Other exclusion criteria included age less than 15 or greater than 65 years, incomplete medical records, co-ingestion of medications or substances known to prolong the QTc interval or alter clinical outcomes, electrolyte imbalances (hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia), and preexisting comorbidities. This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent for the use of patient data was obtained from all patients upon hospital admission. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval Number: IR.SBMU.RETECH.REC.1404.092, Date: 27.04.2025).

Sample Size Calculation

A priori sample size estimation was performed using the following standard formula for comparison of two independent means:

$$N_{\text{per group}} = 2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^{2/} \Delta^2$$

where $Z1-\alpha/2$ represents the two-sided significance level (α), $Z1-\beta$ corresponds to the desired power ($1-\beta$), σ is the standard deviation of QTc dispersion (in ms), and Δ is the minimal clinically important difference between groups (in ms). Substituting these values into the formula yielded an estimated sample size of 63 patients per group (a total of 126 participants). However, due to institutional limitations on data access, electrocardiographic data were available only for 100 eligible patients.

ABBREVIATIONS

ACVE	Adverse cardiovascular events
AUC	Area under the curve
ECG	Electrocardiogram
ED	Emergency Department
hERG	Human ether-a-go-go-related gene
ICU	Intensive Care Unit
IQR	Interquartile range
MMT	Methadone maintenance therapy
QTc	Corrected QT
QTcd	QTc dispersion
ROC	Receiver operating characteristic
TdP	Torsades de pointes
TPe	Tpeak–Tend

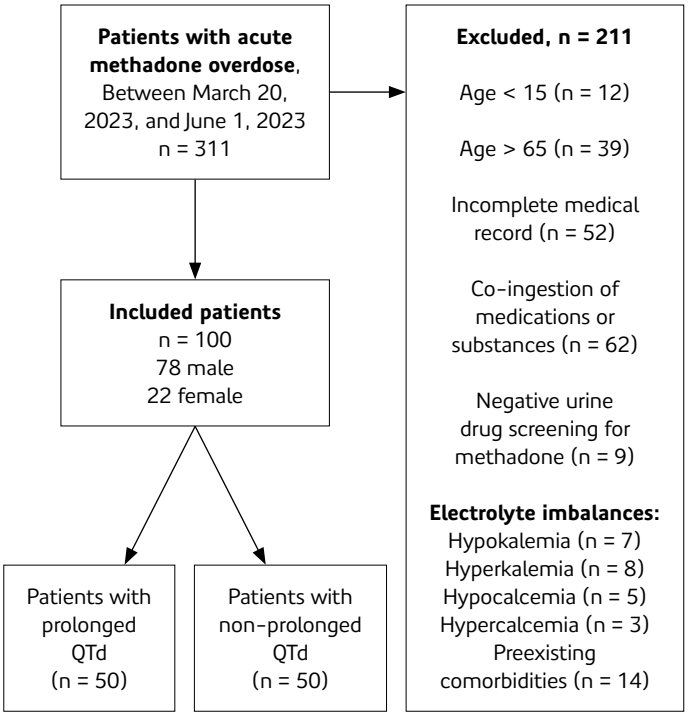


Figure 1. Flowchart of patient selection and inclusion process.

Data Collection

Demographic variables such as age, sex, history of substance use, ingested methadone dose, and the interval between methadone intake and emergency department presentation were collected from patient records by a primary researcher and independently verified by a second researcher. Additionally, vital signs on Emergency Department (ED) admission and primary outcomes were documented, including tracheal intubation, ICU admission, hospitalization duration, and in-hospital mortality.

Electrocardiogram (ECG) Analysis

A researcher, blinded to patient outcomes and clinical characteristics, analyzed the initial ECGs performed in the ED. An attending cardiologist subsequently rechecked each ECG. QT intervals were assessed in all 12 leads from the start of the QRS complex to the termination of the T wave. In the presence of a U wave, the QT measurement was taken to the lowest point between the T and U waves. To account for heart rate variability, the QT interval was adjusted using Bazett's equation, where QTc is obtained by dividing the observed QT duration by the square root of the RR interval ($QTc = QT / \sqrt{RR}$). QTcd was assessed by subtracting the minimum from the maximum QTc interval across all 12 ECG leads, with prolongation defined as a QTcd exceeding 60 ms.[1,12] Patients were then categorized into prolonged and non-prolonged QTcd groups, and all extracted data were compared between the two groups.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software, version 27 (IBM Corp., Chicago, IL, USA) was used for statistical analysis. Continuous variables with a normal distribution (determined by Kolmogorov-Smirnov and Shapiro-Wilk tests) are presented as mean ± SD, and those with a non-normal distribution are presented as median and interquartile range (IQR). Comparisons between groups were conducted using the independent t-test for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. The Chi-square test or Fisher's exact test was applied to analyze categorical data. Statistical significance was defined as a P-value < 0.05. Receiver operating characteristic (ROC) curves were constructed to evaluate the ability of QTc dispersion to predict ICU admission, intubation, and in-hospital mortality. The area under the curve (AUC), sensitivity, specificity, and optimal cutoff values were determined. To assess the predictive value of QTcd for major clinical outcomes, we categorized patients based on the occurrence or non-occurrence of each outcome, including death, intubation, and ICU admission. For each outcome, QTcd and other covariates were included in the univariate analysis. In cases where QTcd yielded a p-value under 0.2, QTcd and all other covariates meeting the same threshold underwent multivariate logistic regression to identify those with independent predictive significance. Given the small number of outcome events, Firth's penalized logistic regression was used to reduce small-sample bias.

Results

A total of 311 patients presented to Loghman-Hakim Hospital Poisoning Center with acute methadone overdose between March 20, 2023 and June 1, 2023. Of these, 211 were excluded based on the defined exclusion criteria. The final study population included 100 patients (Figure 1), categorized into two groups: those with QTcd > 60 ms (prolonged QTcd group, n = 50) and those with QTcd ≤ 60 ms (non-prolonged QTcd group, n = 50). The cohort had a mean age of 34.83 ± 14.16 years, and 78% of participants were male. The baseline characteristics of the patients are presented in Table 1.

The mean QTcd was 64.26 ± 24.55 ms, which was significantly higher than the mean in the normal population (33.4 ± 20.3 ms, P < 0.001). There was no significant difference in age (P = 0.09) or gender distribution (P = 0.81) between the prolonged and non-prolonged QTcd groups. No patients developed TdP during hospitalization. The mean time from methadone consumption to ED admission was 8.45 ± 8.34 hours, and the mean methadone dose was 240.21 ± 296.19 mg, with no significant intergroup differences (P = 0.72 and P = 0.11, respectively).

On admission to the ED, systolic and diastolic blood pressures, respiratory rates, and oxygen saturation levels were similar between the two groups, with no significant differences detected (all P > 0.05). However, the prolonged QTcd group had a significantly higher pulse rate than the non-prolonged QTcd group (P = 0.03). Hospitalization duration ranged from 1 to 48 days, without significant differences between groups (P = 0.83). There were four deaths, six patients who were intubated during the hospitalization period, and eight patients who required ICU admission. These outcomes did not differ significantly between the two groups (Table 1).

In the univariate analysis, QTcd had a p-value < 0.2 for intubation and ICU admission. Therefore, QTcd and all other covariates with a p-value < 0.2 were included in the multivariate analysis to identify independent predictors of these outcomes. However, the multivariate analysis revealed no significant associations between the covariates and intubation or ICU admission (all P >

Table 1. Baseline characteristics, vital signs, electrocardiogram parameters, and clinical outcomes of the patients

Variables	Prolonged QTcd group (n = 50)	Non-prolonged QTcd group (n = 50)	*P*
Age, mean (SD) (years)	37.38 (14.78)	32.28 (13.18)	0.09
Gender, n (%)			0.81
Male	40 (80)	38 (76)	
Female	10 (20)	12 (24)	
Addiction history, n (%)			0.37
Yes	26 (52)	19 (38)	
No	12 (24)	16 (32)	
Unknown	12 (24)	15 (30)	
Methadone dose, mean (SD) (mg)	245.13 (204.89)	234.55 (378.56)	0.11
Time from methadone consumption to ED, mean (SD) (hours)	7.90 (6.82)	9.03 (9.74)	0.72
Vital signs at admission			
Systolic blood pressure, median (IQR) (mmHg)	115 (24)	110 (20)	0.79
Diastolic blood pressure, median (IQR) (mmHg)	75 (10)	70 (19)	0.87
Pulse rate, median (IQR) (beats/min)	**90 (17)**	**85 (18)**	**0.03**
Respiratory rate, median (IQR) (breaths/min)	16 (4)	16 (4)	0.81
O_2 saturation, median (IQR) (%)	96 (4)	96 (7)	0.70
ECG parameters			
QTc interval minimum, mean (SD) (ms)	371.32 (27.84)	376.21 (30.35)	0.50
QTc interval maximum, mean (SD) (ms)	**454.08 (31.18)**	**421.99 (32.32)**	**<0.001**
QTcd, mean (SD) (ms)	**82.75 (20.61)**	**45.78 (9.77)**	**<0.001**
Clinical outcomes			
Patients intubated, n (%)	3 (6)	5 (10)	0.71
Patients transferred to ICU, n (%)	1 (2)	5 (10)	0.20
Hospitalization period, median (IQR) (days)	1 (1)	1 (1)	0.83
Death, n (%)	3 (6)	1 (2)	0.61

ECG, Electrocardiogram; IQR, Interquartile range; mg, Milligram; min, Minutes; mmHg, Millimeter Hg; ms, Milliseconds; n, Number; ED, Emergency department; ICU, Intensive care unit; SD, Standard deviation.

Table 2. Association between intubation and Intensive Care Unit admission with clinical features

Dependent variables	Independent variables	OR (95% CI)	*P*
Intubation	Methadone dose	1.00 (0.99–1.00)	0.97
	O_2 saturation	0.97 (0.70–1.33)	0.85
	Hospitalization period	0.56 (0.18–1.73)	0.31
	QTcd	0.95 (0.89–1.01)	0.14
ICU admission	O_2 saturation	1.00 (0.99–1.00)	0.98
	Hospitalization period	1.00 (0.99–1.00)	0.98
	QTcd	1.00 (0.99–1.00)	0.97

ICU, Intensive care unit; CI, Confidence interval; OR, Odds ratio.

0.05). The odds ratios (OR) and 95% confidence intervals (CI) for each variable are presented in Table 2.

To minimize potential bias related to the small number of adverse outcomes, Firth's penalized logistic regression was applied. Separate models were constructed for in-hospital mortality, need for intubation, and ICU admission, including methadone dose, oxygen saturation on admission, hospitalization period, and QTcd as covariates. None of the variables showed a statistically significant independent association with any of the three outcomes after adjustment (Table 3).

ROC curve analysis demonstrated that QTc dispersion had good discriminative ability for ICU admission (AUC = 0.809; optimal cutoff = 43.6 ms; sensitivity = 85.1%; specificity = 66.7%) but lower performance for intubation (AUC = 0.651) and mortality (AUC = 0.573). The derived cutoff values and diagnostic indices are summarized in Table 4 and Figure 2.

Discussion

This study sought to assess the prognostic significance of QTcd in acute methadone toxicity by investigating its association with major clinical outcomes, including mortality, ICU admission, intubation, and length of hospital stay. Our findings indicate that although patients with acute methadone poisoning had significantly increased QTcd compared to the normal population, there was no significant correlation between QTcd and adverse clinical outcomes. Although QTc dispersion was our primary parameter, we acknowledge that additional electrocardiographic

Table 3. Firth's penalized logistic regression results for predictors of in-hospital mortality, intubation, and Intensive ICU admission

Dependent variables	Independent variables	OR (95% CI)	*P*
Intubation	Methadone dose	0.99 (0.99–1.00)	0.35
	O_2 saturation	1.08 (0.87–1.35)	0.44
	Hospitalization period	0.90 (0.33–2.49)	0.85
	QTcd	0.98 (0.87–1.10)	0.75
ICU admission	Methadone dose	0.99 (0.99–1.00)	0.35
	O_2 saturation	1.08 (0.87–1.35)	0.44
	Hospitalization period	0.90 (0.33–2.49)	0.85
	QTcd	0.98 (0.87–1.10)	0.75
Mortality	Methadone dose	0.99 (0.99–1.00)	0.35
	O_2 saturation	1.08 (0.87–1.35)	0.44
	Hospitalization period	0.90 (0.33–2.49)	0.85
	QTcd	0.98 (0.87–1.10)	0.75

ICU, Intensive care unit; QTcd, QTc dispersion; OR, Odds ratios; CI, Confidence intervals.

Table 4. ROC analysis for corrected QTcd predicting clinical outcomes

Outcomes	AUC	Cut-off (ms)	Sensitivity (%)	Specificity (%)
Intubation	0.651	43.6	84.8	50.0
ICU admission	0.809	43.6	85.1	66.7
Mortality	0.573	62.6	75.0	54.2

ROC, Receiver operating characteristic; QTcd, QT interval dispersion; ICU, Intensive care unit; AUC, Area under the curve.

indices such as Tpeak–Tend (TPe) could provide complementary insights into ventricular repolarization heterogeneity.[13] This study adds to current knowledge on methadone-induced cardiac repolarization changes and their prognostic implications in toxicological emergencies.

Previous studies have consistently shown an association between QT interval prolongation and methadone use. While Krantz et al.[1] found that methadone maintenance therapy is significantly associated with QTc interval prolongation, a study in Japan[13] reported that QTc increased insignificantly in cancer patients receiving small to modest doses of methadone. However, their study focused on chronic methadone users rather than acute poisoning cases. In contrast, our study specifically examined acute methadone overdose. Manini et al.[14] demonstrated that a prolonged QTc in poisoned patients is a predictor of adverse cardiovascular events, including myocardial injury, dysrhythmias, and cardiac arrest. Farsi et al.[3] investigated the association between prolonged QTc and adverse outcomes of methadone overdose, such as death, endotracheal intubation, and respiratory arrest, identifying QTc as a strong predictor of intubation and respiratory arrest. In our study, we examined the association between QTcd and adverse outcomes in cases of acute methadone overdose.

Both increased QTcd and QTc intervals have been reported in association with methadone use.[1,5] QTcd prolongation has been observed in both acute and chronic methadone exposure.[1,5] Dorooshi et al.[15] found that QTcd measured at admission did not differ significantly between patients based on long-term methadone use; however, it increased significantly in chronic users 24 hours after hospitalization. QTcd is a non-invasive indicator of myocardial repolarization heterogeneity and can predict the risk of arrhythmia.[8] In our study, the mean QTc dispersion among methadone-poisoned patients (64.26 ± 24.55 ms) was significantly greater than that reported in the general population (33.4 ± 20.3 ms),[16,17] supporting the notion that methadone significantly affects ventricular repolarization.

Methadone-induced QT prolongation and abnormal ventricular repolarization primarily result from its inhibitory effects on the human ether-a-go-go-related gene (hERG) potassium channels, which are crucial for the rapid phase of the delayed rectifier potassium current (IKr). By blocking these channels, methadone delays phase 3 of the cardiac action potential, resulting in delayed repolarization and a heightened risk of arrhythmias such as TdP.[18,19]

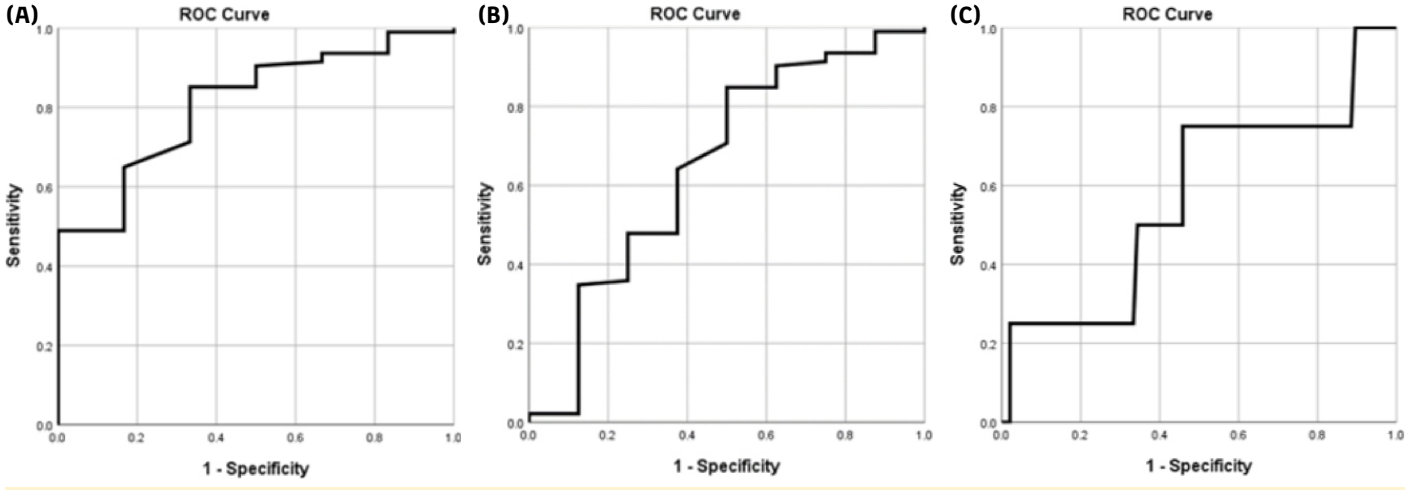


Figure 2. Receiver operating characteristic (ROC) curve for corrected QT interval dispersion (QTcd) to predict intubation (A), Intensive Care Unit (ICU) admission (B), and death (C).

