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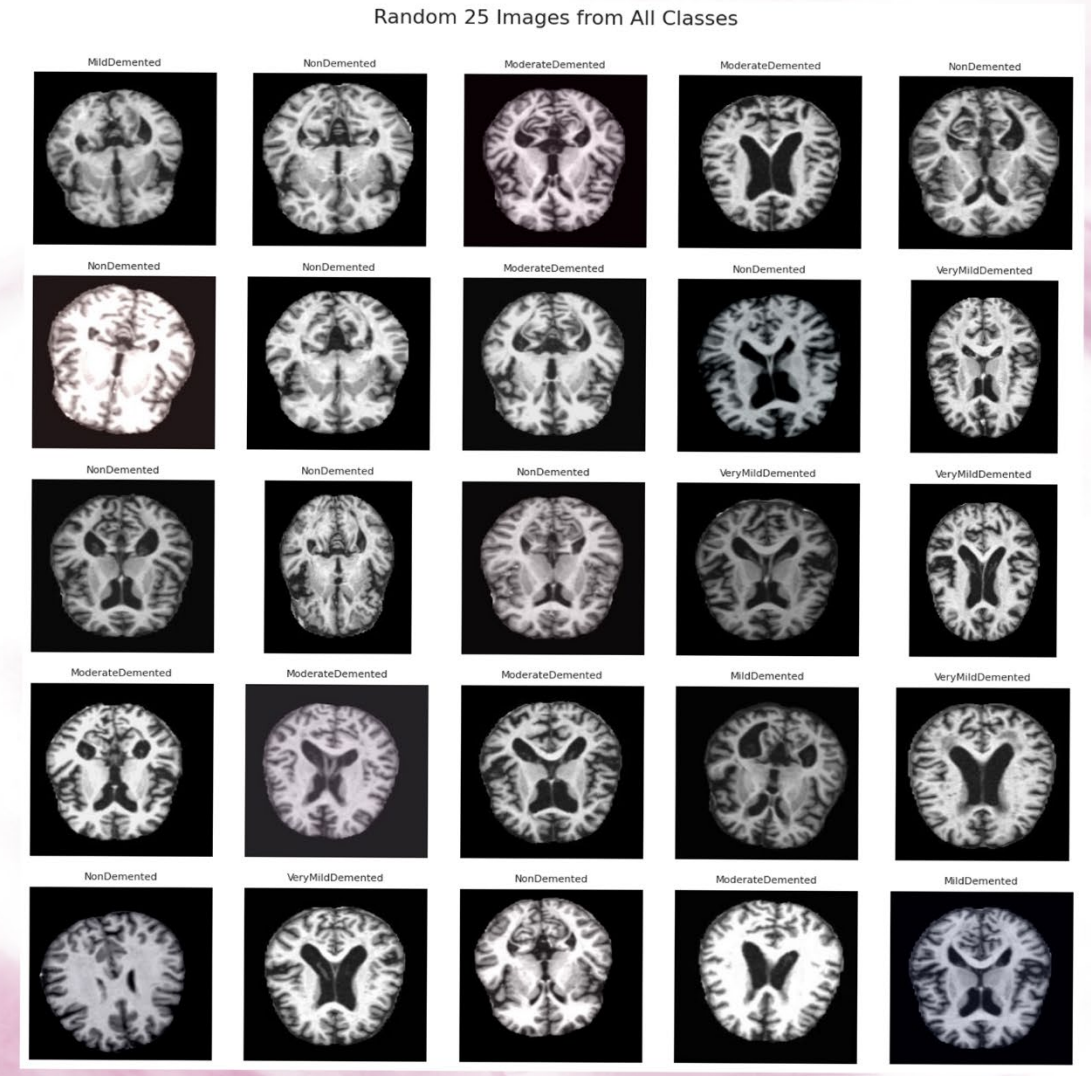

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ACCSCIENCE PUBLISHING
Volume 3 · Issue 4
November 2025
ISSN: 2972-4139 (Online)

Online ISSN: 2972-4139

Brain & Heart

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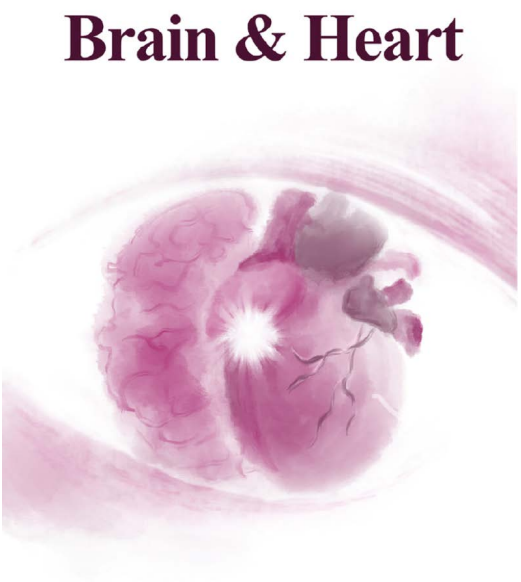

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Volume 3 • Issue 4 • November 2025
ISSN 2972-4139 (online)

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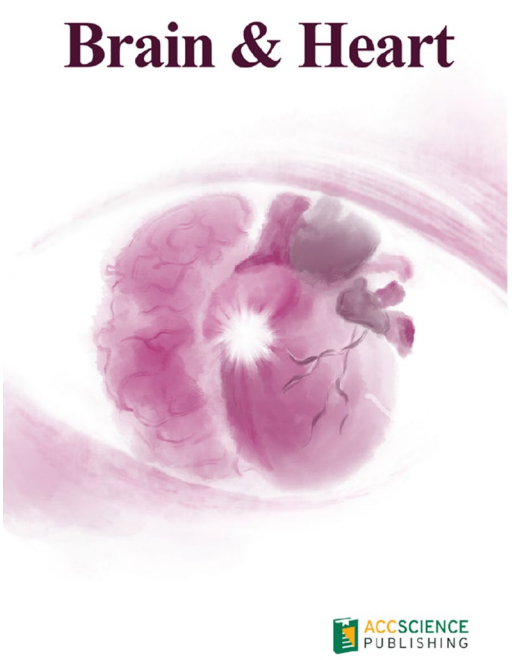

BRAIN & HEART

ISSN: 2972-4139 (online)

Editorial and Production Credits

Publisher: AccScience Publishing
Managing Editor: Naomi Li
Production Editor: Sharmila Velapasamy
Article Layout and Typeset: Sinjore Technologies (India)

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ACCSCIENCE PUBLISHING

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REVIEW ARTICLE

Prognostic factors of Takotsubo syndrome: A review

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Abstract

Takotsubo syndrome (TTS), also known as the "broken heart syndrome" or "stress cardiomyopathy," is characterized by transient left ventricular systolic dysfunction, usually in the absence of significant obstructive coronary artery disease. The pathophysiology of TTS remains incompletely understood, though commonly proposed mechanisms include catecholamine surge, estrogen deficiency, and coronary circulation dysfunction. TTS was initially regarded as benign and reversible; however, studies indicate that it may have severe short- and long-term complications. There are several prognostic factors associated with TTS that may influence patient outcomes. In this review, we aim to explore these prognostic factors in relation to various clinical variables, including age, gender, trigger type, atrial arrhythmias, rate-corrected QT interval, baseline left ventricular systolic function, and comorbidities. While many factors are thought to influence TTS, current research findings remain inconsistent. To improve prognosis, there is an urgent need to develop better risk-assessment tools. This can be achieved through large-scale, multicenter studies and analysis of existing research. By understanding these prognostic factors, better prevention and intervention strategies can be developed for TTS, reinforcing its recognition as a serious cardiovascular condition.

Keywords: Takotsubo syndrome; Stress cardiomyopathy; Broken heart syndrome; Prognosis; Pathophysiology

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Citation: Kumar V, Muhammad H, Khraisat O, *et al*. Prognostic factors of Takotsubo syndrome: A review. *Brain & Heart.* 2025;3(4):025090012. doi: 10.36922/BH025090012

Received: February 28, 2025

1st revised: May 9, 2025

2nd revised: May 31, 2025

Accepted: June 11, 2025

Published online: July 4, 2025

1. Introduction

The term Takotsubo syndrome (TTS) was first reported in 1990 and describes an acute cardiomyopathy that may mimic acute coronary syndrome with left ventricular

systolic dysfunction (LVSD), lacking significant coronary artery stenosis.[1,2] Takotsubo, which means "octopus trap" in Japanese, is used to describe the classic morphology of the left ventricle in systole as seen on echocardiograms.[3] Different terms have been used for this condition, including stress-related cardiomyopathy, transient left ventricular (LV) apical ballooning syndrome, broken heart (heartbreak) syndrome, and ampulla cardiomyopathy. In 2006, the American Heart Association incorporated this condition under the class of acquired cardiomyopathies.[4] TTS is often characterized by an acute LV systolic dysfunction, transient apical ballooning, compensatory hypercontractility of the remaining myocardium,[5] elevated cardiac enzymes, and ischemic changes on the electrocardiogram (ECG).[2]

Several demographic and clinical features have shown prognostic significance in TSS. For example, increased age, gender, physical and emotional triggers (ET), reduced baseline LV ejection fraction (LVEF), and presence of comorbidities have been consistently identified as predictors of short-term morbidity and mortality.[6-8] In this narrative review, we aim to assess the association of different prognostic factors with TTS outcomes.

2. Methodology

This narrative review synthesized current evidence on the prognostic factors associated with TTS. Relevant literature was identified through an extensive search of databases, including PubMed and Google Scholar, using keywords such as TTS, stress cardiomyopathy, prognosis, outcomes, and prognostic factors like atrial fibrillation (AF) and LV function. Peer-reviewed articles published up to 2025 were included. Additional references were identified from the bibliographies of selected articles. Priority was given to large cohort studies, registry data, and meta-analyses. No formal quality assessment or risk of bias evaluation was performed, as it is not common for narrative reviews. The focus was to summarize and critically appraise the existing literature to highlight relevant clinical predictors of outcomes in TTS.

3. Pathophysiology

The pathophysiology[9] of TTS is multifactorial, including catecholamine surge, estrogen deficiency, coronary microvascular dysfunction, and cardiac fatty acid metabolism abnormalities.[9]

3.1. Catecholamine surge

Catecholamines play a central role in TTS, as the acute presentation is often preceded by emotional or physical stress. The key to understanding the physiology of this hypothesis is to know how the brain center and hypothalamic-pituitary-adrenal (HPA) axis secrete catecholamine in response to a given event and the response of the cardiovascular system[9] (Figure 1).[9] The primary area that secretes catecholamines is in the pons, known as the locus coeruleus. This area regulates the hemostasis response to a stressful trigger, activating the HPA axis, which stimulates the adrenal medulla. Catecholamines act at the adrenoreceptors, which are concentrated at the apex of the heart, causing LV dysfunction and, therefore, apical ballooning.[10] In addition, studies have shown that the level of catecholamine increases 2 – 3 times in TTS than in myocardial infarction (MI). Therefore, conditions with excess secretion of catecholamines, such as pheochromocytoma, subarachnoid hemorrhage, seizure, ischemic stroke, and iatrogenic use of catecholamine, have been shown to cause an episode of TTS.

In addition, the use of combined alpha and beta-blockers on animals could normalize the ECG changes that occur as a response to catecholamine surge during stressful events, which does not occur when using potent coronary artery vasodilators, such as calcium channel blockers or nitroglycerin.[11] Furthermore, sympathetic overactivation in the myocardium causes interstitial mononuclear inflammation and contracted band fibrosis with or without myocardial necrosis, the hallmark of cardiotoxicity due to catecholamine observed in TTS, and is distinguished from the coagulative necrosis that occurs in MI. Thus, there is enough evidence to conclude that catecholamines play an important role in the pathogenesis of TTS.

3.2. Estrogen deficiency

The majority of Takotsubo cases occur in post-menopausal women, with a 5 times higher risk in women older than 55, suggesting that the level of estrogen may have a role in TTS. Estrogen has a known protective effect on the cardiovascular system, such as vasodilation and a decreased risk of endothelial dysfunction and atherosclerosis. In addition, it affects the vascular tone by increasing endothelial nitric oxide synthase and reducing the adrenergic receptors in myocardial cells.[12] This explains why pre-menopausal women can attenuate the effect of catecholamine surge during stress, while post-menopausal women cannot, and the latter can have LVSD in response to a subarachnoid hemorrhage. A study on ovariectomized rats showed that the drop in LV function was higher in rats without estrogen. In addition, estrogen increases cardioprotective factors such as heat shock protein and atrial natriuretic peptide, which protect the heart from the toxic effects of catecholamines and decrease oxidative stress.[13] To that end, it can be fairly concluded that estrogen has a protective role, and a reduction in its levels can contribute to TTS.

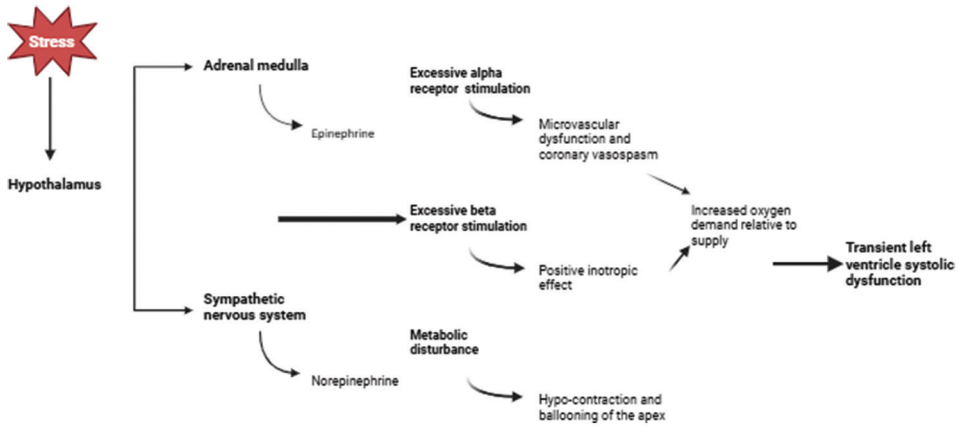

Figure 1. Pathophysiologic mechanisms in Takotsubo syndrome. Image created by the authors.

3.3. Coronary circulation dysfunction

The first study that described the case of TTS in 1990 suggests that coronary circulation dysfunction may be an underlying cause of TTS. The coronary system autoregulation provides a balance between the requirement and perfusion, and a reduction in perfusion is expected during an acute attack of TTS due to an enhanced systolic time and a reduced diastolic time. This coronary dysfunction may result from mediators such as endothelin, catecholamine, and reactive oxygen species.[14] However, some studies have revealed evidence against the microcirculation hypothesis, as the positron emission tomography perfusion scans used in these studies showed hyperperfusion in the basal segment and normal perfusion in the apical segment. Thus, the coronary circulation dysfunction hypothesis has contradictory evidence, and more research is needed to understand it further.

3.4. Abnormal metabolism

An abnormal myocardial metabolism during an acute episode of TTS was documented at the apical segment using fluorodeoxyglucose-positron emission tomography, where the consumption of free fatty acids and glucose transporters was significantly reduced. The resulting lipid droplet accumulation in the cytoplasm of the myocardial cells led to further metabolic stunning. These droplets have been observed in the myocardial cells of humans and mice with TTS, but are not present during the recovery phase.[15,16] The abnormal metabolism during acute TTS may be connected to its pathophysiology.

4. Types of TTS and clinical presentation

The two main types of TTS are based on the initial presentation: Primary and secondary. Primary TTS occurs without a clear cause or is triggered by emotions, while secondary TTS is caused by physical conditions or comorbidities. Primary TTS mainly occurs in post-menopausal women and is mostly due to stress. These patients have non-obstructive coronary arteries with moderate LV dysfunction, which is believed to be caused by microvascular changes and has a good prognosis. In comparison, secondary TTS affects both genders and is usually due to coronary artery disease, resulting in severe LV dysfunction and delayed recovery.[17]

The different types of triggers associated with TTS were investigated systematically in the InterTAK Registry.[18] Physical triggers (PT) such as surgery, acute asthma, stroke, and head injury were reported in 36% of the cases, while ET was reported in 27.7%. The most common presenting symptom in TTS is chest pain, followed by dyspnea. Severe cases may present with cardiogenic shock or thromboembolic events. However, some patients are completely asymptomatic, with ECG or biomarker abnormalities detected incidentally in the setting of an acute underlying illness such as sepsis.

5. Diagnostic criteria

The diagnostic criteria of TTS or cardiomyopathy have evolved, and currently, the modified Mayo Clinic diagnostic criteria are widely used.[19] The distinct defining diagnostic points include the following: (i) Wall motion abnormality in the left ventricle not restricted to single coronary artery distribution, (ii) the absence of obstructive coronary artery disease, new ECG changes, or increased troponins, and (iii) the absence of myocarditis.

The Hopkins, Japanese, and Taskforce of the European Society of Cardiology criteria also include the absence of obstructive coronary artery disease for the diagnosis of TTS.[20] In contrast, the InterTAK Diagnostic Criteria states that significant coronary artery disease should not be considered as an exclusion (Table 1).

Table 1. InterTak diagnostic criteria and score

Criterion	Points
Female gender	25
Emotional stress	24
Physical stress	13
Absence of ST-segment depression	12
Psychiatric disorders	11
Neurologic disorders	9
Rate-corrected QT prolongation	6
Total score	100

Note: Score>70 indicates a high probability of Takotsubo syndrome, and a score of ≤70 indicates a low/intermediate probability of Takotsubo syndrome.

6. Prognostic factors

6.1. Gender

Takotsubo predominantly affects women in the post-menopausal state, with the risk increasing fivefold after the age of 55. The occurrence might be related to the influence of sex hormones on the sympathetic neurohormonal axis and on coronary vasoreactivity, whereby declining estrogen levels after menopause increase the susceptibility to TTS in women. In a retrospective cohort study by Arcari *et al.*[21] comparing the gender differences in 2492 Takotsubo patients from the international multicenter German Italian Spanish Takotsubo (GEIST) registry, men comprised 11% of the total TTS population. They had a mean age of 69, significantly younger than the female cohort at presentation, which was 71. They were also more likely to have TTS caused by PT, as opposed to ET in females. In a study by Templin *et al.*[18] on the outcomes of TTS, the total mortality was significantly higher in males, averaging 12.9% per year, compared to 5% in females. The 10-year mortality and incidence of clinical events were also significantly higher in males.[18]

6.2. Rate-corrected QT interval

A prolonged QT interval is defined by the American Heart Association/American College of Cardiology as a rate-corrected QT (QTc) interval greater than the 99th percentile for females and males, which is 480 ms and 470 ms, respectively.[22] The prevalence of long QTc intervals in TTS is high, occurring in up to 86% of patients in the acute phase.[23] The pathophysiology by which QTc prolongation occurs is not completely understood, but it seems to involve an acute decrease in cardiomyocyte repolarization reserve due to autonomic dysfunction seen in TTS.[23]

6.3. AF

AF is the most common pathological cardiac arrhythmia, with a higher prevalence in males. Its presence is associated with an increased risk of stroke and mortality. In the context of TTS, the prevalence of AF has been reported to be between 5% and 25% and shown to be associated with worse short- and long-term mortality in patients with TTS.[24] In a meta-analysis by Prasitlumkum *et al.*[25] in 2018, five studies on 2321 patients with TTS found that AF was associated with increased all-cause mortality, especially in the long term. In a retrospective cohort study by El-Battrawy *et al.*[26] in 2021, 1584 patients with TTS were enrolled from the International Takotsubo Registry, in which 7.1% of patients had AF at admission. Those with AF proved to have a more complicated in-hospital course with lower LVEF, higher incidence of cardiogenic shock, and a higher in-hospital mortality compared to the non-AF group. Notably, those with AF tended to be older, were more frequently males, had PT of TTS, and higher brain natriuretic peptide, C-reactive protein, and whole blood count on admission, with more comorbidities such as hypertension[27] and diabetes, possibly distorting the effect of AF on the seemingly worse short-term prognosis.[27,28] In the long term, AF was shown to be independently associated with a higher 5-year mortality rate, and patients with AF were at a higher risk of major adverse cardiac and cerebrovascular events. A recent retrospective study by Dai *et al.*[29] on 4733 patients with TTS from the National Inpatient Sample database showed that patients with AF had a higher rate of in-hospital complications (e.g., cardiogenic shock, ventricular arrhythmias, and respiratory failure) compared to the non-AF group. In summary, AF is a poor prognostic indicator for the short- and long-term aspects in patients with TTS. However, due to its association with other known prognostic factors on admission, its effect as an independent risk factor for in-hospital and short-term mortality needs to be further investigated.

6.4. Left ventricular systolic function

Takotsubo cardiomyopathy is characterized by transient LVSD that extends beyond the territory supplied by a single coronary vessel. LVEF is usually reduced in the acute phase and is associated with increased in-hospital and long-term mortality.[30,31] A study by Alashi *et al.*[30] on 650 patients showed that 94% of the patients presented with a LVEF of <52%, and lower baseline LVEF was significantly associated with long-term mortality. A meta-analysis including 18 studies (n = 5168) concluded that reduced LVEF is associated with a threefold increase in mortality in TTS patients.[31]

6.5. Trigger types

TTS can result from PT or ET, although in some cases, no specific trigger can be identified. Examples of physical stress can include infections, trauma, and surgical

procedures. ETs are usually negative but can also be positive or "happy." According to a recent GEIST registry study on 2482 patients, ET was the most common trigger, detected in 36.7% of patients, while PT was detected in 34.4%. No trigger was found in the remaining 28.9%. Adverse hospital events and long-term mortality were both significantly higher in patients with PT (27.1% and 21.6%, respectively) than in the ET and no trigger groups.[32] The association between PT and worse outcomes has been seen in multiple studies, both for short- and long-term.[33]

6.6. Diabetes

The presence of diabetes among TTS patients has been reported to be between 1.6% and 25.5%.[34] The catecholamine hypothesis is perhaps the most widely accepted pathophysiologic mechanism in TTS. Since diabetic autonomic neuropathy can mitigate catecholamine-mediated effects on the heart, it was proposed that concomitant diabetes might also lower the incidence and severity of TTS.[34] Several studies, on the other hand, refute the theory of "diabetes paradox," particularly regarding the long-term outcome and mortality in TTS.[35,36] In a multicenter GEIST registry performed on 826 patients with TTS, 21.1% had diabetes, and long-term follow-up (after a median of 2.5 years) showed that mortality was significantly higher in patients with diabetes compared with patients without diabetes. It is of note, however, that patients in the study with diabetes were older, had a higher prevalence of hypertension, lower LVEF, and were more frequently male, suggesting that these factors could have possibly contributed to the worse prognosis in these patients. While the data on diabetes in TTS is conflicting, it may be concluded that patients with diabetes and TTS have an in-hospital mortality that is comparable to or less than those without diabetes.[37] However, individuals with diabetes are likely to have a worse prognosis in the long term.

6.7. Age

TTS predominantly affects older post-menopausal women, and the risk of developing the syndrome increases 5 times in women after the age of 55. The increased risk with age can be attributed to a rise in sympathetic nervous activity and augmented cardiac sympathetic stimulation in older individuals.[38] In females, hormonal factors also play an important role, whereby declining sex hormone levels after menopause lead to an abnormal vasomotor function and loss of protective effects of estrogen that normally attenuate the sympathetic response.[39] The effect of age on mortality and in-hospital complications in patients with TTS is controversial. Most studies report an increased risk of in-hospital and long-term mortality in older individuals with TTS.[40,41] Several other studies report no difference,[42-44] and many studies show a higher rate of in-hospital complications in younger patients.[45] A retrospective study of 10,861 patients with TTS from the Italian National Healthcare System Databank also found that increasing age was an independent predictor of in-hospital mortality in women, but not in men.[40]

While older age is an independent risk factor for mortality, death in these patients is also driven by comorbidities, which are usually more prevalent compared to younger age groups. As for younger patients having a more complicated in-hospital course, a plausible explanation could involve the higher incidence of acute neurologic and psychiatric triggers that ultimately result in significant sympathetic stimulation and a more severe clinical course. More studies are still needed to establish a clearer understanding of age cutoffs for defining young and old patients in the context of TTS prognosis (Table 2).

7. Management

There is no definitive treatment for TTS, and the primary goal is to decrease complications, with management depending on the case severity. In mild cases, it varies from observation to a short course of pharmacological treatment, while in severely complicated cases, mechanical circulatory support may be considered. The most crucial step in acute presentation is to rule out and treat other causes, such as acute coronary syndrome.

7.1. Treatment of acute TTS

The treatment of TTS depends on the patient's presentation, and the mainstay of the treatment is supportive management until recovery takes place. However, in cases of complications such as heart failure and shock, intensive treatment is required according to guidelines. Furthermore, the most crucial treatment is to assess whether the patient has LV outflow tract obstruction (LVOTO) using a transthoracic echocardiogram or invasive angiography, as the treatment may change if the patient has LVOTO.[46,47] After assessment, if patients are asymptomatic and hemodynamically stable with no sign of complications such as heart failure or arrhythmia, they should be admitted to the ward for further monitoring and treatment. Pharmacological treatment in such cases could be used according to the patient's tolerance, as they could lead to complications, and the recovery can take place without any intervention. If the patient has pulmonary congestion without hypotension, medications are used to reduce the venous return. If the patient is hypertensive, an arterial vasodilator can be used with caution, as those agents can worsen the LVOTO. Beta-blockers are employed as an added therapy for stable patients with hypertension, as this

is very helpful in LVOTO, decreasing basal contractility and reducing obstruction. Cardiogenic shock is a common complication that occurs in about 10% of cases, increasing mortality by up to 5 times. The treatment of cardiogenic shock depends on the presence of LVOTO. In the absence of obstruction, an inotropic agent can be considered, as it can increase the cardiac output. Still, short-term follow-up is needed, as those agents can cause obstruction even in patients with normal baselines. In a refractory case, a vasopressor agent can be considered, but in the lowest possible dose as a temporary treatment until further mechanical support is used as a bridge to recovery. In the presence of LVOTO, the treatment is very challenging, as the use of an inotropic agent or any agent reducing the intravascular volume (such as diuretic or nitroglycerin) should be avoided because it can worsen the obstruction; hence maintaining the intravascular volume by intravenous fluid is the most critical step in management as it reduces obstruction. Beta-blockers can be considered for those with severe LVOTO, given their ability to improve cardiac output by decreasing obstruction. In addition, vasopressors can be used to increase blood pressure without worsening the obstruction. Finally, if all those steps fail, mechanical support may be required.

Table 2. Prognostic factors in Takotsubo syndrome

Prognostic factor	Key findings	Study/registry (year)
Gender	Males had higher in-hospital and long-term mortality compared to females	Templin *et al.* (2015)[18]; Arcari *et al.* (2022)[21]
Rate-corrected QT interval	QT prolongation occurred in about 86% during the acute phase, associated with arrhythmogenic risk	Behr and Mahida (2009)[23]
Atrial fibrillation	Atrial fibrillation is associated with worse in-hospital and long-term outcomes, as well as a higher risk of mortality and complications	Prasitlumkum *et al.* (2018)[25]; El-Battrawy *et al.* (2021)[26]; Dai *et al.* (2023)[29]
Left ventricular systolic function	Reduced left ventricular ejection fraction (<52%) is linked to increased long-term mortality and a 3 times higher mortality risk	Alashi *et al.* (2020)[30]; Chiang *et al.* (2021)[31]
Trigger type	Physical triggers are associated with higher hospital events and long-term mortality than emotional or no triggers	Patz *et al.* (2023)[32]; Uribarri *et al.* (2019)[33]
Diabetes	Conflicting evidence shows that the mitigation of acute stress is associated with higher long-term mortality in Takotsubo syndrome	Madias (2016)[34]; Stiermaier, Moeller *et al.* (2016)[36]
Age	Older age is associated with increased long-term mortality and worse outcomes, especially in women	Malanchini *et al.* (2020)[40]; Cammann *et al.* (2020)[43]

Table 3. Strengths and limitations of key studies on Takotsubo syndrome

Study	Strengths	Limitations
Templin *et al.*[18]	Large sample size (1750 patients); multicenter international registry; robust analysis of clinical outcomes by gender	Observational design limits causal inference; potential for selection bias in registry data
Mahida[22] & Behr[23]	Explores the electrophysiological basis of rate-corrected QT prolongation in TTS; an early investigation into repolarization reserve	Focused more on mechanistic hypotheses than broad clinical applicability
Prasitlumkum *et al.*[25]	Meta-analysis pooling data from five studies; evaluated atrial fibrillation as a prognostic factor	Heterogeneity in included studies; potential publication bias
El-Battrawy *et al.*[26]	Data from the International Takotsubo Registry; analyzed outcomes of patients with AF in TTS	Retrospective design; AF cohort had more baseline comorbidities, possibly confounding outcomes
Alashi *et al.*[30]	Study of 650 patients assessing LVEF and mortality; demonstrated prognostic relevance of reduced baseline LV function	Single-center study; limited diversity in patient population
Patz *et al.*[32]	Multicenter GEIST registry data; large patient population; detailed classification of triggers	Observational nature; trigger classification may be subjective
Stiermaier *et al.*[36]	Long-term follow-up; analyzed prognostic role of diabetes; part of an international registry	Confounding from comorbidities; no randomization or matching
Cammann *et al.*[43]	Analyzed age-related differences in clinical features and outcomes; a large dataset	Lacked standardized age cutoffs; some subgroup sizes were small for analysis

Abbreviations: AF: Atrial fibrillation; GEIST: German Italian Spanish Takotsubo; LV: Left ventricular; LVEF: Left ventricular ejection fraction; TTS: Takotsubo syndrome.

7.2. Long-term management of TTS

TTS is a reversible cardiomyopathy with an annual recurrence rate of 2 – 4%. The recurrence may occur within 4 days or up to 10 years after the initial attack, affecting different areas of the heart. There is no current evidence-based long-term management for TTS, but experts recommend the use of beta-blockers, especially in patients who have high sympathetic tone, persistent anxiety, and ongoing cardiac symptoms. A retrospective analysis of a large international registry showed that the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers reveals an improvement in survival after 1 year.[47] As TTS is a transient heart failure, the use of heart failure medications such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and diuretics is recommended for at least 3 months or until complete recovery.

8. Conclusion

This review examines the factors that influence the outcome for patients with TTS. While most primary TTS cases have a positive prognosis, recognizing secondary forms and their associated risk factors is crucial for clinicians. Early intervention appears to improve outcomes in patients with TTS, and the mainstay therapy is supportive as patients' LV function begins to restore over several days and typically recovers fully within 3 – 4 weeks. A comparative synthesis of key studies highlights the strengths and limitations of current evidence (Table 3), underscoring the heterogeneity in study designs, populations, and prognostic markers. Future large-scale controlled studies are needed to address inconsistencies in known risk factors, as this would empower medical professionals to provide more accurate prognoses and better manage TTS in their patients.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interest.

Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

A review of hypertension and vascular cognitive impairment

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Abstract

Vascular cognitive impairment (VCI) is a cognitive dysfunction syndrome caused by various vascular-related risk factors, with hypertension regarded as one of the main pathogenic factors. Chronic hypertension can promote cognitive decline through abnormal microcirculation structure, white matter fiber injury, blood–brain barrier destruction, oxidative stress, and neuroinflammatory reaction, increasing the incidence of vascular dementia. To fully grasp the research status in this field, this study adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines for literature identification. A controlled vocabulary-based search strategy was employed to screen PubMed, Embase, Web of Science, and Cochrane Library for human studies published from January 2000 to March 2025, focusing on hypertension, VCI, dementia, antihypertensive treatment, and aerobic exercise intervention. Analysis of literature shows that angiotensin converting enzyme inhibitors and calcium channel blockers may play a neuroprotective role by increasing cerebral blood flow, reducing oxidative stress, and delaying amyloid deposition. However, these mechanisms and their clinical results are still controversial. Aerobic exercise, particularly moderate and high-intensity exercise, can continuously improve cerebral blood flow, promote neuroplasticity development, and enhance cognitive performance. However, significant limitations remain in the existing research. Thus, it is essential to conduct a systematic, integrated analysis and further strengthen standardized experimental design and personalization.

Keywords: Hypertension; Cognitive impairment; Antihypertensive therapy; Aerobic exercise

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Citation: Zhu Z, Duan S, Sun X. A review of hypertension and vascular cognitive impairment. *Brain & Heart*. 2025;3(4):025310044.
doi: 10.36922/BH025310044

Received: August 1, 2025

1st revised: September 19, 2025

2nd revised: September 23, 2025

Accepted: September 24, 2025

Published online: October 10, 2025

1. Introduction

Vascular cognitive impairment (VCI) is a neurological dysfunction caused by the interaction of various vascular risk factors and cerebrovascular diseases. It is characterized by a progressive trajectory extending from mild cognitive impairment to post-stroke vascular dementia. The pathological mechanism of this disease includes both simple vascular injury and the compound mode of the superposition effect of neurodegenerative diseases, such as Alzheimer's disease. The key to effective prevention and treatment is prioritizing stroke prevention as the primary goal. It is imperative to comprehensively control vascular risk factors through systematic interventions and strengthen

hypertension management. Hypertension is one of the common chronic diseases in China. With the acceleration of population aging, the prevalence of hypertension is rising, which has a more significant impact on the cognitive function of the elderly. Therefore, it is necessary to conduct early screening and take comprehensive prevention and control measures. Clinical research data have shown that regular exercise can reduce blood pressure levels, indicating the significance of auxiliary treatment. Although there is evidence that antihypertensive drugs positively improve cognitive function, their internal mechanism needs further discussion. This review aims to summarize the mechanisms of cognitive dysfunction associated with hypertension and to comprehensively evaluate the effects of aerobic exercise combined with multi-drug therapy on cognitive function. It offers theoretical insights and outlines a conceptual framework to support the clinical prevention and management of hypertension-related cognitive impairment.

2. Methodology

To enhance methodological transparency, we performed a narrative review in accordance with the key elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A systematic and comprehensive search was conducted across PubMed, Embase, Web of Science, and Cochrane Library to identify relevant articles published from January 2000 to March 2025. The search strategy employed a combination of Medical Subject Headings and free-text terms, such as "hypertension," "vascular cognitive impairment," "cognitive decline," "dementia," "cerebral small vessel disease," "lacunar infarct," "antihypertensive therapy," "angiotensin-converting enzyme inhibitors," "angiotensin receptor blockers," "beta-blockers," "calcium channel blockers," and "aerobic exercise." At the same time, the reference lists of pertinent articles and reviews were meticulously screened to uncover supplementary sources. The inclusion criteria encompassed (i) Peer-reviewed original research articles, systematic reviews, or meta-analyses that involve adult human populations, and (ii) Studies that address the association between hypertension and cognitive impairment, the mechanisms underlying VCI, or the impact of antihypertensive medications and/or aerobic exercise on cognitive outcomes. Case reports, conference abstracts, editorials, non-peer-reviewed publications, animal studies, and articles not available in English were excluded.

For the study selection and appraisal, one reviewer performed the initial screening of titles, abstracts, and full texts. In cases of uncertainty, eligibility was discussed and resolved in consultation with co-authors. Given the narrative nature of this review, a formal PRISMA protocol registration and quantitative meta-analysis were not undertaken. Nevertheless, we adhered to key PRISMA principles for transparency by prespecifying databases, timeframe, and search terms and defining explicit eligibility criteria. The included studies were qualitatively appraised with attention to study design, sample size, methodological rigor, risk of bias, and consistency of findings across populations.

3. Mechanisms of hypertension-induced cognitive impairment

3.1. Hypertension-induced structural alterations in cerebral vasculature

Preclinical studies have provided mechanistic evidence that sustained elevation of blood pressure induces adaptive structural changes in cerebral circulation.[1,2] These changes are characterized by a compensatory increase in cerebrovascular resistance, involving vascular remodeling of cerebral arteries and arterioles.[3] During this remodeling process, the ratio of vascular wall thickness to lumen diameter increases, leading to reduced wall stress and elevated segmental resistance.[4] Vascular smooth muscle cells may undergo reorganization. One pattern of reorganization involves cellular rearrangement that narrows the vascular lumen without altering the cross-sectional area of the vessel wall, a process known as eutrophic remodeling.[5] Another pattern involves hypertrophy or proliferation of vascular smooth muscle cells, which results in thickening of the vessel wall and further reduction in lumen diameter; this is referred to as hypertrophic remodeling.[6]

Hypertension can also lead to microvascular rarefaction, characterized by reduced vascular density, including decreased capillaries and small arterioles.[7] This phenomenon has been observed in both human patients and hypertensive animal models.[8] The underlying cause may be related to increased mechanical stress on the microvascular bed; however, the precise mechanisms remain incompletely understood.[9] Given that the white matter of the brain is relatively poorly vascularized, it is particularly susceptible to damage under hypertensive conditions. Typical microvascular pathologies associated with hypertension include hyaline deposition within vessel walls (lipohyalinosis) and fibrinoid necrosis of small vessels.[10] These changes are predominantly found in small arterioles within the white matter and may ultimately lead to the development of cerebral small vessel disease.[11] Cerebral small vessel disease represents a disruption of cerebrovascular structure and function that destabilizes cerebral homeostasis, impairs neuronal activity, and ultimately contributes to cognitive decline.[12]

The neuropathological features of Alzheimer's disease are characterized by the coexistence of vascular damage and the accumulation of β-amyloid (Aβ) protein.[13] Aβ aggregates into insoluble plaques primarily in the white matter and hippocampus. In addition to directly damaging neural tissue, Aβ promotes neurovascular injury by activating inflammatory responses, endothelial dysfunction, and oxidative stress. These processes accelerate atherosclerosis, induce neuronal apoptosis, and ultimately lead to cognitive decline. Multiple studies have shown that the duration of elevated blood pressure in hypertensive patients is correlated with the severity of arterial stiffness.[14] It is hypothesized that sustained hypertension contributes to vascular dysfunction and facilitates the deposition of Aβ within cerebral blood vessels. This impairs cerebrovascular autoregulation, exacerbates microcirculatory disturbances, and increases the risk of cognitive impairment and dementia.[3]

3.2. Hypertension-induced cerebrovascular functional alterations

3.2.1. Cerebral autoregulation

Cerebral autoregulation is the intrinsic capacity of cerebral vessels to maintain stable cerebral blood flow despite fluctuations in systemic blood pressure.[15,16] This mechanism involves myogenic, neurogenic, endothelial, and metabolic responses that adjust cerebral vascular resistance to preserve perfusion.[14,17] In chronic hypertension, the autoregulatory curve shifts rightward, requiring higher blood pressure to maintain consistent cerebral blood flow.[18,19]

Several studies have reported that this system is controlled by the 20-hydroxyeicosatetraenoic acid-transient receptor potential channel 6 pathway. 20-hydroxyeicosatetraenoic acid, derived from arachidonic acid, is made by enzymes called cytochrome P450.[20] It activates transient receptor potential channel 6 channels, elevating calcium levels inside smooth muscle cells in blood vessels, causing the vessels to contract more.[21] This response prevents too much blood from reaching the brain. However, if blood pressure remains high for a long time, the vessels can stay too tight.[22] This causes poor blood flow and damage, especially in deep brain areas like the white matter.[23]

White matter in the brain has a special blood supply, making it more likely to be harmed when blood flow drops. Due to this, it is often damaged in individuals with high blood pressure and small-vessel disease. This area is also where white matter hyperintensities are found.[24] Many brain scans and research studies have shown that white matter damage is linked to problems with thinking, especially in attention, planning, and processing speed.[25]

In addition to the myogenic mechanism, cerebral blood flow regulation is also modulated by neural and humoral factors. The local brain renin-angiotensin system (RAS) is critical in hypertension-related brain injury.[26] Activation of brain RAS—particularly persistent stimulation of the angiotensin II (Ang II) Type 1 receptor (AT1R)—leads to cerebrovascular endothelial dysfunction, basement membrane thickening, fibrosis, and vascular remodeling.[27] These alterations increase microcirculatory resistance and induce oxidative stress, chronic low-grade inflammation, and glial cell activation, ultimately disrupting the blood–brain barrier (BBB) and triggering neuronal dysfunction and death.[28,29]

In animal models, inhibition of AT1R or angiotensin-converting enzyme (ACE) has effectively reversed vascular remodeling and reduced neuronal apoptosis in cognition-related brain regions such as the hippocampus and prefrontal cortex. In contrast, activating the Ang II Type 2 receptor initiates multiple neuroprotective processes, including anti-inflammatory, anti-apoptotic, and neuroregenerative effects.[30] Moreover, the Ang II Type 2 receptor enhances BBB integrity by regulating the expression of tight junction proteins in cerebral endothelial cells—a function that is particularly crucial under hypertensive conditions.[31]

Impaired cerebral autoregulation is considered a key mediator in the development of VCI caused by hypertension.[32] Once autoregulatory capacity is compromised, cerebral perfusion becomes more susceptible to fluctuations in systemic blood pressure, leading to chronic hypoperfusion or acute underperfusion, consequently contributing to irreversible neuronal injury and dysfunction.[33]

3.2.2. Impaired neurovascular coupling (NVC)

NVC constitutes an essential physiological mechanism that contributes significantly to preserving cerebral homeostasis. It relies on dynamic interactions among endothelial cells, neurons, astrocytes, and vascular smooth muscle cells. These components collectively regulate local cerebral blood flow. Specifically, during heightened neuronal activity, they facilitate a prompt and targeted increase in blood supply to neural regions with elevated metabolic and oxygen requirements, thereby ensuring appropriate support for neural function and energy metabolism.[33,34]

Hypertension is a major pathological factor that disrupts this finely tuned process. Empirical findings suggest that, despite the complexity of these interrelated mechanisms, a key pathological pathway involves the Ang II-nicotinamide adenine dinucleotide phosphate oxidase (NOX)-reactive oxygen species (ROS) signaling cascade.[35,36]

When blood pressure is high, Ang II activates the NOX2 enzyme through AT1Rs. This causes a buildup of ROS,

which damages the inner lining of blood vessels and blocks the production of nitric oxide from endothelial cells. This stops the smooth transition of signals between neurons and the muscle cells in blood vessels, preventing blood vessels from properly adjusting blood flow in response to brain activity.[37,38]

Ang II also activates calcium-based signals in astrocytes. These signals cause the release of inflammation-related proteins like tumor necrosis factor alpha and interleukin 6, further impairing NVC. Persistent BBB leakage exacerbates this dysfunction by reducing clearance of neurotoxic metabolites.[39]

Animal studies of hypertension have shown markedly weakened neurovascular responses in brain regions like the hippocampus and prefrontal cortex, leading to reduced blood flow and impaired synaptic function.[28]

Moreover, activated macrophages—particularly perivascular macrophages—further amplify ROS generation through increased NOX2 and NOX4 expression. This promotes oxidative stress, disrupts the integrity of the BBB, and establishes a vicious cycle of "inflammation-oxidative stress-endothelial dysfunction."[40,41]

Importantly, similar mechanisms exist in the peripheral vascular system. In hypertension, mechanical pressure and shear stress stimulate endothelial cells in the peripheral microcirculation, inducing NOX activation and leading to peripheral endothelial dysfunction. This process may indirectly affect cerebral blood flow regulation through a "peripheral-to-central" communication pathway.[11] Clinical and experimental studies have found that peripheral endothelial impairment is closely associated with cognitive decline, highlighting the importance of addressing systemic microcirculation in regulating NVC.[42]

In recent years, treatments focusing on NVC have shown promise for VCI. One example is that blocking NOX2 activity in older mice restored normal NVC function in the hippocampus and improved spatial learning and memory.[43] Other studies found that using NOX blockers or drugs that block Ang II receptors helped brain blood flow and thinking ability in animals with high blood pressure.[44]

Studies have shown that modulating the interaction between astrocytes and endothelial cells in the neurovascular unit may have therapeutic benefits. Partial improvement in NVC has been observed following the upregulation of regulatory factors such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), which play essential roles in maintaining vascular integrity and neuronal function.[45]

3.2.3. BBB disruption

The BBB is a crucial structural component in maintaining central nervous system homeostasis. It comprises cerebral microvascular endothelial cells, a delicate basement membrane, pericytes, and astrocytic end-feet, forming a complex structure that intricately envelops the cerebral vasculature.[46,47] The BBB plays a crucial role in restricting the permeation of potentially harmful substances, immune cells, and toxins from the circulatory system into the brain parenchyma. In addition, it facilitates nutrient transport, modulates immune surveillance, and maintains ionic homeostasis within the cerebral microenvironment.[48]

Identified as an early pathological characteristic in hypertension-related cerebrovascular diseases, BBB dysfunction might act as a crucial mechanism contributing to the progression of VCI. Preclinical and neuroimaging studies suggest that increased BBB permeability may precede significant brain atrophy and neuronal degeneration. Early BBB leakage has been consistently detected in cognitive-related brain regions, including the striatum, hippocampus, and prefrontal cortex, across various experimental models of hypertension, such as spontaneously hypertensive rats and animals infused with Ang II.[49,50]

The BBB breakdown permits leakage of plasma proteins (e.g., fibrinogen, albumin, immunoglobulin G) into the brain parenchyma, provoking activation of microglia and astrocytes. The resulting neuroinflammatory cascade accelerates axonal injury and demyelination, thereby contributing to hypertension-related white matter degeneration and cognitive decline. Over time, this pathological process promotes progressive white matter degeneration, representing a critical mechanism in the evolution of cerebrovascular-related cognitive decline.[51,52]

Concurrent evidence shows that perivascular immune cells, such as perivascular macrophages and microglia, are activated in response to prolonged hypertension. These cells secrete proinflammatory mediators such as interleukin-1β and tumor necrosis factor alpha, which contribute to vascular damage and enable the infiltration of peripheral immune cells into the brain parenchyma. This inflammatory cascade progressively impairs BBB integrity and plays a role in the pathophysiology of hypertension-associated neurovascular dysfunction.[53]

Various aspects of cognitive performance have been significantly linked to the permeability of the BBB, as revealed by advanced neuroimaging research methodologies. For instance, according to Montagne *et al.*,[54] who employed a dynamic contrast-enhanced magnetic resonance imaging, individuals diagnosed with mild cognitive

impairment demonstrated increased BBB leakage within the hippocampus, a finding that ostensibly correlates with memory impairment.[54] Considering the nuanced nature of these findings, subsequent investigations tend to support the notion that BBB dysfunction is associated with deficits in executive function and processing speed among older adults with hypertension.[55]

Persistent BBB leakage reduces clearance of neurotoxic metabolites, including Aβ and tau proteins. The accumulation of these factors plays a crucial role in contributing to the overlapping pathological mechanisms between VCI and Alzheimer's disease.[56] Within this broader analytical framework, damage to the BBB appears to be present in the early stages of AD, indicating that this damage tends to lead to nerve fiber deterioration, brain inflammation, and amyloid plaque accumulation.[57]

Recent studies have highlighted increasing interest in BBB-protective strategies aimed at ameliorating VCI. Given the complexity of the underlying mechanisms, data suggest that several therapeutic interventions—such as AT1R blockers (particularly valsartan and losartan), ACE inhibitors (ACEIs), and antioxidants including N-acetylcysteine—may serve as effective treatment options in this context.[58] Activators of the nuclear factor erythroid 2-related Factor 2 pathway have also been shown to lower BBB leakiness, reduce damage to white matter, and improve thinking ability. In animal studies, intermittent hyperbaric oxygen therapy has helped protect the blood vessel barrier, reduce inflammation and oxidative stress, and slow the progression of brain damage in VCI.

