



## **CLINICAL PHARMACOLOGICAL APPROACHES TO THE TREATMENT OF MYOCARDIAL INFARCTION**

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### **ABSTRACT**

*This article reviews the modern clinical pharmacological basis for the treatment of myocardial infarction (MI). It examines dual antiplatelet therapy and individualized, bleeding-risk-based duration strategies, the pharmacogenetic basis of individual response to clopidogrel (CYP2C19), anti-inflammatory therapy with colchicine, and the emerging role of SGLT2 inhibitors in post-MI care, drawing on major clinical trials published between 2023 and 2025. The review further discusses safety considerations, drug interactions, and patient-selection criteria for each therapeutic approach, and outlines a framework for personalized post-MI pharmacotherapy that integrates genetic, inflammatory, and metabolic risk markers.*

### **1. Introduction**

Over the past two to three decades, the strategy for treating myocardial infarction has changed fundamentally. Whereas earlier management focused almost exclusively on restoring coronary blood flow (reperfusion), clinical pharmacology today occupies a central role at every stage of care — from the acute period through long-term secondary prevention. Drug selection increasingly takes into account not only overall efficacy but also the patient's individual genetic characteristics, degree of systemic inflammation, and comorbid conditions. This approach reflects the broader shift toward precision, or individualized, medicine. Importantly, this shift is not merely theoretical: it is increasingly codified in major international guidelines, reflected in updated risk-stratification tools, and supported by an expanding evidence base spanning genomics, inflammation biology, and cardiometabolic pharmacology.



This evolution has been driven by several converging developments: the maturation of pharmacogenomics as a clinically actionable discipline, a growing body of evidence implicating residual inflammatory risk as an independent driver of recurrent ischemic events even after successful revascularization and lipid-lowering therapy, and the unexpected cardioprotective signal observed with SGLT2 inhibitors — a drug class originally developed for glycemic control. Together, these developments have expanded the post-MI pharmacological armamentarium well beyond the traditional pillars of antiplatelet therapy, beta-blockade, renin–angiotensin system inhibition, and statin therapy.

This review focuses on four areas that best illustrate this shift toward individualized post-MI pharmacotherapy: dual antiplatelet therapy and its risk-adapted duration, pharmacogenetic testing for clopidogrel response, anti-inflammatory therapy with colchicine, and the emerging role of SGLT2 inhibitors. A summary of the principal trials discussed is provided in Table 1.

## 2. Dual Antiplatelet Therapy (DAPT)

### 2.1 Mechanistic basis and standard regimens

The foundation of standard post-MI pharmacotherapy is dual antiplatelet therapy (DAPT) — the combination of acetylsalicylic acid (aspirin), which irreversibly inhibits platelet cyclooxygenase-1, with an inhibitor of the platelet P2Y<sub>12</sub> receptor (clopidogrel, ticagrelor, or prasugrel). Blocking both pathways produces more complete suppression of platelet aggregation than either agent alone, which is essential during the period of highest stent thrombosis and recurrent ischemic risk following an acute coronary event.

### 2.2 Individualizing therapy duration

The updated 2025 joint guideline from the American Heart Association and the American College of Cardiology places particular emphasis on individualizing the duration and composition of antiplatelet therapy according to the patient's bleeding risk, representing a substantial update to the earlier 2016 recommendations. Risk-stratification tools such as the PRECISE-DAPT score and the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria are increasingly used to identify patients who may benefit from shortened DAPT duration — as brief as one to three months — followed by P2Y<sub>12</sub> inhibitor monotherapy, versus patients at low bleeding risk and high ischemic risk who may benefit from extended or intensified therapy.

### 2.3 De-escalation strategies

Alongside duration individualization, “de-escalation” strategies — switching from a potent P2Y<sub>12</sub> inhibitor (ticagrelor or prasugrel) to clopidogrel after the initial high-risk period, either unguided or guided by platelet-function or genetic testing — have gained increasing acceptance as a means of reducing bleeding risk in the chronic phase without a clinically meaningful increase in ischemic events. Trials evaluating guided de-escalation have generally shown that this approach can lower bleeding rates while preserving ischemic protection, reinforcing the principle that antiplatelet intensity should decline over time as the highest-risk period recedes.



Ticagrelor monotherapy after a short initial period of DAPT has been particularly well studied in this context, with several large trials showing preserved ischemic protection alongside meaningfully lower rates of clinically relevant bleeding compared with continued dual therapy through twelve months.