Methadone's effect on cardiac repolarization has been well established in chronic opioid users, emphasizing the arrhythmogenic risks associated with prolonged QT intervals.[20,21] However, in our study of acute methadone poisoning, no cases of TdP were observed despite significant QTcd prolongation. This finding aligns with Soroosh et al.,[2] who observed no cases of TdP in acute methadone overdose, potentially due to the transient nature of repolarization abnormalities in acute settings compared to chronic exposure.

Risk assessment in poisoned patients is both challenging and essential for reducing mortality while optimizing hospital resource allocation.[5,14] The prognostic role of QTcd in methadone poisoning has been investigated alongside other cardiotoxic agents, such as tricyclic antidepressants, antipsychotics, benzodiazepines, and various toxins.[5,14] However, our study is novel in its specific focus on methadone. In these toxicities, increased QTcd has been associated with heightened arrhythmic risk and poor clinical outcomes. Consistent with our findings, Hassanian-Moghaddam et al.[5] demonstrated that QTcd does not appear to be a reliable predictor of death in cases of acute cardiotoxic poisoning. However, they identified an association between QTcd prolongation and the subsequent development of complications, including refractory hypotension and right bundle branch block. Manini et al.[14] showed that QTcd was significantly higher in poisoned patients who experienced at least one adverse cardiovascular event compared to the control group. Nevertheless, QTcd was not identified as an independent predictor of such events. Despite these associations, QTcd remains an inconsistent predictor of adverse outcomes across different toxicological settings. Our findings reinforce this uncertainty, as QTcd in methadone-poisoned patients did not correlate with mortality or ICU admission. Further research is needed to establish standardized QTcd thresholds and validate its utility as a prognostic marker in acute methadone poisoning.

Recent evidence has expanded the understanding of electrocardiographic predictors in acute cardiotoxicities. Lashin et al.[22] developed a six-predictor nomogram to estimate the risk of adverse cardiovascular events (ACVE) among patients poisoned with various cardiotoxic agents. Their model incorporated three ECG parameters, including ST-segment changes, prolonged QTc interval, and widened QRS complex, alongside clinical and biochemical variables, achieving 89.2% predictive accuracy for ACVE. Interestingly, despite evaluating several ECG indices, they reported no significant association between ACVE and other ECG abnormalities, such as QT dispersion. Similarly, El-Sarnagawy et al.[23] found that both QTd and QTdc failed to correlate with in-hospital mortality, ICU admission, or ACVE components. Their ROC analysis confirmed the superiority of QTc over QTd for outcome prediction, although the discriminatory power remained limited. Consistent with these findings, our results revealed no independent association between QTc dispersion and major clinical outcomes in acute methadone toxicity. Taken together, these studies suggest that dispersion-based indices may have limited prognostic reliability in acute poisoning, whereas QTc-related measures, especially when combined with clinical and biochemical parameters, may better reflect true cardiac risk.

In our study, a significantly elevated heart rate was observed in the prolonged QTcd group relative to the non-prolonged group, consistent with existing literature on the interplay between heart rate and ventricular repolarization variability.[16] However, as numerous studies have indicated, the exact relationship between heart rate and QTcd remains unresolved.[24,25] While heart rate correction formulas such as Bazett's attempt to standardize QT interval measurements, they may introduce inconsistencies when applied to QTc dispersion.[26,27] In our study, the observed increase in heart rate among patients with prolonged QTcd may reflect underlying autonomic dysregulation or compensatory mechanisms related to methadone toxicity rather than a direct causal relationship between heart rate and QTcd. Future investigations should further explore the role of autonomic function and its impact on QTcd to enhance the clinical utility of this parameter in risk stratification.

In addition, we performed ROC analyses to evaluate the discriminative ability of QTc dispersion for predicting major in-hospital outcomes. The ROC curves demonstrated good discriminative performance for ICU admission (AUC = 0.809), but only modest accuracy for intubation (AUC = 0.651) and poor accuracy for mortality (AUC = 0.573). These findings suggest that, while QTc dispersion may reflect subclinical myocardial repolarization abnormalities that could identify patients at higher risk for intensive care needs, it lacks sufficient discriminatory power to serve as a stand-alone prognostic tool for severe outcomes such as death.

Limitations

It is important to recognize the limitations of this study, particularly the potential for selection bias due to its retrospective design. Since the results are based on hospital-registered files, the accuracy and reliability of the collected data may require careful consideration and review. Additionally, while we used a strict QTcd cutoff (> 60 ms) to define prolongation, other studies have used varying thresholds, which could contribute to differences in reported associations with clinical outcomes. Another limitation was the absence of prior ECGs, which prevented the assessment of QTcd changes from baseline. Furthermore, only baseline ECGs obtained at admission were analyzed, as serial recordings were not consistently available across cases. Another limitation of our study was the unavailability of TPe interval measurements, which have been proposed as additional markers of repolarization heterogeneity. Unfortunately, TPe data were not consistently available in our dataset and therefore could not be analyzed. Some potential prognostic variables, including electrolyte imbalances and concurrent QT-prolonging medications, were unavailable for all patients and therefore not included in regression models. Larger-scale prospective studies are required to clarify the prognostic value of QTcd in methadone overdose.

Conclusion

Our study demonstrates that acute methadone overdose is associated with significantly increased QTcd. However, QTcd did not predict major clinical outcomes such as mortality, ICU admission, or intubation. These findings suggest that although methadone toxicity affects ventricular repolarization, the prognostic utility of QTcd in acute methadone poisoning remains uncertain. Further research is needed to elucidate the clinical relevance of QTcd and its role in risk stratification for patients with acute opioid toxicity.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval Number: IR.SBMU.RETECH.REC.1404.092, Date: 27.04.2025).

Informed Consent: Written informed consent for the use of patient data was obtained from all patients upon hospital admission.

Conflict of Interest: The authors declare no conflicts of interest related to this work.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Use of AI for Writing Assistance: No artificial intelligence (AI)–assisted technologies were used for data analysis, figure generation, or the scientific content of this manuscript. Language and grammar were reviewed using AI-based tools, including Grammarly and ChatGPT, solely for improving readability and clarity.

Author Contributions: Concept – H.Y., M.T.; Design – A. Taherkhani; Supervision – H.Y., M.T.; Data Collection and/or Processing – A. Taherkhani, H.Y.; Analysis and/or Interpretation – A.Taherkhani, A. Tavasol; Literature Review – A. Taherkhani, H.Y.; Writing – A. Taherkhani, S.M.H.; Critical Review – A. Taherkhani, H.Y., A. Tavasol, S.M.H., M.T.

Acknowledgments: The authors thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, for their support and assistance. Special thanks to Dr. L. Gachkar for expert guidance in statistical analysis.

Peer-review: Externally peer-reviewed.

References

1. Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-interval dispersion. *Pharmacotherapy*. 2005;25(11):1523-1529. [CrossRef]
2. Soroosh D, Neamatshahi M, Zarmehri B, Nakhaee S, Mehrpour O. Drug-induced prolonged corrected QT interval in patients with methadone and opium overdose. *Subst Abuse Treat Prev Policy*. 2019;14(1):8. [CrossRef]
3. Farsi D, Mirafzal A, Hassanian-Moghaddam H, Azizi Z, Jamshidnejad N, Zehtabchi S. The correlation between prolonged corrected QT interval with the frequency of respiratory arrest, endotracheal intubation, and mortality in acute methadone overdose. *Cardiovasc Toxicol*. 2014;14(4):358-367. [CrossRef]
4. Taheri F, Yaraghi A, Sabzghabaee AM, et al. Methadone toxicity in a poisoning referral center. *J Res Pharm Pract*. 2013;2(3):130-134. [CrossRef]
5. Hassanian-Moghaddam H, Amiri H, et al. QT dispersion and prognostication of the outcome in acute cardiotoxicities: A comparison with SAPS II and APACHE II scoring systems. *Cardiovasc Toxicol*. 2014;14(2):129-133. [CrossRef]
6. Dadpour B, Hatami Z, Liaghat A, Eshraghi A, Najari F, Najari D. Assessment of QT dispersion in electrocardiogram of patients with acute poisoning of methadone. *TUMJ*. 2019;77(7):453-457.
7. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J*. 1990;63(6):342-344. [CrossRef]
8. Somberg JC, Molnar J. Usefulness of QT dispersion as an electrocardiographically derived index. *Am J Cardiol*. 2002;89(3):291-294. [CrossRef]
9. Statters DJ, Malik M, Ward DE, Camm AJ. QT dispersion: problems of methodology and clinical significance. *J Cardiovasc Electrophysiol*. 1994;5(8):672-685. [CrossRef]
10. Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O. A systematic review of the cardiotoxicity of methadone. *EXCLI J*. 2015;14:577-600.
11. Hassanian-Moghaddam H, Soltaninejad K, Shadnia S, Kabir A, Movahedi M, Mirafzal A. Risk Factors for Mortality and Endotracheal Intubation after Methadone Intoxication. *Basic Clin Pharmacol Toxicol*. 2016;118(3):231-237. [CrossRef]
12. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957-2963. Erratum in: *JAMA*. 1994;271(17):1321. [CrossRef]
13. Yamanaka E, Chino S, Takasusuki T, Hamaguchi S, Yamaguchi S. Effect of Methadone on Cardiac Repolarization in Japanese Cancer Patients: A Longitudinal Study. *Cardiol Ther*. 2020;9(1):119-126. [CrossRef]
14. Manini AF, Nelson LS, Skolnick AH, Slater W, Hoffman RS. Electrocardiographic predictors of adverse cardiovascular events in suspected poisoning. *J Med Toxicol*. 2010;6(2):106-115. [CrossRef]
15. Dorooshi G, Shirmohammadi M, Gheshlaghi F, Otroshi A, Zoofaghari S, Eizadi-Mood N. Cardiovascular Complications Following Acute Methadone Poisoning in Patients with and Without a History of Long-term Methadone Use. *J Res Pharm Pract*. 2024;13(2):58-64. [CrossRef]
16. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol*. 2000;36(6):1749-1766. [CrossRef]
17. Atescelik M, Bozdemir MN, Yildiz M, et al. QT dispersion in carbon monoxide poisoning. *Eur Rev Med Pharmacol Sci*. 2012;16 Suppl 1:25-29.
18. Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. *Pain*. 2003;105(3):499-506. [CrossRef]
19. Antzelevitch C, Shimizu W, Yan GX, Sicouri S. Cellular basis for QT dispersion. *J Electrocardiol*. 1998;30 Suppl:168-175. [CrossRef]
20. Price L, Manuel J, Kurz D, Delate T. Methadone and Cardiac Adverse Outcomes: A Retrospective Study of Patients in a Managed Care Organization (S750). *J Pain Symptom Manage*. 2013;45(2):448. [CrossRef]
21. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage*. 2005;29(4):385-391. [CrossRef]
22. Lashin HI, Elgazzar FM, El Sharkawy SI, Elsawaf SM, Sobh ZK. Development of a risk-prediction nomogram for in-hospital adverse cardiovascular events in acute cardiotoxic agents poisoning. *Toxicol Rep*. 2024;13:101826. [CrossRef]
23. El-Sarnagawy GN, Shaban AE, Lashin HI. Validation of Corrected and Dispersed QT as Predictors of Adverse Outcomes in Acute Cardiotoxicities. *Cardiovasc Toxicol*. 2022;22(1):1-13. [CrossRef]
24. Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JE, Malik M. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. *Pacing Clin Electrophysiol*. 1999;22(9):1397-1401. [CrossRef]
25. Zabel M, Woosley RL, Franz MR. Is dispersion of ventricular repolarization rate dependent? *Pacing Clin Electrophysiol*. 1997;20(10 Pt 1):2405-2411. [CrossRef]
26. Han J, Millet D, Chizzonitti B, Moe GK. Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. *Am Heart J*. 1966;71(4):481-487. [CrossRef]
27. Morgan JM, Cunningham D, Rowland E. Dispersion of monophasic action potential duration: demonstrable in humans after premature ventricular extrastimulation but not in steady state. *J Am Coll Cardiol*. 1992;19(6):1244-1253. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Artificial Intelligence and Guideline-Augmented Prompting in Assessing the Need for Preoperative Cardiology Consultation

Preoperatif Kardiyoloji Konsültasyonu Gerekliliğinin Değerlendirilmesinde Yapay Zeka ve Kılavuz Destekli Komut Yönlendirmesi

ABSTRACT

Objective: With the growing elderly population worldwide, the number of annual surgical procedures has risen substantially, leading to an increase in the demand for preoperative cardiology consultations. In parallel, recent years have witnessed remarkable innovations in cardiology driven by advances in artificial intelligence (AI) and machine learning (ML). In this study, we aimed to evaluate the performance of three widely used AI models: ChatGPT-5, Deepseek-V3, and Gemini 2.0 Pro, in assessing the necessity of cardiology consultation in preoperative patients and to explore the potential contribution of guideline-augmented prompting in this context.

Method: A council consisting of seven cardiologists and seven anesthesiologists was formed. Each physician evaluated 20 preoperative patient scenarios and provided recommendations on whether a separate cardiology consultation was necessary. For each case, the majority decision of the council was accepted as the reference standard. The same scenarios were presented to the three AI models, and their responses were recorded. Subsequently, the AI models with the highest concordance were integrated into the decision framework using guideline-augmented prompting, and the cases were re-evaluated.

Results: Although there was no statistically significant difference, ChatGPT-5 and Gemini 2.0 Pro showed higher concordance than Deepseek-V3 in preoperative consultation decisions (κ = 0.706 and κ = 0.681, respectively; 85% accuracy). Following the integration of guidelines into ChatGPT-5 and Gemini 2.0 Pro, the models were re-evaluated and demonstrated improved performance (κ =0.898, 95% accuracy).

Conclusion: ChatGPT-5, Deepseek-V3, and Gemini 2.0 Pro demonstrated effectiveness in assessing the necessity of cardiology consultation in preoperatively evaluated patients. Moreover, the integration of guideline-augmented prompting was shown to improve the accuracy and reliability of AI model performance.

Keywords: Artificial intelligence, ChatGPT, machine learning, preoperative consultation

ÖZET

Amaç: Yaşlı nüfusun artmasıyla birlikte, tüm dünyada yıllık cerrahi işlemlerin sayısı da önemli ölçüde artmıştır. Bu durum preoperatif kardiyoloji konsültasyonlarının artışına neden olmuştur. Buna paralel olarak, son yıllarda yapay zeka (YZ) ve makine öğrenimi alanındaki gelişmelerin etkisiyle kardiyoloji alanında önemli yenilikler yaşanmıştır. Bu çalışmada, yaygın olarak kullanılan YZ modellerinden ChatGPT-5, Deepseek-V3 ve Gemini 2.0 Pro'nun preoperatif hastalarda kardiyoloji konsültasyonunun gerekliliğini değerlendirmedeki performansını değerlendirmeyi ve bu bağlamda kılavuz destekli komut yönlendirmesinin potansiyel katkısını araştırmayı amaçladık.

