

Opinion

Mechanism-Informed Drug Repurposing in MINOCA: Therapeutic Rationale and Trial Framework for Empagliflozin and Colchicine

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Abstract

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinically important but heterogeneous syndrome associated with substantial long-term morbidity and adverse cardiovascular outcomes. Pharmacologic management remains largely extrapolated from obstructive coronary artery disease, creating a persistent mismatch between treatment strategies and the diversity of underlying mechanisms. Accurate diagnostic adjudication using cardiac magnetic resonance imaging, intracoronary imaging, coronary functional testing, and mechanistic biomarkers is therefore central to a phenotype-guided therapeutic approach. Inflammation, endothelial dysfunction, oxidative stress, autonomic dysregulation, coronary microvascular dysfunction, plaque-related injury, and adverse ventricular remodeling represent potentially targetable biological domains across selected MINOCA phenotypes. Empagliflozin and colchicine exert overlapping but distinct effects on several of these pathways and have demonstrated cardiovascular benefits in related clinical settings; however, direct evidence in MINOCA remains limited and predominantly observational. This article integrates the available mechanistic and clinical evidence into a comparative, phenotype-linked therapeutic framework and proposes a pragmatic trial strategy incorporating diagnostic adjudication, phenotype enrichment, biomarker-guided stratification, and adaptive or factorial designs. The proposed framework is hypothesis-generating and is intended to inform prospective investigation rather than support off-label prescribing or changes to current clinical practice.

Keywords: MINOCA; drug repurposing; coronary microvascular dysfunction; inflammation; empagliflozin; colchicine; precision medicine; adaptive trial design



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1. Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA)

Myocardial infarction with non-obstructive coronary arteries (MINOCA) accounts for approximately 5–15% of acute myocardial infarction presentations and is associated with a substantial clinical burden, with reported major adverse cardiovascular event rates of up to 21.5% [1–6]. MINOCA is also associated with prolonged hospitalization and considerable healthcare costs [7]. Despite its frequency and prognostic significance, its pharmacologic management remains largely extrapolated from obstructive coronary artery disease, reflecting a persistent mismatch between current treatment paradigms and the underlying pathophysiology.

The terminology and conceptual boundaries of MINOCA continue to evolve. Bucciarelli-Ducci et al. recently proposed broadening the concept from myocardial infarction with non-obstructive coronary arteries to myocardial injury with non-obstructive coronary arteries, emphasizing that the initial clinical label may encompass ischemic infarction as well as alternative forms of myocardial injury [8]. This proposal reinforces the need to regard MINOCA as a working diagnosis requiring systematic adjudication rather than as a definitive etiological diagnosis. In the present manuscript, the established term MINOCA is retained, but the proposed therapeutic framework is restricted to patients in whom an ischemic mechanism remains plausible or has been demonstrated.

MINOCA is not a single disease entity but a heterogeneous syndrome encompassing multiple mechanisms, including plaque disruption, coronary vasospasm, coronary microvascular dysfunction, spontaneous coronary artery dissection, coronary embolism, and supply–demand mismatch [1,9,10] (Figure 1). This mechanistic diversity complicates therapeutic development because trials that do not account for biological heterogeneity may dilute treatment effects and produce false-negative findings. Conducting definitive randomized trials in MINOCA is also challenging because of the complexity of diagnostic adjudication and the large sample sizes required for adequately powered clinical outcomes.