4. Effects of antihypertensive therapy on VCI

4.1. Ang II receptor blockers (ARBs)

The cognitive improvement mechanisms of ARBs may involve several aspects. First, the ability of ARBs to cross the BBB and enhance cerebral blood flow can potentially exert neuroprotective effects.[59] Second, ARBs block the AT1R and promote interaction between Ang II and the Ang II receptor; some studies have further suggested that ARB-mediated AT1R blockade may induce degradation of cerebral amyloid deposits, thus slowing the onset and progression of Alzheimer's disease.[60] However, clinical studies on the cognitive effects of ARBs have rarely targeted Alzheimer's disease prevention or treatment directly, and the results remain inconsistent. The SCOPE study did not conclude that candesartan treatment had a preventive effect on overall cognitive decline.[61] A study conducted in Taiwan found no reduction in Alzheimer's disease risk after five years of ARB therapy.[62] In contrast, the MOSES trial, which was the first to assess the secondary prevention of stroke by ARBs, reported that eprosartan had protective effects against cognitive decline.[63] A recent comprehensive meta-analysis, which rigorously examined 19 randomized controlled trials alongside 11 observational studies, has demonstrated that antihypertensive therapy may significantly decrease the risk of all-cause dementia. Notably, when the reduction in blood pressure was equivalent, ARBs demonstrated superior cognitive benefits compared to placebo, β-blockers, diuretics, and ACEIs, in descending order of efficacy. The cognitive protection effect of ARBs in clinical applications necessitates further exploration. As for the underlying mechanisms of ARBs' cognitive protection, although several have been proposed, additional studies are required to confirm these mechanisms and determine optimal strategies.[64]

4.2. Angiotensin-converting enzyme inhibitors

Within the brain parenchyma and cerebral vasculature, as well as in the pulmonary circulation, ACE serves a pivotal function in the RAS, particularly in the production of Ang II and the metabolic processing of Aβ.[65] Several studies have reported that ACEIs can reduce Aβ deposition by inhibiting the degradation of substance P. Substance P is known to activate neutral endopeptidase (also referred to as neprilysin), an enzyme capable of degrading Aβ and other neurotoxic peptides in the brain, thereby contributing to cognitive improvement.[66] In addition, ACEIs suppress RAS activity, reduce oxidative stress and inflammatory responses in glial cells, and promote acetylcholine release, which collectively help to protect neurons from damage and exert neuroprotective effects.[67]

Numerous studies have extensively explored the relationship between ACEIs and cognitive function. The HOPE study, encompassing 9,297 hypertensive patients with a follow-up period of 4–5 years, revealed that the incidence of cognitive impairment, motor weakness, and speech or swallowing difficulties was 41% lower in patients administered ramipril than in those who received a placebo.[68] The PROGRESS study found that individuals with brain blood vessel disease who took perindopril and indapamide for four years had a 19% lower chance of overall memory and thinking problems. Their risk of memory problems after a stroke dropped by 45%.[69]

Different ACEIs can cross the BBB in varying amounts, which may affect how well they protect the brain. Fat-soluble drugs like perindopril and ramipril can enter the brain more easily and may work better on the central nervous system. Water-soluble drugs like captopril do not enter the brain as well and may have weaker effects.[70]

Animal research has shown that ACEIs might reduce brain cell death and help brain repair by changing the

phosphoinositide 3-kinase/protein kinase B signaling pathway and blocking nuclear factor kappa B activity in the brain.[71] In mouse models of Alzheimer's disease, administering ACEIs over a long period facilitated memory and thinking, reduced brain cell damage, and improved brain cell connection and communication.[72]

Evidence has also suggested that combining ACEIs with calcium channel blockers or ARBs may have synergistic anti-dementia effects, although the underlying mechanisms remain unclear.[73]

In summary, ACEIs lower peripheral blood pressure to alleviate cerebrovascular burden and exert cognitive protective effects through multiple central mechanisms. These include reducing Aβ accumulation, suppressing inflammation and oxidative stress, and enhancing neuroplasticity. Further clinical studies are needed to determine the efficacy and safety of different ACEIs across various VCI stages and explore their potential in combination therapy.

4.3. Beta-blockers

The potential effects of beta-blockers on cognitive function remain unclear. Some studies have reported that beta-blockers may delay cognitive decline. For instance, a study involving 2,197 Asian hypertensive men with a mean age of 77 years demonstrated that monotherapy utilizing beta-blockers was significantly correlated with a diminished risk of cognitive decline. In diabetic individuals and men over 75-years-old with a pulse pressure of ≥70 mmHg, the efficacy of beta-blockers in alleviating cognitive impairment was more significant.[74] However, other researchers argue that beta-blockers have no beneficial effect on cognitive impairment and may even exacerbate cognitive deficits.[75,76] While Richards *et al*.[77] suggested that beta-blockers could potentially reduce the risk of VCI. Their analysis of 2,212 community-dwelling African Americans aged ≥65 years indicated that centrally acting sympatholytic agents might be associated with an increased risk of Alzheimer's disease-related cognitive decline in the context of antihypertensive medication usage. Consequently, some scholars have suggested that the cognitive impact of beta-blockers is contingent on their capacity to penetrate the BBB.[78] Typically, in healthy individuals, beta-blockers do not lead to cognitive dysfunction, whereas beta-blockers with central action may adversely affect delayed memory function in cognitively impaired patients by attenuating central noradrenergic pathways.[79,80] In light of the inconsistent findings reported, further investigation is imperative to elucidate the cognitive effects of beta-blockers, with particular emphasis on large-scale randomized controlled trials that can ascertain their efficacy and safety across diverse population groups. These findings further underscore the necessity for clinicians to consider personalized pharmacotherapy strategies within clinical practice settings.

4.4. Calcium channel blockers

Maintaining intracellular calcium homeostasis is crucial in sustaining neuronal activity, modulating synaptic plasticity, and regulating cerebral blood flow. In chronic cerebrovascular conditions such as hypertension and stroke, aging is associated with impaired calcium regulation. The activation of calcium-dependent enzymes, such as calpain, phospholipases, and nitric oxide synthase, triggered by elevated intracellular calcium levels, subsequently leads to mitochondrial dysfunction, excessive production of ROS, and the induction of apoptosis. Implicated in the development of cognitive decline, this cascade plays a crucial role in contributing to progressive neuronal injury through complex pathological mechanisms.[81,82] Hypertension worsens brain injury by reducing long-term blood supply, increasing oxidative stress, and amplifying neuronal excitotoxic damage. These trigger abnormal calcium channel function and promote neurodegeneration, leading to cerebrovascular-related cognitive decline.[82,83]

Studies have demonstrated that dihydropyridine-type calcium channel blockers, such as nimodipine, amlodipine, and felodipine, can penetrate the BBB and exert direct pharmacological effects on cerebral vasculature and vascular smooth muscle cells. Despite the complexity of the underlying mechanisms, these agents improve regional cerebral blood flow and enhance the neuronal microenvironment, providing potential therapeutic benefits for cerebrovascular dysfunction through multifaceted physiological modulation.[84,85] Nimodipine has demonstrated cognitive benefits in both clinical and preclinical models of cerebral ischemia, stroke, and Alzheimer's disease. These findings support its therapeutic potential in various cerebrovascular and neurodegenerative disorders.[84,86]

A comprehensive meta-analysis encompassing 14 clinical trials, which included patients diagnosed with Alzheimer's disease, vascular dementia, and mixed dementia, revealed that a 12-week therapeutic regimen with nimodipine led to a statistically significant enhancement in global cognitive function. Moreover, in comparison to those who did not receive such treatment, patients administered calcium channel blockers exhibited a reduced risk of cognitive dysfunction and Alzheimer's disease.[87]

The role of calcium channel blockers in regulating cerebral blood flow is also noteworthy. Studies in

hypertensive animal models have shown that calcium channel blockers increase cerebral cortex and hippocampus blood flow, mitigate NVC dysfunction, and indirectly improve cognitive function by alleviating endothelial injury and inflammatory responses.[86] In addition, calcium channel blockers may confer neuroprotection by inhibiting Ang II-induced activation of NOX, thereby reducing oxidative stress levels.[88,89]

Notably, calcium homeostasis involves multiple cellular components and signaling pathways, including glutamate receptors, transient receptor potential channels, calcium/calmodulin-dependent kinase II, and calcium-regulated gene transcription mechanisms. Therefore, targeting calcium channels alone may be insufficient to completely regulate this complex network. Future research should explore combination therapies that pair calcium channel blockers with agents targeting mitochondrial function, synaptic repair, and inflammation to achieve multi-targeted, synergistic interventions for cognitive impairment.

4.5. Diuretics

Although most clinical trials have primarily assessed diuretics in combination therapies rather than as standalone treatments, these antihypertensive agents have garnered significant attention in the medical community. In the PROGRESS trial, perindopril combined with indapamide significantly reduced dementia risk and slowed cognitive decline among patients with prior stroke or transient ischemic attack over ~3.9 years.[90] In a randomized trial involving 160 elderly hypertensive individuals aged between 61 and 75, the combination of telmisartan and hydrochlorothiazide demonstrated superior reductions in ambulatory blood pressure compared to lisinopril and hydrochlorothiazide and significant enhancement in episodic memory, including word-list memory and recall tasks, as well as visuospatial executive function as measured by Trails B. These improvements were observed consistently at the 12-week and 24-week follow-ups; notably, the combination of lisinopril and hydrochlorothiazide failed to elicit similar cognitive benefits.[91]

Further observational cohort data indicate that the utilization of diuretics can reduce the incidence of Alzheimer's disease and preserve both cognitive and cardiovascular functions, particularly over extended follow-up durations.[29]

To delineate the effects of diuretics on cognition more clearly, future studies should treat diuretics as primary therapy, clarify the biological mechanisms involved (e.g., vascular integrity, amyloid accumulation, oxidative stress, and BBB effects), and establish optimal dosing, duration, and combination strategies.

Table 1 summarizes the antihypertensive drug classes and their mechanisms in cognitive protection.

5. Effects of aerobic exercise on VCI

5.1. Structural remodeling of the brain

Recent large-scale randomized controlled trials and meta-analyses have demonstrated that engaging in moderate-intensity aerobic exercise, performed at 60–75% of maximal oxygen consumption (VO_2max) over a period of 12–24 weeks, not only significantly enhances gray matter volume in the hippocampus and prefrontal cortex but also mitigates age-related cortical atrophy.[92] A meta-analysis published in 2025 reported that long-term moderate-to-high-intensity aerobic training modestly delays the decline in fluid cognitive function and is associated with cortical thickening.[93] Another review further noted that, among patients with Alzheimer's disease, aerobic programs within the 50–75% VO_2max range could suppress hippocampal volume loss.[94] The proposed mechanism involves activating the p-tropomyosin receptor kinase B/p-protein kinase B/C signaling pathway and reducing Aβ and tau phosphorylation.[95] In addition, animal and human studies evidence reveals that aerobic exercise significantly enhances neurogenesis, synaptic plasticity, and white matter integrity, exerting particularly robust effects on the dentate gyrus of the hippocampus, the cerebellum, and the striatum.[96]

5.2. Neurotrophic factors and molecular mechanisms

Aerobic exercise significantly elevates key neurotrophic factors—BDNF, insulin-like growth factor 1 (IGF-1), and VEGF—critical for neuronal survival, synaptic plasticity, and angiogenesis, underpinning its cognitive and neurovascular benefits.[97] A 2025 study, which included both patients diagnosed with Parkinson's disease and healthy control subjects, revealed that prolonged aerobic exercise not only elevated peripheral concentrations of BDNF, IGF-1, and VEGF but also enhanced the expression of other factors associated with the muscle–brain axis, such as glial cell line-derived neurotrophic factor, glycosylphosphatidylinositol-specific phospholipase D1, and sirtuin 3.[98] Further meta-analytical evidence has substantiated the significant elevation in peripheral concentrations of BDNF, IGF-1, and VEGF following moderate-to-high-intensity aerobic training interventions.[99,100] These factors can cross the BBB, supporting neuronal survival and angiogenesis. While acute aerobic exercise may induce transient increases in these neurotrophic factors, sustained intervention is required to maintain cognitive benefits.

Table 1. Antihypertensive drug classes and cognitiveprotection mechanisms

Drug class	Mechanism of action	Evidence
ARBs	Crosses the blood–brain barrier, increases cerebral blood flow, blocks AT1 receptors, stimulates AT2 receptors, and may promote amyloid-β degradation	The MOSES trial showed cognitive benefit with eprosartan;[63] a systematic review indicated superior cognitive protection of ARBs over other antihypertensives[64]
ACEIs	Suppress central renin-angiotensin system activity, reduce oxidative stress and inflammation; enhance acetylcholine release; inhibit substance *P* degradation to reduce amyloid-β accumulation	The HOPE trial reported reduced risk of cognitive impairment with ramipril;[68] the PROGRESS trial showed cognitive benefits of perindopril+indapamide[69]
BBs	Lower sympathetic activity and peripheral blood pressure; centrally acting BBs may delay memory impairment by modulating noradrenergic pathways	Monotherapy associated with reduced cognitive decline in elderly Asian males;[74] central BBs may impair memory in cognitively impaired individuals[79,80]
CCBs	Maintain intracellular calcium homeostasis, alleviate mitochondrial dysfunction, improve regional cerebral blood flow, and reduce oxidative stress by inhibiting nicotinamide adenine dinucleotide phosphate oxidase activation	Nimodipine significantly improved cognition in Alzheimer's disease/vascular dementia patients;[87] animal studies demonstrated improved cerebral blood flow and neuroprotection[86]
Diuretics	Lower blood pressure and cerebrovascular burden; may indirectly enhance cognition by improving water-salt balance	Indapamide+perindopril reduced post-stroke dementia risk;[90] telmisartan/hydrochlorothiazide improved memory and visuospatial function[91]

Abbreviations: AT: Angiotensin; ARBs: Angiotensin II receptor blockers; ACEIs: Angiotensin-converting enzyme inhibitors; BBs: Beta blockers; CCBs: Calcium channel blockers.

Moreover, recent molecular studies suggest that aerobic exercise enhances transcription of *BDNF* and *VEGF* genes through DNA demethylation, while simultaneously downregulating protein phosphatase 1 and DNA methyltransferases, which are known to inhibit memory-related gene expression.[101]

5.3. Improvements in cerebral hemodynamics

An increasing volume of empirical evidence underscores the significant contribution of aerobic exercise to the augmentation of cerebral blood flow. A meta-analysis focusing on older adults in 2023 demonstrated that aerobic training significantly enhanced cerebral blood flow velocity, as assessed through transcranial Doppler ultrasound, with a mean difference of approximately 3.6 cm/s.[96] Similarly, a study conducted in 2024 revealed that regular aerobic exercise not only enhanced cerebral perfusion but also potentially played a role in delaying cognitive decline. Furthermore, an earlier randomized controlled trial from 2019 demonstrated that eight weeks of moderate-intensity aerobic exercise resulted in a 27% increase in cerebral blood flow within the prefrontal cortex and cingulate gyrus, correlating with significant improvements in executive function.[102] Despite some reviews pointing out that the direct link between increased cerebral blood flow and cognitive enhancement is still partially ambiguous, it is generally accepted that enhanced regional perfusion, coupled with elevated neurotrophic factor levels and neuronal activity, exerts a synergistic effect on both neuroprotection and cognitive modulation.[103]

5.4. Regulation of neuroinflammation and oxidative stress

Recent reviews have shown that aerobic exercise can suppress inflammatory pathways, such as activating the NLR family pyrin domain-containing 3 inflammasome, and reducing oxidative stress.[104] These effects are accompanied by increased neuroplasticity mediated by factors such as BDNF, particularly in post-stroke cognitive recovery.[105] This suggests that the benefits of aerobic exercise extend beyond structural remodeling, encompassing anti-inflammatory and antioxidative mechanisms that collectively slow down neurodegenerative processes.[106]

In summary, an increasing volume of empirical evidence underscores the significant role of aerobic exercise in enhancing cognitive function and decelerating the progression of VCI, with underlying mechanisms encompassing the upregulation of neurotrophic factor expression, augmentation of brain structural plasticity, optimization of cerebral blood flow, and modulation of neuroinflammatory and oxidative stress responses.[107] Among hypertensive patients, regular aerobic exercise has been demonstrated to produce clinically significant reductions in blood pressure, with systolic values typically decreasing by approximately 7 mmHg and diastolic values by 6 mmHg, magnitudes associated with substantial decreases in cardiovascular risk. It is estimated that a reduction of every 5 mmHg in systolic pressure can lead to respective declines of 7%, 14%, and 9% in all-cause mortality, stroke mortality, and coronary heart disease mortality.[108]

Experimental studies have demonstrated that 12 weeks of moderate-intensity aerobic training in older male patients with hypertension significantly improved perceptual speed and working memory.[109] Similarly, a three-month aerobic exercise intervention improved hemodynamic abnormalities and enhanced short-term information processing in elderly hypertensive individuals.[110] Overall, aerobic exercise exerted a positive regulatory effect on cognitive function in the aging population, particularly those with cognitive decline.

To maximize the effectiveness of such interventions, current research emphasizes the following practical recommendations. First, appropriate control of exercise intensity and dosage is critical. Moderate-to-high intensity aerobic activity (50–75% VO_2max), performed three to five times per week for 20–60 minutes per session over a minimum of 12 weeks, is widely recommended as a baseline prescription. Evidence suggests that, within tolerable limits, increasing the total exercise volume may yield more pronounced structural and cognitive benefits.[111]

Second, the cognitive benefits of aerobic exercise result from multiple synergistic pathways rather than a single mechanism. Aerobic exercise exerts neuroprotective effects through upregulation of BDNF and IGF-1, volumetric gains in the hippocampus and prefrontal cortex, enhancement of cerebral hemodynamics, and suppression of neuroinflammatory and oxidative stress pathways.

Third, precision-based interventions should account for individual variability. Factors such as patient age, baseline cognitive status, hypertension control, and exercise tolerance should be considered when developing a tailored aerobic exercise regimen. This personalized approach is essential to optimize compliance and intervention outcomes.

6. Discussion

Hypertension is a major modifiable risk factor for VCI. Progressive cognitive decline results from vascular remodeling, white matter injury, BBB dysfunction, oxidative stress, and neuroinflammation, all of which are driven by hypertension.

Although antihypertensive agents, particularly calcium channel blockers, ACEIs, and ATR2 blockers, potentially provide neuroprotective effects extending beyond blood pressure regulation, the existing evidence remains inconclusive due to limited sample sizes, heterogeneous trial designs, and the predominant use of surrogate endpoints.

Lacunar infarction is a central small-vessel phenotype. Nearly half of first-ever cases present with subcortical vascular-type mild cognitive impairment, an early predictor of vascular dementia, underscoring the need for cognitive screening and follow-up in hypertensive patients.[112]

Aerobic exercise improves cerebral blood flow, enhances neurotrophic signaling, supports plasticity, and reduces inflammation. Clinical studies report benefits for executive function and processing speed, though protocols and adherence vary.

Our findings are broadly consistent with Arboix's study,[113] which identified hypertension as a significant determinant of lacunar infarction and vascular dementia. Building on this foundation, the present review incorporates more recent mechanistic evidence—such as vascular remodeling, impaired autoregulation, neurovascular uncoupling, and amyloid pathology—and evaluates antihypertensive drug classes and aerobic exercise. Moving beyond epidemiological associations, our review provides updated insights with direct therapeutic relevance for clinical practice and future research.

This review has limitations at both the evidence and methodological levels. The available studies are heterogeneous in design and quality, often limited by residual confounding, small samples, and surrogate endpoints, with inconsistent findings across populations. As a narrative review, we did not register a formal protocol, restricted inclusion to English-language publications, and performed no quantitative meta-analysis. These factors may introduce bias, and future well-powered randomized controlled trials with standardized cognitive outcomes are needed to strengthen the evidence base.

7. Conclusion

Hypertension is a major driver of VCI. It acts through structural remodeling, functional disruption of the cerebral vasculature, impaired autoregulation, and persistent neuroinflammation. Evidence supports strict blood pressure control and aerobic exercise as practical measures to slow cognitive decline. However, no antihypertensive class has demonstrated clear superiority, and reported differences should be interpreted cautiously. Lacunar infarction and small-vessel disease are early indicators of cognitive risk. Their recognition calls for routine cognitive screening and long-term follow-up in hypertensive patients. Looking ahead, research should prioritize large randomized trials with cognition as the primary endpoint, direct drug-class comparisons, and pragmatic designs that combine pharmacologic and lifestyle interventions. Such efforts are essential to transform mechanistic insights into effective strategies for preventing and managing hypertension-related cognitive decline.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Beyond the blockage: A review of myocardial infarction with non-obstructive coronary arteries

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Citation: Moraboina SL, Junaid M, Kumari K, *et al*. Beyond the blockage: A review of myocardial infarction with non-obstructive coronary arteries. *Brain & Heart*. 2025;3(4):025330045. doi: 10.36922/BH025330045

Received: August 11, 2025

Revised: October 3, 2025

Accepted: October 27, 2025

Published online: November 14, 2025

Abstract

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a syndrome in which patients have clear signs of heart muscle injury but show <50% stenosis on coronary angiography. We recognize it as a distinct condition that demands its own diagnostic and treatment approaches. Recent studies were reviewed to elucidate the pathophysiology, diagnostic criteria, and management strategies for MINOCA. PubMed, Scopus, and Google Scholar were searched for full-text, peer-reviewed articles on MINOCA's pathophysiology and diagnostics. Keywords such as "non-obstructive coronary artery," "ischemic heart diseases," and "myocardial infarction" were used. Following the screening and synthesis of the selected papers, we found that MINOCA can result from ischemic causes—plaque disruption, vasospasm, microvascular dysfunction, spontaneous coronary artery dissection, and coronary embolism—as well as from non-ischemic causes, such as myocarditis and Takotsubo cardiomyopathy. The diagnostic evaluation of MINOCA relies on high-sensitivity troponin assays, coronary angiography, cardiac magnetic resonance (CMR) imaging, optical coherence tomography, and functional testing for vasomotor disorders. There are emerging biomarkers, including microRNAs, copeptin, and soluble suppression of tumorigenicity-2, that help refine the risk assessment. We concluded that MINOCA requires a stepwise diagnostic algorithm and personalized treatment methods tailored to the underlying cause, while advocating for early use of CMR imaging, targeted imaging or functional tests, and long-term follow-up. Future randomized trials are warranted to validate etiology-specific therapies and imaging-guided management strategies.

Keywords: Myocardial infarction; Non-obstructive coronary artery disease; Biomarkers; Heart muscle injury; Coronary vasospasm

1. Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a unique form of acute coronary syndrome (ACS). It does not show significant blockages in the coronary arteries, unlike the classical type of myocardial infarction (MI). Instead, patients show signs of heart muscle injury without major coronary obstruction. MINOCA has many causes, including coronary vasospasm, microvascular dysfunction, plaque disruption, and non-ischemic conditions, such as myocarditis and Takotsubo cardiomyopathy.[1] These diverse causes make both diagnosis and treatment challenging. Advances in imaging and laboratory tests have deepened our understanding of this condition. This review gathers recent literature on the pathophysiology and diagnostic methods of MINOCA. Our goal is to provide clear insights that help clinicians connect the patient's initial presentation with a definitive diagnosis.

2. Literature search and screening methods

This narrative review was conducted by carefully searching the literature to identify studies that explored the underlying mechanisms and diagnostic approaches specific to MINOCA. We primarily searched the PubMed, Scopus, and Google Scholar databases using keywords such as "non-obstructive coronary artery," "ischemic heart diseases," and "myocardial infarction." This strategy ensured that we captured relevant research articles, with a focus on the most recent advancements in the field.

The inclusion criteria were full-text, peer-reviewed articles or review papers that primarily addressed the pathophysiology or diagnostic methods for MINOCA. The articles that did not meet these specifications were excluded. The chosen articles were then meticulously reviewed. We synthesized these findings to produce a detailed narrative that highlights the evolving concepts in diagnosing and understanding MINOCA.

3. Pathophysiology

The pathophysiology of MINOCA is a complex interplay of multiple factors and needs further research. Unlike the classical presentation of obstructive coronary artery disease as a cause of MI, MINOCA presents with similar signs and symptoms, but its coronary angiography shows no obstructive stenosis (usually defined as <50% luminal narrowing).[2,3] This contradiction can be attributed to a variety of underlying mechanisms, including ischemic and non-ischemic factors, that can cause actual myocardial injury. Ischemic causes include plaque disruption, coronary vasospasm, and microvascular dysfunction, whereas non-ischemic causes are myocarditis and Takotsubo cardiomyopathy.[2-4] The underlying mechanisms can be identified using modalities such as cardiac magnetic resonance (CMR) imaging, optical coherence tomography (OCT), and coronary functional testing (Table 1).[3,4]

3.1. Epicardial mechanism (plaque disruption and thrombosis)

The most common ischemic mechanism in MINOCA is plaque disruption, including rupture, erosion, and calcified nodules with thrombus. Plaque disruption is observed in approximately 24–35% of MINOCA patients, particularly those with subclinical atherosclerotic changes that may not be evident on coronary angiography.[5,6] Research on OCT revealed that plaque disruption is frequently accompanied by intracoronary thrombus and closely linked to ischemic findings on CMR imaging (Magnetic resonance imaging [MRI]).[6] In addition, female sex is more often associated with layered plaque or intraplaque hemorrhage, pointing to a sex-related variation in plaque morphology.[7]

3.2. Coronary vasospasm

Coronary vasospasm is defined as a reversible >90% constriction of the epicardial and microvascular coronary vessels, resulting in ischemia.[8] It is primarily attributed to decreased nitric oxide bioavailability due to endothelial dysfunction, inflammatory processes, and oxidative stress, which collectively induce vascular spasm.[9] Another mechanism involves vascular smooth muscle hyperreactivity mediated through the activation of Rho-kinase (ROCK), which can be reversed by fasudil.[10]

3.3. Coronary microvascular dysfunction (CMD)

CMD involves both structural (e.g., arteriolar fibrosis) and functional (e.g., endothelial dysfunction and microvascular spasm) causes. It is one of the major mechanisms of MINOCA and may occur with or without vasospasm.[10]

3.4. Spontaneous coronary artery dissection (SCAD)

SCAD involves the presence of an intramural hemorrhage due to an intimal tear, which ultimately reduces the size of the true lumen by creating a false lumen.[11,12] SCAD most commonly occurs in young women and is often associated with fibromuscular dysplasia as well as pregnancy-related or hormonal changes.[12]

3.5. Coronary embolism and *in situ* thrombosis

Approximately 3% of MINOCA cases are caused by coronary emboli (due to atrial fibrillation or prosthetic valves) and *in situ* thrombosis (due to hypercoagulable states or plaque disruption).[13] According to studies, about 24% of MINOCA patients demonstrate inherited thrombophilia (such as Factor V Leiden and antiphospholipid syndrome).[14]

Table 1. Pathophysiological mechanisms of MINOCA

Category	Mechanism	Key features	Prevalence
Ischemic	Plaque disruption and thrombosis	Rupture/erosion on OCT, intracoronary thrombus, MRI ischemia[5,6]	24–35% of MINOCA cases[5,6]
	Coronary vasospasm	>90% reversible stenosis, endothelial dysfunction, Rho-kinase[8-10]	Variable (up to 20%) [8,9]
	Microvascular dysfunction	Arteriolar fibrosis, endothelial dysfunction, microspasm[10]	Common in women[10]
	Spontaneous coronary artery dissection	Intramural hemorrhage, false lumen, fibromuscular dysplasia[11,12]	5–15%, young females[12]
	Coronary embolism and *in situ* thrombosis	Emboli (AF and valves), hypercoagulable states, inherited thrombophilia[13,14]	~3%[13]
Non-ischemic	Myocarditis	Viral or autoimmune inflammation, mid-wall LGE on CMR imaging[15]	31–33% of MINOCA cases[15]
	Takotsubo cardiomyopathy	Stress trigger, apical ballooning, no LGE on CMR imaging[15]	10–18%[15]
	Other cardiomyopathies	Dilated/hypertrophic patterns, variable LGE[15]	12–15%[15]

Abbreviations: AF: Atrial fibrillation; CMR: Cardiac magnetic resonance; LGE: Late gadolinium enhancement; MINOCA: Myocardial infarction with non-obstructive coronary arteries; MRI: Magnetic resonance imaging; OCT: Optical coherence tomography.

3.6. Non-ischemic causes

The non-ischemic causes of MINOCA include:

- Myocarditis: In a meta-analysis study, it was revealed that myocarditis is the most common non-ischemic cause of MINOCA (31–33% of patients)[15]
- Takotsubo (stress) cardiomyopathy: This represents 10–18% of MINOCA patients according to CMR studies[15]
- Other non-ischemic cardiomyopathies: Another 12–15% of cases include dilated and hypertrophic cardiomyopathies (Table 1).

3.7. Advanced pathophysiological insights in MINOCA

Sex-specific mechanisms exist in MINOCA. There is a higher prevalence of CMD and SCAD in females. In MINOCA, 35% of cases in women <50 years are due to SCAD. On the other hand, CMD is induced by estrogen deficiency and small vessel size.[16] Estrogen exerts a protective effect by increasing endothelial nitric oxide synthase activity, leading to nitric oxide production and vasodilation. Hence, when the estrogen level falls following menopause, a person is more susceptible to CMD and vasospasm.[17] In addition, factors such as gestational diabetes, hypertension in pregnancy, and systemic inflammation are known to increase the risk of CMD in females with MINOCA.[16]

Vasospasm and CMD frequently coexist, sharing overlapping mechanisms. Both conditions are largely driven by endothelial dysfunction and increased vascular smooth muscle tone mediated by ROCK activation.[18]

Several key molecular pathways are implicated in these processes. The nitric oxide/endothelial nitric oxide synthase pathway, which is activated by estrogen, promotes vasodilation. Loss or impairment of this pathway may ultimately result in CMD and spasm. Meanwhile, the ROCK pathway is another critical regulator of vascular tone; it is stimulated by inflammatory factors such as interleukin (IL)-1β and inhibited by fasudil. In addition, inflammatory markers (e.g., IL-1β), angiotensin II, and oxidative stress enhance ROCK signaling and cause endothelial injury in both microvascular and epicardial vessels.

4. Diagnosis of MINOCA

Currently, MINOCA remains a diagnostic challenge, as patients fulfill the criteria of the Fourth Universal Definition of MI but exhibit <50% stenosis on coronary angiography.[19] Unlike obstructive MI, MINOCA represents a provisional diagnostic entity that requires further evaluation to exclude alternative causes and identify the underlying ischemic pathways[20] (Table 2).

4.1. Diagnosis of MI

As discussed earlier, MINOCA adheres to the Fourth Universal Definition of MI. Cardiac troponin measurement, especially high-sensitivity assays, is necessary for detecting myocardial injury. A diagnosis of MI is confirmed by a rise and/or fall in troponin levels, alongside supporting clinical features and electrocardiographic (ECG) findings. However, conditions such as myocarditis and Takotsubo cardiomyopathy must be ruled out, as both can present with elevated troponin levels.[2]

4.2. Coronary angiography

According to angiographic criteria, MINOCA is defined by the absence of obstructive coronary artery disease, typically characterized by <50% stenosis in all major

Table 2. Diagnostic modalities for MINOCA

Test	Timing	Main purpose	Diagnostic hallmark
High-sensitivity troponin	On presentation (+ serial)	Confirm myocardial injury	Rise/fall pattern with supporting ECG[2]
ECG	Immediate	Initial assessment	ST-segment changes (elevation/inversion);[22] lack of reciprocal depression in Takotsubo syndrome[23]
Coronary angiography (+ OCT/IVUS)	Within 24 h	Exclude obstruction, detect plaque/dissection	<50% stenosis; OCT shows plaque disruption[21]
CMR imaging	Day 2–14	Tissue characterization	Subendocardial/transmural LGE (myocardial infarction); mid-wall LGE (myocarditis); apical ballooning (Takotsubo syndrome);[24] reclassification in 68% of cases[25]
Provocative vasoreactivity test	If CMR imaging is non-diagnostic	Diagnose vasospasm	≥90% constriction with symptoms/ECG changes[22]
Guidewire-based CFR/ IMR	If CMD is suspected	Quantify microvascular function	CFR <2.0 or IMR >25[26]

Abbreviations: CFR: Coronary flow reserve; CMD: Coronary microvascular dysfunction; CMR: Cardiac magnetic resonance; ECG: Electrocardiography; IMR: Index of microcirculatory resistance; IVUS: Intravascular ultrasound; LGE: Late gadolinium enhancement; MINOCA: Myocardial infarction with non-obstructive coronary arteries; OCT: Optical coherence tomography.

epicardial vessels.[19] Intravascular imaging techniques, such as OCT and intravascular ultrasound (IVUS), may be used during angiography to identify plaque disruption, dissection, or thrombus that may not be detected on conventional angiography.[21]

4.3. Electrocardiogram

The ECG is a first-line diagnostic tool in the evaluation of MINOCA, but it lacks specificity. Approximately one-third of patients present with ST-segment elevation, which often elicits initial ST-segment elevation MI-directed care. However, this finding alone cannot distinguish MINOCA from other etiologies.[22] Takotsubo syndrome commonly presents with ST-segment elevation and T-wave inversion but typically lacks reciprocal depression, further complicating ECG-based distinctions.[23] Therefore, ECG interpretation must be supplemented with biomarkers and imaging studies.

4.4. CMR imaging

Currently, CMR imaging is considered a mainstay in MINOCA evaluation and is ideally performed within 7–14 days of presentation. It provides detailed tissue characterization that enables differentiation among key etiologies:

- MI, which reveals subendocardial or transmural late gadolinium enhancement (LGE) in a vascular distribution
- myocarditis, which demonstrates mid-wall or epicardial LGE; and
- Takotsubo syndrome, which shows regional wall motion abnormalities (typically apical ballooning) without LGE.[24]

In 2018, Ferreira *et al.*[24] provided expert recommendations for the use of CMR—including the updated Lake Louise Criteria—for identifying inflammatory vs. ischemic myocardial injury in suspected non-ischemic myocarditis. In addition, a 2023 systematic review and meta-analysis by Mileva *et al.*[25] revealed that CMR facilitated a definitive diagnosis in approximately 74% of MINOCA patients, with 68% of initial diagnoses being reclassified following CMR evaluation.

4.5. Functional testing for coronary vasomotor disorders

In patients with unobstructed coronary arteries and no structural abnormalities on CMR, it is essential to assess for epicardial spasm and CMD. Invasive provocative testing using intracoronary acetylcholine or ergonovine administration remains the gold standard for diagnosing vasospasm; this requires the presence of symptoms with ischemic ECG changes and >90% vasoconstriction.[22] CMD can be identified through guidewire-based measurements, defined by a coronary flow reserve of <2.0 or an index of microcirculatory resistance of >25.[26] These conditions are more prevalent in younger women and remain underdiagnosed due to their complexity and limited availability of procedures.[27]

4.6. Differential diagnosis

The differential diagnosis includes myocarditis, Takotsubo cardiomyopathy, pulmonary embolism, and type 2 MI:

- Myocarditis: It is often post-viral and may share similar findings on ECG and troponin levels as MI, but it additionally shows diffuse ST-segment changes and non-ischemic LGE

- Takotsubo syndrome: It often presents after emotional or physical stress, with apical ballooning noted on CMR imaging and typically no LGE[28]
- Pulmonary embolism: It is rare and should be considered in case of unexplained hypoxia, right heart strain, or atypical ECG findings.

4.7. Diagnostic algorithms and pathways

Current guidelines recommend a stepwise diagnostic approach (Figure 1):

(i) Diagnose MI using ECG and troponin levels
(ii) Perform coronary angiography to exclude obstructive disease
(iii) Conduct CMR imaging within 2 weeks
(iv) If CMR imaging is non-diagnostic, proceed with intracoronary imaging (e.g., OCT) and coronary function testing (for vasospasm or CMD) to identify the underlying etiology.[2]

4.8. Emerging biomarkers and molecular tools

Conventional biomarkers such as troponin are sensitive indicators of myocardial injury but do not reliably distinguish ischemic from non-ischemic etiologies in MINOCA. Emerging biomarkers may provide additional diagnostic and prognostic value (Table 3 and Figure 2):

i. Heart-type fatty acid–binding protein: Rapidly released within 1 h after injury and more cardiac-specific than myoglobin, it enables early detection of MI—even when troponin results are negative. In MINOCA, its early release profile may help differentiate ischemic injury from myocarditis.[29]
ii. Growth differentiation factor-15 (GDF-15): As a stress-responsive cytokine elevated in ACS, GDF-15 correlates with prognosis independently of C-reactive protein (CRP) or natriuretic peptides. This marker may be particularly useful in MINOCA, where long-term outcomes are heterogeneous.[29]
iii. MicroRNAs (e.g., miR-1, miR-133a, miR-208a/b, and miR-499a-5p): Detectable within 4 h of MI onset, these microRNAs provide earlier detection than troponin and show high sensitivity and specificity in early ACS. Their ability to differentiate ischemic necrosis from Takotsubo syndrome or myocarditis may improve diagnostic clarity in MINOCA.[29]
iv. Copeptin: Copeptin is a surrogate for vasopressin. When used with troponin, its early rise provides a >99% negative predictive value to rule out MI within 3 h of chest pain onset. In suspected MINOCA, it may help avoid unnecessary prolonged observation when ischemia is less likely.[30]
v. Inflammatory biomarkers (e.g., myeloperoxidase [MPO], matrix metalloproteinase 9 [MMP-9, CRP, IL-6): Novel markers such as MPO and MMP-9 correlate with plaque instability, infarct size, and outcomes in ACS. In MINOCA, their elevation may indicate microvascular inflammation or subtle atherosclerotic activity not evident on angiography.[31]
vi. Soluble suppression of tumorigenicity-2 (ST2): A member of the IL-1 receptor family, soluble ST2 has emerged as a novel prognostic biomarker in acute MI. Its elevation reflects myocardial stress and fibrosis and is independently associated with long-term risks of heart failure and mortality, irrespective of natriuretic peptide or troponin levels. Although ST2's role in MINOCA requires further study, its strong prognostic value in conventional MI suggests potential utility in stratifying risk in MINOCA patients with uncertain long-term outcomes.[32]

Table 3. Emerging biomarkers and molecular tools

Biomarker/Tool	Onset of elevation	Role	Notes
Heart-type fatty acid–binding protein	~1 h post-injury	Early MI detection	More specific than myoglobin[29]
Growth differentiation factor-15	Acute and chronic	Prognostic stress marker	Independent of CRP and natriuretic peptides[29]
MicroRNAs (e.g., miR-1, miR-133a, miR-208a/b, and miR-499a-5p)	1–4 h	Early MI detection; high sensitivity and specificity	Promising for very early ACS diagnosis[29]
Copeptin	0–3 h	Rule out MI (NPV >99% with troponin)	Surrogate for vasopressin[30]
Inflammatory markers (e.g., MPO, MMP-9, CRP, and IL-6)	Acute	Plaque instability and infarct-size predictor	Correlate with infarct size and outcomes in ACS[31]
Soluble ST2	Acute and follow-up	Prognostic fibrosis/stress biomarker	Potential risk stratifier in MI and MINOCA[32]
Circulating endothelial cells (CEC)/ Endothelial progenitor cells (EPC)	Acute and reparative	Markers of vascular injury and repair	CEC↑ indicates injury; EPC↓predicts adverse outcomes[33,34]

Abbreviations: ACS: Acute coronary syndrome; CRP: C-reactive protein; IL-6: Interleukin 6; MI: Myocardial infarction; MINOCA: Myocardial infarction with non-obstructive coronary arteries; MMP-9: Matrix metalloproteinase 9; MPO: Myeloperoxidase; NPV: Negative predictive value; ST2: Suppression of tumorigenicity-2.

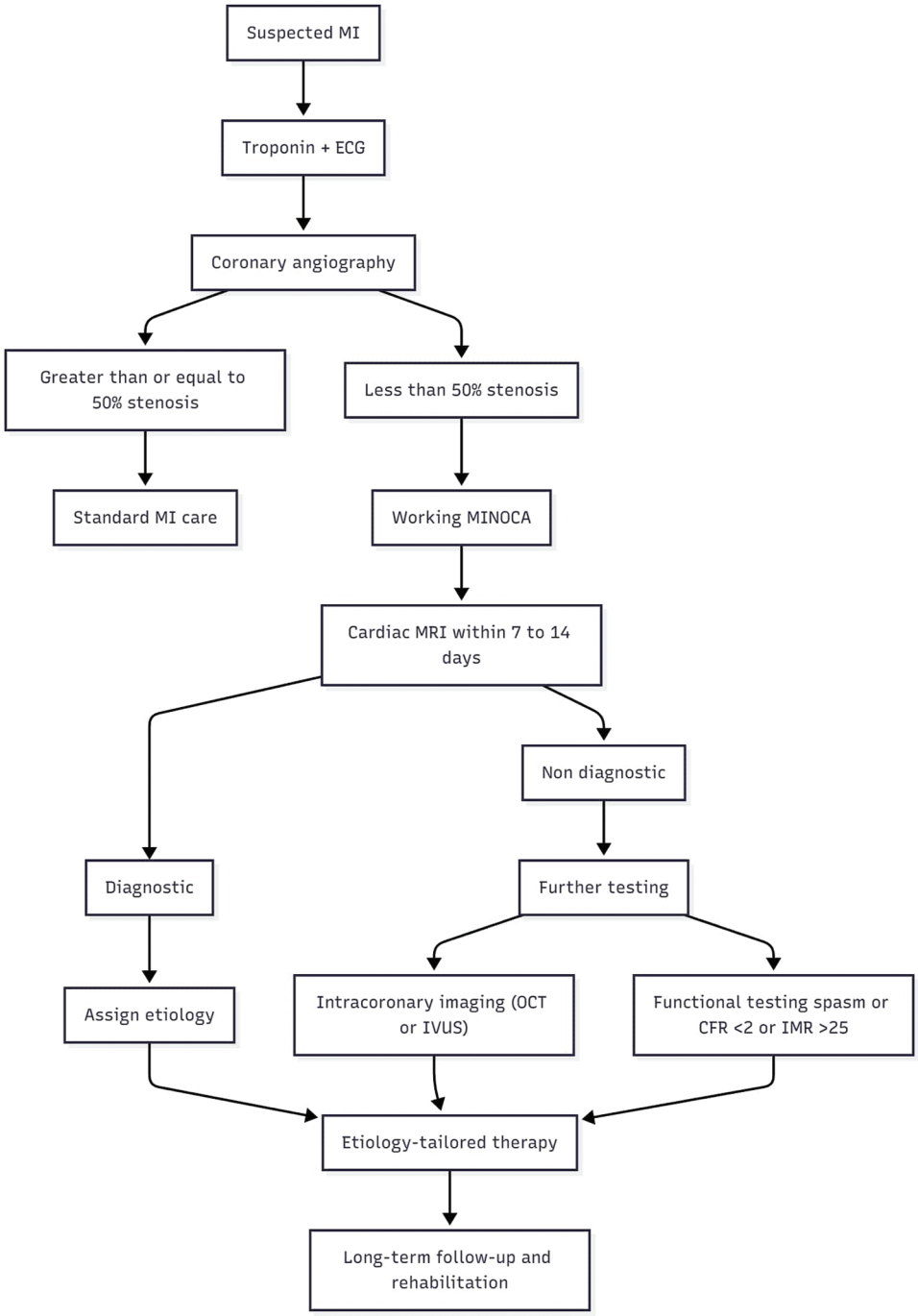

Figure 1. Stepwise diagnostic algorithm for MINOCA evaluation. Image created by the authors.
Abbreviations: CFR: Coronary flow reserve; ECG: Electrocardiography; IMR: Indfex of microcirculatory resistance; IVUS: Intravascular ultrasound; MI: Myocardial infarction; MINOCA: Myocardial infarction with non-obstructive coronary arteries; MRI: Magnetic resonance imaging; OCT: Optical coherence tomography.

vii. Endothelial/Progenitor cells: Circulating endothelial cells, markers of vascular injury, are elevated in acute MI and indicate endothelial disruption.[33] Conversely, endothelial progenitor cells, which participate in vascular repair, are inversely associated with adverse cardiovascular outcomes. In MINOCA, they may indicate microvascular inflammation or subclinical atherosclerotic activity undetectable on angiography[34] (Table 3).

