



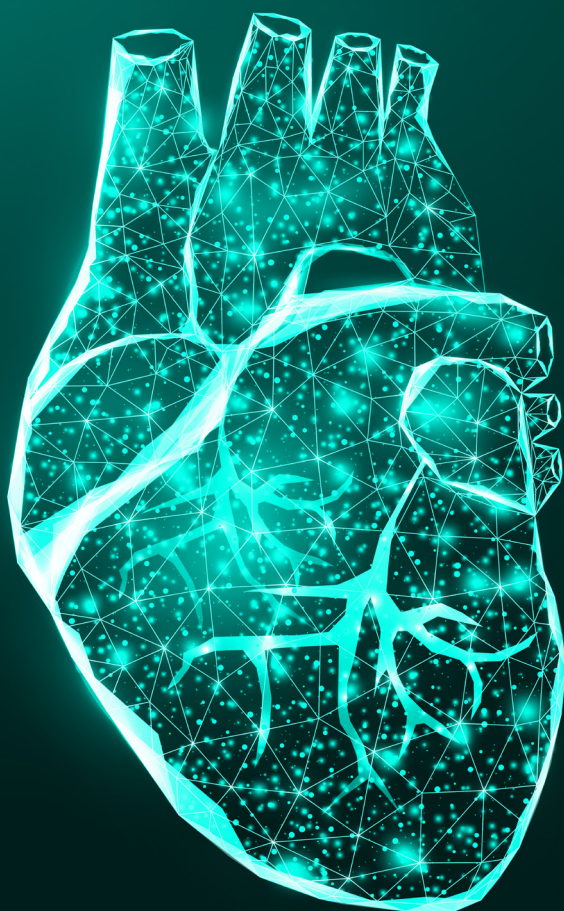
# INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

VOLUME: 10

ISSUE: 4

DECEMBER 2024



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Web: www.galenos.com.tr  
Publisher Certificate Number: 14521  
Publication Date: December 2024  
ISSN: 2405-8181 E-ISSN: 2405-819X  
International scientific journal published quarterly.

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OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

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The journal is published online.

**Owner:** Ömer Kozan on behalf of the Cardiovascular Academy Society

**Responsible Manager:** Mehdi Zoghi

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DOI: 10.4274/ijca.2024.63825

Int J Cardiovasc Acad 2024;10(4):82-90

# Current Clinical Perspectives on Takotsubo Syndrome: Comprehensive analysis of Diagnosis, Management, and Pathophysiology

 Harsahaj Singh Wilkhoo,  Harshavardhini Visvanathan,  Swastika Chatterjee,  Suhaib Hussain,  Priyanshi Gundaniya,  Vetrichelvan Francis,  Bharat Singh,  Ashwini Anil Pillai

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## Abstract

Takotsubo syndrome (TTS), commonly referred to as stress-induced cardiomyopathy or broken heart syndrome, is a disorder characterized by acute left ventricular (LV) failure and apical ballooning that tends to occur due to extreme psychological or physical stress. Mainly affecting postmenopausal women, it has great similarities with other cardiac conditions like acute coronary syndrome. However, it has characteristic and distinct pathophysiology and disease progression. A wide range of diagnostic methods can be used, ranging from radiologic imaging to important biomarkers and biochemical analysis. These include cardiac magnetic resonance imaging, coronary angiography, echocardiography, echocardiogram, and inflammatory and cardiac biomarkers. There is a significant role for catecholamines in diagnosis. Key features include transient LV dysfunction and characteristic apical ballooning on imaging. The etiology involves a catecholamine surge leading to myocardial toxicity and microvascular dysfunction. Risk factors include age, sex, and stress, with additional associations such as pheochromocytoma and certain thyroid disorders. Management focuses on supportive care and pharmacological interventions, including beta-blockers, angiotensin converting enzyme inhibitors, and anticoagulants. Despite a good short-term prognosis, this condition can lead to severe complications and even sudden cardiac death. Long-term prognosis varies, with factors like reduced LV ejection fraction as well as old age affecting outcomes. This review summarizes the most updated information and is crucial for understanding TTS's diagnostic and therapeutic strategies. This review underlines the pathophysiology, risk factors, management strategies, and importance of nutritional management. Future research is recommended for improving diagnostic and therapeutic strategies, emphasizing early and accurate detection to mitigate risks and enhance patient outcomes.

**Keywords:** Takotsubo syndrome, cardiomyopathy, stress-induced cardiomyopathy, broken heart syndrome, cardiology, left ventricular dysfunction

## INTRODUCTION

Takotsubo syndrome (TTS) is a relatively rare but potentially life-threatening cardiac event. Characterized as an acute dysfunction of the left ventricular (LV) caused by dilation of the apex of the LV and the proximal myocardium.<sup>[1]</sup> TTS is often known as stress-induced cardiomyopathy or broken heart syndrome. In recent years, it has gained attention due to its

life-threatening complications and mortality potential. It is often associated with extreme emotional stress, which could result in severe LV impairment.<sup>[1]</sup> It often mimics the symptoms of acute coronary syndrome (ACS), making it important to have an accurate differential diagnosis. The most common manifestations of TTS are angina and dyspnea which worsens with exertion.<sup>[2,3]</sup> In terms of electrocardiogram (ECG) findings, TTS mimics the findings of ST-elevated ACS. The diagnosis is

**To cite this article:** Wilkhoo HS, Visvanathan H, Chatterjee S, Hussain S, Gundaniya P, Francis V, Singh B, Pillai AA. Current Clinical Perspectives on Takotsubo Syndrome: Comprehensive analysis of Diagnosis, Management, and Pathophysiology. Int J Cardiovasc Acad. 2024;10(4):82-90



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**Received:** 02.09.2024  
**Revised:** 15.10.2024  
**Accepted:** 30.10.2024  
**Published Online:** 16.12.2024



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often made by coronary angiography, which excludes coronary artery disease (CAD). Echocardiography findings show a great dilation of the left ventricle, which resembles a Japanese octopus trap or takotsubo.<sup>[2,4]</sup> The exact etiology of TTS remains unclear to date. However, it is linked to high levels of chronic stress or cases dealing with the sudden loss of a close person.<sup>[3]</sup> Drugs like angiotensin-converting enzyme inhibitors are seen to be giving promising results in terms of long-term prognosis. Other pharmacologic interventions like dual antiplatelet therapy are also beneficial treatment options.<sup>[2,5]</sup> This review provides in-depth and recent information about these management strategies. This review aims to provide the most recent updates on TTS and address gaps in the current literature.

## 1. Epidemiology

TTS was first described in 1990. It was observed to develop in any age group among males or females of any ethnicity. Approximately 90% of the patients were female, and 80% were aged >50 years. Surprisingly, this syndrome is also reported in children. TTS is more prevalent in women than men by 10%.<sup>[6-8]</sup> However, studies in Japan have found that TTS is more common in men in Japan.<sup>[9-11]</sup>

The exact reason why females are more prone to TTS is still not known but studies indicate that a low estrogen level in postmenopausal females can be the reason, as estrogen is essential in the regulation of sympathetic functioning and microvascular flow from the endothelial mechanisms. Some studies suggest an increase in sympathetic nervous system activity with age, especially in females, and that cardiac stimulation is enhanced because of an imbalance in neuronal norepinephrine homeostasis. As females age, there is a significant decrease in vagal tone and sensitivity of the baroreflex together with an associated rise in sympathetic activation causing the susceptibility of the myocardium to increase the levels of catecholamines.<sup>[8,12]</sup> From the data on TTS from different regions of the world according to National Institutes of Health reports 85-90% of the patients are females within the age group 65-70 years old. The probability of TTS recurrence ranges from 0% to 22%. Studies suggest a link between pheochromocytoma and TTS, as it has a 17.7% recurrence rate due to undiagnosed pheochromocytoma. The yearly rate of recurrence was seen to be 1.5% and the incidence of recurrence was increased by 1.2% at 6 months and 5% by 6 years.<sup>[13]</sup> Increasing anxiety and stress levels experienced in the Western populations resulted in a higher prevalence of TTS. During the coronavirus disease-19 (COVID-19) pandemic, the incidence of TTS has increased by 2 to 3 folds due to social isolation, stress, financial crisis, anxiety, and quarantine compared to before COVID-19.

## 2. Pathogenesis

The pathogenesis of TTS is complex and yet not entirely known. Several processes have been proposed as potential causes of TTS, such as sympathetic overactivity accompanied by elevated catecholamine levels, coronary spasm, microvascular dysfunction, reduced estrogen levels, inflammation, or compromised myocardial fatty acid metabolism.<sup>[14]</sup> However, it is believed that several processes play a role in TTS growth. Up to two-thirds of patients report experiencing preceded emotional or physical stress. This stressor includes natural disasters, death of a loved one, financial issues, previous surgery, trauma, and conditions associated with the central nervous system. This results in an excess of catecholamine being released, causing a catecholamine surge.<sup>[15]</sup> This condition is characterized by a shift in  $\beta$ -2-adrenoceptor signaling from Gs to Gi, resulting in negative inotropy and LV contractile dysfunction. This condition is called stimulus trafficking. The alpha-adrenergic receptors in the coronary vasculature's smooth muscle cells are activated by both norepinephrine and epinephrine, resulting in coronary vasoconstriction. These spasms can reduce blood flow to the myocardium, mimicking myocardial infarction (MI). Immediate coronary vasospasm occurs in 5-10% of patients, indicating that most do not experience it.<sup>[8]</sup> A previous study showed abnormally high levels of plasma catecholamines and stress-related neuropeptides in individuals with TTS compared with Killip class III ACS patients.<sup>[16]</sup> This suggested a connection between TTS and excessive catecholamine levels. The catecholamine surge leads to a cascade of events, starting from direct myocardial toxicity and microvascular and coronary artery dysfunction. Among the emitted catecholamines, only a small amount enters the bloodstream. The majority of it is sent straight to the myocardium's adrenoceptor by the sympathetic nerve endings, which release it into the nerve terminals. Catecholamine enters myocardial cells through  $\beta$ -adrenergic receptors and triggers a pathway that increases calcium influx, leading to cellular damage and toxicity.<sup>[15]</sup>

Catecholamines and endothelin predominantly cause vasoconstriction in the coronary microvasculature through  $\alpha$ 1-receptors and endothelin receptor type A. This indicates that acute microcirculatory disruption may play a significant role in TTS. Numerous non-invasive and invasive techniques have confirmed that coronary microvascular abnormalities could be responsible for TTS pathogenesis. However, whether microvascular dysfunction is the primary cause or secondary is still unclear.<sup>[17]</sup> Studies have suggested that perfusion of the myocardium examined while angiography is more compromised in patients with TTS than in patients with ST-segment elevation MI (STEMI) who show cardiac reperfusion. At the same time, it is less compromised than in patients with STEMI showing obstruction of microvasculature.<sup>[18]</sup> Microcirculatory dysfunction was prevalent during the acute phase of cardiomyopathy, and

microvascular damage was as severe as that in STEMI patients. Similarly, there have been reports of increased thrombolysis in MI (TIMI) frame counts and aberrant grades of TIMI myocardial perfusion. A quantitative coronary flow evaluation using the TIMI frame count (TFC) demonstrated prolonged corrected TFC in either the left anterior descending (LAD) artery alone or in all three coronary arteries.<sup>[19-21]</sup>

As estrogen provides a cardioprotective effect, a decrease in estrogen levels has been found to increase the susceptibility of cardiac myocyte to catecholamines.<sup>[10,22]</sup> This may be seen to be more prevalent among females. TTS associated with pheochromocytoma is a known but rare event. It is part of the Paraganglioma family of tumors and causes the gland to produce an excessive number of catecholamines. Studies have suggested rare cases of TTS after stroke. According to a study, 0.1% of patients develop TTS after 4 weeks following stroke.<sup>[23]</sup> Thyrotoxicosis can have adverse effects in the cardiovascular system. Takotsubo cardiomyopathy may present as a symptom of thyroid storm, possibly due to elevated levels or increased sensitivity to catecholamines.<sup>[24-26]</sup> Studies have contributed to understanding how the cardiovascular system responds to unexpected severe stress. It is observed that normal myocardial tissue generates most of its energy from fatty acid metabolism and 10% from glucose metabolism. TTS appears to be moving away from fatty acid metabolism toward glucose.<sup>[27]</sup> Inflammation is another mechanism that has drawn attention. Findings from cardiac magnetic resonance imaging (MRI) show myocardial edema, necrosis, and fibrosis. Microvascular dysfunction, evidenced by prolonged TIMI frame count and abnormal coronary flow patterns, contributes to the pathogenesis of the disease. TTS can also represent aborted MI, where imaging techniques like intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have revealed underlying atherosclerotic plaques and coronary vasospasm.<sup>[28-31]</sup>

### 3. Risk Factors

Strong evidence indicates that TTS is caused by extreme mental or physical stress. Other predisposing factors like cardiovascular risk factors, also play a role.<sup>[32]</sup> Risk factors include age, gender, diabetes mellitus, lung diseases, and even chronic kidney disease. These factors are associated with recurrence or even death in TTS.<sup>[33]</sup> Additionally, the risk of TTS increases with age >55 years, smoking, alcohol abuse, and anxiety. Cannabinoid use, including non-dependent cannabis, is linked to increased Traditional Chinese medicine risk, affecting cardiovascular function. Marijuana use is associated with transient LV ballooning and significant morbidity, contributing to the complexity and prognosis.<sup>[34]</sup> Comorbidities such as obesity, hypertension, dyslipidemia, psychological disorders, and malignancies. Other associated

conditions include neurologic and thyroid diseases. Some surgeries and interventions can also increase the risk of developing TTS. In some cases, immediate postoperative use of epinephrine and dobutamine as well as atrioventricular valve surgery. Although rare, precise and personalized risk assessment plans should be made for such patients.<sup>[32,34]</sup> TTS is less likely to recur if managed properly. Compared with individuals with no recurrence of TTS, those with recurrent TTS were more likely to have no clear stressful trigger at admission. Stroke, although with a lesser prevalence among patients with TTS based on a study, was observed to be associated with TTS. According to a study, these individuals were seen to be having a significantly higher risk of stroke and death.<sup>[35,36]</sup> Sudden cardiac death (SCD) is also seen to be associated with TTS as the most severe complication among patients with TTS. TTS patients have a greater risk for SCD because they have extended QT intervals, which may result in torsades de pointes, as well as other ECG abnormalities including diffuse negative T-waves and larger QRS complexes. Bradyarrhythmias, existing comorbidities, associated CAD or vasospasm, significant LV dysfunction, and sympathomimetic consumption.<sup>[37]</sup> TTS tends to involve psychological disorders such as depression and nervousness. Cognitive-behavioral therapy combined with cardiovascular rehabilitation may be more effective in improving mental health and reducing negative thinking than cardiac rehab alone. Ongoing research, such as PLEASE (NCT04425785), is investigating the beneficial effects of regimented fitness and mental health programs.<sup>[38]</sup> Hypertension is common in patients with recurrent TTS. Being overweight and having chronic kidney disease are linked to a worse prognosis, whereas hyperlipidemia is linked to fewer problems; data are limited. The influence of diabetes mellitus on TTS prognosis is yet unknown, indicating the need for additional research to better understand these interactions.<sup>[39,40]</sup>

TTS is a prominent variant of MI with non-obstructive coronary arteries (MINOCA) and is affected by a variety of risk factors. Severe angina, defined as two or more occurrences within 24 hours, is an independent predictor of TTS in patients with MINOCA. Furthermore, mental stress and psycho-emotional problems play an important role in TTS development. Other significant risk factors include age >55 years, anxiety, and underlying cardiovascular disease. Comorbidities, such as hypertension, diabetes, and chronic renal disease, can increase the risk of TTS. Furthermore, cardiac MRI combined with biomarkers and ECG anomalies can help identify TTS within MINOCA instances. Pulmonary embolism has also been identified as a possible cause of MINOCA, with some cases matching TTS.<sup>[41-44]</sup>

Recent research suggests a complex link between myocarditis and TTS. Myocarditis may cause TTS and is also a defining

hallmark of this condition. The inflammatory theory in TTS is supported by evidence of transitory apical wall thickening caused by cardiac edema and catecholamine spillover. Some researchers contend that cardiac inflammation in TTS may be a result of mechanical disruption rather than a primary trait. Despite their different pathologies, patients with TTS tend to be older, have a larger female preponderance, and have a higher fatality rate than patients with myocarditis. The association between TTS and myocarditis is still being investigated, with some studies indicating that many myocarditis patients may be TTS.<sup>[20,45-47]</sup>

#### 4. Diagnosis Using Radiological Imaging and Electrocardiography

TTS can be diagnosed with a combination of many clinical evaluations. One of them is imaging, which is also performed so that we can exclude other heart conditions like ACS, immediately.

##### 4a. X-Ray

An X-ray commonly displays apical ballooning, which is a reversible condition associated with TTS. At systole, the left ventricle's center and apex expand out, referred to as apical ballooning, whereas the area above, known as the base, shrinks normally. The design resembles a Takotsubo pot used to collect octopuses.<sup>[48]</sup>

##### 4b. Electrocardiography

Inverted T-waves are seen in both the limb and precordial leads, a frequent feature of TTS with apex balloon-like dilation. Potential ECG abnormalities include ST-segment elevation, ST-segment depression, left bundle branch block, and prolonged QT interval. TTS can occasionally present with normal ECG findings, but our data indicate that it resembles ischemia in the anterior distribution.

Initially, the ECG changes resembled a lot of ACS. These are ST elevations, inverting T-waves, and left bundle branch blocks. ST elevation and T-wave inversion are not specifically localized in this case. Certain ongoing alterations can be categorized as follows: stage 1 involves ST deviation, stage 2 involves progressive T-wave inversion and QTc prolongation, and stage 3 comprises gradual resolution of T-wave and QTc alterations over several weeks or months. Ventricular arrhythmias, including torsade de pointes, can occur in the hyperacute phase. They are often associated with prolonged QTc but not necessarily related to it. TTS often presents with less prominent ST elevation and more diffuse T-wave inversions, making it challenging to distinguish from ACS solely based on ECG findings. Over time, beyond the acute phase, TTS often involves the resolution of ST elevation, as well as broad and deep T-wave inversions, which are frequently linked with QT prolongation. Although transient Q-waves may occur, but they are infrequent.<sup>[50]</sup>

##### 4c. Echocardiography

Echocardiographic imaging of a patient with TTS may reveal mitral valve alterations. These are LV outflow tract (LVOT) obstruction and systolic anterior motion (SAM). The hallmark pattern involves akinesia at the apex of the heart, followed by akinesia at the base. This apical ballooning trend may resemble LAD-distribution ischemia. The images also show SAM and turbulence across the LVOT, which indicates LVOT obstruction. Echocardiography can assess the severity, location, and nature of wall motion anomalies in TTS. Approximately 20% of individuals with apical-to-mid-cavity ballooning and basal hyperkinesis experienced increased LVOT blockage. Contrast drugs can help distinguish wall motion anomalies and detect LV thrombus, which can occur abruptly or later. Other advanced techniques, such as speckle-tracking echocardiography, indicate that the left ventricle's twist indices are aberrant, as are deformations. Cardiac deformation indicators that remain abnormal during recovery suggest heart failure with preserved ejection fraction.<sup>[51,52]</sup>

##### 4d. Cardiac Magnetic Resonance

On MRI, four distinct patterns of abnormal movement and ballooning were observed. The apical is the most common ventricle, followed by the biventricular, midventricular, and basal. Cardiac MRI using gadolinium contrast helps differentiate TTS from acute MI and myocarditis. TTS does not show late gadolinium enhancement, revealing fibrosis, unlike MI or myocarditis. A characteristic thin transmural band of fibrosis can be detected at the junction of the hyperkinetic base and dyskinetic apex or mid-cavity, both acutely and at follow-up. Cardiac magnetic resonance (CMR) can accurately detect right ventricular involvement and identify left and right ventricular thrombi. This method is frequently used to visualize minor pericardial effusions. On CMR, TTS is characterized by severe myocardial edema, which gradually diminishes over 5-6 months throughout recovery.<sup>[52,53]</sup>

##### 4e. Coronary Angiography and Left Ventriculography

Coronary angiography is performed to confirm whether the patient has MI or not because takotsubo cardiomyopathy can mimic this disease. This phenomenon should be considered when individuals present with sudden chest pain and other STEMI-like symptoms but coronary angiography shows a normal or non-obstructive coronary artery. ST segment elevation on ECG and associated symptoms are indicators of myocardial ischemia, which requires prompt assessment with a cardiologist. Coronary angiography may be normal; however, CAD does not rule out the diagnosis of TTS. TTS diagnosis is often accomplished after coronary angiography, which may show normal or non-obstructive CAD. There may be less acuteness in TTS presentations, such as with non-



specific ECG findings or elevated biomarkers, which can make physicians avoid performing coronary imaging. In cases where cardiac catheterization is not feasible or safe, defining the coronary anatomy using noninvasive angiography is recommended for suspected TTS. In patients with TTS, CAD, which occurs in approximately 15% of cases, requires a link between angiography findings and wall motion anomalies. Left ventriculography is another important imaging technique that typically shows mild LV end-diastolic pressure elevation with mild to moderate ballooning of the cardiac apex, suggesting a possible case of TTS. Modern intravascular imaging techniques, such as OCT and IVUS, may rule out plaque rupture, which is not characteristic of TTS. The majority of cases present with apical or midventricular dyskinesia and basal sparing as a hallmark of TTS. Other forms include reverse or mid-ventricular presentations, isolated right ventricular involvement, and focal LV participation.<sup>[52,54,55]</sup> The modified Mayo Clinic diagnostic criteria are used when a patient is suspected of having an acute MI but cardiac catheterization reveals no coronary blockage, as mentioned in Table 1.<sup>[56,57]</sup>

### 5. Diagnosis Using Hormonal Analysis and Biomarkers

TTS is usually diagnosed either primarily or secondary to coronary heart disease. The therapeutic implications of recovery time are uncertain; however, developing data suggest that full recovery may be slower and less complete than originally thought. Apart from radiologic imaging, certain biomarkers and hormonal analyses are important to consider. These contain certain cardiac biomarkers, inflammatory biomarkers, brain natriuretic peptide (BNP), and catecholamines to name some.<sup>[51]</sup>

#### 5a. Cardiac and Inflammatory Biomarkers

Along with ECG findings, TTS is associated with an increase in certain biomarkers, indicating myocardial damage. Creatine kinase is elevated in approximately 56% of patients with TTS. Cardiac Troponin is almost universally elevated in TTS because of the greater sensitivity of contemporary assays. The troponin levels were modest, peaking at approximately 60 times the upper limit of normal (ULN). In patients with

acute STEMI, troponin levels can be elevated up to 400 times the ULN. This pattern can also be observed during non-STEMI. Troponin-ejection fraction product (TEFP) is another method for differential diagnosis. If TEFP is 250 or higher, it correctly identified STEMI 95% of the time and non-STEMI cases (like TTS) 87% of the time, with an overall accuracy of 91%. This makes TEFP a reliable tool for accurate diagnosis in clinical settings.<sup>[55]</sup>

#### 5b. Brain Natriuretic Peptide Levels

BNP levels were higher in TTS than in STEMI. These levels may indicate the extent of myocardial dysfunction and damage. These levels may increase for months after the acute case. NT-proBNP levels are notably higher in patients with the apical variant than in those with the atypical variant. This difference may indicate more significant acute LV enlargement and myocardial stretching.<sup>[52,55]</sup>

#### 5c. The Role of Catecholamines in Takotsubo Syndrome

Plasma catecholamine levels for epinephrine, norepinephrine, and dopamine are found to be 2-3 times higher in TTS than in individuals having Killip class III acute heart failure after MI and about 7-34 times higher than normal ranges. Not all studies consistently reported elevated catecholamine levels as it was not one of the primary reliable biomarkers to indicate TTS.<sup>[29,55]</sup>

### 6. Management and Postdischarge Follow-up

The overall aim of management is to stabilize the patient and prevent recurrence. This can be achieved through comprehensive and personalized cardiac risk assessment. Initial management of TTS involves supportive care that aims to address the triggers. It is combined with pharmacological interventions, such as  $\beta$ -blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs). ACE inhibitors and ARBs are suggested for their potential benefits in improving LV function and reducing cardiovascular mortality.<sup>[10,58]</sup> However, the effectiveness of  $\beta$ -blockers in decreasing mortality or recurrence remains debatable. Inotropes are favored vasopressors in individuals with complex conditions, particularly those with LVOT obstruction, with  $\beta$ -blockers being the safer choice. For individuals at high risk of thromboembolism, anticoagulation therapy is indicated, often beginning with low-molecular-weight heparin and progressing to oral anticoagulants for up to 3 months. In cases of cardiogenic shock, mechanical support devices should be considered immediately. Although the future outlook is generally good, with a majority of patients regaining LV function, ongoing treatment necessitates regular monitoring and follow-ups.<sup>[3,59]</sup>

Post-discharge follow-up is usually indicated within 1 month to check for any residual abnormalities using ECG and

**Table 1: Revised Mayo Clinic criteria for the diagnosis of Takotsubo syndrome<sup>[57]</sup>**

	Criteria
1	Transient dyskinesia of the left ventricle midsegment
2	Regional wall motion abnormalities beyond a single epicardial vascular distribution
3	Absence of obstructive coronary artery disease or acute plaque rupture
4	New electrocardiographic abnormalities or modest troponin elevation
5	Absence of pheochromocytoma and myocarditis

echocardiogram, with subsequent visits within 3 to 6 months depending on the patient’s recovery. Patients at high risk or with chronic symptoms may benefit from cardiopulmonary exercise testing and annual examinations. Statins are recommended in patients with CAD. Moreover, aspirin with antiplatelet drugs may reduce major cardiovascular events, but their impact on TTS-specific outcomes is unknown. Hormone therapy, notably estrogens, and novel medicines such as angiotensin-neprilysin receptor inhibitors, SGLT2 inhibitors, and novel mineralocorticoid receptor antagonists are all being investigated for their potential role in TTS management. Multidisciplinary management is essential for managing difficult situations involving psychiatric problems, cancer, or other major illnesses.<sup>[4,59-61]</sup>