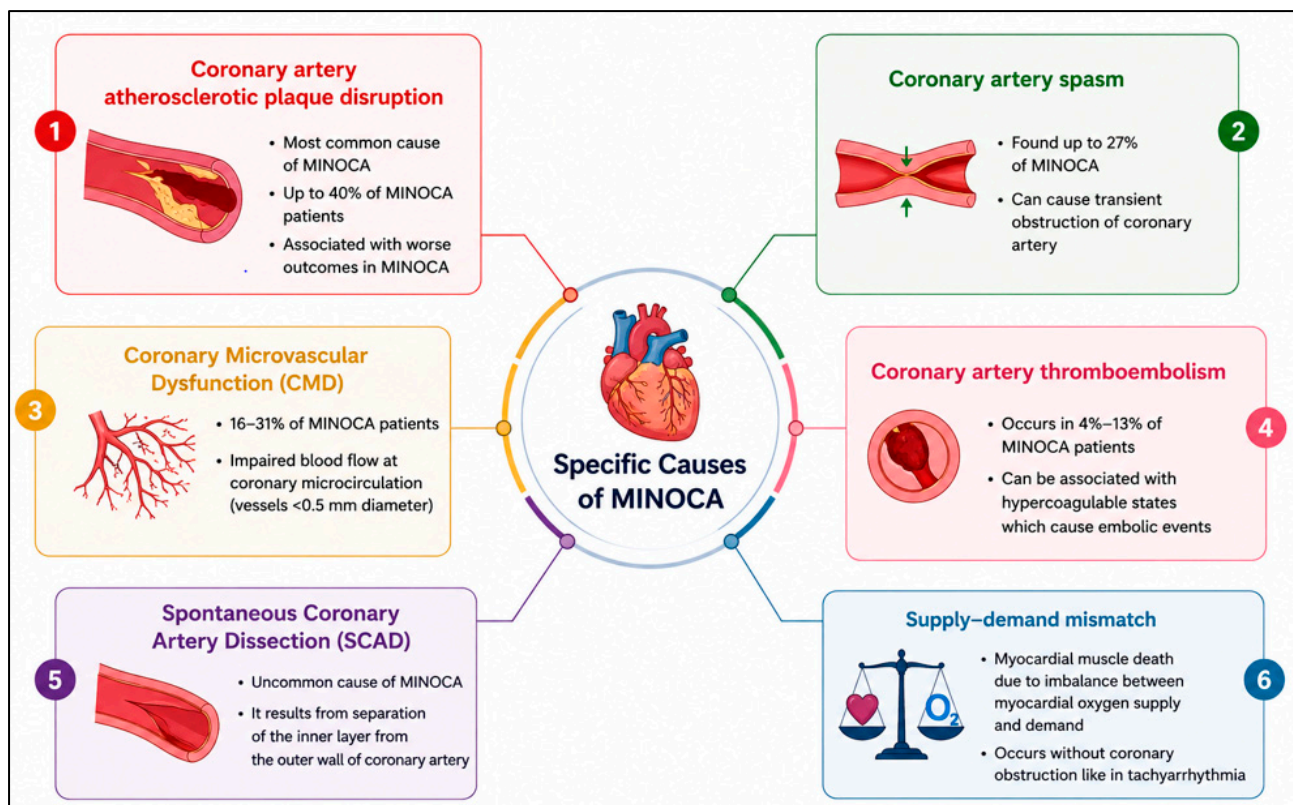


Figure 1. Principal mechanisms and etiologic subtypes underlying the MINOCA syndrome.

Emerging mechanistic evidence implicates inflammation, endothelial dysfunction, oxidative stress, autonomic dysregulation, and coronary microvascular impairment as recurring contributors to myocardial injury and adverse outcomes across selected MINOCA phenotypes [1,10]. These observations suggest that therapies targeting shared biological pathways, rather than a single angiographic lesion, warrant prospective evaluation. Accordingly, this manuscript develops a hypothesis-generating framework for evaluating the repurposing of empagliflozin and colchicine in systematically adjudicated and phenotyped MINOCA populations. The framework is intended to guide future research and does not advocate off-label prescribing or changes to current clinical practice. The principal

original contribution of this article is the integration of empagliflozin and colchicine into a comparative, phenotype-linked therapeutic framework rather than a further description of their individual pleiotropic effects. To our knowledge, this is the first review to combine their complementary biological rationale with a pragmatic blueprint for prospective, mechanism-informed trials in MINOCA.

2. Diagnostic Adjudication and Mechanism-Based Phenotyping in MINOCA

MINOCA should be regarded as a working diagnosis rather than a final disease entity. Although coronary angiography confirms the absence of obstructive epicardial coronary disease, it does not identify the underlying mechanism responsible for myocardial injury. Consequently, a mechanism-informed therapeutic strategy requires systematic diagnostic adjudication to exclude non-ischemic mimics and define the predominant ischemic mechanism before treatment selection.

Cardiac magnetic resonance (CMR) imaging is central to contemporary MINOCA evaluation because it differentiates ischemic myocardial infarction from myocarditis, Takotsubo syndrome, and other non-ischemic causes of myocardial injury while simultaneously characterizing infarct size, myocardial edema, fibrosis, ventricular function, and adverse remodeling [11]. In a prospective study of women with MINOCA, the combined use of optical coherence tomography (OCT) and CMR identified a potential underlying mechanism in 84.5% of patients, highlighting the complementary diagnostic value of multimodality assessment [11].

Intracoronary imaging complements CMR when an epicardial coronary mechanism is suspected. OCT and intravascular ultrasound (IVUS) can detect plaque rupture, plaque erosion, intracoronary thrombus, layered plaque, calcified nodules, and spontaneous coronary artery dissection that may not be apparent on conventional angiography. Integrating intracoronary imaging with CMR therefore substantially improves diagnostic yield and reduces the proportion of patients with unexplained MINOCA [12].

When coronary vasomotor dysfunction or coronary microvascular dysfunction is suspected, invasive coronary functional testing provides valuable physiological information by identifying epicardial spasm, microvascular spasm, impaired coronary flow reserve, or increased microvascular resistance [12,13]. These investigations are particularly relevant when evaluating therapies targeting endothelial dysfunction or coronary microvascular disease. The objective is not to perform every investigation in every patient, but rather to establish a sufficiently robust phenotype to minimize biological heterogeneity in future therapeutic trials.

Despite increasing recognition of phenotype-guided management, access to advanced diagnostic investigations remains highly variable worldwide. In our recent international survey involving 329 cardiology professionals from 44 countries, high-income-country status emerged as the strongest independent predictor of routine CMR, intracoronary imaging, and coronary functional testing. These findings indicate that implementation of mechanism-guided MINOCA care is influenced not only by scientific recommendations but also by healthcare resources, institutional infrastructure, and access to specialized expertise [14].

The diagnostic process is therefore inseparable from treatment evaluation. Failure to adjudicate the mechanism may dilute treatment effects, create apparent therapeutic neutrality, and expose patients with non-target phenotypes to interventions that are unlikely to provide benefit.

3. Mechanism-Phenotype Framework: Targetable Pathways in MINOCA

A mechanism-informed approach requires linking therapeutic hypotheses to clinically relevant MINOCA phenotypes.