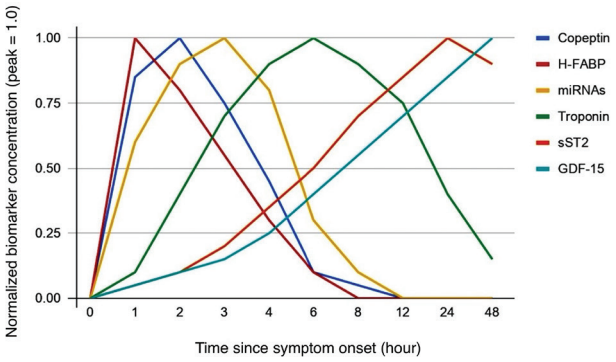

Figure 2. Temporal rise of cardiac biomarkers in MINOCA. Image created by the authors.
Abbreviations: GDF-15: Growth differentiation factor-15; H-FABP: Heart-type fatty acid–binding protein; MINOCA: Myocardial infarction with non-obstructive coronary arteries; sST2: Soluble suppression of tumorigenicity-2.

In summary, a thorough diagnostic approach that includes imaging, intracoronary assessment, and clinical context is essential to uncover the underlying etiology of MINOCA. Early use of CMR imaging, followed by targeted testing when initial investigations are inconclusive, ensures accurate classification and guides appropriate management.

5. Management

The management of MINOCA presents a unique clinical challenge due to its heterogeneous etiologies and distinct pathophysiological mechanisms. Unlike type 1 MI, MINOCA is not a single disease but rather a syndrome requiring accurate diagnostic evaluation before starting treatment. Therefore, standardized treatment protocols are not appropriate. Instead, management should be customized according to the root cause, such as plaque disruption, microvascular dysfunction, coronary spasm, myocarditis, or Takotsubo syndrome. Nevertheless, a comprehensive therapeutic approach is often used in the acute setting while the specific etiology remains unknown.[2,35]

5.1. General medical therapy

Guided by principles of limiting myocardial injury and optimizing secondary prevention, the initial treatment of MINOCA frequently resembles that of type 1 MI until a specific etiology is confirmed. However, the efficacy of this approach remains uncertain and is still a topic of ongoing investigation. Clinicians must strike a balance between early empirical treatment and the need to refine treatment based on diagnostic clarity, as highlighted in recent studies.[36,37]

5.1.1. Aspirin

Aspirin is commonly prescribed for its proven benefit in atherothrombotic episodes and favorable safety profile. Its efficacy in non-atherosclerotic conditions such as myocarditis and vasospasm, however, has not been established.[38,39]

5.1.2. Statins

Statins are recommended for the majority of MINOCA patients, especially when an atherosclerotic component is suspected, owing to their pleiotropic effects, including plaque stabilization, anti-inflammatory action, and endothelial function improvement. A 2022 meta-analysis showed that statin therapy was associated with a notable decrease in all-cause mortality and major adverse cardiovascular events (MACE) in MINOCA cases.[40]

5.1.3. Beta-blockers

Beta-blockers are commonly prescribed post-MINOCA, especially when myocardial stress or ischemia is suspected. A meta-analysis conducted in 2022 found that beta-blocker therapy was associated with a 19% reduction in all-cause mortality (hazard ratio [HR]: 0.81; 95% confidence interval [CI]: 0.66–0.99).[41] However, more reliable and randomized evidence is still pending; the MINOCA-BAT trial is currently underway to evaluate how beta-blockers (and angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARBs]) affect this population's challenging clinical outcomes.[42]

5.1.4. ACEi/ARBs

In MINOCA patients, ACEi and ARBs are recommended. According to the SWEDEHEART registry study, ACEi/ARBs therapy was associated with a 22% reduction in mortality in MINOCA cases.[43] In addition, the Korean registry study reported a lower mortality rate in MINOCA patients who were prescribed ACEi/ARBs on discharge.[44]

5.1.5. Dual antiplatelet therapy (DAPT)

The efficacy of DAPT in MINOCA remains uncertain. A 2025 meta-analysis of seven studies (n = 12,307) showed a non-significant trend of decreased MACE with DAPT (HR: 0.82; 95% CI: 0.66–1.03).[45] Furthermore, registry data revealed that up to 55% of MINOCA patients are prescribed DAPT at discharge, though its clinical benefit remains uncertain.[46]

Recent studies suggest a role for cardioprotective agents, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors, particularly in patients with left ventricular dysfunction following MI or those with cardiometabolic comorbidities. A 2025 meta-analysis demonstrated a 21% reduction in all-cause mortality among patients receiving SGLT2 inhibitors after MI, regardless of the timing of initiation.[47]

5.2. Etiology-specific management

5.2.1. Coronary vasospasm

Calcium-channel blockers, including dihydropyridines and non-dihydropyridines, are considered the first-line therapy to suppress vasospastic episodes.[48,49] Long-acting nitrates are also effective in relieving symptoms, though tolerance and endothelial dysfunction may develop.[50] In refractory cases, alternative agents such as nicorandil, cilostazol, magnesium, and Rho-kinase inhibitors (e.g., fasudil) have demonstrated therapeutic efficacy in small clinical trials.[49,50]

5.2.2. CMD

CMD is managed by improving endothelial function and alleviating ischemia. ACEI/ARBs and statins exhibit a vascular protective effect. Symptomatic relief can be achieved with beta-blockers, calcium channel blockers, and ranolazine, which, although supported by limited evidence, have shown benefits in reducing angina. In addition, other strategies, such as lifestyle modification, stress reduction, and cardiac rehabilitation, are also crucial for long-term symptom control.[27]

5.2.3. Plaque disruption (rupture/erosion)

Standard secondary prevention strategies are recommended for patients with plaque disruption detected on OCT or IVUS. DAPT with aspirin and purinergic receptor type Y, subtype 12 (P2Y12) inhibitor is advised for 12 months.[49] Moreover, high-intensity statins are used for plaque stabilization, while beta-blockers and ACEi are utilized in the presence of left ventricular dysfunction. Despite the absence of significant stenosis, these patients remain at risk for future cardiovascular events.[21]

5.2.4. Takotsubo syndrome

In Takotsubo syndrome, supportive treatment is primarily employed. Acute phase treatment includes beta-blockers, ACEi, and diuretics in the presence of heart failure.[51] Anticoagulation is recommended in cases with apical ballooning or severe left ventricular dysfunction. However, the routine use of antiplatelet agents or statins is discouraged unless there are coexisting cardiovascular risk factors.[52]

5.2.5. SCAD

As the majority of patients with SCAD heal spontaneously, conservative management is preferred for clinically stable patients.[49] In cases of ongoing ischemia or hemodynamic instability, invasive procedures, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting, may be necessary. Beta-blockers may reduce arterial wall stress and lower the risk of recurrence. According to the expert consensus from the American Heart Association, patients who do not undergo PCI or stenting should receive single antiplatelet therapy rather than dual therapy, whereas standard ACS antiplatelet protocols apply when intervention is performed. In addition, screening for fibromuscular dysplasia is advised in all cases.[53] Although pregnancy-associated SCAD is rare, it is a severe condition that presents with worse ACS outcomes compared to SCAD in non-pregnant individuals. The optimal management strategies for pregnancy-associated SCAD remain uncertain, underscoring the need for further research to develop evidence-based management guidelines for this condition.[54]

5.2.6. Myocarditis

Management of myocarditis includes supportive care and guideline-directed therapy. In cases of giant cell or autoimmune myocarditis, immunosuppressive therapy is utilized. Antithrombotic therapy is generally not required unless arrhythmias or thromboembolic complications are present. Exercise should be restricted until clinical remission is achieved, typically for at least one month, with a tailored approach to accelerate recovery[55] (Table 4).

5.3. Key differences in MINOCA management: ESC 2024 versus AHA/ACC 2025 guidelines

The European Society of Cardiology (ESC) 2024 guideline recommends secondary prevention for all MINOCA patients. According to the guideline, therapeutic agents such as aspirin, statins, ACEis, ARBs, and beta-blockers are recommended for most patients unless a specific reason precludes their use. The ESC recommends routine functional testing for conditions such as vasospasm and microvascular problems.[55]

The American Heart Association/American College of Cardiology (AHA/ACC) 2025 guideline recommends MINOCA treatment based on the exact cause. Aspirin and statins are recommended only if MINOCA is caused by plaque disruption or atherosclerosis. ACEis, ARBs, and beta-blockers are recommended based on each patient's condition, such as heart failure and high blood pressure. Advanced imaging techniques, such as CMR imaging and specific tests, are recommended to identify the cause of MINOCA.[56]

The ESC recommends a one-size-fits-all approach to protect all patients, while the AHA/ACC recommends a more individualized strategy, tailoring medicines and diagnostic tests to the patient's specific condition.

5.3.1. Cardiac rehabilitation

Exercise-based cardiac rehabilitation has been shown to significantly improve outcomes in MINOCA patients.

Table 4. Management strategies in MINOCA by etiology

Etiology	First-line therapy	Additional/Alternative options
Plaque disruption	DAPT (12 months), high-intensity statin[21]	β-blocker, ACEi if left ventricular dysfunction[21]
Vasospasm	Calcium-channel blocker[48]	Long-acting nitrate, nicorandil, fasudil[50]
CMD	ACEi/ARB, statin[27]	β-blocker, CCB, ranolazine; [27] lifestyle and rehabilitation
SCAD	Conservative management[53]	β-blocker, antiplatelet; [53] screen for fibromuscular dysplasia
Myocarditis	Supportive care[55]	Immunosuppression (for giant cell/autoimmune myocarditis), avoid antithrombotics if no risk[55]
Takotsubo	Supportive treatment (e.g., β-blocker and ACEi) [52]	Diuretics in cases with heart failure; anticoagulants in cases with severe left ventricular dysfunction[52]
Embolism/thrombosis	Anticoagulant[13]	Investigate for AF, thrombophilia workup[14]

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blockers; CCB: Calcium channel blocker; CMD: Coronary microvascular dysfunction; DAPT: Dual antiplatelet therapy; MINOCA: Myocardial infarction with non-obstructive coronary arteries; SCAD: Spontaneous coronary artery dissection.

In a randomized trial of 524 MINOCA patients assigned to a home-based exercise program group and a control group, the exercise group showed significantly higher physical health scores, along with approximately a 50% reduction in all-cause mortality and a 40% reduction in MACE over a 3-year follow-up, compared with controls.[57] These findings suggest that cardiac rehabilitation improves the quality of life and reduces adverse cardiovascular effects.

5.3.2. Prognosis and long-term follow-up

Previously, MINOCA was regarded as a benign condition, but it is now recognized to be associated with adverse cardiovascular outcomes. The 12-month incidence of MACE varies between 4% and 15%, and recurrent chest pain, rehospitalization, and reinfarction are not uncommon. Female patients constitute the majority of MINOCA cases and often experience a greater symptom burden and higher psychosocial distress. Prognosis is poor in patients with reduced left ventricular ejection fraction, evidence of myocardial damage on CMR imaging, or myocarditis. Thus, individualized risk assessment is crucial for long-term management.[3]

Close follow-up is essential to detect recurrence, optimize secondary prevention, and identify evolving pathology. Repeat CMR imaging or echocardiography may be indicated in patients with initial myocardial damage, persistent symptoms, or unknown etiology. Women, in particular, should receive regular follow-ups due to the increased frequency of angina, psychological stressors, and potential under-treatment. Further management should include risk factor control, adherence monitoring, and screening for anxiety or depression. A multidisciplinary approach is recommended to improve both physical and emotional recovery.[43]

5.4. Gaps in evidence and future directions

There is a growing need for randomized controlled trials specifically targeting MINOCA subtypes, such as vasospasm, microvascular dysfunction, and plaque disruption. Such studies are essential to identify effective therapies and to avoid the application of management plans designed for obstructive MI populations.

The role of advanced imaging also warrants further investigation. While modalities such as intracoronary OCT and CMR imaging have proven valuable for diagnosis, current evidence does not confirm that imaging-guided therapy improves clinical outcomes. Emerging biomarkers represent another promising frontier. Although their clinical utility remains under study, novel biomarkers such as GDF-15, copeptin, and soluble ST2 show promise in improving risk stratification and guiding individualized therapy in MINOCA.[2]

6. Conclusion

As a diverse and clinically relevant syndrome, MINOCA has proven to be a challenge to conventional diagnostic and therapeutic approaches. Multiple mechanisms, such as coronary vasospasm, microvascular dysfunction, and plaque disruption, are involved in its pathophysiology. Accurate diagnosis depends on the integration of advanced imaging techniques, such as CMR imaging and intracoronary OCT, along with thorough clinical assessment.

Management should be individualized based on the underlying etiology. While general medical therapy may benefit many patients, targeted therapies, such as vasodilators for spasm or conservative care in SCAD, are crucial. Outcomes can be further optimized through cardiac rehabilitation, long-term follow-up, and psychosocial support.

Despite extensive research in understanding MINOCA, significant knowledge gaps remain. Therefore, future studies, such as randomized clinical trials, should focus on specific MINOCA subtypes, the impact of imaging-guided therapies, and the clinical utility of emerging biomarkers. Such efforts will advance diagnostic accuracy, refine therapeutic strategies, and ultimately enhance prognosis in this frequently neglected population.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Orthostatic hypotension in clinical practice: Definitions, pathophysiology, outcomes, and future directions

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Abstract

Orthostatic hypotension (OH) is a common but underrecognized disorder defined by an abnormal fall in blood pressure on standing. It reflects impaired autonomic and cardiovascular adaptation to postural change, leading to transient cerebral hypoperfusion. Beyond immediate symptoms such as dizziness and syncope, OH is associated with long-term risks including falls, fractures, cognitive decline, and cardiovascular morbidity. This review synthesizes current evidence on epidemiology, definitions, pathophysiology, diagnostic approaches, management strategies, and future directions. Four phenotypes, including initial, classical, delayed, and delayed recovery, represent a clinical continuum from transient to sustained autonomic failure. Diagnosis relies primarily on the active standing test, with tilt-table and beat-to-beat monitoring enhancing detection of atypical forms. Home and ambulatory blood pressure monitoring provide additional insight into supine hypertension and postprandial patterns. Management prioritizes symptom control and prevention of complications through stepwise strategies: Lifestyle modification, volume and salt expansion, compression therapy, and pharmacological agents such as midodrine, droxidopa, and fludrocortisone. Drug selection and dosing must account for comorbid hypertension and supine hypertension risk. Recent research highlights phenotype-specific prognostic differences and emerging options, including pyridostigmine, atomoxetine, and device-based abdominal compression. Digital phenotyping through home or beat-to-beat monitoring may enable personalized management. The evolving understanding of OH underscores the importance of individualized, evidence-based care aimed at functional improvement and reduction of adverse outcomes rather than strict normalization of blood pressure.

Keywords: Orthostatic hypotension; Supine hypertension; Phenotyping; Tilt-table testing; Digital monitoring

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Citation: Sarıhan A, Kalçık M, Çelik MC, Yetim M, Bekar L, Karavelioğlu Y. Orthostatic hypotension in clinical practice: Definitions, pathophysiology, outcomes, and future directions. *Brain & Heart.* 2025;3(4):025410058. doi: 10.36922/BH025410058

Received: October 7, 2025

Revised: October 29, 2025

Accepted: October 31, 2025

Published online: November 17, 2025

1. Introduction

Orthostatic hypotension (OH) is not merely limited to clinical definitions; it significantly reduces quality of life, leads to traumatic falls, shortens life expectancy, and increases the risk of various health problems, particularly cardiovascular diseases.[1] For these reasons,

the early recognition, comprehensive evaluation, and development of management strategies for OH are of great importance for both clinical practice and public health.

The prevalence of OH in the general population is approximately 5–10%. However, its incidence increases markedly with age; prevalence rises to 20–30% in individuals over 70 years of age, and may reach 40–50% in those aged 85 years and older. Among residents of long-term care facilities, the rates increase to 25–30%, while in those with neurodegenerative disorders such as Parkinson's disease or dementia; prevalence may reach even more striking levels.[2,3]

From a clinical perspective, OH is important not only because it produces symptoms but also due to its long-term effects. Prospective data show that OH increases morbidity due to falls and fractures, predisposes to cognitive decline, and is independently associated with cardiovascular mortality.[4-6]

The presence of hypertension increases the risk of developing OH. Underlying mechanisms include vascular stiffness, autonomic nervous system dysfunction, and the effects of antihypertensive medications.[7] Nevertheless, recent randomized controlled trials have shown that intensive blood pressure treatment does not absolutely increase the frequency of OH, but rather its cardiovascular benefits predominate. Therefore, asymptomatic OH alone does not justify the relaxation of antihypertensive treatment.[5,8]

1.1. Methodology of the review

This narrative review was conducted through a structured search of the PubMed, Scopus, and Google Scholar databases. The search included articles published between 2000 and 2025, using the following keywords and combinations: "orthostatic hypotension," "neurogenic orthostatic hypotension," "supine hypertension," "autonomic dysfunction," "tilt-table test," and "blood pressure variability." Additional references were identified from the bibliographies of relevant reviews and guidelines. Both clinical studies and major consensus statements were included to provide a comprehensive synthesis of definitions, mechanisms, diagnostic methods, and management strategies.

2. Definition and classification

OH is defined as a reduction of ≥20 mmHg in systolic blood pressure (SBP) or ≥10 mmHg in diastolic blood pressure (DBP) within 3 min of standing up from the supine or resting position, or on tilting to an angle of ≥60°. This criterion has long been accepted and is referenced in many current guidelines.[9,10]

However, OH is not restricted to this classical definition; it can be classified into several subtypes based on clinical and pathophysiological characteristics:

- Initial OH: Within the first 15 s of standing, a fall of ≥40 mmHg SBP or ≥20 mmHg DBP occurs, which rapidly recovers. This form is generally transient and characterized by short-lived symptoms, and has been defined particularly in studies using continuous (beat-to-beat) blood pressure recordings.[11] Recent expert consensus has suggested that the term "immediate orthostatic hypotension" may more accurately describe this phenomenon, as the blood pressure drop occurs within the first seconds of standing.[12] This terminology is gaining attention as an alternative to the traditional "initial" term used in earlier literature and guidelines.
- Classical OH: Occurring between 30 s and 3 min after standing, meeting the ≥20/10 mmHg criteria. This is the most common type encountered in clinical practice.[9]
- Delayed OH: Falls in blood pressure that occur beyond 3 min of standing, often considered to represent milder forms of autonomic failure.[9,11]
- Delayed blood pressure recovery: Blood pressure falls after standing but takes longer than 15 s to return to baseline; therefore, stabilization of the fall is delayed.[9]

In addition, OH can be categorized by etiology into two main groups:

- Neurogenic OH: Due to autonomic nervous system dysfunction. Disorders affecting the central or peripheral nervous system (*e.g.*, Parkinson's disease, multiple system atrophy (MSA), autonomic syndromes, diabetic neuropathy) fall into this group.[13]
- Non-neurogenic OH: Secondary to causes such as volume depletion (dehydration, blood loss), cardiac dysfunction, drug effects (diuretics, vasodilators, antihypertensives), or electrolyte disturbances.[9,13]

The definition and classification of OH are clinically relevant, as each subtype may differ in prognostic value, therapeutic approach, and management. The classical form is most commonly encountered, whereas initial and delayed forms are less frequent but may be overlooked, particularly in symptomatic patients. The main phenotypic categories and their diagnostic thresholds are summarized in Table 1.

3. Pathophysiology

OH occurs as a result of inadequate physiological responses to the sudden hemodynamic effects of gravity on standing. Under normal conditions, approximately 300–800 mL of blood pools in the legs and splanchnic region. This

reduces venous return and, consequently, stroke volume; if compensatory mechanisms are insufficient, a marked fall in systemic arterial pressure ensues.[14,15] The main compensatory mechanisms during postural change and the pathophysiologic disturbances responsible for OH are illustrated in Figure 1.

3.1. Normal compensatory mechanisms

In healthy individuals, several simultaneous mechanisms are activated in response to standing:

- Baroreflex response: Baroreceptors in the carotid sinus and aortic arch sense the drop in pressure and, through the medulla oblongata, increase sympathetic activity while reducing parasympathetic tone. As a result, heart rate rises, myocardial contractility increases, and arterial and venous vessels constrict.[2,16]
- Arterial and venous tone: Vasoconstriction of peripheral arterioles supports blood pressure by increasing peripheral resistance, while increased

Table 1. Clinical phenotypes of orthostatic hypotension

Phenotype	Definition/criteria	Clinical relevance	References
Initial OH	≥40 mmHg SBP or ≥20 mmHg DBP fall within first 15 s, rapid recovery	Often transient; beat-to-beat BP monitoring required	11
Classical OH	≥20/10 mmHg fall within 3 min of standing	Most common form in practice	9
Delayed OH	BP fall occurs >3 min after standing	May represent early/mild autonomic dysfunction	9,11
Delayed BP Recovery	BP fall after standing, recovery >15 s	Suggests impaired compensatory kinetics	9

Abbreviations: BP: Blood pressure; DBP: Diastolic blood pressure; OH: Orthostatic hypotension; SBP: Systolic blood pressure.

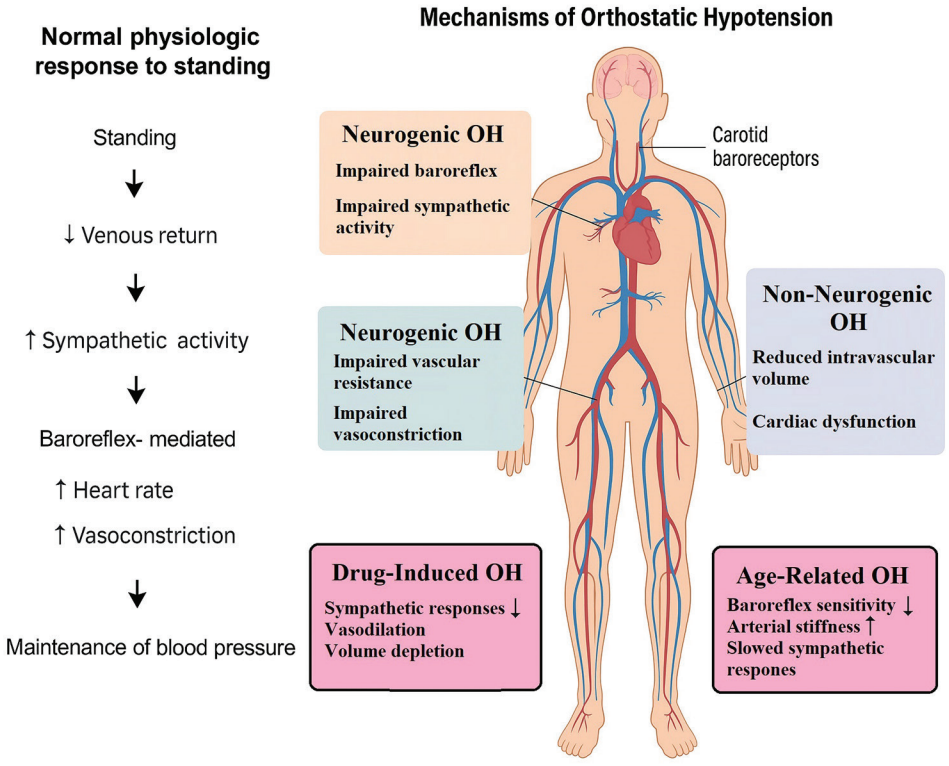

Figure 1. Overview of normal compensatory responses to standing and key pathophysiologic mechanisms, leading to orthostatic hypotension. The left panel illustrates the normal physiological response to standing, in which venous pooling triggers baroreceptor-mediated sympathetic activation, leading to increased heart rate and vasoconstriction that maintain blood pressure. Carotid baroreceptors play a central role in initiating compensatory reflexes. The right panel summarizes the principal mechanisms underlying orthostatic hypotension (OH). Neurogenic OH results from impaired baroreflex function or defective sympathetic vasoconstriction. Non-neurogenic OH arises from reduced intravascular volume or cardiac dysfunction. Drug-induced OH involves attenuation of sympathetic responses, vasodilation, or volume depletion, while age-related OH reflects decreased baroreflex sensitivity, arterial stiffness, and slowed sympathetic responses. Image created by the authors.

venous tone limits pooling. Splanchnic venous capacitance is particularly critical in this regard.[2]

- Hormonal regulation: With prolonged standing, the renin–angiotensin–aldosterone system is activated. Angiotensin II is a potent vasoconstrictor; aldosterone promotes sodium retention to support intravascular volume. Vasopressin (ADH), released from the posterior pituitary, further contributes by promoting water retention.[14]
- Muscle pump: Rhythmic contractions of the calf muscles propel venous blood upward through the deep veins, thereby supporting venous return. This mechanism is absent during prolonged immobility in the upright position, increasing the risk of OH.[14]

3.2. Pathophysiological disturbances

The development of OH reflects inadequacy or impairment of the above compensatory mechanisms:

- Neurogenic OH: Results from autonomic nervous system dysfunction. Parkinson's disease, MSA, pure autonomic failure, and diabetic neuropathy are among the most frequent causes. In this setting, norepinephrine release from sympathetic nerve terminals is reduced, leading to impaired vascular response and insufficient heart rate increase. Clinically, heart rate rises minimally (<10–15 bpm) on standing.[16,17]
- Non-neurogenic OH: Here, the nervous system is intact, but effective circulating volume is reduced. Conditions such as dehydration, blood loss, diuretic therapy, and advanced heart failure fall into this group; compensatory reflexes may remain intact, but the baseline reserve is inadequate.[7]
- Drug-induced OH: Antihypertensives (especially alpha-blockers, diuretics, nitrates), dopaminergic agents, and certain antidepressants may cause OH by suppressing sympathetic responses or inducing vasodilation.[7] Polypharmacy, especially in older adults, further amplifies this effect.
- Age-related changes: With advancing age, baroreflex sensitivity diminishes, arterial stiffness increases, and sympathetic responses are slowed. In addition, venous valve incompetence and a tendency toward venous pooling become more prominent. These changes explain the higher prevalence of OH in elderly populations.[2,18]
- Supine hypertension paradox: Patients with neurogenic OH often exhibit concomitant supine hypertension. The paradox of high blood pressure while supine but marked hypotension on standing complicates diagnosis and therapeutic strategies.[18]

3.3. Special situations

- Postprandial hypotension: Following meals, splanchnic vasodilation and increased blood flow predispose especially elderly and autonomic failure patients to OH.
- Post-exercise hypotension: Abrupt cessation of activity eliminates the muscle pump, thereby exacerbating venous pooling.
- Delayed OH: Slow-onset blood pressure falls occurring after more than 3 min of standing are often an early sign of autonomic dysfunction.[17]

4. Clinical findings

The clinical presentation of OH spans a wide spectrum. The most common manifestations are symptoms of orthostatic intolerance: Dizziness on standing, lightheadedness, unsteadiness, blurred or blackened vision, tinnitus, headache, difficulty concentrating, fatigue, and presyncope.[8,18,19] Symptoms typically develop within a few seconds to a few minutes and resolve rapidly on returning to the supine position.[2,18,19]

In more severe cases, syncope may occur, which is an important risk factor for falls and traumatic fractures, particularly in the elderly.[2,6] OH may also cause acute slowing of cognitive function and confusion; in the long term, recurrent episodes have been associated with dementia and cognitive decline.[6,20]

The severity and onset of symptoms are closely related to provoking factors. Morning hours, postprandial periods (postprandial hypotension), hot environments, abrupt cessation of exercise, alcohol intake, and prolonged motionless standing are the principal triggers that exacerbate OH symptoms.[2,18,21]

In addition to symptoms, certain clinical clues are diagnostically informative. The heart rate response provides insight into the underlying mechanism: in neurogenic OH, despite a drop in blood pressure, the increase in heart rate is minimal (<10–15 bpm), whereas in OH due to volume loss or medications, compensatory tachycardia is more prominent.[8,18,21] On physical examination in the orthostatic position, narrowing of pulse pressure, cool–pale extremities, and unsteady gait may be observed.

A particularly common finding in neurogenic OH is concomitant supine hypertension. In this situation, patients exhibit hypertensive values while supine but develop marked hypotension on standing; this paradox complicates both the symptom profile and therapeutic strategies.[10,19]

5. Diagnostic approach

If there is active clinical suspicion, the first step is the bedside active standing test: After at least 5 min of supine rest, the patient is brought to the standing position, and blood pressure and pulse are measured at the 1st and 3rd min. A fall of ≥20 mmHg SBP or ≥10 mmHg DBP constitutes the diagnostic criterion.[8,15,21]

If the bedside test is normal but clinical features persist, or if initial or delayed forms are suspected, beat-to-beat non-invasive blood pressure monitoring or tilt-table testing is recommended. Tilt testing is particularly used to provoke symptoms and findings and helps distinguish among different orthostatic forms.[8,21,22]

In individuals with hypertension, the diagnostic approach should be supplemented by home blood pressure monitoring or ambulatory blood pressure monitoring (ABPM), as orthostatic variability and patterns such as supine hypertension may only be captured at home or on ambulatory monitoring.[8,23]

The heart rate response is also an important clue during diagnostic evaluation: If the increase in heart rate accompanying the blood pressure fall is <10–15 beats/min, this favors neurogenic OH; larger increases suggest volume loss or non-neurogenic causes.[8,21,23]

In addition, the medication history (particularly diuretics, vasodilators, and antihypertensives) should be reviewed during clinical assessment; if drug effects contribute to orthostatic drops, dose adjustments may be required.[21,23]

Laboratory and basic tests may assist diagnosis: Complete blood count (anemia), electrolytes, renal function, glucose/HbA1c, and thyroid function.[21] If necessary, autonomic function testing (Valsalva maneuver, deep breathing test, quantitative sudomotor axon reflex test, heart rate variability tests) can further characterize autonomic dysfunction.[21,22] A summary of diagnostic modalities, including bedside, tilt, ambulatory, and autonomic function testing, is provided in Table 2.

6. Cardiovascular effects

OH is not merely a cause of symptomatic intolerance; in prospective studies, it has shown significant correlations with cardiovascular events, heart failure, coronary disease, and all-cause mortality.[5,10,24]

In community-based cohort studies, the presence of OH has been associated with increased mortality. For instance, in the meta-analysis by Angelousi *et al.*,[25] overall mortality was 36% higher among individuals with OH (HR ≈ 1.36). This finding suggests that OH may serve as a prognostic marker across diverse populations.

Regarding heart failure, some observational studies have reported a strong association between OH and the incidence of heart failure. Cross-sectional studies have identified OH as a risk factor predicting the development of heart.[26] Moreover, increased risks of coronary artery disease and arrhythmia in association with OH have been observed in various cohort analyses.[10,24]

However, conflicting findings also exist in the literature. For example, a meta-analysis confirmed the association of OH with cardiovascular events but suggested that in subgroups receiving intensive blood pressure lowering, OH did not increase risk.[5] Another study found no significant association between OH and cardiovascular events among individuals on intensive antihypertensive therapy.[24]

A recently published study presented separate analyses of cardiovascular events for initial (within the first 15 s) and sustained forms of OH in individuals aged ≥50 years. This study indicates that risk may differ according to the OH phenotype.[27]

In addition, links have been reported between OH and subclinical atherosclerosis: correlations have been found between the magnitude of postural blood pressure drop and carotid intima–media thickness and plaque burden.[28] This suggests that OH may reflect direct hemodynamic stress and endothelial dysfunction.

Taken together, the presence of OH, particularly when accompanied by advanced age, hypertension, and cardiovascular risk factors, has clinical importance

Table 2. Diagnostic approach in orthostatic hypotension

Step/test	Methodology	Diagnostic value	References
Active standing test	BP and HR at first and third minute after standing	First-line, bedside, high specificity	8,14,20
Tilt-table test	Supine→60–70° tilt; continuous BP/HR monitoring	Differentiates initial/delayed forms	8,20,21
Home/ABPM	24-h or home BP monitoring	Detects supine hypertension, postprandial OH	8,22
Autonomic function tests	Valsalva, HR variability, QSART	Confirms neurogenic OH	20,21

Abbreviations: ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; HR: Heart rate; OH: Orthostatic hypotension; QSART: Quantitative sudomotor axon reflex test.

for long-term follow-up plans and risk stratification. Nevertheless, further prospective, controlled studies are needed to establish the independent prognostic effect of OH.

7. Treatment and management

The treatment of OH primarily aims to relieve symptoms, prevent falls, and enhance functional capacity rather than to normalize blood pressure values. Management begins with identification and correction of reversible factors. Drugs that may worsen OH, such as diuretics, vasodilators, alpha-blockers, and nitrates, should be reduced, discontinued, or substituted when possible. Patients should be assessed for hypovolemia and underlying conditions such as heart failure, adrenal insufficiency, or gastrointestinal fluid loss, and these should be corrected before specific therapy is initiated.[10,29] The stepwise therapeutic framework integrating lifestyle, pharmacologic, and special-case strategies is outlined in Table 3.

Lifestyle and non-pharmacological measures form the cornerstone of management and are recommended for all patients, either alone or in combination with medication. Adequate hydration (2–3 L/day) and liberal salt intake expand plasma volume, while rapid ingestion of 300–500 mL of water can acutely increase blood pressure through the osmopressor reflex. Behavioral strategies such as rising slowly, pausing before standing fully, avoiding hot environments and postprandial standing, and performing physical counter-maneuvers (leg crossing, calf and quadriceps contractions) help mitigate symptoms. Abdominal compression garments reduce venous pooling more effectively than lower-extremity stockings, and elevating the head of the bed by 10–20 cm minimizes nocturnal hypertension. Moderate physical activity and resistance training support venous return and improve orthostatic tolerance.[8,10,15,21]

Pharmacological therapy is reserved for patients with persistent symptoms despite optimal non-drug measures. Treatment must be individualized according to the OH type, comorbidities, and the presence of supine hypertension. Fludrocortisone enhances sodium retention and intravascular volume but carries risks of fluid overload and heart failure. Midodrine, a selective alpha-1 agonist, effectively increases vascular tone and is widely used, particularly in neurogenic OH. Droxidopa, a norepinephrine precursor, augments sympathetic tone and is beneficial in peripheral sympathetic failure. Pyridostigmine, an acetylcholinesterase inhibitor, and atomoxetine, a norepinephrine reuptake inhibitor, may be useful adjuncts, with pyridostigmine offering symptom control without exacerbating supine hypertension.[8,10,13,21,30-34] It should be noted that the availability of some pharmacologic agents discussed (*e.g.*, droxidopa, ampreloxetine) may vary between countries, and therapeutic choices should be adapted according to local drug accessibility and regulatory approval.

Therapeutic strategies should begin with low doses and gradual titration. The coexistence of supine hypertension necessitates short-acting agents and avoidance of late-day dosing. Combination therapy, such as midodrine plus fludrocortisone or adjunctive pyridostigmine, may enhance efficacy. Blood pressure should be monitored in both supine and upright positions, and side effects assessed regularly. In older adults or those with renal dysfunction, fluid and drug adjustments require particular caution.[21,30]

Special considerations include the management of patients with concomitant hypertension, in whom antihypertensive therapy should not be universally withdrawn but rather optimized through timing and agent selection. In inpatient or acute settings, careful fluid administration, gradual postural transitions, and supportive head-up positioning are essential. In neurogenic OH, treatment must balance symptomatic benefit with the risk of supine hypertension, guided by individualized assessment of autonomic dysfunction and medication burden.[10,21,29,30] The principal pharmacologic options, including their mechanisms of action, common starting doses, adverse effects, and levels of evidence, are summarized in Table 4.

8. Future directions

In recent years, research in OH has accelerated along two lines: (i) more refined phenotyping and prognostic

Table 3. Management of orthostatic hypotension

Level	Interventions	Key points	References
Lifestyle & non-pharmacological	↑ Fluid/salt, water bolus, slow rising, counter-maneuvers, compression stockings, head-up sleeping	First-line, universal	8,10,20
Pharmacological	Fludrocortisone, midodrine, droxidopa, pyridostigmine, atomoxetine	Individualized; consider supine HTN	10,20,29-33
Special cases	OH+hypertension; inpatient management; elderly/frail patients	Careful dose adjustment, avoid overtreatment	20,28,29

Abbreviation: OH: Orthostatic hypotension.

Table 4. Pharmacologic management of orthostatic hypotension

Agent	Mechanism of action	Common starting dose	Major side effects	Level of evidence	References
Midodrine	α_1-adrenergic agonist→increases vascular tone	2.5–10 mg orally, 2–3×/day	Supine hypertension, piloerection, scalp tingling	High	8,10,20,29
Fludrocortisone	Mineralocorticoid→sodium and water retention→expands plasma volume	0.05–0.2 mg/day	Edema, hypokalemia, heart failure exacerbation	Moderate	10,20,29
Droxidopa	Synthetic NE precursor→augments sympathetic tone	100–600 mg 3×/day	Headache, hypertension	High	8,10,12,30
Pyridostigmine	Acetylcholinesterase inhibition→enhances ganglionic transmission	30–60 mg 2–3×/day	GI upset, muscle cramps	Moderate	10,20,31,32
Atomoxetine	NE reuptake inhibition→increases sympathetic outflow	18–40 mg/day	Insomnia, tachycardia, anxiety	Low–moderate	32,33

Abbreviations: GI: Gastrointestinal; NE: Norepinephrine.

modeling, and (ii) novel/improved pharmacological and device-based therapies. The line of evidence with direct impact on clinical practice has been a shift toward more precise characterization and more personalized therapeutic strategies through the systematic use of delayed/initial forms, heart rate response-based distinctions, and home/ambulatory monitoring.[8,15]

- Regarding prognostic updates: Throughout the 2020s, evidence has strengthened that classical and delayed OH are long-term risk markers: Major reviews and guidelines emphasize that delayed OH may represent an early/mild phenotype of autonomic dysfunction and may be associated with increased long-term mortality.[10,15] In addition, in an elderly cohort with coronary artery disease, OH was associated with a significant increase in cardiovascular mortality risk, supporting the notion that these phenotypes point not only to symptoms but also to hard outcomes.[35] Nonetheless, recent analyses indicating that OH does not necessarily increase event risk in the context of intensive antihypertensive therapy suggest that aggressive blood pressure control may be safe in appropriately selected patients.[5]
- New evidence and combinations in therapy: From 2023 to 2025, combination approaches have come to the fore: the combination of pyridostigmine + midodrine has shown additive benefit in orthostatic blood pressure reduction compared to monotherapies.[32] Comparative data between midodrine and droxidopa are accumulating; recent syntheses report that midodrine more robustly increases upright SBP but carries a higher risk of supine hypertension, whereas droxidopa appears more neutral in this regard.[31] On the other hand, safety signals regarding midodrine in heart failure with reduced ejection fraction (HfrEF, associations with more hospitalizations and mortality) have been published, necessitating more cautious use in patients with concomitant heart failure.[36]
- Norepinephrine transporter (NET) inhibitors and new molecules: In a recent double-blind, randomized crossover study, atomoxetine did not demonstrate superiority over placebo, limiting the translation of previous encouraging acute effects into routine practice.[33,34] By contrast, Phase 3 programs for ampreloxetine, a long-acting NET inhibitor, in neurogenic OH associated with MSA are ongoing; analyses reported between 2023 and 2025 indicate improvements in composite OH symptom scores, while final efficacy/safety conclusions await completion of ongoing trials.[37]
- Device-based/technological solutions: The hemodynamic efficacy of abdominal compression had been demonstrated in earlier randomized data; in 2024–2025, usability and safety-focused studies of inflatable abdominal binder designs were published. These platforms open a new area in terms of daily wearability and tailoring the effective pressure level to the patient.[38-40] In addition, home/ambulatory and beat-to-beat monitoring technologies facilitate routine detection of phenotypes such as initial OH and delayed recovery, accelerating the transition to the era of "digital phenotyping"; a 2024 American Heart Association statement supports the integration of these monitors into decision-making, particularly in hypertensive adults.[8]
- Personalization and targeted therapy in the near future: The forthcoming focus will be on developing "risk–benefit balanced" strategies that account for phenotype (neurogenic vs. non-neurogenic; initial/classical/delayed), coexisting supine hypertension, and comorbidities (especially HFrEF). Positioning NET inhibitors in selected subgroups (*e.g.*, MSA), testing device–drug combinations (*e.g.*, short-acting midodrine + personalized abdominal compression), and adequately powered prospective studies on long-term outcomes (falls, fractures, cardiovascular events, cognition) represent the greatest unmet needs in the field.[8,31,32,35-41]

Future research priorities should focus on addressing several unresolved questions regarding OH, particularly the delayed subtype. Delayed OH appears to represent an early or partial form of autonomic failure, yet its natural history, clinical trajectory, and potential reversibility remain poorly characterized. Longitudinal studies using continuous or ambulatory blood pressure monitoring could clarify whether delayed OH consistently progresses to classical OH and whether early lifestyle or pharmacological intervention can modify this course.[14]

Biomarker development is another unmet need. Although indices such as heart rate variability, plasma norepinephrine levels, and endothelial stress markers (*e.g.*, EASIX, inflammatory ratios) have shown promise, none have yet been validated for routine clinical use. Future work should aim to establish reproducible, phenotype-specific biomarkers to distinguish neurogenic from non-neurogenic forms and to predict symptom burden, cardiovascular risk, and treatment response. Integration of digital phenotyping and machine learning-based autonomic profiling could further improve predictive accuracy.[42]

Targeted management strategies should be explored in patient subgroups with particularly high unmet needs, such as those with co-existing supine hypertension, neurodegenerative disorders, or frailty. These populations are often excluded from clinical trials but face the greatest risk of adverse outcomes and therapeutic complications. Pragmatic, phenotype-driven studies assessing individualized dosing schedules, device-based compression technologies, and novel sympathomimetic or neuroprotective agents could help refine management algorithms.[10,15]

In summary, the future direction of OH research should move toward longitudinal characterization, biomarker-driven diagnosis, and precision-based therapy, with a focus on vulnerable subgroups and real-world applicability.

9. Conclusion

OH represents a systemic disorder rather than a simple postural fall in blood pressure. Its growing prevalence with aging and its impact on quality of life, morbidity, and cardiovascular outcomes highlight the need for structured screening and individualized management. Accurate diagnosis relies on standardized measurements, particularly the active standing test and, when necessary, tilt-table or beat-to-beat monitoring. Recognition of distinct phenotypes, including initial, classical, delayed, and delayed recovery, is essential, as each carries different prognostic and therapeutic implications.

Pathophysiologically, OH results from disturbances in autonomic, vascular, and hormonal mechanisms that maintain upright perfusion. The coexistence of supine hypertension, especially in neurogenic OH, remains a major therapeutic challenge. In practice, symptom-oriented treatment aimed at improving postural tolerance is prioritized over strict normalization of blood pressure. Non-pharmacological strategies, fluid and salt optimization, behavioral adjustments, compression therapy, and head-up sleeping form the foundation of care. Pharmacological options, including midodrine, droxidopa, and fludrocortisone, should be selected and titrated cautiously, considering comorbidities and the risk of supine hypertension. Adjunctive use of pyridostigmine or atomoxetine may provide additional benefit in selected patients.

Future management should advance toward phenotype-specific and personalized approaches that integrate home or ambulatory monitoring, wearable compression systems, and digital phenotyping. Standardized diagnostic criteria, long-term outcome studies, and pragmatic clinical trials targeting falls, fractures, cardiovascular events, and cognition are critical next steps. Early recognition and evidence-based, individualized therapy remain key to improving functional outcomes and reducing the overall burden of OH.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist in composing and refining the figures. The authors carefully reviewed and edited all AI-generated contents and take full responsibility for the content of the publication.