### 3. Pharmacogenomics: Individual Variation in Response to Clopidogrel

#### 3.1 Metabolic basis

Clopidogrel is not itself pharmacologically active; it is a prodrug that requires hepatic biotransformation, primarily via the CYP2C19 enzyme, into its active metabolite. Patients carrying loss-of-function variants in the gene encoding this enzyme (“poor metabolizers”) achieve markedly reduced platelet inhibition, and numerous studies have confirmed that this is associated with an increased risk of stent thrombosis and recurrent infarction. Conversely, carriers of gain-of-function alleles (“ultrarapid metabolizers”) may be at increased risk of bleeding due to enhanced drug activation. The prevalence of loss-of-function alleles such as CYP2C19\*2 and \*3 varies substantially across populations, being notably higher among East and Central Asian populations than among individuals of European ancestry — a fact with direct relevance to clinical practice in the region.

#### 3.2 Testing and clinical implementation

In 2024, the American Heart Association issued a formal scientific statement recommending CYP2C19 genetic testing prior to prescribing a P2Y<sub>12</sub> inhibitor, particularly in patients undergoing percutaneous coronary intervention. Point-of-care genotyping platforms, which can return results within one to two hours, have made testing feasible even in the acute-care setting, and several health systems have integrated pre-emptive or rapid genotyping into routine post-PCI pathways. According to current practice guidance, patients found to carry a “poor metabolizer” variant are generally recommended to receive an alternative agent such as ticagrelor or prasugrel in place of clopidogrel.

#### 3.3 Ongoing debate

It should be noted, however, that the 2025 updated American guideline has not yet formally incorporated this genetic testing recommendation as a mandatory step, and debate continues among specialists regarding its cost-effectiveness, logistical feasibility across diverse healthcare settings, and applicability across different ethnic populations. A 2026 guideline developed by the CERSI-PGx consortium has proposed a structured framework for translating CYP2C19 genotype results into actionable prescribing recommendations, which may help standardize implementation going forward. Beyond CYP2C19, research into additional pharmacogenomic determinants of cardiovascular drug response — including variants affecting statin-associated myopathy risk and beta-blocker metabolism — suggests that genotype-informed prescribing may eventually extend well beyond antiplatelet therapy alone, further reinforcing the value of building genotyping infrastructure now.

### 4. Anti-inflammatory Therapy: The Emerging Role of Colchicine



#### 4.1 Rationale

Persistent low-grade inflammation following myocardial infarction has been recognized as an independent driver of recurrent ischemic events, distinct from residual atherogenic lipid burden. This understanding has renewed interest in targeting the inflammatory component of atherosclerosis directly, rather than relying solely on lipid-lowering therapy.

#### 4.2 Mechanism and trial evidence

Colchicine, a centuries-old anti-gout medication, acts primarily through inhibition of microtubule polymerization and suppression of the NLRP3 inflammasome, thereby reducing interleukin-1 $\beta$  and downstream interleukin-6-mediated inflammatory signaling implicated in plaque instability. The 2019 COLCOT trial demonstrated that colchicine 0.5 mg daily, initiated after myocardial infarction, significantly reduced the risk of major cardiovascular complications, with the greatest benefit observed when the drug was started within the first three days after infarction. These findings were broadly consistent with the earlier LoDoCo2 trial in patients with chronic coronary disease. The 2024 European Society of Cardiology guideline incorporated low-dose colchicine as a Class IIa recommendation for secondary prevention.

#### 4.3 Safety considerations

Despite this favorable evidence, colchicine's adoption has been tempered by safety concerns, including gastrointestinal intolerance (particularly diarrhea), rare but serious myotoxicity, and clinically important drug–drug interactions — most notably with strong CYP3A4 inhibitors (such as certain macrolide antibiotics and antifungals) and with statins, which can increase the risk of myopathy when co-administered. Renal impairment further increases the risk of toxicity and requires dose adjustment or avoidance. Careful medication reconciliation is therefore essential before initiating colchicine in post-MI patients, who are typically already receiving multiple interacting drugs, including high-intensity statins. Dose reduction or avoidance is generally advised in patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup>, and periodic monitoring of blood counts and liver function is reasonable during the first months of therapy, particularly in older adults, in whom age-related declines in renal clearance and polypharmacy further increase the likelihood of clinically significant interactions.

#### 4.4 Continuing uncertainty

Recently published large-scale trial data have added further nuance to this discussion, and the precise role of colchicine — including optimal patient selection, timing of initiation, and long-term safety in broader populations — remains an area of active scientific debate rather than settled practice.