3.1. Plaque Disruption Phenotype

Plaque disruption is among the most frequently recognized ischemic mechanisms within MINOCA and may remain angiographically underestimated despite biologically active atherosclerotic disease [1,10,15]. Inflammation, endothelial dysfunction, oxidative stress, and thrombo-inflammatory activation may contribute to recurrent ischemic risk even in the absence of flow-limiting stenosis [15]. Colchicine provides a biologically plausible anti-inflammatory strategy, while empagliflozin may complement this through endothelial and cardiometabolic effects. Careful phenotypic characterization is therefore essential to minimize mechanistic heterogeneity and improve interpretation of therapeutic response in future studies.

Following the identification of these overlapping pathophysiological pathways, a mechanism-informed drug repurposing strategy may represent a pragmatic approach for therapeutic investigation in MINOCA, particularly given the challenges associated with conducting large-scale randomized trials in this heterogeneous population. Empagliflozin and colchicine exhibit complementary biological effects relevant to several mechanisms implicated in MINOCA, including inflammation, endothelial dysfunction, oxidative stress, autonomic dysregulation, coronary microvascular dysfunction, and plaque-related vascular injury. Although neither agent is currently established therapy for MINOCA, their mechanistic profiles and cardiovascular effects observed in related clinical settings provide a biologically plausible rationale for prospective evaluation in carefully phenotyped MINOCA populations.

3.2. Inflammatory Phenotype

Inflammation appears to have prognostic significance in MINOCA, as elevated inflammatory markers such as the neutrophil-to-lymphocyte ratio and C-reactive protein have been associated with worse clinical outcomes, including higher rates of MACE [16,17]. These observations support evaluation of anti-inflammatory strategies in phenotypes where systemic or vascular inflammation is prominent. Colchicine has a well-described anti-inflammatory mechanism and has been positioned as an affordable anti-inflammatory agent for atherosclerosis with broad cardiovascular event-prevention evidence [18,19]. Accordingly, incorporating inflammatory biomarkers such as hs-CRP into enrollment or stratification strategies may help reduce biological heterogeneity and improve the ability of studies to detect treatment effects in MINOCA populations.

3.3. Microvascular and Endothelial Dysfunction Phenotype

Coronary microvascular dysfunction and endothelial impairment are increasingly recognized across the spectrum of non-obstructive coronary syndromes, including selected MINOCA presentations [20]. Dysfunction may arise from impaired endothelium-dependent vasodilation, abnormal microvascular resistance, structural microvascular remodeling, inflammation, and oxidative stress [21]. These abnormalities may contribute to recurrent ischemia, persistent symptoms, impaired myocardial perfusion, and potentially adverse ventricular remodeling.

SGLT2 inhibitors exert anti-inflammatory, metabolic, neurohormonal, myocardial energetic, and post-infarction cardioprotective effects extending beyond glucose lowering. Experimental evidence suggests that these effects may include modulation of arrhythmic vulnerability, transient post-infarction SGLT2 expression, mitochondrial energetics, and

adverse ventricular remodeling, although their clinical relevance to MINOCA remains uncertain [22–26]. These observations provide biological plausibility for investigating empagliflozin in MINOCA populations characterized by coronary microvascular dysfunction, endothelial impairment, or concomitant ventricular dysfunction or adverse remodeling.

Where feasible, incorporation of coronary flow reserve, index of microvascular resistance, acetylcholine testing, stress imaging, and mechanistic biomarkers may facilitate phenotype enrichment and permit assessment of pathway engagement in future studies.

3.4. Vasospastic Phenotype

Coronary vasospasm is an established ischemic mechanism within the MINOCA spectrum and may remain unrecognized because angiography can appear normal outside an active episode [1,10]. Its pathophysiology reflects a complex interaction among vascular smooth muscle hyperreactivity, endothelial dysfunction, impaired nitric oxide signaling, oxidative stress, inflammation, and autonomic imbalance [20,21,27].

Intracoronary acetylcholine provocation testing can identify both epicardial and microvascular spasm. In prospective MINOCA and INOCA cohorts, acetylcholine testing has demonstrated a low incidence of predominantly mild and transient complications and may also identify patients at increased risk of subsequent clinical events [28,29].

Empagliflozin and colchicine should not be regarded as substitutes for established antispasm therapies such as calcium-channel blockers. Their relevance in this phenotype is instead hypothetical and relates to possible modulation of upstream endothelial, inflammatory, oxidative, and autonomic pathways. Accordingly, future studies should evaluate these agents only as adjunctive mechanism-targeted strategies in carefully phenotyped populations, ideally with vasospasm confirmed by physiologic or provocation testing [1,10].

3.5. SCAD and Sex-Associated Phenotypes

Spontaneous coronary artery dissection is an important MINOCA mechanism, particularly among younger and middle-aged women. It is pathophysiologically distinct from atherosclerotic plaque disruption, coronary vasospasm, and inflammatory microvascular dysfunction. Contemporary literature emphasizes its strong female predominance and its association with pregnancy, emotional or physical stressors, and fibromuscular dysplasia [30].

Neither empagliflozin nor colchicine has an established disease-modifying role in SCAD. This phenotype should therefore be separately adjudicated rather than included indiscriminately in trials aimed at inflammation, metabolic stress, or coronary microvascular dysfunction. Sex-specific evaluation remains important more broadly because women are disproportionately represented in MINOCA and may have different distributions of SCAD, vasomotor dysfunction, microvascular disease, and stress-related mechanisms.