Yöntem: Yedi kardiyolog ve yedi anestezi uzmanından oluşan bir konsey oluşturuldu. Her hekim, 20 preoperatif hasta senaryosunu değerlendirdi ve kardiyoloji konsültasyonunun gerekli olup olmadığına dair önerilerde bulundu. Her vaka için konseyin çoğunluk kararı referans standart olarak kabul edildi. Aynı senaryolar üç YZ modeline sunuldu ve yanıtları kaydedildi. Ardından, en yüksek uyum gösteren YZ modellerine kılavuz destekli komut yönlendirmesi kullanılarak güncel kılavuzlar entegre edildi ve vakalar yeniden değerlendirildi.

Bulgular: İstatistiksel olarak anlamlı bir fark olmamasına rağmen, ChatGPT-5 ve Gemini 2.0 Pro, ameliyat öncesi konsültasyon kararında Deepseek-V3'ten daha yüksek uyum gösterdi (κ = 0,706, κ = 0,681; %85 doğruluk). Kılavuzların ChatGPT-5 ve Gemini 2.0 Pro'ya entegre edilmesinin ardından modeller yeniden değerlendirildi ve performanslarında iyileşme izlendi (κ = 0,898, %95 doğruluk).

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

Mehmet Uğur Çalışkan[1]
Ceren Yağmur Doğru Yılmaz[2]
Halenur Sarıbaş[3]
Elmas Kaplan[4]
Ceren Özdemir Al[5]
Ertan Andaç Al[5]

[1]*Department of Cardiology, Kızılcahamam State Hospital, Ankara, Türkiye*
[2]*Department of Cardiology, Çorum Erol Olçok State Hospital, Çorum, Türkiye*
[3]*Department of Cardiology, Ardahan State Hospital, Ardahan, Türkiye*
[4]*Department of Cardiology, Çankırı State Hospital, Çankırı, Türkiye*
[5]*Department of Cardiology, Nazilli State Hospital, Aydın, Türkiye*

Corresponding author:
Mehmet Uğur Çalışkan
✉ ugurkobian@gmail.com

Received: August 25, 2025
Accepted: December 25, 2025

Cite this article as: Çalışkan MU, Doğru Yılmaz CY, Sarıbaş H, Kaplan E, Özdemir Al C, Al EA. Artificial Intelligence and Guideline-Augmented Prompting in Assessing the Need for Preoperative Cardiology Consultation. *Turk Kardiyol Dern Ars.* 2026;54(3):268-271.

DOI: 10.5543/tkda.2025.70041

Sonuç: ChatGPT-5, Deepseek-V3 ve Gemini 2.0 Pro'nun preoperatif hastalarda kardiyoloji konsültasyonu gerekliliğini değerlendirmedeki etkinliği kanıtlanmıştır. Kılavuz destekli komut yönlendirmesi YZ modellerinin doğruluğunu arttırmaktadır.

Anahtar Kelimeler: Yapay zekâ, ChatGPT, makine öğrenimi, preoperatif konsültasyon

Advances in modern medicine have significantly contributed to an increase in average life expectancy. As a consequence, the number of patients requiring major surgical procedures has also risen steadily over the years. It is estimated that worldwide, more than 300 million patients undergo surgical operations annually.[1] The number of preoperative cardiology consultations has also increased due to the higher prevalence of comorbidities in elderly patients and the associated increased risk of ischemic events.[2] The 2022 European Society of Cardiology (ESC) Non-Cardiac Surgery Guidelines and the 2024 American College of Cardiology (ACC) Non-Cardiac Surgery Guidelines, in conjunction with a multidisciplinary approach, outline which patients should be referred to cardiology for consultation during the preoperative assessment.[1,3]

Artificial intelligence (AI), which has been gaining ground in recent years, is a computer technology that attempts to solve problems by means of human-like thinking abilities.[4] AI has introduced key concepts such as machine learning (ML) and deep learning (DL). Although these terms are closely related and often used interchangeably, they represent different approaches and levels of complexity within the broader field of AI. ML is a technology that allows AI to generate insights or predictions from existing data by developing algorithms that best represent the underlying patterns within a dataset.[5] DL can be defined as an advanced form of ML that enables more comprehensive analysis by combining more data.[6] In the field of cardiology, AI and ML have increasingly become the focus of research, serving a variety of purposes such as the interpretation of radiological and echocardiographic images, automated analysis of electrocardiograms (ECG), and the management and risk stratification of specific patient populations.[7,8] Several studies in the literature have investigated the feasibility and potential clinical utility of AI in the risk assessment of preoperative patients.[9] However, to date, no clinical studies have specifically investigated the ability of AI and guideline-augmented prompting to evaluate the necessity of preoperative cardiology consultation.

In this study, we aimed to evaluate the performance of three widely used AI models (ChatGPT-5, Deepseek-V3, and Gemini 2.0 Pro) in assessing the necessity of cardiology consultation in preoperative patients and to explore the potential contribution of guideline-augmented prompting in this context.

Materials and Methods

A cardiologist developed 20 standardized patient scenarios that included detailed information on each patient's age, sex, diagnosis, planned surgical procedure, physical examination findings, medical history, and additional anamnesis questions (Supplementary Material: Patient Scenarios). These scenarios were designed to simulate real-world clinical conditions and served as the basis for evaluating the necessity of preoperative cardiology consultation. A council was established consisting of 14 physicians, including seven anesthesiologists from three different centers and seven cardiologists from four different centers. Each council member was individually presented with the patient scenarios and asked to provide a recommendation for each case in the format of "cardiology consultation required" or "not required." All members responded independently, indicating the decision they would make when evaluating the patient in each scenario, without following any predefined algorithm. The responses were compiled by an independent cardiologist, and for each scenario, the decision supported by the majority vote was accepted as the reference standard (Supplementary Material: Council Decision).

A standardized directive was provided to commonly used AI systems (ChatGPT-5, Deepseek-V3, and Gemini 2.0 Pro):

> *"I need your help. You are an anesthesiologist. I will give you 20 patient scenarios. In these scenarios, I want you to indicate which patients require preoperative consultation with cardiology."*

Each model was tested separately using this standardized prompt (Supplementary Material: ChatGPT-5, DeepSeek-V3, and Gemini 2.0 Pro Answers). Following the initial evaluations, the responses obtained from the AI models were compared with the reference standard established by the expert panel. As a result of this analysis, the AI systems that demonstrated the closest agreement with the council's decisions were selected. Subsequently, the 2022 European Society of Cardiology (ESC) and 2024 American College of Cardiology/American Heart Association (ACC/AHA) Non-Cardiac Surgery Guidelines were incorporated into the models using guideline-augmented prompting.[1,3] Integration was achieved by manually uploading the guideline documents into the system. The same 20 case scenarios were then presented again, and the model's guideline-based responses were obtained and compared with the initial responses. The models were also asked to indicate the differences compared to their previous assessments (Supplementary Material: ChatGPT-5 and Gemini 2.0 Pro with Integration of Clinical Guidelines).

ABBREVIATIONS

ACC	American College of Cardiology
AI	Artificial intelligence
DL	Deep learning
ECG	Electrocardiograms
ESC	European Society of Cardiology
ML	Machine learning

Statistical Analysis

Data analysis was conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). For each AI model, the accuracy rate was calculated as the proportion of responses that were in complete agreement with the reference standard established by the expert council. Cohen's kappa coefficient was calculated to evaluate the models' agreement with the council's decisions. Kappa values were interpreted according to the classification of Landis and Koch (1977) as < 0.20 poor, 0.21–0.40 low, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 excellent agreement. The McNemar test was applied to compare the distribution of decisions among the AI models. In all statistical analyses, a p value < 0.05 was considered indicative of statistical significance.

Results

In the study, the expert council determined that cardiology consultation was necessary in 8 of the 20 patient scenarios. Among the artificial intelligence models, ChatGPT-5 recommended consultation in 11 cases, Deepseek-V3 in 10 cases, and Gemini 2.0 Pro in seven cases. The comparative distribution of the AI models' recommendations versus the council's reference decisions is summarized in Table 1.

The consistency of all three AI models with the council's reference decisions was found to be statistically significant (P < 0.05). Among the models, the highest consistency was observed with ChatGPT-5 (κ = 0.706, 85% accuracy). Although Gemini 2.0 Pro demonstrated the same accuracy rate as ChatGPT, its Cohen's kappa value was slightly lower (κ = 0.681, 85% accuracy). After integrating the 2022 ESC and 2024 ACC non-cardiac surgery guidelines into ChatGPT-5 and Gemini 2.0 Pro, both models were re-evaluated and showed improved performance (κ = 0.898, 95% accuracy).

When comparing the decision distributions among the models, no statistically significant differences were found between ChatGPT-5 and the other models (P > 0.05) (Table 2).

Table 1. Comparison and compatibility analysis between artificial intelligence model decisions and council decisions

Model	Kappa	Agreement level	Accuracy (%)	*P*
ChatGPT-5	0.706	Good	85%	0.001
Deepseek-V3	0.600	Moderate	80%	0.006
Gemini 2.0 Pro	0.681	Good	85%	0.002
ChatGPT-5 (integrated guidelines)	0.898	Excellent	95%	<0.001
Gemini 2.0 Pro (integrated guidelines)	0.898	Excellent	95%	<0.001

Table 2. Comparison of decision distributions among artificial intelligence models

Compared models	*P*
ChatGPT-5 vs. Deepseek-V3	1.000
ChatGPT-5 vs. Gemini 2.0 Pro	0.125
Deepseek-V3 vs. Gemini 2.0 Pro	0.250

Discussion

In this study, we investigated the feasibility of using AI models and the impact of guideline-augmented prompting on assessing the necessity of preoperative cardiology consultation. Our findings demonstrated that all three widely used AI models: ChatGPT-5, Deepseek-V3, and Gemini 2.0 Pro, showed statistically significant consistency with the expert panel's decisions (P < 0.05), indicating that these models are feasible tools for supporting decision-making in this field. Although there was no statistically significant difference in performance when the models were compared directly (P > 0.05), ChatGPT-5 and Gemini 2.0 Pro demonstrated higher accuracy compared with DeepSeek-V3. The limited sample size remains a constraint and may affect the generalizability of these results. Moreover, integrating guideline-augmented prompting with current clinical guidelines further enhanced performance, increasing accuracy from 85% to 95%.

Recent clinical investigations have highlighted that ChatGPT may demonstrate superior performance compared to other general-purpose AI models, particularly in the evaluation of clinical case scenarios.[10,11] In a study conducted by Pierri et al.,[11] the performance of ChatGPT-4o, Claude 3.5, and Gemini Flash 1.5 AI models were compared in the field of general cardiology using a set of 70 questions. The results demonstrated that ChatGPT-4o outperformed the other two models in terms of accuracy and consistency. However, no model demonstrated professional-level reliability. In another study conducted by Kozaily et al.,[12] the performances of ChatGPT-3.5 and Google Bard AI models were compared using 30 questions related to the diagnosis, prognosis, and treatment of heart failure. The findings indicated that ChatGPT provided more accurate responses overall. However, it was also observed that some recommendations generated by both models were either inconsistent with current clinical guidelines or contradicted real-world clinical practice. In our study, no statistically significant differences were found when comparing the decisions of the three models.

Machine learning and deep learning hold significant potential in the field of medicine. These approaches not only allow for comprehensive analysis of large-scale datasets but also facilitate the integration of years of accumulated clinical knowledge and experience. This enables the identification of previously unrecognized relationships within clinical decision-support processes and facilitates the development of predictive models. Moreover, these AI-based approaches not only enhance the processing and interpretation of existing data, but also support the generation of new hypotheses and the creation of predictive datasets applicable to a wide range of clinical scenarios.[13,14] In a study conducted by Yoon et al.,[15] preoperative anesthesia assessment notes for 717,389 patients were retrospectively reviewed. Using these notes, the ChatGPT-4, BioClinicalBERT, and ClinicalBigBird models were trained with ML methods, and their performances were subsequently compared with those of expert anesthesiologists and assistant anesthesiologists. The study demonstrated that AI models performed significantly better than assistant physicians and similarly well as specialist physicians. In our study, the same AI models were re-evaluated after the integration of guideline-augmented prompting. This approach demonstrated the positive impact of guideline-augmented prompting on model performance and outcome

accuracy. Both ChatGPT-5 and Gemini 2.0 Pro, when used with guideline-augmented prompting, produced identical responses. The only discrepancy from the council's decision occurred in Case 1, involving acute appendicitis. While the council did not request cardiology consultation due to the urgent nature of the surgery, the guideline-integrated AI systems recommended consultation based on the elevated perioperative cardiovascular risk. If AI models are to be consulted on specific topics, integrating relevant literature or data into the model beforehand increases the consistency and clinical applicability of the responses obtained.

Although advances in AI models are highly promising, they have also raised a number of ethical concerns and debates. In particular, sharing patient data with these systems introduces the risk of cyberattacks and data breaches, which may seriously compromise patient privacy, data security, and confidentiality.[16] AI models such as ChatGPT, Deepseek, and Gemini are designed as general-purpose systems and therefore cannot be held accountable for incorrect or inappropriate decisions, a limitation that may pose a potential risk of harm to patients in clinical practice. However, although the ultimate responsibility for patient management lies with the physician, AI models can serve as valuable tools by facilitating information exchange on important cardiovascular diseases, providing clinical insights, and supporting decision-making processes.[17] The results of our study also support the notion that AI systems supported by guideline-augmented prompting can assist physicians in preoperative assessment.

The primary limitation of this study is the limited sample size, which diminishes statistical power and reduces the generalizability of the findings. Larger-scale studies are needed to validate these results and further evaluate the clinical applicability of artificial intelligence–based decision support systems. Nevertheless, the novelty of being the first study to evaluate the necessity of cardiology consultation in preoperative patient assessment and to investigate the impact of guideline-augmented prompting using the same model underscores the significance and originality of our work.

Conclusion

Commonly used AI models such as ChatGPT-5, Deepseek-V3, and Gemini 2.0 Pro demonstrated effectiveness in assessing the necessity of cardiology consultation in preoperatively evaluated patients. Moreover, guideline-augmented prompting further improved the accuracy and reliability of AI model performance.

Online Supplementary Link: Supplementary may be accessed via this link.

Ethics Committee Approval: This study did not involve patient data; therefore, ethics committee approval was not required.

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

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: No financial support was received for the research, authorship, and/or publication of this article.

Use of AI for Writing Assistance: No use of AI-assisted technologies was declared by the authors.