### 5. SGLT2 Inhibitors: A New Horizon in Post-Infarction Care

#### 5.1 Background and proposed mechanisms

Sodium–glucose cotransporter-2 (SGLT2) inhibitors (dapagliflozin, empagliflozin) were initially developed for glycemic control in type 2 diabetes but have since become firmly established in the treatment of heart failure, owing to mechanisms extending well beyond



glucose lowering — including natriuresis and volume modulation, a shift toward ketone-body utilization as an efficient myocardial fuel source, reduction of cardiac preload and afterload, and anti-inflammatory and anti-fibrotic effects on the myocardium. These pleiotropic mechanisms have prompted active investigation of SGLT2 inhibitors in the acute and post-myocardial infarction setting.

### 5.2 Trial evidence

A large 2025 meta-analysis published in the *European Heart Journal — Cardiovascular Pharmacotherapy*, encompassing more than 11,000 post-infarction patients, found that all-cause mortality was reduced by 14% among patients receiving an SGLT2 inhibitor, with significant improvement in left ventricular function observed at 12 weeks. The greatest benefit was seen in patients with comorbid diabetes or elevated NT-proBNP levels. These pooled findings should, however, be interpreted alongside the two largest dedicated post-MI outcome trials: EMPACT-MI, which randomized more than 6,500 patients but did not meet its primary composite endpoint of all-cause mortality and heart-failure hospitalization, although it did show a meaningful reduction in heart-failure hospitalizations across the spectrum of ejection fraction; and DAPA-MI, in which dapagliflozin improved a hierarchical composite outcome driven mainly by weight reduction and lower incident diabetes, but showed no mortality benefit. This divergence between the meta-analytic signal and the neutral primary results of the largest individual trials indicates that the evidence for routine SGLT2 inhibitor use after myocardial infarction is still maturing rather than conclusive.

### 5.3 Safety and patient selection

Clinically relevant safety considerations for SGLT2 inhibitors include an increased risk of genital mycotic infections, volume depletion in patients also receiving diuretics, and — although rare — euglycemic diabetic ketoacidosis, which requires clinician awareness given its atypical presentation with near-normal glucose levels. Careful attention to renal function and hydration status is warranted when initiating therapy in the acute post-MI setting. Temporary discontinuation is generally advised during acute illness, periods of reduced oral intake, or planned surgery, in keeping with established “sick-day” guidance for this drug class, and clinicians should counsel patients accordingly at the time of prescription.

### 5.4 Outstanding questions

Nevertheless, specialists emphasize that definitive conclusions regarding routine, unselected use of this drug class across the entire post-infarction population should await the results of ongoing large randomized controlled trials, which will help clarify optimal timing of initiation, the magnitude of benefit in patients without diabetes or heart failure, and long-term safety.

## 6. Toward Personalized Post-Myocardial Infarction Pharmacotherapy

The four therapeutic domains reviewed above — antiplatelet therapy, pharmacogenomics, anti-inflammatory treatment, and metabolic modulation via SGLT2 inhibition — illustrate a broader shift away from a uniform, “one-size-fits-all” pharmacological regimen toward a



stratified approach informed by the individual patient's bleeding and ischemic risk, genetic metabolizer status, residual inflammatory burden, and metabolic comorbidities. Integrating these domains into a coherent clinical pathway will require close collaboration between clinical pharmacologists, cardiologists, and laboratory medicine specialists, as well as investment in point-of-care testing infrastructure and clinician education.

From a health-systems perspective, realizing this integrated model will also require attention to workflow design: embedding genotype results, inflammatory markers, and renal or metabolic parameters directly into electronic prescribing systems, so that clinicians receive actionable, patient-specific guidance at the point of care rather than having to consult disparate data sources. Multidisciplinary post-MI clinics, in which cardiologists, clinical pharmacologists, and pharmacists jointly review each patient's risk profile before hospital discharge, offer one practical model for operationalizing this approach and have been associated with improved adherence to guideline-directed therapy in early experience.