3.6. Coronary Thromboembolic Phenotype

Coronary thromboembolism represents another mechanistically distinct subtype and may occur in association with atrial fibrillation, valvular disease, intracardiac thrombus, thrombophilia, infective endocarditis, or other embolic sources [31]. Its diagnostic evaluation may include careful angiographic review, echocardiography, rhythm assessment, and targeted investigation for an embolic or hypercoagulable source. Because this phenotype is not primarily driven by the pathways targeted by empagliflozin or colchicine, it should be separated from inflammatory, plaque-related, and microvascular phenotypes in therapeutic trials.

3.7. Patients with Left Ventricular Dysfunction or Adverse Remodeling

Heart failure is an important adverse outcome after MINOCA, and available observational evidence suggests that myocardial injury, left ventricular dysfunction, and adverse remodeling may contribute to subsequent risk [6,32]. Cardiac magnetic resonance imaging and echocardiography play complementary roles in characterizing ventricular function, infarct size, myocardial fibrosis, edema, and remodeling, while facilitating differentiation of ischemic from non-ischemic myocardial injury [33]. This data may be particularly relevant to empagliflozin because SGLT2 inhibitors reduce heart failure hospitalization across a broad range of ejection fractions and have shown favorable heart failure-related signals after acute myocardial infarction. In contrast, colchicine may be more relevant when heart failure vulnerability coexists with a prominent inflammatory or plaque-related phenotype rather than as a primary heart failure therapy. Future MINOCA studies could therefore evaluate ventricular function, NT-proBNP, and CMR-derived remodeling indices as enrichment or stratification variables when testing empagliflozin.

4. Evidence of Cardiovascular Benefit of SGLT2 Inhibitors

SGLT2 inhibitors were initially developed as glucose-lowering therapies but have subsequently demonstrated cardiovascular and renal benefits extending beyond glycemic control. Proposed cardioprotective mechanisms include improved myocardial energetics, natriuresis and hemodynamic unloading, reduced glucotoxicity, modulation of sympathetic and renin–angiotensin–aldosterone system activity, attenuation of inflammation and oxidative stress, improved endothelial function, and favorable effects on ventricular remodeling [22,34].

Large cardiovascular outcome and heart failure trials have established cardiovascular and renal benefits of SGLT2 inhibitors across diverse patient populations [23,35–38].

Many of the cardiovascular effects discussed in this review are likely to represent SGLT2 inhibitor class effects rather than properties unique to empagliflozin. Empagliflozin was selected as the principal candidate because it has extensive cardiovascular and heart failure outcome evidence, has been specifically evaluated after acute myocardial infarction in EMMY and EMPACT-MI, and has supporting experimental evidence related to post-infarction remodeling, immune modulation, and myocardial energetics. Evidence involving dapagliflozin, including DAPA-MI, is included to place the hypothesis within the broader SGLT2 inhibitor class. Thus, the proposed framework is empagliflozin-focused but does not exclude the possibility that other SGLT2 inhibitors may have similar relevance.

Data evaluating SGLT2I in acute myocardial infarction populations remain limited. In AMI PROTECT Registry of diabetic patients with acute MI undergoing Percutaneous Coronary Intervention (PCI), SGLT2 inhibitor use was associated with a 43% lower adjusted risk of MACE [35]. In EMMY trial ($n = 476$), patients with acute MI were assigned to empagliflozin vs. placebo, the primary outcome was NT Pro-BNP as a surrogate marker of HF, Empagliflozin was associated with a 15% greater reduction in NT-proBNP over 26 weeks compared with placebo [95% CI -4.4% to -23.6%], in addition to significant improvement in structural and functional echocardiographic parameters [36].

More recently, randomized trials evaluating SGLT2 inhibitors initiated early after acute MI have reported neutral effects on primary composite endpoints but consistent signals toward heart failure risk reduction. In EMPACT-MI trial, which included 6522 patients, empagliflozin demonstrated a favorable safety profile and a notable reduction in heart failure hospitalizations compared with placebo. Over a median follow-up of 17.9 months, the primary composite endpoint of all-cause mortality or heart failure hospitalization occurred in 8.2% of the empagliflozin group versus 9.1% in the placebo group (HR: 0.90; 95% CI: 0.76–1.06; $p = 0.21$). Heart failure hospitalization was nominally lower in the

empagliflozin group (3.6% vs. 4.7%; HR: 0.77; 95% CI: 0.60–0.98), suggesting a specific benefit in reducing heart failure-related morbidity, yet heart failure hospitalization was an exploratory signal rather than achieving the primary endpoint [37].

In the DAPA-MI trial (4017 patients), dapagliflozin achieved a win ratio of 1.34 (95% CI: 1.20–1.50; $p < 0.001$) for its primary hierarchical composite outcome [38]. Modified during the trial due to low event accrual, this result was solely driven by cardiometabolic outcomes (such as new-onset diabetes and weight reduction). Dapagliflozin did not reduce cardiovascular death or heart failure hospitalizations, with the hard composite remaining virtually identical between the groups (2.5% vs. 2.6%; HR: 0.95; 95% CI: 0.64–1.40) [38].