**6a. Nutritional Management for Patients with Takotsubo Syndrome**

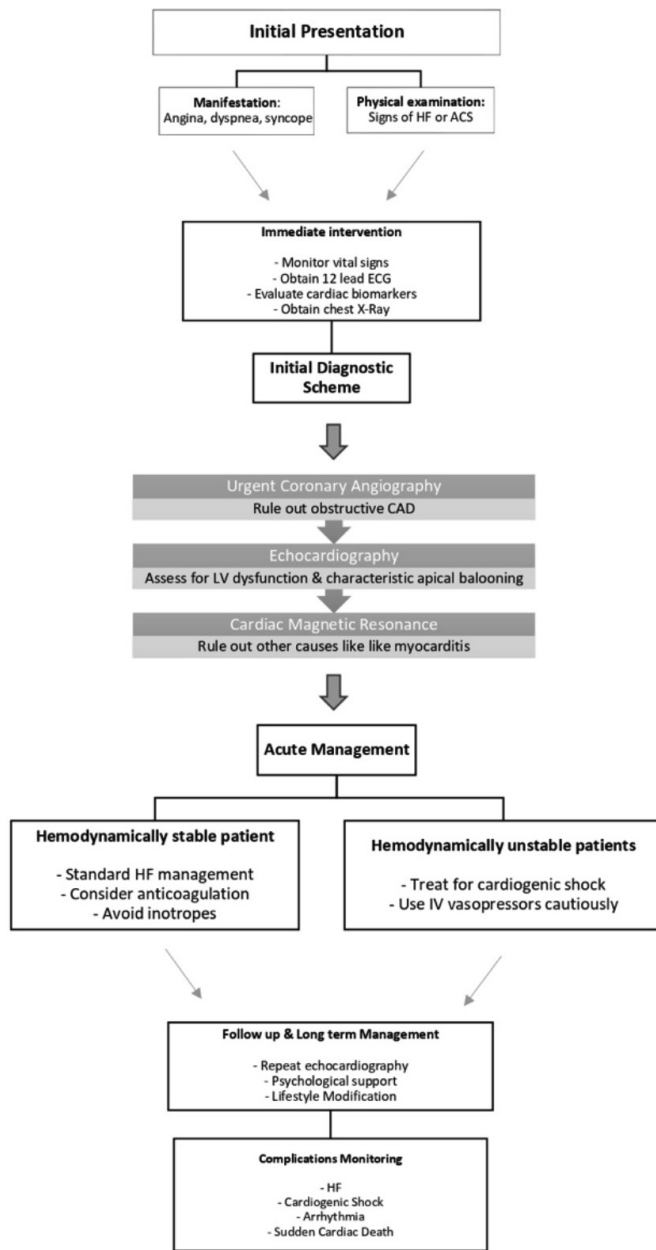
A personalized dietary plan for managing TTS should be provided that includes many important factors. In general, this plan aimed to individualize dietary adjustments based on both physical and emotional factors that specifically affected each patient. Sodium restriction to prevent fluid retention, with a focus on reducing salt intake and avoiding processed foods. Incorporating heart-healthy spices, herbs, and phenol-rich fruits like red, purple, and citrus fruits can provide beneficial antioxidant benefits. Limiting fructose intake to 25-30 g per day is important to prevent excessive uric acid production, which can affect cardiovascular health. Probiotics and prebiotics, such as those found in fermented dairy products, support gut health and aid in the elimination of toxins. The management of fat intake is crucial. Emphasizing the intake of polyunsaturated fats while avoiding trans fats and minimizing cooking methods that produce harmful advanced glycation end products is one of the most important nutritional recommendations. Maintaining electrolyte balance through potassium-rich diets is essential, and regular monitoring advised.<sup>[39,61-64]</sup>

**6b. Schematic Algorithm for the Management of Takotsubo Syndrome**

The schematic diagram of TTS management provides an organized way to diagnose and manage it, as shown in Figure 1. The findings highlight the importance of early detection of symptoms and other associated presentations. Using various diagnostic techniques, such as coronary angiogram and echocardiography, a physician can differentiate TTS from other conditions with similar presentations. Using this scheme, physicians can implement appropriate therapeutic modalities for both hemodynamically stable and unstable patients. It also addresses long-term care as well as related complications.<sup>[15,65,66]</sup>

**7. Prognosis**

The prognosis of TTS is no longer as positive as it was once due to multiple complications and mortality-related conditions. Patients with TTS have a lower LV ejection fraction. An LV ejection fraction (LVEF) below %35 at admission has been identified as a predictor of both short- and long-term outcomes.<sup>[67]</sup> However, some studies have found that LVEF 35% was an independent predictor of mortality among patients with TTS.



**Figure 1:** Schematic algorithm for the management of Takotsubo syndrome  
 ACS: Acute coronary syndrome, CAD: Coronary artery disease, HF: Heart failure, IV: Intravenous, LV: Left ventricle, ECG: Electrocardiogram

Recently, the registry on TTS database, which was launched by a Spanish research group, discovered that cardiogenic shock is associated with both short- and long-term prognoses among these patients.<sup>[68,69]</sup> Reduced systolic blood pressure upon admission is considered a prognostic indication.<sup>[65]</sup> Furthermore, in multivariate studies, elderly age remained an independent prognostic factor. This disease is induced by a decrease in  $\beta$ -1 adrenergic receptor density. The increasing prevalence of mitral regurgitation (MR) in elderly patients requires particular medical attention. MR in these patients usually occurs due to the SAM of the mitral anterior leaflet, anchoring by papillary muscle displacement, and regional or global ventricular dysfunction. Some studies have identified long-term prognosis for patients with TTS. These patients had a similar long-term mortality rate as those with ACS. In addition, TTS that is typically caused by stress has a good short- and long-term outlook. In terms of prognosis, TTS requires a personalized treatment strategy and follow-up. Patients were seen to have the same in-hospital mortality rate as those with ACS, but patients with TTS had a higher survival rate post-discharge.<sup>[70-73]</sup>

## CONCLUSION

TTS is a complex cardiac event often misdiagnosed as ACS. Mainly seen to affect women in the postmenopausal age, it can be triggered due to severe stress, leading to transient LV dysfunction. The exact pathogenesis is not known. The proposed mechanisms involve catecholamine surges, microvascular dysfunction, and estrogen deficiency. Diagnosis requires imaging, such as echocardiography and cardiac MRI, along with biomarkers. TTS management focuses on supportive care, stressor management, and medications like ACE inhibitors and beta-blockers. TTS can lead to serious complications and even death. Future research should refine diagnosis, management protocols, and prevention strategies to improve prognosis and overall quality of life.

## Footnotes

### Authorship Contributions

Concept: H.S.W., Design: H.S.W., H.V., S.C., S.H., P.G., V.F., Data Collection or Processing: H.S.W., H.V., S.C., S.H., P.G., V.F., Analysis or Interpretation: H.S.W., H.V., S.C., S.H., P.G., V.F., Literature Search: H.S.W., H.V., S.C., S.H., P.G., V.F., B.S., A.A.P., Writing: H.S.W., H.V., S.C., S.H., P.G., V.F., B.S., A.A.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2024.83703

Int J Cardiovasc Acad 2024;10(4):91-101

# Prognostic Value of Circulating Osteogenic Proteins for Stratifying Coronary Artery Calcification Risk

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## Abstract

Increasing evidence suggests a common physiological process for bone and coronary artery calcification (CAC), implying the role of bone metabolism markers in subclinical atherosclerosis development. However, the association between bone turnover markers and the development of CAC has remained controversial, as seen in various studies. Because CAC measurement has both financial burden and radiation exposure risk in individuals with suspected cardiovascular disease (CVD), applying the diagnostic role of osteogenic markers in predicting abnormal CAC would improve treatment adherence and reduce the rate of CVD mortality. In this review, we begin by describing the current understanding of the molecular mechanisms of bone markers in the etiology of CAC. Furthermore, we summarize bone-associated regulatory factors at the molecular level as novel therapeutic targets for CAC. In addition, we focused on the current results on the prognostic role of novel mediators of osteogenic activity in determining the risk of CAC as a preclinical factor of atherosclerotic CVD. Accumulating evidence suggests the role of bone marker-mediated pathways in the progression of CAC, which may lead to early diagnosis of CVD complications and the establishment of innovative targets for pharmacological therapy. Indeed, miRNAs and lncRNAs, as novel therapeutic interventions, can be a research priority in regulating bone metabolism at the gene expression level to attenuate high CAC and improve CVD outcomes.

**Keywords:** Bone marker, osteoprotegerin, RANKL, fetuin-A, calcium score, non-coding RNAs

## INTRODUCTION

Coronary artery calcification (CAC) is a prominent feature of atherosclerosis and is not the only principal cause of coronary artery disease (CAD) but also leads to increased mortality and

atherosclerosis outcomes.<sup>[1]</sup> The baseline coronary artery calcium score is the most robust marker in the subclinical prediction of calcium in the walls of the heart's arteries, which is a significant factor in increasing the risk of CAD.<sup>[2,3]</sup>

**To cite this article:** Prognostic Value of Circulating Osteogenic Proteins for Stratifying Coronary Artery Calcification Risk.

Int J Cardiovasc Acad. 2024;10(4):91-101



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**Received:** 12.10.2024

**Revised:** 29.11.2024

**Accepted:** 03.12.2024

**Published Online:** 16.12.2024



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Using the coronary artery calcium score, individuals can be appropriately classified based on CAC categories that predict atherosclerotic cardiovascular disease in both sexes, ages, and races with similar magnitude impacts. Hence, preventive therapy may be beneficial for patients with elevated risk of CAC.<sup>[4-6]</sup> Accordingly, the potential role of CAC in the early diagnosis of patients with CAD burden will substantially reduce mortality and provide suitable care. Clinical studies have confirmed that artery mineralization is an active, complex process similar to bone formation, as both appear to share common signaling pathways, transcription factors, and extracellular matrix mediators. An emerging body of evidence suggests that bone markers, including matrix Gla protein (MGP), osteocalcin (OCN), osteoprotegerin (OPG), receptor activator of NF- $\kappa$ B ligand (RANKL), osteopontin (OPN), fetuin-A, bone morphogenetic proteins (BMPs), and alkaline phosphatase (ALP), could be considered as predictors of CAC prevalence.<sup>[7-14]</sup> However, the association between bone turnover markers and the development of CAC has remained controversial, as shown in various studies.<sup>[14-16]</sup> As the prediction of artery calcification is related to the concentration of bone metabolism markers and leads to early diagnosis of individuals at high risk of developing CAC, this review discusses the potential role of bone metabolism markers in stratifying the risk of CAC. The molecular mechanisms of bone turn over markers in the etiology of CAC and bone-associated regulatory factors at the molecular level were investigated as novel therapeutic targets for coronary calcification.

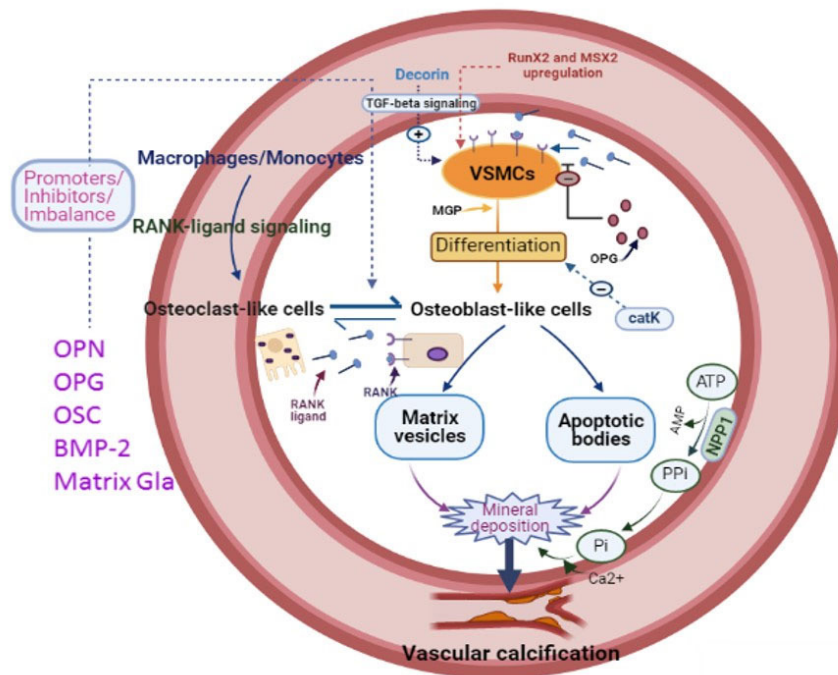
## 1. Bone Metabolism Markers and Mechanistic Insights into Coronary Artery Calcification

In the majority of human tissues, including bone (osteoblasts) and the vasculature (endothelial and vascular smooth muscle cells, or VSMC), OPG, a soluble glycoprotein, is widely expressed.<sup>[17]</sup> tumor necrosis factor (TNF)-related apoptosis-inducing ligand, which is expressed by VSMC and T cells, is bound by OPG, a member of the TNF family, to counteract its pro-apoptotic effects.<sup>[18]</sup> RANK receptors, which are found on the surface of osteoclasts, monocytes, and dendritic cells, are coupled to RANKL, which is expressed in osteoblastic, stromal, and T-cells.<sup>[19]</sup> The interaction can initiate intracellular signaling cascades, including the NF- $\kappa$ B pathway, and initiate the activation of osteoclast differentiation.<sup>[20]</sup> OPG can compete with RANKL for binding to the receptor and prevents RANK/RANKL interaction, thereby inhibiting osteoclast differentiation and bone resorption is the outcome.<sup>[19]</sup> Since several similarities were observed between osteoporotic bone loss and arterial mineral accumulation, OPG and RANKL were suggested as key markers involved in CAC<sup>[21,22]</sup> (Figure 1). Fetuin-A is a glycoprotein that is synthesized in the liver and mainly found in bone tissue. It plays an important role in bone mineralization.<sup>[23,24]</sup> This protein is a carrier of lipids in the blood and can mediate inflammatory

responses.<sup>[25,26]</sup> Fetuin-A binds to TGF- $\beta$  and BMP, inhibits bone mineralization, and is considered a calcification inhibitor.<sup>[27,28]</sup> Because the binding ability of fetuin-A to calcium and phosphorus in the circulation could enhance their solubility and, in turn, inhibit coronary calcification, this protein was noticed as a candidate marker for assessing the risk of CAC.<sup>[29]</sup> The most prevalent non-collagenous peptide in the mineralized matrix of bone is OCN. OCN has been shown to be a marker of arterial calcification, and compared with healthy controls, patients with coronary atherosclerosis have higher levels of OCN on the surface of their endothelial progenitor cells (EPC).<sup>[30]</sup> Endothelial cells, fibroblasts, VSMCs, and chondrocytes express MGP, a 14-kDa  $\gamma$ -carboxylated protein that was first isolated from bone. This protein contains five glutamine and three serine residues. To become fully functional, MGP must be phosphorylated and undergo a glutamate carboxylation process that is dependent on vitamin K. MGP potentially acts in several ways to regulate calcium deposition.<sup>[31]</sup> The mechanism for the strong calcification inhibition activity of MGP was explained by Price et al.<sup>[32]</sup>, who suggested that further calcium precipitation could be prevented by binding MGP to the calcium phosphate crystal nuclei. The other mechanism for the inhibitory effect of MGP on calcification is the binding of MGP to bone morphogenetic protein-2 (BMP-2) and its inactivation of this pro-mineralization factor.<sup>[33]</sup> Bone morphogenetic proteins (BMPs) are derived from the - $\beta$  like growth factors family. BMPs are secreted by endothelial cells, smooth muscle cells, and foamy cells in atherosclerotic vascular areas.<sup>[34]</sup> Because they contribute to calcification, BMP-2, BMP4, and later BMP 5, 6, and 7 have the highest correlation with vascular disease among the proteins in this family. BMP-2 is a crucial molecule that controls vascular calcification and bone development.<sup>[35]</sup> OPN is an extracellular matrix protein that functions as a proinflammatory cytokine. In addition to binding to osteoblasts, OPN is also involved in most systemic inflammatory processes and tissue remodeling.<sup>[36]</sup> It has been indicated that OPN is a potent calcification inhibitor because it can potentially increase the speed of calcium and other mineral dissolution by accelerating the expression of monocyte's carbonic anhydrase II enzyme and acidifying the extracellular surrounding.<sup>[37]</sup> ALP is a ubiquitous enzyme found in most tissues. ALP increases the level of phosphate in the extracellular surroundings.<sup>[38]</sup> Binding calcium to these extra phosphates induces calcification via the formation of calcium crystals.<sup>[39,40]</sup>

## 2. Molecular Factors Involved in Bone Metabolism Regulation as Therapeutic Targets in CAC

Over the last few years, noncoding RNAs (ncRNAs) have been of interest as novel therapeutic targets because they contribute to cellular processes by regulating gene expression.<sup>[41,42]</sup> Although a number of blood markers have been linked to an elevated risk of cardiovascular endpoints, few have been demonstrated



**Figure 1:** RANKL-RANK interactions initiate intracellular signaling cascades including NF- $\kappa$ B required for osteoclast differentiation and activity. OPG can compete with RANKL for binding to the receptor and inhibits RANK/RANKL, thereby preventing osteoclast differentiation and bone resorption. MGP binds to BMP-2 and inactivates this pro-mineralization factor. Among other effects, BMP-2, a member of the transforming growth factor-beta (TGF-beta) superfamily, promotes osteogenic conversion of VSMCs via the MSX2 transcription factor. BMP-2 5, 6, and 7 have the highest association with vascular disease due to their contributing role in calcification. Fetuin-A binds to TGF- $\beta$  and BMP and prevents bone mineralization and calcification. High levels of OCN are located on the surface of endothelial progenitor cells (EPC) in coronary atherosclerosis. OCN can be undercarboxylated (ucOCN) due to low activity of the vitamin K-dependent carboxylase enzyme or vitamin K deficiency. ucOCN has less affinity to hydroxyapatite and is more readily released into circulation than OCN. It was indicated that OPN is a potent inhibitor of calcification as it can potentially increase the speed of calcium dissolution and other minerals by accelerating the expression of monocyte's carbonic anhydrase II enzyme and acidifying the extracellular surrounding. ENPP1 could hydrolyze extracellular ATP and release PPI, which inhibit hydroxyapatite crystals by binding to their Pi sites, leading to prevent vascular mineralization. Decorin regulates transforming growth factor- $\beta$  activity. During atherosclerosis and restenosis, extracellular decorin associates with SMC and collagen types I and III in the fibrous cap and with SMC and macrophages in the core region

RANKL: Receptor-activator of NF- $\kappa$ B ligand, OPG: Osteoprotegerin, MGP: Matrix gla protein, OCN: Osteocalcin, ucOCN: Undercarboxylated osteocalcin, OPN: Osteopontin, BMP-2: Bone morphogenetic protein-2

to have significant clinical implications or diagnostic value that would influence patient care.<sup>[6]</sup> As a result, novel biomarkers that can be utilized to evaluate the likelihood of atherosclerosis, the advancement of CAD, and the effectiveness of treatment are highly sought for.<sup>[7,8]</sup> Numerous studies have demonstrated the tight relationship between regulatory ncRNAs, such as microRNAs (miRNAs) (miRNA/miRs), short interfering RNAs (siRNAs), and long non-coding RNAs (lncRNAs), and the occurrence and progression of cardiovascular disorders. Recent studies on lncRNAs and miRNAs in cardiac disease have advanced rapidly.<sup>[9]</sup> MiRNA and lncRNA expression signatures in tissues and blood may play a role in disease diagnosis, prognosis, and treatment evaluation. In the cardiovascular system, ncRNAs are critical for the development of the heart and arteries as well as for the pathophysiology of cardiac disorders like CAD.<sup>[10,11]</sup> Because

of their regulatory function in disease development, ncRNAs—a class of genetic, epigenetic, and translational regulators—obtain both short and long transcripts and offer fascinating potential as biomarkers.<sup>[13]</sup> Because ncRNAs, particularly miRNAs and lncRNAs, are persistent in bodily fluids like plasma, they may be used as disease biomarkers. Numerous studies have demonstrated the important roles of certain miRNAs and lncRNAs in the development of the heart and arteries as well as in the pathophysiology of the heart. To identify novel targets for the therapy of heart disease, we have compiled the most recent research findings here, with an emphasis on the molecular mechanism of miRNAs and lncRNAs in CAD. Small noncoding ribonucleic acid molecules called miRNAs, which have a length of 20-22 base pairs, are essential for controlling posttranscriptional levels of gene expression because they can



either prevent mRNA translation or cause mRNA destruction. In rare circumstances, miRNAs may improve a gene's transcription or translation of a gene, increasing the amount of the protein product.<sup>[14]</sup> A growing body of research indicates that miRNAs play a crucial role in controlling important signaling and lipid homeostasis pathways that change the ratio of atherosclerotic plaque advancement to reversal.<sup>[15]</sup> Crucially, miRNAs are involved in the control of endothelial cell inflammation and plaque development, in addition to lipoprotein metabolism.<sup>[16,17]</sup> Furthermore, leukocyte recruitment-one of the first harmful processes in atherosclerosis-is regulated by miRNAs.<sup>[17]</sup> In accordance with the ncRNA classification, lncRNAs are defined as ncRNAs longer than 200 base pairs. Despite the fact that the majority of lncRNAs have an unknown function, it is now evident that these molecules play crucial roles in many biological processes. lncRNAs can control gene expression programs by a number of methods, including alternative splicing, posttranscriptional gene regulation, epigenetic alterations of DNA, and mRNA stability and translation.<sup>[18,19]</sup> Considering their well-established functions in transcriptional control, lncRNAs are essential for many cellular processes, such as development, migration, apoptosis, and proliferation.<sup>[18]</sup> Because lncRNAs are now known to modulate the expression of genes that encode proteins, they can either favorably or adversely affect the expression of the genes they target.

Recently, the results of an animal study demonstrated that miR103a could reduce osteogenic trans-differentiation in VSMCs by inhibiting the expression of Runx2, an osteogenesis transcription factor that induces calcification. As it was indicated that Runx2 levels are significantly enhanced in calcified atherosclerotic plaques<sup>[43]</sup>, inhibiting the expression of this transcription factor could be a research priority to identify promising combinations between related miRs and CAC incidence. Similar to the results of this study, another *in vitro* study showed that inhibiting miR32 could remarkably decrease the levels of Runx2 as well as the levels of BMP2, OPN, and MGP; therefore, vascular calcification was attenuated.<sup>[44]</sup> Interestingly, the result of an experimental study in 2021 showed that miR-223-3p could target the interleukin-6 (IL-6)/STAT3 signaling pathway and inhibit the osteogenic switch in VSMCs, thereby finding the associated miRs with STAT3 signaling pathway could potentially target atherosclerotic vascular calcification and can be considered a novel pharmacological intervention for CAC treatment.<sup>[45]</sup>

Lately, a study by Wicik et al.<sup>[46]</sup> applied correlation network analysis of 51 women that 21 of them had high CAC score and identified four bone metabolism genes, including PTGER3, FGFR1, ONECUT2, and SGCD, as the most contributed genes with other regulators of CAC. As demonstrated by the results of this study, the interaction of miRs and lncRNAs with these genes and signaling pathways could be considered novel

therapeutic targets for reducing high CAC scores and improving cardiovascular disease (CVD) outcomes among patients.<sup>[46]</sup> PTGER3 contributes to the formation of prostaglandin receptors and the calcium signaling pathway, which can play an important role in cellular processes related to calcification in the arterial walls.<sup>[47,48]</sup> An emerging body of evidence from an *in vivo* study indicated that PTGER3 is less expressed during osteogenic activity and atherosclerosis, suggesting that manipulation of this gene expression could be a therapeutic target in altering the calcium signaling pathway during CAC.<sup>[47]</sup> Furthermore, FGFR1 plays a crucial role in bone calcification by acting as a receptor for FGF23, a bone-derived hormone that regulates the level of phosphate. The inhibition of FGFR1 expression leads to dysfunction in phosphate concentration and elevated calcification levels. Thus, targeting the expression of FGFR1 as a modulator factor could lay the foundation for novel therapeutic interventions against CAC.<sup>[49]</sup> The cumulative result of a study in an animal model demonstrated that SGCD contributes to the intracellular pathway related to calcification and myocardial dysfunction by regulating the signaling pathways in the cardiac muscle membrane.<sup>[50]</sup> Moreover, it was shown that ONECUT2 is a key driver in the molecular process of advanced CAD and aortic valve calcification, and interfering with the expression of FGFR1 and PTGER3 plays a role as a novel key regulator of CAC incidence.<sup>[46,51]</sup>

### 3. Prognostic Role of Osteogenic Activity Mediators in Determining the Risk of CAC

This review identified numerous observational studies investigating the association between OPG level and CAC risk in three different populations, including asymptomatic subjects, patients with type 2 diabetes, and individuals with a history of CVD.

#### 3.1. Association between OPG and CAC in individuals with type 2 diabetes

According to a prospective cohort study involving 510 patients with type 2 diabetes, OPG was found to be an independent significant marker for predicting the risk of CAC [odds ratio (OR) = 2.84 (2.2-3.67),  $P < 0.01$ ].<sup>[9]</sup> The cumulative results from the cross-sectional studies demonstrated the significant contribution of elevated OPG levels in identifying the enhanced risk of CAC incidence.<sup>[52-54]</sup> On the other hand, a clinical study with 168 participants reported that OPG was not correlated with CAC incidence.<sup>[55]</sup> However, the causality relationship between CAC and OPG could not be confirmed by these cross-sectional studies, and the strong association between OPG and CAC among patients with type 2 diabetes should be further evaluated in prospective cohort studies and clinical trials with larger sample sizes. The characteristics of the included studies are presented in the Table 1.

