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The Role of Calcium Channel Blockers as Non-Antiplatelet Therapy in MINOCA Patients: A Review of Current Clinical Evidence

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ABSTRACT

Myocardial infarction with non-obstructive coronary arteries (MINOCA) represents a heterogeneous clinical entity with diverse underlying pathophysiological mechanisms. Recent evidence has demonstrated that MINOCA accounts for approximately 2.7% to 15% of acute myocardial infarction presentations, particularly affecting younger patients and women with significant long-term morbidity and mortality. While dual antiplatelet therapy has traditionally been the cornerstone of acute coronary syndrome management, emerging data question the efficacy of antiplatelet agents in MINOCA given the heterogeneous nature of underlying etiologies, many of which do not involve platelet-mediated thrombosis. Calcium channel blockers (CCBs), as non-antiplatelet agents, represent a promising alternative therapeutic strategy, particularly in MINOCA phenotypes characterized by epicardial coronary vasospasm and coronary microvascular dysfunction. This review synthesizes current evidence on the mechanism of action of CCBs in the context of MINOCA pathophysiology, examines existing clinical trials evaluating CCB efficacy in MINOCA populations, and discusses potential sex- and age-specific considerations in CCB therapy. CCBs show considerable potential as first-line therapy for vasospasm-mediated MINOCA and warrant further investigation in adequately powered randomized controlled trials.

Keywords: calcium channel blockers; coronary vasospasm; microvascular dysfunction; MINOCA

1. INTRODUCTION

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is defined as an acute myocardial infarction based on the Third Universal Definition of Myocardial Infarction, with non-obstructive coronary arteries that show no lesion reaching 50 percent in any major epicardial vessel, and no alternative clinical condition that explains the acute presentation [1]. MINOCA accounts for approximately 2.7% to 15% of all acute myocardial infarction (AMI) presentations, with most studies reporting a prevalence around 5-9% [2]. The epidemiological significance of MINOCA is underscored by recent meta-analytical evidence demonstrating a pooled prevalence of 8.92% among patients undergoing coronary angiography, with MINOCA patients being younger, predominantly female, and presenting with atypical chest pain and dyspnea compared to patients with myocardial infarction and obstructive coronary artery disease (MIOCA) [3]. The pathophysiological mechanisms underlying MINOCA are remarkably diverse and can be stratified into atherosclerotic and non-atherosclerotic etiologies [4]. The current standard approach to MINOCA management has historically relied upon applying treatment strategies developed for myocardial infarction with obstructive coronary artery disease, including dual antiplatelet therapy, high-intensity statin therapy, beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [5]. However, the mechanistic rationale for antiplatelet therapy in MINOCA is substantially weaker than in atherosclerotic plaque rupture-mediated infarction [6].

Calcium channel blockers represent a pharmacologically distinct therapeutic class that addresses fundamental pathophysiological mechanisms in specific MINOCA phenotypes, particularly those characterized by vasomotor dysfunction [7]. The appeal of CCBs in MINOCA management becomes apparent when considering the high prevalence of epicardial and microvascular vasospasm in MINOCA populations [8]. Increasing evidence indicates that coronary spasm and vasomotor dysfunction may account for more than half of MINOCA cases [9]. When compared with dual antiplatelet therapy, which primarily addresses thrombotic pathways of questionable relevance in

vasospasm-mediated MINOCA, CCBs directly target the pathophysiological mechanism (vascular smooth muscle hypercontractility) responsible for producing ischemia and myocardial infarction in these patients [4]. These pleiotropic effects position CCBs as particularly rational therapeutic agents in MINOCA, where inflammation, evidenced by elevated C-reactive protein, B-type natriuretic peptide, and fibrinogen levels, appears to be a key pathophysiological mechanism.