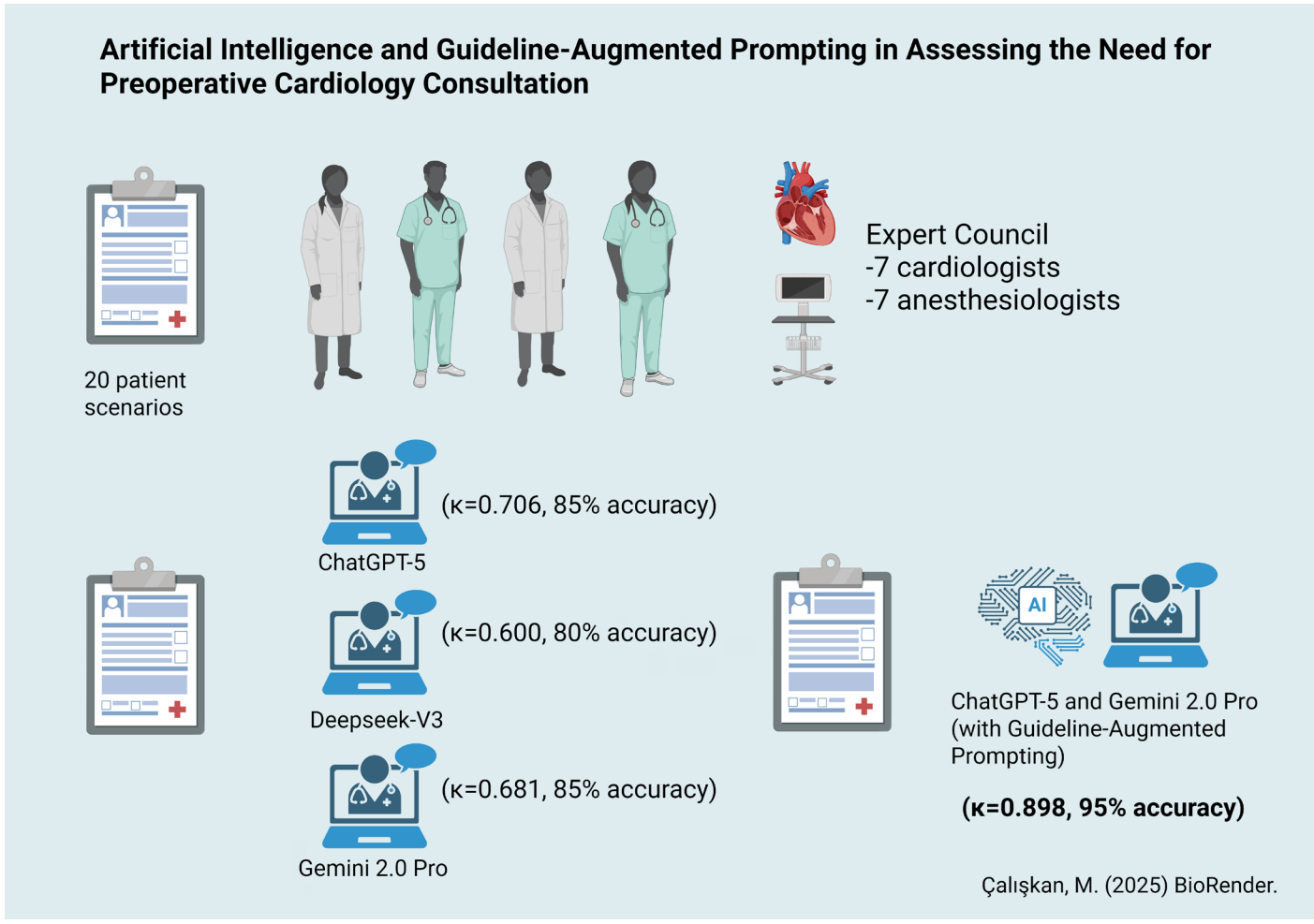
Author Contributions: Concept – M.U.Ç.; Design – M.U.Ç.; Supervision – C.Y.D.Y.; Resource – E.K.; Materials – E.K.; Data Collection and/or Processing – C.Ö.A.; Analysis and/or Interpretation – H.S.; Literature Review – E.A.A.; Writing – M.U.Ç.; Critical Review – M.U.Ç.

Peer-review: Externally peer-reviewed.

Data Availability Statement: All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

References

1. Halvorsen S, Mehilli J, Cassese S, et al.; ESC Scientific Document Group. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J*. 2022;43(39):3826-3924. Erratum in: *Eur Heart J*. 2023;44(42):4421. [CrossRef]
2. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators; Spence J, LeManach Y, Chan MTV, et al. Association between complications and death within 30 days after noncardiac surgery. *CMAJ*. 2019;191(30):E830-E837. [CrossRef]
3. Writing Committee Members; Thompson A, Fleischmann KE, Smilowitz NR, et al. 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management for Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2024;84(19):1869-1969. Erratum in: *J Am Coll Cardiol*. 2024;84(24):2416.
4. Hamet P, Tremblay J. Artificial intelligence in medicine. *Metabolism*. 2017;69S:S36-S40. [CrossRef]
5. Choi RY, Coyner AS, Kalpathy-Cramer J, Chiang MF, Campbell JP. Introduction to Machine Learning, Neural Networks, and Deep Learning. *Transl Vis Sci Technol*. 2020;9(2):14.
6. Currie G, Hawk KE, Rohren E, Vial A, Klein R. Machine Learning and Deep Learning in Medical Imaging: Intelligent Imaging. *J Med Imaging Radiat Sci*. 2019;50(4):477-487. [CrossRef]
7. Johnson KW, Torres Soto J, Glicksberg BS, et al. Artificial Intelligence in Cardiology. *J Am Coll Cardiol*. 2018;71(23):2668-2679. [CrossRef]
8. Kaçar MN, Ulusoy İ, Yayla Ç. A Review on the Estimation of Coronary Fractional Flow Reserve Using Artificial Intelligence. *Turk Kardiyol Dern Ars*. 2025;53(4):275-280. [CrossRef]
9. Abdel Malek M, van Velzen M, Dahan A, et al. Generation of preoperative anaesthetic plans by ChatGPT-4.0: a mixed-method study. *Br J Anaesth*. 2025;134(5):1333-1340. [CrossRef]
10. Pay L, Yumurtaş AÇ, Çetin T, Çınar T, Hayıroğlu Mİ. Comparative Evaluation of Chatbot Responses on Coronary Artery Disease. *Turk Kardiyol Dern Ars*. 2025;53(1):35-43. [CrossRef]
11. Pierri MD, Galeazzi M, D'Alessio S, et al. Evaluating Large Language Models in Cardiology: A Comparative Study of ChatGPT, Claude, and Gemini. *Hearts*. 2025;6(3):19. [CrossRef]
12. Kozaily E, Geagea M, Akdogan ER, et al. Accuracy and consistency of online large language model-based artificial intelligence chat platforms in answering patients' questions about heart failure. *Int J Cardiol*. 2024;408:132115. [CrossRef]
13. Cascarano A, Mur-Petit J, Hernández-González J, et al. Machine and deep learning for longitudinal biomedical data: a review of methods and applications. *Artif Intell Rev*. 2023;56(2):1711-1771. [CrossRef]
14. Sadr H, Nazari M, Khodaverdian Z, et al. Unveiling the potential of artificial intelligence in revolutionizing disease diagnosis and prediction: a comprehensive review of machine learning and deep learning approaches. *Eur J Med Res*. 2025;30(1):418. [CrossRef]
15. Yoon SB, Lee J, Lee HC, Jung CW, Lee H. Comparison of NLP machine learning models with human physicians for ASA Physical Status classification. *NPJ Digit Med*. 2024;7(1):259. [CrossRef]
16. Siafakas N, Vasarmidi E. Risks of Artificial Intelligence (AI) in Medicine. *Pneumon*. 2024;37(3):1-5. [CrossRef]
17. Madaudo C, Parlati ALM, Di Lisi D, et al. Artificial intelligence in cardiology: a peek at the future and the role of ChatGPT in cardiology practice. *J Cardiovasc Med (Hagerstown)*. 2024;25(11):766-771. [CrossRef]


Artificial Intelligence and Guideline-Augmented Prompting in Assessing the Need for Preoperative Cardiology Consultation
20 patient scenarios
Expert Council
-7 cardiologists
-7 anesthesiologists
ChatGPT-5
(κ=0.706, 85% accuracy)
Deepseek-V3
(κ=0.600, 80% accuracy)
Gemini 2.0 Pro
(κ=0.681, 85% accuracy)
AI
ChatGPT-5 and Gemini 2.0 Pro (with Guideline-Augmented Prompting)
(κ=0.898, 95% accuracy)
Çalışkan, M. (2025) BioRender.

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Management of Bradycardia Before Transcatheter Aortic Valve Implantation in a Patient with Mechanical Tricuspid and Mitral Valve Replacement

Mekanik Triküspit ve Mitral Kapak Replasmanı Olan Bir Hastada Transkateter Aort Kapak İmplantasyonu Öncesi Bradikardi Yönetimi

ABSTRACT

Transcatheter aortic valve implantation (TAVI) has proven to be a safe and effective treatment, particularly in patients with aortic stenosis and moderate to high surgical risk scores. One potential complication after TAVI is bradyarrhythmia due to high-grade atrioventricular block, which may necessitate permanent pacemaker (PM) implantation. We present a case of a patient with symptomatic intermittent pauses and severe aortic stenosis who underwent permanent PM implantation via the coronary sinus prior to TAVI, due to a history of mechanical tricuspid and mitral valve replacements. The subsequent TAVI procedure was successful, and the patient remained stable without periprocedural complications.

Keywords: Aortic stenosis, pacemaker, valve disease

ÖZET

Transkateter aort kapak implantasyonu (TAVI), özellikle cerrahi risk skoru orta ila yüksek olan aort darlığı hastalarında güvenli ve etkili bir yöntem olduğunu kanıtlamıştır. TAVI sonrası olası komplikasyonlardan biri, yüksek dereceli atriyoventriküler bloktan kaynaklanan bradiaritmidir. Bu durumdaki bazı hastalar kalıcı kalp pili (PM) implantasyonu gerektirebilir. Bu durumda, semptomatik aralıklı duraklamalar ve şiddetli aort darlığı olan, mekanik triküspit ve mitral kapak replasmanı öyküsü nedeniyle TAVI öncesinde koroner sinüs yoluyla kalıcı PM implantasyonu uygulanan ve ardından başarılı bir TAVI geçiren bir vaka sunduk. Hasta, işlem sırasında herhangi bir komplikasyon yaşamadan stabil kaldı.

Anahtar Kelimeler: Aort darlığı, kalp pili, kapak hastalığı

CASE REPORT
OLGU SUNUMU

Mert Doğan
Uğur Canpolat
Ahmet Hakan Ateş
Mehmet Levent Şahiner
Ergün Barış Kaya
Kudret Aytemir

Department of Cardiology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye

Corresponding author:
Mert Doğan
✉ drmertd@gmail.com

Received: April 19, 2025
Accepted: July 27, 2025

Cite this article as: Doğan M, Canpolat U, Ateş AH, Şahiner ML, Kaya EB, Aytemir K. Management of Bradycardia Before Transcatheter Aortic Valve Implantation in a Patient with Mechanical Tricuspid and Mitral Valve Replacement. *Turk Kardiyol Dern Ars.* 2025;54(3):272-276.

DOI: 10.5543/tkda.2025.60402

Transcatheter aortic valve implantation (TAVI) is a safe and effective procedure, especially for patients with aortic stenosis (AS) who have intermediate to high surgical risk scores.[1] A known complication following TAVI is bradyarrhythmia resulting from high-grade atrioventricular (AV) block.[2] We present a case of a patient with symptomatic intermittent pauses and severe AS who underwent permanent pacemaker (PM) implantation via the coronary sinus (CS) prior to TAVI, due to a history of mechanical tricuspid and mitral valve replacements (TVR and MVR), followed by an uneventful and successful TAVI procedure.

Case Report

A 68-year-old female with a history of myelodysplastic syndrome, mechanical TVR and MVR surgery, and atrial fibrillation was admitted to our center with complaints of shortness of breath, classified as New York Heart Association Class II. Physical examination revealed a mechanical prosthetic valve sound and a severe systolic murmur in the aortic focus on auscultation. Laboratory tests showed a hemoglobin level of 10.1 g/dL, a platelet count of 51 × 10^3 U/L, and a brain natriuretic peptide (BNP) level of 109 pg/mL. A 12-lead electrocardiogram (ECG) on admission demonstrated atrial fibrillation with a ventricular rate of 50 bpm and a QRS duration of 90 ms (Figure 1). The patient's 24-hour Holter monitoring revealed a total of 37 pauses ranging from 2.5 to 3 seconds

in duration (Figure 2). These pauses were strongly associated with clinical symptoms including presyncope, dizziness, and severe fatigue, which occurred concurrently with the patient's complaints of shortness of breath and were temporally correlated with the documented pauses. Transthoracic echocardiography (TTE) showed a left ventricular ejection fraction of 60%, with a significantly enlarged left atrial anteroposterior diameter of 90 mm. The right ventricle was also dilated, with a mid-cavity diameter of 30 mm and a basal diameter of 43 mm. The mechanical tricuspid and mitral valves were functioning normally. However, the aortic valve was heavily calcified, with mild aortic valve insufficiency and severe aortic stenosis, (characterized by an aortic valve area of 0.7 cm^2, a peak gradient of 72 mmHg, and a mean gradient of 39 mmHg). The European System for Cardiac Operative Risk Evaluation II (EURO-SCORE II) and the Society of Thoracic Surgeons (STS) score were calculated as 12.04% and 10.8%, respectively. Therefore, the patient was deemed high surgical risk by the heart team, and a decision was made to proceed with TAVI. Given the patient's documented symptomatic bradyarrhythmia with significant pauses, and the presence of a mechanical tricuspid valve prosthesis that precluded conventional transvenous right ventricular lead placement, the heart team decided to implant a single-chamber permanent PM via the CS approach, two weeks prior to the scheduled TAVI procedure. This pre-emptive strategy was deemed essential for both periprocedural temporary rapid ventricular pacing during valve deployment and potential post-procedural bradyarrhythmia management. A left axillary vein puncture was performed, and a 9F delivery sheath (Attain Command™ + SureValve™ integrated valve, Medtronic, Minneapolis, MN, USA) was introduced. Severe dilation of the right heart chambers (right ventricular [RV] mid: 30 mm, RV base: 43 mm) hindered CS cannulation using standard CS catheters, necessitating the use of a steerable radiofrequency ablation catheter for successful access. Despite these efforts, optimal CS venography could not be achieved due to distorted cardiac anatomy and the absence of an occlusion balloon. The guidewire was advanced to the most distal accessible location, identified as the anterior interventricular branch of the CS. Lead placement in this branch was successfully accomplished with acceptable electrical parameters (Medtronic, Minneapolis, MN, USA; threshold: 2.3 V, impedance: 805 Ω, sensing: 17.8 mV),

ABBREVIATIONS

AS	Aortic stenosis
AV	Atrioventricular
BNP	Brain natriuretic peptide
CS	Coronary sinus
ECG	Electrocardiogram
EURO-SCORE II	European System for Cardiac Operative Risk Evaluation II
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MVR	Mitral valve replacement
PM	Pacemaker
RBBB	Right bundle branch block
RV	Right ventricular
SAVR	Surgical aortic valve replacement
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation
TTE	Transthoracic echocardiography
TVR	Tricuspid valve replacements

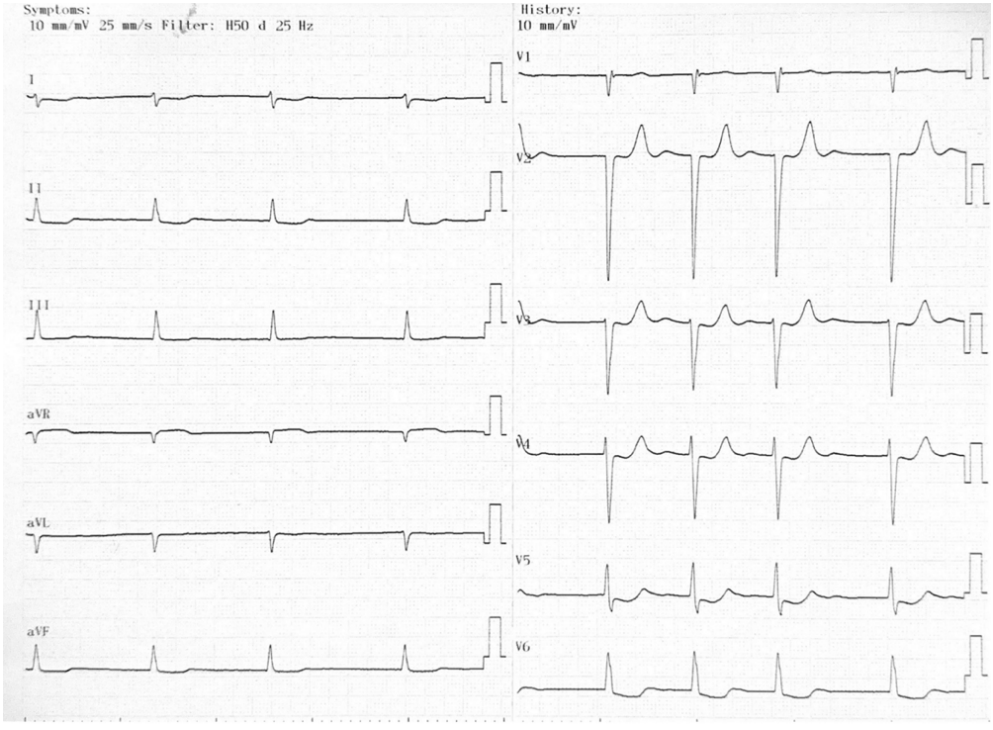


Figure 1. Twelve-lead electrocardiogram before the transcatheter aortic valve implantation (TAVI) procedure showing atrial fibrillation, a ventricular rate of 50 bpm, and a QRS duration of 90 ms.