Table 1 summarizes the principal trials and guidance documents underpinning the therapeutic strategies discussed in this review.

| Trial / Source                     | Intervention                                     | Population                                                     | Key Finding                                                                                                                    |
|------------------------------------|--------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| COLCOT (2019)                      | Colchicine<br>0.5 mg/day vs<br>placebo           | Patients within<br>30 days of MI                               | Significant reduction<br>in major cardiovascular<br>events; greatest benefit<br>when started within 3<br>days                  |
| LoDoCo2 (2020)                     | Colchicine<br>0.5 mg/day vs<br>placebo           | Chronic<br>coronary disease                                    | Reduced composite<br>cardiovascular endpoint,<br>supporting anti-<br>inflammatory strategy                                     |
| 2025 meta-analysis (EHJ-CVP)       | SGLT2<br>inhibitor vs<br>standard care           | >11,000 post-<br>infarction patients<br>(pooled analysis)      | 14% reduction in all-<br>cause mortality;<br>improved LV function<br>at 12 weeks                                               |
| EMPACT-MI (2024) / DAPA-<br>MI     | SGLT2<br>inhibitor<br>initiated early<br>post-MI | >10,000<br>combined post-<br>infarction patients<br>(two RCTs) | Primary composite<br>endpoints not met;<br>EMPACT-MI reduced<br>HF hospitalizations,<br>DAPA-MI showed no<br>mortality benefit |
| AHA Scientific Statement<br>(2024) | CYP2C19<br>genotyping<br>before P2Y12            | Patients<br>undergoing PCI                                     | Recommends<br>genotype-guided<br>selection of alternative                                                                      |



| Trial / Source                          | Intervention               | Population                       | Key Finding                                                                             |
|-----------------------------------------|----------------------------|----------------------------------|-----------------------------------------------------------------------------------------|
|                                         | inhibitor selection        |                                  | P2Y12 inhibitor in poor metabolizers                                                    |
| 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline | Risk-adapted DAPT duration | Acute coronary syndrome patients | Individualizes DAPT duration/composition by bleeding risk; updates 2016 recommendations |

Table 1. Overview of key clinical trials and guidance documents discussed in this review.

#### 7. Implementation Considerations in Resource-Limited Settings

The translation of these individualized strategies into routine practice is particularly challenging in low- and middle-income healthcare systems, where access to rapid CYP2C19 genotyping, inflammatory biomarker panels, and newer agents such as ticagrelor, prasugrel, colchicine, and SGLT2 inhibitors may be constrained by cost, supply, or laboratory infrastructure. In such settings, clopidogrel often remains the default P2Y12 inhibitor for practical and economic reasons, which makes awareness of population-level CYP2C19 allele frequencies especially important: clinicians practicing in regions with a higher prevalence of loss-of-function alleles should maintain a lower threshold for suspecting inadequate platelet inhibition and for considering alternative agents when genetic testing is unavailable, based on clinical risk factors such as recurrent stent thrombosis or early recurrent ischemia.

Similarly, where colchicine and SGLT2 inhibitors are not yet part of standard post-MI protocols, their introduction may need to be prioritized according to local disease burden and cost-effectiveness data rather than adopted uniformly. International guideline bodies increasingly acknowledge this heterogeneity, and future guidance is likely to include tiered recommendations that distinguish core, broadly applicable interventions from optional or resource-dependent add-on therapies. Strengthening local clinical pharmacology training, together with the development of national or regional formularies that reflect the latest evidence, will be essential to ensure that patients in resource-limited settings are not left behind as post-MI pharmacotherapy continues to individualize.

#### 8. Limitations and Future Directions

Several challenges remain before these individualized strategies can be fully realized in routine practice. Genetic and inflammatory biomarker testing are not yet universally available, particularly outside specialized centers, and their cost-effectiveness in diverse healthcare systems requires further study. Head-to-head comparisons of genotype-guided versus platelet-function-guided antiplatelet strategies remain limited. Long-term safety data for colchicine and SGLT2 inhibitors in broad, unselected post-MI populations are still accumulating. Future research should prioritize pragmatic trials that evaluate the real-world feasibility and cost-effectiveness of integrated, biomarker-guided post-MI pharmacotherapy pathways, as well as



implementation studies examining how best to embed rapid genotyping and inflammatory-risk assessment into routine acute coronary care.

#### 9. Conclusion

The modern clinical pharmacology of myocardial infarction treatment is evolving simultaneously along several fronts: tailoring antiplatelet therapy to individual bleeding risk, selecting medications based on genetic characteristics, introducing new therapies that target the inflammatory process, and uncovering the cardioprotective potential of established antidiabetic drugs. These trends indicate that, in the future, rather than a uniform regimen applied to every patient with myocardial infarction, an individualized pharmacotherapy strategy — one that accounts for a patient's genetic profile, degree of inflammation, and comorbid conditions — will increasingly take precedence.

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