Table 1: Characteristics of the studies evaluating the association between bone turnover markers and CAC								
Author (year)	Country	Age (year)	Population	Study design	Follow-up	Marker	Main finding	Reference number
Anand (2006)	UK	52.7	T2DM free of symptoms of cardiovascular disease	Prospective cohort, n=510	18±5 months	OPG	OPG levels retained a strong association with elevated CAC scores.	[9]
Berezin (2013)	Ukraine	58.34±9.60	Subjects with documented asymptomatic CAD	Prospective cohort, n=126	-	OPG OPN	OPG and OPN independently associated with coronary artery calcification.	[59]
Ishiyama (2009)	Japan	60.85	T2DM	Cross-sectional, n=168	-	OPG OPN	OPG was not a significant independent determinant of CAC. OPN was a significant independent determinant of CAC.	[55]
Jung (2009)	Korea	57.2±11.2	T2DM	Cross-sectional, n=110	-	OPG	CAC and OPG were significantly correlated with each other.	[52]
Maser (2015)	USA	62.5	T2DM	Cross-sectional, n=50	-	OPG OCN ucOCN	OPG is a useful serum biomarker for identifying those at increased risk of arterial calcification. OCN and ucOCN were not significant marker for CAC.	[53]
Pesaro (2018)	Brazil	57.95	Asymptomatic subjects	Cross-sectional, n= 130	-	OPG MGP RANKL Fetuin-A	MGP and RANKL were associated with CAC. No association was found between OPG or fetuin-A and CAC burden.	[58]
Diederichsen (2017)	Denmark	55.39±5.01	Asymptomatic subjects	Prospective cohort, n= 1006	5 years	OPG	OPG has no predictive value for CAC among asymptomatic subjects.	[57]
Mohammadpour (2012)	Iran	56.52±11.05	CAD	Cross-sectional, n=50	-	OPG RANKL	OPG level and RANKL/OPG ratio was correlated with CAC, but RANKL was not a significant marker.	[22]
Lieb (2010)	USA	61	Free of CVD	Prospective cohort (Framingham Study), n=3250	4.6 years	OPG RANKL	Prevalence of CAC increased non significantly with RANKL quartiles. OPG quartiles showed a weak association with CAC prevalence.	[54]

Table 1: Continued

Author (year)	Country	Age (year)	Population	Study design	Follow-up	Marker	Main finding	Reference number
Ix (2012)	USA	62±10	Free of CVD	Cohort [Multi-ethnic study of atherosclerosis (MESA)], n= 2457	3.2 years	Fetuin-A	Fetuin-A is inversely associated with CAC severity, while no associations were found between fetuin-A and CAC incidence or progression.	[29]
Ix (2011)	USA	70±11	Free of CVD	Cohort, n= 1375	4.6 years	Fetuin-A	Fetuin-A was associated with CAC severity.	[12]
Abedin (2007)	USA	44.75	Free of CVD	Prospective Cohort (Dallas study) , n= 3386	2 years	OPG	OPG is independently associated with CAC.	[56]
Esteghamat (2014)	Iran	56.8±11.2	CAD	Cross-sectional, n=155	-	OPG	Strong and independent association between CCS and OPG.	[60]
Nazemi (2018)	Iran	57.2±10.2	CAD	Cross-sectional, n= 83	-	BMP-2 BMP-7	BMP-2, BMP-7 were significantly associated with CAC.	[10]
Panh (2017)	France	60.9±10.8	Free of CVD	Cross-sectional, n=500	-	ALP OCN ucOCN	ALP was a significant marker for CAC but OCN and ucOCN were not associated with CAC.	[65]
Kiselova-Kaneva (2020)	Bulgaristan	62.12±12.00	CVD	Cross-sectional, n=99	-	ucMGP	CAC and ucMGP was not significantly associated with each other.	[68]
UZ (2009)	Turkey	49.5±10.9	Suspected CAD patients	Cross-sectional, n=64	-	OPN Fetuin-A	OPN was significantly correlated with CAC, but fetuin-A was not associated with CAC.	[14]
Mohammadpour (2018)	Iran	57.13±10.7	CAD	Cross-sectional, n=83	-	ENPP1	ENPP1 was significantly associated with CAC.	[71]
Kuipers (2015)	Trinidad and Tobago	62.9±8	Afro-Caribbean men	Case-control, n=191	-	Sclerostin	Sclerostin was a significant associated factor for CAC.	[72]
Nazemi (2018)	Iran	57.2±10.2	CAD	Cross-sectional, n=84	-	Decorin	No significant association between CAC and decorin was observed.	[70]

Table 1: Continued

Author (year)	Country	Age (year)	Population	Study design	Follow-up	Marker	Main finding	Reference number
Mori (2010)	Japan	62.4±10.4	Recently underwent coronary angiography	Cross-sectional, n=92	-	Fetuin-A	The correlation between CAC and Fetuin-A was indicated significant.	[61]
Okura (2010)	Japan	61	Essential hypertension	Cross-sectional, n=92	-	ucOCN	ucOCN and CAC were independently associated with each other.	[67]
Cho (2015)	Korea	51.8±8.2	Asymptomatic patients	Cross-sectional, n=162	-	OCN ucOCN	ucOCN was associated with CAC in men.	[66]
Jono (2004)	Japan	64±11	Suspected CAD patients	Cross-sectional, n=115	-	MGP	MGP was an associated marker for CAC severity.	[7]
Krajnc (2019)	Slovenia	59±8	T2M	Cohort, n=45	18 months	Fetuin-A	CAC progression was independently associated with Fetuin-A.	[62]

T2DM: Type 2 diabetes, CAC: Coronary artery calcification, CVD: Cardiovascular disease, CCS: Coronary calcium score, CAD: Coronary artery disease, OPG: Osteoprotegerin, MGP: Matrix gla protein, ucMGP: Undercarboxylated MGP, OPN: Osteopontin, OCN: Osteocalcin, ucOCN: Undercarboxylated osteocalcin, BMP: Bone morphogenetic protein, ALP: Alkaline phosphatase, RANKL: Receptor-activator of NF- $\kappa$ B ligand

### 3.2. OPG and CAC risk in asymptomatic patients

The association between CAC and plasma OPG was evaluated in a Dallas heart study among 3,386 participants, and it was demonstrated that elevated OPG levels independently enhanced the risk of CAC prevalence by 39%.<sup>[56]</sup> In addition, multivariate analysis by a prospective cohort study in a population of 3250 asymptomatic subjects indicated that OPG quartiles could weakly increase the prevalence of CAC and suggested serum OPG concentration as a predictive marker for CVD and mortality in the clinical health care system.<sup>[54]</sup> In contrast, the incidence odds ratio for coronary artery calcium score at baseline and follow-up was evaluated using the OPG level in 1006 individuals and revealed that OPG was an insignificant factor for CAC incidence.<sup>[57]</sup> Likewise, in a cross-sectional study with a population of 130 subjects, no significant association was found between OPG and CAC among asymptomatic individuals.<sup>[58]</sup> Overall, OPG might be a potential predictor of the risk of CAC, thereby identifying subclinical CVD burden.

### 3.3. Association between OPG and CAC risk in patients with CAD

As observed in studies on patients with CAD, a positive significant association was demonstrated between OPG and the incidence of CAC. The cohort study involving 126 patients with CAD indicated a positive correlation between OPG and CAC, in which elevated OPG levels could enhance the prevalence of CAC by 45%.<sup>[59]</sup> The study by Esteghamat et al.<sup>[60]</sup> recruited 155 subjects

and demonstrated that OPG could be an independent detector of CVD mortality by predicting CAC prevalence. On the other hand, a study by Mohammadpour et al.<sup>[22]</sup> involving 50 patients with ischemic coronary disease reported a significant negative association between serum OPG and total CAC ( $P = 0.03$ , Correlation coefficient =  $-0.468$ ), suggesting a protective effect of OPG on vascular calcification. They claimed that although OPG could not be a diagnostic marker for CAC incidence, the RANKL: OPG ratio might be a diagnostic marker for evaluating the risk of CAC in patients with a previous history of CAD.<sup>[22]</sup> Owing to limited and controversial findings, the ability of OPG to predict coronary artery calcium scores in CVD patients has yet to be established.

### 4. Association between RANKL and the Risk of CAC

Several studies have investigated the correlation between RANKL and CAC and have indicated that RANKL cannot be recognized as a reliable bone turnover marker for identifying the risk of CAC. As observed in a study by Lieb et al.<sup>[54]</sup> with a population of 3250 individuals having no symptoms of CVD at baseline, no significant correlation was confirmed between the prevalence of CAC and the RANKL quartiles after 4.6 years of follow-up. Furthermore, a cross-sectional study in 2012 found no significant association between CAC and RANKL in patients with ischemic heart disease.<sup>[22]</sup> In contrast, in a clinical study by Pesaro et al.<sup>[13]</sup>, investigating osteogenic proteins among 170 participants without known CAD, RANKL was recognized as a positive significant factor for the detection of CAC after

fully adjusting for potential CVD confounders. Thus, a high level of RANKL increased the risk of CAC [OR=1.75 (1.04; 2.94),  $P = 0.03$ ] and suggested RANKL as a novel marker for identifying subclinical CVD burden among individuals. An additional analysis conducted on 70 participants (40 acute MI patients and 30 controls) revealed that RANKL concentration was not significantly correlated with MI or 1-2 months post-MI.<sup>[13]</sup> Overall, the results of the studies identifying the association of RANKL or RANKL: OPG ratio with CAC were inconsistent and inclusive. Hence, conducting additional clinical investigations can benefit the existing gap and provide robust evidence.

## 5. Fetuin A Level and Elevated Incidence of CAC

The hypothesized relationship between fetuin-A and the severity of CAC and CVD burden has been widely investigated in clinical settings. Accordingly, a prospective cohort study was conducted on 1375 participants without known prevalence of clinical CVD, and the protective effect of fetuin-A on CAC was determined. Based on our results, 31% of the risk of CAC severity was reduced by high levels of circulating fetuin-A.<sup>[12]</sup> Furthermore, a study by Mori et al.<sup>[61]</sup> confirmed the protective effect of fetuin-A on CAC by reducing the incidence of CAC by up to 46% in patients who recently underwent coronary angiography. In addition, a significant negative association between fetuin-A and relative CAC progression was also verified in type 2 diabetic patients comparing baseline and 18-month follow-up (coefficient for the relative change in calcium score=-0.345,  $P = 0.02$ ).<sup>[62]</sup> As demonstrated in a cross-sectional study of 88 non-dialyzed individuals with diabetic nephropathy, enhanced prevalence and severity of CAC were observed among individuals with diabetic nephropathy compared with diabetic controls. Hence, there was a direct, potent association between fetuin-A levels and the CAC score ( $r=0.22$ ,  $P = 0.038$ ) which is dependent on the status of nephropathy.<sup>[63]</sup> In line with these studies, inversely independent associations were identified between plasma fetal fetuin-A concentrations and CAC severity. For each SD higher fetuin-A level, there was a 12% decline in CAC severity in fully adjusted models for conventional risk factors of CVD in addition to kidney function and lifestyle variables. However, no association was found between fetuin-A and the incidence or progression of CAC.<sup>[29]</sup> Despite the observed significant associations between fetuin-A and CAC in previously described studies, a clinical study with 64 patients with suspected CVD indicated no significant correlation between fetuin-A and CAC incidence ( $r=0.17$ ,  $P = 0.22$ ).<sup>[14]</sup> The result of comparing the baseline data and a 7-year follow-up indicated that serum fetuin-A concentrations were not associated with the risk of cardiovascular events among 2647 individuals recruited from the multi-ethnic study of atherosclerosis cohort [HR=1.01 (0.84; 1.23)].<sup>[64]</sup> Additionally, in a study by Pesaro et al.<sup>[58]</sup>, an association between fetuin-A and abnormal coronary

artery calcium score was not found in both univariate and multivariate analyses.

## 6. OCN Connection to CAC Development

The possible association between carboxylated OCN (ucOCN) and the incidence of CAC remains controversial. However, total OCN did not significantly predict CAC development among the evaluated studies. As observed in a cross-sectional study recruiting 50 patients with type 2 diabetes, no significant correlation was reported between CAC and OCN or ucOCN by logistic regression analysis.<sup>[53]</sup> Moreover, the study by Panh et al.<sup>[65]</sup> among 500 asymptomatic participants indicated the same results: neither OCN nor ucOCN was not associated with abnormal coronary artery calcium score. However, ucOCN was a significant indicator of CAC prevalence in two cross-sectional studies. By investigating the relationship between CAC incidence and ucOCN levels among 162 asymptomatic healthy men, 29% of CAC prevalence was associated with ucOCN.<sup>[66]</sup> Likewise, in a population with essential hypertension, ucOCN was responsible for 18% of CAC incidence, demonstrating that ucOCN is a potential marker for predicting CVD outcomes.<sup>[67]</sup>

## 7. MGP and Risk of CAC Incidence

Few studies have investigated the association between MGP and carboxylated MGP and CAC development among patients diagnosed with CVD and those without known CVD. Accordingly, the multivariate analysis for MGP in 170 patients indicated that MGP could increase the risk of CAC by more than triple times (OR= 3.12 (1.20-8.11),  $P = 0.02$ ).<sup>[13]</sup> In parallel, the presence of MGP among 115 patients with suspected coronary artery disease decreased the severity of CAC ( $P < 0.001$ ), suggesting a contributing role of MGP in vascular calcification and reflecting subclinical CVD diagnosis in clinical settings.<sup>[7]</sup> However, an increasing trend of ucMGP was observed with a high score of coronary artery calcium among 99 patients with CVD, which was not statistically significant in this cross-sectional study.<sup>[68]</sup> The causality relationship between MGP and CAC could not be addressed by these cross-sectional studies and should be investigated by high-quality prospective cohorts and clinical trials.

## 8. The Relationship between OPN and CAC Development

OPN reflected a possible association with identifying CAC burden and providing an opportunity for early diagnosis of CVD incidence among patients. By comparing the data between baseline and follow-up using Cox regression analysis, we found that an elevated level of OPN can increase the risk of CAC by 14% among 126 individuals with a history of CAD.<sup>[69]</sup> Likewise, a cross-sectional study that recruited 64 patients with CAD supported the positive association of OPN with CAC incidence.<sup>[14]</sup> Moreover, using linear regression analyses, the relationship

between OPN and CAC was evaluated in patients with type 2 diabetes, indicating that OPN was a significant determinant of coronary artery calcium score and CVD burden ( $P < 0.0001$ ).<sup>[55]</sup>

### 9. Association between BMP Levels and Abnormal Coronary Artery Calcium Score

Because limited studies have evaluated the association between BMPs and CAC, we obtained relevant cross-sectional literature. This pilot study included 83 patients with CAD aged >40 years. The plasma concentrations of BMP-2, BMP-7, and the Agatston score were measured, and linear regression analysis demonstrated a positive correlation of BMP-2 and BMP-7 with total CAC ( $P < 0.001$ ).<sup>[10]</sup> However, this association should be verified by additional cohort studies that recruit a large number of individuals.

### 10. ALP and CAC risk

As observed in a cross-sectional study that evaluated the tertiles of ALP and calcium scores among 500 individuals without any signs of CAD, high ALP levels could be considered a potential risk factor for coronary calcification [OR=3.84 (2.01-7.54),  $P = 0.001$ ]. In order to identify the risk of high coronary artery calcium scores among patients under statin therapy and without a statin, logistic regression analysis showed that ALP was significantly associated with abnormal coronary artery calcium scores among patients not administering lipid-lowering therapy, whereas the association was not significant in the statin treatment group.<sup>[65]</sup> Due to limited data identifying the role of ALP in determining the patients exposed to high risk of CAC, further studies are needed to confirm the association.

### 11. Association between Other Bone Markers and CAC Risk

The prognostic role of novel bone turnover markers, including decorin, ENPP1, sclerostin, and Gremlin-1 were also investigated in determining the risk of CAC. Circulating decorin concentrations were investigated in our laboratory after recruiting 84 patients with CAD. The results of the study showed no significant correlation between serum decorin levels and the Agatston score ( $r = -0.121$ ,  $P = 0.28$ ).<sup>[70]</sup> Recently, in our previous study, the association between ENPP1 and CAC was assessed among 83 patients diagnosed with CAD (80.7% non-diabetic patients), and a negative correlation was found between ENPP1 and the prevalence of total CAC. Our findings indicated that serum ENPP1 concentrations could be useful markers for identifying subclinical CVD burden in patients without diabetes.<sup>[71]</sup> Multivariate analysis showed that elevated serum sclerostin levels could increase the risk of CAC by 76% in 191 Afro-Caribbean men.<sup>[72]</sup> Moreover, the contribution role of Gremlin-1 as an extracellular antagonist of BMPs was demonstrated by our previously described study. The high concentrations of serum Gremlin-1 may consider a predictor of

decreased risk of CAC. Further studies with larger populations are necessary to verify this association.<sup>[73]</sup>

## CONCLUSION

Because CAC measurement is rather expensive and patients are exposed to radiation, applying the prognostic role of bone turnover markers in predicting elevated coronary artery calcium score could improve treatment adherence and reduce the rate of CVD mortality. Accumulating evidence supports the role of bone marker-mediated pathways in the progression of CAC, which facilitates early diagnosis of CVD complications and the establishment of innovative targets for pharmacological therapy. Indeed, miRNAs and lncRNAs, as novel therapeutic interventions, can be a research priority in regulating bone metabolism at the gene expression level to attenuate high CAC and improve CVD outcomes.

## Ethics

### Authorship Contributions

Concept: A.H.M., A.H.M., N.O., Design: D.W., A.I.M., N.O., Data Collection or Processing: S.S., F.V., N.S., D.W., A.I.M., Analysis or Interpretation: S.S., F.V., N.S., D.W., A.I.M., A.H.M., N.O., Literature Search: S.S., F.V., N.S., Writing: S.S., F.V., A.H.M., N.O.

## Footnotes

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2024.53824

Int J Cardiovasc Acad 2024;10(4):102-114

# Effect of Blood Pressure Control on Left Atrial Function Assessed by 2D Echocardiography in Newly Diagnosed Patients with Systemic Hypertension

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## Abstract

**Background and Aim:** The objective of this study was to investigate the impact of appropriate blood pressure (BP) control on left atrial (LA) function in recently diagnosed individuals with systemic hypertension (HTN), as assessed by two-dimensional (2D) speckle echocardiography and electrocardiography.

**Materials and Methods:** The study included 50 patients who were recently diagnosed with systemic arterial HTN and sought medical attention at Ain Shams University Hospital. The patients' demographic information, risk factors, general and local examinations, 12-lead electrocardiograms (ECG), 2D speckle tracking ECGs, and laboratory measurements were evaluated. Following six months of appropriate BP control in accordance with Joint National Committee 10, the patients were followed up.

**Results:** Peak atrial longitudinal strain (PALS) increased in the current study, with a mean change of  $35.04 \pm 4.33$  to  $38.92 \pm 5.52$  and a  $P$ -value  $< 0.001$ . The mean peak atrial contraction, picture archiving and communication system (PACS) strain, increased from  $17.38 \pm 4.67$  to  $20.46 \pm 4.39$ , with a  $P$ -value of less than 0.001. The mitral peak early (E) and septal mitral annular velocities ( $e'$ ) and their average  $E/e'$  decreased with a change in the mean from  $8.8 \pm 0.93$  to  $7.8 \pm 1.16$ , with a  $P$ -value of less than 0.001. The mean LA stiffness index (LASI) decreased from  $0.24 \pm 0.04$  to  $0.2 \pm 0.03$ , with a  $P$ -value less than 0.001. The ECG follow-up showed no discernible change in the  $P$ -wave's duration or amplitude with  $P$ -values of 0.135 and 0.785, respectively.

**Conclusion:** The results of this study showed that patients with HTN may benefit from speckle tracking imaging to identify mild impairment of LA function. PALS, PACS,  $E/e'$ , and LASI improve in hypertensive patients when BP is well controlled. Additional studies are necessary to enhance the comprehension of LA function assessed via speckle tracking echocardiography, particularly in predicting atrial fibrillation and evaluating the risk of heart failure.

**Keywords:** Hypertension, left atrium strain, left atrium stiffness index, intra-atrial conduction delay

## INTRODUCTION

Hypertension (HTN) can insidiously affect the body for an extended period before the onset of any clinical manifestations. If left uncontrolled, it can cause severe complications, including disability, diminished quality of life, and even fatal events, such as myocardial infarction and stroke.<sup>[1]</sup> Transthoracic

echocardiography (TTE) remains the primary imaging technique for assessing left atrial (LA) volume index (LAVI) and functional capacity. Nevertheless, TTE has introduced innovative methods for the anatomical and functional evaluation of the LA, including the calculation of the LA strain index (LASI) derived from global longitudinal strain (GLS) measurements.<sup>[2]</sup> The

**To cite this article:** Mousa M, Salam ZA, ElSawye M, Omran A, Aly K. Effect of blood pressure control on left atrial function assessed by 2D Echocardiography in newly diagnosed patients with systemic hypertension. Int J Cardiovasc Acad. [Epub Ahead of Print]



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**Received:** 26.08.2024  
**Revised:** 15.10.2024  
**Accepted:** 31.10.2024  
**Published Online:** 16.12.2024



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LA can be conceptualized as a dynamic extension of the left ventricle (LV), playing a pivotal role in optimizing LV filling and overall cardiac function through its reservoir, conduit, and booster pump phases. This tri-phasic mechanism relies not only on LV diastolic and systolic performance but also on the inherent characteristics of the LA. Consequently, any disruption in ventricular function or changes in loading conditions can influence the interplay between the LA and ventricle.<sup>[3]</sup> Enlargement of the LA has been definitively linked to an increased risk of ischemic stroke and cardiovascular disorders.<sup>[4]</sup> Speckle tracking echocardiography (STE) facilitates a direct, angle-independent assessment of myocardial deformation, yielding sensitive and highly reproducible indices of myocardial fiber dysfunction. This technique addresses many of the limitations associated with strain measurements derived from Doppler imaging.<sup>[5]</sup>

## MATERIALS AND METHODS

This prospective observational study aimed to assess the effect of adequate blood pressure (BP) control on LA function, as measured by two-dimensional (2D) echocardiography, in newly diagnosed patients with systemic HTN.

The current study included 50 patients with established systemic arterial HTN. All patients were adequately controlled on medications during follow-up. Proper history of demographic data, risk factors, current treatment, and general and local examination with emphasis on heart rate (HR), BP and heart sounds.

Approval was obtained from the ethical committee at Ain Shams University Faculty of Medicine Research Ethics Committee before starting the research (approval number: MS 87/2023, date: 15.02.2023).

Informed written consent was obtained from all participants, ensuring their full adherence to appropriate privacy and confidentiality standards.

The inclusion criteria were as follows: both sexes, age >18 years, and recently diagnosed systemic arterial HTN within 6 to 12 months, on antihypertensive medications uncontrolled according to Joint National Committee (JNC) 8 guidelines.<sup>[6]</sup> The exclusion criteria encompassed the following: patients younger than 18 years, those diagnosed with chronic coronary syndrome or acute coronary syndrome, patients with valvular disease, patients with atrial arrhythmias, patients exhibiting a LV ejection fraction (EF) below 50%, and those with comorbidities such as thyroid dysfunction.

A comprehensive checklist was used to assess all relevant clinical data pertaining to the patients. This documentation was compiled, and the data were systematically entered into

a computerized system to establish a structured database for all individuals. Measures were subsequently implemented to ensure the strict confidentiality of the collected data.

**All patients who provided written informed consent were subjected to the following at baseline:** A thorough history was obtained, encompassing clinical and demographic information, such as sex and age, as well as risk factors and comorbidities, including diabetes, dyslipidemia, smoking, obesity, and the presence of a family history of relevant conditions.

**Duration of the study:** Study started from October 2022 to July 2023, collection of the patients at baseline from October 2022 to November 2022, follow-up electrocardiogram (ECG) and echocardiography were done after 6 months from proper control of BP to be below 140 systolic BP and below 90 diastolic BP according to JNC 8 guidelines.<sup>[6]</sup>

Comprehensive physical examination including vital signs including BP, HR and auscultation of the heart and lungs.

**Investigations:** Twelve lead surface ECG: with special emphasis on *P*-wave amplitude and *P*-wave duration, complete blood count, creatinine, sodium, and potassium, trans-thoracic echocardiography.

**2D STE:** A Vivid e95 GE Healthcare cardiac ultrasound system with a multifrequency transducer (3-8 MHz) was used to perform echocardiography. All patients underwent a standard TTE study in the four windows (parasternal, apical, subcostal, and suprasternal). All the studies were conducted by a single cardiologist.

Conventional 2D echocardiography was used to capture apical four- and two-chamber views of the LA at relatively high frame rates (60-80 frames per second). After tracing the LA endocardium in both views, the region of interest (ROI) was adjusted to the LA. The ROI was determined by extending the LA endocardial and epicardial surfaces at their junctions, particularly in areas of discontinuity in the LA wall, such as the regions corresponding to the pulmonary veins and the LA appendage.

The ROI was segmented into six parts, resulting in 12 segments that were analyzed. The software generated individual longitudinal strain curves for each segment along with the global strain for each view. Additionally, it was utilized to assess the peak atrial longitudinal strain (PALS), representing LA systolic strain, and peak atrial contraction strain (PACS), corresponding to late diastolic strain.

Mitral peak early (E) and atrial contraction (A) flow velocities, as well as septal mitral annular velocities ( $e'$ ), were used as indicators for assessing diastolic function. Mitral inflow patterns were recorded using pulsed-wave Doppler echocardiography to

capture early diastolic inflow velocity (E), velocity during A, and the ratio of E to A waves (E/A).

The LAVI was determined using the biplane area-length technique and was derived from the apical 4- and 2-chamber views. Volumetric measurements were performed during end systole from the frame immediately before mitral valve opening, after which the volume was adjusted for body surface area.

LV systolic function was assessed via 2D imaging in both apical 4-chamber and 2-chamber views using the biplane method of discs, following the modified Simpson rule.

The LA emptying fraction (LAEF) was calculated using biplane Simpson’s method with the following formula: (LA maximum volume-LA minimum volume)/LA maximum volume × 100.