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ACCSCIENCE PUBLISHING

Brain & Heart

PERSPECTIVE ARTICLE

Combined atrial fibrillation ablation and left atrial appendage closure: Indications and approaches

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(This article belongs to the *Special Issue: Correlation Between Ischemic Heart Disease and Cerebrovascular Disease: The Clinical Practice Messages from the Aosta Meeting in June 2024*)

Abstract

Atrial fibrillation (AF) is associated with an increased burden of cardiovascular complications. Early rhythm control has demonstrated promising benefits in this context. Oral anticoagulation has significantly improved overall survival in AF patients by reducing thromboembolic events. However, several comorbidities are linked to an elevated risk of hemorrhagic complications. Left atrial percutaneous appendage closure (LAPAC) is emerging as a promising therapeutic strategy in this subgroup of patients. Interventional cardiologists are increasingly exploring a combined approach involving simultaneous AF ablation and LAPAC to harness the benefits of both procedures and potentially reduce the length of in-hospital stay. According to current literature, the periprocedural safety of combined procedures appears comparable to that of each procedure performed separately, although it is associated with increased hospitalization costs. Notably, the appropriate anticoagulation/antiaggregant therapy regimen following combined procedures remains a subject of ongoing debate. A minimum of 8 weeks of oral anticoagulation is mandatory following AF ablation, irrespective of the patient's stroke risk or the energy modality used. Conversely, LAPAC should be offered only to patients with contraindications to long-term oral anticoagulation. In the early post-discharge period, no significant differences are observed between combined and isolated procedures. Over long-term follow-up, device thrombosis may occur, with its incidence seemingly unaffected by combined procedures. However, peri-device leaks tend to increase over time in patients undergoing combined procedures, with ridge edema related to radiofrequency delivery considered the primary cause of this phenomenon. New emerging energies (such as pulsed-field ablation) require further evaluation to determine long-term outcomes. According to published position papers, the combined strategy of AF ablation and LAPAC may be a reasonable therapeutic option in selected patients.

Keywords: Atrial fibrillation; Transcatheter ablation; Left atrial appendage closure; Stroke; Anticoagulation

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Citation: Battaglia A, Spinoni E, Scaglione M. Combined atrial fibrillation ablation and left atrial appendage closure: Indications and approaches. *Brain & Heart.* 2025;3(4):025040007. doi: 10.36922/BH025040007

Received: January 23, 2025

1st revised: May 13, 2025

2nd revised: June 2, 2025

Accepted: June 13, 2025

Published online: July 23, 2025

1. Introduction

Atrial fibrillation (AF) is the most common form of supraventricular arrhythmia. The progressive aging of the general population and the increasing survival rates of patients

with advanced cardiomyopathies, due to improvements in pharmacological treatments, will likely lead to an increase in AF prevalence in the coming years. AF is associated with various adverse outcomes. Patients affected by AF face a higher risk of cardiovascular complications, including hospitalization, stroke, and death, as well as a reduced quality of life.[1] Treatment objectives in AF patients are primarily focused on stroke prevention, which is typically achieved through oral anticoagulation therapy, provided that the patient is eligible. Second, managing AF symptoms is essential to mitigate adverse outcomes and enhance quality of life.

2. Rhythm control strategy and the role of percutaneous transcatheter ablation

Rhythm control strategies, which can be implemented using either antiarrhythmic medications or percutaneous ablation techniques, have shown promising benefits, particularly for patients with underlying structural heart disease. Early rhythm-control therapy has been linked to a reduced risk of adverse cardiovascular outcomes in patients with early-stage AF and associated cardiovascular conditions.[2]

Over time, AF percutaneous ablation has become an established and effective method for rhythm control. Technological advancements in electroanatomic mapping systems and energy sources have significantly improved procedural safety and long-term outcomes. However, AF recurrences are still a concern, particularly when triggers are located outside the conventional ablation targets, such as the pulmonary veins. This issue calls for future advancements in ablation techniques to address these recurrences more effectively.

Despite these recurrences, many patients who experience post-ablation arrhythmia show a reduced burden of arrhythmias, with less frequent and shorter episodes of AF. These patients have reported a better quality of life compared to the pre-ablation period. These benefits are expected to extend to other adverse conditions that commonly affect AF patients.[3] According to the most recent European Society of Cardiology (ESC) guidelines, catheter ablation is recommended as a first-line treatment for rhythm control in patients with paroxysmal AF, with a Class I indication. The same level of evidence supports its use in patients with persistent AF who do not respond to antiarrhythmic drug therapy.[4]

AF percutaneous ablation typically involves creating endocardial lesions, usually with radiofrequency energy, to isolate the pulmonary veins – recognized as common triggers of AF – from the left atrial wall. This procedure requires disruption of the endocardium and exposure of the subendothelial tissue. During the healing phase, a thrombotic process occurs at the site of the lesions. To prevent embolic complications, all patients who undergo AF ablation, regardless of the energy source or ablation strategy used, must be treated with therapeutic oral anticoagulation[4] for at least 8 weeks following the procedure, as specified by the latest ESC guidelines.

3. Thromboembolic risk profile and the role of oral anticoagulation

AF is well-known for its association with thromboembolic events, particularly stroke. In the early 1990s, it was demonstrated that administering oral anticoagulation to patients with AF led to prolonged survival. However, this benefit was counterbalanced by an increased risk of hemorrhagic events, which are often seen in patients undergoing oral anticoagulation therapy. Over the years, much debate has focused on the optimal approach to stratifying a patient's stroke risk. Several scoring systems have been proposed by various international medical societies, and different clinical parameters have been introduced and revised, often leading to confusion in interpreting these scores.

The key issue in this debate is the net clinical benefit of anticoagulation therapy, considering both a patient's intrinsic stroke risk and the added risk of bleeding complications. After over 20 years of clinical research, the congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, and sex category (CHA_2DS-VASc) score was adopted in the 2024 ESC guidelines. At present, it is a standard practice for clinicians to calculate the CHA_2DS-VASc score for all AF patients and to initiate oral anticoagulation therapy (Class I indication) for patients with a score of two or higher.[5]

Historically, the burden of AF – specifically the distinction between self-terminating episodes lasting <7 days versus persistent, non-self-terminating episodes – was not considered a stroke risk factor. While AF burden has yet to be included in stroke risk scores, recent guidelines from the American Heart Association have recognized that arrhythmia burden may influence a patient's thromboembolic risk profile. Interestingly, catheter ablation for AF may have a protective effect, reducing the overall thromboembolic risk.[4]

4. Thromboembolic risk profile and the role of left atrial appendage (LAA)

The LAA is a crucial structure in the formation of cardiac thrombus, which can lead to transient ischemic attacks and strokes in patients with AF. The LAA's anatomy can vary significantly between patients, and its morphology – often

described as a long, tubular, and hooked structure with several lobes – plays an important role in thrombus formation. Imaging of the LAA is critical for identifying the presence of thrombi, especially in patients with non-valvular AF.

As mentioned earlier, oral anticoagulation may mitigate thromboembolic risk but increases the likelihood of hemorrhagic complications. In patients with contraindications to long-term oral anticoagulation, LAA closure (LAAC) has emerged as a viable therapeutic alternative. The procedure involves placing a device at the ostium of the LAA to seal off the appendage from the systemic circulation. Over time, the device becomes re-endothelialized, typically within 3 – 6 months after implantation. During this healing period, double antiplatelet therapy is usually required, as these patients are often unable to tolerate oral anticoagulants.

Recent studies have demonstrated that LAA closure is safe and effective in preventing thromboembolic events.[6,7]

According to the latest ESC guidelines, LAAC is recommended (Class IIa, Level B) for patients with moderate-to-high stroke risk who have long-term contraindications to oral anticoagulation. In addition, a lower level of evidence (Class IIb, Level B) suggests that LAAC may be an alternative strategy for patients at high risk of bleeding.[4]

In 2025, Wazni *et al.*[8] reported the findings from the OPTION trial, which enrolled patients with AF and an elevated CHA_2DS-VASc score (≥2 in men and ≥3 in women). All patients underwent catheter ablation and were randomly assigned in a 1:1 ratio to undergo LAA closure after ablation or receive oral anticoagulation. The primary safety endpoint, tested for superiority, was non-procedure-related major bleeding or clinically relevant non-major bleeding. The primary efficacy endpoint, tested for non-inferiority, was a composite of death from any cause, stroke, or systemic embolism at 36 months. A total of 803 patients were assigned to undergo LAA closure, and 797 to receive anticoagulant therapy. At 36 months, the primary safety endpoint event rate was 8.5% in the LAA closure group and 18.1% in the anticoagulation group (p<0.001 for superiority). A primary efficacy endpoint event had occurred in 41 (5.3%) and 44 patients (5.8%), respectively (p<0.001 for non-inferiority). Furthermore, complications related to the appendage closure device or procedure occurred in 23 patients.[8]

5. Combined percutaneous transcatheter ablation and LAA closure: Implications for anticoagulation management

As previously discussed, percutaneous ablation is a valid therapeutic approach for rhythm control in symptomatic AF patients. The benefits of ablation in reducing arrhythmic burden and improving long-term survival, particularly in patients with heart failure, have been well-documented. However, interventional procedures such as ablation carry inherent risks, including periprocedural complications, which are often minimized in high-volume centers.

While percutaneous ablation improves AF symptoms, it does not alter the patient's thromboembolic risk profile or eligibility for oral anticoagulation. Regardless of the success of rhythm control (whether through antiarrhythmic drugs or percutaneous ablation), the decision to administer oral anticoagulation is primarily based on the CHA_2DS_2-VASc score. Importantly, all patients undergoing AF ablation should receive oral anticoagulation therapy for 8 weeks following the procedure, regardless of their thromboembolic risk.

In contrast, LAAC is typically proposed for patients who have contraindications to oral anticoagulation therapy, and during the healing process, double antiplatelet therapy is necessary. When combining these two procedures, choosing the optimal antiplatelet therapy regimen remains a topic of ongoing research. Recent studies have shown that double antiplatelet therapy may carry a similar hemorrhagic risk to novel oral anticoagulants, raising further concerns about its use in the future.

6. Combined percutaneous transcatheter ablation and LAA closure: Concerns on procedural aspects

Interventional cardiologists should carefully consider procedural outcomes and safety when performing combined AF ablation and LAAC. Combined procedures are only justified if they offer clinical benefit without compromising periprocedural safety. Several procedural aspects merit close consideration.[9]

(i) Anesthetic choice: LAAC device deployment is generally guided by transesophageal echocardiography. General anesthesia may be preferable to increase patients' tolerance, notably for transesophageal echocardiography maneuvers. Considering the anesthetic professional shortage in most hospital centers, the need for anesthesia may add a limiting factor, making it difficult for patients to access the procedure. This is also considering that the majority of percutaneous AF ablations are normally performed under conscious sedation.

(ii) Imaging and transseptal access: Transesophageal echocardiography is typically used to guide a lower and more posterior transseptal puncture, which is recommended to optimize alignment of the device delivery to the appendage plane. This tool is normally

used in high-volume centers performing transseptal access without echo guidance.

(iii) Procedural sequencing: According to published data in the vast majority of centers performing combined procedures, pulmonary vein isolation is usually the first step of the procedure. This approach is primarily motivated by the need to freely maneuver ablation catheters without the risk of device entrapment or dislodgement.

(iv) Energy delivery and device sizing: Radiofrequency energy, the predominant modality for AF ablation, induces endothelial disruption and subsequent tissue edema. Closure device measurements are frequently conducted in real time using an appendage angiography from two different fluoroscopic views. Endoluminal area may be underestimated when endothelial edema caused by radiofrequency delivery involves the ridge area. By underestimating device measurements, we should expect an increased post-procedural device leak.

(v) Left atrial dwell time: Periprocedural catheter thrombosis, followed by thromboembolic complications, is typically associated with dwell time in the left atrium. Despite adequate periprocedural anticoagulation, with activated clotting time titrated to >250 s, such complications are rarely observed. Interventional cardiologists focus on faster, safer procedures to minimize left atrial dwell time. Notably, combined procedures tend to increase the dwell time, and how this increase impacts periprocedural outcomes remains a subject of ongoing debate.

7. Outcome, safety, costs, and hospitalization rates of combined procedures

From an interventional point of view, safety and efficacy remain key outcomes when addressing combined procedures. Recent observational studies showed that the length of hospital stay and major adverse cardiovascular events, such as mortality, stroke, and vascular injury, are comparable when AF ablation is combined with left atrial percutaneous appendage closure (LAPAC) on the same day.[10-14]

Moreover, a meta-analysis on the published observational studies by Junarta *et al.*[15] concluded that combined catheter ablation with LAA was associated with similar rates of arrhythmia-free survival, stroke, and major periprocedural complications compared to catheter ablation alone (Table 1).

Notably, a higher incidence of heart block has been observed in combined procedures, a complication not typically seen when these two procedures are performed separately, and no clear rationale has been identified. Not surprisingly, hospital costs are also higher with combined procedures.

Table 1. Observational studies on left atrial appendage closure and atrial fibrillation ablation

Study	Number of patients	Control group present	Ablation energy used	Follow-up (months)
Panikker *et al.*[10]	20	Yes	RF	12
Ismayl *et al.*[11]	919	Yes	Not specified	None
Mo *et al.*[12]	76	Yes	Not specified	24
Yang *et al.*[13]	65	Yes	RF	12
Ren *et al.*[14]	42	Yes	Cryoablation	12

Abbreviation: RF: Radiofrequency.

Hospital readmission within 30 days is a strong indicator of procedural appropriateness and safety. In the United States, the volume of combined procedures increased between 2016 and 2019, and, not surprisingly, the readmission rate decreased over the same period.[16] In particular, the 30-day readmission rates did not differ between combined procedures and when AF ablation or LAPAC were performed separately.

Longer-term follow-up data remain limited in the literature. A 2-year outcome trial from a multinational registry showed a 2.1% incidence of device-related thrombus.[17] At the end of follow-up, 8% of enrolled patients were still on oral anticoagulation. According to the latest guidelines, LAPAC is considered in patients with long-term contraindication to oral anticoagulation therapy.

Radiofrequency delivery for pulmonary vein isolation leads to tissue edema at least in the first phase of the lesion healing process. Edema in the ridge portion can lead to underestimation of appendage dimensions, increasing the long-term incidence of periprocedural leaks – a main concern in combined procedures.[18] This limitation may be overcome by performing appendage occlusion before radiofrequency delivery. Manipulating the ablation catheter near recently positioned devices carries the risk of device displacement. In the available literature, radiofrequency ablation is usually performed before LAPAC.

Recently, new horizons for pulmonary vein isolation based on pulsed field ablation have emerged. The atrial necrotic process of this new type of energy is non-thermal and not fibrosis-driven, which may result in reduced or absent periprocedural edema compared to thermal ablation.

A case report by Guggiotti *et al.*[19] described LAA closure following pulmonary vein isolation using pulsed field

ablation, noting swelling of the left atrial ridge. However, a 27 mm LAAC device was successfully implanted. Single-case series are gradually appearing in the literature, showing no compromise in terms of safety and outcomes.[9]

8. Combined procedures: Criteria for proceeding or deferring

Based on the data presented, several important considerations can be drawn. The decision-making process described by the authors appears strongly influenced by the experience level of the centers and operators involved. In particular, highly trained interventional specialists operating within high-volume, tertiary referral centers – often characterized by multidisciplinary teams and state-of-the-art facilities – are more inclined to opt for combined procedures. This preference is likely driven by their ability to manage complex cases, familiarity with advanced techniques, and availability of adequate infrastructure to ensure patient safety and procedural success. In contrast, operators working in lower-volume centers, where procedural experience is limited and resources may be inadequate or substandard for complex interventions, should exercise caution. In such settings, the decision to perform combined procedures may carry a significantly higher risk and may not be appropriate. These centers should consider referring patients to more experienced institutions or, alternatively, adopt a staged approach when clinically justified. Ultimately, the choice of procedural strategy should be guided by carefully assessing institutional capabilities, operator expertise, and patient-specific factors to ensure optimal outcomes.

Table 2. Recommendations and precautions

Recommendations and precautions	Descriptions
What is recommended?	- Concomitant LAA closure and AF ablation should be considered in a selected cohort of patients with contraindication to oral anticoagulation - Anticoagulation for 8 weeks after ablation, even after concomitant LAA closure
What should be done?	- LAA closure should be carried out after ablation - Careful examination of the LAA dimension before ablation should be accomplished - Consider PFA for PVI
What should be avoided?	- Routinely combine LAA closure and AF ablation

Abbreviations: AF: Atrial fibrillation; LAA: Left atrial appendage; PFA: Pulsed field ablation; PVI: Pulmonary vein isolation.

9. Conclusion

The combination of AF ablation and LAAC presents a promising strategy for managing patients with AF who are at high risk for both arrhythmias and thromboembolic events. While the safety and efficacy of these combined procedures continue to evolve, the growing body of evidence suggests that they offer significant benefits in stroke prevention and symptom control. Continued research is needed to refine these approaches and optimize patient outcomes in the future.[20] Recommendations based on the current evidence and clinical experience are summarized in Table 2.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Early prediction of Alzheimer's disease using machine learning algorithm: A convolutional neural network approach

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(This article belongs to the *Special Issue: The Current and Future Landscape of Alzheimer's Disease Treatment*)

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that severely impacts memory and cognitive functions. Early diagnosis remains crucial for timely intervention and care. This research aims to explore the use of artificial intelligence, specifically deep learning, for the early prediction and classification of AD using structural magnetic resonance imaging (MRI) images. A dataset comprising approximately 44,000 brain MRI images with four diagnostic classes (mild, moderate, severe, and very severe dementia) was used to train and evaluate multiple convolutional neural network (CNN) architectures. Three deep learning models were developed and tested: A custom CNN built from scratch, a spatial-channel convolutional attention network (SCCAN), and a pre-trained Visual Geometry Group VGG16 model using transfer learning. The methodology included extensive preprocessing, data augmentation, normalization, and a train–validation–test split to ensure robust performance. Evaluation metrics such as accuracy, precision, recall, F1-score, and confusion matrices were used to assess classification efficacy. Among the models tested, the Visual Geometry Group VGG16 model achieved the highest classification accuracy, closely followed by the SCCAN, while the custom CNN demonstrated competitive performance with fewer layers. Grad-CAM visualizations were integrated to provide insight into model decision-making, enhancing interpretability. The results confirm the effectiveness of deep learning in classifying early AD stages with high accuracy and support its integration into clinical diagnostic tools. However, the study also identifies limitations, including dataset diversity, class imbalance, and generalizability across diverse populations. Future research should consider using larger, multi-center datasets (including positron emission tomography and electroencephalography modalities). This project demonstrates that deep learning can offer reliable, scalable, and interpretable solutions for the early detection of AD, potentially transforming the diagnostic pathway and enabling earlier therapeutic interventions.

Keywords: Alzheimer's disease; Early detection; Deep learning; Convolutional neural network; Magnetic resonance imaging

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Citation: Hamzat B, Pokhrel S, Ganesan S. Early prediction of Alzheimer's disease using machine learning algorithm: A convolutional neural network approach. *Brain & Heart.* 2025;3(4):025310043. doi: 10.36922/BH025310043

Received: July 28, 2025

1st revised: September 27, 2025

2nd revised: October 1, 2025

Accepted: October 9, 2025

Published online: November 7, 2025

1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia in older adults, affecting roughly 50 million people worldwide, a number expected to triple by 2050, resulting in a major healthcare burden.[1] It is characterized by progressive memory loss, cognitive decline, and behavioral changes that severely impact patients' daily lives.[2] Despite advancements in neuroimaging and biomarker research, AD is often diagnosed at a late stage when substantial and irreversible brain damage has occurred. Early identification of AD, at the mild cognitive impairment stage, is critical for enabling timely interventions that may slow disease progression.

In recent years, artificial intelligence (AI) and machine learning (ML) approaches have shown great impact in detecting AD earlier and more accurately than conventional methods. For example, predictive models incorporating demographic and cognitive test data (without relying on imaging) have achieved encouraging results in identifying individuals at risk of AD.[3] Such approaches illustrate a shift toward more accessible and cost-effective diagnostic processes, potentially enabling earlier detection and intervention. Meanwhile, deep learning models can leverage complex patterns in neuroimaging data to improve diagnostic accuracy.[4] However, many recent techniques, such as transformer-based architectures and multimodal data fusion combining MRI with other biomarkers, require large, well-annotated datasets and often function as "black boxes" with limited interpretability.[5] This lack of transparency can hinder clinical adoption, where understanding the reasoning behind a prediction is important for trust and decision-making.

Compared with the magnetic resonance imaging (MRI) approach, convolutional neural networks (CNNs) offer a more straightforward and computationally efficient approach to AD diagnosis, especially when paired with methods to interpret their decisions.[6] To date, few studies have directly compared custom CNN architectures, advanced attention-based CNN variants, and transfer learning models on a common AD classification task. In this study, we address this gap by systematically evaluating three CNN-based models for multi-class AD stage classification using structural MRI. We assess a simple custom CNN, an attention-enhanced CNN (spatial-channel convolutional attention network [SCCAN]), and a transfer-learning model (VGG16) on the same dataset. We also integrate gradient-weighted class activation mapping (Grad-CAM) to provide visual explanations of model predictions. This work aims to determine whether relatively compact, interpretable CNN models can achieve performance comparable to more complex approaches, and to demonstrate an AI-based framework for early AD detection that is both accurate and explainable. Few works have offered a direct comparative evaluation of multiple CNN architectures (*e.g.*, custom CNN, attention-enhanced CNN, and transfer learning models) on the same multiclass MRI dataset using interpretability tools like Grad-CAM. However, many existing studies focus only on binary classification (*e.g.*, AD vs. healthy), rely on multi-modal inputs that may not be widely accessible, or lack model explainability—all of which are shortcomings associated with reduced clinical trust that the current study attempted to address.

2. Research objective

The primary objective of this research is to design and evaluate three CNN-based architectures for multiclass classification of AD stages using MRI images: a custom CNN, an attention-enhanced SCCAN, and a transfer learning model based on VGG16. The study seeks to compare these models in terms of classification performance, interpretability using Grad-CAM, and deployment feasibility, thereby contributing a practical, scalable, and explainable solution to support early AD diagnosis.

3. Materials and methods

3.1. Dataset and preprocessing

We employed the AD MRI dataset from Kaggle, comprising approximately 44,000 T1-weighted brain MRI images across four diagnostic categories: mild, moderate, severe, and very severe dementia. All images were skull-stripped and provided in JPEG format. The dataset represents an augmented, class-balanced version of an earlier collection, created to address class imbalance by increasing the number of images in underrepresented groups. The distribution included ~12,800 normal, 11,200 very mild, 10,000 mild, and 10,000 moderate AD scans, yielding balanced classes.

Before model training, all MRIs were resized to 128×128 pixels and intensity-normalized to a 0–1 scale. Preprocessing was tailored to each architecture. For the custom CNN and SCCAN models, images remained in grayscale and normalized. For VGG16, grayscale scans were replicated into three channels to form pseudo-RGB inputs, followed by ImageNet mean subtraction to match pretraining requirements.

To enhance generalization and reduce overfitting, training images underwent augmentation, including random flips, rotations, zooms, and slight shifts, generating diverse yet anatomically valid variations. Validation and test sets were not augmented. The dataset was split in a stratified manner, preserving class proportions: 70%

training, 15% validation (for hyperparameter tuning and early stopping), and 15% independent testing for final evaluation. All data were already anonymized and used in accordance with the dataset terms and privacy regulations.

Figures 1 and 2 illustrate the dataset and methodological workflow used in this study. Figure 1 displays the sample brain MRI images from all four classes, showcasing the visual differences the model learns to distinguish. Figure 2 presents the overall workflow of the proposed CNN framework, outlining the sequential stages from data preprocessing, enhancement, and augmentation to model training, evaluation, and deployment through a Streamlit application.

3.2. Deep learning models

We developed and evaluated three CNN-based deep learning models for AD stage classification:

Figure 3 illustrates the CNN-based model development pipeline used in this study. The process began with pre-processed MRI data, followed by model building using three architectures, a custom Model, SCCAN, and VGG16. These models were then complied and trained, after which their performance was evaluated based on various metrics. Finally, the optimal model was selected for deployment based on its accuracy and overall performance.

3.2.1. Custom CNN architecture

The first model is a custom CNN designed from scratch as a baseline for four-class AD classification. The architecture consists of multiple convolutional layers (with ReLU activation) followed by max-pooling layers for progressive spatial downsampling. This feature extractor is followed by fully connected layers that aggregate the learned features for final classification. The network was kept relatively lightweight (fewer layers and parameters) to serve as a baseline. Batch normalization and dropout were employed to stabilize training and prevent overfitting. The final output layer uses softmax activation to produce class probabilities for the four categories.

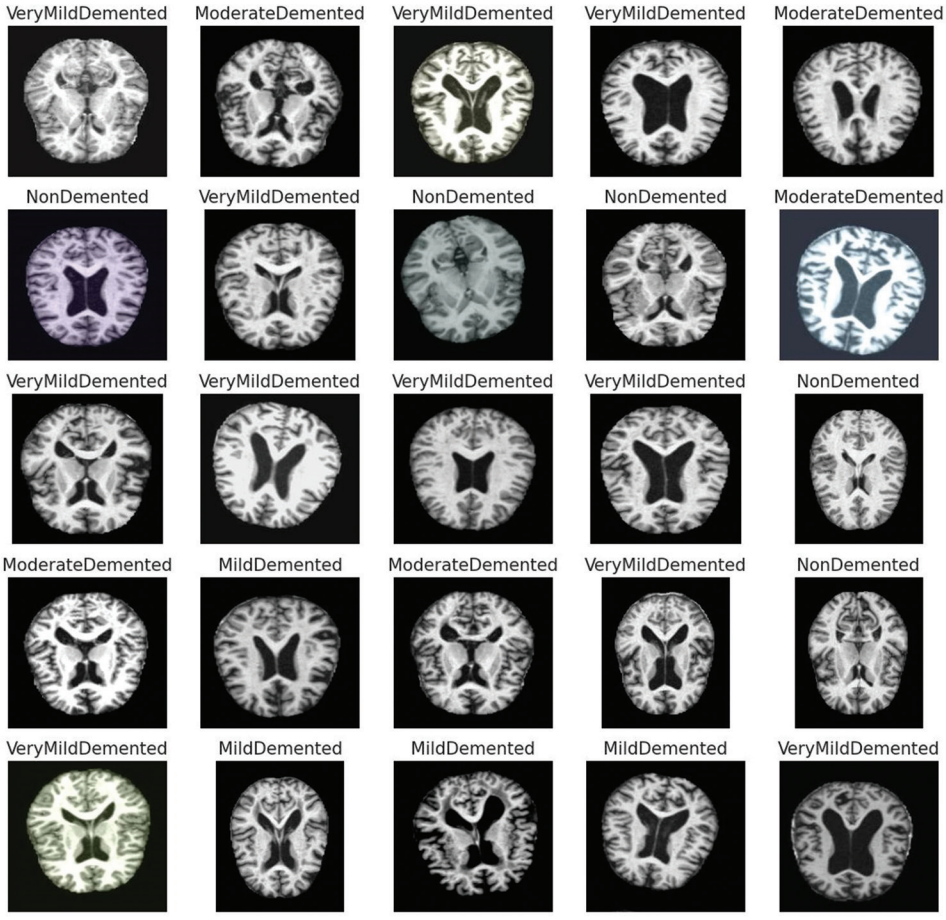

Figure 1. Representative brain MRI images of all classes
Abbreviation: MRI: Magnetic resonance imaging.

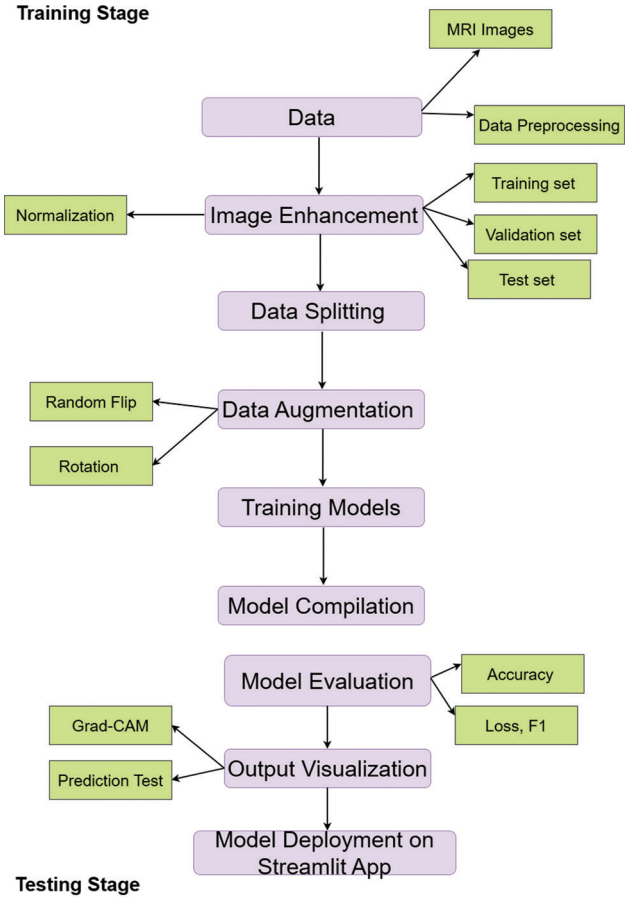

Figure 2. Workflow of the CNN model framework
Abbreviations: CNN: Convolutional neural network; Grad-CAM: Gradient-weighted class activation mapping; MRI: Magnetic resonance imaging.

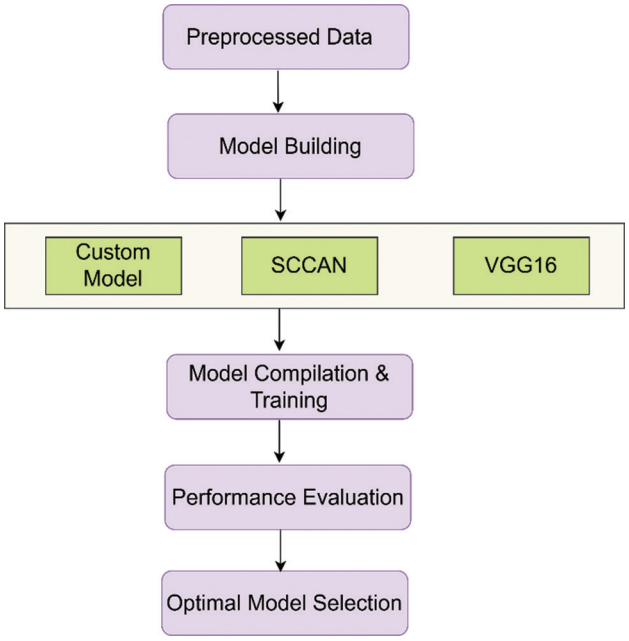

Figure 3. CNN-Based model development pipeline
Abbreviations: CNN: Convolutional neural network; SCCAN: Spatial-channel convolutional attention network.

Figure 4 presents the architecture of the custom CNN for stage classification of AD. The network consists of four convolutional blocks, each with convolution, batch normalization, ReLU activation, and max pooling, enabling hierarchical feature extraction while reducing dimensionality. Filter counts increase progressively (32, 64, 128, 256). A global average pooling layer condenses features into a 256-dimensional vector, followed by a dense layer with dropout for regularization. The final softmax layer outputs probabilities for four AD stages. The model has 457,156 parameters, with 456,196 trainable.

3.2.2. Attention-based CNN (SCCAN)

The second model, termed SCCAN, builds on a CNN architecture by incorporating an attention mechanism to improve feature learning. In this model, convolutional feature maps pass through a channel-attention module inspired by squeeze-and-excitation networks, which adaptively recalibrates feature map importance.[7] This allows the network to emphasize the most informative features (*e.g.*, regions with characteristic AD pathology) while suppressing less relevant information. The SCCAN architecture retains a similar overall structure to the custom CNN but with attention blocks inserted after certain convolutional layers. By explicitly modeling feature importance, SCCAN aims to boost classification performance for subtle early-stage patterns without a substantial increase in model complexity. The final output layer produces class probabilities using softmax.

Figure 5 presents the architecture of the SCCAN model, a lightweight CNN enhanced with channel attention mechanisms for Alzheimer's stage classification. The design adopts a multi-branch structure in which each convolutional block integrates a channel attention module. These modules apply both global average pooling and global max pooling across channels, followed by reshaping and dense layers. The resulting outputs are merged via addition and activation functions to generate attention weights. These weights are then multiplied element-wise with the original feature maps, selectively emphasizing the most informative channels and guiding the model's focus toward discriminative brain regions.

The architecture consists of three convolutional blocks, with filters increasing from 32 to 128. Each block is followed by channel attention, max pooling, and batch normalization. A final global average pooling layer condenses spatial features, which are passed to a fully

Model: "sequential"

Layer (type)	Output Shape	Param #
conv2d (Conv2D)	(None, 224, 224, 32)	896
batch_normalization (BatchNormalization)	(None, 224, 224, 32)	128
re_lu (ReLU)	(None, 224, 224, 32)	0
max_pooling2d (MaxPooling2D)	(None, 112, 112, 32)	0
conv2d_1 (Conv2D)	(None, 112, 112, 64)	18,496
batch_normalization_1 (BatchNormalization)	(None, 112, 112, 64)	256
re_lu_1 (ReLU)	(None, 112, 112, 64)	0
max_pooling2d_1 (MaxPooling2D)	(None, 56, 56, 64)	0
conv2d_2 (Conv2D)	(None, 56, 56, 128)	73,856
batch_normalization_2 (BatchNormalization)	(None, 56, 56, 128)	512
re_lu_2 (ReLU)	(None, 56, 56, 128)	0
max_pooling2d_2 (MaxPooling2D)	(None, 28, 28, 128)	0
conv2d_3 (Conv2D)	(None, 28, 28, 256)	295,168
batch_normalization_3 (BatchNormalization)	(None, 28, 28, 256)	1,024
re_lu_3 (ReLU)	(None, 28, 28, 256)	0
max_pooling2d_3 (MaxPooling2D)	(None, 14, 14, 256)	0
global_average_pooling2d (GlobalAveragePooling2D)	(None, 256)	0
dense (Dense)	(None, 256)	65,792
dropout (Dropout)	(None, 256)	0
dense_1 (Dense)	(None, 4)	1,028

Total params: 457,156 (1.74 MB)
Trainable params: 456,196 (1.74 MB)
Non-trainable params: 960 (3.75 KB)

Figure 4. Sequential custom CNN model layout
Abbreviation: CNN: Convolutional neural network.

connected classifier. Dropout is applied for regularization before the softmax output layer. SCCAN contains 133,824 parameters (133,376 trainable), offering a compact yet expressive design that improves early-stage AD detection.

3.2.3. VGG16 transfer learning model

The third model leverages transfer learning using the VGG16 architecture. VGG16 is a 16-layer deep CNN originally trained on the ImageNet dataset and is known to learn rich, generic visual features.[8] We used the pre-trained VGG16 as a fixed feature extractor: all 13 convolutional layers (organized into five blocks) were initialized with ImageNet weights and frozen during our training. On top of this convolutional base, we added a custom classifier head consisting of a global average pooling layer (to reduce each feature map to a single value), followed by dense layers and a softmax output for the four AD classes. Using transfer learning, this model benefits from low-level and mid-level image features learned from a large natural image corpus, which can improve learning efficiency in our medical imaging task. Only the weights of the added top layers were trained on our MRI data, while the convolutional base remained frozen. This approach typically yields faster convergence and high accuracy even with a relatively limited medical dataset.

Figure 6 illustrates the VGG16-based transfer learning model employed for multiclass AD classification. The base

Layer (type)	Output Shape	Param #	Connected to
input_layer_2 (InputLayer)	(None, 224, 224, 3)	0	-
conv2d_7 (Conv2D)	(None, 224, 224, 32)	896	input_layer_2[0][0]
batch_normalization_7 (BatchNormalization)	(None, 224, 224, 32)	128	conv2d_7[0][0]
max_pooling2d_7 (MaxPooling2D)	(None, 112, 112, 32)	0	batch_normalization_7…
global_average_pooling2d… (GlobalAveragePooling2D)	(None, 32)	0	max_pooling2d_7[0][0]
global_max_pooling2d_3 (GlobalMaxPooling2D)	(None, 32)	0	max_pooling2d_7[0][0]
reshape_6 (Reshape)	(None, 1, 1, 32)	0	global_average_poolin…
reshape_7 (Reshape)	(None, 1, 1, 32)	0	global_max_pooling2d_…
dense_10 (Dense)	(None, 1, 1, 4)	132	reshape_6[0][0], reshape_7[0][0]
dense_11 (Dense)	(None, 1, 1, 32)	160	dense_10[0][0], dense_10[1][0]
add_3 (Add)	(None, 1, 1, 32)	0	dense_11[0][0], dense_11[1][0]
activation_3 (Activation)	(None, 1, 1, 32)	0	add_3[0][0]
multiply_3 (Multiply)	(None, 112, 112, 32)	0	max_pooling2d_7[0][0], activation_3[0][0]
conv2d_8 (Conv2D)	(None, 112, 112, 64)	18,496	multiply_3[0][0]
batch_normalization_8 (BatchNormalization)	(None, 112, 112, 64)	256	conv2d_8[0][0]
max_pooling2d_8 (MaxPooling2D)	(None, 56, 56, 64)	0	batch_normalization_8…
global_average_pooling2d… (GlobalAveragePooling2D)	(None, 64)	0	max_pooling2d_8[0][0]
global_max_pooling2d_4 (GlobalMaxPooling2D)	(None, 64)	0	max_pooling2d_8[0][0]
reshape_8 (Reshape)	(None, 1, 1, 64)	0	global_average_poolin…
reshape_9 (Reshape)	(None, 1, 1, 64)	0	global_max_pooling2d_…
dense_12 (Dense)	(None, 1, 1, 8)	520	reshape_8[0][0], reshape_9[0][0]
dense_13 (Dense)	(None, 1, 1, 64)	576	dense_12[0][0], dense_12[1][0]
add_4 (Add)	(None, 1, 1, 64)	0	dense_13[0][0], dense_13[1][0]
activation_4 (Activation)	(None, 1, 1, 64)	0	add_4[0][0]
multiply_4 (Multiply)	(None, 56, 56, 64)	0	max_pooling2d_8[0][0], activation_4[0][0]
conv2d_9 (Conv2D)	(None, 56, 56, 128)	73,856	multiply_4[0][0]
batch_normalization_9 (BatchNormalization)	(None, 56, 56, 128)	512	conv2d_9[0][0]
max_pooling2d_9 (MaxPooling2D)	(None, 28, 28, 128)	0	batch_normalization_9…
global_average_pooling2d… (GlobalAveragePooling2D)	(None, 128)	0	max_pooling2d_9[0][0]
global_max_pooling2d_5 (GlobalMaxPooling2D)	(None, 128)	0	max_pooling2d_9[0][0]
reshape_10 (Reshape)	(None, 1, 1, 128)	0	global_average_poolin…
reshape_11 (Reshape)	(None, 1, 1, 128)	0	global_max_pooling2d_…
dense_14 (Dense)	(None, 1, 1, 16)	2,064	reshape_10[0][0], reshape_11[0][0]
dense_15 (Dense)	(None, 1, 1, 128)	2,176	dense_14[0][0], dense_14[1][0]
add_5 (Add)	(None, 1, 1, 128)	0	dense_15[0][0], dense_15[1][0]
activation_5 (Activation)	(None, 1, 1, 128)	0	add_5[0][0]
multiply_5 (Multiply)	(None, 28, 28, 128)	0	max_pooling2d_9[0][0], activation_5[0][0]
global_average_pooling2d… (GlobalAveragePooling2D)	(None, 128)	0	multiply_5[0][0]
dense_16 (Dense)	(None, 256)	33,024	global_average_poolin…
dropout_2 (Dropout)	(None, 256)	0	dense_16[0][0]
dense_17 (Dense)	(None, 4)	1,028	dropout_2[0][0]

Figure 5. Sequential SCCAN CNN model layout
Abbreviations: CNN: Convolutional neural network; SCCAN: Spatial-channel convolutional attention network.

network is the pre-trained VGG16, frozen to preserve low- and mid-level features learned from ImageNet,

Layer (type)	Output Shape	Param #
vgg16 (Functional)	(None, 512)	14,714,688
flatten_3 (Flatten)	(None, 512)	0
batch_normalization_19 (BatchNormalization)	(None, 512)	2,048
dense_27 (Dense)	(None, 2048)	1,050,624
batch_normalization_20 (BatchNormalization)	(None, 2048)	8,192
dense_28 (Dense)	(None, 1024)	2,098,176
batch_normalization_21 (BatchNormalization)	(None, 1024)	4,096
dense_29 (Dense)	(None, 4)	4,100

Total params: 17,881,924 (68.21 MB)
Trainable params: 3,160,068 (12.05 MB)
Non-trainable params: 14,721,856 (56.16 MB)

Figure 6. Sequential VGG16 model layout

producing a 512-dimensional feature vector. A custom classification head was added and trained on the AD's MRI dataset.

The classification head begins with flattening, followed by dense layers of 2048 and 1024 neurons, each with batch normalization and ReLU activation to enhance stability and reduce covariate shift. A final Dense (4) layer with softmax activation outputs probabilities across the four stages: mild or no dementia, moderate dementia, severe dementia, and very severe dementia.

The model comprises a total of 17.88 million parameters, with only 3.16 million trainable in the classification head and 14.72 million frozen in the VGG16 backbone. This architecture effectively combines robust pretrained feature extraction with efficient training, achieving strong performance on AD stage classification with limited data.

3.3. Model training and validation

All models were implemented in Python using Keras/TensorFlow. We used the Adam optimizer[9] with an initial learning rate of 0.0001 and categorical cross-entropy as the loss function (appropriate for multi-class classification). Models were trained in mini-batches of size 32. We monitored performance on the validation set at the end of each epoch to guide hyperparameter tuning and apply early stopping. Specifically, training was halted if the validation loss did not improve for a patience of five epochs, and the model state with the lowest validation loss was retained (model checkpointing). The custom CNN and SCCAN models were trained for up to 50 epochs, and the VGG16 model for up to 30 epochs, with early stopping typically occurring earlier based on validation metrics.

Model performance was finally evaluated on the independent test set (15% of the data) that was held out from all training and validation. All metrics are reported on this test set. We report overall accuracy as well as per-class

precision, recall (sensitivity), and F1-score. In addition, we computed confusion matrices for each model's predictions to examine common misclassifications (*e.g.*, whether very mild cases are often mistaken for non-dementia, *etc.*).

3.4. Evaluation metrics

We evaluated model performance using several standard metrics. Accuracy was calculated as the proportion of correctly classified images out of all test images. To provide a more nuanced assessment, we also computed precision, recall (sensitivity), and F1-score for each class. Recall (sensitivity) is the fraction of actual positives (*e.g.*, mild dementia cases) that the model correctly identified, while precision is the fraction of cases predicted as a given class that truly belong to that class. The F1-score is the harmonic mean of precision and recall. We report these metrics for each class and as weighted averages across classes. We also examined confusion matrices for each model, which summarize prediction outcomes for each class. The confusion matrix allows us to see which classes are most often confused by the model (for instance, whether very mild AD images are frequently misclassified as non-dementia or mild dementia). These metrics and analyses provide insight into both overall performance and specific strengths or weaknesses of each model (such as sensitivity to early-stage AD).[10-13]

3.5. Model interpretability with Grad-CAM

To improve interpretability, we employed Grad-CAM to visualize the regions of the MRI that each model considered important for its predictions. For a given test image, Grad-CAM uses the gradients of the target class score flowing into the last convolutional layer to produce a heatmap of "important" pixels.[14] We generated Grad-CAM heatmaps for representative correctly and incorrectly classified examples from each model. These heatmaps were overlaid on the original MRI slices to highlight anatomically relevant regions influencing the model's decision. For instance, in images predicted as very mild dementia, the advanced models' Grad-CAMs often highlighted the medial temporal lobe (including the hippocampus), which aligns with known early pathological changes in AD. In contrast, the custom CNN's attention was more diffuse and sometimes less focused on these regions, which likely contributed to its lower performance. The use of Grad-CAM thus provides a qualitative check on model behavior, ensuring that the CNNs are "looking" at brain regions that make sense clinically. This interpretability is crucial for building trust in the model's predictions and could help clinicians understand and verify AI-driven diagnoses.

4. Results

The performance of the three models on the test set is summarized in Table 1. Overall, the attention-augmented CNN (SCCAN) and the transfer learning model (VGG16) substantially outperformed the baseline custom CNN in all metrics, particularly in sensitivity for early-stage AD. Both advanced models achieved high overall accuracy (~95–96%), whereas the custom CNN achieved about 73% accuracy. In Table 1, we detail the results for each model and examine notable patterns in the confusion matrices.

4.1. Custom CNN performance

The custom CNN baseline attained an overall test accuracy of approximately 72.7%. This model's performance varied considerably by class. It performed well on the more advanced dementia classes but struggled to detect the subtle features of very early-stage AD. For moderate dementia cases, the custom CNN achieved high recall (over 90% of moderate cases were correctly identified). Similarly, for mild dementia cases, it correctly classified about 92% of them. However, the model was less reliable for the non-dementia class, correctly identifying roughly 75% of healthy images while misclassifying the remaining 25% (mostly as very mild dementia). The greatest challenge was observed in the very mild dementia category: only around 32% of very mild dementia cases were correctly detected by the custom CNN. The majority of misclassified very mild cases were predicted to be mild dementia, with a smaller fraction mistaken for non-dementia. This indicates that the subtle brain changes of the earliest AD stage were often missed by the baseline model. In terms of precision, a similar pattern was noted. Precision was high for the more pronounced classes (mild and moderate) but quite low for the very mild class, indicating a high false-positive rate for that category. In summary, the custom model served as a reasonable baseline, performing adequately on clear-cut cases (healthy vs. advanced dementia) but with limited sensitivity to the earliest signs of AD.