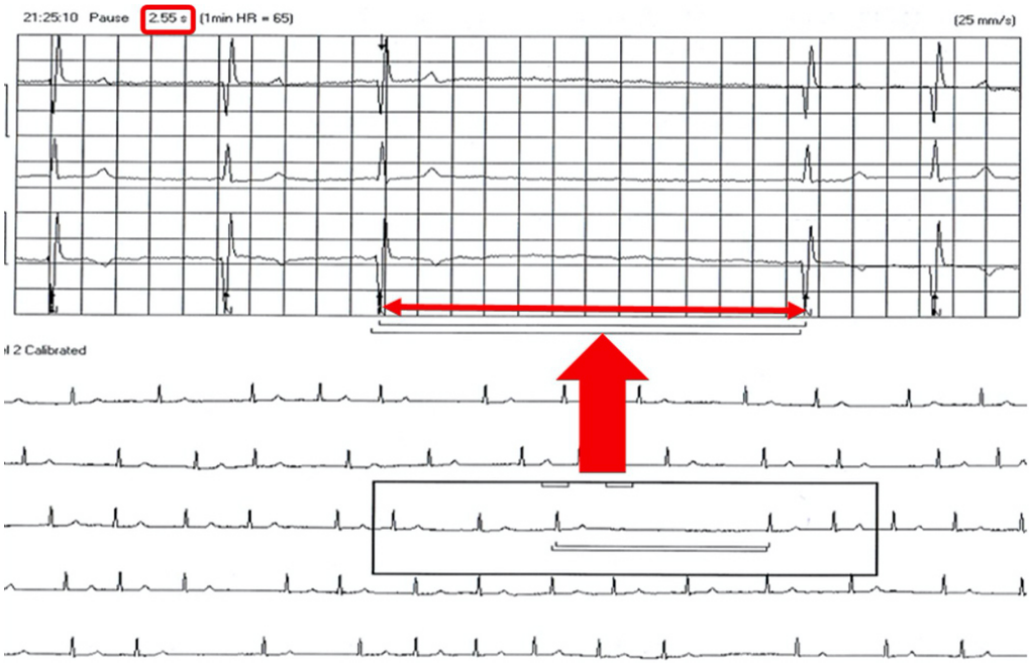


Figure 2. Twenty-four-hour Holter monitoring demonstrating a 2.6-second ventricular pause during atrial fibrillation.

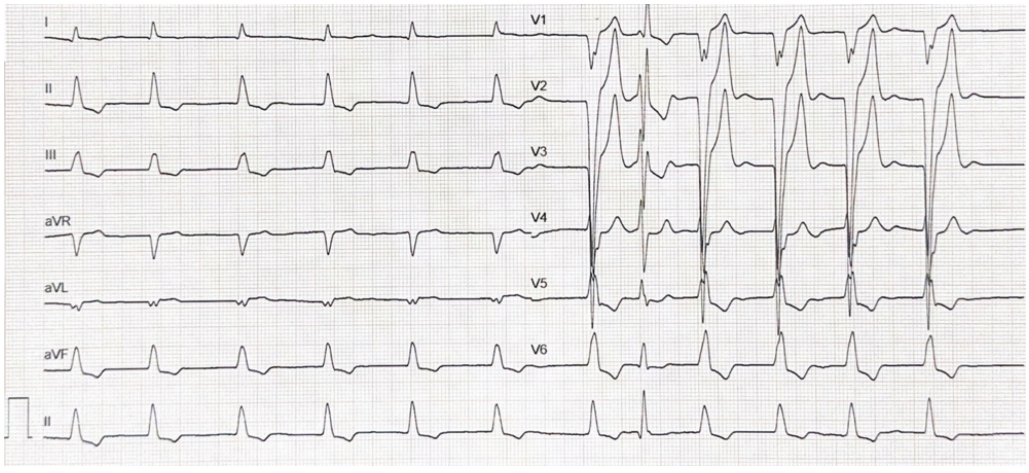


Figure 3. Twelve-lead electrocardiogram immediately after the transcatheter aortic valve implantation (TAVI) procedure showing atrial fibrillation, new-onset left bundle branch block, and a QRS duration of 150 ms.

providing adequate pacing support for both the TAVI procedure and the management of symptomatic pauses (Supplementary Video 1). After confirming acceptable sensing and pacing parameters, the lead was connected to the pulse generator, and the procedure was successfully completed using a standard approach. One week later, the patient underwent a successful TAVI procedure under anesthesia. A 29-mm self-expandable aortic prosthetic valve (Medtronic, CoreValve Evolut, USA) was successfully implanted (Supplementary Video 1). Ventricular overdrive pacing was performed via the previously implanted permanent PM during valve implantation. Postprocedural aortography revealed minimal aortic valve insufficiency. A post-procedural peak-to-peak transaortic gradient of 12 mmHg was measured. There were no periprocedural complications. Post-TAVI 12-lead ECG revealed a new-onset left bundle branch block (LBBB) with a QRS duration of 150 ms (Figure 3). However, on the second day, the 12-lead ECG showed intermittent ventricular pacing rhythm due to pauses, along with improvement of the LBBB (Figure 4). The patient was discharged uneventfully 48 hours later.

Discussion

The TAVI procedure was first performed and reported by Cribier et al. in 2002.[3] With increasing clinical experience and advancements in technology, TAVI has become widely adopted across the globe. During the TAVI procedure, various conduction system abnormalities, including bundle branch blocks and atrioventricular blocks, may occur due to the anatomical

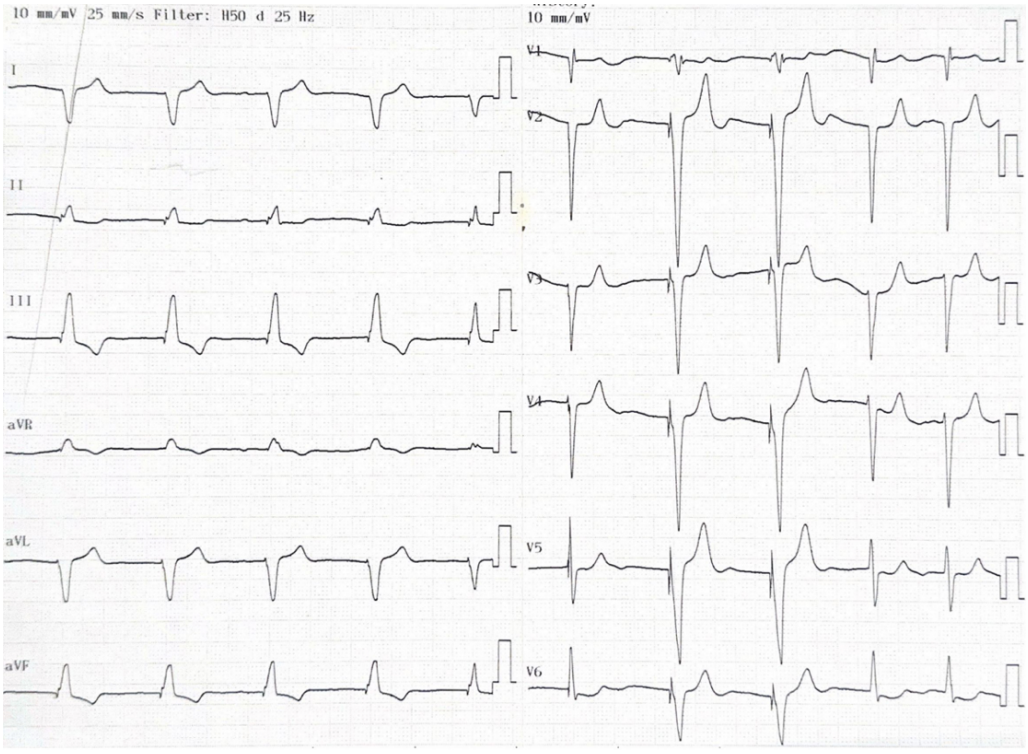


Figure 4. Twelve-lead electrocardiogram on the second day after transcatheter aortic valve implantation (TAVI) demonstrating an intermittent pacemaker rhythm and improvement of the left bundle branch block.

proximity. While surgical aortic valve replacement (SAVR) remains the preferred option for patients with low surgical scores (STS, EURO-SCORE), TAVI is a safe and effective alternative for appropriately selected elderly patients across all risk groups. Potential complications following TAVI include vascular injury, stroke, aortic valve insufficiency, bleeding, and valve malposition.[4] According to a meta-analysis, the rate of permanent PM implantation after TAVI is approximately 15%.[5] Predictive factors for the development of high-degree block after TAVI include right bundle branch block (RBBB), LBBB, intraventricular conduction delay, bifascicular block, atrial fibrillation with a low ventricular rate, male gender, and use of self-expandable valve prostheses.[6] Despite advancements in technology and procedural techniques, high-degree AV block and the subsequent need for permanent PM implantation remain relevant concerns following TAVI. Although permanent PM implantation is not required in most cases of newly developed LBBB after TAVR, studies and current guidelines indicate that the risk of permanent PM implantation is higher in patients with a QRS duration > 150 ms, PR duration > 240 ms, atrial fibrillation (AF), and a left ventricular ejection fraction (LVEF) < 40%.[7] Furthermore, ventricular overdrive pacing is routinely required during valve implantation, and periprocedural temporary transvenous pacing may be necessary in some patients. Therefore, a transvenous temporary PM electrode is generally placed in the right ventricle. However, the presence of a mechanical TVR before TAVI poses an obstacle to this approach for both overdrive ventricular pacing and temporary or permanent pacing after the procedure. Overdrive ventricular pacing during valve implantation can be achieved via a guidewire placed inside the left ventricle; however, this method cannot be used for temporary pacing after the procedure. Catheter ablation targeting atrial arrhythmias has been described in the literature as an effective treatment strategy for patients with refractory ventricular pauses, particularly in cases of bradycardia mediated by vagal reflexes.[8] Left atrial enlargement, especially with a diameter exceeding 50 mm, is a significant predictor of poor outcomes following catheter ablation for atrial fibrillation.[9] Our patient presented with severe left atrial dilatation (> 90 mm), which constituted a major limiting factor for ablation therapy. Additionally, the patient would have required a permanent PM in the event of developing high-grade atrioventricular block due to mechanical compression of the AV node following TAVI. Therefore, in our case, permanent PM implantation via the CS was performed two weeks prior to the TAVI procedure. Studies have shown that ventricular electrode implantation via the CS is a safe and effective method in patients where right ventricular pacing is not feasible due to tricuspid valve disease (e.g. atresia, severe stenosis) and/or TVR.[10] Alternative pacing modalities in patients with mechanical TVR present significant technical challenges. Epicardial lead placement is another option that can be prophylactically performed during tricuspid valve surgery; however, it requires a more invasive procedure and is generally associated with higher pacing thresholds.[11] More recently, leadless PM implantation through mechanical tricuspid valves has been reported in isolated cases, though this approach has not gained widespread acceptance due to limited data regarding potential effects on valve function.[12] To ensure safety, a permanent PM was implanted via the CS route prior to the TAVI procedure in our patient. The TAVI procedure was then successfully performed one week later, with no periprocedural complications observed.

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

Informed Consent: The patient was fully informed about the publication of this case in the literature and provided both written and verbal consent.

Conflict of Interest: Kudret Aytemir: Proctoring for Medtronic, Abbott, and Biosense Webster. Uğur Canpolat: Proctoring for Biotronik and Medtronic. Mehmet Levent Şahiner: Proctoring for Medtronic. Other authors have nothing to disclose.

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

Use of AI for Writing Assistance: No artificial intelligence technologies were utilized in the preparation of this manuscript.

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

Peer-review: Externally peer-reviewed.

Video 1. (A) Difficult venography performed via the standard delivery sheath showing the coronary sinus (CS) venous branches. (B) Due to difficulty advancing the CS electrode into the lateral branches because of small diameters, the CS electrode was implanted into the anterior interventricular branch of the CS. (C) Successful transcatheter aortic valve implantation (TAVI) with minimal aortic insufficiency observed post-procedure.

References

1. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol*. 2011;9(1):15-29. [CrossRef]
2. Young Lee M, Chilakamarri Yeshwant S, Chava S, Lawrence Lustgarten D. Mechanisms of Heart Block after Transcatheter Aortic Valve Replacement - Cardiac Anatomy, Clinical Predictors and Mechanical Factors that Contribute to Permanent Pacemaker Implantation. *Arrhythm Electrophysiol Rev*. 2015;4(2):81-85. [CrossRef]
3. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002;106(24):3006-3008. [CrossRef]
4. Young MN, Inglessis I. Transcatheter Aortic Valve Replacement: Outcomes, Indications, Complications, and Innovations. *Curr Treat Options Cardiovasc Med*. 2017;19(10):81. [CrossRef]
5. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. *J Cardiovasc Electrophysiol*. 2012;23(4):391-397. [CrossRef]
6. Alabdaljabar MS, Eleid MF. Risk Factors, Management, and Avoidance of Conduction System Disease after Transcatheter Aortic Valve Replacement. *J Clin Med*. 2023;12(13):4405. [CrossRef]
7. Glikson M, Nielsen JC, Kronborg MB, et al.; ESC Scientific Document Group. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2021;42(35):3427-3520. Erratum in: *Eur Heart J*. 2022;43(17):1651. [CrossRef]
8. Hocini M, Sanders P, Deisenhofer I, et al. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation*. 2003;108(10):1172-1175. [CrossRef]
9. Bajraktari G, Bytyçi I, Henein MY. Left atrial structure and function predictors of recurrent fibrillation after catheter ablation: a systematic review and meta-analysis. *Clin Physiol Funct Imaging*. 2020;40(1):1-13. [CrossRef]
10. Noheria A, van Zyl M, Scott LR, et al. Single-site ventricular pacing via the coronary sinus in patients with tricuspid valve disease. *Europace*. 2018;20(4):636-642. [CrossRef]
11. Bazire B, Para M, Raffoul R, et al. Prophylactic epicardial pacemaker implantation in tricuspid valve replacement. *Eur J Cardiothorac Surg*. 2023;64(6):ezad344. [CrossRef]
12. Hwang J, Han S, Park HS, Lee CH, Kim IC, Jang WS. Implantation of a leadless pacemaker in a patient with mechanical tricuspid valve. HeartRhythm *Case Rep*. 2022;8(4):284-287. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

A Noonan Syndrome Mimicking Acute Coronary Syndrome

Akut Koroner Sendromu Taklit Eden Bir Noonan Sendromu

ABSTRACT

Noonan syndrome is a genetic disorder that can present with a wide range of clinical manifestations, making diagnosis challenging. This article presents the case of a 29-year-old male who presented with chest pain and ST-segment elevation, initially raising suspicion for acute coronary syndrome. However, coronary angiography revealed only ectasia of the coronary arteries, with no other pathological findings. A detailed physical examination and echocardiography revealed a pulmonary murmur, pectus excavatum, and café-au-lait spots. Additionally, both echocardiography and cardiac magnetic resonance imaging (MRI) showed localized left ventricular hypertrophy. Genetic testing identified a heterozygous missense variant in the *PTPN11* gene, leading to the diagnosis of Noonan syndrome. This case highlights the importance of thorough physical examination and multimodal imaging in the diagnosis of Noonan syndrome.

Keywords: Electrocardiogram, Noonan syndrome, physical examination

ÖZET

Noonan Sendromu, geniş bir klinik yelpazede farklı semptomlarla kendini gösterebilen ve bu nedenle tanısı zorlayıcı olan genetik bir bozukluktur. Bu yazıda, göğüs ağrısı ve ST-segment elevasyonu ile başvuran 29 yaşındaki bir erkek hasta sunulmuştur. İlk aşamada akut koroner sendrom tanısı düşünülmüş ancak koroner anjiyografi sonuçlarında koroner arterlerde ektazi dışında herhangi bir patolojik bulguya rastlanmamıştır. Detaylı fizik muayene ve ekokardiyografi ile hastada pulmoner odakta üfürüm, pektus ekskavatum ve cafe-au-lait lekeleri gözlemlenmiş, ayrıca ekokardiyografide ve kardiyak MRI'da sol ventrikülde lokalize hipertrofi saptanmıştır. Yapılan genetik incelemede *PTPN11* geninde heterozigot varyant tespit edilerek hastaya Noonan sendromu tanısı konulmuştur. Bu vaka, Noonan Sendromu tanısında ayrıntılı fizik muayenenin ve multimodalite görüntüleme tekniklerinin kullanımının önemini vurgulamaktadır.