In a propensity-matched TriNetX analysis, SGLT2 inhibitor exposure among patients coded as MINOCA was associated with lower 1-year rates of composite cardiovascular outcomes, recurrent MI, heart failure exacerbation, and all-cause hospitalization, while mortality was not significantly different and a small increase in atrial fibrillation events was observed. These findings should be interpreted as hypothesis-generating because retrospective database analyses are vulnerable to misclassification, treatment-selection bias, and residual confounding; causality should not be inferred [39].

Given the overlap between post-MI remodeling pathways and MINOCA-related endothelial and microvascular dysfunction, SGLT2 inhibitors represent a biologically plausible strategy for prospective evaluation rather than an established therapy in this population (Figure 2).

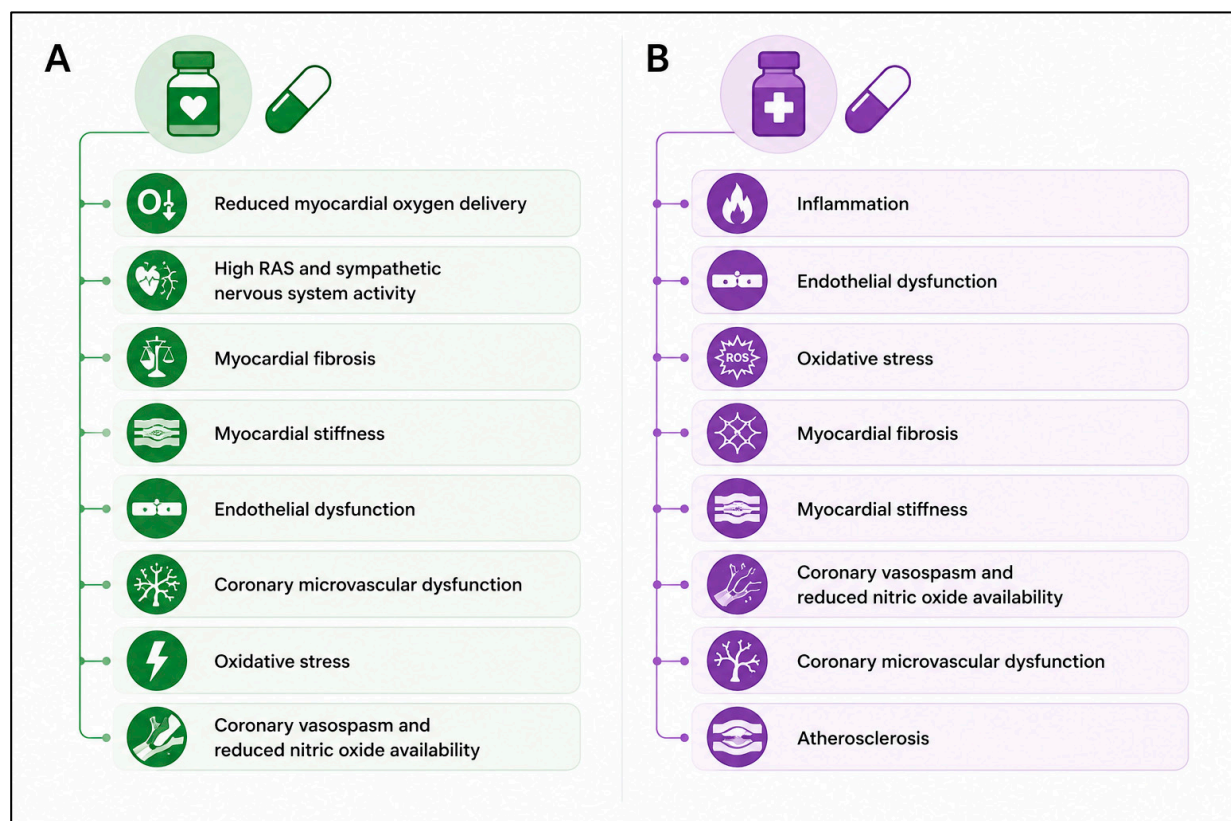


Figure 2. Proposed mechanism-specific therapeutic targets of empagliflozin (A) and colchicine (B) across the MINOCA pathophysiological spectrum.

5. Evidence of Cardiovascular Benefit of Colchicine

Colchicine is an established anti-inflammatory therapy with increasing cardiovascular relevance [40]. Its potential role in MINOCA is biologically plausible because inflammation,

endothelial dysfunction, impaired vasomotor regulation, oxidative stress, and atherosclerotic activity overlap with mechanisms implicated in MINOCA pathophysiology [41].

The inflammatory response during and after MI can worsen ischaemia-reperfusion injuries, which increase infarct size and worsen prognosis [42]. Colchicine can reduce the negative impacts of ischaemia through its anti-inflammatory, antiplatelet, anti-arrhythmic impact, anti-atherosclerotic and anti-fibrotic effects [40,42].

In LoDoCo and LoDoCo2 trials, colchicine reduced combined cardiovascular outcomes, including MI, stroke and CV death, coronary revascularization and out-of-hospital cardiac arrest in patients with stable ischemic heart disease (IHD) [43,44]. COLCOT trial showed that colchicine use in post-MI can reduce MACE by 23% [45]. However, in another trial assessing infarct size post-MI, using colchicine was not associated with significant reduction in myocardial infarct size [46].

COVERT-MI trial recruited 192 patients with STEMI post primary PCI for colchicine vs. placebo; there was no significant difference in left ventricular remodeling assessed by Cardiac Magnetic Resonance Imaging (CMR) after 3 months [46]. However, colchicine use was for only 5 days [46].