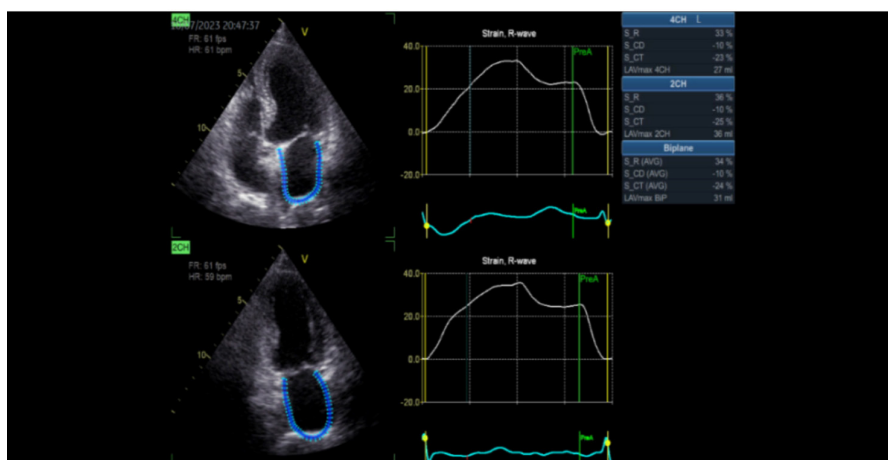
**LA maximum volume:** LA volume at end-systole immediately before mitral valve opening.

**LA minimum volume:** LA volume at end-diastole immediately before mitral valve closure.

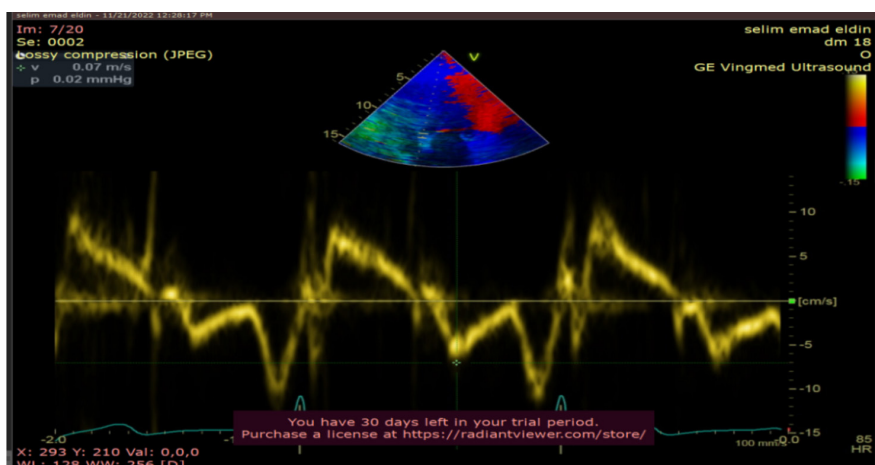
The LA stiffness index (LASI) was calculated based on GLS. The LASI was calculated as the ratio of E/e’ to LA-GLS (Figures 1-5).

**Follow-up data:** All enrolled patients should have their BP properly controlled according to the JNC 8 guidelines and follow-up BP after one week of increasing the medication dose and then monthly at our outpatient clinics.

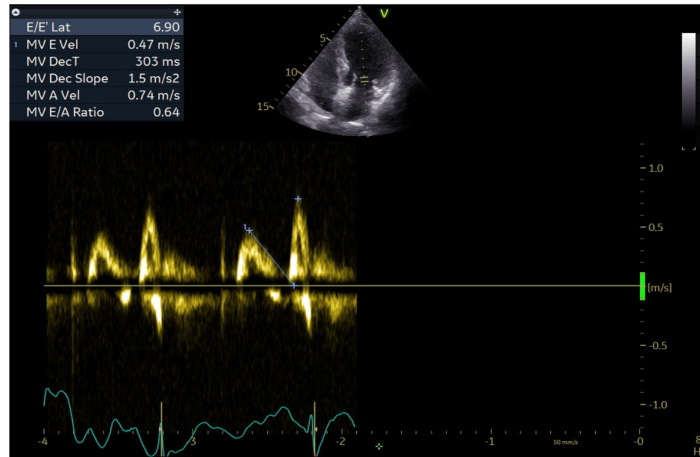
ECG and echocardiography assessments were performed for all patients with the above-mentioned baseline parameters reassessed after 6 months of properly controlled BP, and then both data were compared for each patient (Figure 6).



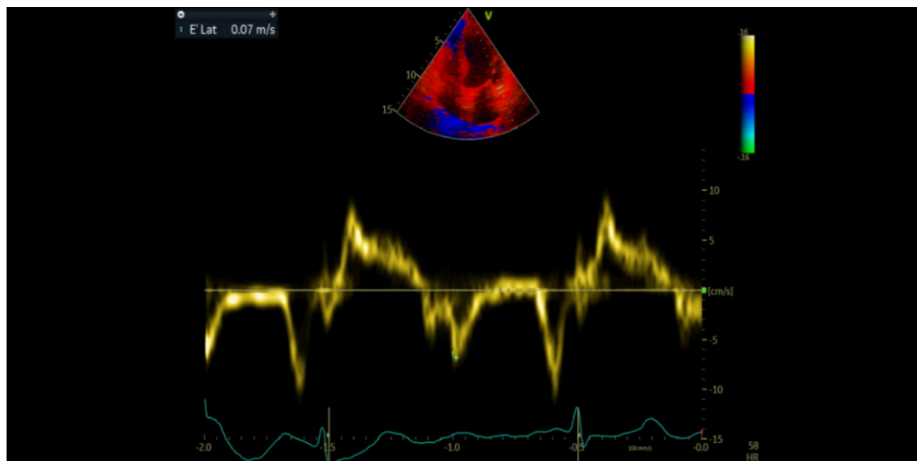
**Figure 1:** LA strain in apical 4 and apical 2 chamber views  
 LA: Left atrial



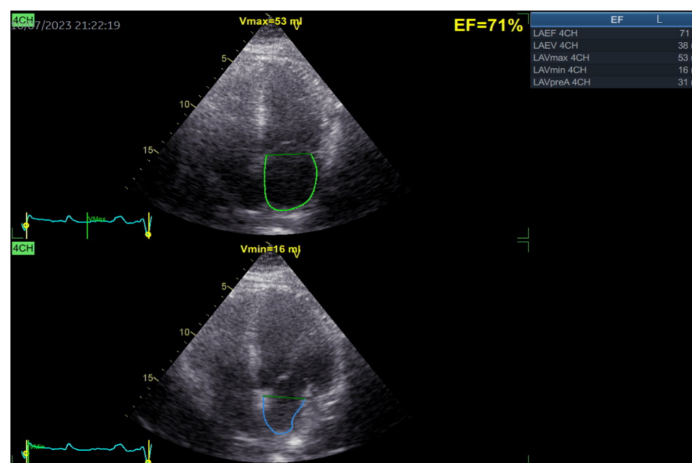
**Figure 2:** Tissue Doppler analysis of the septal mitral annulus to calculate septal e’ in apical 4 chamber (follow-up study of patient number 8)  
 e’: Mitral annular velocities



**Figure 3:** Pulsed-wave Doppler spectra on the tips of the mitral valve in apical 4 chambers view to calculate the A and E waves  
*E: Mitral peak early, e': Mitral annular velocities, A: Atrial contraction*



**Figure 4:** Tissue Doppler analysis of the lateral mitral annulus to calculate lateral e' in apical 4 chambers view  
*e': Mitral annular velocities*



**Figure 5:** Apical 4 chamber view calculating left atrium maximum and minimum volumes and emptying fraction  
*EF: Ejection fraction, LAEV: Left atrial ellipsoid volume, LAEF: Left atrial emptying fraction, LAV: Left atrial volume*

### Statistical Analysis

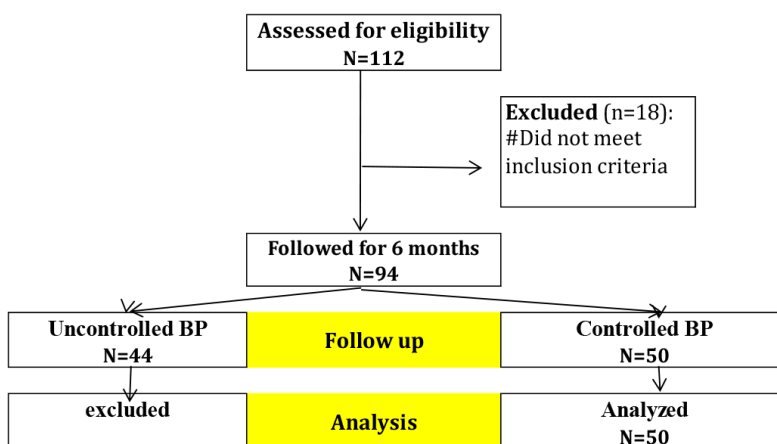
The data were obtained, revised, coded, and entered using the Statistical Package for Social Science (IBM SPSS) version 20. For parametric data, qualitative variables were expressed as numbers and percentages, whereas quantitative variables were summarized as means, standard deviations, and ranges. For non-parametric data, medians with interquartile ranges (IQR) were reported. To compare two groups with qualitative data, the chi-square test was used, and the Fisher exact test was used when the expected frequency in any cell was below 5. For quantitative data with a parametric distribution, an independent t-test was applied to compare the two groups, and the Mann-Whitney test was used for non-parametric data comparisons. For comparisons of quantitative data with parametric distributions across more than two groups, one-way ANOVA was used, while the Kruskal-Wallis test was employed for nonparametric data. The confidence interval was set at 95%,

with a 5% margin of error. Therefore, statistical significance was interpreted as follows:  $P > 0.05$ : non-significant,  $P < 0.05$ : significant (S); and  $P < 0.01$ : highly significant.

### RESULTS

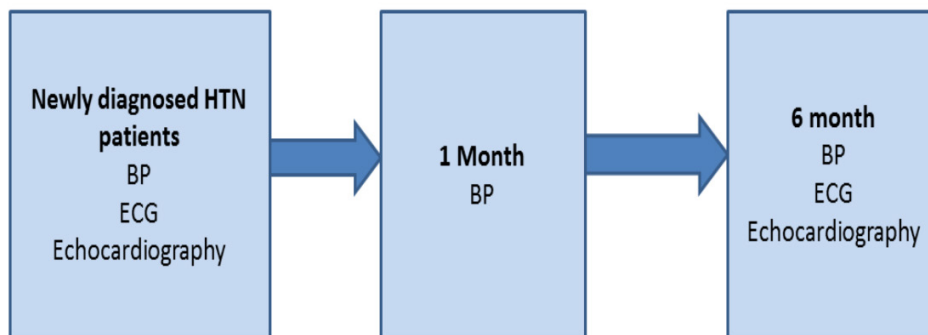
The study was conducted on 50 patients newly diagnosed with uncontrolled systemic HTN. Presented to the outpatient clinic to properly control BP according to the JNC 8 guidelines, history and examination were performed according to the protocol shown in (Figure 7).

**Description of baseline and follow-up BP after 6 months for the patients:** The baseline mean systolic BP was  $149.5 \pm 24.9$ /mean diastolic BP mean was  $90.1 \pm 11.0$ , at the end of follow-up, the mean systolic BP was  $134.4 \pm 15.7$ /mean diastolic BP was  $79 \pm 9$  mm Hg ( $P = 0.005$  Systolic BP and  $P = 0.01$  diastolic BP) (Figure 8).



**Figure 6:** Study design

BP: Blood pressure



**Figure 7:** Flow chart and duration of the current study

BP: Blood pressure, ECG: Electrocardiogram, HTN: Hypertension

**Description of demographic data and risk factors among all studied populations:** The mean age of the study population was 51.26 years ±6.39 ranging from 40 to 62, with 28% males and 72% females. Eleven patients (22%) were smokers.

All the patients included in our study had uncontrolled BP above 140/90 mmHg at the time of examination and then proper BP control below 140/90 mmHg with lifestyle modification and medications. BP measurements at follow-up were performed monthly at our outpatient clinic (Table 1).

**Description of the baseline ECG and Echocardiography parameters for the patients:** Baseline ECG parameters included the amplitude of the P-wave, which ranged from 0.16 mV to 0.21 mV, the mean was 0.19±0.01 (all with in normal range below 0.25 mV), and the P-wave duration, which ranged from 80 ms to 100 ms with a mean 89.22±5.96 (all with in normal range).

Baseline echocardiography parameters included the following: EF ranged from 55% to 66% with a mean 60.92±3.47, PALS (reservoir strain) ranged from 22 to 43 with a mean 35.04±4.33, PACS ranged from 7 to 25 with a mean 17.38±4.67, E wave ranged from 0.4 m/s to 1.02 m/s with a mean 0.68±0.17, A wave ranged from 0.59 m/s to 1.08 m/s with a mean 0.82±0.12, E/A wave ranged from 0.57 to 1.19 with a mean 0.83±0.16, E/e' ranged from 6.21 to 10 with a mean 8.8±0.93, empty fraction ranged from 53% to 70% with a mean 64.68±5.02, LAVI ranged from 20 mL/m<sup>2</sup> to 33 mL/m<sup>2</sup> with a mean 27.12± 2.97 and LASI ranged from 0.18 to 0.33 with a mean 0.24±0.04 (Table 2).

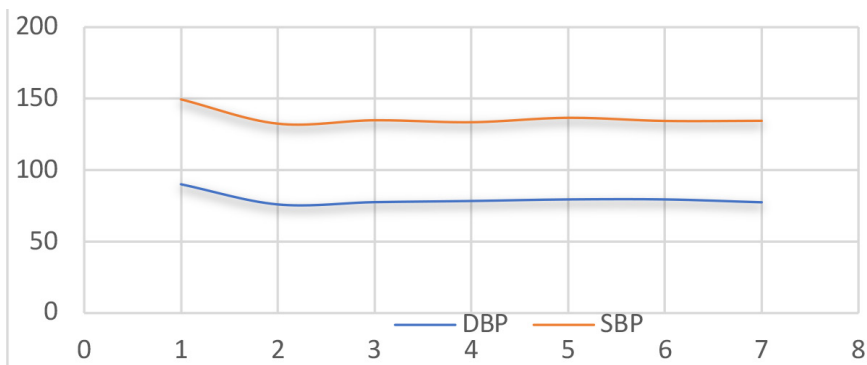
**Description of ECG parameters at baseline and after 6 months of properly controlled BP:** There was no statistically significant difference between the P-wave duration and amplitude at baseline and six month follow-up after proper control of BP. The P-wave duration and amplitude were within the normal range (Table 3).

**Description of echocardiography parameters at baseline and after 6 months of properly controlled BP:** There was a strong relationship between control of BP and changes in PALS, PACS, E/e', and LASI, as shown: PALS showed an increase with change of the mean from 35.04±4.33 to 38.92±5.52 with P-value below 0.001. PACS showed an increase with change of the mean from 17.38±4.67 to 20.46±4.39 with P-value below 0.001 (Figure 9). E/e' showed a decrease with change of the mean from 8.8±0.93 to 7.8±1.16 with P-value below 0.001 (Figure 10). LASI showed a decrease with change of the mean from 0.24±0.04 to 0.2±0.03 with P-value below 0.001 (Figure 11). There was no statistically significant difference between baseline executive function and 6 months after implantation of the modified biplane Simpson method (Table 4).

**Table 1: Demographic data and characteristics of the study population**

		Total no. =50
Age	Mean ± SD	51.26±6.39
	Range	40-62
Sex	Female	36 (72.0%)
	Male	14 (28.0%)
BMI	Mean ± SD	30.74±4.68
	Range	24-41
Duration since diagnosis	6 month	30 (60.0%)
	1 year	20 (40.0%)
Drugs	BB (bisoprolol)	26 (52.0%)
	ACEI and ARBs	18 (36.0%)
	CCB	6 (12.0%)
Smoker	Non-smoker	88 (78.0%)
	Smoker	11 (22.0%)

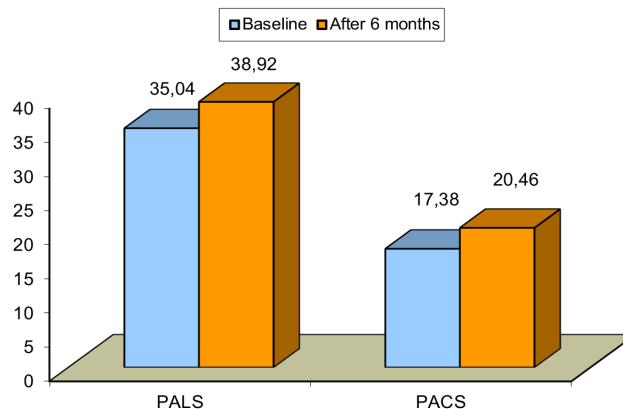
ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers, CCB: Calcium channel blocker, BMI: Body mass index, SD: Standard deviation, BB: Beta-blockers



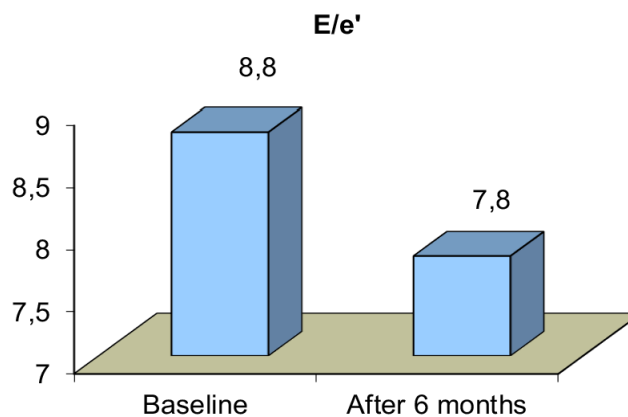
**Figure 8:** Showing blood pressure at baseline and during follow-up monthly  
 DBP: Diastolic blood pressure, SBP: Systolic blood pressure

Table 2: Baseline ECG and ECHO parameters among the study patients		
Baseline		Total no =50
<b>ECG</b>		
Wave amplitude (mV)	Mean ± SD	0.19±0.01
	Range	0.16-0.21
P-wave duration (ms)	Mean ± SD	89.22±5.96
	Range	80-100
<b>ECHO</b>		
EF %	Mean ± SD	60.92±3.47
	Range	55-66
PALS	Mean ± SD	35.04±4.33
	Range	22-43
PACS	Mean ± SD	17.38±4.67
	Range	7-25
E wave	Mean ± SD	0.68±0.17
	Range	0.4-1.02
A wave	Mean ± SD	0.82±0.12
	Range	0.59-1.08
e'	Mean ± SD	0.08±0.02
	Range	0.06-0.11
E/e'	Mean ± SD	8.8±0.93
	Range	6.21-10
E/A	Mean ± SD	0.83±0.16
	Range	0.57-1.19
Diastolic Dysfunction	No	8 (16.0%)
	Yes	42 (84.0%)
LAVI	Mean ± SD	27.12±2.97
	Range	20-33
Emptying fraction	Mean ± SD	64.68±5.02
	Range	53-70
Maximum Volume	Median (IQR)	34 (29-44)
	Range	14-55
Minimum Volume	Median (IQR)	12 (8-14)
	Range	3-23
LASI	Mean ± SD	0.24±0.04
	Range	0.18-0.33

ECG: Electrocardiogram, ECHO: Echocardiography, EF: Executive function, PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, e': Mitral annular velocities, E: Mitral peak early, A: Atrial contraction, LAVI: Left atrial volume index, LASI: Left atrial strain index, SD: Standard deviation, IQR: Inter quantile range, no.: Number



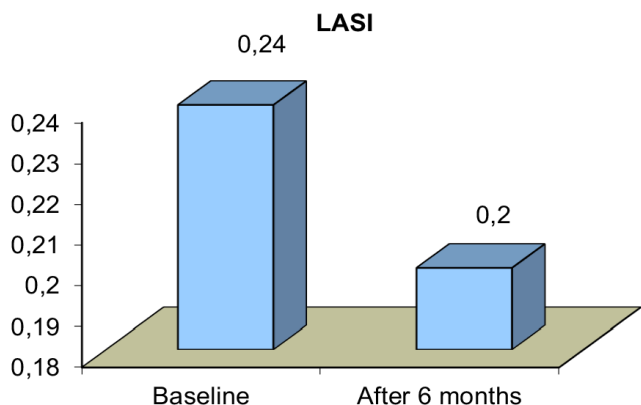
**Figure 9:** PALS and PACS at baseline and follow-up after 6 months  
*PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain*



**Figure 10:** E/e' at baseline and follow-up after 6 months  
*e': Mitral annular velocities, E: Mitral peak early*

Table 3: Baseline electrocardiogram and follow-up after 6 months among the studied patients							
		Baseline	After 6 months	Change %	Test value	P-value	Sig.
				Median (IQR)			
Wave amplitude (mV)	Mean ± SD	0.19±0.01	0.19±0.01	0 (0-0)	-1.520*	0.135	NS
	Range	0.16-0.21	0.16-0.21				
Wave duration (ms)	Mean ± SD	89.22±5.96	89.30±5.89	0 (0-0)	-0.275*	0.785	NS
	Range	80-100	80-100				

P-value > 0.05: Non-significant (NS), \*: Paired t-test, SD: Standard deviation, IQR: Inter quantile range, Sig.: Significance



**Figure 11:** LASI at baseline and follow-up after 6 months  
*LASI: Left atrial strain index*

**Description of the correlation between age, body mass index (BMI) and Echo parameters:** The E and A waves had a positive correlation with age coefficient of 0.4, with a *P*-value of 0.002 for the E wave and 0.001 for the A wave, yet it showed mild change. The E wave was higher in patients with a BMI 30 kg/m<sup>2</sup>, with a *P*-value of 0.034 (Table 5).

**Description of the different drugs in relation to changes in echocardiographic parameters:** Gender, smoking status, and drug type showed no statistically significant correlation with changes in echocardiography parameters after 6 months of proper BP control (Table 6-8).

**Table 4: ECHO at baseline and follow-up after 6 months of properly controlled blood pressure among the study patients**

		Baseline	After 6 months Median (IQR)	Change %	Test value	<i>P</i> -value	Sig.
EF %	Mean ± SD	60.92±3.47	60.92±3.47	-	0.000	1.000	NS
	Range	55-66	55-66				
PALS	Mean ± SD	35.04±4.33	38.92±5.52	7.71 (3.33-13.89)	-7.768*	<0.001	HS
	Range	22-43	27-53				
PACS	Mean ± SD	17.38±4.67	20.46±4.39	10 (7.14-26.67)	-9.182*	<0.001	HS
	Range	7-25	10-32				
E wave	Mean ± SD	0.68±0.17	0.69±0.16	2.27 (-12.86-15.15)	-0.215*	0.830	NS
	Range	0.4-1.02	0.45-1.07				
A wave	Mean ± SD	0.82±0.12	0.84±0.15	0 (-9.46-7.41)	-0.931*	0.357	NS
	Range	0.59-1.08	0.6-1.16				
e'	Mean ± SD	0.08±0.02	0.08±0.01	0 (-10-12.5)	-0.522*	0.604	NS
	Range	0.06-0.11	0.06-0.11				
E/e'	Mean ± SD	8.8±0.93	7.8±1.16	-9.01 (-16.38- -3.09)	6.484*	<0.001	HS
	Range	6.21-10	5.1-9.8				
E/A	Mean ± SD	0.83±0.16	0.83±0.16	-0.59(-11.54-14.93)	0.149•	0.882	NS
	Range	0.57-1.19	0.61-1.4				
Diastolic dysfunction	No	8 (16.0%)	8 (16.0%)	-	0.000*	1.000	NS
	Yes	42 (84.0%)	42 (84.0%)				
LAVI	Mean ± SD	27.12±2.97	27.12±2.97	-	0.000	1.000	NS
	Range	20-33	20-33				
Emptying fraction	Mean ± SD	64.68±5.02	64.68±5.02	-	0.000	1.000	NS
	Range	53-70	53-70				
Maximum volume	Median (IQR)	34 (29-44)	34 (23-38)	-5.41 (-17.78-6.67)	-1.733#	0.083	NS
	Range	14-55	13-54				
Minimum volume	Median (IQR)	12 (8-14)	11 (6-13)	0 (-26.67-8.33)	-1.345#	0.179	NS
	Range	3-23	2-23				
LASI	Mean ± SD	0.24±0.04	0.2±0.03	-13.64 (-24- -8)	9.090*	<0.001	HS
	Range	0.18-0.33	0.16-0.31				

*P*-value > 0.05: NS: Non-significant, *P*-value < 0.05: Significant, *P*-value < 0.01: Highly significant (HS), •: Paired t-test, #: Wilcoxon signed ranks test, \*: Chi-square test, ECHO: Echocardiography, EF: Executive function, PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, e': Mitral annular velocities, E: Mitral peak early, A: Atrial contraction, LAVI: Left atrial volume index, LASI: Left atrial strain index, SD: Standard deviation, IQR: Inter quantile range, Sig.: Significance



**Table 5: Correlations of changes in ECHO parameters with age and BMI among the studied parameters**

Change %	Age		BMI	
	r	P-value	r	P-value
P-wave	-0.146	0.313	-0.068	0.639
P-R interval	-0.063	0.664	-0.053	0.716
PALS	-0.277	0.051	-0.107	0.460
PACS	0.011	0.940	0.085	0.558
E wave	0.421**	0.002	0.301*	0.034
A wave	0.450**	0.001	0.127	0.381
e'	0.202	0.160	0.230	0.108
E/e'	0.147	0.307	0.127	0.381
E/A	0.032	0.826	0.010	0.943
Maximum volume	-0.058	0.689	-0.172	0.233
Minimum volume	-0.165	0.253	0.136	0.348
LASI	0.193	0.178	-0.042	0.774

P-value > 0.05: Non-significant (NS), P-value < 0.05: Significant, P-value < 0.01: Highly significant (HS), \*\*:Spearman correlation coefficient, \*: Chi-square test, ECHO: Echocardiography, PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, e': Mitral annular velocities, E: Mitral peak early, A: Atrial contraction, LASI: Left atrial strain index, BMI: Body mass index