2. REVIEW CONTENT

2.1 Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA)

Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) is the term for a clinical presentation of acute myocardial infarction (MI) without significant obstructive coronary artery disease, which is defined as less than 50% stenosis on coronary angiography. While ruling out other non-ischemic causes, including myocarditis, Takotsubo cardiomyopathy, or pulmonary embolism, the diagnosis must satisfy the universal criteria for acute MI, which include an increase and/or fall in cardiac troponin with evidence of myocardial ischemia [10, 11]. MINOCA is considered a preliminary diagnosis that needs more evaluation to determine the underlying cause [12]. Advanced imaging, especially cardiac magnetic resonance, optical coherence tomography, and intravascular ultrasound, is frequently necessary to clarify the etiology and direct tailored treatment because traditional angiography may overlook subtle plaque disruption, microvascular dysfunction, or vasomotor disorders [13]. The complex and multifaceted pathogenesis of myocardial infarction with non-obstructive coronary arteries (MINOCA) is caused by several atherosclerotic and non-atherosclerotic mechanisms in the absence of severe epicardial coronary artery stenosis [14].

The pathophysiological mechanisms underlying MINOCA are remarkably diverse and can be stratified into atherosclerotic and non-atherosclerotic etiologies [15]. MINOCA is a heterogeneous syndrome with both atherosclerotic and non-atherosclerotic etiologies. Atherosclerotic MINOCA is primarily caused by plaque disruption mechanisms such as plaque erosion, plaque rupture, and calcified nodules, which can be identified by optical coherence tomography (OCT). These atherosclerotic causes are associated with worse clinical outcomes, including higher rates of major adverse cardiac events (MACE) like target lesion revascularization and rehospitalization [16, 17]. Non-atherosclerotic MINOCA includes mechanisms such as spontaneous coronary artery dissection, coronary artery spasm, coronary microvascular dysfunction, thromboembolism, and supply-demand mismatch, often linked to non-ischemic myocardial injury patterns on cardiac magnetic resonance imaging (CMR) [4, 18]. Coronary microvascular dysfunction, a key non-atherosclerotic mechanism, may also have a genetic predisposition and plays a significant role in MINOCA pathophysiology and prognosis [18]. Multi-modality imaging combining OCT and CMR improves identification of the underlying cause in most MINOCA cases, distinguishing ischemic (mostly atherosclerotic) from non-ischemic etiologies, which is crucial for guiding targeted therapy [19].

2.2 Calcium Channel Blocker's Mechanism of Action in MINOCA

(1) *Calcium Channel Blockade and Vascular Smooth Muscle Relaxation*

The fundamental mechanism by which calcium channel blockers exert vasodilatory effects operates through selective inhibition of voltage-dependent calcium channels in vascular tissue, particularly the L-type calcium channels that mediate calcium influx into vascular smooth muscle cells [20]. Calcium channel blockers are classified into three distinct pharmacological classes based on their specific binding sites within the calcium channel complex and their respective tissue selectivities: the dihydropyridines (such as nifedipine, amlodipine, and benidipine), which demonstrate high selectivity for vascular smooth muscle calcium channels; the phenylalkylamines (represented by verapamil), which show relatively greater effects on cardiac conduction tissue; and the benzothiazepines (diltiazem), which occupy an intermediate position [21]. The dihydropyridine class possesses particular advantage in coronary vasospasm management owing to their preferential action on vascular calcium channels relative to cardiac muscle, thereby avoiding the negative inotropic and chronotropic effects more prominent with non-dihydropyridine agents [22]. In terms of mechanism, when vascular smooth muscle cells are depolarized, L-type calcium channels open and permit calcium influx, leading to elevation of intracellular calcium concentration [23]. This calcium binds to calmodulin to activate myosin light chain kinase (MLCK), which phosphorylates the regulatory light chain of myosin, enabling actin-myosin cross-bridge formation and contraction. By blocking calcium entry through these channels, CCBs reduce intracellular calcium availability and prevent MLCK activation, thereby promoting vascular smooth muscle relaxation and vasodilation [23].