In a meta-analysis of 10 RCTs (12,819 patients) using colchicine in patients with IHD with median follow-up of 6 months reduced MACE by 31%, MI by 23%, and stroke by 52%; however, uncertainty remained regarding non-cardiovascular mortality and other safety outcomes [47].

A retrospective cohort analysis evaluated colchicine exposure and cardiovascular outcomes in patients coded as MINOCA [48]. Although the reported associations support biological plausibility, they remain hypothesis-generating; observational designs cannot exclude residual confounding, treatment-selection bias, or diagnostic misclassification. Confirmation in prospectively adjudicated MINOCA cohorts is required before any practice implications can be considered.

Given the central role of inflammation, endothelial dysfunction, and plaque-related vascular injury in selected MINOCA phenotypes, colchicine represents a biologically plausible therapeutic candidate for prospective evaluation rather than an established treatment in this population (Table 1) (Figure 2).

Table 1. Mechanism-informed diagnostic and therapeutic framework for major MINOCA phenotypes.

Phenotype/Mechanism	Typical Clues	Key Investigations	Relevance to Empagliflozin/Colchicine Hypothesis
Plaque disruption	ACS presentation; mild or irregular plaque; regional ischemic injury	OCT or IVUS; CMR	Colchicine may be most relevant to inflammatory/plaque-active disease; empagliflozin may provide complementary endothelial and remodeling effects
Epicardial vasospasm	Rest angina; transient ST changes; episodic ischemia	Acetylcholine or ergonovine provocation where appropriate	Neither drug is an established antispastic therapy; upstream endothelial, inflammatory, oxidative, and autonomic modulation may warrant study

Table 1. Cont.

Phenotype/Mechanism	Typical Clues	Key Investigations	Relevance to Empagliflozin/Colchicine Hypothesis
Microvascular spasm/CMD	Persistent or recurrent angina; abnormal flow reserve; non-obstructive angiography	CFR; IMR; acetylcholine testing; stress CMR or PET where available	Empagliflozin may be more relevant to endothelial, metabolic, microvascular, and patients with LV dysfunction, adverse remodeling, or increased HF risk; colchicine may be relevant when inflammation coexists
SCAD	Younger or middle-aged woman; pregnancy-associated or stress-related presentation; long smooth narrowing	Expert angiographic review; OCT/IVUS only when necessary and safe; CMR	Not a primary target phenotype for either proposed therapy; should be adjudicated separately
Coronary thromboembolism	Atrial fibrillation; valve disease; thrombophilia; embolic source	Echocardiography; rhythm monitoring; targeted thrombophilia/embolic evaluation	Not a primary target for either drug; requires mechanism-specific antithrombotic management
Supply–demand mismatch	Tachyarrhythmia; anemia; hypoxia; sepsis; hypertensive crisis	Clinical adjudication; CMR when diagnosis remains uncertain	Not a direct target phenotype; treatment should address the precipitating condition
Inflammatory phenotype	Elevated hs-CRP or NLR; plaque-related or vascular inflammatory features	Inflammatory biomarkers; OCT/CMR according to presentation	Colchicine is the more directly aligned candidate
LV dysfunction or adverse remodeling	LV dysfunction; increased NT-proBNP; edema; adverse remodeling	Echocardiography; CMR; NT-proBNP	Empagliflozin is the more directly aligned candidate because of HF and post-MI evidence

Abbreviations: ACS, acute coronary syndrome; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IMR, index of microcirculatory resistance; IVUS, intravascular ultrasound; LV, left ventricular; MINOCA, myocardial infarction with non-obstructive coronary arteries; NLR, neutrophil-to-lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OCT, optical coherence tomography; PET, positron emission tomography; SCAD, spontaneous coronary artery dissection.

6. Comparative Therapeutic Framework: Empagliflozin and Colchicine

The available evidence suggests that empagliflozin and colchicine should be viewed as complementary rather than competing therapeutic candidates. Although both agents share anti-inflammatory, endothelial-protective, antioxidative, and anti-remodeling properties, their principal biological strengths appear to differ.

Empagliflozin is primarily aligned with phenotypes characterized by coronary microvascular dysfunction, endothelial impairment, metabolic stress, ventricular dysfunction, or adverse remodeling, reflecting its established cardiometabolic and heart failure benefits together with favorable effects on myocardial energetics and neurohormonal activation.

Conversely, colchicine appears more directly suited to inflammatory and plaque-related phenotypes because its principal therapeutic effect is suppression of vascular inflammation and thrombo-inflammatory activation, mechanisms that may contribute

to plaque disruption and recurrent ischemic events despite the absence of obstructive coronary disease.

Importantly, these mechanistic profiles are not mutually exclusive. Several biological pathways, including inflammation, endothelial dysfunction, oxidative stress, myocardial fibrosis, stiffness, and vasomotor dysfunction, are shared by both agents, suggesting that combination therapy could represent a rational strategy for selected patients in whom multiple pathogenic mechanisms coexist. (Table 2).

Table 2. Comparative therapeutic profiles of empagliflozin and colchicine in proposed MINOCA phenotypes.