**Table 6: Relationship between sex and changes in ECHO parameters among the study patients**

Change %		Sex		Test value	P-value	Sig.
		Female	Male			
		no=36	no=14			
PALS	Median (IQR)	1.28 (-2.86-12.13)	3.45 (0-13.51)	-0.400#	0.689	NS
	Range	-23.91-34.29	-18.52-40.54			
PACS	Median (IQR)	8.7 (-4.55-18.93)	0 (0-10)	-0.674#	0.500	NS
	Range	-33.33-157.14	-37.5-87.5			
E wave	Median (IQR)	4.17 (-9.93-14.72)	-3.51 (-15.71-20.45)	-0.735#	0.462	NS
	Range	-24.74-30	-36.11-25			
A wave	Median (IQR)	0 (-10.64-7.41)	1.33 (-3.53-7.46)	-0.606#	0.545	NS
	Range	-98.72-37.29	-11.84-17.86			
e'	Median (IQR)	0 (0-14.29)	0 (-14.29-0)	-1.639#	0.101	NS
	Range	-45.45-66.67	-27.27-33.33			
E/e'	Median (IQR)	-1.46 (-15.89-4.67)	-9.49 (-26.44-3.06)	-1.383#	0.167	NS
	Range	-25.29-43.33	-43.33-42.77			
E/A	Median (IQR)	-1.38 (-11.54-5.75)	5.42 (-13.64-17.54)	-0.627#	0.531	NS
	Range	-27.36-37.25	-35.11-22.58			
Maximum volume	Median (IQR)	-2.27 (-17.24-7.75)	-12.39 (-20.69- -2.17)	-1.405#	0.160	NS
	Range	-32.08-80	-36.36-33.33			
Minimum volume	Median (IQR)	0 (-26.43-33.33)	-16.03 (-26.67- -6.25)	-1.432#	0.152	NS
	Range	-81.82-228.57	-44.44-53.33			
LASI	Median (IQR)	-8.55 (-16.59-4.88)	-12.5 (-30.3-0)	-1.364#	0.173	NS
	Range	-32.14-35	-37.5-29.41			

P-value > 0.05: NS: Non-significant, P-value < 0.05: Significant, P-value < 0.01: Highly significant (HS), #: Mann-Whitney test, ECHO: Echocardiography, PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, e': Mitral annular velocities, E: Mitral peak early, A: Atrial contraction, LASI: Left atrial strain index, SD: Standard deviation, IQR: Inter quantile range

**Table 7: Relation between types of drugs and changes in ECHO parameters among the study patients.**

		Drugs			Test value	P-value	Sig.
		BB	ACEI and ARBs	CCB			
		no=26	no=18	no=6			
PALS	Median (IQR)	5.88 (-2.7-12.9)	0 (-11.11-13.51)	1.72 (-2.5-3.45)	2.126#	0.345	NS
	Range	-23.91-34.29	-18.52-40.54	-4.88-5			
PACS	Median (IQR)	8.89 (0-26.09)	0 (-18.75-10.53)	0 (0-8.33)	1.653#	0.438	NS
	Range	-33.33-57.14	-37.5-157.14	0-8.33			
E wave	Median (IQR)	6.54 (-7-21.28)	-3.51 (-15.71-14.29)	5.45 (-4.26-13.33)	2.023#	0.364	NS
	Range	-24.74-30	-36.11-25	-4.26-13.33			
A wave	Median (IQR)	0 (-9.46-15.58)	1.52 (-1.27-7.46)	-11.84 (-98.72-1.33)	4.888#	0.087	NS
	Range	-27.71-37.29	-15.24-17.86	-98.72-1.33			
e'	Median (IQR)	0 (0-14.29)	0 (-11.11-12.5)	0 (-27.27-22.22)	0.531#	0.767	NS
	Range	-45.45-33.33	-14.29-66.67	-27.27-22.22			
E/e'	Median (IQR)	1.05 (-16.38-11.95)	-14.18 (-15.89-0)	-7.3 (-9.49-3.06)	2.395#	0.302	NS
	Range	-25.29-43.33	-43.33-42.77	-9.49-3.06			
E/A	Median (IQR)	-1.38 (-10.47-16.46)	0.41 (-13.64-4.29)	17.54 (-11.54-22.58)	2.401#	0.301	NS
	Range	-27.36-37.25	-35.11-14.93	-11.54-22.58			
Maximum volume	Median (IQR)	0 (-17.78-20.69)	-3.36 (-13.16-3.33)	-17.24 (-17.78--11.63)	5.150#	0.076	NS
	Range	-32.08-80	-36.36-33.33	-32.08--11.63			
Minimum volume	Median (IQR)	0 (-7.69-33.33)	-6.25 (-26.67-8.33)	-33.09 (-53.85--21.74)	4.157#	0.125	NS
	Range	-81.82-228.57	-50-155.56	-53.85-53.33			
LASI	Median (IQR)	-10.1 (-17.39-5.26)	-9.2 (-29.63-0)	-6.08 (-10-0)	1.017#	0.601	NS
	Range	-32.14-35	-37.5-29.41	-15-0			

P-value > 0.05: NS: Non-significant, P-value < 0.05: Significant, P-value < 0.01: Highly significant (HS), #: Kruskal-Wallis test, ECHO: Echocardiography, PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, e': Mitral annular velocities, E: Mitral peak early, A: Atrial contraction, LASI: Left atrial strain index, SD: Standard deviation, IQR: Inter quantile range, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers

**Table 8: Relation between smoking and changes in ECHO parameters among the study patients.**

Change %		Smoker		Test value	P-value	Sig.
		No	Yes			
		no=39	no=11			
PALS	Median (IQR)	5 (-2.86-12.9)	3.23 (-11.11-5)	-0.645#	0.519	NS
	Range	-23.91-40.54	-18.52-20.69			
PACS	Median (IQR)	8.7 (-4.55-26.09)	0 (-18.75-8.33)	-1.425#	0.154	NS
	Range	-33.33-157.14	-37.5-87.5			
E wave	Median (IQR)	5.26 (-12.86-15.15)	-3.51 (-15.71-5.45)	-1.136#	0.256	NS
	Range	-26.58-30	-36.11-20.45			
A wave	Median (IQR)	0 (-9.46-9.86)	1.33 (-3.9-3.03)	-0.035#	0.972	NS
	Range	-98.72-37.29	-11.84-7.46			
e'	Median (IQR)	0 (-9.09-14.29)	0 (-14.29-12.5)	-0.942#	0.346	NS
	Range	-45.45-66.67	-27.27-33.33			
E/e'	Median (IQR)	-2.27 (-16.38-5.88)	-9.49 (-15.02-3.06)	-0.996#	0.319	NS
	Range	-35-43.33	-43.33-42.77			
E/A	Median (IQR)	-1.18 (-11.54-5.75)	14.93 (-13.64-17.54)	-0.785#	0.433	NS
	Range	-27.36-37.25	-35.11-22.58			

**Table 8: Continued**

Change %		Smoker		Test value	P-value	Sig.
		No	Yes			
		no=39	no=11			
Maximum volume	Median (IQR)	0 (-17.24-11.11)	-13.16 (-20.69--2.17)	-1.699≠	0.089	NS
	Range	-36.36-80	-32.08-33.33			
Minimum volume	Median (IQR)	0 (-26.67-33.33)	-16.67 (-35.71--6.25)	-1.800≠	0.072	NS
	Range	-81.82-228.57	-44.44-53.33			
LASI	Median (IQR)	-8 (-17.39-5)	-15 (-30.3-0)	-1.771≠	0.076	NS
	Range	-32.14-35	-37.5-0			

*P*-value > 0.05: NS: Non-significant, *P*-value < 0.05: Significant, *P*-value < 0.01: Highly significant (HS), ≠: Mann-Whitney test, ECHO: Echocardiography, PALS: Peak atrial longitudinal strain, PACS: Peak atrial contraction strain, e': Mitral annular velocities, E: Mitral peak early, A: Atrial contraction, LASI: Left atrial strain index, SD: Standard deviation, IQR: Inter quantile range

### DISCUSSION

HTN is a complex, multifactorial condition with considerable heterogeneity. This condition poses a major global public health challenge because of its widespread prevalence and strong association with increased cardiovascular risk. The burden of cardiovascular morbidity and mortality is intensified by delayed diagnosis, inadequate awareness, and poor BP management in affected individuals, thereby placing further strain on healthcare systems and resources.

The LA is vulnerable to both structural and functional changes in individuals with HTN.<sup>[7]</sup> The effect of HTN on LA function has been explored to a limited extent, particularly in hypertensive patients with normal LA dimensions. Therefore, this study was designed to evaluate LA function in patients with normal or mildly enlarged LA using deformation imaging techniques. Strain rate imaging has emerged as a reliable tool for accurately measuring regional myocardial function, independent of the tethering effect and cardiac rotational dynamics. However, only a few studies have focused on quantifying LA function in hypertensive patients to date.<sup>[8]</sup>

**LA functional parameters and systemic arterial HTN:** The association between well-controlled HTN and LA functional assessment has been minimally explored in the literature. HTN often results in both LA enlargement and compromised functionality. Nevertheless, alterations in LA function initiate in the early stages, even before measurable changes in atrial dimensions are observed. Identifying subclinical LA dysfunction early is crucial because it provides an opportunity to maintain the reservoir function of the LA in hypertensive individuals without LA dilation.<sup>[8]</sup>

In this study, our objective was to identify early signs of LA dysfunction in hypertensive patients with optimal BP control, with “early” defined as preceding significant structural alterations in LA size, specifically reflected by LA volume. To assess LA function, 2DSTE. Furthermore, we aimed to

establish a correlation between various risk factors and clinical parameters observed in hypertensive individuals and their impact on LA strain function. Adequate BP control was achieved after 6 months of follow-up, with a substantial drop in both mean systolic and diastolic measurements with a delta change of -15.4 mmHg systolic and -11.1 mmHg diastolic, and a *P*-value of 0.005 and 0.01 respectively. This modest decrease in androgen binding protein (ABP) had a significant effect on LA strain measurements, as will be discussed.

**The PALS:** In the current study, PALS was improved in the hypertensive group at the 6-month follow-up controlled on medications compared with the baseline. PALS showed an increase with change of the mean from 35.04±4.33 to 38.92±5.52 with *P*-value 0.001.

These outcomes aligned with the findings of Taamallah et al.,<sup>[9]</sup> the hypertensive group, with values of 31.23±9.93 in hypertensive group versus 46.43±11.06 in the control group (*P* = 0.000).

This was in concordance with the study done in 2020 by Sahin et al.<sup>[10]</sup> which was done in 30 hypertensive patients and follow-up done after 12 weeks of BP control showed an increase in LA reservoir strain (%) mean at baseline (31.4±8.8) then mean after 12 weeks (34.7±9.6) with a *P*-value of 0.020.

**The peak atrial contraction strain (PACS):** In the current study, PACS was improved in the hypertensive group at the 6-month follow-up controlled on medications compared with the baseline. PACS showed an increase with change of the mean from 17.38±4.67 to 20.46±4.39 with *P*-value 0.001.

This contrasts with the findings presented by Taamallah et al.<sup>[9]</sup> in 2021, in which their study demonstrated no statistically significant difference between the hypertensive and non-hypertensive cohorts in terms of peak strain values, reported as 16.73±3.84% and 15.29±2.75%, respectively (*P* = 0.07).

**E/e' and arterial HTN:** In the current study, a short-term follow-up of 6 months showed a significant decrease in E/e' with a change in the mean from  $8.8 \pm 0.93$  to  $7.8 \pm 1.16$  with  $P$ -value 0.001.

This is in concordance with Piskorz et al.<sup>[11]</sup> who showed that the frequency of an E/e' ratio  $>14$  was reduced from 38 patients (13.3%) to 3.6% ( $P < 0.001$ ) in medium to long-term follow-up with a mean of 5 years.

**LASI and arterial HTN:** In our study, short-term follow-up after 6 months of properly controlled arterial HTN showed a significant decrease in LASI. LASI showed a decrease with change of the mean from  $0.24 \pm 0.04$  to  $0.2 \pm 0.03$  with  $P$ -value 0.000. These findings are consistent with the results of Sun et al.,<sup>[12]</sup> which revealed that the LASI was notably elevated in non-dippers [0.29 (0.21, 0.41)] compared with dippers [0.26 (0.21, 0.33)], with a statistically significant difference ( $P < 0.05$ ).

### Type of Medications and Echocardiography Parameters

In our study, different types of drugs showed no statistically significant differences between the types of drugs and changes in echocardiographic parameters after 6 months of proper BP control below 140/90 mmHg. This result is in concordance with that of Degirmenci et al.<sup>[13]</sup> and showed no significant difference between patients on irbesartan and patients on nebivolol. This finding highlights the importance of ABP control in the selection of medication.

### Age and Echocardiography Parameters

In our study, the only significance was that the E and A waves were higher in age groups 50 and older, with a  $P$ -value of 0.002 for the E wave and 0.001 for the A wave. In concordance with our study in 2021, Piskorz et al.<sup>[11]</sup> showed that E and A waves were higher in the age group above 55.

### Study Limitation

The cohort of patients in this study was comparatively limited, and the research was conducted at a single center with a short follow-up period. It was better to perform ambulatory BP monitoring. It is also recommended to assess the effect of BP control on LA strain parameters. All patients enrolled in the current study were newly diagnosed hypertensive patients with no significant co-morbidities; however, other risk factors should have been addressed, such as dyslipidemia and DM in a sub-analysis. LV hypertrophy was not correlated with LA functions in this study, as all candidates were newly diagnosed hypertensive patients. This should be addressed in future research.

## CONCLUSION

The current study demonstrated that speckle tracking imaging can be used to detect subtle impairment of LA function in

patients with HTN. Proper control of BP in hypertensive patients leads to improvement in LA strain parameters (PALS, PACS, E/e' and LASI). The clinical applicability of assessing LA function through STE in hypertensive patients warrants additional research to refine the role of LA evaluations in predicting atrial fibrillation and assessing the risk of heart failure with preserved EF.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ain Shams University Faculty of Medicine Research Ethics Committee (approval number: MS 87/2023, date: 15.02.2023)

**Informed Consent:** Informed consent was obtained.

### Footnotes

### Authorship Contributions

Concept: M.M., Z.A., K.A., Design: Z.A., K.A., Data Collection or Processing: M.E., A.O., Analysis or Interpretation: M.M., Literature Search: M.E., Writing: M.M.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2024.83097

Int J Cardiovasc Acad 2024;10(4):115-122

# An Evaluation of Cases with a Claim of Medical Malpractice Related to the Cardiology Department Reported by the First Forensic Medicine Expert Committee of the Forensic Medicine Institute between 2012 and 2014

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## Abstract

**Background and Aim:** There are few studies in literature related to medical malpractice in Turkey. There is insufficient information in literature about malpractice in the field of cardiology, not only in Turkey but throughout the world. The aim of this study was to examine claims of medical malpractice related to cardiology and reports on this subject prepared by the First Forensic Medicine Expert Committee of the Forensic Medicine Institute.

**Materials and Methods:** A retrospective examination was performed on 160 cases with a claim of malpractice related to cardiology branch doctors, with reports by the First Forensic Medicine Expert Committee of the Forensic Medicine Institute between 2012 and 2014.

**Results:** The examined cases comprised 58.8% males and 41.2% females. Malpractice was determined in 5.6% of the cases. The rate of malpractice claims was high in the Marmara region, in private hospitals, and among specialist doctors. The most common complaint at hospital was chest and arm pain. During the diagnostic process, the most common primary diseases were coronary artery disease (n=75, 76.9%) and heart failure (n=13, 8.1%).

**Conclusion:** Medical malpractice claims are currently rapidly increasing in Turkey. The complaint process can have severe physical and psychological negative effects for both the patient and the healthcare professional. Therefore, it is important to examine, analyze, and evaluate cases of malpractice to be able to prevent and overcome them.

**Keywords:** Cardiology, malpractice, forensic medicine, autopsy

## INTRODUCTION

The term “malpractice” is derived from the Latin words, “male” and “praxis” and is used for the erroneous or defective actions of a member of any profession. In recent years, the subject of malpractice has been examined from educational,

management, ethical, social, and legal perspectives and has been interpreted in different ways. At the 44<sup>th</sup> General Board Meeting of the World Medical Association in 1992, the definition of malpractice was accepted as “harm to the patient during treatment by the physician not performing standard

**To cite this article:** Kılıç F, Hösükler E, Altın İ, Üzün İ. An Evaluation of Cases with a Claim of Medical Malpractice Related to The Cardiology Department Reported by the First Forensic Medicine Expert Committee of the Forensic Medicine Institute between 2012 and 2014. Int J Cardiovasc Acad. 2024;10(4):115-122



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**Received:** 03.10.2024**Revised:** 18.11.2024**Accepted:** 25.11.2024**Published Online:** 16.12.2024

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practices, lack of competence, or not treating the patient”, and it was emphasized that this must be differentiated from complications seen during medical care and treatment not due to physician error.<sup>[1,2]</sup>

The term malpractice refers to neglect by members of professions such as doctors, dentists, engineers, and lawyers. Medical malpractice is behavior by a healthcare provider (doctor, dentist, chemist, midwife, nurse, etc.) below the standards of the profession. To be classified as medical malpractice, 4 components must be considered:

1. Is the action legal?
2. Is there a mistake?
3. Has harm been caused?
4. Is there a causal link between the harm and the action?<sup>[3]</sup>

Prior to the “Regulation on the Procedures and Principles Regarding the Investigation of Healthcare Professionals Due to Medical Procedures and Practices and the Recourse of Compensation Paid by the Administration” number 31867 published in the Official Gazette dated 15.06.2022, applications regarding medical malpractice were made to the relevant Chief Public Prosecutor. After an initial examination of the physician according to the place of work at a private hospital, state hospital, charitable trust hospital, or university hospital, the right to prosecute was decided, and proceedings were initiated. In addition to physicians working in private hospitals, following a preliminary investigation by the hospital, the prosecution of the physician permitted to be investigated could be conducted by the Chief Public Prosecutor. After this point, when expert opinion reports were required, they were requested from the Istanbul Forensic Medicine Institute Directorate and prepared by a panel of 3 experts including at least one professor from the relevant departments of university hospitals. In cases resulting in death, an expert opinion was sought from the First Expert Committee of Istanbul Forensic Medicine Institute.<sup>[1,2,4]</sup>

The number of medical malpractice cases is increasing in Turkey, as throughout the world. Because the public now has easy access to information, people do not question whether the information obtained is correct or false. They may be misdirected by lawyers, and there are increased amounts of compensation demanded.<sup>[4,5]</sup>

An expert is a person with specialized knowledge who assists the Public Prosecutor in solving a problem, in circumstances permitted by the court, judge, and law. The expert service in Turkey is provided mainly by expert witnesses or institutions on the subject. In medical malpractice investigations, the experts and expert committees determine whether or not any harm occurring in the patient is due to the medical practice applied

or whether the applied practice was deficient or not. These committees make decisions by evaluating statements from the patient and witnesses together with the medical documents, films, and laboratory reports of the patient, and if there was an autopsy, the autopsy findings.<sup>[6,7]</sup>

In this study, a retrospective examination was made of medical malpractice reports of cases resulting in death related to the cardiology department, which were submitted to the First Forensic Medicine Expert Committee of the Forensic Medicine Institute (FMI First FMEC) between 2012 and 2014.

## METHODS

A retrospective examination was conducted on 160 cases with claims of medical malpractice, which were discussed and decided by the FMI First FMEC between 2012 and 2014. The cases were examined in respect of age at the time of the event, gender, date of the event, relationship of the complainant to the patient, reason for the complaint, the healthcare institution at which they presented, the academic title of the doctor against whom the claim was made, complaint on presentation, diagnosis on presentation, whether or not medical malpractice occurred, complications that developed, the effect of the presence of complications on the error rate, autopsy status, the effect of autopsy on the error rate, and the reason for medical malpractice.

## Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 21.0 software (Statistical Package for the Social Sciences). Descriptive statistical methods were used in the analysis of the study data, and results were stated as mean  $\pm$  standard deviation, median, minimum, and maximum values, or number (n) and percentage (%). In the qualitative data comparisons, relationships between two or more groups of variables were examined using the Pearson’s chi-square test, the Yates’ continuity correction test, and Fisher’s exact test. Findings were presented in tables and graphs. A value of  $P < 0.05$  was set as statistically significant.

This study was based on a thesis entitled, “An evaluation of cases with a claim of medical malpractice related to the cardiology department reported by the First Forensic Medicine Expert Committee of the Forensic Medicine Institute between 2012 and 2014”.

The records in this study were evaluated according to the laws before the “Presidential Decree on the Organization of Ministries, Related Institutions and Organizations and Other Institutions and Organizations”, published in the Official Gazette number 30379, dated 15/07/2018, and the “Regulation on the Procedures and Principles Regarding the Investigation

of Healthcare Professionals Due to Medical Procedures and Practices and the Recourse of the Compensation Paid by the Administration” published in the Official Gazette number 31867, dated 15/06/2022.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institute of Forensic Medicine Scientific Research Committee (approval number: 21589509/1019, date: 15.12.2015).

### RESULTS

The 160 cases evaluated comprised 94 (58.8%) males and 66 (41.2%) females. No information was available regarding the age of 7 cases and the mean age of the remaining 153 cases was determined to be 58.45±17.12 years (range, 12-88 years). Of the 153 cases in which age was known, the largest age group was ≥60 years (n=79, 51.6%) (Figure 1). When the relationship between gender and medical malpractice was evaluated, no statistically significant difference was determined ( $P > 0.05$ ).

When the cases were examined by year, there were seen to be 46 (28.8%) cases reported in 2012, 57 (35.6%) in 2013, and 57 (35.6%) in 2014. When the dates of the events which were the subject of a court case or investigation were examined, they were seen to have occurred between 2003 and 2014. The events of most cases occurred in 2012, and the number of records increased up to that year. In the 3-year period of 2012-2014 of this study, claims of medical malpractice related to the cardiology department showed an increase of 23.9%. When the relationship was examined between the date when the incident occurred and the presence of medical malpractice, the rate of error in incidents occurring in 2010 and previous years was found to be statistically significantly higher than that of other years ( $P = 0.036$ ) (Table 1).

It was determined that 81.9% of the cases were referred by the Public Prosecutor. Of the case files from the judicial authorities, an opinion was requested only about physician error in 67.5%, physician error and causation in 16.3%, physician error and cause of death in 13.1%, and physician error, causation, and cause of death in 3.1%.

In the cases with a claim of medical malpractice, the complainant was usually the spouse and/or children (n=105, 69%), and no reference to the complainant was found in 8 cases. No data were obtained regarding the reason for the complaint in 18 cases, and of the 134 cases with a reason given, the most common was a claim of treatment error (n=47, 35.1%), followed by a claim of lack of care (n=44, 32.8%) (Figure 2).

When the distribution of primary healthcare institutions where the incident occurred was examined, private hospitals (n=89, 55.6%) were determined to be the institutions with the most claims of medical malpractice. No statistically significant difference was determined in the comparison of medical malpractice claims according to healthcare institution ( $P > 0.05$ ) (Table 2).

In the claims of medical malpractice included in this study, the physicians were specialists in 116 (72.5%) cases, more than one doctor was involved in 27 (16.9%) cases, 8 (5%) were professors, 7 (4.3%) were associate professors, and 2 (1.3%) were residents. In the statistical comparison made between the malpractice status and academic degree of the doctors, the malpractice rate of the specialist physicians was determined to be statistically significantly low ( $P = 0.021$ ), and when the claim was against more than one cardiology physician, the rate of malpractice was found to be statistically significantly high ( $P = 0.007$ ) (Table 2).

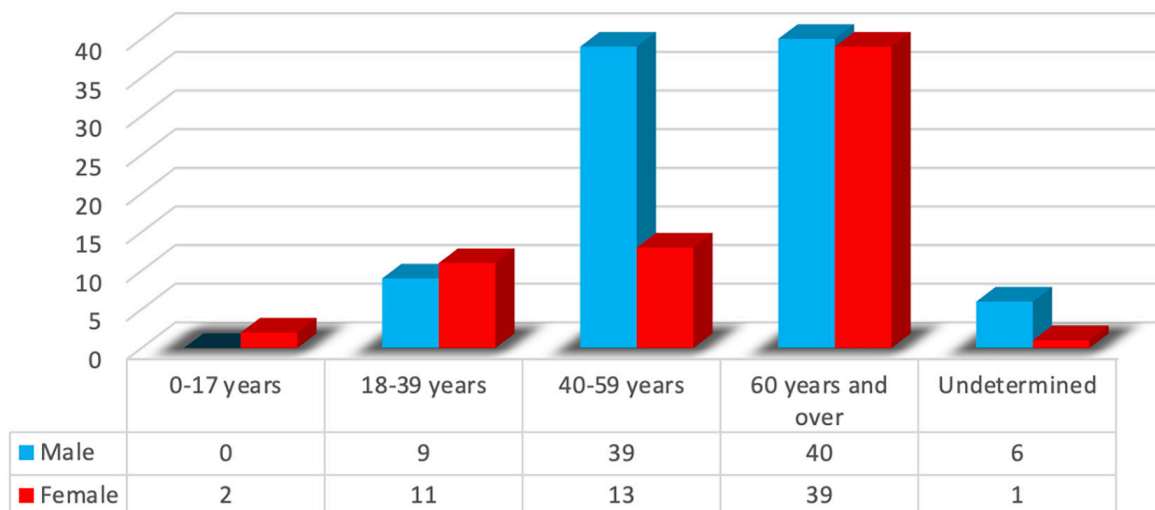


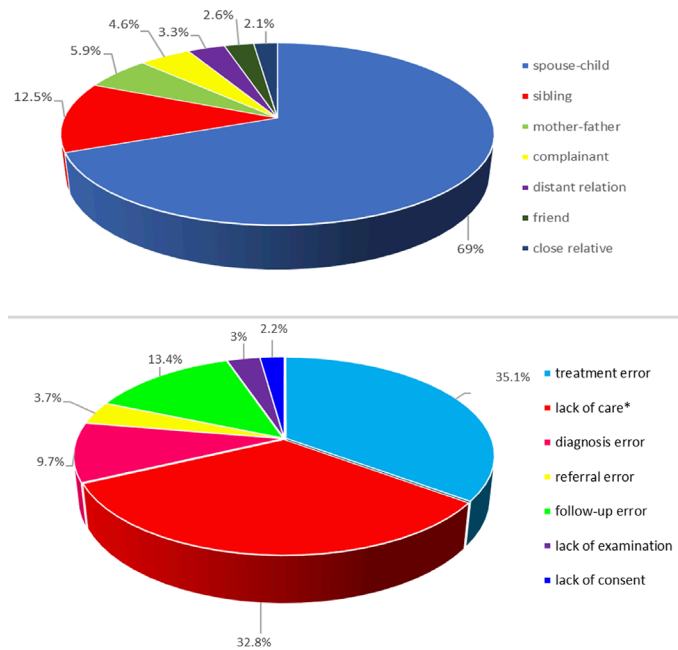
Figure 1: Distribution of the gender and age groups of the cases



**Table 1: Relationships between the date of the event and medical malpractice**

Date of the event	Medical malpractice		P-value*
	Present	Absent	
2010 and previously	5	33	0.036
2011	3	33	0.424
2012	1	44	0.447
2013	0	30	0.210
2014	0	10	1.000
<b>Total</b>	<b>9</b>	<b>150</b>	

Fisher's exact test, \*P < 0.05



**Figure 2:** Distribution of the complainants and reasons for the complaint

\*The doctor himself was not sufficiently interested, did not give sufficient information, behaved impolitely etc.