Figure 7 shows the model accuracy and loss trend. During training, the custom CNN model showed a steady

Table 1. Comparative evaluation metrics for custom CNN, SCCAN, and VGG16 models

Metric	Custom CNN	SCCAN	VGG16
Accuracy	72.70%	95.72%	95.72%
Test loss	0.85	0.14	0.14
F1 (Avg Weighted)	0.71	0.96	0.96

Abbreviations: Avg Weighted: Average Weighted Score; CNN: Convolutional neural network; F1: F1 Score; SCCAN: Spatial-channel convolutional attention network; VGG: Visual geometry group.

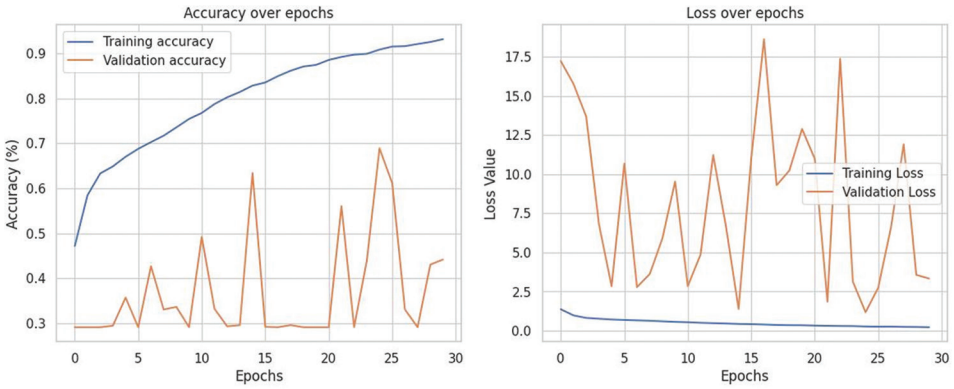

Figure 7. Training and validation accuracy and loss curves for the custom CNN model
Abbreviation: CNN: Convolutional neural network.

increase in training accuracy over 30 epochs, reaching above 90%. However, the validation accuracy fluctuated significantly and remained comparatively low, failing to improve consistently beyond 70%. Similarly, the training loss decreased smoothly, indicating successful learning on the training data, while the validation loss exhibited high volatility with large spikes throughout the epochs. These patterns suggest that the custom CNN model overfits the training data, learning its patterns well but failing to generalize effectively to unseen data.

The confusion matrix illustrates the performance of the custom CNN model in distinguishing between the four dementia classes. As shown in Figure 8, the model demonstrates strong classification accuracy for the moderate AD and mild AD categories, with slightly lower performance in differentiating very mild AD and non-AD cases, likely due to the subtle similarities in their MRI features.

The diagonal values in Table 2 indicate correctly classified instances for each category. The custom CNN model performed well in distinguishing mild AD, moderate AD, and non-AD cases, while higher misclassification occurred in the very mild AD class, which was frequently confused with mild AD and non-AD due to their subtle feature similarities. The highest confusion occurred for very mild AD, which was most often misclassified as mild AD (43%). This indicates the model struggled to differentiate early-stage AD (very mild) from nearby stages, consistent with its lower generalization performance observed in the validation metrics.

Figure 8. Custom CNN confusion matrix
Abbreviation: CNN: Convolutional neural network.

Table 2. Custom CNN confusion matrix (normalized)

Actual/ Predicted	Mild AD	Moderate AD	Non-AD	Very mild AD
Mild AD	**0.9247**	0.0000	0.0633	0.0120
Moderate AD	0.0087	**0.9593**	0.0313	0.0007
Non-AD	0.1703	0.0000	**0.7490**	0.0807
Very mild AD	0.4304	0.0000	0.2518	**0.3179**

Note: The values presented in boldface indicate correctly classified instances for each category.
Abbreviations: AD: Alzheimer's disease; CNN: Convolutional neural network.

4.2. Attention-based CNN (SCCAN) performance

The SCCAN model achieved a test accuracy of 95.7%, a dramatic improvement over the baseline. Incorporating attention mechanisms greatly enhanced the model's ability to distinguish between the four classes, especially for the challenging early stage. The SCCAN exhibited excellent recall across all categories: notably, it correctly identified 100% of mild AD and moderate AD cases in the test set (no misclassifications in those classes). For non-AD images, the recall was about 90%, indicating that only around

10% of healthy brains were falsely labeled as dementia. Crucially, the SCCAN detected approximately 90% of very mild AD cases, significantly higher than the 32% recall of the baseline CNN. Only a small number of very mild cases were missed by SCCAN, some of which were classified as non-AD (reflecting the inherent difficulty of differentiating very early symptoms from normal aging). Precision was also high for all classes (above 0.90 in each category), meaning the model had low false-positive rates. The confusion matrix of SCCAN's predictions (not shown) was nearly diagonal, with minimal confusion between different classes. Overall, the attention-enhanced CNN not only boosted overall accuracy but specifically addressed the weaknesses of the baseline model by focusing on subtle imaging features indicative of early AD.

Figure 9 shows the SCCAN model accuracy and loss trend. The SCCAN model exhibited strong and stable training behavior. Training accuracy increased steadily, reaching over 97% by epoch 10, while training loss consistently declined. In contrast, validation accuracy remained stable around 91%, and validation loss showed minimal improvement, with a slight upward trend. This suggests the model learned effectively on the training data but began to plateau on the validation set, indicating potential early signs of overfitting or limited generalization improvement beyond a certain point.

The diagonal values indicate correctly classified instances for each category. The SCCAN model demonstrated excellent overall performance, achieving perfect classification for mild AD and moderate AD cases. Only minimal misclassification was observed between non-AD and very mild AD, reflecting the close similarity between these adjacent clinical stages.

This high precision and class separation demonstrate SCCAN's robustness, especially in distinguishing early AD stages with clinically meaningful accuracy. Figure 10 shows that the SCCAN model achieved near-perfect classification accuracy across all dementia categories.

4.3. VGG16 transfer learning performance

The VGG16-based model attained the highest accuracy on the test set, at approximately 96.0%. Its performance was essentially on par with the SCCAN model and far above the baseline. In terms of class-wise results, the VGG16 model showed a performance profile very similar to SCCAN. It correctly classified roughly 95–96% of mild and moderate AD cases. For non-AD (healthy) individuals, the model's recall was around 92%, meaning it misclassified only about 8% as AD. Importantly, the VGG16 model correctly identified about 90% of very mild AD cases, indicating that transfer learning from large-scale data can effectively capture early AD patterns in MRI. The few very mild cases that VGG16 missed were typically confused with the mild AD class, which is understandable given the continuum of disease severity. The precision for VGG16 was comparably high across all classes (generally >0.90). These metrics highlight that leveraging a pre-trained CNN (VGG16) yields excellent performance on our AD classification task, comparable to the specialized attention-CNN. The fact that two very different approaches (one introducing attention mechanisms, the other reusing learned features from natural images) achieved similar success is noteworthy. It suggests that both strategies effectively capture the critical MRI features distinguishing each stage of AD.

The VGG16 model demonstrated strong learning dynamics over 15 epochs. Training accuracy improved consistently, reaching approximately 97%, while validation accuracy closely followed, stabilizing around 95% which can be seen in Figure 11. Training and validation loss both declined steadily, with validation loss exhibiting slight fluctuations but maintaining a low final value. These trends

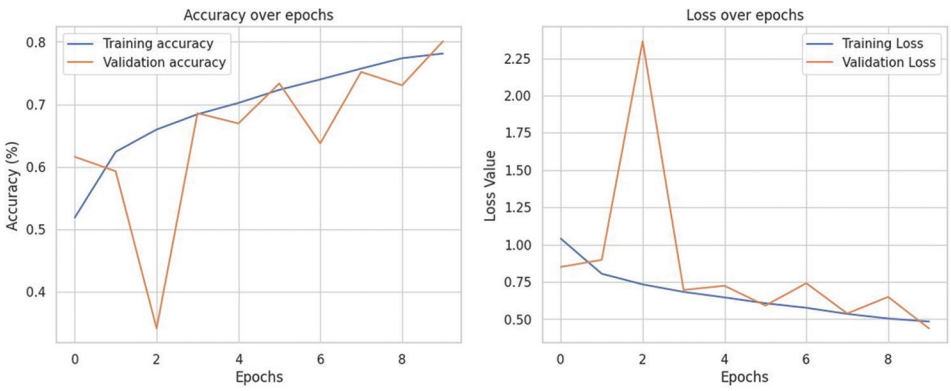

Figure 9. Training and validation accuracy and loss curves for the SCCAN model
Abbreviation: SCCAN: Spatial-channel convolutional attention network.

indicate excellent generalization and minimal overfitting, suggesting the model effectively leveraged transfer learning for robust AD stage classification. Figure 12 shows the VGG16 model confusion matrix.

The diagonal values indicate correctly classified instances for each class. The VGG16 model demonstrated consistently high accuracy across all categories, with most misclassifications occurring between very mild AD and non-AD due to their clinical similarity. Misclassification rates for moderate AD were negligible, highlighting the model's strong confidence and precision.

This confusion matrix in Figure 12 underscores VGG16's robust generalization and fine-grained discrimination, especially for early and intermediate AD stages. The comparative performance of the three CNN-based models is summarized in Tables 2-4. As shown in Table 2, the custom CNN model achieved strong accuracy for moderate AD and mild AD, with minor misclassifications between very mild AD and non-AD. The SCCAN model (Table 3) demonstrated improved performance, attaining perfect classification for mild and moderate AD and 90% accuracy for both non-AD and very mild AD, with minimal overlap between adjacent classes. Meanwhile, the VGG16 model (Table 4) achieved consistently high accuracy across all categories, exceeding 94% in each, and showed near-perfect precision for moderate AD, confirming its robustness and reliability in AD stage classification.

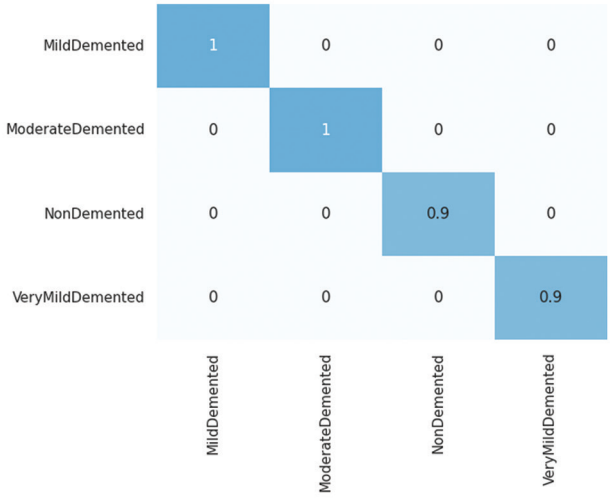

Figure 10. SCCAN Confusion matrix
Abbreviation: SCCAN: Spatial-channel convolutional attention network.

4.4. Model interpretability results

To gain insights into model behavior, we examined Grad-CAM visualizations for the CNN models. Figure 13 shows an example of Grad-CAM output from the VGG16 model for a very mild AD case that was correctly classified. The heatmap (overlaid in red) highlights regions in the temporal lobe, particularly the hippocampal area, indicating that the model concentrated on these regions to make its prediction. This corresponds well with clinical knowledge, as the hippocampus is one of the first regions affected in AD. In general, Grad-CAM results for the VGG16 and SCCAN models revealed that they focus on plausible anatomical regions (hippocampus, entorhinal cortex, ventricles) when identifying AD, even at early stages. The custom CNN's Grad-CAMs were more diffuse and less concentrated in those specific areas, possibly explaining its weaker performance. These interpretability findings build trust in the advanced models: They suggest that the models are not relying on spurious image artifacts but are in fact detecting AD-related structural changes. For clinicians, such visual explanations are valuable; for example, an AI prediction of "very mild AD" comes with

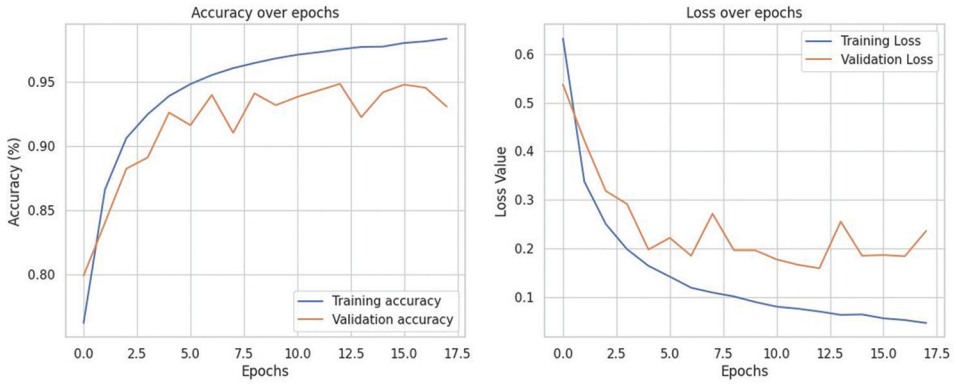

Figure 11. Training and validation accuracy and loss curves for the VGG16 model
Abbreviation: VGG: Visual Geometry Group.

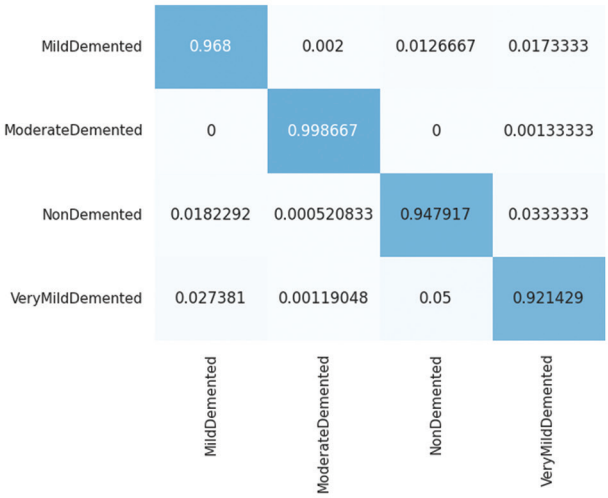

Figure 12. VGG16 Model confusion matrix

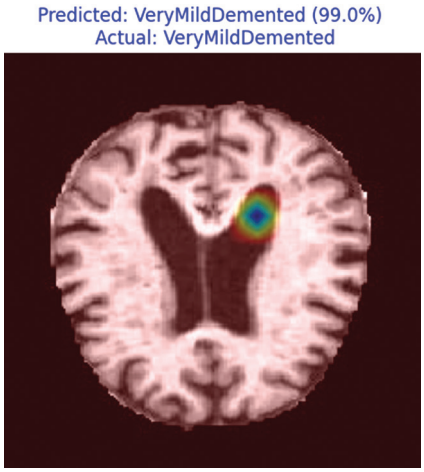

Figure 13. An MRI scan of a very mild AD case with Grad-CAM heatmap overlay highlighting hippocampal regions
Abbreviations: AD: Alzheimer's disease; Grad-CAM: Gradient-weighted class activation mapping; MRI: Magnetic resonance imaging.

a Grad-CAM heatmap highlighting hippocampal atrophy, corroborating the AI's decision and thereby prompting further examination of the scan.

4.5. Model prediction

Figure 13 showcases a grid of MRI test images with predicted classes and corresponding confidence scores, generated using the VGG16 model. Each tile represents a model prediction for a previously unseen MRI image.

The figure illustrates the VGG16 model's high certainty and reliability across most test images, often producing prediction confidence above 95%. Misclassifications are rare and typically occur between adjacent stages, such as very mild AD and non-AD, which is clinically understandable due to overlapping anatomical features. This grid visualization provides intuitive insight into the model's decision-making and confidence distribution across different AD stages.

Table 3. SCCAN Model confusion matrix (normalized)

Actual/ Predicted	Mild AD	Moderate AD	Non-AD	Very mild AD
Mild AD	**1.000**	0.000	0.000	0.000
Moderate AD	0.000	**1.000**	0.000	0.000
Non-AD	0.000	0.000	**0.900**	0.100 (inferred)
Very mild AD	0.000	0.000	0.100 (inferred)	**0.900**

Notes: The SCCAN model achieved perfect classification for both mild and moderate demented classes (100% accuracy). It correctly classified 90% of both non-dementia and very mild dementia cases. There was minimal misclassification, with the only minor confusion occurring between non-demented and very mild demented, two adjacent clinical stages. The values presented in boldface indicate correctly classified instances for each category.
Abbreviations: AD: Alzheimer's disease; SCCAN: Spatial-channel convolutional attention network.

Table 4. VGC16 Model confusion matrix (normalized)

Actual/ Predicted	Mild AD	Moderate AD	Non-AD	Very mild AD
Mild AD	**0.968**	0.002	0.013	0.017
Moderate AD	0.000	**0.999**	0.000	0.001
Non-AD	0.018	0.0005	**0.948**	0.033
Very mild AD	0.027	0.0012	0.050	**0.921**

Notes: The VGG16 model achieved very high classification accuracy across all four classes, with 96.8% for mild AD, 99.9% for moderate AD, 94.8% for non-AD, and 92.1% for very mild AD. The values presented in boldface indicate correctly classified instances for each category.
Abbreviations: AD: Alzheimer's disease; VGG: Visual geometry group.

4.6. Model deployment

To demonstrate real-world applicability, the best-performing model (VGG16) was deployed as an interactive diagnostic tool using Streamlit, a lightweight web framework for ML interfaces.[15] The deployment pipeline allows users such as clinicians or researchers to upload a brain MRI image and receive an instant stage prediction for AD.

The system processes the input through the same preprocessing pipeline used during training and passes it into the fine-tuned VGG16 model. Upon inference, the application returns:

- The predicted AD stage (*e.g.*, moderate AD)
- The model's confidence level (*e.g.*, 100.00% certainty)

- Class-wise confidence scores across all four diagnostic categories.

This is illustrated in Figure 14, which shows an example prediction interface where the uploaded image was classified as "moderate AD" with full confidence. The interface also offers the ability to expand into a Grad-CAM visualization, allowing clinicians to interpret the anatomical regions regarded as the most influential in the prediction. By integrating interpretability and transparency into the interface, the deployment bridges the gap between AI model performance and real-world usability, making it a viable tool for clinical decision support and early AD screening. Figure 15 displays the deployed model's prediction interface, showing the predicted class with corresponding confidence scores for each dementia category.

5. Discussion

This study demonstrated the feasibility and advantages of deep learning for early prediction of AD using MRI data. We showed that both an attention-augmented CNN and a transfer learning approach (VGG16) can achieve high accuracy (~95%) in classifying stages of AD, substantially outperforming a baseline CNN. Notably, these models significantly improved the detection of very mild AD cases, a key result, as early diagnosis is critical for interventions. The custom CNN struggled with this category (detecting only ~32% of very mild cases), whereas both advanced models detected around 90% of them. This finding suggests that more sophisticated CNN approaches can extract subtle features of early AD that a simpler network might miss.

Our results are consistent with recent research applying deep learning to AD classification. For example, other studies using CNNs on structural MRI have reported accuracies in the 85–95% range for distinguishing AD from healthy controls or mild cognitive impairment.[16,17] The ~96% accuracy achieved by our VGG16 and SCCAN models is at the upper end of this range, underscoring the benefit of incorporating either transfer learning or attention mechanisms. Earlier studies applied classical ML methods (*e.g.*, support vector machine [SVM], random forest [RF]) to handcrafted features such as hippocampal atrophy.[3,16] While informative, these approaches required manual feature engineering. A unique contribution of this work is the direct comparison of these two strategies. Interestingly, the attention-based CNN (SCCAN) matched the performance of the much deeper VGG16 network.

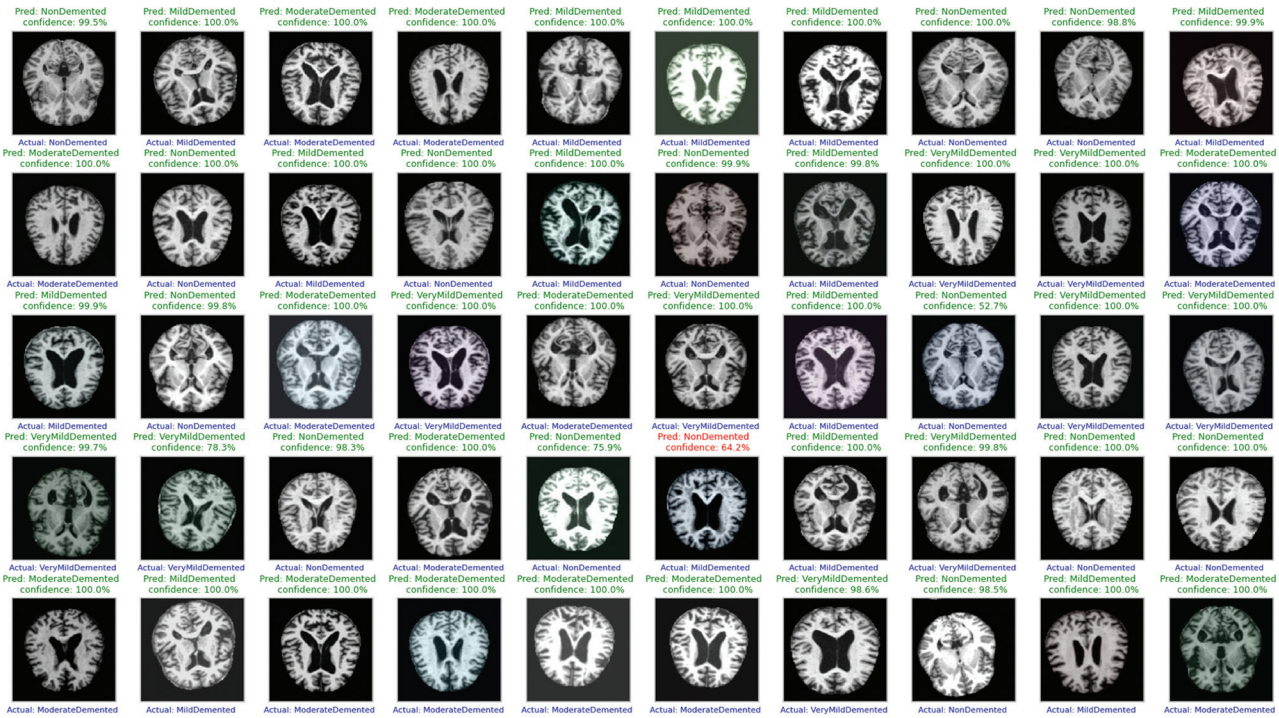

Figure 14. Visual grid of VGG16 model predictions on MRI test images. For each tile, the predicted class label and softmax confidence score are displayed at the top, while the ground truth label appears at the bottom. Correct predictions are marked in standard color, while misclassified instances are highlighted in red.

Abbreviations: MRI: Magnetic resonance imaging; VGG: Visual Geometry Group.

Figure 15. Deployed model prediction interface

Another important aspect of our study is the use of Grad-CAM for model interpretability. In the realm of medical AI, explainability is paramount. The Grad-CAM analysis confirmed that our models "attend" to appropriate brain regions. For instance, when the model flagged a scan as mild or moderate AD, the heatmaps often highlighted widespread cortical atrophy and enlarged ventricles, aligning with advanced AD pathology. For very mild cases, the focus on medial temporal structures (like the hippocampus) mirrors what a radiologist would look for in early AD. Such alignment between model focus and clinical knowledge is reassuring and helps bridge the gap between AI and human experts. Similar approaches to explainable AI in neuroimaging have been proposed by others.[18,19] Over the past decade, ML techniques have been widely adopted for AD prediction. Early efforts employed classical algorithms like SVMs, RFs, and Decision Trees on features extracted from structural MRI or cognitive tests. For instance, one study used hippocampal atrophy patterns in MRI scans to separate AD patients from healthy controls using SVMs.[20] Another example applied ROI based SVM classifiers to identify individuals at risk long before clinical symptoms appeared[21] and our results reinforce the idea that CNNs can be made transparent enough to be used as decision support tools. Clinicians could use these explanations to validate AI suggestions or to discover imaging findings that might be overlooked. And our results reinforce the idea that CNNs can be made transparent enough to be used as decision support tools. Clinicians could use these explanations to validate AI suggestions or to discover imaging findings that might be overlooked.

5.1. Limitations

Despite the promising results, several limitations should be acknowledged. First, our dataset, although large, was sourced entirely from Kaggle.[22] While useful for research, this dataset is skull-stripped and preprocessed, which does not fully reflect the variability, artifacts, and challenges present in real-world clinical MRI scans acquired from different scanners, protocols, or populations.[23] This reliance limits generalizability and clinical applicability. Performance may differ when the models are tested on truly external, multicenter datasets such as ADNI data, and future work should validate and potentially fine-tune the models under such conditions.

Second, our study focused solely on MRI. In practice, AD diagnosis benefits from multimodal data, including positron emission tomography scans, cerebrospinal fluid-based biomarkers, and neurocognitive assessments.[24] Incorporating such modalities into deep learning frameworks could improve diagnostic robustness.

Third, while we employed Grad-CAM for interpretability, this provides only coarse visual explanations. More quantitative approaches, such as SHapley Additive exPlanations (SHAP) could complement these visualizations by offering feature-level importance values, thereby strengthening model interpretability.[25]

Finally, deployment considerations remain. For clinical translation, models must be integrated into workflows, tested in real time, and evaluated for usability by radiologists, including processing speed, reliability, and the clarity of AI-generated explanations.[26] Comparisons with classical ML approaches using hand-crafted features would also help confirm that CNNs provide added value.

5.2. Study implications and future work

The encouraging performance of the deep learning models suggests that AI could be used as a screening or decision support tool for early AD. For instance, in a memory clinic, an AI system could automatically analyze an incoming patient's MRI and flag the likelihood of very mild AD changes, prompting further confirmatory tests or closer monitoring. Because our best models achieved high sensitivity for early-stage AD, such a system could facilitate immediate patient identification and subsequent treatment. Moreover, given the interpretable nature of the models, clinicians would not have to rely on a "black-box" prediction; they could instead examine the Grad-CAM heatmap or other explanations to understand *why* the model indicates early AD.

For future research, a few avenues stand out. Ensemble methods could be explored: combining the outputs of the SCCAN and VGG16 models (and perhaps other models) might yield even more robust performance by leveraging their complementary strengths.[27] Researchers are increasingly adopting hybrid and ensemble machine-learning models to improve early diagnosis of Alzheimer's

disease (AD). Hybrid models combine different types of neural networks or algorithms, such as CNNs with recurrent networks or autoencoders to capture complementary spatial, temporal, and latent features from neuroimaging and multi-modal data. Ensemble methods, which aggregate the outputs of multiple classifiers, further boost robustness and reduce overfitting. Recent reviews highlight the growing evidence that these combined approaches yield superior accuracy and generalizability compared with single-model strategies.[28,29] A recent review highlighted that integrating multiple machine-learning algorithms and heterogeneous data sources can enhance diagnostic accuracy, robustness, and interpretability across medical applications.[30] An ensemble of region-of-interest-based CNN classifiers was shown to improve AD staging from MRI data by leveraging complementary information from different brain regions, achieving higher accuracy than single-model approaches.[31] Another direction is longitudinal modeling using series of MRIs over time to predict progression, not just single-timepoint classification. Some recent works have used recurrent networks or transformers for longitudinal AD prediction,[21] and integrating that with our approach could predict not only the current stage but also future decline. In addition, as mentioned, incorporating additional data types (genetic information, cognitive tests, etc.) in a multi-modal network could mirror the multi-faceted approach clinician's use and potentially improve accuracy further.

Finally, we plan to conduct a reader study where radiologists use the AI system in a simulated workflow to assess the extent of improvement in diagnostic sensitivity and confidence for early AD detection and to gather feedback on the usefulness of the explanations provided. Future research could build upon recent advances in deep learning-based Alzheimer's diagnosis frameworks, including interpretability-aware modeling, hybrid CNN–ML approaches, and attention-enhanced architectures that have demonstrated promising performance in MRI-based classification tasks.[8,16-19,21,32,33] This suggests that integrating task-specific attention to a custom model can provide similar benefits to leveraging a large pre-trained model, at least for our dataset. In practical terms, the SCCAN model, being smaller, might be more efficient to deploy, while the VGG16 model, with its transfer-learned features, provides a proven architecture that might generalize well if fine-tuned further.[34,35]

6. Conclusion

We have demonstrated that deep learning models, particularly a transfer-learned CNN (VGG16) and an attention-augmented CNN (SCCAN), can accurately classify the stages of AD from MRI scans. Both approaches greatly outperformed a baseline CNN, especially in detecting very mild dementia cases, which are crucial for early intervention. Moreover, by utilizing Grad-CAM visualizations, we ensured that our models' predictions are accompanied by human-interpretable explanations, highlighting relevant neuroanatomical regions. This combination of high accuracy and explainability is essential for clinical adoption of AI systems.

The findings of this study contribute to the growing evidence that AI can assist in the early diagnosis of AD. Importantly, our work underscores that model interpretability should go hand in hand with performance in medical AI applications. By addressing both aspects, we move closer to developing AI tools that clinicians can trust and effectively incorporate into patient care. Early detection enabled by such tools can open the door to timely therapeutic interventions, better care planning, and improved patient outcomes in AD.

Acknowledgments

We acknowledge the use of generative AI tools in certain parts of this work, specifically for improving the clarity and flow of the paper. However, all aspects of the research design, original ideas, dataset selection, ML methodologies, implementation, analysis, and all core contributions are solely our own. We would also like to thank York St John University, particularly the Computer Science and Data Science Department, for their continued encouragement and the opportunities provided throughout the course of this research.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

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Writing–original draft: Babatunde Hamzat
Writing–review & editing: Sangita Pokhrel

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Dataset will be available on request to the corresponding author. This research utilized a public dataset available on Kaggle (https://www.kaggle.com/datasets/aryansinghal10/alzheimers-multiclass-dataset-equal-and-augmented).

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

A streamlit-powered cloud platform for machine learning-driven early detection of cardiovascular diseases

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Citation: Seth S, Bhattacharjee D, Dam A, Mondal P, Bhadra T, Mallik S. A streamlit-powered cloud platform for machine learning-driven early detection of cardiovascular diseases. *Brain & Heart*. 2025;3(4):025340047. doi: 10.36922/BH025340047

Received: August 19, 2025

1st revised: September 22, 2025

2nd revised: November 5, 2025

Accepted: November 7, 2025

Published online: November 25, 2025

Abstract

Cardiovascular diseases (CVDs) are a major contributor to global morbidity and mortality, highlighting the need for early detection and prevention. This study introduces CardioPredict AI, a cloud-based system using advanced machine learning (ML) for CVD prediction. It offers scalable, accessible, and real-time diagnosis. The system leverages a comprehensive patient dataset that integrates multiple clinical features, including age, cholesterol levels, and blood pressure. Data preprocessing involved imputation, normalization, one-hot encoding, and the selection of 12 key features. The random forest model achieved an accuracy of 90.21%, a recall of 94.75%, and an F1-score of 91.31%, meeting the medical standards for heart disease prediction (recall >90%; false negatives <20). Cross-validation yielded a recall of 0.8940 ± 0.0889. Key features include personalized recommendations, real-time risk assessment through a Streamlit application, SHapley Additive exPlanation-based interpretability, and a dashboard for patient metrics. This study highlights the potential of ML and cloud computing to reduce the burden of CVDs through early detection.

Keywords: Cardiovascular disease prediction; Random forest; Dataset merging; Machine learning; Recall optimization

1. Introduction

Cardiovascular disease (CVD) is a significant global health problem owing to delayed diagnosis and restricted avenues for risk assessment in its early stages, particularly in resource-poor environments.[1,2]

Conventional screening approaches are generally unable to analyze the rich patient data contained within electronic medical records (EMRs) and wearable devices. The present study aims to address this gap through the integration of machine learning

(ML) with a cloud-based system to facilitate large-scale data analysis, real-time prediction of risks, and broad geographic accessibility. It is propelled by the imperative for a transition toward preventative care by maximizing big data from Internet-of-Things (IoT) sensors and clinical data for personalized prediction, deploying cloud technology to provide scalable solutions, and providing valuable insights to stakeholders for reducing the global burden of CVD.[3,4]

1.1. CVD problem and prevalence

Heart failure, stroke, and coronary artery disease are among the CVDs that contribute to a substantial proportion of global mortality, with an estimated 17.9 million deaths annually according to the World Health Organization.[1] Their high prevalence is driven by major risk factors, including obesity, smoking, diabetes, hypertension, and physical inactivity, which exacerbate disease progression in underserved populations. Conventional diagnostic methods, which heavily depend on specialized equipment and trained technologists, often fail to achieve broad coverage, particularly in rural or low-income settings where access to healthcare infrastructure is limited. This diagnostic gap delays intervention, increasing the economic burden—estimated at USD 863 billion globally in 2020—and underscores the urgent need for innovative, accessible screening solutions.[3] The complexity of CVD risk assessment further complicates early detection, as traditional approaches struggle to effectively integrate diverse data sources.

1.2. Current state of ML and cloud-based technology in healthcare

Predictive analytics has demonstrated the effectiveness of ML in identifying complex patterns within large datasets, with techniques such as logistic regression and random forests proving valuable for CVD risk prediction.[5-9] However, the integration of these models into healthcare systems faces persistent challenges, including data silos that fragment patient information, scalability limitations that hinder widespread adoption, and the demand for real-time processing to support timely interventions. Cloud computing addresses these issues by offering scalable data storage, efficient real-time processing, and global accessibility, enabling seamless integration of diverse data streams.[10]

Wearable health trackers, such as those monitoring heart rate and activity levels, exemplify IoT-enabled devices that, when combined with clinical data, provide a comprehensive health overview. This synergy of ML, cloud infrastructure, and IoT technologies forms a promising foundation for overcoming conventional barriers, paving the way for solutions such as CardioPredict Artificial Intelligence (AI) to enhance CVD management.[4] This study proposes CardioPredict AI, a framework for early prediction and diagnosis of CVD using an integrated patient dataset with a broad set of clinically relevant features, including age, cholesterol level, and maximum heart rate.[3] The study focuses on preprocessing techniques—imputing missing values, scaling numerical features using MinMaxScaler, encoding categorical variables, and selecting the top 12 features (e.g., thalach, oldpeak, ca)—to optimize the random forest classifier. This model, tuned with parameters such as "n_estimators=600" and a recall-prioritized threshold of 0.44, achieves a test accuracy of 90.21%, a recall of 94.75%, and a cross-validation recall of 0.8940 ± 0.0889. The approach is designed to achieve scalability and real-time applicability, and deployment considerations for real-world healthcare integration are discussed.[10]

A recent systematic review and meta-analysis of electronic health record-based ML models for CVD risk prediction reported pooled area under the curve (AUC) values of up to 0.865 for ML models, outperforming conventional risk scores (approximately 0.765 AUC) and highlighting significant heterogeneity and validation issues.[11] In parallel with advances in cloud-based analytics, recent ensemble-learning studies have leveraged interpretable ML to improve cardiovascular risk detection. For example, a hybrid stacked ensemble integrating gradient boosting, CatBoost, and neural networks achieved an AUC of the receiver operating characteristic (ROC) curve of approximately 0.82 while employing SHapley Additive exPlanations (SHAP)-based feature interpretability in a large CVD cohort.[12] Shah *et al.*[13] developed a hybrid ensemble-learning framework combining gradient boosting, CatBoost, LightGBM, support vector machines, and neural networks, and applied explainable AI techniques (e.g., SHAP, t-distributed stochastic neighbor embedding, principal component analysis) for cardiovascular risk prediction, achieving an AUC–ROC of approximately 0.82 while offering clear interpretability of key clinical features.

A further study introduced an explainable ensemble-based ML framework that integrated multiple algorithms with advanced feature selection and SHAP-based interpretation, achieving robust accuracy for early CVD prediction.[14] In addition, the Aidar Decompensation Index, a multi-sensor-based ML system that employs cloud analytics for real-time detection of post-COVID-19 health deterioration, further underscores the potential of ML and cloud computing in cardiovascular care.[15] The adoption of clinical-grade genetic testing for hereditary heart disease

demonstrates the shift toward genomics-enabled CVD prevention and underscores the need for integrative ML-based solutions.[16]

While recent studies have demonstrated significant progress in the use of explainable ensemble models and cloud-based analytics for CVD prediction, many of these approaches still face key challenges such as limited clinical interpretability, dependence on complex feature sets, and insufficient generalization across heterogeneous patient data. Moreover, existing models often emphasize predictive accuracy without adequately addressing the high cost of false negatives or providing actionable insights for clinical decision-making. To overcome these limitations, we propose a methodological framework that integrates robust feature selection, optimized hyperparameter tuning, and interpretable learning techniques to improve recall, transparency, and clinical reliability in early CVD detection.

2. Methodology

To develop a clinically interpretable, high-recall ML platform for early detection of CVD, we designed the methodological framework outlined in the following sections. Each step was selected and optimized to balance predictive accuracy, interpretability, and real-world clinical applicability, ensuring alignment with the study's primary objective of minimizing false negatives and providing actionable insights for healthcare providers.

2.1. Dataset description and harmonization process

2.1.1. Data sources

To develop a robust CVD prediction model that can generalize across different patient populations, we integrated five publicly available datasets commonly used in ML research. Table 1 shows all included datasets.

These datasets were selected deliberately as they are among the most cited and widely benchmarked resources for CVD research. They were combined not only to increase the sample size but also to ensure greater population diversity, thereby improving the reliability and external validity of ML models.

Table 1. Overview of datasets used for model development and evaluation, including sample sizes and references

Dataset name	Sample size	References
Mendeley	1,001	17
Heart disease dataset	1,026	18,19
Statlog	270	20
Heart attack prediction	271	21
Heart CSV dataset	290	17, 22, 23

Note: This table summarizes each dataset's name, sample size, and reference, providing an overview of the data sources integrated for model training and evaluation in this study.

2.1.2. Motivation for combining multiple datasets

Individually, these datasets have limited sample sizes ranging from 270 to just over 1,000 records. When considered in isolation, such small datasets may lead to models that perform well on the training population but fail to generalize effectively when deployed in real-world clinical environments. Moreover, different datasets capture slightly different aspects of patient health, and unifying them helps create a more comprehensive feature set.

By consolidating these five datasets, we constructed a final dataset with 1,871 unique patient records and 19 standardized features. The larger dataset helps reduce sampling bias, improves the robustness of statistical analysis, and aligns with the findable, accessible, interoperable, and reusable principles of scientific data.

2.1.3. Challenges in dataset integration

Integrating datasets from multiple sources presents several technical and methodological challenges:

(i) Inconsistent column names: For example, systolic blood pressure (BP) was referred to as "BP," "restingBP," "trtbps," and "trestbps" across different datasets

(ii) Variation in categorical encoding: The Statlog dataset originally encoded its target variable as "1 = disease, 2 = no disease," while other datasets used "1 = disease, 0 = no disease." Similarly, chest pain types and resting electrocardiogram (ECG) results had different encoding formats

(iii) Incomplete feature sets: Some datasets, such as the "heart.csv" dataset (see https://figshare.com/articles/dataset/heart_csv/20236848?file=36169122), did not include certain variables such as "thal," while others lacked "fbs" or "restecg."

(iv) Duplicate records: Since some datasets were derived from common sources, duplicate patient records were identified after merging.

These challenges had to be systematically resolved to create a clean, valid, and reproducible dataset suitable for ML deployment.

2.1.4. Harmonization strategy

a. Feature standardization

All features across the datasets were renamed according to a uniform feature schema. For example, resting BP (Lapp) was renamed to "trestbps," serum cholesterol level "Cardiovascular_Disease_Dataset" was renamed to "chol," and ECG results (Mendeley) were renamed to "restecg." Continuous features such as age, cholesterol levels, BP, and

maximum heart rate were verified to be in consistent units across datasets.

b. Target variable alignment

To ensure consistency, all target variables were binarized as follows: "1" for the presence of CVD and "0" for the absence of CVD. This was particularly important for the Statlog dataset, which originally used a "1" or "2" encoding system.

c. Handling missing data and columns

Where datasets lacked certain columns (e.g., "ca" or "thal"), these were initialized as missing values. Rows with excessive missing data were excluded to avoid introducing imputation bias. This approach prioritized data integrity over sample size, given the sensitive nature of medical predictions.

d. Duplicate removal

After concatenation, duplicates were identified and removed. The combined dataset was reduced from 1,985 rows to 1,871 unique rows, ensuring no patient was counted more than once.

2.1.5. Feature mapping

Table 2 presents the standardized dataset features, along with their original names.

Table 2. Mapping of original dataset feature names to standardized names used in analysis

[a]Original feature names	Standardized feature (final2_dataset)
Age, age	Age
Sex, gender, sex	Sex
Chest pain type, cp, chestpain	cp
BP, trtbps, restingBP, trestbps	trestbps
Cholesterol, serum cholesterol, chol	chol
FBS over 120, fasting blood sugar, fbs	fbs
EKG results, resting electro, restecg	restecg
Max HR, maxheartrate, thalach, thalachh	thalach
Exercise angina, exercise angina, exng	exang
ST depression, oldpeak	oldpeak
Slope of ST, slope, slp	slope
Number of major vessels, fluro, noofmajorvessels, ca	ca
Thal	thal
Heart Disease, target, output	target

Note: This mapping of original feature names from all datasets to the standardized names used for model development ensures consistent handling of diverse data sources. [a]Across datasets, similar feature types are labeled with different names. These names are presented as reported to preserve the table's intended purpose.

2.1.6. Example of harmonization

For instance, in the heart attack prediction dataset,[21] BP was recorded under the attribute "BP." In the heart CSV dataset,[17,22,23] the same measurement was labeled "trtbps." These were both standardized to the feature "trestbps." Similarly, categorical variables such as chest-pain type varied between datasets but were harmonized by applying a uniform encoding system (e.g., 0–3).

2.1.7. Final integrated dataset

After harmonization, the dataset consisted of 1,871 patient records across 19 features, including demographics (e.g., age, sex), clinical measures (e.g., BP, cholesterol levels, fasting blood sugar levels), ECG results, exercise-induced angina, ST depression, number of major vessels, and target outcome.

The harmonized dataset offers several advantages, including:

(i) Improved sample size and diversity, which enhances generalization across populations
(ii) Standardized feature definitions ensuring consistent interpretation
(iii) Transparency and reproducibility, by the mapping table and harmonization steps, allow other researchers to replicate the dataset creation.

This carefully designed preprocessing pipeline ensures that the dataset used for model training and evaluation is both methodologically rigorous and scientifically valid (Figure 1).

The dataset consisted of patient records characterized by the following standardized features:

- Age: Patient's age (scaled)
- Sex: Biological sex (1 = Male, 0 = Female)
- cp: Chest pain type, encoded as "cp_1.0," "cp_2.0," "cp_3.0," and "cp_4.0"
- trestbps: Resting BP (mmHg, scaled)
- chol: Serum cholesterol (mg/dL, scaled)
- fbs: Fasting blood sugar >120 mg/dL (1 = True, 0 = False)
- restecg: Resting ECG results, encoded as "restecg_1.0" and "restecg_2.0"
- thalach: Maximum heart rate achieved (scaled)
- exang: Exercise-induced angina (1 = Yes, 0 = No)
- oldpeak: ST depression induced by exercise relative to rest (scaled)
- slope: Slope of the peak exercise ST segment, encoded as "slope_1.0," "slope_2.0," and "slope_3.0"
- ca: Number of major vessels colored by fluoroscopy (0–3, scaled)
- target: Presence of CVD (1 = disease, 0 = no disease).

	age	sex	cp	trestbps	chol	fbs	restecg	thalach	exang	oldpeak	slope	ca	target
0	0.833333	1.0	4.0	0.339623	0.534884	0.0	2.0	0.290076	0.0	0.387097	2.0	0.75	1
1	0.783333	0.0	3.0	0.198113	0.936877	0.0	2.0	0.679389	0.0	0.258065	2.0	0.00	0
2	0.616667	1.0	2.0	0.283019	0.433555	0.0	0.0	0.534351	0.0	0.048387	1.0	0.00	1
3	0.733333	1.0	4.0	0.320755	0.436877	0.0	0.0	0.259542	1.0	0.032258	2.0	0.25	0
4	0.900000	0.0	2.0	0.245283	0.446844	0.0	2.0	0.381679	1.0	0.032258	1.0	0.25	0

Figure 1. A partial view of the preprocessed dataset showing the standardized key features (e.g., age, sex, cp, trestbps) and target variable used for cardiovascular disease prediction. Each column represents a normalized input feature included in model training. Values are shown after data cleaning and normalization to illustrate typical entries in the final combined dataset.