Anahtar Kelimeler: Elektrokardiyogram, Noonan sendromu, fizik muayene

CASE REPORT
OLGU SUNUMU

Mustafa Yılmaz[1]
Arda Güler[2]
Elif Ayduk Gövdeli[3]
Mehmet Karacan[4]
Gamze Babur Güler[2]

[1]*Department of Cardiology, Gaziosmanpaşa Research and Training Hospital, İstanbul, Türkiye*
[2]*Department of Cardiology, Mehmet Akif Ersoy Cardiothoracic and Vascular Surgery Training and Research Hospital, Istanbul, Türkiye*
[3]*Department of Cardiology, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom*
[4]*Department of Pediatric Cardiology, Ümraniye Training and Research Hospital, İstanbul, Türkiye*

Corresponding author:
Mustafa Yılmaz
✉ drmustafayilmaz@outlook.com

Received: March 28, 2025
Accepted: May 28, 2025

Cite this article as: Yılmaz M, Güler A, Ayduk Gövdeli E, Karacan M, Babur Guler G. A Noonan Syndrome Mimicking Acute Coronary Syndrome. *Turk Kardiyol Dern Ars.* 2025;54(3):277-281.

DOI: 10.5543/tkda.2025.48459

Noonan syndrome (NS) is an autosomal dominant inherited condition characterized by multisystem involvement. The phenotypic presentation can vary widely, and diagnosis is typically based on a combination of clinical features such as characteristic facial features, short stature, skeletal abnormalities, cardiac defects, and family history (Table 1).[1] The broad spectrum of manifestations can make diagnosis challenging. In this article, we present a case in which a patient initially presented with symptoms mimicking acute coronary syndrome, but without typical features of NS such as short stature, developmental delay, or a family history. The diagnosis was ultimately established through a detailed physical examination and patient history.

Case Report

A 29-year-old male with no known history of chronic illness presented to the emergency department with chest pain, described as pressure-like and constrictive. An initial electrocardiogram (ECG) revealed findings suggestive of ischemia, prompting measurement of high-sensitivity troponin levels, which were within normal limits. Given these findings, coronary computed tomography angiography (CTA) was performed and showed no evidence of coronary plaques or vascular anomalies. A few days later, the patient presented to another hospital with similar

chest pain. An ECG performed at the second hospital revealed ST-segment elevation in the inferior leads and ST-segment depression in the lateral leads (Figure 1A). Due to the severity of the chest pain, conventional coronary angiography (CAG) was promptly performed. CAG revealed ectatic coronary arteries but no evidence of plaques or thrombus (Figure 1B). Additionally, laboratory tests, including D-dimer levels, were within normal limits, effectively ruling out differential diagnoses such as pulmonary embolism and aortic dissection. Thoracic imaging also showed no pulmonary pathology. The patient was started on calcium channel blocker therapy, but his chest pain persisted. Upon a third presentation, physical examination revealed a pulmonary murmur, prompting further evaluation with transthoracic echocardiography (TTE). TTE demonstrated increased wall thickness at the basal anteroseptum, along with turbulent flow and an elevated gradient across the pulmonary valve (Figure 1C). These findings raised suspicion of a genetic cardiomyopathy, leading to a more detailed physical examination. Notably, the patient exhibited left palpebral ptosis, marked pectus excavatum, and café-au-lait spots on the skin (Figure 1D-E-F). Despite these findings, his height was 180 cm, and there was no family history of genetic or chronic diseases. Given the constellation of clinical signs, cardiac magnetic resonance imaging (MRI) was performed, revealing localized thickening of the basal anteroseptum up to 21 mm, with patchy enhancement in the hypertrophic region (Figure 1G-H).

Due to the combination of structural cardiac abnormalities and syndromic features, molecular genetic testing was conducted using a clinical exome approach based on next-generation sequencing (NGS) technology. A heterozygous missense variant was identified in the *PTPN11* (protein tyrosine phosphatase, non-receptor type 11) gene (NM_002834.5): c.1403C>T, resulting in a threonine-to-methionine substitution at codon 468 (p.Thr468Met). This pathogenic variant affects a highly conserved residue within the protein tyrosine phosphatase domain of SHP2 (Src Homology 2-containing Protein Tyrosine Phosphatase 2), a critical component of the RAS/MAPK signaling pathway. Based on these findings, along with clinical and imaging features, a diagnosis of Noonan syndrome was established.

ABBREVIATIONS

CAG	Conventional coronary angiography
CFCS	Cardio-facio-cutaneous syndrome
CTA	Computed tomography angiography
MRI	Magnetic resonance imaging
NS	Noonan syndrome
PVS	Pulmonary valve stenosis
TTE	Transthoracic echocardiography

Discussion

Noonan syndrome is classified among a group of hereditary disorders known as RASopathies, which result from genetic variants affecting the RAS/MAPK signaling pathway. This group includes NS, Costello syndrome, cardio-facio-cutaneous syndrome (CFCS), LEOPARD syndrome (also known as Noonan syndrome with multiple lentigines or NSML), Legius syndrome, and several other related conditions.[2] Although these syndromes share overlapping phenotypic features, they differ in terms of their underlying genetic variants. Among the RASopathies, NS is the most common subtype and is clinically characterized by cardiac anomalies, distinctive facial features, short stature, and developmental delays. The estimated incidence at birth ranges from 1 in 1,000 to 1 in 2,500 live births.[3] NS is typically inherited in an autosomal dominant manner and is often associated with de novo variants; however, a recessive form has also been described more recently.[4] The broad phenotypic variability and the age-related attenuation of some features can complicate clinical diagnosis. Cardiac involvement is one of the hallmark features of Noonan syndrome. Pulmonary valve stenosis (PVS) and hypertrophic cardiomyopathy (HCM) are the most frequently observed cardiac abnormalities, although a range of other structural cardiac defects has also been reported, further expanding the phenotypic spectrum (Table 2).[2]

To date, more than 20 genes have been associated with NS. Among them, *PTPN11*, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, LZTR1, and SOS2 are the most prominent. Nevertheless, in approximately 10%–20% of cases, the causative variant remains unidentified. *PTPN11* was the first gene identified in

Table 1. Diagnostic criteria for Noonan syndrome (van der Burgt, 2007)[15]

Feature	Major criteria	Minor criteria
1. Facial dysmorphism	Typical facial features (age-dependent), including hypertelorism, ptosis, low-set ears, etc.	Suggestive but not typical facial features
2. Cardiac defects	Pulmonary valve stenosis, hypertrophic cardiomyopathy, or typical electrocardiogram (ECG) abnormalities	Other congenital heart defects
3. Height	Height < 3rd percentile	Height < 10th percentile
4. Chest wall	Pectus carinatum or pectus excavatum	Broad chest
5. Family history	First-degree relative with a confirmed diagnosis of Noonan syndrome	First-degree relative with suggestive features of Noonan syndrome
6. Other findings	All three of the following: intellectual disability, cryptorchidism, and lymphatic dysplasia	Any one of: intellectual disability, cryptorchidism, or lymphatic dysplasia

A diagnosis of Noonan syndrome can be made if either of the following combinations is present: Typical facial features (1 major facial criterion) plus one additional major criterion or two minor criteria OR Suggestive facial features plus two major criteria or three minor criteria.

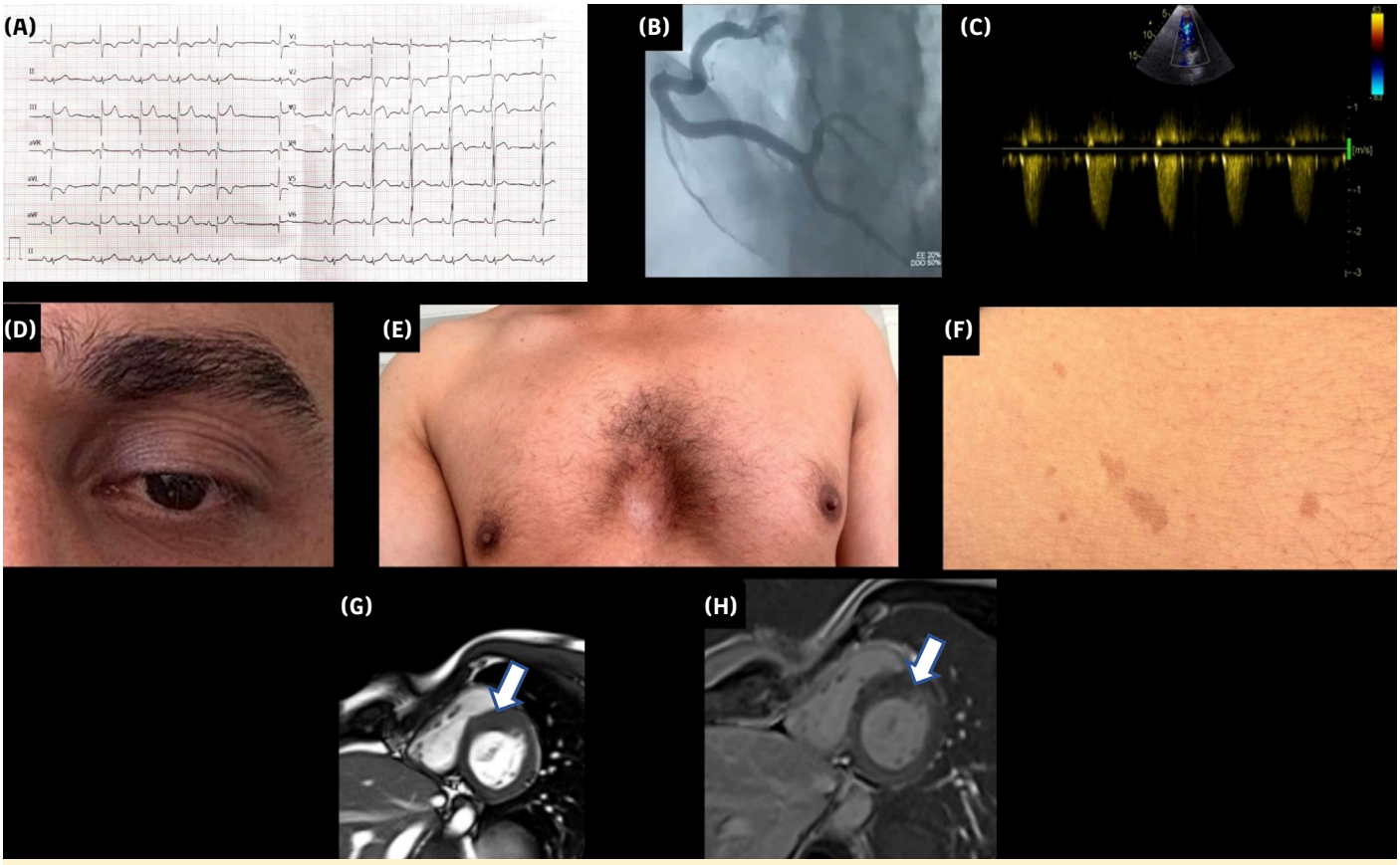


Figure 1. (A) Electrocardiogram (ECG) showing inferior ST-segment elevation. (B) Coronary angiography image demonstrating an ectatic right coronary artery. (C) Doppler echocardiography showing an increased gradient across the pulmonary valve. (D) Ptosis.(E) Pectus excavatum. (F) Café-au-lait spots. (G) Cardiac magnetic resonance imaging short-axis view showing increased wall thickness at the basal anteroseptum (white arrow). (H) Cardiovascular magnetic resonance imaging short-axis view with patchy late gadolinium enhancement in the hypertrophied segment (white arrow).

Table 2. Cardiac involvement in Noonan syndrome[2,12,16]

Cardiac finding	Prevalence (%)	Clinical significance
PVS	~50–60%	Most common defect; often associated with a dysplastic pulmonary valve
HCM	~20–30%	May result in arrhythmias or sudden cardiac death
ASD	~6–10%	Frequently of the ostium secundum type
VSD	~5–10%	Typically small and hemodynamically insignificant
PDA	<5%	May persist beyond infancy
Branch pulmonary artery stenosis	~10%	May coexist with pulmonary valve stenosis (PVS)
Coarctation of the aorta	Rare (~1–2%)	More commonly seen in other RASopathies
Mitral valve abnormalities	Uncommon	Includes mitral valve prolapse and insufficiency
ECG abnormalities	Common (~40–60%)	Includes left axis deviation, RSR' in V1, and prolonged QTc
Arrhythmias	Rare but serious	Typically associated with hypertrophic cardiomyopathy (HCM) or accessory pathways

ASD, Atrial septal defect; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; PDA, patent ductus arteriosus; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

association with NS and remains the most commonly mutated, accounting for approximately 50% of all NS cases and 85% of cases of LEOPARD syndrome (NSML). *PTPN11* encodes SHP2, a cytoplasmic enzyme widely expressed across tissues, which regulates multiple intracellular signaling pathways involved in cell proliferation, differentiation, and survival. SHP2 plays a critical role in normal cardiac development and function, and variants in *PTPN11* are most commonly associated with PVS and HCM.[5,6]

Noonan syndrome is a complex genetic disorder characterized by cardiac anomalies, growth retardation, developmental delays, and neuropsychosocial issues. Long-term follow-up studies have shown that the mortality rate in individuals with NS is approximately three times higher than in the general population. While most deaths are related to severe cardiac conditions, factors such as cognitive impairments, poor educational outcomes, and social isolation also negatively impact quality of life. Therefore, early diagnosis and preventive interventions are crucial in managing NS. However, the phenotypic heterogeneity of the syndrome often complicates the diagnostic process.[7]

In our case, the diagnosis was complicated by several factors. One of the most significant challenges was the patient's chief complaint of chest pain, accompanied by ST-segment elevation in the inferior leads on ECG. While ST elevation on ECG is a critical finding for the diagnosis of myocardial infarction, studies have shown that a significant number of patients with hypertrophic cardiomyopathy also exhibit ST-segment elevation.[8,9] In a study by Yang et al.,[10] ST-segment elevations in patients with HCM were compared to those in patients with myocardial infarction. It was found that ST elevations in HCM patients persisted longer and were more frequently associated with T-wave inversions in multiple leads, distinguishing them from myocardial infarction cases. In our patient, follow-up ECGs showed a persistent ST elevation pattern and T-wave changes in leads V2-V3, findings consistent with those reported by Yang et al.[10] Additionally, electrocardiographic findings such as left axis deviation, small R-waves in the left precordial leads, large S-waves in the right precordial leads, abnormal Q-waves, and/or a wide QRS complex have also been reported in patients with NS.[11]

Another challenge in diagnosis was the patient's normal height. Short stature is a common feature in individuals with NS, particularly in those with *PTPN11* variants. However, some patients may present with normal height, indicating that this feature alone is not sufficient to rule out the diagnosis.[12] The absence of prominent facial features, such as palpebral ptosis, further complicated the diagnostic process. Moreover, the negative family history in this case added another layer of complexity. Nevertheless, as mentioned earlier, de novo variants occur in a considerable number of cases, indicating that a negative family history does not necessarily exclude the condition.

As previously discussed, the diagnostic challenges of NS can often be addressed through detailed anamnesis and a comprehensive physical examination. Despite several complicating factors in our patient's case, key clinical findings played a significant role in reaching the correct diagnosis. The patient exhibited a prominent pectus excavatum, one of the characteristic features of NS.[13] Additionally, the presence of a murmur in the pulmonary area, skin lesions, and mild left palpebral ptosis were crucial diagnostic clues. Although the chest deformity made echocardiographic evaluation more challenging, the use of multimodal imaging, including cardiac MRI, provided valuable insights by revealing localized hypertrophy that might have otherwise been overlooked. The application of advanced imaging techniques, particularly cardiac MRI, was pivotal in identifying subtle hypertrophic changes, underscoring the importance of a multimodal approach in complex diagnostic cases. Furthermore, the presence of coronary artery ectasia, a finding previously reported in NS, offered additional support for the diagnosis.[14]

Conclusion

This case highlights the diagnostic challenges associated with NS, emphasizing the importance of a detailed medical history and comprehensive physical examination in reaching an accurate diagnosis. Given the heterogeneous clinical presentation, it is essential to utilize available diagnostic tools, such as cardiac MRI and other imaging techniques, to support clinical findings. The combination of careful physical assessment and advanced imaging can significantly aid in distinguishing NS from other conditions, ultimately facilitating timely and appropriate management.

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.

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

Use of AI for Writing Assistance: No AI-usage was declared by the authors.

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

Peer-review: Externally peer-reviewed.