However, beyond this classical mechanism, contemporary understanding recognizes that vascular smooth muscle contraction is not exclusively dependent upon calcium influx. The Rho-kinase pathway maintains vascular smooth muscle contraction primarily by inhibiting myosin light chain phosphatase (MLCP), which increases phosphorylation of the myosin light chain (LC20) and promotes sustained contraction. This pathway enables Ca2+ sensitization, meaning contraction is maintained even without increased intracellular calcium, supporting the tonic phase of vascular smooth muscle contraction [24]. Studies investigating coronary artery spasm in related vasospastic conditions have consistently demonstrated elevated Rho-kinase activity during active vasospasm episodes [25]. While CCBs primarily operate through calcium channel blockade,

evidence suggests that normalization of intracellular calcium and reduction of oxidative stress through CCB action may indirectly modulate Rho-kinase-mediated pathways, contributing to their superior efficacy in vasospasm compared to agents acting exclusively through other mechanisms.

(2) *Pleiotropic Anti-Inflammatory and Endothelial Protective Effects of Calcium Channel Blockers*

Beyond their primary mechanism of calcium channel antagonism, emerging pharmacological evidence has illuminated remarkable pleiotropic effects of calcium channel blockers that extend to vascular inflammation, oxidative stress, and endothelial dysfunction, mechanisms increasingly recognized as central to MINOCA pathogenesis. Long-acting dihydropyridine-type calcium channel blockers such as nifedipine, azelnidipine, and benidipine have been demonstrated in both experimental and clinical investigations to inhibit vascular inflammation through multiple molecular mechanisms. Nifedipine, one of the most extensively studied dihydropyridines, has been shown to prevent monocyte chemoattractant protein-1 (MCP-1) production from endothelial cells triggered by tumor necrosis factor-alpha (TNF-α), operating through antioxidative properties that reduce reactive oxygen species generation. Furthermore, nifedipine blocks TNF-α-induced upregulation of vascular cell adhesion molecule (VCAM)-1 messenger RNA expression in human umbilical vein endothelial cells and prevents adherence of lymphoblastic cells to TNF-α-exposed endothelium, thereby reducing leukocyte-endothelial interactions that drive atherogenesis and microvascular inflammation [26].

The anti-inflammatory mechanisms of CCBs appear to operate through inhibition of the local renin-angiotensin system and enhancement of nitric oxide bioavailability [26]. Calcium channel blockades, such as amlodipine and manidipine, have been demonstrated to normalize decreased endothelial nitric oxide synthase (eNOS) expression, attenuate overexpression of inflammatory molecules, including those mediating oxidative stress, and modulate angiotensin-converting enzyme (ACE) expression in vascular tissue [26]. These anti-inflammatory and antioxidant effects were found to be independent of the blood pressure-lowering effects of the drugs, suggesting genuine pleiotropic vascular benefits [26]. In the context of MINOCA, where inflammatory markers, including high-sensitivity C-reactive protein, B-type natriuretic peptide, and fibrinogen, are significantly elevated compared to healthy controls, and where inflammation plays a pathophysiologically central role in driving endothelial dysfunction, microvascular obstruction, and vasospasm, these anti-inflammatory properties of CCBs assume particular importance [27].

The enhancement of endothelial function represents another crucial mechanism through which CCBs may benefit MINOCA patients [26]. Vascular endothelial dysfunction, characterized by reduced nitric oxide bioavailability, increased production of reactive oxygen species, and impaired endothelium-dependent vasodilation, represents a fundamental pathophysiological abnormality across multiple MINOCA etiologies, particularly in coronary microvascular dysfunction and vasospastic disease [27].

Among the diverse pharmacological therapies capable of restoring endothelial function, calcium channel blockers stand alongside angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins [28]. Calcium antagonists improve endothelial activity through enhancement of antioxidant capacity and by increasing nitric oxide bioavailability, as evidenced by radial artery applanation tonometry and pulse wave analysis demonstrating reduced central aortic systolic blood pressure in patients receiving CCB-containing regimens compared to other antihypertensive strategies [29]. Through these combined mechanisms, direct vasodilation via calcium channel blockade, anti-inflammatory effects, oxidative stress reduction, and endothelial function restoration, calcium channel blockers address multiple pathophysiological pathways implicated in MINOCA, providing a mechanistic rationale for their deployment as first-line therapy in vasospasm-mediated disease [27].