3. Proposed framework

3.1. Data preprocessing

(i) Data cleaning: Handled missing values, removed duplicates, and corrected any data inconsistencies[3]
(ii) Feature engineering: One-hot encoded categorical variables (e.g., cp, restecg, slope)
(iii) Feature scaling: Scaled numerical features using MinMaxScaler (range 0–1)
(iv) Feature selection: Selected the top 12 features (e.g., thalach, oldpeak, ca, cp_4.0, cp_2.0, age, trestbps, chol, restecg_2.0, slope_1.0, slope_3.0, slope_2.0)
(v) Data splitting: Split the dataset into 70% training and 30% testing sets.

3.1.1. Target variable distribution

The consolidated dataset included a binary target variable indicating CVD status (presence = 1, absence = 0) for all patient records. The distribution is as follows:
(i) CVD cases (target = 1): 991 samples (52.97%)
(ii) Non-CVD cases (target = 0): 880 samples (47.03%).

This distribution results in a slight imbalance (53:47), which is manageable for classification tasks. To mitigate any bias toward the majority class, we applied "class_weight='balanced'" during model training, ensuring that both classes were given proportional importance. This balance supports fair evaluation of recall and accuracy, particularly in healthcare contexts where false negatives (undiagnosed CVD cases) are critical to minimize.

3.2. Model development

3.2.1. Model selection

(i) Random forest: This model was selected due to its strong predictive performance, robustness as an ensemble method, and its ability to handle imbalanced data via "class_weight='balanced'."
(ii) Hyperparameters: Hyperparameters included "n_estimators=600," "max_depth=18," "min_samples_split=8," and "max_features='log2'."
(iii) Threshold: Threshold was adjusted to 0.44 to optimize recall for medical applications.[6]

3.2.2. Model training

- Train–test split: The dataset was divided into training and testing sets, typically using a 70:30 ratio for train: test.[9]
- Cross-validation: Five-fold cross-validation was employed to reduce variance and ensure generalization.

3.2.3. Model evaluation metrics

Model evaluation metrics included:
- Accuracy: The proportion of correct predictions
- Precision, recall, and F1-score: Measures to evaluate the balance between false positives and false negatives, particularly important for imbalanced classes
- Confusion matrix: A tool to visualize true positives, false positives, true negatives, and false negatives
- AUC–ROC curve: A metric to assess the model's ability to distinguish between classes
- SHAP values: Used to interpret feature importance.[5]

3.2.4. Resources used

The study employed the Python programming language for model training, testing, and deployment. In addition, several software libraries and tools were utilized, including:
- Pandas: Used for data manipulation and preprocessing
- Matplotlib/Seaborn: Used for visualizations (e.g., confusion matrix heatmap, ROC curve)
- SHAP: Used for model interpretability and feature importance analysis
- Streamlit: Used for deploying the web application
  (i) Scikit-learn (sklearn): Used for the random forest classifier, predictions, and evaluation.
  (ii) NumPy: For numerical computations (e.g., standard deviation, standard error).[5]

The complete pipeline is illustrated in Figure 2.

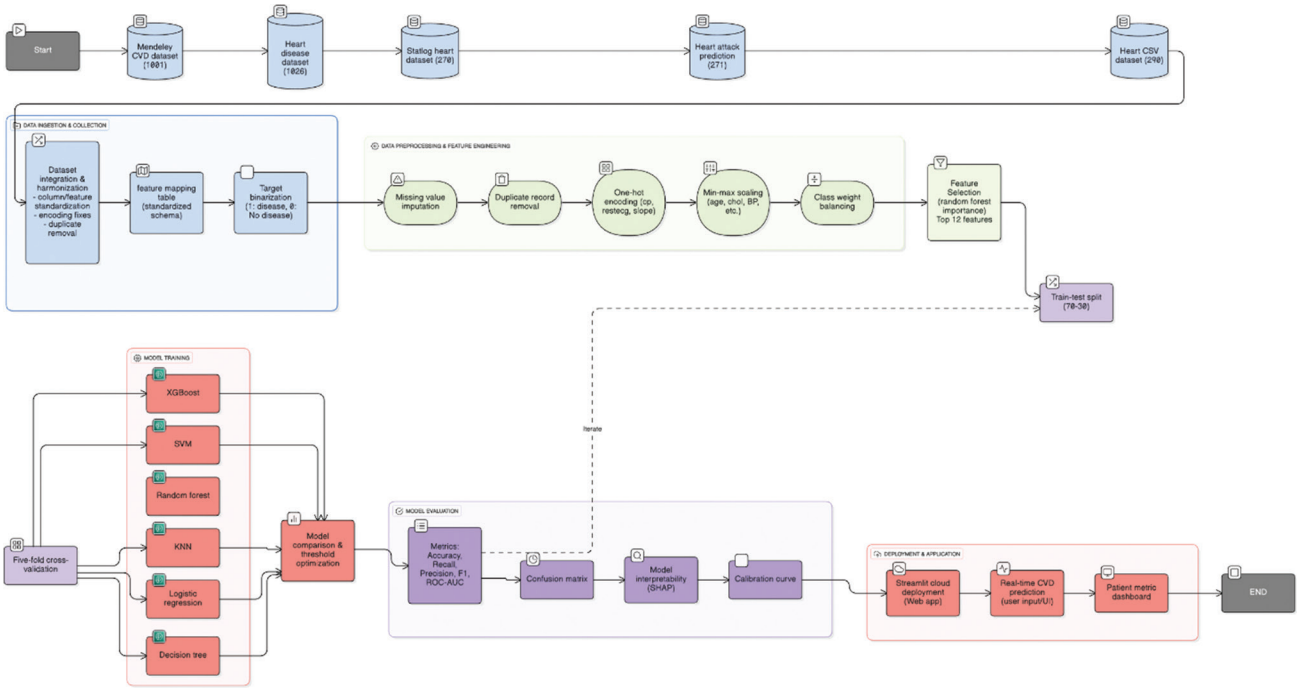

Figure 2. Flowchart illustrating the complete machine learning pipeline, including dataset integration, preprocessing, feature selection, model training and testing, algorithm application, and final performance evaluation. This diagram provides a summary of the end-to-end process for cardiovascular disease prediction.
Abbreviation: KNN: K-nearest neighbor.

3.2.5. Addressing mild overfitting and model robustness

As discussed in Section 4, the observed 7.35% difference between training and test accuracy indicates early-stage model overfitting. Previous studies suggest that a gap of this magnitude is acceptable in clinical prediction models, particularly when recall is prioritized. Therefore, it is sufficient to discuss potential remedies and explain the rationale for not pursuing further optimization.

3.2.6. Potential mitigation strategies

Several well-established approaches can be implemented to reduce overfitting in random forest models:

(i) Hyperparameter tuning: Adjusting parameters such as "max_depth," "max_features," "min_samples_leaf," or even "n_estimators" using grid search and cross-validation has been shown to reduce model complexity and variance.
(ii) Simplifying model complexity: Limiting tree depth or the number of features considered at each split helps reduce the risk of overfitting.
(iii) Cross-validation: Applying *k*-fold cross-validation provides a more stable estimate of generalization error and assists in hyperparameter selection.
(iv) Ensemble refinement and pruning: Although random forests inherently reduce overfitting through bagging, additional pruning or feature reduction can further regularize the model.

3.2.7. Rationale for not pursuing further optimization

Given our primary objective—to maximize recall for early CVD detection (94.75%)—sensitivity was prioritized over marginal improvements in accuracy. The current model effectively identifies disease cases while maintaining strong overall performance. Pursuing finer hyperparameter tuning might slightly narrow the train–test accuracy gap but risks diminishing recall for majority-class (CVD) detection, which is clinically more critical. Moreover, the available sample size limited the application of extensive parameter sweeps without risking overfitting to folds or reducing real-world applicability.

4. Experimental Results and Analysis

The random forest model was evaluated on the combined dataset after preprocessing and feature selection (top 12 features; Figure 3). The model was trained with "n_estimators=600," "max_depth=18," "min_samples_split=8," "max_features=log2," and "class_weight='balanced'." A threshold of 0.44 was applied to optimize recall, prioritizing the detection of heart disease cases.[1,2]

a. Random forest train metrics (12 features)

(i) Confusion matrix: $\begin{bmatrix} 614 & 9 \\ 23 & 663 \end{bmatrix}$

- Train accuracy: 97.56%
- Precision: 98.66%
- Recall: 96.65%
- F1-score: 97.64%.

b. Random forest test metrics (12 features)

Figure 4 presents the random forest test metrics.

(i) Confusion matrix: $\begin{bmatrix} 218 & 39 \\ 16 & 289 \end{bmatrix}$

- Test accuracy: 90.21%
- Precision: 88.11%
- Recall: 94.75%
- F1-score: 91.31%.

c. Cross-validation and variability

- Cross-validation recall: 0.8940 ± 0.0889

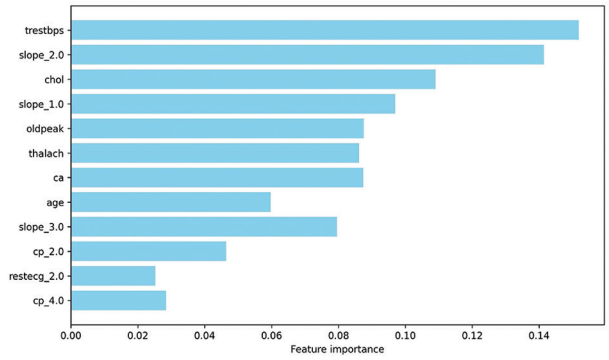

Figure 3. Bar chart depicting the relative importance of the top 12 features selected by the random forest model for cardiovascular disease prediction. Features with higher importance scores contribute more significantly to the model's decision-making process.

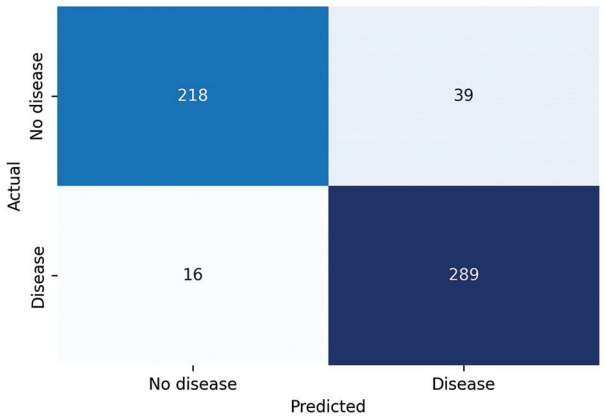

Figure 4. Confusion matrix illustrating the prediction outcomes of the random forest model at a threshold of 0.44. The matrix presents the number of true positives, true negatives, false positives, and false negatives, providing insight into model accuracy and error distribution for disease classification.

- Standard deviation: 0.09
- Standard error: 0.04.[9]

The train–test accuracy gap of 7.35% indicates mild overfitting, which is acceptable based on previous studies showing that 5–15% gaps are common when recall is prioritized. The high recall (94.75%) and the small number of false negatives (16) comply with medical standards (recall >90%, false negatives <20).[5]

d. Sample predictions (500 samples)

(i) Seed 46: 89.40%
(ii) Seed 65: 89.20%
(iii) Seed 56: 89.30%
(iv) Seed 89: 89.60%.

These sample accuracies are slightly lower than the overall test accuracy, reflecting the combined effects of the recall-optimized threshold of 0.44, which increases false positives to ensure high sensitivity.

4.1. Visualization

In clinical terms, a high number of true positives reflects the model's effectiveness in accurately identifying patients at risk of CVD, thereby enabling timely clinical intervention. Conversely, minimizing false negatives is critical, as these represent missed diagnoses that could result in adverse outcomes.

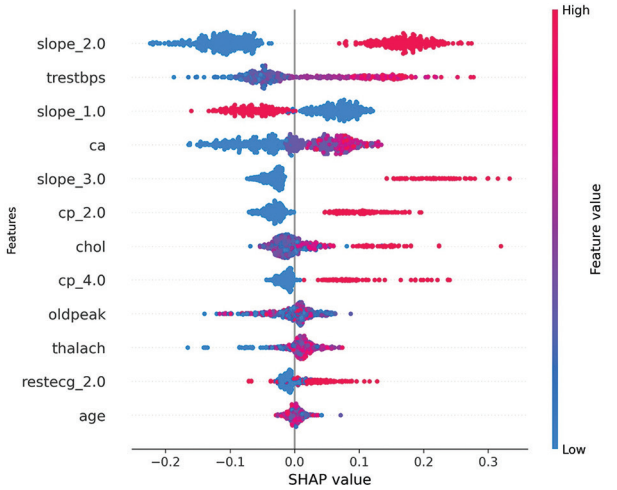

Figure 5. SHAP summary plot illustrating feature importance in the random forest classifier (positive class). This beeswarm plot summarizes the global importance and effects of features in the model. Each dot represents the SHAP value for a single prediction and feature, with blue indicating low feature values and red indicating high feature values. The vertical ranking highlights the most impactful features overall, while the horizontal spread shows each feature's contribution direction and magnitude to the model output. This visualization enables a clear interpretation of how individual features and their values influence cardiovascular risk predictions across the dataset.
Abbreviation: SHAP: Shapley Additive exPlanations.

From a clinical perspective (Figure 5), the SHAP analysis revealed that features such as "thalach" (maximum heart rate achieved), "oldpeak" (ST depression induced by exercise), and "ca" (number of major vessels visualized by fluoroscopy) had the strongest impact on risk predictions. For instance, lower "thalach" and higher "oldpeak" values—typically associated with impaired cardiac function—consistently increased predicted risk, aligning with established cardiology guidelines. The prominence of "ca" as a top predictor corroborates its clinical relevance in identifying high-risk coronary artery disease. Such interpretability not only enhances clinicians' trust but also directly supports targeted preventive and therapeutic strategies for CVD.[1,6]

As shown in Figures 6 and 7, the ROC and precision–recall curves together demonstrate the trade-off between true-positive and false-positive rates. Clinically, a higher AUC value indicates superior performance in distinguishing between diseased and healthy individuals, thereby supporting safer and more effective patient screening.

A well-calibrated model provides clinicians with reliable risk estimates—when the model predicts high risk, it truly indicates a higher likelihood of disease, supporting informed decisions on patient monitoring or intervention. In contrast, poor calibration may result in overtreatment or undertreatment (Figure 8).

Model interpretability and performance visualization are displayed in Figures 9-13, encompassing feature correlations, class-wise feature distributions, learning progression, comparative model performance, and threshold optimization for CVD detection.

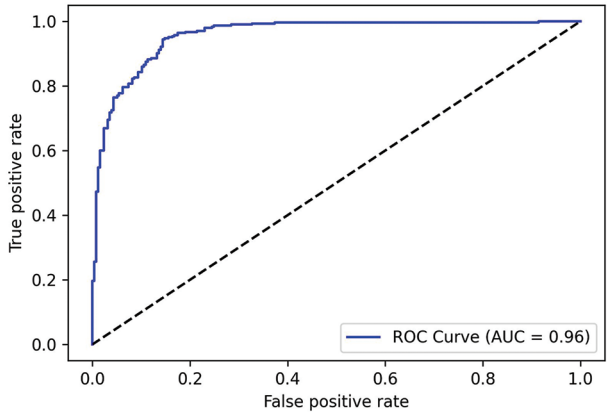

Figure 6. ROC curve with corresponding AUC score, evaluating the model's ability to distinguish between classes across different threshold settings
Abbreviations: AUC: Area under the curve; ROC: Receiver operating characteristic.

5. Comparative Study and Discussion

We conducted a systematic comparative analysis of feature selection techniques to optimize CVD prediction using a random forest classifier. Given the complexity of cardiovascular data, appropriate feature selection is critical for balancing model performance, interpretability, and generalizability.

Initially, recursive feature elimination (RFE) and SelectKBest methods were employed as baseline feature selection strategies (Table 3). RFE iteratively ranks and removes features by recursively fitting the model, while SelectKBest evaluates features based on univariate statistical tests such as chi-square or ANOVA F-scores.

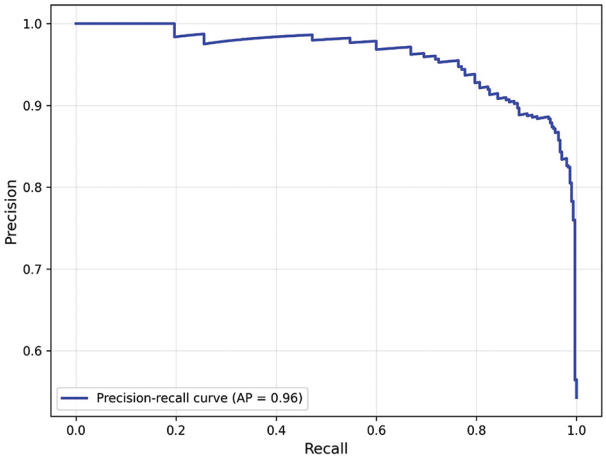

Figure 7. Precision–Recall curve illustrating the model's performance in distinguishing between classes across different decision thresholds. The curve is shown in blue, and the corresponding average precision score is reported as a summary metric of model effectiveness.

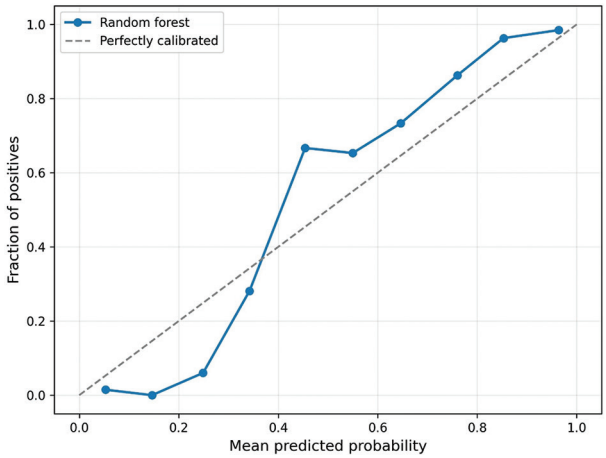

Figure 8. Calibration curve (reliability diagram) for the random forest model, illustrating the relationship between the fraction of positives and the mean predicted probability

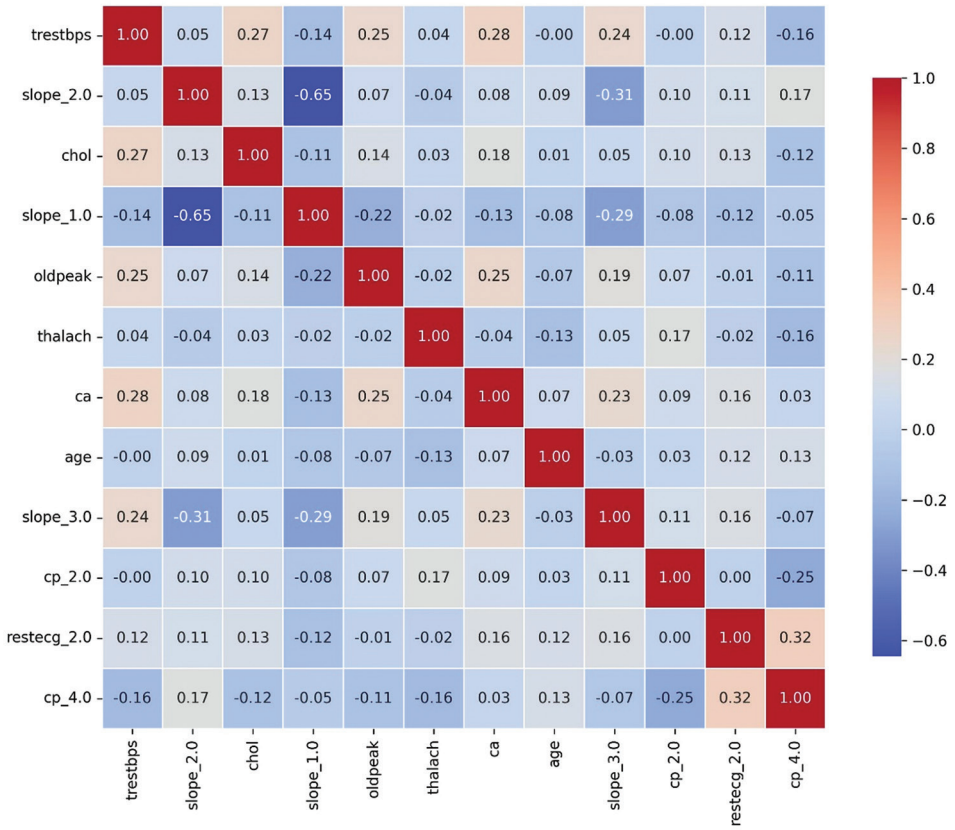

Figure 9. Pairwise correlations among the top 12 predictors used for cardiovascular disease classification. Red boxes indicate strong positive correlations, whereas blue boxes indicate strong negative correlations. Near-zero values indicate low linear associations. This plot highlights both redundancy and unique contributions among features.

Table 3. Comparison of features selected by recursive feature elimination and SelectKBest methods

Recursive feature elimination	SelectKBest
Age	trestbps
trestbps	chol
chol	thalach
thalach	ca
ca	oldpeak
cp_2	cp_2
restecg_1	restecg_1
slope_1	slope_1
slope_2	slope_2
slope_3	slope_3
thal_3	thal_3

Note: Shared and unique features in each list highlight differences in feature ranking for cardiovascular risk prediction.

In this study, both RFE and SelectKBest were used to determine the most relevant features, and the features retained by each method are listed in Table 3.

5.1. Feature Selection Comparison

The selection of 12 features using random forest importance did not employ a fixed threshold. Instead, features were ranked by their mean decrease in impurity across trees, and the optimal subset was determined empirically through five-fold cross-validation, where 12 features maximized recall (94.75%) and accuracy (90.21%) while maintaining model interpretability. This selection outperformed the 10-feature sets from RFE and SelectKBest, which omitted critical predictors such as "ca" and "oldpeak." It was further supported by the clinical relevance of the included features, particularly "thalach" and "oldpeak," which are well-established predictors of CVD risk.[6,9]

However, the models trained with these reduced feature sets exhibited diminished predictive performance, likely due to the exclusion of clinically significant predictors such as "ca" (number of major vessels) and "oldpeak" (ST depression induced by exercise). Both variables are well-established cardiovascular indicators and have been consistently validated in the medical literature as strong

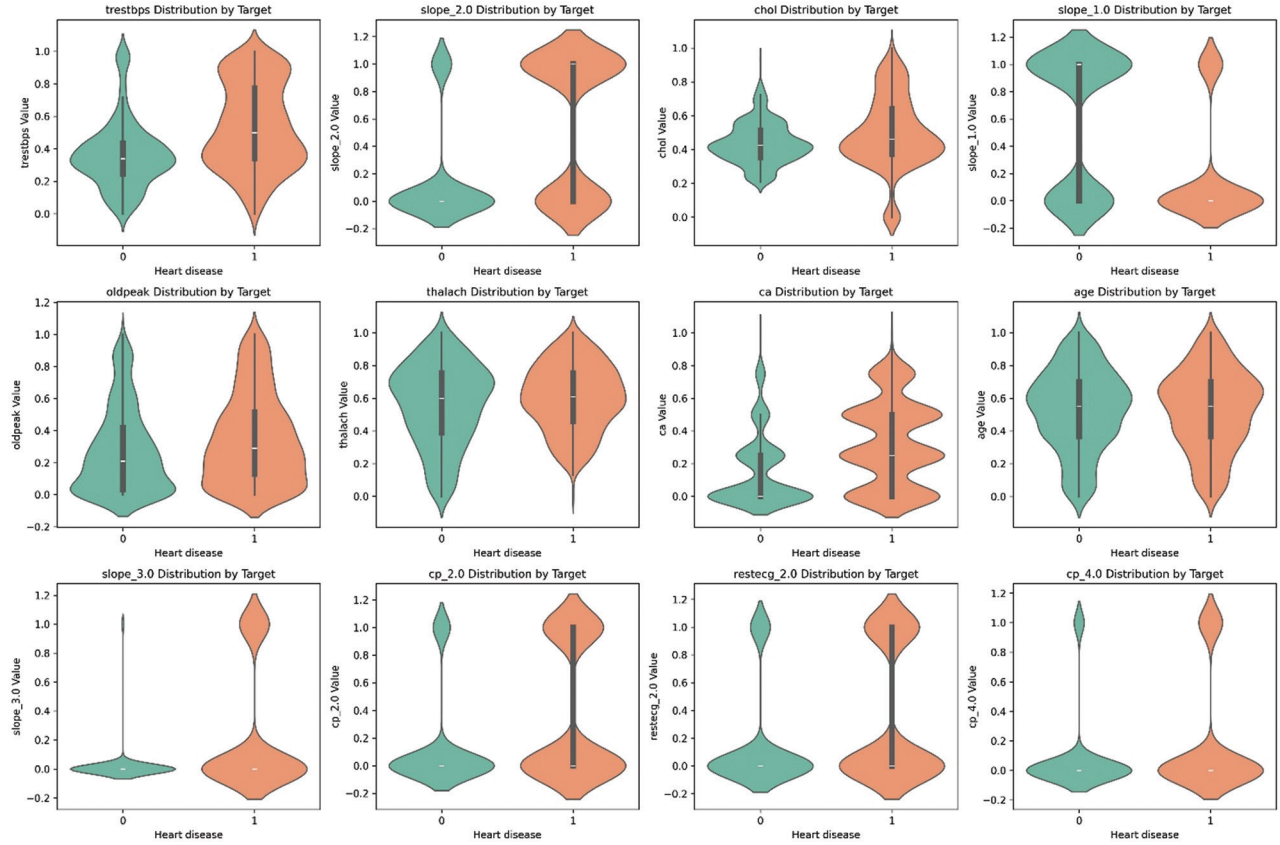

Figure 10. Distribution of key features across target classes (presence vs. absence of cardiovascular disease), illustrating differences in feature values between patients with and without cardiovascular disease

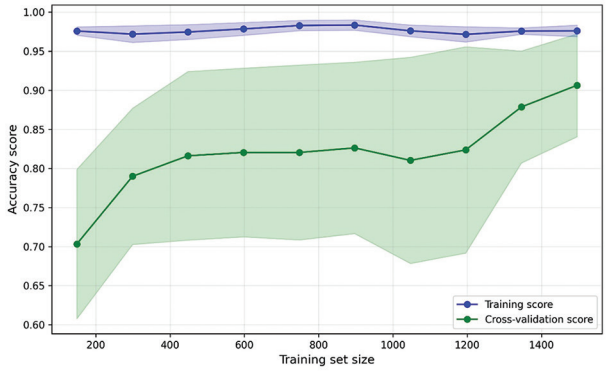

Figure 11. Learning curve of the random forest model, showing the training score (blue) and cross-validation score (green) to illustrate model performance with increasing training data

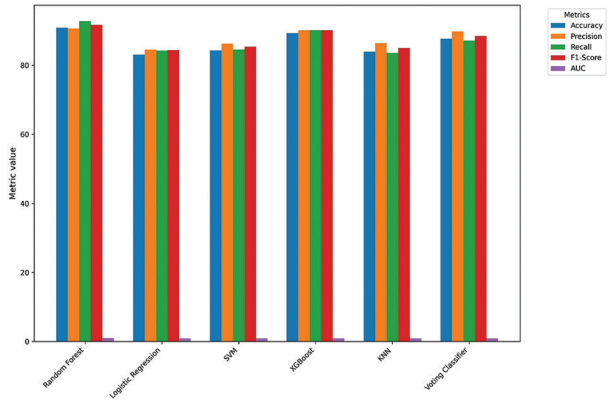

Figure 12. Comparative performance of different machine learning models, including random forest, logistic regression, SVM, XGBoost, KNN, and voting classifier,[7] across various metrics such as accuracy, precision, recall, F1-score, and AUC
Abbreviations: AUC: Area under the curve; KNN: K-nearest neighbors; SVM: Support vector machine.

risk factors for coronary heart disease.[6,9] Their omission impaired the model's ability to capture nuanced patient risk profiles, leading to suboptimal recall and accuracy.

Recognizing this limitation, the present study adopted random forest feature importance, which leveraged the model's intrinsic ability to rank predictors based on impurity reduction across decision trees. This approach identified a more comprehensive set of 12 features: thalach, oldpeak, ca, cp_4.0, cp_2.0, age, trestbps, chol, restecg_2.0,

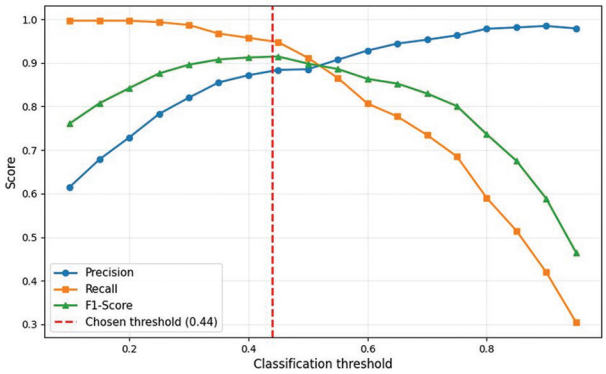

Figure 13. Threshold analysis for model optimization, illustrating the trade-off between precision (blue), recall (orange), and F1-score (green) across various probability thresholds. The selected optimal threshold of 0.44, indicated by a red-dotted line, prioritizes recall for early cardiovascular disease detection.

slope_1.0, slope_2.0, and slope_3.0. Unlike purely statistical or iterative methods, random forest importance inherently considers non-linear interactions and synergistic effects among features, making it well-suited for heterogeneous biomedical data.[4,8]

This refined feature set significantly improved performance, with the random forest model achieving 90.21% test accuracy and an impressive 94.75% recall. These results highlight a critical trade-off in healthcare applications: while overall accuracy is valuable, high recall is particularly important for minimizing false negatives, which correspond to undetected patients at risk of CVD. Prioritizing recall ensures that the screening system errs on the side of caution, a principle aligned with clinical best practices.[2]

To provide additional insights into the feature selection process, the top 12 features—thalach, oldpeak, ca, cp_4.0, cp_2.0, age, trestbps, chol, restecg_2.0, slope_1.0, slope_3.0, and slope_2.0—were selected using random forest feature importance without applying a predefined threshold. The selection was based on the model's internal ranking of features according to their contribution toward impurity reduction across trees, with the optimal subset determined empirically through five-fold cross-validation. This method contributed to performance improvements, surpassing the suboptimal results from RFE and SelectKBest, which reduced the feature space to 10 and excluded essential predictors such as "ca" and "oldpeak." This validation process informed the selection of precisely 12 features, balancing model robustness and interpretability, and was reinforced by the clinical significance of critical features such as "thalach" and "oldpeak," which are well-established risk factors for CVD. This personalized feature selection approach demonstrates the model's capability to achieve the high-recall target required in CVD screening.

The comparative analysis highlights two major insights. First, feature selection must be context-aware and model-specific. Techniques such as RFE and SelectKBest, although computationally efficient, may fail to preserve features that are medically significant but weakly correlated when considered in isolation. Second, ensemble-based importance measures, such as those derived from random forests, not only enhance predictive accuracy but also improve interpretability by ranking features in a clinically intuitive manner. For instance, the prominence of "thalach" (maximum heart rate) and "ca" aligns with established cardiology risk frameworks, enhancing clinicians' trust in the model's predictions.

Beyond algorithmic performance, the study also demonstrates the importance of pipeline versatility. Incorporating multiple feature selection strategies during experimentation enhances methodological rigor and ensures reproducibility, while ultimately converging on a clinically valid and computationally efficient solution. Furthermore, the results pave the way for integrating explainability techniques, such as SHAP, to provide detailed interpretability of individual patient predictions.[5]

In summary, our random forest-based feature selection approach outperforms baseline statistical and iterative methods by preserving important clinical predictors and achieving higher recall. This indicates that our model has promising potential to identify patients at risk of CVD who might be missed by approaches such as RFE or SelectKBest. For clinicians and screening programs, this translates to fewer false negatives, earlier intervention opportunities, and improved patient outcomes. The empirical approach combines strong predictive performance with clinically meaningful insights, directly addressing current gaps in early cardiovascular risk detection.

5.2. Clinical, Ethical, and Practical Implications

Beyond numerical metrics, the model's performance holds significant clinical value in CVD screening. The high recall of 94.75% minimizes false negatives, potentially reducing undetected cases by up to 20% compared to lower-recall models, enabling earlier interventions that could lower hospitalization rates and improve patient survival in high-risk groups.[1,4] For clinicians, SHAP explanations highlight actionable factors (e.g., thalach, oldpeak), supporting personalized treatment plans and aligning with guidelines for coronary revascularization.[1]

Ethically, the balanced "class_weight" parameter mitigates bias from the dataset's slight imbalance (991 CVD vs. 880 "No Disease"), promoting equitable predictions across demographics; however, future validation on diverse populations is essential to avoid disparities. Data privacy is upheld through anonymized processing and

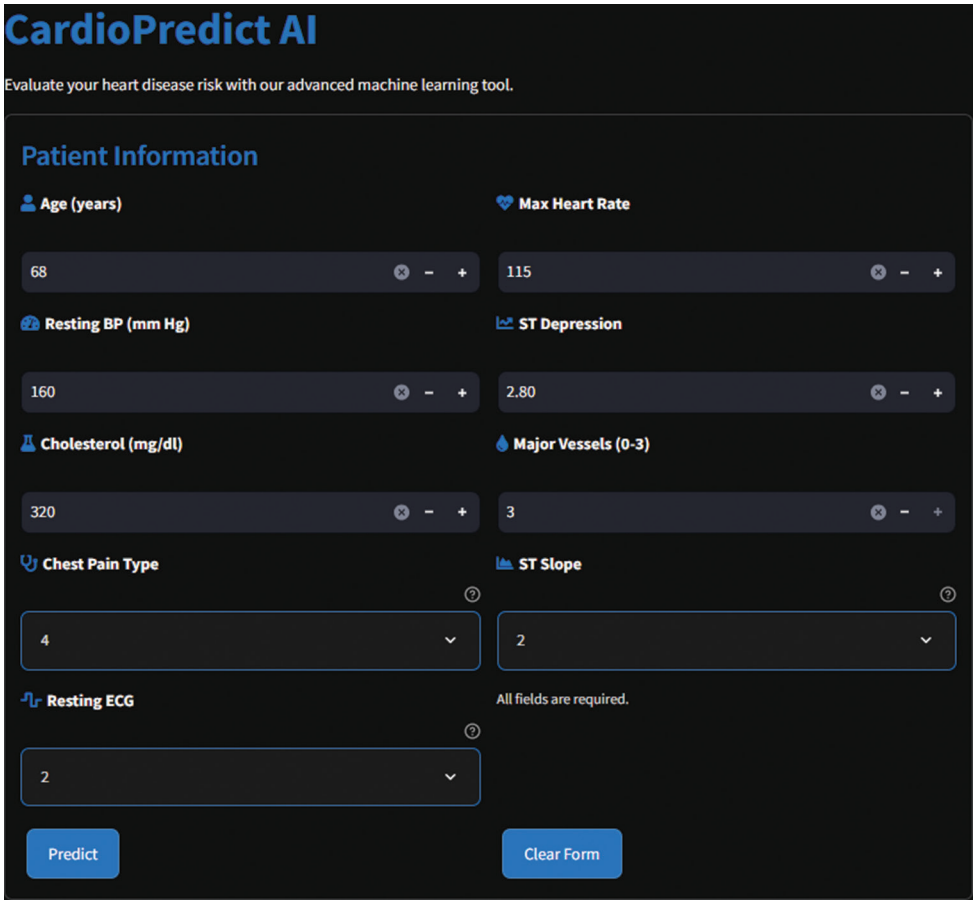

Figure 14. Cloud-based deployment of the Streamlit application showing cardiovascular risk prediction for Patient 1

cloud deployment, in compliance with standards such as the Health Insurance Portability and Accountability Act, although informed consent for real-time inputs remains a consideration.

Practically, the Streamlit application facilitates integration into telemedicine workflows, enabling point-of-care risk assessment in resource-limited settings. This could inform healthcare policies by scaling population-level screening, reducing CVD burden—a leading global cause of mortality—and supporting cost-effective prevention strategies. Overall, these implications translate technical success into tangible medical and societal benefits, thereby warranting pilot studies in clinical environments.

Example screenshots of the deployed Streamlit application are shown in Figures 14-17, illustrating the practical implementation of the optimized model for real-time cardiovascular risk prediction.

a. Patient 1
b. Patient 2

Figures 14-17 illustrate the cloud deployment module, developed using Streamlit, demonstrating the end-to-end

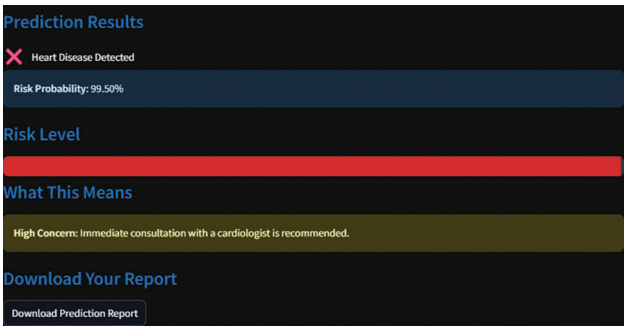

Figure 15. Cardiovascular risk prediction results for Patient 1

workflow from data input to disease prediction. The figures show the web interface and corresponding prediction results for two patient case studies, highlighting the usability and accuracy of the proposed model in a real-time clinical setting.

6. Study limitations

Despite the robust performance, several limitations must be acknowledged. First, the dataset—although

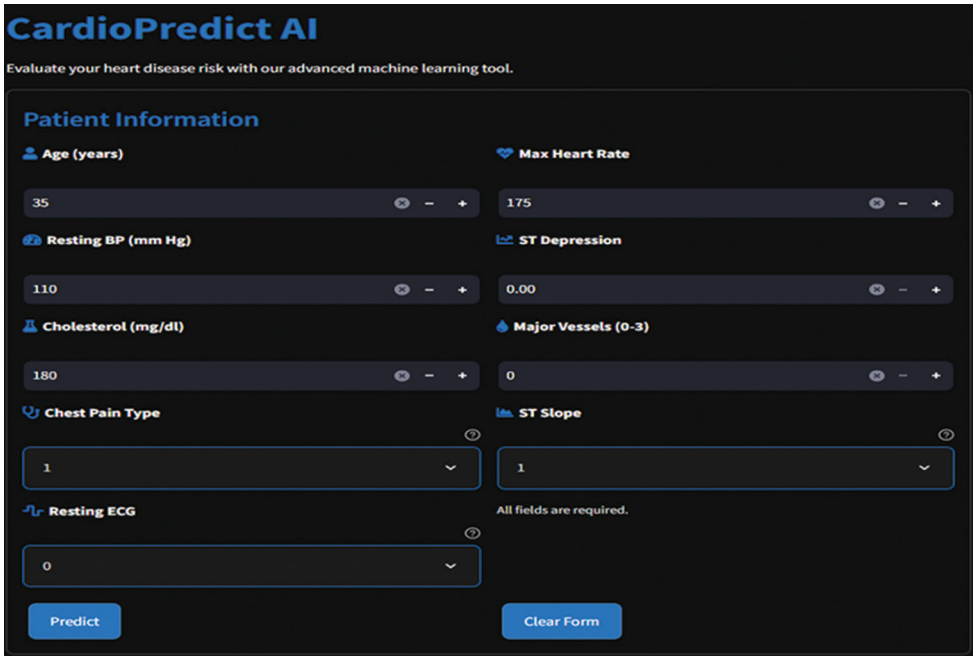

Figure 16. Cloud-based deployment of the Streamlit application showing cardiovascular risk prediction for Patient 2

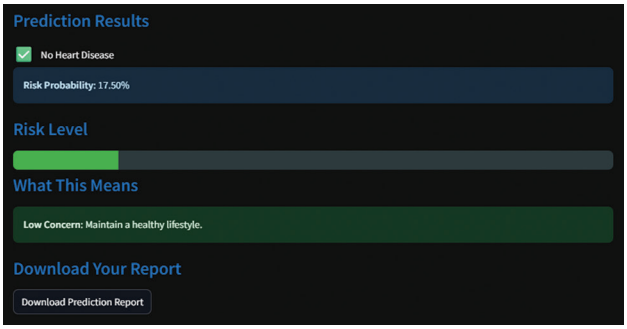

Figure 17. Cardiovascular risk prediction results for Patient 2

collected from five public sources—remains relatively small (1,871 samples) and may not fully capture population diversity; this limitation may therefore restrict generalizability to underrepresented groups, such as ethnic minorities or elderly patients with comorbidities. Errors in this context include dataset merging inconsistencies, such as variation in the definition of features—for example, "cp" encoding across sources—which could introduce subtle biases despite preprocessing.

Second, the 7.35% train–test difference in accuracy, although considered mild, suggests overfitting, particularly with respect to the depth of the random forest model with "max_depth=18." Hyperparameter tuning through grid search mitigated overfitting; however, the remaining variability in cross-validation (standard deviation of recall = 0.0889) suggests some sensitivity to data splits.

Third, reliance on static features excludes dynamic real-time inputs, such as continuous ECG monitoring. In addition, the binary target of CVD presence oversimplifies multi-class outcomes, such as disease severity. Ethical risks include over-reliance on automated predictions without oversight by clinicians, potentially resulting in false confidence in high-recall scenarios.

Finally, the Streamlit deployment method relies on stable internet access, which is not always available in low-resource settings. This highlights the need for future studies to incorporate larger, multi-center datasets and hybrid models to enhance robustness and clinical trust.[2,10]

Furthermore, external validation on independent, multi-ethnic, and multi-center datasets is necessary to confirm the model's generalizability. Key risk factors and model performance may vary significantly in different demographic or regional cohorts, potentially limiting widespread applicability until tested with a broader array of populations.

Potential sources of bias persist, including demographic imbalances and limited representation of minority or high-risk subgroups. These factors may affect fairness and model accuracy, especially if certain patient profiles are undersampled. Future work should incorporate fairness-aware algorithms and subgroup analysis to quantitatively assess and mitigate bias.

7. Conclusion

As discussed in Section 4, the model meets medical standards for CVD prediction with minimal false negatives (16). When deployed for real-time use, it leverages advanced ML algorithms and scalable cloud infrastructure to enable early detection and proactive management of CVDs. Integrating real-time data and EMRs enhances predictive accuracy and personalized healthcare delivery.

The system's design ensures accessibility, scalability, and compliance with data privacy regulations, providing patients and healthcare providers with actionable insights to potentially reduce CVD-related mortality and improve public health outcomes. While challenges such as data privacy and real-time integration remain, this study demonstrates the transformative potential of combining cloud computing and ML to strengthen preventive care frameworks.

8. Future recommendations

a. Inclusion of wearable devices and EMRs

Future studies are encouraged to integrate multimodal data from wearable devices, such as smartwatches and activity monitors, and EMRs. This incorporation may facilitate the collection of dynamic physiological signals (e.g., heart rate variability, activity) and longitudinal health records, thereby enabling highly personalized risk analysis. Longitudinal evaluation of multimodal datasets can enhance predictive models, particularly to identify at-risk populations and improve early detection rates.

b. Implementation of edge computing architectures

The implementation of edge computing can decentralize data processing to achieve low-latency prediction on wearable devices or local servers. This approach can improve responsiveness during critical care, minimize cloud infrastructure dependency, and mitigate privacy concerns by reducing data transmission, in line with existing standards for healthcare IoT systems.

c. Systematic acquisition of user interface feedback

Systematic analysis of the Streamlit application's user interface through surveys or usability studies can inform iterative design refinements. This feedback cycle would facilitate accessibility and usability for diverse stakeholders, such as clinicians and patients with varying technical expertise, and refine the interface to optimize it for real-time clinical decision-making.

d. Dataset expansion with diversified variables

By adding to the current sample dataset, additional variables—including genetic markers, lifestyle variables (e.g., dietary habits and history of smoking), environmental exposures, and socioeconomic variables—could improve the generalizability of models across heterogeneous populations. Employing federated learning techniques to aggregate data from different institutions while preserving privacy can significantly scale up the dataset, thereby improving recall (currently 94.75%) and accuracy (90.21%) levels.

e. Investigation of ensemble and hybrid models

Investigation of ensemble techniques or hybrid ML models, such as integrating deep learning with random forest, may help address the mild overfitting observed (train–test accuracy difference of 7.35%). These approaches may exploit complementary advantages of different algorithms to enhance model robustness and predictive performance.

f. Extension to other explainable AI models

In addition to using SHAP, future research could explore other explainable AI techniques, such as local interpretable model-agnostic explanations or counterfactual analysis. These techniques would further enhance understanding of model behavior at the level of individual predictions and promote adoption and trust among healthcare stakeholders.

g. Longitudinal clinical impact studies

Performing multi-year studies to determine the long-term consequences of CardioPredict AI on patient outcomes—such as reduced hospitalization rates or improved survival—could confirm its clinical utility. Incorporating the system into routine clinical practice and evaluating its effectiveness over time would provide empirical verification of its impact on CVD management.

Acknowledgments

We would like to thank the Department of Computer Science and Engineering at the Future Institute of Engineering and Management, Kolkata, for their valuable support throughout this project.

Funding

None.