References

1. Zenker M, Edouard T, Blair JC, Cappa M. Noonan syndrome: improving recognition and diagnosis. *Arch Dis Child*. 2022;107(12):1073-1078. [CrossRef]
2. Faienza MF, Meliota G, Mentino D, et al. Cardiac Phenotype and Gene Mutations in RASopathies. *Genes (Basel)*. 2024;15(8):1015. [CrossRef]
3. Zenker M. Clinical overview on RASopathies. *Am J Med Genet C Semin Med Genet*. 2022;190(4):414-424. [CrossRef]
4. Johnston JJ, van der Smagt JJ, Rosenfeld JA, et al.; Members of the Undiagnosed Diseases Network; Zenker M, Lee B, Biesecker LG. Autosomal recessive Noonan syndrome associated with biallelic LZTR1 variants. *Genet Med*. 2018;20(10):1175-1185. [CrossRef]
5. Leoni C, Blandino R, Delogu AB, et al. Genotype-cardiac phenotype correlations in a large single-center cohort of patients affected by RASopathies: Clinical implications and literature review. *Am J Med Genet A*. 2022;188(2):431-445. [CrossRef]
6. Asmamaw MD, Shi XJ, Zhang LR, Liu HM. A comprehensive review of SHP2 and its role in cancer. *Cell Oncol (Dordr)*. 2022;45(5):729-753. [CrossRef]
7. Binder G, Grathwol S, von Loeper K, et al. Health and quality of life in adults with Noonan syndrome. *J Pediatr*. 2012;161(3):501-505. e1. [CrossRef]
8. Thygesen K, Alpert JS, Jaffe AS, et al.; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231-2264. [CrossRef]
9. Sheikh N, Papadakis M, Panoulas VF, et al. Comparison of hypertrophic cardiomyopathy in Afro-Caribbean versus white patients in the UK. *Heart*. 2016;102(22):1797-1804. [CrossRef]

10. Yang YQ, Pei YH, Situ QS, Du XZ, Chen XH, He AX. ECG criteria to distinguish hypertrophic cardiomyopathy featured with "Pseudo-STEMI" from acute ST-elevation myocardial infarction. *J Electrocardiol*. 2023;77:10-16. [CrossRef]
11. Vos E, Leenders E, Werkman SR, Udink Ten Cate FEA, Draaisma JMT. The added value of the electrocardiogram in Noonan syndrome. *Cardiol Young*. 2022;32(6):936-943. [CrossRef]
12. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet*. 2013;381(9863):333-342. [CrossRef]
13. Athota JP, Bhat M, Nampoothiri S, et al. Molecular and clinical studies in 107 Noonan syndrome affected individuals with *PTPN11* mutations. *BMC Med Genet*. 2020;21(1):50. [CrossRef]
14. Ly R, Soulat G, Iserin L, Ladouceur M. Coronary artery disease in adults with Noonan syndrome: Case series and literature review. *Arch Cardiovasc Dis*. 2021;114(8-9):598-605. [CrossRef]
15. van der Burgt I. Noonan syndrome. *Orphanet J Rare Dis*. 2007;2:4. [CrossRef]
16. Prendiville TW, Gauvreau K, Tworog-Dube E, et al. Cardiovascular disease in Noonan syndrome. *Arch Dis Child*. 2014;99(7):629-634. [CrossRef]

ARCHIVES OF THE
TURKISH SOCIETY
OF CARDIOLOGY

Official journal of the
TURKISH
SOCIETY OF
CARDIOLOGY

Multimodality Imaging of Neuroendocrine Tumor with Cardiac Metastasis

Kardiyak Metastazlı Nöroendokrin Tümörün Multimodal Görüntülemesi

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 42-year-old man with a biopsy-proven neuroendocrine tumor (NET) presented with progressive dyspnea. Fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrated widespread metastatic disease with multifocal myocardial uptake, predominantly involving the left ventricle (Figure 1A). Transthoracic echocardiography (TTE) revealed multiple intramyocardial hyperechoic masses (Figure 1B, Video 1). Cardiac magnetic resonance imaging showed diffuse intramyocardial metastatic infiltration, with the largest lesion located in the basal anterolateral wall (Figure 1C). Left ventricular ejection fraction was preserved; however, global longitudinal strain (GLS) was reduced (Figure 1D). Combination chemotherapy with etoposide and cisplatin was initiated. Despite a marked reduction in myocardial FDG uptake on post-treatment FDG-PET (Figure 2A), follow-up echocardiography, including strain imaging, demonstrated persistence of intramyocardial hyperechoic masses and ongoing subclinical systolic dysfunction (Figures 2B-C, Video 2).

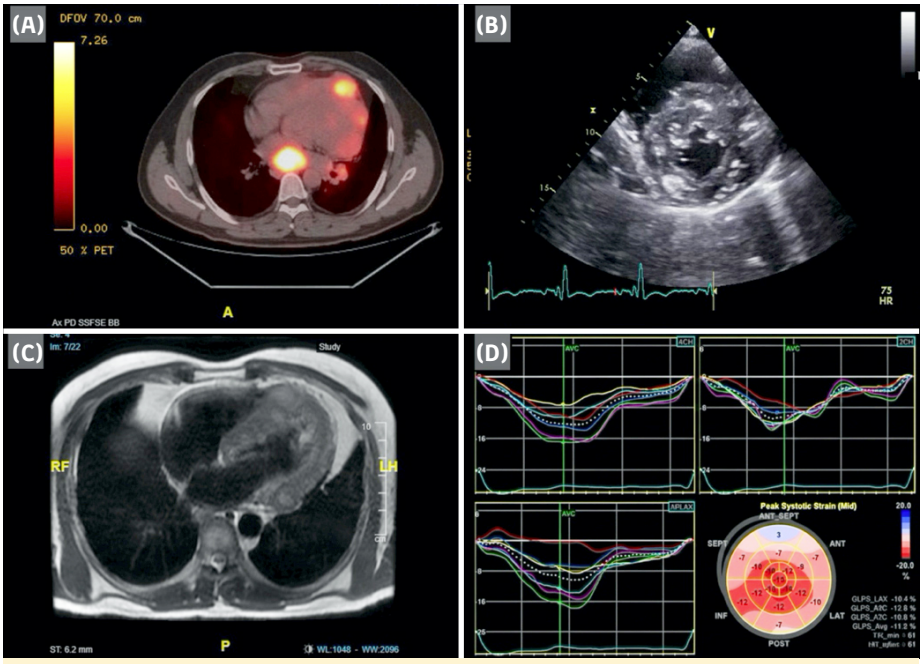


Figure 1. Pre-treatment multimodality imaging of cardiac metastases from a neuroendocrine tumor. (A) Baseline axial fused fluorodeoxyglucose positron emission tomography (FDG-PET) image demonstrating multifocal intense myocardial FDG uptake, predominantly involving the left ventricle. (B) Parasternal short-axis transthoracic echocardiography showing multiple intramyocardial hyperechoic masses. (C) Black-blood spin-echo cardiac magnetic resonance image revealing diffuse intramyocardial metastatic infiltration, most prominent in the basal anterolateral wall. (D) Baseline two-dimensional speckle-tracking analysis showing reduced myocardial tissue deformation, particularly in the basal anteroseptal region (global longitudinal strain: -11.2%).

Uğur Nadir Karakulak[1]
Damla Yalçınkaya Öner[2]
Necla Özer[1]

[1]*Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye*
[2]*Department of Cardiology, Karaman Training and Research Hospital, Karaman, Türkiye*

Corresponding author:
Uğur Nadir Karakulak
✉ ukarakulak@gmail.com

Received: January 08, 2026
Accepted: February 01, 2026

Cite this article as: Karakulak UN, Yalçınkaya Öner D, Özer N. Multimodality Imaging of Neuroendocrine Tumor with Cardiac Metastasis. *Turk Kardiyol Dern Ars.* 2026;54(3):282-283.

DOI: 10.5543/tkda.2026.74315

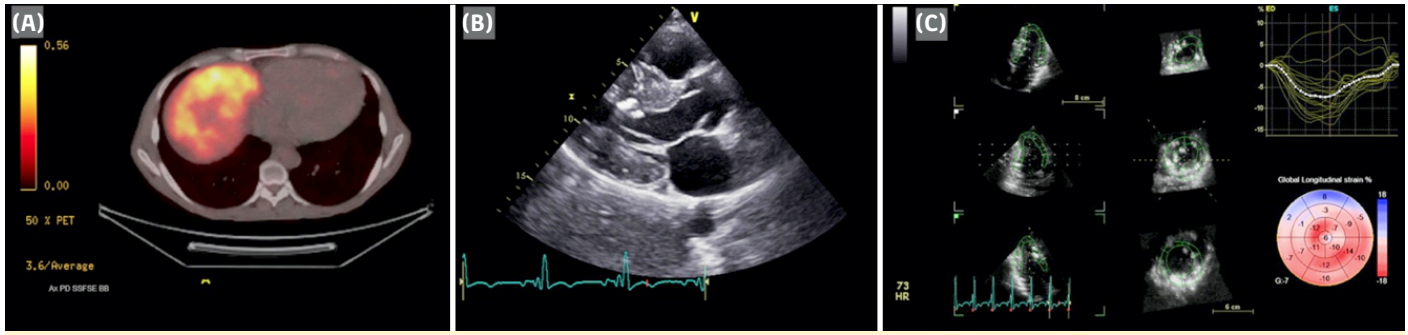


Figure 2. Post-treatment anatomic and metabolic response of cardiac metastases. (A) Follow-up axial fused fluorodeoxyglucose positron emission tomography (FDG-PET) image demonstrating marked reduction in myocardial FDG uptake, consistent with significant metabolic regression. (B) Follow-up parasternal long-axis transthoracic echocardiography showing persistence of intramyocardial hyperechoic masses despite therapy. (C) Follow-up speckle-tracking echocardiography with bull's-eye representation demonstrating persistently reduced global longitudinal strain (−7.0%), indicating ongoing mechanical dysfunction.

This case illustrates that myocardial metastases from NET may persist morphologically despite metabolic remission. Furthermore, echocardiography including strain imaging may substantially underestimate treatment response, whereas FDG-PET serves as a robust marker of therapeutic efficacy in cardiac metastatic disease.

The detection of cardiac involvement in NET requires a high index of clinical suspicion and recognition of specific imaging "red flags." Based on multimodality imaging, the following features should alert clinicians to potential myocardial metastasis:

- **On TTE:** The presence of multiple, round, well-defined hyperechoic masses within the myocardium.
- **On magnetic resonance imaging (MRI):** Diffuse intramyocardial metastatic infiltration, similar to TTE, particularly involving the left ventricular walls.
- **On positron emission tomography (PET) imaging:** Multifocal and intense myocardial FDG uptake, serving as a robust metabolic indicator of metastatic disease in patients with known NET.

Management of cardiac metastasis from NET is primarily dictated by tumor grade and the extent of systemic involvement. Because cardiac metastases frequently coexist with widespread systemic disease, systemic therapy remains the cornerstone of management. In poorly differentiated or aggressive NETs, combination chemotherapy regimens such as etoposide and cisplatin are commonly employed. Surgical resection may be considered for solitary or symptomatic cardiac lesions but is often limited by the multifocal nature of the infiltration.

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

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

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: No use of AI-asssisted technologies was declared by the authors.

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

Peer-review: Internally peer-reviewed.

Video 1. Parasternal short-axis transthoracic echocardiography showing multiple intramyocardial hyperechoic masses.

Video 2. Follow-up parasternal long-axis transthoracic echocardiography demonstrating persistence of intramyocardial hyperechoic masses despite therapy.

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Clock–Time or Sleep–Wake Cycle in the Definition of Dipper and Non-Dipper Classification: A Methodological Perspective

Dipper ve Non-Dipper Sınıflandırmasının Tanımında Saat-Zaman veya Uyku-Uyanıklık Döngüsü: Metodolojik Bir Bakış Açısı

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with interest the study by İliş et al.[1] evaluating dipper and non-dipper blood pressure patterns in hypertensive patients living at moderate altitude. Using ambulatory blood pressure monitoring (ABPM), the authors reported a high prevalence of the non-dipper pattern and demonstrated its association with impaired left ventricular global longitudinal strain (LVGLS), thereby providing valuable insights into subclinical cardiac involvement in this population.

Nevertheless, we would like to highlight a methodological aspect that may be relevant to the interpretation of the reported findings.

In the study, dipper and non-dipper classification was based on fixed clock–time intervals, defined as daytime (06:00–22:00) and nighttime (22:00–06:00). Although the Methods section refers to "awake" and "sleep" periods, no details are provided regarding how these periods were determined in relation to individual sleep–wake cycles. The absence of sleep diaries, patient-reported sleep times, or objective tools such as actigraphy suggests that the classification was effectively based on predefined clock–time intervals.

The concepts of dipper and non-dipper hypertension were first introduced by O'Brien et al.,[2] and in this original description, nocturnal and daytime blood pressure values were assessed using fixed time intervals, consistent with the methodological standards of that period. This approach was subsequently widely adopted. However, reliance on clock–time–based definitions has been discussed in the literature for its limited ability to capture interindividual variability in sleep–wake behavior, particularly in individuals with delayed sleep onset, shift work, or irregular sleep habits, where misclassification may occur.

In contrast, sleep–wake–based assessment relies on comparing blood pressure measurements obtained during an individual's actual sleep and wake periods. Consensus documents on ABPM methodology emphasize that sleep–time and awake–time blood pressure values should be defined according to individualized sleep–wake cycles rather than rigid clock–time intervals.[3] In addition, sleep–wake–based approaches have been shown to reflect circadian blood pressure patterns more accurately and to enhance the prognostic value of ABPM.[4] This perspective is also supported by the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines, which draw attention to the limitations of strict clock–time–based definitions and encourage more individualized, physiologically grounded assessments when feasible.[5]

This methodological consideration becomes particularly relevant when the clinical characteristics of the study population are taken into account. The higher prevalence of advanced age, diabetes mellitus, and chronic obstructive pulmonary disease in the non-dipper group suggests a clinical context in which sleep patterns may be more heterogeneous. Accordingly, the use of clock–time–based classification should be considered when interpreting the reported non-dipper prevalence and the clinical implications derived from the findings.

Ramazan Astan[1]
Ersin Sarıçam[2]
Fehmi Kaçmaz[3]
Erdoğan İlkay[2]

[1]Department of Cardiology, Batman Training and Research Hospital, Batman, Türkiye
[2]Department of Cardiology, Medicana International Ankara Hospital, Ankara, Türkiye
[3]Department of Cardiology, Üsküdar University Faculty of Medicine, İstanbul, Türkiye

Corresponding author:
Ramazan Astan
✉ drastan80@gmail.com

Received: January 16, 2026
Accepted: January 21, 2026

Cite this article as: Astan R, Sarıçam E, Kaçmaz F, İlkay E. Clock–Time or Sleep–Wake Cycle in the Definition of Dipper and Non-Dipper Classification: A Methodological Perspective. *Turk Kardiyol Dern Ars.* 2026;54(3):284–285.

DOI: 10.5543/tkda.2026.62747

In conclusion, the study by İliş et al.[1] offers important information regarding hypertension and circadian blood pressure patterns at moderate altitude. However, the use of fixed clock–time intervals for dipper/non-dipper classification represents a methodological limitation that should be acknowledged when interpreting the results. Future studies incorporating sleep–wake–based definitions may allow for more accurate risk stratification and clearer clinical guidance.

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

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

References

1. İliş D, Arslan A, Artaç İ, et al. Clinical and Demographic Characteristics of Dipper and Non-Dipper Hypertensive Patients at Moderate Altitude. *Turk Kardiyol Dern Ars*. 2026;54(1):33-40. [CrossRef]
2. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet*. 1988;2(8607):397. [CrossRef]
3. International Society for Chronobiology; American Association of Medical Chronobiology and Chronotherapeutics; Spanish Society of Applied Chronobiology, Chronotherapy, and Vascular Risk; Spanish Society of Atherosclerosis; Romanian Society of Internal Medicine; Hermida RC, Smolensky MH, Ayala DE, Portaluppi F. 2013 ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals. *Chronobiol Int*. 2013;30(3):355-410. [CrossRef]
4. Hermida RC, Ayala DE, Smolensky MH. Sleep-time blood pressure: prognostic value and relevance for hypertension management. *Sleep Med Rev*. 2017;33:17-27. [CrossRef]
5. Williams B, Mancia G, Spiering W, et al.; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. Erratum in: *Eur Heart J*. 2019;40(5):475. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications

Hiperlipidemili Yaşlı Hastalarda Kümülatif LDL-C ve Lipoprotein(a): Metodolojik Hususlar ve Klinik Etkileri

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the article by Yurtseven et al.,[1] recently published in the Archives of the Turkish Society of Cardiology, which investigated lipoprotein(a) [Lp(a)] and cumulative low-density lipoprotein cholesterol (LDL-C) as predictors of coronary artery disease (CAD) in statin-naïve elderly individuals with hyperlipidemia.