Domain	Empagliflozin	Colchicine
Principal rationale	Cardiometabolic, endothelial, neurohormonal, remodeling and HF pathways	Inflammation, plaque activity and thrombo-inflammatory pathways
Most plausible phenotype	CMD/endothelial dysfunction; LV dysfunction or adverse remodeling	Inflammatory; plaque disruption; vascular inflammation
Relevant biomarkers	NT-proBNP; LV function; CMR remodeling; CFR/IMR	hs-CRP; NLR; plaque characteristics on OCT
Advantages	Broad HF evidence; renal and hemodynamic effects; post-MI studies	Low cost; oral dosing; established anti-inflammatory action
Main limitations	No randomized MINOCA trial; volume depletion; infections; rare ketoacidosis	No randomized MINOCA trial; GI intolerance; interactions; renal/hepatic considerations; phenotype specificity uncertain
Potential combined use	May complement anti-inflammatory therapy where metabolic and HF risk coexist	May complement SGLT2 inhibition where inflammation and plaque activity coexist

Abbreviations: CFR, coronary flow reserve; CMR, cardiac magnetic resonance; CMD, coronary microvascular dysfunction; GI, gastrointestinal; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IMR, index of microcirculatory resistance; LV, left ventricular; MINOCA, myocardial infarction with non-obstructive coronary arteries; NLR, neutrophil-to-lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OCT, optical coherence tomography; SGLT2, sodium-glucose cotransporter 2.

At present, however, this concept remains hypothetical. Future prospective studies incorporating systematic phenotyping, biomarker-guided enrichment, and mechanistic endpoints will be required to determine whether different MINOCA phenotypes derive differential benefit from either therapy alone or in combination.

7. Mechanism-Informed Trial Blueprint for Drug Repurposing in MINOCA

Future studies evaluating empagliflozin and colchicine in MINOCA should use mechanism-informed and phenotype-stratified designs rather than treating MINOCA as a uniform condition. Eligibility should require structured adjudication to exclude myocarditis, Takotsubo syndrome, and other non-ischemic causes of myocardial injury, followed by classification of the most likely ischemic mechanism using CMR, intracoronary imaging, coronary functional testing, biomarkers, and clinical characteristics as appropriate.

Pragmatic registry-based randomized trials, biomarker-enriched trials, adaptive platform designs, and factorial studies may be more feasible than a single large conventional outcome trial. Stratified randomization could assign patients according to inflammatory, plaque-related, microvascular/endothelial, vasospastic, or heart failure-prone phenotypes. A factorial design could separately evaluate empagliflozin, colchicine, their combination, and usual care while preserving the ability to examine phenotype–treatment interactions.

Electronic health record-enabled trial infrastructure may further support efficient case identification, recruitment, longitudinal follow-up, and outcome ascertainment in prag-

matic MINOCA studies. Its use would nevertheless require validation of diagnostic coding, standardized phenotype definitions, assessment of data completeness, and appropriate governance for data linkage and secondary use [49].

In addition to traditional cardiovascular outcomes such as recurrent myocardial infarction and heart failure hospitalization, future investigations should also consider symptom burden, recurrent angina, and quality-of-life measures, which remain clinically relevant in many patients with MINOCA despite the absence of obstructive coronary disease. Careful safety monitoring will also be important, particularly regarding volume status and arrhythmia signals with SGLT2 inhibitors and gastrointestinal intolerance or drug interactions with colchicine.

Clinical endpoints should include cardiovascular death, recurrent MI, heart failure hospitalization, recurrent angina, symptom burden, functional status, and quality of life. Mechanistic endpoints may include hs-CRP and other inflammatory biomarkers, NT-proBNP, ventricular remodeling, CMR-defined infarct and fibrosis measures, coronary flow reserve, index of microvascular resistance, and endothelial or vasomotor function. Safety outcomes should include volume depletion, renal events, genital infections, ketoacidosis, arrhythmias, gastrointestinal intolerance, cytopenia, and relevant drug interactions.

Trials should prespecify interaction analyses between treatment assignment and phenotype rather than relying exclusively on an overall pooled effect. This would permit identification of therapeutic signals that might otherwise be obscured by the biological heterogeneity of MINOCA.

Ultimately, phenotype-oriented investigation may provide a more realistic framework for evaluating repurposed therapies in MINOCA than broad extrapolation from obstructive coronary artery disease populations (Figure 3).