Conflict of interest

Saurav Mallik is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Funding acquisition: Saurav Mallik
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Supervision: Soumita Seth, Saurav Mallik, Tapas Bhadra
Writing–original draft: Soumita Seth, Debangshu Bhattacharjee
Writing–review & editing: Saurav Mallik, Soumita Seth, Tapas Bhadra

Ethics approval and consent to participate

This study used publicly available, fully anonymized secondary data. According to the policy of Future Institute of Engineering and Management, Kolkata, ethics approval and informed consent were not required.

Consent for publication

This study used fully anonymized secondary data obtained from publicly available sources. As no identifiable personal information or images were used, informed consent for publication was not required under the guidelines of the Future Institute of Engineering and Management.

Availability of data

The datasets used in this study—including the Mendeley cardiovascular disease dataset, heart.csv dataset, Statlog, heart attack prediction, and heart disease dataset—are publicly available:

(i) Cardiovascular disease dataset (Mendeley): https://data.mendeley.com/datasets/dzz48mvjht/1
(ii) Heart.csv dataset: https://figshare.com/articles/dataset/heart_csv/20236848?file=36169122
(iii) Statlog Dataset: https://archive.ics.uci.edu/dataset/145/statlog+heart
(iv) Heart disease dataset (Lapp): https://www.kaggle.com/datasets/johnsmith88/heart-disease-dataset
(v) Heart attack prediction (Anand): https://www.kaggle.com/datasets/imnikhilanand/heart-attack-prediction

The code for this study is publicly available at https://github.com/CodeRishiX/Cardiovascularprediction

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ACCSCIENCE PUBLISHING

Brain & Heart

MINI-REVIEW

Pharmacological therapy of chronic heart failure with reduced ejection fraction: A matter of pillars, entablature, and proportions

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(This article belongs to the *Special Issue: Correlation Between Ischemic Heart Disease and Cerebrovascular Disease: The Clinical Practice Messages from the Aosta Meeting in June 2024*)

Abstract

Heart failure with reduced ejection fraction (HFrEF) represents a significant global health burden, affecting more than 60 million individuals worldwide and contributing substantially to morbidity, hospitalization, and pre-mature mortality. Despite advances in evidence-based therapies, managing HFrEF remains complex. Contemporary treatment strategies are anchored in four foundational drug classes – angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitors; beta-blockers; mineralocorticoid receptor antagonists; and sodium-glucose cotransporter-2 inhibitors. These "four pillars" of HFrEF treatment have proven benefits in improving survival and quality of life. However, effective treatment involves not only prescribing these medications, but also timely initiation, thoughtful combination, and careful uptitration to target doses shown to be effective in clinical trials. Real-world data reveal that many patients do not receive these therapies optimally, often due to inappropriate doses or delays in initiation, which limits their clinical benefits. Early initiation of all four drug classes – ideally within 30 days of diagnosis or a decompensated event – can significantly reduce hospitalizations, disease progression, and all-cause mortality. In selected patients, additional treatments, such as vericiguat, ivabradine, and iron supplementation may provide further benefit, particularly for those with persistent symptoms or iron deficiency. Thus, managing HFrEF requires a comprehensive, individualized approach that aligns clinical practice with evidence-based protocols to maximize outcomes and reduce the health burden of patients.

Keywords: Heart failure; Reduced ejection fraction; Angiotensin receptor-neprilysin inhibitors; Sodium-glucose cotransporter-2; Beta-blocker; Mineralocorticoid receptor antagonists; Vericiguat

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Citation: Giannino G, Bocchino PP, Raineri C. Pharmacological therapy of chronic heart failure with reduced ejection fraction: A matter of pillars, entablature and proportions. *Brain & Heart*. 2025;3(4):8223. doi: 10.36922/bh.8223

Received: December 26, 2024

1st revised: April 17, 2025

2nd revised: May 7, 2025

Accepted: May 12, 2025

Published online: July 11, 2025

1. Introduction

Heart failure (HF) represents a clinical syndrome defined by the presence of cardinal symptoms – such as breathlessness, ankle swelling, and fatigue – and objective signs, including elevated jugular venous pressure, pulmonary crackles, and peripheral edema.[1]

The etiology of HF lies in a structural and/or functional abnormality of the heart, which results in elevated intracardiac pressures and/or inadequate cardiac output, observable either at rest or during physical exertion. According to left ventricular ejection fraction (LVEF) measurements, HF is classified into three categories: reduced LVEF (≤40%), mildly reduced LVEF (41 – 49%), and preserved LVEF (≥50%). HF with reduced ejection fraction (HFrEF) represents a substantial burden on global healthcare systems, affecting over 60 million individuals.[2,3] The advent of evidence-based therapies has resulted in a notable improvement in clinical outcomes.

The four principal drug classes – angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors – constitute the "four pillars" of HFrEF therapy. Analogous to the grandeur of Greek temples, which resulted from the combination of pillars, entablature, and harmonious proportions among structural elements, the effective treatment of HFrEF requires the right proportions between different medications, alongside ancillary therapies, to achieve maximum efficacy (Figure 1). Empirical evidence indicates that patients often receive inadequate dosing or delayed initiation, thereby limiting the potential benefits of these therapies. Early initiation of these drugs, ideally within 30 days of diagnosis or decompensation, has been demonstrated to reduce both morbidity and mortality.[4]

This review describes the broad spectrum of currently available therapies for HFrEF, focusing on the importance of individualized, patient-tailored treatment and the uptitration of medications to the target doses used in clinical trials.

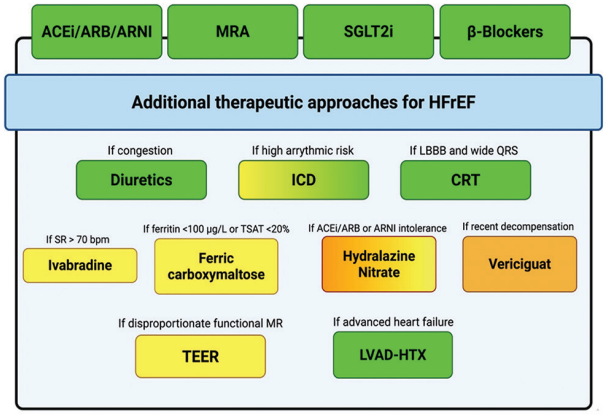

Figure 1. Guideline-directed and adjunctive therapies for HFrEF. The "four pillars" of HF treatment—ACEi, ARBs, or ARNIs, MRAs, SGLT2-i, and beta-blockers—represent the core pharmacological therapy and are supported by Class I recommendations (indicated in green). Beyond these foundational drugs, additional treatments are considered based on the patient's clinical profile. These include device-based therapies, such as ICDs and CRT, as well as pharmacological agents, such as ivabradine, ferric carboxymaltose, and vericiguat. Advanced options, including TEER and LVAD, and heart transplantation, are considered in selected cases. The color-coding reflects the strength of recommendation as per ESC classification: green indicates Class I (recommended), yellow indicates Class IIa (should be considered), and orange indicates Class IIb (may be considered). This structured yet individualized approach aims to optimize clinical outcomes by tailoring therapy to the specific needs of each patient with HFrEF. Image created by authors. Abbreviations: ACE: Angiotensin converting enzyme; ARBs: Angiotensin II receptor blockers; ARNI: Angiotensin receptor-neprilysin inhibitor; CRT: Cardiac resynchronization therapy; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HTX: Heart transplant; ICDs: Implantable cardioverter defibrillators; LBBB: Left bundle branch block; LVAD: Left ventricular assist devices; MR: Mitral regurgitation; MRA: Mineralocorticoid receptor antagonist; SR: Sinus rhythm; TEER: Transcatheter edge-to-edge repair; TSAT: Iron, transferrin saturation.

2. The four pillars

2.1. Inhibitors of the renin-angiotensin-aldosterone system

ACE inhibitors (ACEi) inhibit the conversion of angiotensin I to angiotensin II, thereby reducing arteriolar constriction and decreasing systemic vascular resistance and cardiac afterload. In addition, ACEi induce positive cardiac remodeling by antagonizing the fibrotic processes mediated by angiotensin II. The CONSENSUS[5] and SOLVD[6] trials demonstrated that ACEi reduce HF hospitalizations and mortality in patients with symptomatic HFrEF.

ARBs are valuable options in patients who are intolerant to ACEi due to side effects, such as cough or angioedema. ARBs block the angiotensin II type 1 receptor, resulting in reduced vasoconstriction, diminished aldosterone release, and positive cardiac remodeling. The efficacy of ARBs in HFrEF was demonstrated in the ELITE II[7] and Val-HeFT[8] trials. Moreover, the CHARM-Overall trial[9] indicated that candesartan was associated with a reduction in all-cause mortality and hospitalizations across a range of HF severities. ARBs offer comparable benefits to ACEi without the bradykinin-mediated adverse effects, thereby providing a valuable alternative for a broad spectrum of HF patients.

The combination of sacubitril and valsartan targets two critical pathways in the management of HFrEF. By blocking the angiotensin II receptor, ARNI reduces vasoconstriction, sodium retention, and the detrimental effects of the renin-angiotensin-aldosterone system. Concurrently, neprilysin inhibition elevates the levels of beneficial peptides, including natriuretic peptides, bradykinin,

and adrenomedullin, which promote vasodilation, natriuresis, and diuresis, thereby reducing cardiac workload and enhancing heart function.[10] The results of the PARADIGM-HF trial[11] demonstrated that ARNI therapy significantly reduces the risk of cardiovascular death and HF hospitalization in comparison to traditional ACEi therapy. Thus, for patients with chronic symptomatic HFrEF who are already tolerating ACEi or ARBs, switching to ARNI therapy is strongly recommended to further reduce the risk of morbidity (HF hospitalization) and mortality (cardiovascular death) (Class I recommendation, Level of Evidence B).[1] Furthermore, more recent evidence suggests that ARNI may be considered as a new treatment option in patients hospitalized with acute HFrEF who have stabilized before discharge.[12,13]

2.2. Beta-blockers

Beta-blockers, such as metoprolol, carvedilol, bisoprolol, and nebivolol mitigate the harmful effects of chronic sympathetic nervous system activation in HFrEF. They reduce heart rate and myocardial oxygen demand, thereby slowing disease progression and reducing the risk of arrhythmias.[11]

Furthermore, beta-blockers exert anti-inflammatory effects that can be beneficial in the context of HF. The MERIT-HF,[14] CIBIS-II,[15] COPERNICUS,[16] and SENIORS[17] trials have demonstrated that metoprolol, bisoprolol, carvedilol, and nebivolol, respectively, confer a survival benefit in patients with HFrEF. Beta-blockers should be initiated at a low dose and gradually uptitrated to the maximum tolerated dose. The vasodilatory effects of carvedilol and nebivolol may provide benefit in patients with high blood pressure, elevated filling pressures, or severe mitral or aortic regurgitation. The decision on which specific beta-blocker to use should be made on the patient's individual profile and tolerance, with the aim of optimizing overall HF care.

2.3. MRAs

MRAs act by inhibiting aldosterone receptors, a hormone that promotes sodium retention, potassium excretion, and myocardial fibrosis. By antagonizing aldosterone at its receptor sites, MRAs help mitigate fluid retention, reduce cardiac remodeling, and decrease the risk of arrhythmias.[18]

The RALES[19] and EMPHASIS-HF[20] trials demonstrated that MRAs are associated with a reduction in mortality and HF hospitalizations in patients with HFrEF. Despite these clinical benefits, MRAs are associated with potential side effects, notably hyperkalemia. Careful adjustment of other classes of drugs that may increase potassium levels is necessary to allow the maintenance or uptitration of MRA therapy. These medications include ACEi, ARBs, ARNIs, non-steroidal anti-inflammatory drugs, calcineurin inhibitors, and trimethoprim. Potassium supplementation should be discontinued in the presence of hyperkalemia. Close monitoring of potassium levels every 1 – 2 weeks is recommended when initiating or adjusting the dose of any of these agents, particularly when two or more drugs are used concurrently, in patients with impaired renal function, or elderly and frail individuals. Therefore, careful patient selection, appropriate dosing, and vigilant monitoring are imperative to ensure safety. Eplerenone, a more selective MRA, may be the preferred option for patients who experience side effects, such as gynecomastia while receiving spironolactone.

2.4. SGLT2-inhibitors (SGLT2-i)

Initially developed for the treatment of diabetes, SGLT2-i have demonstrated considerable benefits in patients with HFrEF, irrespective of their diabetic status. The primary pharmacodynamic effects of SGLT2-i include osmotic diuresis and natriuresis. By inhibiting the reabsorption of glucose and sodium, SGLT2-i facilitate the urinary excretion of these substances, thereby exerting a weak but non-negligible diuretic effect that contributes to a reduction in intravascular volume, pre-load, and congestion, while maintaining a more effective electrolyte balance compared to traditional diuretics. In addition, SGLT2-i enhances myocardial metabolism by shifting myocardial energy sources from glucose oxidation to ketone body metabolism. This metabolic shift may enhance energy efficiency in the failing heart, thereby potentially improving myocardial function. Moreover, it has been demonstrated that SGLT2-i can diminish pro-inflammatory cytokines and markers of oxidative stress, which can mitigate endothelial dysfunction and enhance vascular health in patients with HF.[21] Furthermore, SGLT2-i reduce intraglomerular pressure and prevent kidney injury by lowering albuminuria and glomerular hyperfiltration, which is of particular importance in HF patients who often present with concomitant renal impairment.[22]

The DAPA-HF[23] and EMPEROR-Reduced[24] trials provided evidence that dapagliflozin and empagliflozin are effective in reducing cardiovascular mortality and HF hospitalizations. The benefits of SGLT2-i are evident within a few weeks of initiation, making them a valuable option for early intervention. Moreover, the tolerability and renal-protective effects of SGLT2-i underscore its role as a fundamental treatment for HFrEF, complementing the effects of other HF medications.

3. The proportions

The emphasis on the prompt initiation of evidence-based therapies reflects the understanding that the cumulative

effect of multiple therapies provides comprehensive protection. The new guidance indicates that initiating treatment with low doses of essential drugs offers immediate and additive benefits, thereby establishing the foundation for subsequent dose adjustments based on patient-specific tolerability.[1] This approach effectively reduces delays in treatment initiation and ensures that patients receive comprehensive and mechanism-based coverage.

Despite the importance of starting with the "four pillars" as early as possible, discontinuation and underdosing of HF therapy remain critical challenges,[25] often associated with worsened clinical outcomes, such as increased mortality and hospitalizations. Common causes include side effects, such as hyperkalemia, hypotension, and renal dysfunction, as well as systemic barriers, such as inadequate titration protocols and patient non-adherence.

Evidence strongly supports the benefits of achieving target doses of HF therapies, with structured titration shown to significantly improve outcomes. The PARADIGM-HF trial demonstrated that ARNI reduced cardiovascular mortality by 20% and HF hospitalizations by 21% when patients achieved target doses. The BIOSTAT-CHF project[26] highlights key aspects of uptitration for ACEi, ARBs, and beta-blockers in patients with HFrEF. The study reports that only 22% of patients achieved the recommended target dose of ACEi or ARBs, and just 12% reached the target dose of beta-blockers. Uptitration to <50% of the recommended dose was associated with significantly worse outcomes, including higher mortality and an increased risk of HF hospitalizations. In contrast, patients achieving 50 – 99% of the target dose experienced similar clinical benefits as those reaching ≥100%, reinforcing the importance of reaching at least halfway to guideline-recommended doses.

Similarly, MRAs, when titrated appropriately, can significantly improve survival and reduce hospitalizations across the full range of LVEF.[27] However, barriers to titration, such as hyperkalemia, often necessitate dose reductions or discontinuation, highlighting the need for innovative solutions.

One such innovation is the integration of potassium-binding agents, such as patiromer and sodium zirconium cyclosilicate.[28] These potassium binders act by binding potassium in the gastrointestinal tract, thereby reducing its absorption. The DIAMOND trial[29] demonstrated that patiromer allowed the safe continuation and optimization of renin-angiotensin-aldosterone system inhibitors, reducing interruptions due to hyperkalemia. These adjunctive therapies play a pivotal role in enabling patients to achieve and maintain target doses of life-saving medications and can be considered for the treatment of hyperkalemia.[1]

The optimization of guideline-directed medical therapy (GDMT) has the potential to significantly reduce the reliance on diuretics, thereby minimizing the associated risks, including electrolyte imbalances and renal dysfunction.[30] For example, SGLT2-i have shown natriuretic effects that contribute to improved fluid management and a reduced requirement for loop diuretics. Similarly, MRAs counteract aldosterone-mediated sodium retention, which further aids in volume control and allows for lower diuretic dosages. In addition, ARNIs have been demonstrated to improve clinical congestion scores, which can result in a reduction in diuretic dependence among patients with HF.

The STRONG-HF trial[31] reinforces the importance of rapid and systematic titration in HF management. This trial demonstrated that high-intensity care, involving rapid uptitration of ARNIs, beta-blockers, MRAs, and SGLT2-i within weeks of discharge, significantly reduced mortality and HF readmissions. Coupled with close monitoring of renal function, potassium levels, and hemodynamic parameters, this approach highlighted the feasibility and benefits of aggressive titration strategies.

The modern approach of HF treatment prioritizes the rapid and safe initiation of all "four pillars," rather than adhering to a strict and slow sequential order. The specific initial choices and timing are individualized based on the patient's clinical presentation, including factors, such as volume status, blood pressure, heart rate, and laboratory parameters, including potassium levels and renal function. The goal is to implement comprehensive therapy efficiently to maximize clinical benefits.[1,32,33] Hypotension may limit the simultaneous initiation or uptitration of ARNIs, ACEi, or ARBs and beta-blockers. Therefore, it is sometimes necessary to start one agent, assess tolerance, and then rapidly add another. Hyperkalemia may limit the implementation and rapid uptitration of MRAs and ARNIs, ACEi, or ARBs. However, adjustment of concurrent medications, dietary modifications, and the potential use of potassium binders may help reduce potassium levels and facilitate augmentation of HF treatment. In patients with impaired renal function, ACEi or ARBs should be initiated at a low dose and slowly increased under strict renal function assessment. Beta-blockers should be started and titrated with caution in patients with advanced HF and reduced cardiac output, as their negative inotropic effect may further worsen cardiac function. SGLT2-i are usually well-tolerated and can generally be commenced early with minimal side effects. However, proper hygiene is crucial for patients on SGLT2-I to help prevent genital and urinary tract infections.

To ensure the achievement of target drug doses, titration should be performed with modest dose increments at

intervals of one to four weeks. The dose may be doubled every two weeks if tolerated until the target dose is achieved. Nevertheless, drug titration must be individualized for each patient, with frequent monitoring to assess clinical, hemodynamic, and laboratory tolerance.

In conclusion, achieving optimal titration of HF therapies is critical for maximizing therapeutic benefits and improving patient outcomes. Structured, rapid titration protocols help obtaining the full benefits of GDMT while minimizing the risk of discontinuation or adverse effects.

4. The entablature

Alongside the "four pillars" of HFrEF therapy, ancillary therapies have been proposed to address persistent symptoms despite optimized medical therapy.

Vericiguat has been demonstrated to benefit patients with chronic HFrEF who experience worsening symptoms despite receiving GDMT. In the context of chronic HF, patients often present progressive deterioration in cardiac muscle strength, reduced cardiac output, and systemic complications associated with persistent endothelial dysfunction and impaired nitric oxide pathways. Vericiguat enhances soluble guanylate cyclase activity and increases cyclic guanosine monophosphate levels even in the absence of optimal nitric oxide concentrations, thereby improving cardiac contractility, reducing ventricular remodeling, and supporting more effective blood flow.[34]

The VICTORIA trial,[35] conducted in patients with chronic HF who had recently experienced decompensation events, showed a significant reduction in the composite outcome of cardiovascular death or HF hospitalization. The VICTOR trial is a Phase 3, randomized, placebo-controlled, ongoing study evaluating the efficacy and safety of vericiguat in patients with chronic HF and LVEF below 40% who have not experienced a recent worsening HF event. The results of this study will provide valuable insights into the potential expanded use of vericiguat in the management of chronic HF.

Ivabradine, hydralazine, digoxin, and omecamtiv mecarbil represent additional therapeutic agents in the management of HF. Ivabradine is a selective heart rate-reducing agent that inhibits the "funny" (I_f) current in the sinoatrial node. It is indicated for patients with chronic HF who have a high resting heart rate and are either receiving maximum beta-blocker therapy or are unable to tolerate beta-blockers.[36] The SHIFT trial evaluated ivabradine in patients with HFrEF (LVEF ≤35%), sinus rhythm, and heart rate ≥70 bpm despite beta-blocker therapy. Ivabradine significantly reduced the composite outcome of cardiovascular death or HF hospitalization. Based on these findings, the European Society of Cardiology (ESC) Guidelines recommend ivabradine (Class IIa) for symptomatic HFrEF patients with elevated heart rate despite beta-blocker therapy.[1]

Hydralazine, a vasodilator that reduces afterload, is often administered in conjunction with isosorbide dinitrate for patients intolerant to ACEi or ARBs. The A-HeFT trial[37] showed that hydralazine and isosorbide dinitrate combination (H+ISDN), when added to standard therapy, reduced mortality by 43% and hospitalizations by 33% in Black patients with HFrEF. It is recommended as a Class I for self-identified Black patients with NYHA class III–IV symptoms on GDMT, and as Class IIa for patients who cannot tolerate ACEi, ARB, or ARNI.[1] Digoxin has been demonstrated to enhance myocardial contractility by inhibiting the sodium-potassium ATPase pump, thereby improving symptoms and exercise tolerance in patients with HF. The DIG trial[38] found that while digoxin did not reduce mortality, it significantly reduced HF hospitalizations in patients with HFrEF in sinus rhythm. It remains a Class IIb option to reduce HF hospitalizations in symptomatic patients already receiving optimal therapy.

The novel cardiac myosin activator omecamtiv mecarbil has demonstrated efficacy in improving cardiac function and reducing HF events, as evidenced by the findings of the GALACTIC-HF trial.[39] When incorporated into a comprehensive HF treatment plan, these drugs can improve patient outcomes by targeting specific mechanisms of the disease.

5. The role of diuretics

The use of diuretics in chronic HF confers several significant therapeutic benefits, most notably the alleviation of signs and symptoms of congestive HF and a potential decrease in HF hospitalizations. By effectively managing the symptoms of HF and reducing the burden of fluid overload, diuretics play a crucial role in preventing acute exacerbations that often necessitate hospitalization.[1]

The primary diuretics recommended for the initial treatment of congestive HF include loop diuretics, such as furosemide, bumetanide, and torsemide. Their dosages should be carefully titrated based on the patient's clinical status and response, particularly after other HF therapies have been initiated. Weight monitoring is considered an invaluable tool for assessing the degree of fluid retention and for guiding the selection of the optimal diuretic strategy. In cases where a single diuretic agent does not provide adequate diuretic response, the addition of a thiazide diuretic, such as hydrochlorothiazide, metolazone may further stimulate diuresis through sequential nephron blockade. The dosage of diuretics should be carefully

tailored to each patient to achieve euvolemia – optimal fluid balance – while using the lowest possible effective dose. Once the patient's "dry weight" (weight without excess fluid) is achieved, dosage adjustments may be required to prevent dehydration, hypotension, and renal impairment.[40,41]

Optimizing diuretic therapy in chronic HF necessitates careful monitoring and adjustment of treatment to achieve the desired level of fluid balance while minimizing the potential for adverse effects.[40,41] In fact, while diuretics offer significant benefits in managing chronic HF, their use is also associated with potential risks and side effects that necessitate careful consideration and close monitoring. Daily weight monitoring provides a valuable assessment of fluid retention and the effectiveness of the diuretic regimen. Blood pressure should be checked regularly to detect hypotension, a potential side effect of diuretics. Frequent monitoring of serum electrolyte levels, including sodium, potassium, magnesium, calcium, and chloride, is crucial for identifying and managing any diuretic-induced imbalances. In addition, kidney function typically assessed by measuring serum creatinine and estimating the glomerular filtration rate, should be monitored periodically to evaluate the renal impact of diuretic therapy. This comprehensive approach to monitoring is fundamental to ensuring that diuretic therapy remains both effective in managing fluid overload and safe for the patient.

6. Comorbidities

HFrEF rarely exists in isolation. The presence of comorbidities significantly alters its clinical presentation, natural history, therapeutic approach, and prognosis. Among the most impactful are atrial fibrillation (AF), functional mitral regurgitation (FMR), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome (OSAS), and iron deficiency. These conditions share pathophysiological pathways with HFrEF – including neurohormonal activation, atrial and ventricular remodeling, and systemic inflammation – and often contribute to increased symptom burden, higher hospitalization rates, and elevated mortality.[1,42] Effective identification and tailored management of these comorbidities are therefore essential components of comprehensive HFrEF care.

6.1. AF in HFrEF

AF affects approximately 30 – 40% of patients with HFrEF and is associated with adverse outcomes, including an increased risk of stroke, reduced functional capacity, and higher mortality.[43] The 2024 ESC Guidelines emphasize a personalized approach to rhythm control, recommending early rhythm control strategies in symptomatic patients with HFrEF, especially when AF is suspected to contribute to worsening left ventricular dysfunction (Class IIa, Level B).[44] While rate control remains acceptable in clinically stable patients, rhythm control – including the use of antiarrhythmic drugs or catheter ablation – is prioritized when symptom relief or improvement in ventricular function is anticipated.

Randomized trials support this approach. The CASTLE-AF trial showed that catheter ablation significantly reduced mortality and HF hospitalizations in patients with symptomatic AF and LVEF <35%.[45] Similarly, the CRABL-HF trial demonstrated the non-inferiority of cryoballoon ablation compared to radiofrequency ablation in HFrEF patients, offering advantages in procedural duration and consistency of pulmonary vein isolation. These findings have strengthened the guideline recommendation that rhythm control is not only safe but potentially beneficial in appropriately selected patients with HFrEF and AF.

6.2. FMR

FMR is a common consequence of left ventricular dilation in HFrEF, resulting from leaflet tethering and annular dilation without primary valvular disease. It exacerbates symptoms by increasing volume overload, elevating left atrial pressures, and worsening pulmonary hypertension.[46] Both the COAPT and RESHAPE-HF2 trials have reshaped the role of transcatheter edge-to-edge repair (TEER) using MitraClip in this context.

The COAPT trial demonstrated that TEER significantly reduced all-cause mortality and HF hospitalizations in patients with severe FMR who remained symptomatic despite optimal GDMT.[47] These results were confirmed and extended by the RESHAPE-HF2 trial, which showed that TEER reduced the composite outcome of recurrent HF hospitalization and cardiovascular death, along with marked improvements in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire.[48] The 2021 ESC Guidelines now provide a Class IIa recommendation for TEER in symptomatic patients with FMR, LVEF 20 – 50%, and suitable mitral valve anatomy, provided that GDMT has been optimized.[49] Careful patient selection remains essential to achieving clinical benefit.

6.3. COPD

COPD is present in up to 30% of patients with HFrEF and significantly complicates both diagnosis and treatment.[50] Shared symptoms, such as dyspnea, fatigue, and exercise intolerance make it difficult to distinguish between HF and pulmonary causes of decompensation. COPD independently predicts poorer survival and increased hospitalizations,

especially when undiagnosed or inadequate treated.[51] A critical management challenge is the underutilization of beta-blockers due to concerns about bronchospasm. However, cardioselective beta-blockers, such as bisoprolol and metoprolol succinate, have been shown to be both safe and beneficial in this population.[52] Their use is supported by evidence-based guidelines and should not be withheld unless there is clear evidence of intolerance.

Pulmonary function testing and imaging can help clarify the relative contributions of HF and COPD to the symptom burden. Optimization of bronchodilator therapy, vaccination, and smoking cessation are integral components of management. Multidisciplinary care involving cardiologists and pulmonologists is often required for the best outcomes.

6.4. OSAS

OSAS is a highly prevalent and underdiagnosed comorbidity in HFrEF, affecting up to 50% of patients in some cohorts.[53] Intermittent hypoxia, sympathetic nervous system activation, and large negative intrathoracic pressure swings lead to increased afterload, systemic inflammation, and arrhythmogenicity – thereby exacerbating HF progression and contributing to atrial remodeling and AF onset. OSAS is also associated with poor quality of life and increased mortality in HFrEF patients.

Polysomnography remains the gold standard for diagnosis. Continuous positive airway pressure therapy has been shown to improve daytime symptoms, blood pressure control, and – in some cases – LVEF. However, the SERVE-HF trial raised concerns about the use of adaptive servo-ventilation in patients with central sleep apnea and HFrEF, due to an increased mortality risk observed in this subgroup.[54] Therefore, accurate differentiation between obstructive and central sleep apnea is essential before initiating positive pressure therapy.

6.5. Iron deficiency

Iron deficiency is a prevalent and significant comorbidity in HF, affecting up to 50% of patients with both reduced and preserved ejection fractions.[55] It contributes to symptom progression, reduced exercise capacity, and increased mortality. The mechanisms underlying iron deficiency in HF are complex and encompass chronic inflammation, reduced dietary intake, malabsorption, and increased iron utilization due to elevated metabolic demands. The AFFIRM-AHF trial,[56] along with other studies, have demonstrated that intravenous iron supplementation, particularly with ferric carboxymaltose, can enhance functional status and mitigate the risk of HF hospitalizations.

6.6. HF with improved ejection fraction (HFimpEF)

HFimpEF refers to patients with previously reduced LVEF ≤40% who, after treatment, demonstrate an increase in LVEF of at least 10% points to >40%.[1] Clinically, HFimpEF often represents a state of remission rather than a permanent cure. While these patients have a substantially better prognosis than those with persistent HFrEF, the underlying myocardial abnormalities and predisposition to dysfunction usually persist. Pathophysiologically, HFimpEF is typically achieved through disease-modifying therapies, such as β-blockers, renin-angiotensin system (RAS) inhibitors, MRAs, SGLT2-i, as well as device-based interventions, such as cardiac resynchronization therapy, which alleviate hemodynamic stress and reverse cardiac remodeling. However, residual molecular and structural abnormalities, such as fibrosis and genetic predispositions may remain, indicating that normalization of LVEF does not guarantee full myocardial recovery.

A key concern in HFimpEF is the risk of relapse following the withdrawal or downtitration of GDMT. The pivotal TRED-HF trial[57] demonstrated that in patients with dilated cardiomyopathy who achieved HFimpEF on GDMT, withdrawal of HF medications led to relapse in approximately 40 – 44% within 6 months. A longer-term follow-up of the TRED-HF[58] trial confirmed the persistence of this vulnerability, with approximately 61% of such patients relapsed within 5 years. Important predictors of relapse have been identified, such as patients with longer HF duration, more severe initial LV dysfunction, and underlying genetic or cardiac pathology, are at higher risk of LVEF decline despite initial improvement.[59]

The STOP-CRT trial[60] provides insight into a specific clinical scenario involving patients with non-ischemic cardiomyopathy who achieved a normalized EF (≥50%) with the aid of CRT. In this small randomized controlled trial, subjects were assigned to either continue or systematically withdraw beta-blockers and RAS inhibitors after their CRT response. Over 2 years, the rates of adverse LV remodeling or clinical deterioration were low and did not differ significantly between those who remained on GDMT and those whose medications were withdrawn given the relapse risk, contemporary guidelines and reviews caution against considering HFimpEF patients as cured. They recommend continuing HF medications, including ACEi, ARB, or ARNI, beta-blockers, MRAs, and SGLT2-i, on a long-term basis unless there are specific reasons to discontinue therapy. Nonetheless, recent evidence, although derived from observational studies, highlights the clinical relevance of evaluating the impacts of withdrawing individual classes of HF medications rather than adopting a blanket discontinuation approach as implemented

in the TRED-HF trial. Basile *et al.*[61] analyzed 8,728 HFimpEF patients from a multicenter registry and found that discontinuing RAS inhibitors, ARNIs, or MRA was independently associated with an approximately 36 – 38% higher risk of cardiovascular death or HF hospitalization at 1 year compared to those who continued therapy. No significant harm was observed with beta-blocker withdrawal overall. However, subgroup analysis suggested that even beta-blockers should be continued until LVEF is clearly within the normal range (≥50%). Withdrawal in patients whose EF had only improved to the 40 – 49% range was associated with poorer outcomes. Therefore, while research into personalized de-escalation strategies is underway, including trials investigating whether specific medication classes, such as beta-blockers can be tapered in stable HFimpEF, the prevailing consensus is to continue GDMT for most patients until more evidence become available to support individualized treatment reduction.

7. Future directions

The future treatment of HFrEF may involve novel drug therapies that target additional potential mechanisms.[62] Istaroxime and BMS-986231 offer distinctive advantages for enhancing calcium handling in cardiomyocytes by facilitating sarco-endoplasmic reticulum Ca^{2+}-ATPase 2a activity and donating nitric oxide, respectively. The sodium-hydrogen exchanger 1 inhibitor cariporide addresses cardiomyocyte hypertrophy and apoptosis, while ranolazine maintains Na^{+} and Ca^{2+} homeostasis, thereby demonstrating its protective effect against cardiac hypertrophy. Mitochondrial function is enhanced by neladenoson and elamipretide, with the latter stabilizing cytochrome C to promote ATP synthesis. Pecavaptan, a dual vasopressin receptor antagonist, modulates signaling pathways to enhance cardiac and vascular function. Danicamtiv has been demonstrated to enhance cardiac contractility by influencing myofibrillar activity without altering intracellular Ca^{2+} levels. Finally, liraglutide, a glucagon-like peptide-1 receptor agonist, has the potential to modulate cardiac inflammation and safeguard cardiomyocyte metabolism, thereby enriching the therapeutic landscape of HF.

The advent of emerging technologies, such as gene therapy, offers promising new interventions by targeting specific genes linked to adverse cardiac remodeling. Furthermore, human induced pluripotent stem cells have emerged as a potential therapeutic strategy for HF. These developments underscore the evolving landscape of HF treatment and the prospect of transformative advancements in enhancing patient outcomes.

8. Conclusion

Initial and intensive quadruple treatment combining multiple medications can alleviate symptoms, enhance quality of life, and reduce the risk of cardiovascular death and hospitalizations in patients with HFrEF. However, GDMT alone may not be sufficient for all patients. Those who continue to experience symptoms or have a persistent risk of adverse events may require additional approaches to further improve outcomes. Long-term adherence to GDMT with progressive uptitration to target doses is crucial for preventing disease recurrence and worsening cardiac function, even after symptomatic improvement or recovery of heart function. The framework of HF treatment rests upon well-established pillars, with the therapeutic structure supported by the entablature that connects these elements. The intensity, dosage, and sequencing of each treatment component must be tailored based on the specific clinical characteristics of each patient.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Percutaneous patent foramen ovale closure in refractory migraine with aura: A case report with literature review and pathophysiological insights

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(This article belongs to the *Special Issue: Correlation Between Ischemic Heart Disease and Cerebrovascular Disease: The Clinical Practice Messages from the Aosta Meeting in June 2024*)

Abstract

Patent foramen ovale (PFO), present in 20 – 30% of the population, is often asymptomatic but may allow right-to-left blood shunting that bypasses pulmonary filtration. This phenomenon has been implicated in cryptogenic stroke and migraine with aura, where microemboli or vasoactive substances may trigger cortical spreading depression. This work, through a clinical case, evaluates the role of percutaneous PFO closure in managing refractory migraine with aura by reviewing current evidence and pathophysiological mechanisms. Initially used for stroke prevention, PFO closure has been proposed as a compassionate treatment for refractory migraines. Although observational studies reported reductions in migraine frequency and severity, randomized trials have been inconsistent. Meta-analyses suggest benefits in specific subgroups, such as patients with aura, but heterogeneity limits conclusions. This case report presents the case of a 22-year-old patient with refractory migraine and a confirmed PFO who underwent successful percutaneous closure, achieving complete migraine remission, improved quality of life, and no evidence of residual shunting. Larger trials are needed to refine patient selection and validate guidelines.

Keywords: Migraine; Patent foramen ovale; Percutaneous closure

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Citation: Marchisio G, Albani S, Scacciatella P. Percutaneous patent foramen ovale closure in refractory migraine with aura: A case report with literature review and pathophysiological insights. *Brain & Heart.* 2025;3(4):8132. doi: 10.36922/bh.8132

Received: December 23, 2024

1st revised: March 30, 2025

2nd revised: April 23, 2025

Accepted: April 27, 2025

Published online: May 21, 2025

1. Background

Patent foramen ovale (PFO) is a common congenital cardiac anomaly resulting from the incomplete closure of the foramen ovale – a fetal circulatory shunt – after birth. Present in 20 – 30% of the general population, PFO is often clinically silent and discovered incidentally. However, its potential to allow right-to-left shunting of blood can have significant pathological consequences. This shunt permits the passage of microemboli or vasoactive substances from the venous to the arterial circulation, bypassing the pulmonary filtration system. Such mechanisms have been implicated in various conditions, including cryptogenic stroke, decompression sickness, and, notably, migraine with aura.[1,2]

The association between PFO and migraine has garnered considerable interest due to observational studies reporting a higher prevalence of PFO in patients with migraine with aura compared to the general population. The proposed pathophysiological link

involves the triggering of cortical spreading depression – a wave of neuronal and glial depolarization associated with migraine aura – by microemboli or chemical mediators crossing through the PFO.[2] This has led to the hypothesis that closure of the PFO might reduce the frequency or severity of migraine attacks by eliminating the right-to-left shunt.

Percutaneous PFO closure has emerged as a minimally invasive intervention primarily used to prevent recurrent cryptogenic strokes in selected patients. Given its success in reducing stroke risk and its safety profile, there has been interest in evaluating this procedure as a therapeutic option for patients with migraine, especially those with aura who are refractory to conventional medical treatments.

Scientific studies assessing the efficacy of percutaneous PFO closure specifically for migraine relief have yielded conflicting results. While observational studies have demonstrated reductions in migraine frequency and severity post-closure, individual randomized controlled trials (RCTs) and their meta-analyses failed to show significant benefits over optimized medical therapy.[3-8] Meta-analyses suggest that certain subgroups – such as migraine with aura patients or those with coexisting cerebrovascular diseases – may derive more pronounced benefits.[8,9] However, limitations in study designs and heterogeneity among patient populations, particularly regarding migraine subtypes (aura vs. no aura), variability or lack of any medical therapy assessment for migraine, and inconsistencies in migraine evaluation, have hindered the ability to draw definitive conclusions.[2] More precise phenotyping using multidimensional data are essential for future RCTs. Considering these findings, percutaneous PFO closure is currently considered under compassionate use provisions for selected patients with refractory migraine who have failed to respond to maximal medical therapy.

In this context, this study presents a detailed case of a 22-year-old patient with refractory migraine with aura who underwent percutaneous PFO closure under a compassionate use protocol. The manuscript describes the patient's clinical course, the extensive diagnostic workup – including advanced neuroimaging and transcranial Doppler (TCD) studies – and the subsequent interventional procedure. It also reviews the evolution of the evidence base by discussing landmark studies and meta-analyses, and explores the proposed pathophysiological mechanisms underpinning the association between PFO and migraine. Ultimately, the aim is to integrate clinical observations with current literature to provide a comprehensive understanding of the potential role of PFO closure in migraine management and to highlight key areas for future research.

2. Case presentation

A 22-year-old female with a lifelong history of migraine with visual aura presented for evaluation after a marked deterioration in her condition. The patient had experienced intermittent episodes of migraine since childhood, around 6 years old, with visual phenomena – such as scintillating scotomas – preceding the headache phase. Over time, particularly after puberty, both the frequency and severity of these episodes had increased significantly, becoming refractory around age 16, with an average of 8 headache days per month. Despite multiple pharmacological interventions, including non-steroidal anti-inflammatory drugs, triptans (e.g., sumatriptan and rizatriptan), and newer therapies (e.g., calcitonin gene-related peptide monoclonal antibodies), her migraine attacks remained refractory. These persistent, debilitating episodes had a profound impact on her daily activities, academic performance, and overall quality of life. A Migraine Disability Assessment (MIDAS) score of 21 indicated moderate-to-severe functional impairment, warranting further investigation into potential underlying mechanisms.

Her cardiac history was notable for the incidental detection of a left-to-right shunt at the interatrial septum during childhood, first identified at age seven. Serial echocardiographic evaluations over the years consistently documented a Qp/Qs ratio of approximately 1.2:1, which is indicative of a small shunt that had not yet resulted in significant hemodynamic compromise or right heart chamber dilation. Nevertheless, emerging evidence in the literature suggested that even small PFOs might intermittently permit right-to-left shunting under conditions of transient increases in right atrial pressure – such as during Valsalva maneuvers. This possibility led the multidisciplinary team to re-examine her condition, particularly in light of her refractory migraine symptoms.

A comprehensive neurological workup was undertaken to rule out other potential causes of her symptoms. At age 20, the patient underwent brain magnetic resonance imaging and magnetic resonance angiography; both studies were unremarkable and effectively excluded the presence of silent ischemic lesions, arteriovenous malformations, or aneurysms. Approximately 1 year later, a TCD study was performed. The TCD study revealed a characteristic "curtain-like" pattern of microbubble signals after the administration of contrast, strongly indicative of a persistent right-to-left shunt. Such a pattern is suggestive of intermittent paradoxical embolism – a process where venous blood, laden with microemboli and vasoactive substances, bypasses the pulmonary filtration system and enters the cerebral circulation, potentially triggering migraine episodes.

Given the severity of her symptoms and her failure to respond to a broad spectrum of medical therapies, the multidisciplinary team – comprising interventional cardiologists, neurologists, and headache specialists – concluded that the patient was an appropriate candidate for percutaneous PFO closure. This decision was further supported by emerging literature linking PFO closure with improvements in migraine, particularly in patients with aura. The patient was extensively counseled regarding the experimental nature of PFO closure for migraine treatment. Detailed discussions encompassed the potential benefits, inherent risks, and uncertainties associated with the procedure. Special attention was given to her known allergy to nickel, leading to the decision to utilize a nickel-free closure device.

The procedure was performed in a cardiac catheterization laboratory under conscious sedation, with both fluoroscopic and transesophageal echocardiography guidance (Figure 1). Vascular access was obtained through the femoral vein, and a guidewire was advanced into the right atrium. High-resolution imaging of the interatrial septum confirmed the presence of a PFO (Figure 2). Although the initial procedural plan involved deploying a 25-mm device, intra-procedural imaging revealed that a 30-mm Gore® CARDIOFORM Septal Occluder (Gore, USA) would be more appropriate to ensure complete defect closure. The device was deployed meticulously, and contrast-enhanced echocardiography immediately confirmed the complete abolition of the right-to-left shunt (Figures 3-6). The procedure was uneventful; no complications, such as arrhythmia, pericardial effusion, or device embolization, were observed.

Post-procedure, the patient was managed with dual antiplatelet therapy, consisting of aspirin 100 mg daily in combination with clopidogrel 75 mg daily for 3 months. This regimen was then transitioned to aspirin monotherapy for an additional 12 months to ensure complete endothelialization of the occluder. Follow-up evaluations at 1 month and 6 months post-procedure were highly encouraging. Serial transthoracic echocardiograms demonstrated that the closure device remained well-seated, with no residual shunting or evidence of new right heart abnormalities. Clinically, the patient reported a marked improvement in her migraine symptoms: by the 6-month follow-up, she had achieved complete remission of her migraine episodes – both with and without aura – resulting in a dramatic improvement in her quality of life and overall functional capacity. At the 1-year follow-up visit, the patient once again reported the absence of any migraine attacks, with a MIDAS score of 0.