The authors found that male sex, cumulative LDL-C, and elevated Lp(a) independently predict CAD in individuals aged ≥70 years with LDL-C ≥160 mg/dL. The SAFEHEART risk score outperformed SCORE2-OP in this population.[1] Given the ongoing debate regarding statin initiation in elderly patients, these findings are clinically relevant. However, we would like to highlight several methodological and interpretive considerations that warrant further evaluation.

First, the cumulative LDL-C exposure approach, which multiplies a single measurement by age, should be interpreted with caution. The authors acknowledge that this method may overestimate lifelong LDL-C burden, as LDL-C levels tend to increase with age. A single cross-sectional measurement cannot accurately reflect decades-long LDL-C exposure. Mendelian randomization studies by Ference et al.[2] suggest that integrating serial LDL-C measurements over time provides a more physiologically accurate estimate of cumulative exposure.

Second, the SAFEHEART risk equation was developed and validated in patients with familial hypercholesterolemia (FH). However, its application in this cohort—where only 5.4% met the Dutch Lipid Clinic Network criteria for probable FH—raises concerns regarding external validity. The incorporation of Lp(a) into the equation may explain its apparent superiority over SCORE2-OP in this Lp(a)-enriched cohort, rather than reflecting its performance in the broader elderly hyperlipidemia population. Therefore, before recommending its widespread clinical use, SAFEHEART should be prospectively validated in non-FH elderly populations.[3]

Third, the study population was predominantly female (68.3%), which may have influenced the observed effect sizes and limited generalizability to elderly men. Although interaction terms between sex and both Lp(a) and cumulative LDL-C were not statistically significant, the study was likely underpowered to detect such interactions given the sample size of 202 patients. In light of evidence suggesting that sex-specific Lp(a) cut-off values may be warranted for cardiovascular risk stratification, sex-stratified analyses or the inclusion of a larger cohort would strengthen the conclusions.[4]

Fourth, Lp(a) levels were reported in mg/dL rather than nmol/L. Given the well-recognized interindividual variability in Lp(a) particle size, reporting in nmol/L is increasingly preferred in contemporary guidelines and improves cross-study comparability. Additionally, the absence of genetic testing for FH mutations or LPA kringle-IV type 2 (KIV-2) repeat number leaves the molecular basis of elevated Lp(a) uncharacterized in this cohort, thereby limiting mechanistic interpretation.[5]

Fatih Aydın

Department of Cardiology, Eskişehir City Hospital, Eskişehir, Türkiye

Corresponding author:
Fatih Aydın
✉ drfatihaydin@hotmail.com

Received: March 01, 2026
Accepted: March 06, 2026

Cite this article as: Aydın F. Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications. *Turk Kardiyol Dern Ars.* 2026;54(3):286-287.

DOI: 10.5543/tkda.2026.46309

Finally, the retrospective, single-center design involving a referred, symptomatic population introduces Berkson-type bias and limits the generalizability of the findings to community-dwelling elderly individuals. Prospective studies with longitudinal follow-up, incorporating incident cardiovascular events as endpoints rather than prevalent CAD, will be essential to confirm the prognostic utility of cumulative LDL-C and Lp(a) in this age group.

In conclusion, Yurtseven et al.[1] identify Lp(a) and cumulative LDL-C as underappreciated risk indicators in elderly patients with hyperlipidemia. In this vulnerable and growing population, future prospective studies should address the methodological considerations outlined above to strengthen the evidence base for lipid-lowering therapy strategies.

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

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

References

1. Yurtseven E, Ural D, Yaşa G, et al. Lipoprotein(a) and Cumulative Low-Density Lipoprotein Cholesterol as Predictors of Coronary Artery Disease in Statin-Naïve Elderly Individuals with Hyperlipidemia. *Turk Kardiyol Dern Ars*. 2026;54(2):101-108. [CrossRef]
2. Ference BA, Braunwald E, Catapano AL. The LDL cumulative exposure hypothesis: evidence and practical applications. *Nat Rev Cardiol*. 2024;21(10):701-716. [CrossRef]
3. Pérez de Isla L, Alonso R, Mata N, et al. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation*. 2017;135(22):2133-2144. [CrossRef]
4. Yurtseven E, Ural D, Gursoy E, et al. Is There a Need for Sex-Tailored Lipoprotein(a) Cut-Off Values for Coronary Artery Disease Risk Stratification? *Clin Cardiol*. 2024;47(9):e70012. [CrossRef]
5. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J*. 2022;43(39):3925-3946. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Reply to the Letter to the Editor: Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications

Editöre Mektup Yanıtı: Hiperlipidemili Yaşlı Hastalarda Kümülatif LDL-C ve Lipoprotein(a): Metodolojik Hususlar ve Klinik Etkileri

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

Ece Yurtseven[1]
Dilek Ural[1]
Gizem Yaşa[2]
Berk Kabadayı[2]
Özgür Özdemir[2]
Erol Gürsoy[1]
Saide Aytekin[1]
Vedat Aytekin[1]
Meral Kayıkçıoğlu[3]

[1]Department of Cardiology, Koç University Faculty of Medicine, İstanbul, Türkiye
[2] Koç University Faculty of Medicine, İstanbul, Türkiye
[3]Department of Cardiology, Ege University Faculty of Medicine, İzmir, Türkiye

Corresponding author:
Ece Yurtseven
✉ eyurtseven@kuh.ku.edu.tr

Cite this article as: Yurtseven E, Ural D, Yaşa G, et al. Reply to the Letter to the Editor: Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications. *Turk Kardiyol Dern Ars.* 2026;54(3):288-289.

DOI: 10.5543/tkda.2026.17435

To the Editor,

We thank the authors[1] for their interest in our study[2] and for their thoughtful and constructive comments regarding our work. We appreciate the opportunity to clarify several methodological aspects and to further elaborate on the interpretation of our findings.

We agree that estimating cumulative LDL-C exposure using a single measurement multiplied by age may not fully reflect lifelong lipid burden, and we fully acknowledge the authors' concern. However, this limitation was already explicitly stated in our manuscript, where we noted that this approach may lead to a modest overestimation due to age-related increases in LDL-C levels. Our aim was to provide a practical and clinically applicable surrogate marker in a real-world elderly population, where long-term serial lipid measurements are rarely available. Similar approaches have also been reported in the literature.[3] While longitudinal lipid data or Mendelian randomization approaches would provide a more precise estimation, such data are not always feasible in routine clinical practice; therefore, our method should be interpreted as a pragmatic approximation.

Similarly, although the SAFEHEART risk equation was originally developed in a familial hypercholesterolemia population, its use in our study was not intended as a direct external validation but rather as a comparative tool to explore whether the inclusion of lipid-related parameters, particularly Lp(a), improves risk discrimination in elderly individuals with markedly elevated LDL-C levels.[4] Notably, a substantial proportion of our cohort was classified as possible or probable FH, which further supports the relevance of this approach. In addition, Lp(a) levels are known to increase in women after the menopausal transition, which may partly explain the higher Lp(a) levels observed in elderly populations independent of FH.[5] Therefore, it is reasonable that Lp(a) levels in our cohort were higher than those reported in the general population.[6,7] This also supports the clinical relevance of incorporating Lp(a) into risk assessment in this age group. Importantly, we clearly stated in our manuscript that the applicability of SAFEHEART in non-FH elderly populations requires prospective validation, and our findings should be interpreted as hypothesis-generating rather than definitive.

We also acknowledge that the predominance of female participants may influence generalizability, a point that was already clearly discussed in the limitations section of our manuscript. Although interaction analyses between sex and both Lp(a) and cumulative LDL-C were not statistically significant, we agree that the study may be underpowered to detect subtle interactions and that larger, more balanced cohorts would provide further insight into potential sex-specific effects.

Regarding Lp(a) measurement, values were reported in mg/dL in accordance with the standardized assay used in our center's routine clinical practice. We agree that reporting in nmol/L would improve comparability across studies; however, this limitation was already explicitly acknowledged in our manuscript. Current consensus documents also emphasize the variability in Lp(a) particle size and the challenges in standardization across assays.[8]

Similarly, the absence of genetic testing for FH mutations or LPA variants was acknowledged, and we agree that such data would provide additional mechanistic insight.

Finally, we fully agree that the retrospective, single-center design and the inclusion of a referred, symptomatic population may introduce selection bias, including Berkson-type bias. This issue was already extensively addressed in the limitations section of our manuscript. We clearly stated that our cohort represents a higher-risk, physician-referred elderly population, and therefore the findings may not be directly generalizable to community-dwelling individuals. Importantly, our aim was not to provide population-level risk estimates but rather to identify clinically relevant markers associated with prevalent CAD in a real-world elderly cohort, where decision-making regarding lipid-lowering therapy remains challenging.

In conclusion, we appreciate the authors' valuable comments, which highlight important methodological considerations. As emphasized in our manuscript, our findings should be interpreted within the context of the study design and its limitations, many of which were already acknowledged. We believe that our study contributes to the ongoing discussion on cardiovascular risk stratification in elderly individuals by suggesting that cumulative LDL-C exposure and Lp(a) may provide additional clinically relevant information beyond traditional risk scores. Further prospective studies are warranted to validate these findings.

References

1. Aydın F. Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications. *Turk Kardiyol Dern Ars*. 2026;54(3):286–287.
2. Yurtseven E, Ural D, Yaşa G, et al. Lipoprotein(a) and Cumulative Low-Density Lipoprotein Cholesterol as Predictors of Coronary Artery Disease in Statin-Naïve Elderly Individuals with Hyperlipidemia. *Turk Kardiyol Dern Ars*. 2026;54(2):101-108. [CrossRef]
3. Yamaji T, Yusoff FM, Kishimoto S, et al. Association of cumulative low-density lipoprotein cholesterol exposure with vascular function. *J Clin Lipidol*. 2024;18(2):e238-e250. [CrossRef]
4. Pérez de Isla L, Alonso R, Mata N, et al. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation*. 2017;135(22):2133-2144. [CrossRef]
5. Yurtseven E, Ural D, Gursoy E, et al. Is There a Need for Sex-Tailored Lipoprotein(a) Cut-Off Values for Coronary Artery Disease Risk Stratification? *Clin Cardiol*. 2024;47(9):e70012. [CrossRef]
6. Kayıkçıoğlu M, Yurtseven E. The Burden of Lipoprotein (a) in Türkiye: What We Know and What We Need to Learn. *Turk Kardiyol Dern Ars*. 2024;52(6):390-393. [CrossRef]
7. Güngör B, Şimşek B, Çınar T, et al. Assessment of Lipoprotein (a) Levels in Patients with Atherosclerotic Cardiovascular Disease: Single Center Experience from Türkiye. *Turk Kardiyol Dern Ars*. 2024;52(6):384-389. [CrossRef]
8. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J*. 2022;43(39):3925-3946. [CrossRef]

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Pulmo: Patient Education in Pulmonary Hypertension via Artificial Intelligence–Based Digital Characters

Pulmo: Yapay Zeka Tabanlı Dijital Karakterler Aracılığıyla Pulmoner Hipertansiyonda Hasta Eğitimi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

Patients with pulmonary hypertension (PH) and their caregivers often encounter technical, complex, and emotionally overwhelming terminology when seeking information; this can inadvertently increase anxiety and hinder understanding.[1,2]

The key innovation of the Pulmo project lies in the strategic use of an anthropomorphic lung character, designed through artificial intelligence, to mediate the patient's relationship with medical information. The character's persona was meticulously crafted to be warm, explanatory, trustworthy, and mildly humorous, with the aim of transforming the learning experience from a formal, didactic session into a comfortable dialogue with a trusted peer.

Figure 1. Pulmo's different characters: (A) Pulmo; (B) Chef Pulmo; (C) Yogi Pulmo; (D) Traveler Pulmo.

The visual identity and personality of Pulmo were established through an iterative process involving large language models (e.g., ChatGPT) for initial conceptualization. Advanced generative AI tools (e.g., Gemini) were subsequently employed to create diverse stylistic variations, such as depicting Pulmo in different roles (e.g., a chef for nutrition content, a yoga instructor for respiratory information) (Fig. 1). This approach ensured that the character remained visually engaging and contextually relevant across various topics, while strictly maintaining a consistent and recognizable core identity to preserve the audience's trust.[3]

All content is prepared by pulmonary hypertension specialists to ensure clinical accuracy and compliance with current guidelines and is subsequently reviewed by the same specialists after AI processing. Only after this human-centered validation is the information translated into simplified, accessible language.

The Grok AI tool was used to generate natural, fluent, and engaging animations, utilizing facial expressions and gestures to reinforce messaging and increase relatability. Additionally, subtitles were systematically added to all videos to ensure accessibility for users who may be unable to listen to audio content due to their environment or circumstances. Despite being active on Instagram (@mypulmo) for only one month and currently providing content only in Turkish, Pulmo has already reached 425 followers. A YouTube channel has also been created to reach a wider audience and offer content in different languages (https://youtube.com/@mypulmo?si=6-Dl386gfB2NPr4P).

Serdar Kula

Department of Pediatric Cardiology, Gazi University Faculty of Medicine, Ankara, Türkiye

Corresponding author:
Serdar Kula
✉ kula@gazi.edu.tr

Received: January 07, 2026
Accepted: March 07, 2026

Cite this article as: Kula S. Pulmo: Patient Education in Pulmonary Hypertension via Artificial Intelligence–Based Digital Characters. *Turk Kardiyol Dern Ars.* 2026;54(3):290–291.

DOI: 10.5543/tkda.2026.07902

Table 1. Sample questions asked by patients to Pulmo

Secondary pulmonary hypertension was diagnosed. What is secondary pulmonary hypertension?
Why is it so difficult to access medication for pulmonary hypertension?
What should patients with pulmonary hypertension eat?
Is it safe for a patient with pulmonary hypertension to keep a cat at home?
Which vaccines should we receive?
What is NT-proBNP? What does a decrease indicate?
Can we use flu medication when we have the flu?
Which herbal teas are beneficial for patients with pulmonary hypertension?
Would using a triflo device be beneficial?
How far should I walk during the 6-minute walk test?
What should I do to treat anemia?
How much water should I drink daily?
Can undergoing an ablation cause pulmonary hypertension?
I want to do Pilates; is it safe?

Although the project is still in its early stages, the limited feedback received indicates that patients frequently ask Pulmo questions about symptom management and lifestyle changes (Table 1).

At this stage, the study does not include a quantitative or systematic evaluation of its impact (i.e., improvements in knowledge level, behavioral change, or clinical outcomes). A formal evaluation of clinical outcomes and patient knowledge retention is planned. The current implementation of Pulmo is limited to a single language (Turkish) and a restricted number of social media platforms, which may limit the generalizability of the findings. Although the content is designed to be broadly accessible, its effectiveness across different age groups, biological sex, educational backgrounds, and levels of digital health literacy has not yet been systematically assessed. As an early-stage initiative, Pulmo has not yet evaluated whether engagement and comprehension differ across patient subgroups, such as age, biological sex, educational level, or digital health literacy. While the use of short-form content enhances engagement, it may also carry a risk of oversimplifying complex medical concepts, and sex-specific educational needs in PH have not yet been clearly addressed.

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

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

References

1. Canbeyli F, Atasayan V, Tokgoz S, et al. Health-related quality of life and parental depression in children with pulmonary arterial hypertension. *Pediatr Pulmonol*. 2022;57(2):544-550. [CrossRef]
2. Ford HJ, Brunetti C, Ferrari P, et al. Exploring the patient perspective in pulmonary hypertension. *Eur Respir J*. 2024;64(4):2401129. [CrossRef]
3. Wang YF, Hsu YF, Fang KT, Kuo LT. Gamification in medical education: identifying and prioritizing key elements through Delphi method. *Med Educ Online*. 2024;29(1):2302231. [CrossRef]