The complaints of the patients at the time of first pre-treatment at the healthcare institution were mostly chest and/or arm pain (n=86, 53.8%), followed by shortness of breath (12.5%) (Table 3). When the primary disease diagnosis was examined in cases that resulted in death for which an expert opinion was requested in respect of a medical malpractice claim, the most common diagnosis was coronary artery disease (CAD) (n=75, 76.9%), followed by heart failure (n=12, 7.5%) and cardiac arrest (n=13, 8.1%) (Table 3). When the involvement of the cardiology physicians in the treatment was examined, it was determined that 95 (59.4%) were the primary responsible physician, and 6 (40.6%) consulting physicians participated in the treatment. No statistically significant difference was observed in the medical

**Table 2: Distribution of healthcare institutions where cases were treated and followed up and the academic titles of physicians against whom a claim was made**

		Medical malpractice		P-value*
		Present	Absent	
Hospital	Private hospital	5	84	1.000 <sup>a</sup>
	State hospital	1	38	0.455 <sup>a</sup>
	University hospital	1	6	0.340 <sup>a</sup>
	Training and research hospital*	2	22	0.626 <sup>a</sup>
	<b>Total</b>	<b>9</b>	<b>150</b>	
Academic degree	Professor	1	7	0.379 <sup>a</sup>
	Associate professor	0	7	1.000 <sup>a</sup>
	Specialist	3	112	0.021 <sup>d</sup>
	Resident	0	2	-
	More than one doctor	5	22	0.007 <sup>d</sup>
<b>Total</b>	<b>9</b>	<b>150</b>		

<sup>a</sup>Fisher's Exact test, <sup>d</sup>Yates' continuity correction test, \* P > 0.05  
*'In 27 cases where the claim was made against more than one doctor, a total of 65 doctors were involved (33 specialists, 20 residents, 1 assistant associate professor, 4 associate professors, 7 professors)*

malpractice status according to the type of participation of the physician (P > 0.05).

Of the 160 cases with a claim of medical malpractice related to the cardiology department, medical treatment was only applied to 105 (65.6%) patients and medical + surgical treatment to 55 (34.4%). No statistically significant difference was observed in the medical malpractice status according to the type of treatment (P > 0.05) (Table 4).

The presence of complications was evaluated. Complications were determined to have developed during treatment in 36 (22.5%) cases, and no complications developed during medical procedures in 124. No statistically significant difference was determined in the medical malpractice status according to the complication rates (P > 0.05) (Table 4). A great range of complications was observed in the 36 cases that developed complications, with the most frequent being cardiac arrest (n=8, 22.2%), followed by ventricular fibrillation (n=4, 11.1%), infection (n=4, 11.1%), and surgery-related vascular injury (n=4, 11.1%).

In the evaluations of malpractice made by the First FMEC of the FMI, the exact cause of death could not be determined in 1 case as no autopsy was performed; therefore, it was reported in this case that there was insufficient medical evidence for proof of medical malpractice. Of the remaining 159 cases, the decision of no medical malpractice was made in 150 (94.3%) cases (Figure 3).

**Table 3: Distribution of complaints at the time of first presentation and diagnoses of cases**

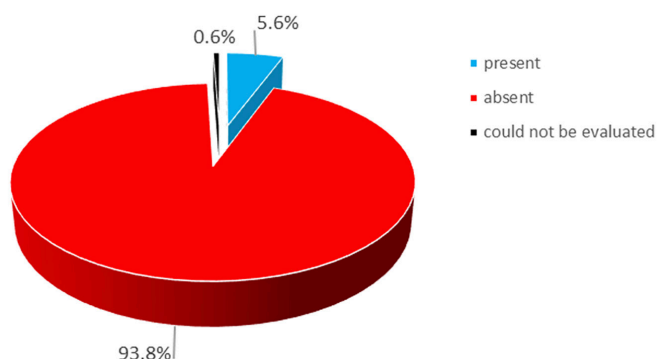
Diagnosis	n	%	Complaint	n	%
Coronary artery disease	75	46.9	Chest-arm pain	86	
Heart failure	13	8.1	Shortness of breath	20	
Cardiac arrest	12	7.5	Abdominal pain and diarrhea	8	
Aortic aneurysm dissection	8	5	Nausea, vomiting	7	
Heart valve disease	6	3.7	Headache, dizziness	6	
Diagnosis could not be performed	4	2.5	Back pain	5	
Congenital heart disease	3	1.9	Palpatations	4	
Rhythm and transmission disorders	3	1.9	Arrest	4	
Peripheral artery diseases	3	1.9	Follow-up examination	3	
Other*	33	20.6	Other	13	
Total	160	100		160	

\*Other (cardiomyopathy, endocarditis, pericarditis, myocarditis, vascular injury, hypertension, cerebrovascular disease, foreign body aspiration, primary pulmonary hypertension, etc.)

**Table 4: Evaluation of the treatments and complications according to the medical malpractice status**

		Medical malpractice		P-value*
		Absent	Present	
Treatment	Medical	100	4	0.317 <sup>a</sup>
	Surgical + Medical	50	5	
Total		150	9	
Complications	Present	34	2	1.000 <sup>b</sup>
	Absent	116	7	
Total		150	9	

<sup>a</sup>Yates' continuity correction test,  $P > 0.05$ , <sup>b</sup>Fisher's exact test, \* $P > 0.05$



**Figure 3: Distribution of the decisions made in respect of medical malpractice**

The opinions given in respect of medical malpractice were determined to be diagnosis error in 6 (66.7%) of the 9 cases, follow-up error in 2 (22.2%) and treatment error in 1 (11.1%). In the detailed examination of the reasons for errors, not making a timely diagnosis was determined to be the most frequent erroneous action (Table 5).

In the 9 cases with confirmed medical malpractice, the most common diagnosis was CAD (n=6, 66.7%). Of these cases, malpractice was determined as a diagnosis error in 3, follow-up error in 2, and treatment error in 1. In 13 (8.1%) patients with a claim of medical malpractice related to heart failure, the claim was not verified. Of 8 (5%) patients with a diagnosis of aorta aneurysm-dissection, malpractice was determined in 2 (25%). In the 9 cases with medical malpractice confirmed by the FMI First FMEC reports, the error types and diagnoses made by the healthcare institution were examined. Errors in diagnosis, treatment, and follow-up were most common in patients diagnosed with CAD (Figure 4).

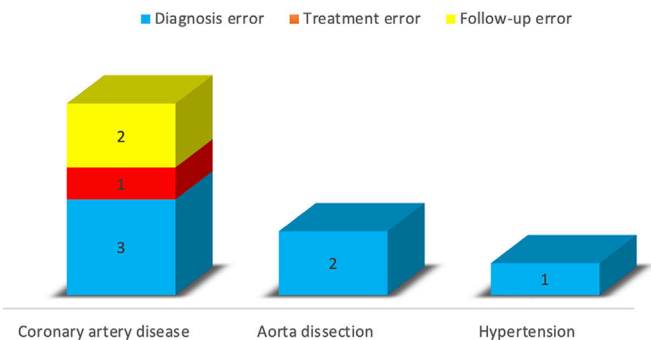
The autopsy status was evaluated for cases with a claim of medical malpractice, and it was determined that autopsy was performed in 59 (36.9%) cases and not in 101 (63.1%). Two exhumed cases were evaluated in the autopsy group. To evaluate the contribution of autopsy to the decision of the medical malpractice claim, groups were formed according to the agreement between clinical and autopsy diagnoses. Group 1: clinical diagnosis confirmed by autopsy; Group 2: clinical diagnosis changed by autopsy or there was no clinical diagnosis and diagnosis was made in the autopsy; Group 3: diagnosis could not be made by autopsy, whether or not there was a clinical diagnosis. According to these groupings, malpractice was determined in 4 (8.5%) cases in Group 1, with no statistically significant difference compared to the other groups ( $P = 1.000$ ,  $P > 0.05$ ) and in 1 (9.1%) case in Group 2 ( $P = 1.000$ ,  $P > 0.05$ ) (Table 6).

## DISCUSSION

In recent years, there has been a rapid increase in claims of medical malpractice in Turkey, similar to throughout the world. The complaints process from beginning to end can cause severe physical and psychological negative effects on both the patient

**Table 5: Distribution of error types in the cases with medical malpractice**

Medical malpractice classification		n	%
Diagnostic error	Not making timely diagnosis	4	44.5
	Not requesting the necessary tests	2	22.2
Treatment error	Starting treatment late	1	11.1
Follow-up error	No referral/referral without care	1	11.1
	Early discharge	1	11.1



**Figure 4.** Distribution of the malpractice error types according to the diagnosis made by the healthcare institution

**Table 6: Compatibility of clinical and autopsy diagnoses used to determine cause of death**

		Medical malpractice		P-value*
		Absent	Present	
Groups	Group 1	43	4	1.000
	Group 2	10	1	1.000
	Group 3	1	0	-
Total		54	5	

Yates continuity correction test, \*P > 0.05

and the physician.<sup>[3,8,9]</sup> Therefore, the examination, analysis, and evaluation of cases of malpractice is extremely important to be able to prevent and overcome these processes.

Previous studies in Turkey have reported that most cases are male. In studies worldwide related to the cardiology department, some have reported a greater frequency of male gender, while others have shown a greater frequency of female gender.<sup>[10-13]</sup> Although male patients accounted for the majority of cases in the current study, the difference between the genders was very small. This finding was attributed to the fact that heart diseases are more common in males than in females.

Previous studies on the age distribution of cases of malpractice claims have shown that cases occurred in the fifth and sixth decades of life.<sup>[14]</sup> The majority of the current study patients were in their sixth decade of life, which is consistent with the literature. Many of the cardiology medical malpractice claims

were closely consistent with the increase in middle-aged cardiology patients with heart disease in the general population demographic data.

When previous studies in Turkey were examined, it was determined that most claims of medical malpractice were in private hospitals, followed by state hospitals and tertiary-level hospitals.<sup>[15-17]</sup> Consistent with these findings in literature, the most claims of medical malpractice in the current study were found to be in private hospitals, followed by second-level state hospitals and tertiary-level healthcare institutions (training and research hospitals and university hospitals). In the years covered by this study, a direct investigation could be initiated by the Public Prosecutor’s office regarding complaints related to doctors working in private hospitals. This difference was thought to be due to the studies being conducted at the stage of files coming to the Public Prosecutor or court.

Most complaints in previous studies were seen to have been made by the patients themselves and then later by the spouse and children. The reasons for the complaints have been reported to most often be treatment errors and lack of care.<sup>[8,18,19]</sup> In the current study, when the cases resulting in death were evaluated, the complaints were made most often by the spouse and children, and the most frequent reason was a claim of treatment error. This was thought to be because when a patient’s condition continued or worsened, close relatives believed that the treatment applied was wrong.

In some studies in Turkey, it has been reported that claims of medical malpractice sent to the FMI are most often sent by the Public Prosecutor.<sup>[8,10,11]</sup> Consistent with these data in the literature, 81.9% of the cases in the current study had been sent from the Public Prosecutor. The reason for this can be attributed to advances in the legal system, and most cases do not require prosecution at this level.

In previous studies, the number of cases related to medical malpractice has been determined to increase each year.<sup>[8,11,14]</sup> In the years in which the incident occurred, which were examined in the current study, the most cases were in 2012, and there was seen to be an increase in cases up to that year. This was thought to be due to the greater availability of information, the greater quest for patient rights, and especially high amounts of financial compensation.

When the diseases are examined causing a claim of medical malpractice related to cardiology, it has been seen that the most claims of medical malpractice were in cases with CAD.<sup>[12,13,18]</sup> In the current study, the primary disease diagnoses were examined in the cases for which an expert opinion was requested in respect of a claim of medical malpractice, and consistent with the literature, the most common diagnosis was of CAD. This finding was attributed to the fact that CAD

is the most frequently occurring heart disorder. In the current study, CAD was the most common diagnosis (n=6, 66.7%). Of these cases, an error in diagnosis was determined in 3, an error in follow-up in 2, and an error in treatment in 1. The range of patient complaints in CAD and the presence of additional diseases can mask some symptoms. Therefore, these types of situations can be misleading in the diagnosis of CAD.

When the diseases causing a claim of medical malpractice related to cardiology are examined, heart failure has been seen to follow CAD and is the reason for claims of medical malpractice at a low rate.<sup>[12,13,18]</sup> In the current study, the claims of medical malpractice associated with heart failure were ranked second with 13 (8.1%) cases, and it was decided that there was no malpractice in any of these cases. This was attributed to the relatively easy diagnosis and treatment of heart failure being relatively easy and well-known compared to other diseases.

Large vascular pathologies, such as aortic aneurysm dissection, which are characterized by chest or back pain and can be difficult to diagnose or be misdiagnosed, are diagnoses which are an uncommon cause of claims of medical malpractice.<sup>[20,21]</sup> In 8 (5%) cases of the current study there was a diagnosis of aorta aneurysm dissection, and in 2 (25%) of these there was determined to have been a diagnosis error. Aortic aneurysm dissection is not observed as frequently as CAD, and diagnosis can be difficult because it can mimic several clinical conditions.

Previous studies in Turkey have reported rates of medical malpractice of 15-40% in the branches of neurology, pediatric health and diseases, anesthesia, orthopedics, plastic surgery, ophthalmology, urology, gynecology, and obstetrics and general surgery.<sup>[10,11,22-26]</sup> In a thesis related to "Malpractice in Cardiovascular Diseases", malpractice was reported at the rate of 30.3% in the branch of cardiology.<sup>[27]</sup> In the current study, the physician malpractice rate was found to be 5.6%. This showed significant differences in the rates of medical malpractice according to the specialist branch and scope of studies performed. The reason for the lower rate of malpractice in the current study compared with previous studies related to cardiology was thought to be the inclusion of only cases that resulted in death.

Treatment errors have been seen more often in general surgery, neurosurgery, and urology, and diagnostic errors in neurology, pediatric health and diseases, and gynecology and obstetrics in previous studies in Turkey.<sup>[10,11,22-24]</sup> In cardiology in Turkey, treatment/follow-up errors have been reported to be the most frequent with the most errors in treatment.<sup>[27]</sup> In cardiology medical malpractice claims linked to the decision of the American Insurance data, diagnostic error was reported to be most commonly associated with CAD.<sup>[28]</sup> The results of the current study showed that the most frequent error made

by cardiology physicians was in the diagnostic process (n=6, 66.7%). This was followed by errors in the follow-up process (n=2, 22.2%) and errors in the treatment process (n=1, 11.1%). Due to greater errors in the diagnostic process and high amounts of compensation, physicians may apply defensive-type practices to reduce the complaints of patients and their families and protect themselves from cases that are opened.<sup>[29]</sup> As no data on studies in Turkey related to defensive medical practices are available in the easily available literature, no further comment can be made on this point.

Previous studies on cardiology have shown that death is the primary reason for court cases. High mortality rates of 31-75% are striking.<sup>[12,13,18]</sup> That mortality rates are this high in medical malpractice claims in cardiology in particular increase the importance of autopsy in cardiology because autopsy is accepted as one of the most reliable methods in the prosecution of medical malpractice claims.<sup>[30-32]</sup> In cases with a claim of medical malpractice resulting in death in Turkey, the rate of autopsies performed varies between 42.6% and 74%.<sup>[10,11,22-24]</sup>

Autopsy was performed on 59 (36.9%) patients in the current study, but not on 101 (63.1%). It was thought that the low rate of autopsy in this study could be because the patient's relatives encountering an unexpected death did not immediately think about complaining about the event, that they do not have sufficient information about the procedure, that they do not want an autopsy for emotional reasons or especially because of religious beliefs, or associated with incorrect thoughts such as thinking that the physician requires permission from the family for an autopsy, and an autopsy would reveal errors of the physician.

### Study Limitations

This study has several limitations that should be considered. These features include the fact that it was a single-center study with a relatively small sample size and that the study was retrospective.

### CONCLUSION

Claims of medical malpractice are continuously increasing, and this has negative physical and psychological effects for healthcare personnel. Studies on this subject can provide guidance and help protect healthcare workers from potential negative effects. From a scan of the literature there were seen to be very few references on this subject, and therefore, it can be considered that increasing these types of studies will be able to guide clinicians.

### Ethics

**Ethics Committee Approval:** This study was conducted in accordance with the principles of the Declaration of Helsinki

and was approved by the Institute of Forensic Medicine Scientific Research Committee (approval number: 21589509/1019, date: 15.12.2015).

**Informed Consent:** Retrospective study.

## Footnotes

## Authorship Contributions

Concept: F.K., İ.Ü., Design: F.K., İ.Ü., Data Collection or Processing: F.K., E.H., Analysis or Interpretation: F.K., E.H., İ.Ü., Literature Search: İ.A., İ.Ü., Writing: İ.A., İ.Ü.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2024.18291

Int J Cardiovasc Acad 2024;10(4):123-131

# Impact of Atherosclerotic Burden on Long-term Major Adverse Cardiovascular and Cerebrovascular Events

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## Abstract

**Background and Aim:** Atherosclerotic burden is a key determinant of long-term cardiovascular outcomes. The objective of this study was to investigate the association between atherosclerotic burden and the incidence of major adverse cardiovascular and cerebrovascular events (MACCE) in patients undergoing simultaneous diagnostic angiography of multiple vascular territories.

**Materials and Methods:** This retrospective study included 153 consecutive patients who underwent concurrent angiography of the coronary, peripheral, carotid, subclavian, and renal arteries at a tertiary care hospital between January 2010 and March 2020. The patients were divided into two groups based on their atherosclerotic burden: the low group (<4 points, n=95) and the high group ( $\geq 4$  points, n=58). The primary outcome was all-cause long-term mortality over a median follow-up period of 5.97 years. The secondary endpoint was the occurrence of MACCE at long-term follow-up.

**Results:** A primary outcome event occurred in 34 of 58 patients (58.6%) in the high group and in 37 of 95 patients (38.9%) of 95 patients in the low group ( $P = 0.018$ ). MACCE occurred in 40 of 58 patients (69.0%) in the high group and in 42 of 95 patients (44.2%) in the low group ( $P = 0.003$ ). Propensity score matching demonstrated that the high group exhibited significantly higher primary outcome (59% vs. 33%,  $P = 0.007$ ) and MACCE incidence (69% vs. 39%,  $P = 0.001$ ) compared to the low group.

**Conclusion:** Among patients who underwent simultaneous diagnostic angiography of multiple vascular territories, those with a high atherosclerotic burden had a higher risk of MACCE and mortality than those with a low atherosclerotic burden over a median follow-up of 5.97 years.

**Keywords:** Atherosclerotic burden, major adverse cardiovascular and cerebrovascular events (MACCE), diagnostic angiography

## INTRODUCTION

Atherosclerosis is a significant contributor to global morbidity and mortality, exerting a considerable impact on a range of cardiovascular diseases, including coronary artery disease (CAD), stroke, and peripheral artery disease (PAD).<sup>[1,2]</sup> Despite the advent of novel medical interventions, the prevalence of atherosclerosis continues to increase, underscoring the need for a more profound understanding of its influence on long-term cardiovascular outcomes.<sup>[3,4]</sup> The severity of arterial stenosis,

often referred to as atherosclerotic burden, has emerged as a crucial determinant of outcomes.<sup>[5,6]</sup>

Recent studies have highlighted the strong correlation between elevated atherosclerotic burden and the risk of major adverse cardiovascular and cerebrovascular events (MACCE), including myocardial infarction (MI), stroke, and cardiovascular mortality.<sup>[7,8]</sup> This risk is particularly pronounced in patients with multi-vessel disease, in whom the likelihood of MACCE is significantly higher than that in those with single-vessel involvement.

**To cite this article:** Esin F, İnce HS, Kırış T, Çelik A, Karaca M. Impact of Atherosclerotic Burden on Long-term Major Adverse Cardiovascular and Cerebrovascular Events. Int J Cardiovasc Acad. 2024;10(4):123-131



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**Received:** 10.09.2024  
**Revised:** 21.11.2024  
**Accepted:** 25.11.2024  
**Published Online:** 16.12.2024



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[9] Assessment of atherosclerotic burden across different vascular territories, including the coronary, peripheral, carotid, subclavian, and renal arteries, provides a more comprehensive evaluation and may enhance the prediction of long-term outcomes.

It is of paramount importance to comprehend the implications of a high atherosclerotic burden, not only for the assessment of the risk of MACCE, but also for the effective addressing of the broader challenges it presents to healthcare systems on a global scale.<sup>[10,11]</sup> This knowledge is vital for the improvement of risk stratification techniques and the formulation of management strategies, particularly in high-risk populations identified through comprehensive diagnostic angiography.<sup>[12,13]</sup>

The current study aimed to evaluate the relationship between atherosclerotic burden and long-term MACCE among patients undergoing simultaneous diagnostic angiography of multiple vascular territories.

## METHODS

### Study Design and Population

This retrospective study was conducted at a single tertiary care hospital with the objective of assessing the impact of atherosclerotic burden on long-term MACCE. The study population consisted of 153 consecutive patients aged 18 years or older who underwent simultaneous diagnostic angiography of the coronary, peripheral, carotid, subclavian, and renal arteries between January 2010 and March 2020. Patients were excluded from the study if their medical records were incomplete, if they had a known diagnosis of congenital heart disease, or if they had significant valvular heart disease to minimize the potential confounding effects of these factors. Incomplete medical records, particularly those lacking comprehensive diagnostic data, may obscure the true extent of atherosclerotic burden, leading to potential misclassification. Similarly, congenital or valvular heart disease can independently influence the risk of MACCE, which may complicate the interpretation of the results. The study protocol was reviewed and approved by the Ethics Committee of İzmir Katip Çelebi University and the participating hospital (decision number: 0213, date: 25.04.2024). In view of the retrospective nature of the study, the requirement for informed consent was waived.

### Data Collection

A comprehensive data set comprising demographic information, clinical characteristics, and laboratory parameters extracted from the hospital's electronic health records. A two-step verification process was employed to ensure the accuracy of the data, thereby reducing the risk of data entry errors and misclassification. This process involved the initial extraction of

data, which was then subjected to independent review by a second member of the research team. Furthermore, the use of medications was recorded to account for potential confounding factors.

### Atherosclerotic Burden

The extent of atherosclerosis was quantified based on the degree of stenosis observed in angiographic assessments of the coronary, peripheral, carotid, subclavian, and renal arteries.<sup>[14]</sup> A standardized scoring system was used for each vascular territory.

- Coronary arteries: The burden of CAD was evaluated by examining the major coronary arteries, namely the left main coronary artery, left anterior descending artery, left circumflex artery, and right coronary artery. A single coronary artery with a degree of stenosis of at least 50% was awarded a score of 1, whereas stenosis of at least 50% in two or more coronary arteries was awarded a score of 2.

The assessment of peripheral arteries was conducted in a similar manner. The same scoring system was applied to the peripheral arteries (e.g., femoral and iliac arteries), whereby one point was assigned for each artery with a minimum of 50% stenosis and two points for bilateral stenosis.

- Carotid, subclavian, and renal arteries: Similarly, these territories were evaluated, and stenosis scores were assigned based on the extent of narrowing observed. A score of 1 point was assigned for a minimum of 50% stenosis in any of the aforementioned arteries, while a score of 2 points was assigned for bilateral stenosis.

The total number of points awarded across all vascular territories was calculated for each patient, resulting in their categorization into two groups: those with a low atherosclerotic burden (less than four points, n=95) and those with a high atherosclerotic burden (equal to or greater than four points, n=58).

### Angiographic Procedures

All angiographic procedures were performed by experienced interventional cardiologists in accordance with standard techniques. Coronary angiography was conducted via femoral or radial access, while peripheral, carotid, subclavian, and renal angiography was performed using selective catheterization and contrast injection. All angiographic examinations were conducted using the Siemens Artis zee floor angiography system (Siemens Healthineers, Erlangen, Germany). The latest developments in digital subtraction angiography have enhanced imaging quality while reducing radiation exposure, and these advances have been integrated into our protocols. The angiographic images were analyzed by two independent reviewers who were unaware of the patient outcomes, thereby

ensuring an objective assessment of the degree of stenosis in each vascular territory. Any discrepancies in the interpretation of images were resolved through consensus.

Angiographic severity of peripheric artery lesions was evaluated using the Trans-Atlantic Inter-Society Consensus II classification.<sup>[15]</sup> The carotid artery stenosis on carotid angiography was measured at the most stenotic segment of the internal carotid artery according to NASCET methods using electronic calipers on a picture archiving and communication system image.<sup>[16]</sup> Between the anterior-posterior and lateral views of the CAS, the more stenotic view was selected for the measurement of CAS%. CAD and renal artery disease were determined on the basis of visual assessment of stenosis severity by the operator performing the procedure.

### Outcome Measures

The primary endpoint was all-cause long-term mortality. The secondary endpoint was the occurrence of long-term MACCE at a median follow-up period. MACCE was defined as a composite of all-cause mortality, myocardial reinfarction [defined as either ST elevation myocardial infarction (STEMI) or non-STEMI target vessel revascularization, defined as any repeat revascularization in the epicardial vessel, main branch or side branches], hospitalization with heart failure, and cerebrovascular events (including the occurrence of new neurological deficits such as stroke or transient ischemic attack, confirmed through radiological imaging). The composite endpoint was evaluated based on the time to initial occurrence. Clinical follow-up information was obtained by reviewing medical records or telephone interviews. Clinical visits were conducted in person or via telephone at 3-month intervals during the initial 12-month period following MI, and at six-month intervals thereafter. In the event of loss to follow-up, data pertaining to mortality or MACCE were confirmed by consulting the National Death Records and National Social Security Institution.