(3) *Clinical Evidence in Vasospastic Angina and Coronary Vasospasm Models*

The clinical evidence base for CCB efficacy in coronary vasospasm derives substantially from investigation of vasospastic angina and experimental models of coronary artery spasm, conditions sharing fundamental pathophysiological mechanisms with vasospasm-mediated MINOCA. Calcium channel blockers are recognized as the first-line pharmacological treatment for coronary artery spasm, and this evidence has been extensively validated through decades of clinical experience and mechanistic investigation [30]. In comparative studies examining multiple calcium channel blockers regardless of type and formulation, CCBs, whether dihydropyridines, phenylalkylamines, or benzothiazepines, have consistently demonstrated effectiveness at preventing vasospasm-induced angina attacks [30]. The efficacy of CCBs in preventing coronary spasm has been further corroborated by mechanistic studies demonstrating that these agents prevent calcium ion (Ca^{2+}) entry into vascular smooth muscle cells by blocking L-type voltage-gated channels, causing sustained vasodilation [30].

Beyond prevention of angina symptoms, observational follow-up studies have documented that CCB-mediated control of coronary vasospasm translates into substantial improvements in clinical outcomes in vasospastic angina. A pivotal registry study following 70% of Japanese patients with vasospastic angina for a mean of 80.5 months demonstrated a significant association between CCB use and both improvement in survival and reduced occurrence of acute myocardial infarction compared with patients receiving no CCB therapy [31]. These findings indicate that control of vasospasm through CCB therapy prevents progression to myocardial infarction

in predisposed populations [31]. Notably, CCB use has been associated with decreased risk of stent thrombosis after drug-eluting stent implantation within one year, with the underlying mechanism thought to involve prevention of vasospasm-mediated thrombotic events [30].

In a study of patients with MINOCA undergoing intracoronary acetylcholine provocation testing, the prevalence of epicardial or microvascular coronary vasospasm reached 50-70%, substantially exceeding the prevalence in stable patients without obstructive coronary artery disease (21.3% vs. 7%, p = 0.002) [9]. These epidemiological findings underscore that vasospasm represents a major MINOCA mechanism, justifying first-line CCB therapy in identified vasospasm-positive patients [9].

The most recent randomized evidence supporting etiology-specific therapy in MINOCA derives from the PROMISE trial, the first randomized controlled trial specifically designed to evaluate optimal management strategies in MINOCA patients [7]. In this multicenter randomized trial, 101 patients with acute coronary syndrome and non-obstructive coronary arteries were randomized 1:1 to either stratified treatment comprising comprehensive diagnostic workup aimed at identifying the underlying aetiology (utilizing stress testing, intracoronary provocation testing, and cardiac magnetic resonance imaging) followed by aetiology-guided therapy, or to standard care [7]. Of these, 92 patients were confirmed as MINOCA and included in the final analysis [7].

The diagnostic workup in the stratified treatment arm successfully identified underlying aetiology in 80% of patients (36 of 45 cases), with epicardial coronary vasospasm identified as the most frequent aetiology in 16 patients (35.6%), followed by atherosclerotic plaque instability in 10 patients (22.2%), spontaneous coronary artery dissection in 6 patients (13.3%), coronary embolism in 2 patients (4.4%), and microvascular spasm in 2 patients (4.4%) [7]. Notably, all 16 patients presenting with epicardial coronary spasm received calcium channel blockers as primary therapy, with the remainder receiving other pharmacological agents tailored to their specific etiologies (such as dual antiplatelet therapy for atherosclerotic plaque disruption or anticoagulation for coronary thromboembolism) [7]. In contrast, the standard care group was predominantly managed with dihydropyridine CCBs prescribed for concomitant hypertension rather than targeting specific MINOCA etiology [7].