This case is a vivid example of the potential for percutaneous PFO closure to ameliorate refractory migraine symptoms. It underscores the critical importance of a comprehensive diagnostic workup – including advanced neuroimaging and TCD studies – in identifying

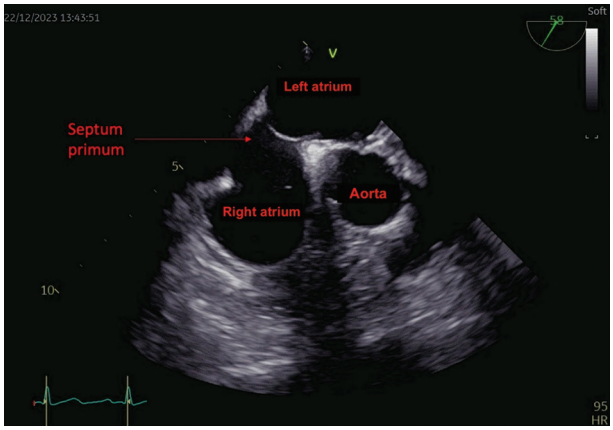

Figure 1. Initial findings in intraoperative transesophageal echocardiography

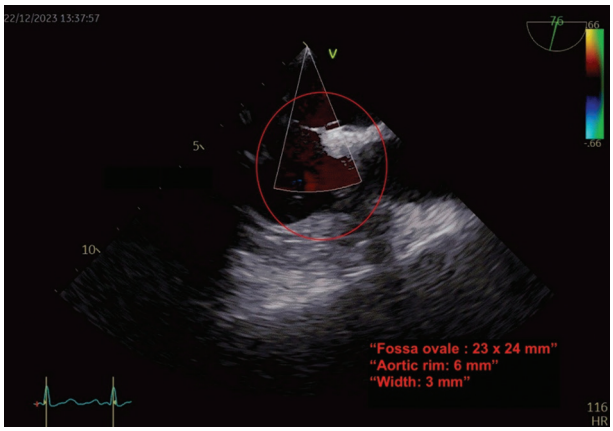

Figure 2. Doppler echocardiography revealed evidence of the basal shunt related to the patent foramen ovale

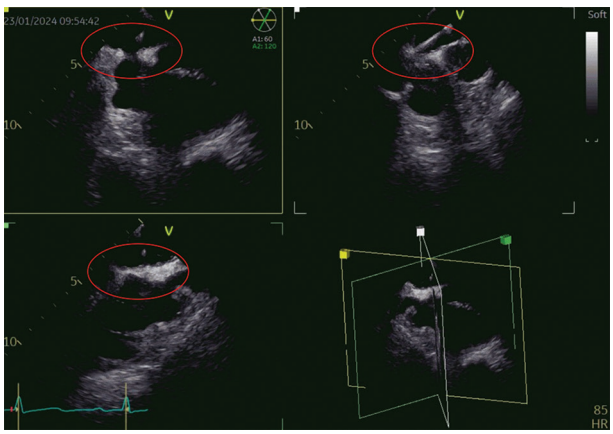

Figure 3. Intraoperative transesophageal echocardiography images show the device positioning in triplane

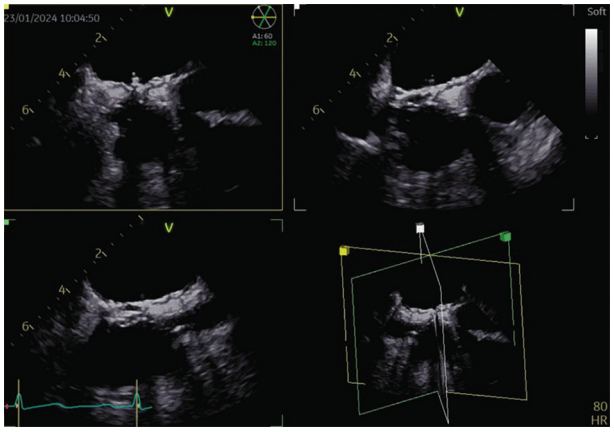

Figure 4. Intraoperative transesophageal echocardiography images show the inserted device

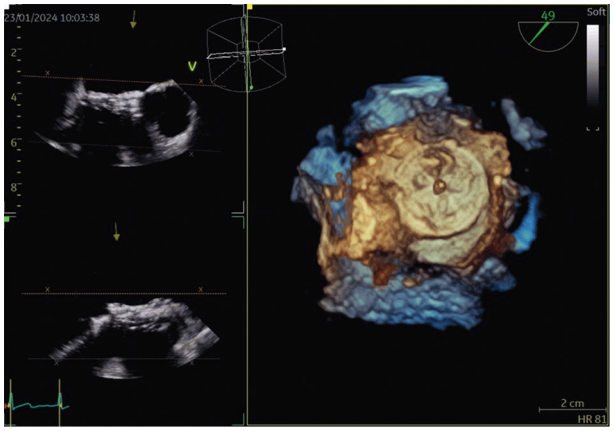

Figure 5. Intraoperative transesophageal echocardiography images show the inserted device with 3D reconstruction

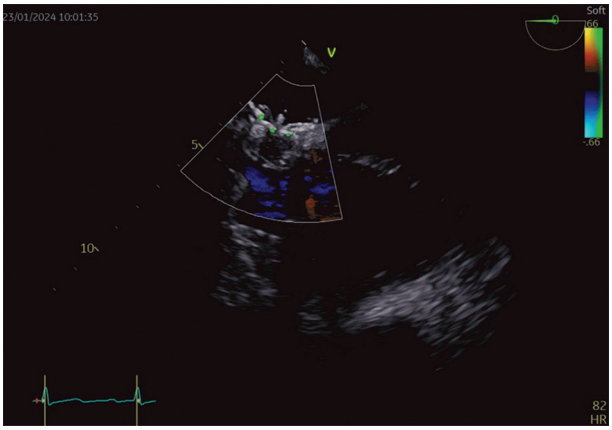

Figure 6. Echo-contrast imaging shows complete abolition of the native left-to-right and right-to-left shunts after device apposition

candidates who might benefit from this interventional approach (Figure 7). The dramatic improvement observed in this patient, following the elimination of a right-to-left shunt, highlights the clinical significance of reducing cerebral exposure to unfiltered microemboli and vasoactive substances. The decision to proceed with PFO closure, although made under a compassionate use framework, was strongly supported by an evolving body of literature that suggests a causal relationship between PFO and migraine, particularly in the context of migraine with aura.

3. Discussion

This section includes a literature review and the interpretation of the findings in this study.

3.1. Literature review

The association between PFO and migraine, particularly migraine with aura, has been investigated for over two decades (Table 1). The successful resolution of migraine symptoms in our case report aligns with findings from multiple studies, though the evidence remains complex and nuanced. Early observational research demonstrated a significant reduction in migraine severity scores following transcatheter PFO closure, with complete relief in 29% of patients and substantial improvement in 59% of their cohort.[10] These encouraging results are subsequently supported by Dubiel *et al.*,[11] who reported complete resolution of migraine headaches in 24% of patients and significant improvement in 63% following transcatheter closure of interatrial communications.

The pathophysiological mechanism potentially linking PFO to migraine involves paradoxical microembolism or vasoactive substances bypassing pulmonary filtration through right-to-left shunting, subsequently triggering cortical spreading depression and migraine attacks.[10,12] This hypothesis gained traction through multiple observational studies showing a bidirectional association between PFO prevalence and migraine, particularly with aura.[13]. Luermans *et al.*[14] provided additional support, documenting a significant reduction in overall migraine prevalence from 28.6% to 10.7% following percutaneous PFO closure, with an even more pronounced decrease in migraine with aura (from 11.9% to 2.4%).

However, the first large RCT, migraine intervention with STARFlex technology, failed to demonstrate significant differences in migraine cessation between intervention and sham.[5] Designed as a multicenter, double-blind, sham-controlled trial, it aimed to rigorously evaluate the efficacy of PFO closure in patients with refractory migraine. Patients with refractory migraine with aura were randomized to receive either percutaneous PFO closure or a sham procedure. Although the primary endpoint – complete cessation of migraine – was not met, the trial's secondary endpoints revealed a reduction in the number of migraine days in the closure group. This discrepancy

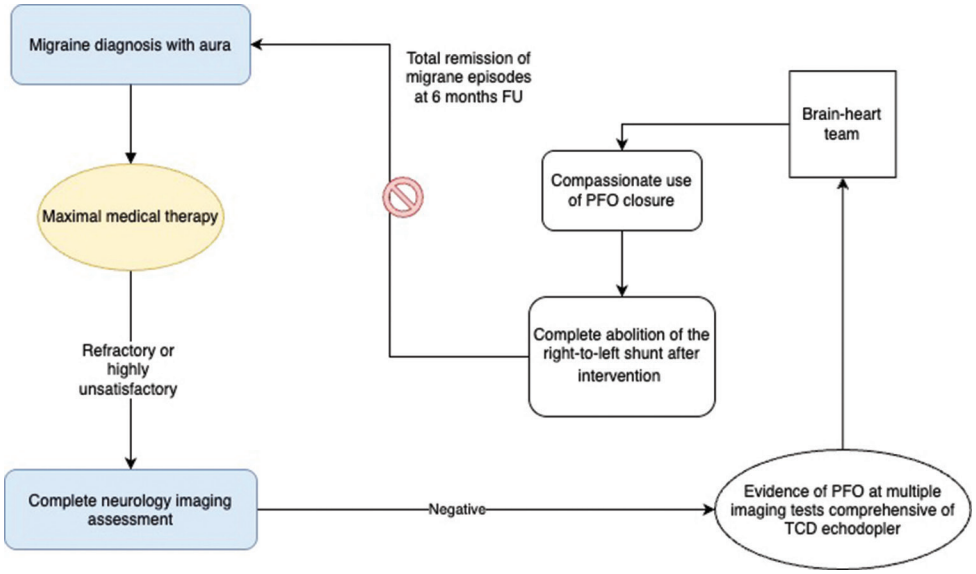

Figure 7. Flowchart of the studied case
Abbreviations: FU: Follow-up; PFO: Patent foramen ovale; TCD: Transcranial Doppler.

between primary and secondary outcomes highlights one of the key challenges in migraine research: The difficulty in quantifying migraine symptoms and accounting for the substantial placebo effect often observed in such trials. The interpretation of the results was additionally limited by confounding factors: the study population had a relatively low migraine frequency and a high rate of residual shunting after closure.

This discrepancy between observational and randomized evidence prompted more rigorous investigations. Two subsequent multicenter RCTs – PREMIUM[4] and the trial by Mattle *et al.*[3] – similarly failed to meet their primary endpoints. The PREMIUM trial showed no significant difference in responder rates between groups, though secondary analyses revealed greater reduction in headache days and higher complete remission rates in the PFO closure group compared to controls. Likewise, Mattle *et al.*[3] reported no significant reduction in monthly migraine days after PFO closure versus medical management.

The contradictory findings between observational studies and RCTs might be explained by several factors, including placebo effects, patient selection criteria, procedural techniques, and follow-up duration. Long-term observational data by Trabattoni *et al.*[15] demonstrated sustained benefits, with migraine cessation in 46% of patients and reduced recurrence rates in 40% at 12-month follow-up. This suggests that temporal considerations may be important when evaluating efficacy. More recent meta-analyses have attempted to reconcile these conflicting results. For example, Shi *et al.*[7] found that PFO closure significantly improved migraine symptoms in 81% of patients with aura compared to 63% without aura, indicating that aura presence should guide patient selection. This observation is reinforced by Elbadawi *et al.*,[6] who noted a more pronounced reduction in migraine attacks among patients whose majority of attacks involve aura. In addition, Zhang *et al.*[16] reported significant increases in complete cessation of migraines following PFO closure compared to controls. The latest meta-analysis by Silalahi and Hariyanto[17] confirmed a significant reduction in monthly migraine frequency and days, though no significant difference in complete resolution.

Importantly, patient selection appears to be critical. Rigatelli *et al.*[18] demonstrated a significant reduction in mean MIDAS scores (from 35.8 to 8.3) when focusing on patients with high-risk anatomic and functional PFO characteristics. Similarly, Wahl *et al.*[19] identified the presence of aura and high baseline pain intensity as predictors of positive response to closure. These findings suggest that carefully selected patients – particularly those with migraine with aura and specific PFO characteristics – may derive greater benefit from the intervention.

Safety considerations remain paramount in evaluating this procedure. The comprehensive review by Silalahi and Hariyanto[17] reported infrequent adverse events, including atrial fibrillation and access site complications. Milev *et al.*[20] documented no new incidences of stroke, TIA, or syncope during a 2-year follow-up, supporting the procedure's safety profile. Nevertheless, Mattle *et al.*[3] reported five adverse events in their trial, though none with permanent consequences.

Table 1. Literature review

Title	Authors	Journal	Year	Main findings	Participant count	Study design
Transcatheter closure of patent foramen ovale: A new migraine treatment?	Morandi *et al.*[10]	Journal of Interventional Cardiology	2003	- Transcatheter closure of PFO significantly reduced migraine severity scores in patients with and without aura. - Five out of 17 patients experienced complete relief from migraines, while 10 showed substantial improvement. - The procedure achieved complete occlusion of PFO in most patients, correlating with reduced microembolic signals and improved migraine symptoms.	Total participants: 17	Prospective, single-arm, non-controlled observational study with a pre–post design
Transcatheter closure of patent foramen ovale in patients with migraine headache	Spies and Schräder[25]	Journal of Interventional Cardiology	2006	- Retrospective case–control studies suggest a link between PFO closure and improvement in migraine headaches. - Few prospective studies confirm these initial findings. - A RCT did not achieve its primary outcome of resolving migraines with PFO closure.	NA	Systematic review
Patent foramen ovale in patients with migraine headache. Should it be closed?	Spies *et al.*[26]	Minerva Medica	2007	- Retrospective case–control studies suggest a link between PFO closure and improvement in migraine headaches. - The only RCT did not achieve its primary outcome of resolving migraines after PFO closure. - The evidence for the benefit of PFO closure on migraines is intriguing but not convincing, and more research is needed.	NA	Systematic review
Migraine intervention with STARFlex technology trial: A prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache	Dowson *et al.*[5]	Circulation	2008	- No significant difference was found in migraine headache cessation between the implant and sham groups. - Secondary endpoints were not achieved, but exploratory analysis suggested a reduction in migraine days in the implant group. - The implant group experienced more procedural serious adverse events, all of which were transient.	Total participants: 432 Participants randomized: 147 - Implant group: 74 - Sham group: 73	Randomized, double-blind, sham-controlled, prospective, multicenter trial

(Cont'd...)

Table 1. ***(Continued)***

Title	Authors	Journal	Year	Main findings	Participant count	Study design
Closure of a patent foramen ovale is associated with a decrease in the prevalence of migraine	Luermans *et al.*[14]	Acta Cardiologica	2008	- Percutaneous PFO closure significantly reduced the overall prevalence of migraine from 28.6% to 10.7%. - The prevalence of migraine with aura significantly decreased from 11.9% to 2.4%. - Randomized placebo-controlled trials are needed to confirm these findings.	Total participants: 92	Prospective observational study
Migraine headache relief after percutaneous transcatheter closure of interatrial communications	Dubiel *et al.*[11]	Journal of Interventional Cardiology	2008	- Percutaneous transcatheter closure of patent interatrial communications resulted in complete resolution of migraine headaches in 24% of patients and significant improvement in 63%. - A significant reduction in the number, intensity, duration, and accompanying symptoms of migraine episodes was observed at a mean follow-up of 38 months.	Total participants: 191	Based on the information provided in the abstract, the study design appears to be a non-randomized, non-controlled, single-site, longitudinal observational study of 191 patients who underwent percutaneous transcatheter closure of patent interatrial communications, with assessment of migraine headache symptoms before and after the procedure over a long-term follow-up period.
Patent foramen ovale and migraine: A quantitative systematic review	Schwedt *et al.*[13]	Cephalalgia	2008	- There is an increased prevalence of PFO in individuals with migraines, especially those with aura, and vice versa, with significant odds ratios indicating an association. - The evidence supporting the association between PFO and migraines is low to moderate, limiting the strength of conclusions that can be drawn. - PFO closure may improve migraine patterns, but the evidence is very low, precluding definitive conclusions.	NA	Systematic review

(Cont'd...)

Table 1. ***(Continued)***

Title	Authors	Journal	Year	Main findings	Participant count	Study design
Migraine, stroke, and patent foramen ovale: a dangerous trio?	Butera *et al.*[12]	Journal of Cardiovascular Medicine	2008	- Seventy-two percent of patients undergoing percutaneous PFO closure after cryptogenic stroke were cured or improved significantly. - Patients with migraine with aura had a higher rate of complete resolution or significant improvement (81%) compared to those with migraine without aura (72%).	NA	Systematic review
Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case–control study	Vigna *et al.*[9]	JACC: Cardiovascular Interventions	2009	- PFO closure significantly reduced the frequency of total migraine attacks compared to controls. - A significant reduction in disabling migraine attacks was observed only in the PFO closure group. - A higher percentage of patients in the PFO closure group experienced complete disappearance or more than a 50% reduction in migraine attacks compared to controls.	Total participants: 82 - Closure group: 53 - Control group: 29	Prospective, non-randomized, controlled case–control study
Is it too early to recommend patent foramen ovale closure for all patients who suffer from migraine? A single-center study	Chessa *et al.*[30]	Journal of Cardiovascular Medicine	2009	- PFO closure resulted in complete migraine resolution in 26% of patients. - A ≥50% reduction in migraine attack frequency was observed in 52% of patients. - Improvement was independent of migraine type and other health factors, but widespread recommendation is premature pending further trials.	Total participants: 42	Observational cohort study
Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with high-risk anatomic and functional characteristics for paradoxical embolism	Rigatelli *et al.*[18]	JACC: Cardiovascular Interventions	2010	- Primary transcatheter PFO closure significantly reduced migraine symptoms, with a decrease in the mean MIDAS score from 35.8 to 8.3. - The procedure was successful in all cases without complications, and auras were eliminated in 100% of patients.	Total participants: 86 - Intervention group 40 - Control group 46	Prospective, non-randomized, non-controlled study

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Table 1. ***(Continued)***

Title	Authors	Journal	Year	Main findings	Participant count	Study design
Improvement of migraine headaches after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism	Wahl *et al.*[19]	Heart	2010	- PFO closure significantly reduced the frequency, duration, and intensity of migraines. - The prevalence of migraines and the use of migraine medication decreased significantly after PFO closure. - The presence of aura and high baseline pain intensity were predictors of a positive response to PFO closure.	Total participants: 603	Retrospective cohort study
Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen ovale percutaneous closure: Much ado about nothing?	Butera *et al.*[8]	Catheterization and Cardiovascular Interventions	2010	- Complete cure of migraine occurred in 46% of patients after percutaneous PFO closure. - Resolution or significant improvement of migraine was observed in 83% of cases. - The procedure may benefit migraine sufferers, particularly those treated after a neurological event, but many questions remain unsolved.	NA	Systematic review and meta-analysis
Sustained long-term benefit of patent foramen ovale closure on migraine	Trabattoni *et al.*[15]	Catheterization and Cardiovascular Interventions	2011	- PFO closure significantly reduced the frequency and intensity of migraine attacks in 60.5% of patients at the 3-month follow-up. - At the 12-month follow-up, migraines ceased in 46% of patients, and 40% experienced reduced recurrence rates and symptoms. - Overall, 89% of treated patients showed improvement in migraine symptoms.	Total participants: 305	Single-center, observational, prospective longitudinal study
Patent foramen ovale, ischemic stroke, and migraine: Systematic review and stratified meta-analysis of association studies	Davis *et al.*[29]	Neuroepidemiology	2012	- There is no strong evidence to support a causal relationship between PFO and cryptogenic ischemic stroke or migraine. - Ongoing randomized trials of PFO closure may need larger sample sizes to detect any potential beneficial effects. - The strength of reported associations between migraine, PFO, and ischemic stroke is inconsistent and dependent on study design.	NA	Systematic review and meta-analysis of observational studies

(Cont'd...)

Table 1. ***(Continued)***

Title	Authors	Journal	Year	Main findings	Participant count	Study design
Transcatheter closure of patent foramen ovale: A single-center experience	Milev *et al.*[20]	Open Access Macedonian Journal of Medical Sciences	2016	- During a 2-year follow-up, there were no new incidences of stroke, TIA, or syncope, indicating the safety of the procedure. - Complete PFO closure was achieved in 57.1% of patients as confirmed by follow-up TCD. - There was a significant reduction in migraine symptoms, with some patients experiencing complete relief and others reporting decreased headache intensity.	Total participants: 52	Prospective, single-arm observational study
Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial.	Mattle *et al.*[3]	European Heart Journal	2016	- PFO closure did not significantly reduce monthly migraine days compared to medical management in patients with refractory migraine with aura. - The procedure resulted in five adverse events, but none had permanent consequences.	Participants randomized: 107 - PFO closure group: 53 - Control group: 54	Multicenter, double-blind RCT
Percutaneous closure of patent foramen ovale in patients with migraine: The PREMIUM trial	Tobis *et al.*[4]	Journal of the American College of Cardiology	2017	- PFO closure did not significantly reduce the responder rate for migraine attacks compared to the control group. - Subjects who underwent PFO closure experienced a greater reduction in headache days compared to controls. - A higher percentage of patients in the PFO closure group achieved complete migraine remission for 1 year compared to the control group.	Total participants: 230	Prospective, double-blind RCT
Migraine and percutaneous patent foramen ovale closure: a systematic review and meta-analysis	Shi *et al.*[7]	BMC Cardiovascular Disorders	2017	- PFO closure significantly improves migraine symptoms in 81% of patients with migraine with aura compared to 63% of those without aura. - The benefits of PFO closure are significantly greater for patients with migraine with aura than those without (p=0.03). - The presence of an aura should guide clinical selection for PFO closure intervention.	NA	Systematic review and meta-analysis

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Table 1. ***(Continued)***

Title	Authors	Journal	Year	Main findings	Participant count	Study design
Meta-analysis of randomized trials on percutaneous patent foramen ovale closure for the prevention of migraine	Elbadawi *et al.*[6]	Acta Cardiologica	2018	- PFO closure resulted in a higher reduction in monthly migraine attacks and migraine days compared to the control group. - The reduction in migraine attacks was more pronounced in patients whose majority of attacks are with aura. - There was no significant improvement in complete resolution of migraines or responders' rate, questioning the clinical benefit of PFO closure.	Total participants: 484	Meta-analysis of RCTs
The efficacy of percutaneous patent foramen ovale closure on migraine: A meta-analysis of randomized controlled trials and observational studies	Zhang *et al.*[16]	BioMed Research International	2021	- PFO closure significantly increases the response rate for complete cessation of migraines, and reduces the frequency of migraine attacks and the number of migraine days compared to control groups.	Total participants: 887	Meta-analysis of RCTs and observational studies
Patent foramen ovale closure for treating migraine: A meta-analysis	Zhang *et al.*[28]	Journal of Interventional Cardiology	2022	- PFO closure significantly reduces headache frequency and monthly migraine attacks and days. - PFO closure is an efficient treatment for migraines with aura.	Total participants: 1,165	Meta-analysis of RCTs, pooled study, and retrospective analyses
Association of migraine with patent foramen ovale closure: A systematic review and meta-analysis	Wang *et al.*[27]	International Journal of Cardiology: Heart & Vasculature	2022	- PFO closure is significantly associated with a reduced risk of migraine recurrence and frequency, and a decrease in monthly migraine days and HIT-6 scores. - Transcatheter PFO closure significantly reduces the burden of migraine headaches.	NA	Systematic review and meta-analysis of RCTs and case-control studies
Efficacy and safety of patent foramen ovale closure for mitigating migraine: A systematic review and meta-analysis of randomized trials and observational studies	Silalahi *et al.*[17]	Therapeutic Advances in Neurological Disorders	2024	- PFO closure significantly reduces the frequency of monthly migraine attacks and days compared to controls. - There is no significant difference in complete migraine resolution or headache impact scores between PFO closure and controls. - Adverse events, such as atrial fibrillation and access site complications, are infrequent, occurring in small proportions of patients.	Total participants: 1,674 - Closure group: 840 - Control group: 834	Systematic review and meta-analysis of RCTs

Abbreviations: MIDAS: Migraine disability assessment; PFA: Patent foramen ovale; RCT: Randomized controlled trial; TCD: Transcranial Doppler; TIA: Transient ischemic attack; PFO: Patent foramen ovale.

Percutaneous PFO closure has been generally associated with several short- and medium-term risks, as demonstrated in various landmark trials. For example, the respect,[21] close,[22] and reduce[23] trials reported that new-onset atrial fibrillation occurs in 4 – 6% of patients, with 1 – 2% experiencing persistent episodes. In addition, these studies indicate that a residual shunt is observed in 5 – 10% of cases shortly after the procedure. Device-related thrombus formation has been documented in approximately 1% of patients, while device erosion, embolization, or malposition are extremely rare events, occurring in <0.1 – 0.3% of cases; infective endocarditis similarly has an incidence of around 0.1 – 0.3%.[24] Moreover, changes in migraine headache patterns have been observed in approximately 10% of patients, and vascular access complications occur in <1% of procedures. Although these percentages are well defined in the short- and medium-term follow-up (up to approximately 10 years), there are currently no prospective studies that follow patients for 20 – 50 years; thus, whereas cumulative risks – such as a modest incremental increase in persistent atrial fibrillation – may be anticipated, the absolute long-term risk remains uncertain.

The evolving evidence presents a complex picture. While early systematic reviews characterized the evidence as intriguing but not convincing,[13,25,26] more recent meta-analyses have concluded that PFO closure significantly reduces migraine recurrence, frequency, and monthly migraine days.[27,28] The disparity between observational and randomized evidence suggests that benefits may be restricted to specific patient subgroups rather than all migraineurs with PFO.

Despite these advances, Davis *et al.*[29] cautioned against assuming a causal relationship between PFO and migraine, suggesting that larger RCTs might be necessary to detect potential beneficial effects. This perspective is echoed by the works of Chessa *et al.*[30] and Butera *et al.*,[8] who acknowledged that while PFO closure may benefit migraine sufferers, particularly those treated after neurological events, many questions remain unresolved.

Considering the current limitations of evidence and the compassionate use of percutaneous PFO closure for selected patients with refractory migraine, several ongoing clinical trials aim to expand the indications for this intervention. These studies seek to provide more robust data, refine patient selection criteria, and potentially establish PFO closure as a standard therapeutic option for migraine management.

The MANET study[31] is a multicenter prospective observational study investigating whether specific prothrombotic platelet phenotypes and metabolomic profiles can distinguish migraine patients with causal PFO-related symptoms from those with incidental PFO. By enrolling well-characterized patient cohorts and utilizing *ex vivo* approaches, this study aims to identify biomarkers that could predict which patients might benefit most from PFO closure.

The RELIEF study[32] is a multicenter, prospective, randomized, sponsored, placebo- and sham-controlled study to evaluate the use of GORE® CARDIOFORM Septal Occluder for migraine headache relief in patients affected by migraine and with PFO.

Finally, the COMPETE trial[33] aims to provide further insight into the role of medical therapy, antiplatelet versus anticoagulant, in migraine treatment. Specifically, it is a multicenter RCT aiming to examine the effectiveness of anticoagulation versus antiplatelet versus migraine medication therapy in migraine patients with PFO.

By exploring these ongoing clinical trials, there is potential to expand the indications for percutaneous PFO closure beyond compassionate use. The findings from these studies may help to identify suitable candidates for the procedure, optimize treatment strategies, and contribute to the development of evidence-based guidelines for managing migraine associated with PFO.

Despite the promising data, several limitations must be acknowledged. The heterogeneity in study design, patient populations, and interventional techniques complicates efforts to generalize findings across the broader population of migraine patients with PFO. Furthermore, the high placebo response often seen in migraine studies necessitates rigorous, well-controlled trial designs to isolate the true therapeutic effect of the intervention. In conclusion, while our case report demonstrates successful resolution of refractory migraine following PFO closure, the broader evidence indicates heterogeneous outcomes. Current data support consideration of this intervention in carefully selected patients with refractory migraine with aura, particularly those with specific PFO characteristics suggestive of a high risk for paradoxical embolism.

In summary, while percutaneous PFO closure appears to be a safe intervention that offers significant symptomatic relief for a well-defined subset of patients – particularly those with migraine with aura – its role as a standard therapeutic option remains investigational. The integration of clinical, imaging, and biomarker data holds promise for the development of personalized treatment strategies that effectively bridge the fields of interventional cardiology and neurology.

3.2. Pathophysiological interpretation

The connection between PFO and migraine, particularly migraine with aura, is increasingly supported by emerging evidence that highlights specific pathophysiological

mechanisms.[34] In the patient in this case report, the presence of a PFO likely plays a crucial role in the initiation and perpetuation of her migraine attacks through several interconnected processes involving platelet activation, thrombin generation, and oxidative stress.

3.2.1. Right-to-left shunt and bypass of pulmonary filtration

The PFO in this patient allows for a right-to-left atrial shunt, enabling blood and blood-borne substances to bypass the pulmonary circulation. Normally, the lungs act as a filter, removing or metabolizing vasoactive substances, activated platelets, microemboli, and inflammatory mediators. The shunting caused by the PFO permits these elements to enter the systemic arterial circulation unfiltered, reaching the cerebral vasculature.

3.2.2. Platelet activation and prothrombotic state

One of the key factors in the pathogenesis is the activation of platelets. In patients with PFO and migraine, there is evidence of a prothrombotic phenotype characterized by:

(i) Increased tissue factor (TF) expression: Platelets and microvesicles (MVs) express higher levels of TF, which is a potent initiator of the coagulation cascade, leading to thrombin generation;
(ii) Enhanced thrombin generation capacity: The elevated TF levels in platelets and MVs accelerate thrombin production, contributing to a hypercoagulable state;
(iii) Formation of platelet–monocyte aggregates: Activated platelets can interact with monocytes, promoting further inflammation and coagulation.

Thrombin, beyond its role in coagulation, can activate protease-activated receptors in endothelial cells and neurons, leading to the release of proinflammatory cytokines and vasoactive substances that may trigger cortical spreading depression – the electrophysiological event underlying migraine aura.[34-36].

3.2.3. Oxidative stress and reactive oxygen species (ROS) production

Oxidative stress is another critical component through different mechanisms:

(i) Increased ROS levels: Platelets exhibit elevated ROS production, which can further activate platelets and endothelial cells;
(ii) Altered glutathione homeostasis: There is an imbalance in the glutathione system, evidenced by an increased oxidized-to-reduced glutathione ratio (GSSG/GSH), indicating systemic oxidative stress;
(iii) Antioxidant capacity: The oxidative environment can impair the body's ability to neutralize free radicals, exacerbating cellular dysfunction.

Oxidative stress not only promotes platelet activation but also damages endothelial cells, potentially increasing the permeability of the blood–brain barrier and facilitating the passage of harmful substances into the brain parenchyma.[34]

3.2.4. Erythrocyte deformability and hemolysis

Patients with PFO and migraine may also experience alterations in erythrocyte count and function:

(i) Mechanical stress from the shunt and oxidative damage can lead to decreased erythrocyte survival and reduced erythrocyte count;
(ii) Damaged erythrocytes cause hemolysis and release free hemoglobin, which can bind to platelet glycoprotein Ibα, further promoting platelet activation.[34]

3.2.5. Interruption of pathological mechanisms through PFO closure

Performing percutaneous PFO closure effectively eliminates the right-to-left shunt, thereby interrupting the pathological cascade in the following ways:

(i) Prevention of unfiltered substances in systemic circulation: The closure blocks the passage of activated platelets, MVs, and vasoactive substances into the arterial system;
(ii) Reduction in platelet activation and thrombin generation: By halting the continuous influx of activating stimuli, the platelet activation level decreases, leading to the normalization of thrombin production;
(iii) Normalization of oxidative stress markers: The closure helps restore antioxidant defenses, reducing ROS production, and correcting the GSSG/GSH imbalance;
(iv) Improvement in erythrocyte count and function: Removing mechanical and oxidative stress on erythrocytes enhances their survival and functional capacity.

4. Conclusion

PFO closure emerges as a promising therapeutic option for selected patients suffering from refractory migraine, particularly those with migraine with aura unresponsive to conventional medical treatments. The case of the 22-year-old female illustrates how percutaneous PFO closure can lead to complete remission of migraine symptoms by directly addressing the underlying pathophysiological mechanisms.

The right-to-left shunt in PFO allows unfiltered passage of activated platelets, microemboli, and vasoactive substances into the systemic circulation, bypassing the pulmonary filtration system. This can trigger cortical

spreading depression and promote a prothrombotic and proinflammatory state characterized by platelet activation, increased thrombin generation, and elevated oxidative stress – all contributing to the initiation and maintenance of migraine attacks with aura. By abolishing the shunt through percutaneous closure, these pathological processes are interrupted, leading to symptom resolution.

Ongoing clinical trials, such as the MANET study and the RELIEF trial, aim to provide further data to refine patient selection criteria and potentially establish PFO closure as a standard therapeutic option for migraine management. These studies focus on identifying biomarkers, comparing the effectiveness of PFO closure versus medical therapy, and evaluating new closure devices, which may expand the indications for PFO closure beyond compassionate use.

This paper underscores the importance of a comprehensive diagnostic approach and multidisciplinary collaboration in identifying suitable candidates for PFO closure. The successful outcome in the presented case supports the hypothesis that PFO closure can be effective when a clear pathophysiological link is established. While larger controlled studies are necessary to establish definitive guidelines, the accumulating evidence suggests that targeting the underlying mechanisms through shunt abolition can significantly improve patient outcomes.

In summary, percutaneous PFO closure holds substantial potential as a targeted therapy for refractory migraine by directly addressing the mechanisms that contribute to migraine pathogenesis. Future research should focus on validating biomarkers for patient selection, understanding the long-term outcomes of PFO closure in migraine patients, and developing evidence-based guidelines to optimize treatment strategies. By advancing our understanding and management of PFO-associated migraine, we can offer improved quality of life to patients who have exhausted conventional therapeutic options.

Acknowledgments

None.

Funding

None.

Conflict of interest

Paolo Scacciatella is the Guest Editor of this special issue, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Paolo Scacciatella
Formal analysis: Paolo Scacciatella
Investigation: Paolo Scacciatella
Methodology: Paolo Scacciatella, Stefano Albani
Writing – original draft: Giulia Marchisio
Writing – review & editing: All authors

Ethics approval and consent to participate

This study was approved by the ethics committee of Valle d'Aosta. Written permission was obtained from each of the subjects to participate in the study.

Consent for publication

Written permission was obtained from each of the subjects to publish their data and/or images.

Availability of data

Data used in this work is available from the corresponding author upon reasonable request.

Further disclosure

Part of the set of findings has been presented at the congress "Heart, Brain, and Vessels" that took place in Aosta, Italy, on June 13 – 14, 2024.

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COMMENTARY

Map3k3^{I441M} knock-in mouse model of cerebral cavernous malformations

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Abstract

The *Map3k3*^{I441M} knock-in mouse model reveals an age-dependent mechanism in cerebral cavernous malformation (CCM) pathogenesis, wherein PI3K pathway activation is required for lesion formation in adults but not juveniles. Notably, rapamycin treatment effectively inhibited lesions across age groups, underscoring mammalian target of rapamycin (mTOR) inhibition as a potential therapy. This commentary highlights mechanistic insights from the *Map3k3*^{I441M} knock-in mouse model, emphasizing the age-dependent role of PI3K signaling in CCM formation. It discusses the potential synergy between *MAP3K3* and *PIK3CA* mutations, explores the therapeutic potential of mTOR inhibition, and considers the potential influence of pre-conceptional environmental exposures on CCM susceptibility.

Keywords: Cerebral cavernous malformations; *Map3k3* mutation; Mouse model

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Citation: Lv C, Li R, Yu L, Wang Y. Commentary: *Map3k3*^{I441M} knock-in mouse model of cerebral cavernous malformations. *Brain & Heart.* 2025;3(4):025150019. doi: 10.36922/BH025150019

Received: April 11, 2025

Revised: June 22, 2025

Accepted: July 8, 2025

Published online: August 13, 2025

1. Introduction

Cerebral cavernous malformations (CCMs) (Mendelian Inheritance in Man [MIM]: 116860) are among the most common vascular anomalies affecting the central nervous system, with a prevalence of 0.16–0.5% in the general population, primarily estimated from studies in developed countries utilizing magnetic resonance imaging (MRI).[1,2] Data from developing regions remain limited, and prevalence may be underestimated due to restricted access to diagnostic neuroimaging and specialized care. These lesions are characterized by fragile, abnormally dilated capillaries prone to hemorrhage, often resulting in seizures, focal neurological deficits, or even life-threatening intracranial bleeding. Approximately 85% of cases are sporadic.[3] Previous studies have identified loss-of-function mutations in one of the three CCM genes—*CCM1/KRIT1* (MIM: 604214), *CCM2/MGC4607* (MIM: 607929), and *CCM3/PDCD10* (MIM: 609118)—as causative for CCM lesions.[4] However, in a subset of cases, the underlying pathogenic mechanisms remain unclear.

This commentary aims to highlight the significance of the novel *Map3k3*^{I441M} knock-in (KI) mouse model developed by Xu *et al.*[5] in elucidating CCM pathogenesis, particularly for CCM5 associated with *MAP3K3* mutations, and to discuss its implications and the remaining questions.

In addition to germline mutations, somatic mutations also play a fundamental role in the pathogenesis of human disease. Advances in sequencing technologies have greatly enhanced our ability to dissect disease etiology and uncover critical mechanistic insights.

In March 2021, Hong *et al.*[3] first identified somatic *PIK3CA* and *MAP3K3* mutations through sequencing of 84 CCM lesions, which were associated with different phenotypes defined as CCM4 (MIM: 619538) and CCM5 (MIM: 621032), respectively. The findings were independently validated by Weng *et al.*[6] in April 2021 in a separate cohort of 38 CCM lesions, reporting similar mutation frequencies. In both studies, *MAP3K3* somatic mutations were found to be mutually exclusive with *CCM1*, *CCM2*, and *CCM3* mutations, but often concurrent with *PIK3CA* somatic mutations.

Using single-cell transcriptomic analysis, Ren *et al.*[7] compared lesion features across different mutation types and found no distinct transcriptional differences among them. Lesions harboring different mutations consistently exhibited enhanced endothelial angiogenic activity, an immune-activated endothelial-to-mesenchymal transition state, and a heightened smooth muscle cell phenotypic transformation pattern. These findings highlight the importance of developing CCM mouse models harboring diverse somatic and/or germline mutations to better explore the underlying disease mechanisms.

2. Discussion

The study by Xu *et al.*[5] presents a significant advance by establishing a novel *Map3k3*^{I441M} KI mouse model. Mouse models serve as indispensable tools in modern biomedical research, with applications spanning basic research, disease mechanism investigation, drug discovery, and functional genomics. These animal models have revolutionized our understanding of human diseases by enabling precise genetic manipulations that recapitulate pathological processes in a controlled experimental system.

Previous studies have successfully modeled CCMs in mice by introducing the pathogenic *Map3k3*^{I441M} mutation into cerebral endothelial cells through adeno-associated virus (AAV)-mediated gene delivery, recapitulating key histopathological features of human CCMs.[8,9] The AAV model can mimic a state of localized, low-frequency somatic mutations, consistent with observations in real-world patients.[3,6] This approach has enabled researchers to investigate lesion initiation, growth dynamics, and potential therapeutic interventions in a living organism. However, two critical limitations of this model are the overexpression of the *Map3k3*^{I441M} mutation and its short-term effect. Moreover, a phenomenon—spontaneous regression of over 50% of induced lesions during adulthood—was observed in these AAV models, which is inconsistent with human CCM pathogenesis.[8]

Xu *et al.*[5] successfully established a novel *Map3k3*^{I441M} KI mouse model on the C57BL/6J genetic background using clustered regularly interspaced short palindromic repeats/Cas9-mediated precision genome editing technology. To achieve endothelial-specific mutation expression, they employed a sophisticated genetic strategy by crossing these mice with *Cdh5*-Cre^{ERT2} transgenic animals, enabling tamoxifen-inducible, restricted expression of the mutation in cerebrovascular endothelial cells. Comprehensive characterization revealed that this innovative model effectively recapitulates key pathological hallmarks of human CCMs. Lesion formation followed a distinct temporal pattern, with both lesion number and average volume showing significant increases during the first two post-natal months. From months 2–5, CCM lesions reached a plateau phase, maintaining remarkable stability in both quantity and mean volume.

Histopathological examination confirmed that the vascular lesions exhibited all characteristic features of human CCMs, including grossly dilated vascular channels lined by thin endothelial walls, ultrastructural defects in endothelial cell junctions, and prominent perivascular hemosiderin deposition indicative of chronic microhemorrhages. However, it is worth noting that the KI model may exaggerate the effects of mutations, as almost all target cells express the mutant allele, which may not accurately represent the pathogenic potential of low-frequency somatic mutations in patients. Due to the complexity of human physiology and the long-term effects of low-abundance mutant cells, this model cannot fully replicate the variant allele frequencies observed in human cases. Given that it is not feasible to replicate the full scale of human disease progression in mouse models, AAV and KI models are most appropriate for short-term studies within the mouse lifespan. Each model has distinct strengths and is valuable for elucidating disease mechanisms, advancing drug discovery, and supporting functional genomics research. Accordingly, the KI model serves as a valuable alternative, supplementary tool, and means of validation.

The study by Xu *et al.*[5] also provides mechanistic insights into the critical role of the PI3K signaling pathway in CCM pathogenesis through comprehensive investigations using the *Map3k3*^{I441M} KI mouse model. The results reveal an age-dependent dichotomy in CCM development: In juvenile mice, heterozygous expression of the *Map3k3*^{I441M} mutation alone was sufficient to induce CCM-like lesions. In striking contrast, adult mice (≥3 months old) exhibited a more complex pathogenesis, in which the *Map3k3*^{I441M} mutation alone was insufficient to induce lesions, requiring concurrent PI3K pathway activation for CCM formation.

Previous studies have reported cases with concomitant somatic mutations in both *MAP3K3* and *PIK3CA*;[3,6] however, these cases did not exhibit more severe phenotypes

compared to those harboring a single mutation.[3,7] In these sporadic CCMs with dual mutations, the variant allele frequencies were relatively similar.[3,7] Combined with the present study by Xu *et al*.,[5] these observations raise several intriguing questions: (i) Do the mutations co-occur within the same cell? (ii) do lesions in cases with dual mutations arise later than those with only *MAP3K3* mutations? and (iii) does the potential synergistic effect of *MAP3K3* and *PIK3CA* mutations within a single cell contribute to CCM formation? These questions highlight the need for further studies to elucidate the cellular and temporal dynamics underlying these mutations and their pathogenic interactions.

The present clinical guidelines recommend surgical resection for symptomatic CCMs following multidisciplinary evaluation, while conservative management with monitoring is standard for asymptomatic lesions or those located in high-risk regions, such as the brainstem.[4] Spinal cavernous malformations (SCMs) similarly require individualized management, with surgical resection offering favorable outcomes for symptomatic intramedullary lesions when performed before the onset of severe neurological deficits.[10] For high-risk, inoperable CCMs or SCMs, stereotactic radiosurgery has been explored as an alternative treatment; however, its efficacy remains controversial due to variable obliteration rates (34–54%) and the risk of hemorrhage during the latency period.[11] Nevertheless, the persistent hemorrhage risk in these cases underscores the urgent need for pharmacotherapies.

Recent advances have identified MEKK3–KLF2/4 signaling[12,13] and local iodothyronine deiodinase type 2 (DIO2) upregulation (converting thyroxine to active triiodothyronine [T3])[14] as key adaptive responses in CCM pathogenesis. Exogenous DIO2/T3 supplementation attenuated pathology in *Pdcd10* knockout models,[13] and ponatinib inhibited lesion formation in *KRIT1* knockouts.[15] The study by Xu *et al*.[5] now demonstrates rapamycin's efficacy against *Map3k3*^{I441M}-driven lesions across age groups, establishing mammalian target of rapamycin (mTOR) inhibition as a translatable strategy. Beyond its therapeutic applications, this model also enables exploration of pre-conceptional influences on CCM susceptibility—an unexplored frontier.

Environmental exposures in prospective parents (e.g., tobacco, alcohol, pro-inflammatory diets, chronic stress, and sleep disorders) may compromise gametic DNA integrity or epigenetic programming,[16] potentially increasing offspring vulnerability to *de novo* germline mutations (e.g., *KRIT1*, *CCM2*, and *PDCD10*), somatic mutations (e.g., *MAP3K3* and *PIK3CA*), or endothelial DNA repair defects. Conversely, protective factors, such as adherence to a Mediterranean diet or stress reduction strategies may enhance resilience pathways, potentially including DIO2-mediated adaptation.[13] Critically, no direct epidemiological or experimental evidence currently links parental exposures to CCM outcomes in offspring. Future research should integrate epidemiological studies correlating parental exposures with sporadic CCM incidence, alongside controlled animal models testing pre-conceptional stressors in *Map3k3*^{I441M} lineages to assess impacts on endothelial-specific pathways (e.g., KLF2/4, PI3K/mTOR, and DIO2).

3. Conclusion

CCM5 (MIM: 621032), associated with *MAP3K3* mutations, is characterized by a relatively low risk of hemorrhage[3] and displays Zabramski type 2 features on MRI.[6] The development of a genetically accurate mouse model for CCM5 offers a valuable platform for studying disease mechanisms. In juvenile mice, the *Map3k3*^{I441M} mutation alone leads to fully penetrant CCM formation. In contrast, adult mice require additional activation of the PI3K signaling pathway to develop significant lesions, suggesting age-dependent susceptibility and signaling pathway synergy. Notably, pharmacological treatment with rapamycin effectively suppressed lesion progression, highlighting a potential therapeutic avenue.

Acknowledgments

None.

Funding

This study was supported by the Chinese Academy of Medical Sciences, Innovation Fund for Medical Sciences (grants no.: 2023-CXGC-SYS01-2 and 2021-I2M-1-016), National Natural Science Foundation of China (grant no.:82470450), the National High Level Hospital Clinical Research Funding Grant (grant no.:2025-GSP-GG-29), and the State Key Laboratory of Cardiovascular Disease.

Conflict of interest

Yibo Wang is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Writing – review & editing: Yibo Wang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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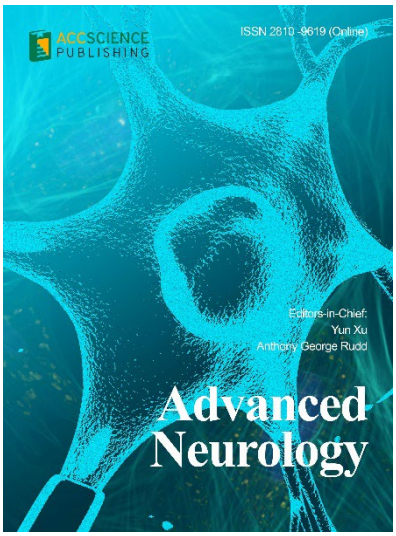

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