### Statistical Analysis

Continuous variables were presented as the mean  $\pm$  standard deviation, and categorical variables were presented as number of patients and percentage of the total number. The Student's t-test or the Mann-Whitney U test was used to compare values between the two groups, as appropriate. The chi-square test was used to compare categorical variables. Propensity score matching was used to create a matched dataset comprising low and high groups. The following covariates were considered to achieve a balance between the groups: diabetes mellitus (DM), hypertension (HT), chronic kidney disease (CKD), beta blocker usage at discharge, mineralocorticoid receptor antagonist (MRA) usage at discharge, creatinine (Cr), and total cholesterol

at admission. Propensity score matching yielded a sample of 57 and 58 patients in the low group and 58 patients in the high group. The cumulative incidence of the primary and secondary endpoints was estimated using the Kaplan-Meier method. A two-sided *P*-value of 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA) and R software.

## RESULTS

The mean age of the low atherosclerotic burden group (95 patients) was  $63.34 \pm 8.50$  years, whereas the high atherosclerotic burden group (58 patients) had a mean age of  $64.83 \pm 7.95$  years (*P* = 0.282). Among the included patients, 85.6% were male (*P* = 0.113). The median follow-up period was 5.97 years (interquartile range: 3.77-7.82 years).

The demographic characteristics of the patients before matching are presented in Table 1. Patients with a high atherosclerotic burden were more likely to have HT (83% vs. 53%, *P* < 0.001), DM (52% vs. 35%, *P* = 0.038), and CKD (16% vs. 3%, *P* = 0.006) than those with a low atherosclerotic burden. The prevalence of CAD was significantly higher in the group with a high atherosclerotic burden (95% vs. 52%, *P* < 0.001), as was the prevalence of carotid artery stenosis (100% vs. 38%, *P* < 0.001). Furthermore, patients with a high burden exhibited a lower left ventricular ejection fraction (LV EF%) ( $54.91 \pm 9.62\%$  vs.  $57.42 \pm 6.31\%$ , *P* = 0.053) and were more frequently on beta-blocker therapy (74.1% vs. 49.5%, *P* = 0.003).

Table 2 presents the laboratory characteristics of the study population. The laboratory findings indicated that patients in the high-burden group exhibited elevated Cr levels ( $1.00 \pm 0.24$  mg/dL vs.  $0.87 \pm 0.20$  mg/dL, *P* < 0.001). Furthermore, there were statistically significant differences in the levels of total cholesterol ( $222.07 \pm 57.69$  mg/dL vs.  $185.02 \pm 43.27$  mg/dL, *P* < 0.001) and low-density lipoprotein cholesterol ( $137.22 \pm 45.73$  mg/dL vs.  $111.42 \pm 39.70$  mg/dL, *P* < 0.001) between the two groups (Table 2).

Regarding clinical outcomes, the mortality rate prior to matching was higher in this group (58.6% vs. 38.9%, *P* = 0.018, Table 1, Figure 1). The incidence of MACCE was significantly higher in the high atherosclerotic burden group before matching (69.0% vs. 44.2%, *p* = 0.003, Table 1, Figure 2). The matching process based on propensity scores yielded 57 and 58 patients in the low group and 58 patients in the high group (Tables 3, 4). The results demonstrated that the mortality and MACCE rates remained higher in the high group than in the low group (59% vs. 33%, *P* = 0.007; 69% vs. 39%, *P* = 0.001, respectively; Table 3, Figures 3, 4).



**Table 1: Baseline demographics and clinical characteristics stratified by atherosclerotic burden before matching**

Parameters	Atherosclerotic burden <4 (n=95)	Atherosclerotic burden ≥4 (n=58)	P-value
Age (years)	63.34±8.50	64.83±7.95	0.282
Gender (male) n (%)	78 (82.1%)	53 (91.4%)	0.113
Diabetes mellitus, n (%)	33 (35)	30 (52)	0.038
Hypertension, n (%)	50 (53)	47 (83)	<0.001
Stroke history n (%)	34 (36)	27 (47)	0.187
Smoking frequency (%)	53 (55.8)	34 (59.6)	0.641
COPD incidence (%)	10 (10.5)	12 (20.7)	0.082
Chronic kidney disease (%)	3 (3)	8 (16)	0.006
Peripheral arterial disease (%)	63 (66)	58 (100)	<0.001
Peripheral arterial intervention n (%)	23 (24)	14 (24)	0.872
Coronary artery disease (%)	49 (52)	55 (95)	<0.001
Coronary intervention n (%)	24 (25)	24 (42)	0.007
Renal artery stenosis (%)	5 (5)	1 (2)	0.274
Subclavian artery stenosis (%)	7 (7)	3 (5)	0.594
Carotid artery stenosis, n (%)	36 (38)	58 (100)	<0.001
Carotid artery intervention, n (%)	20 (21)	35 (61)	<0.001
LVEF (%) mean ± SD	57.42±6.31	54.91±9.62	0.053
History of MI n (%)	11 (11.6)	8 (13.8)	0.687
Antiplatelet therapy, n (%)			0.067
Acetylsalicylic acid n (%)	17 (18)	2 (3)	
Acetylsalicylic acid plus clopidogrel (%)	60 (63)	45 (78)	
Clopidogrel	11 (12)	7 (12)	
Anticoagulant levels (%)	2 (2.1)	0 (0)	0.266
ACE inhibitors, n (%)	29 (30.5)	20 (34.5)	0.611
ARBs n (%)	17 (17.9)	8 (13.8)	0.506
MRA n (%)	1 (1.1)	5 (8.6)	0.019
Beta-blockers n (%)	47 (49.5)	43 (74.1)	0.003
Statin level (%)	57 (60)	42 (74)	0.578
MACCE, n (%)	42 (44.2)	40 (69.0)	0.003
Mortality n (%)	37 (38.9)	34 (58.6)	0.018
Coronary revascularization rate (%)	3 (3.2)	9 (15.5)	0.006
Hospitalization for heart failure, n (%)	1 (1.1)	5 (8.6)	0.019
Follow-up stroke or TIA, n (%)	3 (3.2)	1 (1.7)	0.590
Recurrent MI n (%)	5 (5.3)	4 (6.9)	0.677

COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, ACE inhibitors: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, MRA: Mineralocorticoid receptor antagonists, MACCE: Major adverse cardiac and cerebrovascular events, TIA: Transient ischemic attack

## DISCUSSION

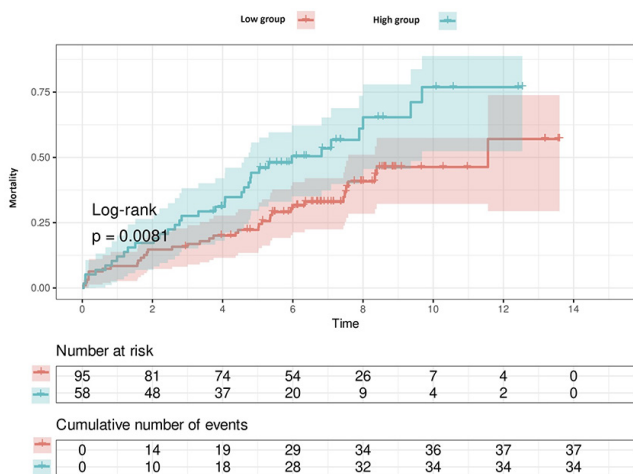
The results of this retrospective analysis showed a significant correlation between an elevated atherosclerotic burden and an increased risk of long-term MACCE and all-cause mortality in patients undergoing simultaneous diagnostic angiography of multiple vascular territories over a median follow-up of 5.97 years.

The role of atherosclerotic burden as a predictor of adverse cardiovascular outcomes is well established, and its involvement in the development of ischemic heart disease, stroke, and PAD has been extensively documented in the literature.<sup>[17,18]</sup> Angiographic studies have revealed that patients with 50% or greater stenosis have a much higher event rate than those with non-obstructive disease. In our study, CAD was more common in patients with a higher atherosclerotic burden.<sup>[19,20]</sup>

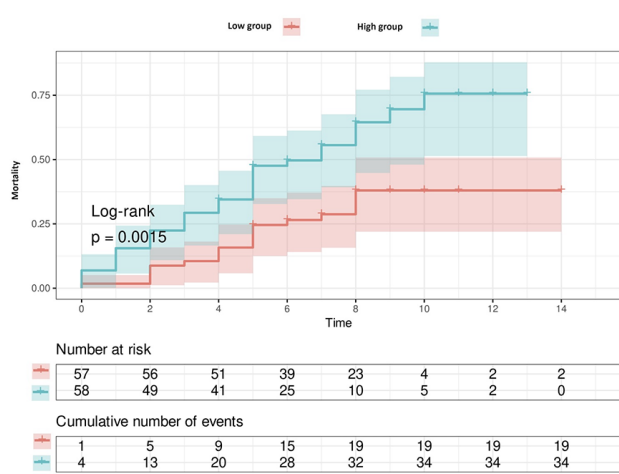
**Table 2: Comprehensive laboratory and clinical parameters stratified by atherosclerotic burden before matching**

Parameter	Atherosclerotic burden <4 (n=95)	Atherosclerotic burden ≥ 4 (n=58)	P-value
WBC (x10 <sup>3</sup> /μL) mean ± SD	8.57±2.12	8.62±2.17	0.893
HB (g/dL) mean ± SD	13.37±1.90	12.98±2.24	0.260
PLT (x10 <sup>3</sup> /μL) mean ± SD	254.65±84.40	265.07±76.89	0.445
CR (mg/dL) mean ± SD	0.87±0.20	1.00±0.24	<0.001
Total cholesterol level (mg/dL) mean ± SD	185.02±43.27	222.07±57.69	<0.001
HDL (mg/dL) mean ± SD	40.64±13.20	40.92±14.95	0.906
LDL (mg/dL) mean ± SD	111.42±39.70	137.22±45.73	<0.001
TRI (mg/dL) mean ± SD	172.85±126.07	188.55±92.03	0.412

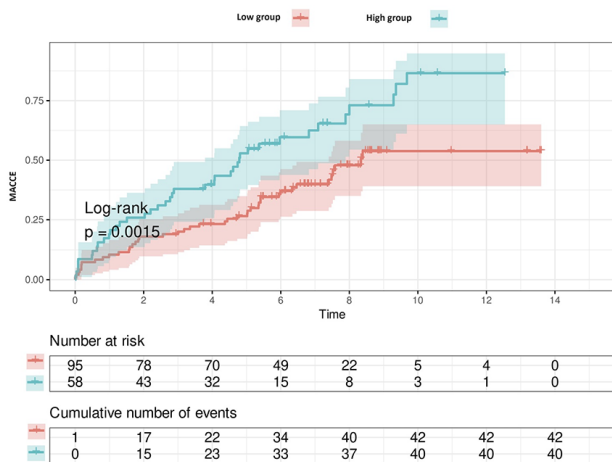
WBC: White blood cells, HB: Hemoglobin, PLT: Platelet count, Cr: Creatinine, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TRI: Triglycerides



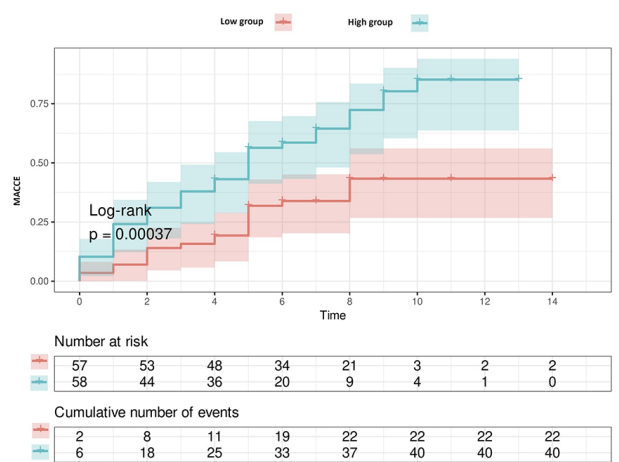
**Figure 1:** Mortality in all groups before matching



**Figure 3:** Mortality in all patients after matching



**Figure 2:** MACCE before matching  
 MACCE: Major adverse cardiovascular and cerebrovascular events



**Figure 4:** MACCE in all patients after matching  
 MACCE: Major adverse cardiovascular and cerebrovascular events

**Table 3. Baseline demographics, clinical characteristics atherosclerotic burden after matching**

Parameters	Atherosclerotic burden <4 (n=57)	Atherosclerotic burden ≥4 (n=58)	P-value
Age (years)	62.7±7.3	64.8±7.8	0.144
Gender (male) n (%)	52 (91)	53 (91)	0.977
Diabetes mellitus, n (%)	19 (33)	30 (52)	0.046
Hypertension, n (%)	27 (47)	48 (83)	<0.001
Stroke history n (%)	21 (37)	27 (47)	0.291
Smoking frequency (%)	35 (62)	34 (60)	0.7611
COPD incidence (%)	7(12)	12 (20.7%)	0.225
Chronic kidney disease (%)	1 (2)	8 (16)	0.009
Peripheral arterial disease (%)	37 (65)	58 (100)	<0.001
Peripheral arterial intervention n (%)	12 (21)	14 (24)	0.882
Coronary artery disease (%)	33 (58)	55 (95)	<0.001
Coronary intervention n (%)	17 (30)	24 (42)	0.192
Renal artery stenosis (%)	2 (4)	1 (2)	0.548
Subclavian artery stenosis (%)	4 (7)	3 (5)	0.679
Carotid artery stenosis, n (%)	19 (33)	58 (100)	<0.001
Carotid artery intervention, n (%)	11 (19)	35 (61)	<0.001
LVEF (%) Mean ± SD	57.5 ± 5.3	54.9 ± 9.6	0.072
History of MI n (%)	6 (11)	8 (14)	0.592
Antiplatelet therapy, n (%)			0.077
Acetylsalicylic acid n (%)	10 (18)	2 (3)	
Acetylsalicylic acid plus clopidogrel (%)	37 (65)	45 (78)	
Clopidogrel level (%)	8 (14)	7 (12)	
Anticoagulant levels (%)	0 (0)	0 (0)	-
ACE inhibitors, n (%)	19 (33)	20 (35)	0.896
ARBs n (%)	2 (14)	8 (14)	0.970
MRA n (%)	0 (0)	5 (9)	0.023
Beta-blockers n (%)	32 (56)	43 (74)	0.003
Statin level (%)	40 (71)	42 (74)	0.886
MACCE, n (%)	22 (39)	40 (69)	0.001
Mortality n (%)	19 (33)	34 (59)	0.007
Coronary revascularization rate (%)	3 (5)	9 (16)	0.072
Hospitalization for heart failure, n (%)	1 (2)	5 (9)	0.098
Follow-up stroke or TIA, n (%)	0 (0)	1 (2)	0.319
Recurrent MI n (%)	3 (5)	4 (7)	0.714

COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, ACE inhibitors: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, MRA: Mineralocorticoid receptor antagonists, MACCE: Major adverse cardiac and cerebrovascular events, TIA: Transient ischemic attack

The underlying pathophysiological mechanisms driving these associations include chronic inflammation, endothelial dysfunction, and plaque instability, all of which contribute to the progression of atherosclerosis and the subsequent occurrence of cardiovascular events.<sup>[20,21]</sup> It is of great importance to assess the extent of atherosclerotic burden across multiple vascular territories, as significant atherosclerosis in one region is typically indicative of widespread disease, thereby amplifying the

overall risk of cardiovascular complications.<sup>[21,22]</sup> These findings highlight the importance of comprehensive cardiovascular risk assessment in clinical practice, particularly for patients with multi-territory vascular involvement.

The Reduction of Atherothrombosis for Continued Health (REACH) Registry, an international registry, found that 15% of stable outpatients with atherothrombosis or multiple risk factors for atherothrombosis exhibited polyvalvular disease.<sup>[23]</sup>

**Table 4: comprehensive laboratory and clinical parameters stratified by atherosclerotic burden after matching**

Parameter	Atherosclerotic burden <4 (n=57)	Atherosclerotic burden ≥4 (n=58)	P-value
WBC (x10 <sup>3</sup> /μL) Mean ± SD	8.5±2.0	8.6±2.2	0.654
HB (g/dL) Mean ± SD	13.6±1.7	13.0±2.2	0.091
PLT (x10 <sup>3</sup> /μL) Mean ± SD	256.4±83.1	265.1±76.9	0.560
CR (mg/dL) Mean ± SD	0.90±0.2	1.00±0.24	<0.001
Total cholesterol level (mg/dL) Mean ± SD	187.6±46.4	222.1±57.7	<0.001
HDL (mg/dL) Mean ± SD	40.4±12.9	40.9±15.0	0.828
LDL (mg/dL) Mean ± SD	112.6±42.4	137.2±45.7	0.003
TRI (mg/dL) Mean ± SD	185.3±148.8	188.6±92.0	0.889

WBC: White blood cells, HB: Hemoglobin, PLT: Platelet count, Cr: Creatinine, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TRI: Triglycerides

The REACH registry indicated that the presence of polyvalvular disease was associated with a 99% increased risk of MACE at the 4-year follow-up in these patients.<sup>[23]</sup> The prospective, randomized trials, including Liraglutide Effect and Action in Diabetes: The Evaluation of Cardiovascular Results and Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53, demonstrated an elevated risk of major adverse cardiovascular events in patients with DM and polyvalvular disease.<sup>[24-27]</sup> As in the aforementioned studies, patients with a high atherosclerotic burden in our study were associated with an increased incidence of poor cardiovascular outcomes in patients undergoing simultaneous diagnostic angiography of multiple vascular territories. In contrast to other studies, our study included patients who underwent simultaneous angiography for coronary, carotid, and peripheral arteries.

Patients with a higher atherosclerotic burden were more likely to have cardiovascular risk factors, such as tobacco use, HT, dyslipidemia, and diabetes. These risk factors are strongly associated with a higher atherosclerotic burden, suggesting a common underlying pathophysiology. Additionally, the prevalence of CKD was higher in these patients in the present study. CKD accelerates the progression of atherosclerosis through several mechanisms, including chronic inflammation and oxidative stress. Additionally, dysregulated mineral metabolism plays a role in this process, leading to vascular calcification and increased arterial stiffness. These processes can exacerbate vascular damage and enhance plaque vulnerability.<sup>[28]</sup> It remains unclear whether the elevated mortality rates are attributable to the presence of multiple comorbidities or the underlying atherosclerotic burden.

The present study revealed a significant association between atherosclerotic burden and the presence of PAD, CAD, and carotid artery stenosis. Each of these conditions was significantly correlated with an increased risk of MACCE. This finding is consistent with the observations of Curcio et al.,<sup>[29]</sup> who emphasized that PAD is not only a marker of systemic

atherosclerosis but also a significant predictor of cardiovascular events such as MI and stroke, due to its involvement in both coronary and cerebral arteries. Similarly, it has been demonstrated that CAD and PAD are pivotal factors in elevated cardiovascular risks and adverse outcomes in patients with significant atherosclerotic burden.<sup>[30]</sup>

The present study identified significant associations between atherosclerotic burden and the use of specific medications, including beta-blockers and MRAs. Patients with a higher atherosclerotic burden were more frequently prescribed beta-blockers and MRAs, in accordance with current guidelines that recommend these therapies for high-risk cardiovascular patients. While beta-blockers are commonly prescribed for CAD, their benefits may be particularly pronounced in subgroups such as those with recent MI, as reported by Godoy et al.<sup>[31]</sup> Furthermore, Andersson et al.<sup>[32]</sup> demonstrated that beta-blockers remain effective in reducing cardiovascular events across patients with significant atherosclerotic burden, thereby reinforcing their importance in this population. MRAs have also been demonstrated to markedly diminish adverse cardiovascular outcomes, particularly in patients with heart failure and extensive atherosclerosis.<sup>[31,33]</sup> Moreover, the importance of lipid management in reducing MACCE, particularly among high-risk populations with substantial atherosclerotic burden, has been well established in recent guidelines. Both Mach et al.<sup>[34]</sup> and Lloyd-Jones et al.<sup>[35]</sup> emphasize the pivotal role of intensive lipid-lowering therapies in preventing cardiovascular events, particularly in patients with extensive atherosclerosis across multiple vascular territories.

### Study Limitations

It should be noted that the present study is not without limitations. First, as a retrospective study, there is the possibility of selection bias. Second, the relatively small number of patients may have reduced the statistical power of the analyses. Third, the study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the

findings. Lastly, there are no data on inflammatory markers known to be associated with atherosclerotic burden and adverse cardiac events. It is recommended that future research address these issues to gain a more comprehensive understanding of the association between atherosclerotic burden and long-term cardiovascular outcomes in these patients.

## CONCLUSION

In conclusion, the prognosis of patients with a higher atherosclerotic burden was significantly worse than that of patients with a lower atherosclerotic burden. It is important to improve the detection and treatment of these patients. It is incumbent upon clinicians to maximize the use of preventive therapies endorsed by societal guidelines in such patients.

## Ethics

**Ethics Committee Approval:** The study protocol was reviewed and approved by the Ethics Committee of İzmir Katip Çelebi University and the participating hospital (decision number: 0213, date: 25.04.2024).

**Informed Consent:** Retrospective study.

## Footnotes

### Authorship Contributions

Concept: F.E., H.S.İ., T.K., A.Ç., M.K., Design: F.E., H.S.İ., T.K., A.Ç., M.K., Data Collection or Processing: F.E., H.S.İ., T.K., A.Ç., Analysis or Interpretation: T.K., M.K., Literature Search: F.E., A.Ç., Writing: F.E., H.S.İ., T.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2024.51523

Int J Cardiovasc Acad 2024;10(4):132-138

# Association between Vitamin D Deficiency and Angiographic Severity in Patients with Coronary Artery Disease

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## Abstract

**Background and Aim:** This study explored the correlation between vitamin D status and the severity of coronary artery disease (CAD), as well as left ventricular function in patients with acute coronary syndrome (ACS).

**Materials and Methods:** This prospective observational study included 102 patients diagnosed with ACS admitted to an Indian tertiary care facility from January 2021 to December 2021. Upon admission, the researchers collected baseline data of the patients and measured serum vitamin D levels. CAD severity was evaluated using Gensini and SYNTAX scores, and left ventricular ejection fraction (LVEF) was measured using echocardiography.

**Results:** The study cohort had a median age of 56.5 years, with males comprising 62.7% of the total patient population. Anterior wall myocardial infarction was the most common presentation (59.8%), and 32.4% of patients had double vessel disease (DVD). The median vitamin D level was 18.3 ng/mL (interquartile range 12.7-26.8). Patients with vitamin D deficiency ( $\leq 20$  ng/mL) exhibited significantly higher Gensini (46.5-94) and SYNTAX (7.5-38) scores than those with optimal levels ( $> 30$  ng/mL) ( $P < 0.001$ ). A notable inverse correlation was found between vitamin D levels and both Gensini ( $r = -0.572$ ,  $P < 0.001$ ) and SYNTAX ( $r = -0.787$ ,  $P < 0.001$ ) scores. Reduced vitamin D levels were linked to decreased LVEF ( $P = 0.018$ ) and a higher incidence of multivessel disease, particularly DVD ( $P = 0.009$ ).

**Conclusion:** This study revealed a significant negative correlation between low vitamin D status, CAD severity, and left ventricular dysfunction in patients with ACS. These results suggest that low vitamin D status indicates vitamin D deficiency and plays a crucial role in the occurrence and progression of coronary atherosclerosis.

**Keywords:** Acute coronary syndrome, coronary artery disease, coronary angiography, ventricular dysfunction, left, vitamin D

## INTRODUCTION

Acute coronary syndrome (ACS) accounts for a large proportion of morbidity and mortality worldwide. Among them, atherosclerosis is a significant cause of myocardial infarction leading to majority cases of mortality.<sup>[1,2]</sup> Hypertension, dyslipidemia, smoking, diabetes, and a history of cardiovascular disease are some well-established risk factors of ACS.<sup>[3]</sup>

Researchers have discovered new inflammatory markers like vitamin D, which is a fat-soluble vitamin playing a vital role in numerous physiological processes apart from its importance calcium homeostasis.<sup>[4]</sup> Several mechanisms that contribute to progression of cardiovascular diseases include its anti-inflammatory, anti-thrombotic, and anti-hypertensive properties, as well as its ability to modulate endothelial function and vascular calcification.<sup>[5]</sup>

**To cite this article:** Sahani KK, Gupta H. Association between Vitamin D Deficiency and Angiographic Severity in Patients with Coronary Artery Disease. Int J Cardiovasc Acad. 2024;10(4):132-138



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**Received:** 05.09.2024

**Revised:** 03.12.2024

**Accepted:** 04.12.2024

**Published Online:** 16.12.2024



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Hence, early identification and appropriate management of vitamin D deficiency in ACS patients may have the potential to improve clinical outcomes and prevent complications. However, the results have been inconsistent, with some studies failing to establish a significant relationship between vitamin D levels and clinical outcomes in patients with ACS. This study aimed to investigate the association between vitamin D levels and the extent of coronary artery disease (CAD) and left ventricular dysfunction in patients with ACS.

## METHODS

### Study Design and Population

This prospective observational study was performed at a tertiary care center in India between January 2021 and December 2021. All patients admitted to intensive cardiac care unit with a diagnosis of ACS, including unstable angina, ST segment elevation myocardial infarction, and non-ST segment elevation myocardial infarction, were included in the study. Patients with chronic kidney disease, known parathyroid hormone disorders, or who were taking calcium or vitamin D supplements were excluded from the study. After obtaining written informed consent, 102 eligible patients were enrolled in the study. The study adhered to the principles of the

Declaration of Helsinki and was approved by the Institutional Ethics Committee M.K.C.G. Medical Collage (number: 1005, date: 18.12.2020).

### Data Collection

For each patient, baseline clinical data, including age, sex, weight, blood pressure, and risk factors. ACS diagnosis was confirmed using clinical history, electrocardiogram findings, and elevated cardiac enzyme levels. We calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration and measured the left ventricular ejection fraction (LVEF) via echocardiography during the initial hospitalization.