The primary endpoint, change in angina-related health status at 12 months measured by Seattle Angina Questionnaire summary score (SAQSS), showed significantly greater improvement in the stratified treatment group compared to standard care (mean between-group difference +9.38, 95% confidence interval 6.81 to 11.95; p<0.001) [7]. This finding demonstrates that tailored, etiology-guided therapy, including targeted CCB use for vasospasm-identified patients, produces superior clinical outcomes in angina burden reduction compared to standard undifferentiated acute coronary syndrome protocols [7]. While the study size was limited and the follow-up duration was 12 months, the results provide the first randomized evidence supporting the superiority of etiology-guided management in MINOCA, establishing a rational framework wherein CCBs should be preferentially deployed in vasospasm-positive cases [7].

(4) *Coronary Microvascular Dysfunction and CCB Efficacy*

In addition to epicardial coronary vasospasm, coronary microvascular dysfunction (CMVD) represents a major contributor to MINOCA pathophysiology. CMVD presents with functional abnormalities characterized by increased propensity for vasoconstriction at the microvascular level, impaired endothelium-dependent and independent coronary vasodilation, and increased coronary microvascular resistance secondary to structural factors [4]. From the therapeutic standpoint, patients presenting with CMVD-mediated MINOCA may benefit from calcium channel blockers as first-line therapy for symptomatic relief, combined with complementary agents targeting endothelial function, such as angiotensin receptor blockers or ACE inhibitors (Squires et al., 2025). The mechanistic rationale derives from the fact that microvascular dysfunction involves both structural changes (vascular remodeling, extramural compression) and functional abnormalities (vasomotor dysfunction, impaired vasodilation), and CCBs address the vasomotor component of this pathology through their capacity to promote microvascular smooth muscle relaxation and enhance nitric oxide-mediated vasodilation [4].

Clinical management guidelines for MINOCA recommend that patients with coronary microvascular dysfunction, whether diagnosed through coronary flow reserve measurement, stress perfusion imaging, or intracoronary acetylcholine provocation testing, may be prescribed beta-blockers and calcium channel blockers as first-line pharmacotherapy, often supplemented with medications enhancing endothelial function such as ACE inhibitors or angiotensin receptor blockers [32]. The rationale for combining CCBs with endothelial function-enhancing agents reflects recognition that multiple pathophysiological pathways require targeting: CCBs address the vasomotor component, while renin-angiotensin system blockade enhances nitric oxide availability and reduces oxidative stress, addressing the endothelial dysfunction component of CMVD [33].

(5) *Sex- and Age-Specific Considerations in CCB Efficacy*

Important sex and age-related differences have emerged in cardiovascular drug responses, with particular relevance for CCB deployment in MINOCA, where female predominance is notable. Women represent approximately 44.8-53% of MINOCA patients, substantially higher than the 30.2% female

prevalence in MIOCA, and female patients are typically older than male MINOCA patients by approximately 8 years, with a higher prevalence of comorbidities including diabetes, hypertension, and obesity. A post-hoc analysis of the ACS1 study comparing antihypertensive efficacy of the angiotensin receptor blocker azilsartan versus the calcium channel blocker amlodipine by age and sex demonstrated that control rates in the amlodipine group were significantly higher than in the azilsartan group in female patients aged 60 years and older. The multivariate analysis in this study showed that female sex was a determinant of a greater blood pressure-lowering effect of amlodipine, regardless of age. These sex-specific differences in CCB efficacy may have implications for MINOCA management, particularly given the female predominance in MINOCA presentation and the concentration of older female patients with MINOCA.

Regarding age-specific considerations, recent studies examining MINOCA in very young patients (≤40 years) have identified distinct demographic and clinical features, with findings suggesting limited prescribing of guideline-recommended secondary prevention medications in young MINOCA populations. For young MINOCA patients presenting with vasospasm-mediated disease, calcium channel blockers emerge as particularly attractive first-line therapy, avoiding the potential complications of long-term dual antiplatelet therapy in younger populations. A comprehensive retrospective study examining sex differences in MINOCA outcomes found that at 3-year follow-up, male patients with MINOCA experienced higher rates of adverse events, including death and myocardial infarction, despite being significantly younger than female MINOCA patients, with male sex identified as an independent predictor of both death and recurrent myocardial infarction. These sex-specific outcome differences underscore the importance of tailored therapeutic strategies that account for distinct pathophysiological and prognostic profiles in male versus female MINOCA patients.