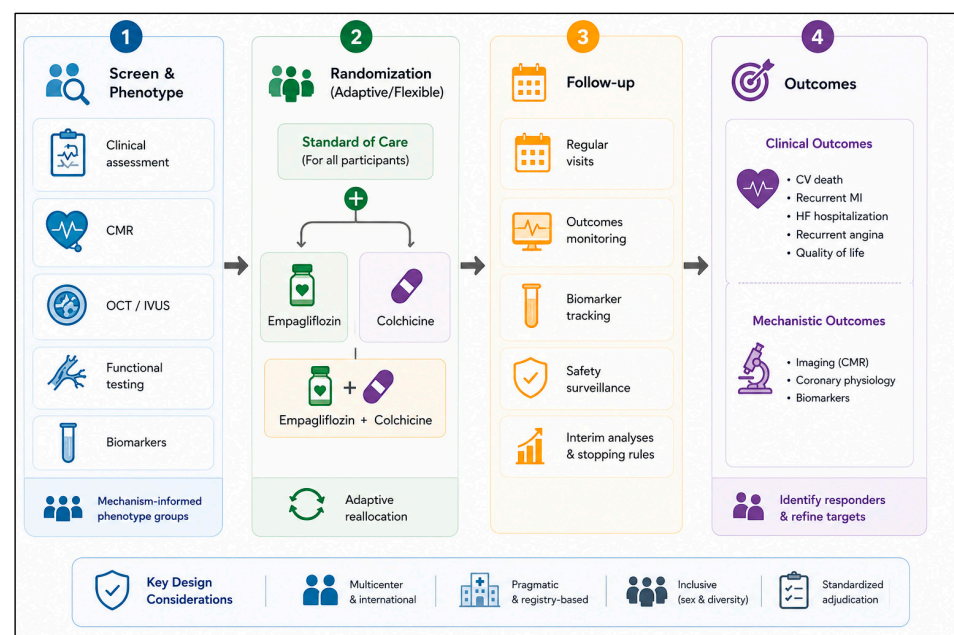


Figure 3. Proposed blueprint for phenotype-guided clinical trials evaluating empagliflozin and/or colchicine in MINOCA. The numbered panels illustrate the sequential stages of the proposed trial framework: (1) systematic screening and mechanism-based phenotyping; (2) adaptive or flexible randomization with standard-of-care therapy for all participants; (3) prospective follow-up, safety surveillance, and biomarker assessment; and (4) evaluation of clinical and mechanistic outcomes to identify treatment-responsive phenotypes and refine future therapeutic strategies. Arrows indicate the proposed progression of the study workflow. **Abbreviations:** CMR, cardiac magnetic resonance; HF, heart failure; IVUS, intravascular ultrasound; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; OCT, optical coherence tomography.

8. Future Directions

The next phase of MINOCA research should move from broad syndromic classification toward precision-oriented therapeutic investigation. This will require integration of clinical presentation, sex, imaging, coronary physiology, inflammatory status, ventricular function, and comorbidity burden into reproducible phenotypic frameworks.

Biomarker-guided strategies may be particularly valuable. Inflammatory markers such as hs-CRP or the neutrophil-to-lymphocyte ratio may help identify patients for anti-inflammatory evaluation, whereas NT-proBNP, ventricular dysfunction, CMR-defined remodeling, or microvascular indices may identify subgroups more biologically aligned with SGLT2 inhibition. These markers should initially be regarded as enrichment and stratification tools rather than validated treatment-selection tests.

Adaptive and platform trials could allow several candidate therapies to be studied across multiple mechanistic subgroups within a shared infrastructure. Such approaches may be more efficient than repeatedly testing therapies in unselected MINOCA cohorts and may permit discontinuation of ineffective strategies while expanding promising phenotype-specific treatment arms.

The implementation of such designs must account for unequal access to CMR, intracoronary imaging, and coronary functional testing. Resource-adapted diagnostic pathways, centralized imaging or physiology adjudication, and flexible eligibility strategies may therefore be required to enable participation from centers without comprehensive advanced diagnostic infrastructure [15].

Real-world observational findings involving SGLT2 inhibitors and colchicine remain hypothesis-generating. Their greatest value lies in helping prioritize prospective questions, define safety signals, and inform sample-size assumptions. They should not be interpreted as evidence of treatment efficacy until confirmed in carefully adjudicated prospective studies.

9. Conclusions

MINOCA is a heterogeneous working diagnosis encompassing distinct ischemic mechanisms as well as conditions that may ultimately be reclassified as non-ischemic myocardial injury. This heterogeneity makes systematic diagnostic adjudication essential before mechanism-targeted therapies can be evaluated.

Empagliflozin and colchicine offer complementary rather than interchangeable therapeutic hypotheses. Empagliflozin may be most relevant to microvascular, endothelial, remodeling, and heart failure-prone phenotypes, whereas colchicine may be more directly aligned with inflammatory and plaque-related mechanisms. However, neither agent has established efficacy in prospectively adjudicated MINOCA populations.

Future studies should integrate CMR, intracoronary imaging, coronary functional testing, biomarkers, and phenotype-stratified trial designs. Adaptive, registry-based, or factorial approaches may provide a practical path toward determining whether either agent—or their combination—can improve clinically meaningful outcomes in selected MINOCA subgroups.

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Abbreviations

The following abbreviations are used in this manuscript:

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ARR	Absolute Risk Reduction
CA	Coronary Angiography
CFR	Coronary Flow Reserve
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance
CMD	Coronary Microvascular Dysfunction
CRP	C-Reactive Protein
cTn	Cardiac Troponin
CV	Cardiovascular
CVD	Cardiovascular Disease
ECG	Electrocardiography
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GI	Gastrointestinal
HF	Heart Failure
HR	Hazard Ratio
hs-CRP	High-Sensitivity C-Reactive Protein
IHD	Ischemic Heart Disease
IMR	Index of Microvascular Resistance
IVUS	Intravascular Ultrasound
LV	Left Ventricular
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MINOCA	Myocardial Infarction with Non-Obstructive Coronary Arteries
NLR	Neutrophil-to-Lymphocyte Ratio
NT-proBNP	N-Terminal Pro-B-Type Natriuretic Peptide
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
RAS	Renin–Angiotensin–Aldosterone System
RCT	Randomized Controlled Trial
SCAD	Spontaneous Coronary Artery Dissection
SGLT2	Sodium–Glucose Cotransporter 2
SGLT2I	Sodium–Glucose Cotransporter 2 Inhibitor(s)
STEMI	ST-Segment Elevation Myocardial Infarction

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