### Laboratory and Angiographic Assessments

Upon admission, venous blood samples were collected to measure serum vitamin D levels. All patients underwent coronary angiography during their hospital stay. CAD assessment was performed with the help of two methods: Gensini score (GS) and SYNTAX score. The GS was calculated using a standardized algorithm that considered the degree of luminal narrowing and the significance of the affected coronary artery segments. Figure 1 outlines the step-by-step calculation process.<sup>[6]</sup> The SYNTAX scoring system is a detailed

STEP 1 Calculation of the severity score for each lesion ≥ 25% and adjustment for total occlusions or 99% obstructive lesions receiving collaterals			
Degree of stenosis (%)	Receiving collaterals	Adjustment for collaterals	Severity Score
1-25	-	0	1
26-50	-	0	2
51-75	-	0	4
76-90	-	0	8
91-99	no	0	16
99	yes	-8	8
100	no	0	32
100	yes, and normal source vessel	-16	32-16=16
100	yes, and 25% stenosis source vessel	-12	32-12=20
100	yes, and 50% stenosis source vessel	-8	32-8=24
100	yes, and 75% stenosis source vessel	-4	32-4=28
100	yes, and 90% stenosis source vessel	-2	32-2=30
100	yes, and 99% stenosis source vessel	-1	32-1=31
STEP 2 A multiplying factor is applied to each lesion score based upon its location in the coronary tree			
Segment	Right Dominance	Left Dominance	
RCA proximal	1	1	
RCA mid	1	1	
RCA distal	1	1	
PDA	1	1	
PLB	0.5	0.5	
Left Main	5	5	
LAD proximal	2.5	2.5	
LAD mid	1.5	1.5	
LAD apical	1	1	
1 <sup>st</sup> Diagonal	1	1	
2 <sup>nd</sup> Diagonal	0.5	0.5	
LCx proximal	2.5	3.5	
LCx mid	1	2	
LCx distal	1	2	
Obtuse Marginal	1	1	
STEP 3 Sum of all the lesion severity scores			

**Figure 1:** Procedure for calculating the Gensini score; (A) step 1: Lesion severity assessment- for lesion ≥25% and total occlusions or 99% obstructive lesions receiving collaterals. (B) step 2: Apply a multiplication factor to each lesion score, the factor varies based on the lesions position in coronary system (C) step 3: Total of all the lesion severity scores



method for evaluating CAD. This numerical assessment reflects both the intricacy and extent of lesions in the coronary arteries. This score was determined using a computer program with sequential, interactive questions, as shown in Figure 2, which illustrates the algorithm's 12 main components.<sup>[7]</sup>

**Definition**

Vitamin D status is typically calculated by assessing serum 25(OH)D levels, with concentrations below 30 nmol/L generally considered deficient, 30-50 nmol/L insufficient, and above 50 nmol/L adequate, according to guidelines set by major health organizations such as The European Food Safety Authority, Endocrine Society, Institute of Medicine, and the Scientific Advisory Committee on Nutrition.<sup>[8]</sup>

**Statistical Analysis**

IBM® SPSS® Statistics software was used for data analysis. Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as frequencies and percentages. The Kolmogorov-Smirnov test was used to examine the relationships between vitamin D levels and various clinical characteristics, angiographic findings (Gensini and SYNTAX scores), and left ventricular dysfunction. We considered *P*-value <0.05 as statistically significant.

**RESULTS**

Our study involved 102 patients comprising 62.7% of male. Table 1 presents an overview of the initial demographic and clinical data of the study participants. Common risk factors

were diabetes (53.9%), hypertension (40.2%), dyslipidemia (32.4%), smoking (31.4%), arrhythmia (16.6%), and thrombosis (15.7%). The median vitamin D concentration was 18.3 ng/mL (IQR 12.7-26.8). Kidney function, as measured by the eGFR, had a median of 90 mL/min/1.72 m<sup>2</sup> (IQR 80.8-99.3). The median ejection fraction was 48% (IQR 42-50.5). The Gensini and SYNTAX scores, which were used to assess CAD, had median values of 64 (IQR 42-82) and 20 (IQR 9.8-24.1) respectively.

Vitamin D status varied among participants; 35.4% were deficient (11-20 ng/mL), 33.3 % had suboptimal levels (21-30 ng/mL), 18.6 % were severely deficient (≤10 ng/mL), and only 12.7% maintained optimal levels (>30 ng/mL).

The correlation between patient vitamin D concentrations and various demographic and clinical factors are presented in Table 2. Vitamin D concentrations were correlated with the extent of CAD. Patients with single vessel disease had significantly higher vitamin D levels (*P* = 0.047), whereas those with double vessel disease (DVD) had lower vitamin D levels (*P* = 0.009). Although not statistically significant, there was a trend toward decreased vitamin D intake in patients with TVD (*P* = 0.188) and left main coronary artery involvement (*P* = 0.660).

A significant association emerged between vitamin D and LVEF. An LVEF of 54% (IQR 48-60 %) was observed in patients with vitamin D levels >30 ng/mL which was considerably higher than those with levels ≤20 ng/mL (median 46-48%, *P* = 0.018).

Table 3 illustrates that patients with the lowest vitamin D levels (≤10 ng/mL) had a substantially higher median GS of 88 (IQR

	Segment No	Right dominance	Left dominance	
<b>1. Dominance</b>	1 RCA proximal	1	0	<b>Diameter reduction*</b>
<b>2. Number of lesions</b>	2 RCA mid	1	0	- Total occlusion
<b>3. Segments involved per lesion</b>	3 RCA distal	1	0	- Significant lesion (50-99%)
<i>Lesion Characteristics</i>	4 Posterior descending artery	1	n.a.	<b>Total occlusion (TO)</b>
<b>4. Total occlusion</b>	16 Posterolateral branch from RCA	0.5	n.a.	- Age >3months or unknown
i. Number of segments involved	16a Posterolateral branch from RCA	0.5	n.a.	- Blunt stump
ii. Age of the total occlusion (>3 months)	16b Posterolateral branch from RCA	0.5	n.a.	- Bridging
iii. Blunt Stump	16c Posterolateral branch from RCA	0.5	n.a.	- First segment visible beyond TO
iv. Bridging collaterals	5 Left Main	5	6	- Side branch (SB) - Yes, SB <1.5mm**
v. First segment beyond the occlusion visible by antegrade or retrograde filling	6 LAD proximal	3.5	3.5	- Yes, both SB < & ≥ 1.5mm
vi. Side branch involvement	7 LAD mid	2.5	2.5	<b>Trifurcations</b>
<b>5. Trifurcation</b>	8 LAD apical	1	1	- 1 diseased segment
i. Number of segments diseased	9 First diagonal	1	1	- 2 diseased segments
<b>6. Bifurcation</b>	9a First diagonal <sup>a</sup>	1	1	- 3 diseased segments
i. Type	10 Second diagonal	0.5	0.5	- 4 diseased segments
ii. Angulation between the distal main vessel and the side branch <70°	10a Second diagonal <sup>a</sup>	0.5	0.5	<b>Bifurcations</b>
<b>7. Aorto-ostial lesion</b>	11 Proximal circumflex artery	1.5	2.5	- Type A, B, C
<b>8. Severe tortuosity</b>	12 Intermediate/ anterolateral artery	1	1	- Type D, E, F, G
<b>9. Length &gt;20mm</b>	12a Obtuse marginal <sup>a</sup>	1	1	- Angulation <70°
<b>10. Heavy calcification</b>	12b Obtuse marginal <sup>b</sup>	1	1	<b>Aorto ostial stenosis</b>
<b>11. Thrombus</b>	13 Distal circumflex artery	0.5	1.5	<b>Severe tortuosity</b>
<b>12. Diffuse disease/small vessels</b>	14 Left posterolateral	0.5	1	<b>Length &gt; 20mm</b>
	14a Left posterolateral <sup>a</sup>	0.5	1	<b>Heavy calcification</b>
	14b Left posterolateral <sup>b</sup>	0.5	1	<b>Thrombus</b>
	15 Posterior descending	n.a.	1	<b>Diffuse disease*/small vessels</b>

**Figure 2:** (A) SYNTAX score algorithm and (B) Scoring system of the SYNTAX score characteristics points

68-92) compared with those with >30 ng/mL, who had a score of just 16 (IQR 6-32) ( $P < 0.001$ ). A similar trend was observed for SYNTAX scores, ranging from a median of 36 (IQR 30-38) in the lowest vitamin D level to those in the highest 5 (IQR 3-11) ( $P < 0.001$ ).

Table 1: Baseline clinical characteristics	
Characteristics	n=102 patients
Male, n (%)	64 (62.7)
<b>Risk factors</b>	
Diabetes, n (%)	55 (53.9)
Hypertension, n (%)	41 (40.2)
Dyslipidaemia, n (%)	33 (32.4)
Smoking, n (%)	32 (31.4)
Arrhythmia, n (%)	17 (16.6)
Thrombosis, n (%)	16 (15.7)
<b>Type of MI</b>	
AWMI, n (%)	61 (59.8)
IWMI, n (%)	17 (16.7)
IWMI + PWMI, n (%)	10 (9.8)
IWMI+ RVMI, n (%)	8 (7.8)
IWMI + PWMI + RVMI, n (%)	6 (5.9)
<b>KILLIP classification</b>	
Class I, n (%)	67 (65.7)
Class II, n (%)	25 (24.5)
Class III, n (%)	0 (0)
Class IV, n (%)	10 (9.8)
<b>NYHA classification</b>	
Class 1, n (%)	65 (63.7)
Class 2, n (%)	26 (25.5)
Class 3, n (%)	11 (10.8)
<b>Coronary artery involvement</b>	
Normal coronary, n (%)	9 (8.8)
SVD, n (%)	32 (31.4)
DVD, n (%)	33 (32.4)
TVD, n (%)	27 (26.5)
LMCA, n (%)	4 (3.9)
Vitamin D, ng/mL [(median (IQR))]	18.3 (12.7-26.8)
eGFR, mL/min/1.73 m <sup>2</sup> [median (IQR)]	90 (80.8-99.3)
LVEF, % [median (IQR)]	48 (42-50.5)
Gensini scores [median (IQR)]	64 (42-82)
Syntax scores [median (IQR)]	20 (9.8-24.1)
Data are expressed as n (%) and median (IQR).	
AWMI: Anterior wall myocardial infarction, DVD: Double vessel disease, eGFR: Estimated glomerular filtration rate, IWMI: Inferior wall myocardial infarction, LMCA: Left main coronary artery, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, NYHA: New York Heart Association, PWMI: Posterior wall myocardial infarction, RVMI: Right ventricular myocardial infarction, SVD: Single vessel disease, TVD: Triple vessel disease	

As shown in Table 4, there was a significant negative correlation between vitamin D levels and both Gensini ( $r=-0.572$ ,  $P < 0.001$ ), and SYNTAX scores ( $r=-0.787$ ,  $P < 0.001$ ), indicating that lower vitamin D levels were associated with more severe CAD.

## DISCUSSION

Vitamin D deficiency is a pervasive health concern affecting diverse demographic groups. While its role was primarily known for calcium regulation, recent research has highlighted the potential significance of vitamin D in CAD. There are studies that suggest links between vitamin D levels and acute myocardial infarction risk and outcomes associated with high rates of illness and death, emphasizing the importance of vitamin D supplementation beyond bone metabolism.<sup>[9]</sup> Our findings support this connection, demonstrating that low vitamin D status is associated with a higher probability of CAD, its angiographic severity, and a greater incidence of vitamin D insufficiency and deficiency among patients, which is consistent with previous studies. In a prior study, 83% of the patients had vitamin D level <30 ng/mL<sup>[10]</sup>. This finding was observed to be similar in our study, in which 87.3% of the patients had vitamin D levels <30 ng/mL. However, Syal et al.<sup>[11]</sup> in their study revealed that a substantial majority of patients (93%) had vitamin D concentrations below 30 ng/mL, which is considered insufficient, and only a small fraction (7%) of patients demonstrated adequate vitamin D levels. Notably, only 12.7% of patients in our study had sufficient vitamin D levels (> 30 ng/mL). Rahman et al.<sup>[12]</sup> observed that most of the male patients exhibited vitamin D concentrations below 30 ng/mL, which demonstrates gender differences in vitamin D levels. However, this finding is in contrast with other research that suggests women typically have lower vitamin D levels. The potential causes postulated were variations in adipose tissue composition, insufficient nutritional composition, reproductive events, and onset of menopause.<sup>[13,14]</sup> In our study, no difference in vitamin D levels was noted among both genders ( $P = 0.425$ ). The present study revealed a significant relationship between decreased vitamin D levels and reduced LVEF, which is a marker of left ventricular dysfunction. These results align with earlier research that has established a correlation between vitamin D insufficiency and a heightened susceptibility to heart failure as well as adverse cardiac remodeling.<sup>[15,16]</sup>

The correlation between vitamin D insufficiency and increased susceptibility to cardiovascular complications have been elucidated. Multiple extensive observational studies, both cross-sectional and longitudinal, have shown a relationship with diminished vitamin D levels and a higher incidence of cardiovascular events.<sup>[10,17]</sup> Furthermore, insufficient vitamin D levels have been identified as a significant biological indicator for elevated rates of various cardiovascular disease risk factors, including hypertension, obesity, diabetes, and

**Table 2: Classification of vitamin D levels according to clinical characteristics**

Variables	Vitamin D level (ng/mL)					P-value
		≤10 (n=19)	11 to 20 (n=36)	21 to 30 (n=34)	>30 (n=13)	
Age, n (%)	<40 years	3 (27.3)	3 (27.3)	2 (18.2)	3 (27.3)	0.266
	40 to 60 years	12 (21.8)	22 (40.0)	16 (29.1)	5 (9.1)	
	>60 years	4 (11.1)	11 (30.6)	16 (44.4)	5 (13.9)	
BMI, median (IQR)	kg/m <sup>2</sup>	28.3 (25.7-31.2)	27.7 (26.3-30.1)	28.8 (27-30.8)	28 (26.6-32.2)	0.519
Gender, n (%)	Male	12 (18.8)	26 (40.6)	18 (28.1)	8 (12.5)	0.425
	Female	7 (18.4)	10 (26.3)	16 (42.1)	5 (13.2)	
Diabetes, n (%)	Yes	8 (14.5)	22 (40.0)	19 (34.5)	6 (10.9)	0.535
	No	11 (23.4)	14 (29.8)	15 (31.9)	7 (14.9)	
Hypertension, n (%)	Yes	5 (12.2)	17 (41.5)	14 (34.1)	5 (12.2)	0.514
	No	14 (23.0)	19 (31.1)	20 (32.8)	8 (13.1)	
Dyslipidaemia, n (%)	Yes	6 (18.2)	13 (39.4)	11 (33.3)	3 (9.1)	0.892
	No	13 (18.8)	23 (33.3)	23 (33.3)	10 (14.5)	
Smoking, n (%)	Yes	6 (18.8)	13 (40.6)	8 (25.0)	5 (15.6)	0.648
	No	13 (18.6)	23 (32.9)	26 (37.1)	8 (11.4)	
Thrombosis, n (%)	Yes	1 (6.3)	5 (31.3)	7 (43.8)	3 (18.8)	0.42
	No	18 (20.9)	31 (36.0)	27 (31.4)	10 (11.6)	
KILLIP class, n (%)	I	15 (22.4)	24 (35.8)	20 (29.9)	8 (11.9)	0.88
	II	3 (12.0)	8 (32.0)	10 (40.0)	4 (16.0)	
	III	0 (0)	0 (0)	0 (0)	0 (0)	
	IV	1 (10.0)	4 (40.0)	4 (40.0)	1 (10.0)	
NYHA class, n (%)	1	10 (15.4)	23 (35.4)	22 (33.8)	10 (15.4)	0.302
	2	6 (23.1)	8 (30.8)	11 (42.3)	1 (3.8)	
	3	3 (27.3)	5 (45.5)	1 (9.1)	2 (18.2)	
SVD, n (%)	Yes	3 (9.4)	8 (25.0)	14 (43.8)	7 (21.9)	0.047
	No	16 (22.9)	28 (40.0)	20 (28.6)	6 (8.6)	
DVD, n (%)	Yes	9 (27.3)	15 (45.5)	9 (27.3)	0 (0)	0.009
	No	10 (14.5)	21 (30.4)	25 (36.2)	13 (18.8)	
TVD, n (%)	Yes	7 (25.9)	12 (44.4)	7 (25.9)	1 (3.7)	0.188
	No	12 (16.0)	24 (32.0)	27 (36.0)	12 (16.0)	
LMCA, n (%)	Yes	0 (0)	2 (50.0)	1 (25.0)	1 (25.0)	0.66
	No	19 (19.4)	34 (34.7)	33 (33.7)	12 (12.2)	
100% cut, n (%)	Yes	2 (16.7)	2 (16.7)	7 (58.3)	1 (8.3)	0.271
	No	17 (18.9)	34 (37.8)	27 (30.0)	12 (13.3)	

Data are expressed as n (%) and median (IQR). P-value <0.05 was considered statistically significant. DVD: Double vessel disease, LMCA: Left main coronary artery, NYHA: New York heart association, SVD: Single vessel disease, TVD: Triple vessel disease

metabolic syndrome. Moreover, inadequate vitamin D concentrations are correlated with determinants of disease progression, including inflammatory responses. The expanding compendium of empirical evidence indicates that vitamin D status may be integral to the maintenance of cardiovascular health.<sup>[18]</sup> In the present investigation, the correlation between diverse risk factors and vitamin D levels was evaluated, and

no statistically significant differences were observed. However, Hussein et al.<sup>[19]</sup> reported that diabetes and dyslipidemia were significantly correlated with vitamin D levels. Our study found a higher prevalence of multivessel disease, particularly DVD, among patients with lower vitamin D levels. This observation is consistent with the findings of Rahman et al.<sup>[12]</sup>, who documented a noteworthy association between vitamin D

**Table 3: Vitamin D levels in relation to GFR, ejection fraction, and angiographic scores**

Variables	Vitamin D level (ng/mL)				P-value
	≤10	11 to 20	21 to 30	>30	
eGFR, mL/min/1.73 m <sup>2</sup> [median (IQR)]	90 (85-94)	88 (80-97.8)	86 (79-99.3)	99 (90-108)	0.088
LVEF, % [median (IQR)]	48 (42-50)	46 (42-48)	48 (44-50)	54 (48-60)	0.018
Gensini scores [median (IQR)]	88 (68-92)	71 (60-82)	58 (46.5-72.5)	16 (6-32)	<0.001
Syntax scores [median (IQR)]	36 (30-38)	23 (20.4-24.5)	11.5 (7.5-18)	5 (3-11)	<0.001

Data are expressed as n (%) and median (IQR). P-value <0.05 was considered statistically significant.  
eGFR: Estimated glomerular filtration rate, LVEF: Left ventricular ejection fraction

**Table 4: Correlation between vitamin D level and coronary artery disease severity scores**

Severity scores	Correlation coefficient	P-value
Gensini score	-0.572	<0.001
Syntax score	-0.787	<0.001

P-value <0.05 was considered statistically significant

levels and the severity of CAD involvement. A previous study showed a significant inverse relationship between vitamin D levels and GS noted ( $r=-0.430$ ,  $P < 0.001$ ).<sup>[19]</sup> Comparable findings were likewise noted in the present investigation. The augmented SYNTAX score, which serves as a metric for evaluating the intricacy of CAD, has been demonstrated to function as an independent prognostic factor for significant adverse cardiac events in individuals diagnosed with ACS.<sup>[2]</sup> The current investigation revealed that vitamin D levels exhibited an inverse correlation with the severity and complexity of CAD, as quantified by the SYNTAX score, which is consistent with the findings observed in our research. Earlier research conducted by Seker et al.<sup>[18]</sup> demonstrated a comparable negative correlation between vitamin D concentrations and SYNTAX scores, with statistical significance ( $r=-0.549$ ,  $P < 0.001$ ). Although the exact processes linking low vitamin D levels to the extent of CAD remain incompletely understood, they likely encompass multiple biological pathways. Vitamin D possesses several beneficial properties that may influence cardiovascular health. These strategies include reducing inflammation, preventing blood clots, lowering blood pressure, and regulating the function of blood vessel linings. Vitamin D also plays a role in controlling calcium deposits in blood vessels. These various effects could potentially impact the formation and advancement of atherosclerosis, which might result in more significant and widespread damage to the coronary arteries.<sup>[18]</sup>

**Study Limitations**

Our study had a single center design and a compatibility-limited sample size, which may have constrained the external validity of the results. Moreover, the study failed to consider potential confounding factors, including dietary habits and sun exposure, which could influence vitamin D levels. The absence

of a control group within the same age group, comparable risk factors, and comprehensive patient data represents a significant methodological limitation of our study. Consequently, further extensive investigations are warranted to confirm these results and explore possible therapeutic implications.

**CONCLUSION**

The present study highlights a significant negative correlation between vitamin D status and the severity of CAD, as evidenced by the Gensini and SYNTAX scores, in patients with ACS. Furthermore, reduced vitamin D levels were associated with decreased LVEF and a higher prevalence of multivessel disease, particularly DVD.

**Ethics**

**Ethics Committee Approval:** The study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee M.K.C.G. Medical Collage (number: 1005, date: 18.12.2020).

**Informed Consent:** Informed consent was obtained from patients.

**Footnotes**

**Authorship Contributions**

Surgical and Medical Practices: K.K.S., H.G., Concept: K.K.S., H.G., Design: K.K.S., Data Collection or Processing: H.G., Analysis or Interpretation: K.K.S., H.G., Literature Search: K.K.S., H.G., Writing: K.K.S., H.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2024.19480

Int J Cardiovasc Acad 2024;10(4):139-140

# Clinical Practices in the Management of NSTEMI-ACS in Turkey: Insights from the READAPT Survey

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**Keywords:** NSTEMI-ACS, pre-treatment, P2Y12 receptor inhibitors, READAPT survey

## To the Editor,

The management of non-ST elevation - acute coronary syndrome (NSTEMI-ACS) remains a critical area of focus, particularly regarding the optimal use of antiplatelet therapy. The study conducted through the REal-world ADOption Survey on Acute antiPlatelet Treatment (READAPT) sheds light on several important issues in the current practice of NSTEMI-ACS management, including the timing of invasive coronary angiography (CAG), the application of pretreatment with P2Y12 inhibitors, and the adherence to European Society of Cardiology (ESC) guidelines. The findings, particularly with respect to Türkiye, provide a valuable perspective on both adherence to guidelines and the practical challenges faced in daily clinical practice.

A key observation from the survey was the widespread use of pre-treatment with oral P2Y12 inhibitors, despite the ESC guidelines suggesting that this is not recommended in routine clinical practice before the coronary anatomy is determined. [1] This discrepancy between guidelines and clinical practice is seen not only in Turkey but also across Europe, where a substantial proportion of patients receive pre-treatment before angiographic confirmation. [2,3] While this approach is common,

it raises concerns about the risk of bleeding, particularly in patients who may require coronary artery bypass surgery or those with specific clinical characteristics. The potential for adverse outcomes, such as bleeding complications, further emphasizes the need for careful risk stratification when deciding on pretreatment strategies.

A web-based survey focusing on the diagnosis, medical treatment, and invasive management of NSTEMI-ACS was created based on a literature review. The questionnaire was accessible on a dedicated online platform from February 4, 2022, to April 15, 2022. The participating countries were Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, Slovenia, Spain, Sweden, Switzerland, the Netherlands, Turkey, and the United Kingdom.

Interestingly, despite the non-recommendation for pretreatment, ticagrelor has emerged as the most frequently used P2Y12 inhibitor, followed by clopidogrel and prasugrel. This highlights an ongoing clinical preference for ticagrelor in many centers, potentially driven by its superior pharmacodynamics and faster onset of action compared to clopidogrel. [4] The use of intravenous P2Y12 inhibitors, such as cangrelor, remains

**To cite this article:** Gökalg M, Çalık AN. Clinical Practices in the Management of NSTEMI-ACS in Turkey: Insights from the READAPT Survey. Int J Cardiovasc Acad. 2024;10(4):139-140



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**Received:** 29.10.2024  
**Revised:** 11.11.2024  
**Accepted:** 15.11.2024  
**Published Online:** 16.12.2024



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relatively low across the board, including in Turkey, where fewer than 10% of patients receive such treatment. This is in line with the lack of direct evidence comparing cangrelor with other oral agents like prasugrel and ticagrelor in NSTEMI-ACS populations, despite their established efficacy in percutaneous coronary intervention (PCI) settings.<sup>[5]</sup>

Additionally, the survey underscores regional variations in the timing of invasive procedures, particularly the timing of CAG and PCI. In Turkey, a high proportion of patients (96%) undergo invasive angiography within 24 hours, which is consistent with the recommendations for early intervention in high-risk patients with NSTEMI-ACS. These findings further reinforce the importance of timely intervention for improving outcomes, as early revascularization remains a cornerstone in reducing mortality and preventing complications.

However, the study also highlighted significant socioeconomic and geographic disparities, particularly among patients in rural areas where healthcare access is limited. These disparities are associated with delayed presentation and consequently worse outcomes. The impact of socioeconomic factors on healthcare delivery should not be underestimated because they can directly affect treatment timeliness and the use of advanced therapies like mechanical circulatory support. Addressing these inequalities should be a priority for healthcare systems so as to ensure that all patients, regardless of their background, have equitable access to optimal care.

In conclusion, while the READAPT survey provides valuable insights into current practices in NSTEMI-ACS management, it also highlights the gaps between guideline recommendations and clinical practices, particularly regarding pretreatment strategies. The need for greater adherence to evidence-based guidelines, along with consideration of individual patient risk factors, remains critical for improving patient outcomes.

Additionally, efforts to address healthcare access disparities, especially in underserved areas, could significantly improve survival rates and reduce the burden of this serious condition.

## Footnotes

## Authorship Contributions

Concept: M.G., A.N.Ç., Design: M.G., A.N.Ç., Analysis or Interpretation: M.G., A.N.Ç., Literature Search: M.G., A.N.Ç., Writing: M.G., A.N.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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