Regarding inflammatory markers and genetic predispositions, limited evidence specifically examining whether inflammatory status or genetic polymorphisms predict differential CCB efficacy in MINOCA currently exists. However, emerging evidence demonstrates that inflammatory markers, including elevated C-reactive protein, B-type natriuretic peptide, and fibrinogen levels, are significantly elevated in MINOCA patients compared to controls, with inflammation identified as a key pathophysiological mechanism in MINOCA. Given the demonstrated anti-inflammatory properties of calcium channel blockers independent of their vasodilatory effects and given the established role of inflammation in MINOCA pathogenesis, inflammatory biomarkers may potentially serve as predictors of CCB responsiveness, though this remains speculative pending dedicated investigation.

2.3 Calcium Channel Blocker versus Antiplatelet Therapy in MINOCA: Comparative Insights

The mechanistic mismatch of antiplatelet therapy in MINOCA is the primary driver for its questioned efficacy. Antiplatelet agents target thrombotic cascades activated by plaque disruption; however, intravascular imaging studies utilizing optical coherence tomography (OCT) have revealed that plaque disruption accounts for only approximately one-third of MINOCA cases. Consequently, for the significant proportion of patients with non-thrombotic etiologies, such as coronary artery spasm or microvascular dysfunction, antiplatelet therapy offers no mechanistic benefit while exposing patients to bleeding risks. This biological plausibility is supported by large-scale observational data. The SWEDEHEART registry, analyzing over 9,000 MINOCA patients, demonstrated that antiplatelet therapy was not associated with a reduction in major adverse cardiac events (Hazard Ratio 0.90, 95% CI 0.74–1.08), contrasting sharply with the significant benefits observed with statins and ACE inhibitors/ARBs. Furthermore, in patients with vasospasm-induced MINOCA, aspirin has been suggested in some experimental models to potentially exacerbate spasm through the inhibition of prostacyclin production, although this remains a subject of debate.

In direct contrast, calcium channel blockers address the functional vascular abnormalities that underpin a majority of non-atherosclerotic MINOCA cases. Comparative data from the PROMISE trial highlights this dichotomy: patients in the "standard care" arm (often receiving antiplatelets based on acute coronary syndrome protocols) had significantly worse angina-related health status at 12 months compared to the "stratified medicine" arm, where vasospasm-positive patients were strictly treated with CCBs. For patients with vasospastic angina, a condition closely overlapping with MINOCA, CCBs have been shown to reduce the frequency of angina attacks and prevent future cardiac events significantly more effectively than nitrates or beta-blockers, the latter of which may paradoxically worsen spasm by leaving alpha-adrenergic vasoconstriction unopposed.

The safety profile further favors CCBs over antiplatelets in appropriate MINOCA phenotypes. The bleeding risk associated with long-term DAPT is well-established, with major bleeding rates ranging from 1-2% annually. Given that MINOCA patients are often younger and more frequently female than MIOCA patients, minimizing iatrogenic bleeding risk is a priority. CCBs, while carrying risks of hypotension or peripheral edema, avoid the cumulative hemorrhagic risk of antithrombotic agents. Therefore, in the absence of confirmed plaque disruption or thromboembolism, the substitution of antiplatelet therapy with CCBs represents a strategy that maximizes mechanistic targeting while minimizing off-target adverse events.

CONCLUSION

Calcium channel blockers represent a pharmacologically rational alternative to antiplatelet therapy in specific MINOCA phenotypes characterized by epicardial coronary vasospasm and coronary microvascular dysfunction. The mechanistic basis for CCB efficacy encompasses direct vascular smooth muscle relaxation through L-type calcium channel blockade, inhibition of calcium-independent contraction through indirect modulation of Rho-kinase pathways, and pleiotropic anti-inflammatory and endothelial protective effects mediated through reduced oxidative stress and enhanced nitric oxide bioavailability.

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