Metabolic Dysfunction at the Culprit Lesion: The Triglyceride–Glucose Index as a Marker of Thrombus Burden and No-Reflow in STEMI

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Abstract

Abstract

Background: Primary percutaneous coronary intervention (PCI) restores epicardial patency in most patients with ST-segment elevation myocardial infarction (STEMI), yet adequate tissue reperfusion is not assured. A large intracoronary thrombus can promote distal embolization, while microvascular obstruction may produce no-reflow despite an angiographically patent infarct-related artery. Both conditions are associated with greater myocardial injury and poorer clinical outcomes. Insulin resistance contributes to endothelial dysfunction, platelet hyperreactivity, inflammation, oxidative stress, impaired fibrinolysis, and microvascular injury. The triglyceride–glucose (TyG) index, calculated from fasting triglyceride and glucose concentrations, offers a simple surrogate measure of this metabolic disturbance.

Main text: This narrative review examines the biological and clinical links connecting the TyG index with coronary thrombus burden and no-reflow in patients undergoing primary PCI for STEMI. Plaque disruption initiates thrombosis, but the magnitude and consequences of thrombus formation are modified by the host metabolic and inflammatory milieu. A higher TyG index may identify patients in whom reduced nitric oxide bioavailability, heightened platelet activation, procoagulant signaling, deficient fibrinolysis, and reperfusion-related microvascular damage converge. Recent observational studies have reported independent associations between elevated TyG values, high angiographic thrombus burden, and coronary no-reflow. Nevertheless, differences in sampling time, fasting status, angiographic definitions, cutoff selection, and covariate adjustment limit direct comparison and preclude adoption of a universal threshold.

Conclusion: The TyG index is an inexpensive and widely accessible candidate biomarker for early risk assessment in STEMI. Current evidence supports an association with thrombotic burden and failed microvascular reperfusion but does not establish causality or demonstrate that TyG-guided treatment improves outcomes. Prospective multicenter studies using standardized measurement and validated incremental-risk analyses are required before routine clinical implementation.

Keywords: Triglyceride–glucose index, ST-segment elevation myocardial infarction, intracoronary thrombus, no-reflow phenomenon, primary percutaneous coronary intervention

1. Introduction

ST-segment elevation myocardial infarction (STEMI) remains one of the most time-critical presentations of coronary artery disease. Its immediate threat arises from persistent coronary occlusion, but its clinical consequences depend on more than reopening the culprit vessel. Contemporary guideline-directed care prioritizes rapid primary percutaneous coronary intervention (PCI), appropriate antithrombotic therapy, and secondary prevention because the duration and completeness of reperfusion strongly influence myocardial salvage and survival [1,2]. Even when PCI achieves a satisfactory angiographic result, however, microvascular perfusion may remain severely compromised.

The initiating event in most cases is disruption of an atherosclerotic plaque, followed by platelet recruitment, thrombin generation, and formation of an obstructive coronary thrombus [3]. Thrombus quantity varies considerably. A large burden complicates lesion crossing and stent deployment, increases the likelihood of distal embolization, and is associated with impaired flow and adverse long-term outcomes [4]. At the tissue level, embolized debris interacts with ischemic endothelial injury, inflammation, edema, vasoconstriction, and reperfusion damage. The resulting no-reflow phenomenon is clinically important because it is linked to larger infarcts, adverse left ventricular remodeling, heart

failure, arrhythmias, and death [5,6].

Prediction remains difficult. Several clinical, laboratory, and angiographic variables are related to thrombus burden or no-reflow, but many become available only after catheterization or have limited discriminatory performance [7]. A biomarker obtained early from routine laboratory testing could therefore complement rather than replace conventional assessment.

Insulin resistance provides a plausible metabolic bridge between atherothrombosis and defective reperfusion. It is accompanied by diminished endothelial nitric oxide activity, inflammatory activation, oxidative stress, platelet hyperreactivity, and an imbalance between coagulation and fibrinolysis [8]. The triglyceride–glucose (TyG) index was introduced as a practical surrogate for insulin resistance and showed agreement with the hyperinsulinemic–euglycemic clamp, the reference method for assessing insulin sensitivity [9]. Its calculation requires only fasting triglyceride and glucose values, making it attractive in settings where insulin assays or specialized metabolic testing are unavailable.

The cardiovascular scope of the TyG index has expanded from chronic risk estimation to acute coronary disease. In patients with STEMI treated by primary PCI, recent studies have associated higher TyG values with high intracoronary thrombus burden and angiographic no-reflow [10,11]. The evidence is promising but still limited, predominantly observational, and vulnerable to variation in definitions and timing. This review integrates the pathobiology of STEMI, coronary thrombosis, and microvascular reperfusion failure with emerging evidence regarding the TyG index. It also considers the potential clinical role of TyG measurement and the methodological requirements needed before the marker can be incorporated into routine STEMI pathways.

2. From Atherosclerotic Plaque to Occlusive Coronary Thrombosis

Atherosclerosis is a chronic inflammatory disease of the arterial wall rather than a simple process of passive lipid storage. Retention and modification of apoB-containing lipoproteins stimulate endothelial activation, monocyte recruitment, foam-cell formation, smooth-muscle responses, and extracellular-matrix remodeling. The resulting plaques differ substantially in composition and biological activity [3]. The older concept that a single morphological “vulnerable plaque” can reliably predict a future event has therefore been replaced by a broader view that incorporates plaque phenotype, systemic susceptibility, and the thrombotic response of the host [12].

Plaque rupture and superficial erosion are the principal substrates of acute coronary thrombosis. Rupture exposes a necrotic core rich in tissue factor and thrombogenic material. Erosion involves loss or dysfunction of the endothelial layer over an otherwise intact fibrous cap and commonly produces a platelet-rich thrombus [13]. Culprit morphology also appears to influence inflammatory risk and subsequent clinical behavior [22]. Regardless of the initiating substrate, platelet adhesion is rapidly followed by activation, aggregation, thrombin generation, and fibrin formation. When endogenous anticoagulant and fibrinolytic mechanisms cannot contain this response, the thrombus enlarges and may completely interrupt epicardial flow.

Abrupt cessation of coronary perfusion deprives the dependent myocardium of oxygen and metabolic substrates. Adenosine triphosphate production falls, ionic gradients deteriorate, intracellular calcium accumulates, and contractile function fails. Persistent ischemia produces progressive necrosis from the subendocardium toward the epicardium. Rapid reperfusion is therefore essential, but reperfusion itself can add injury through reactive oxygen species, mitochondrial permeability transition, calcium overload, inflammation, and endothelial dysfunction [14,18]. The final infarct is consequently determined by the ischemic interval, collateral flow, myocardial demand, embolic burden, microvascular integrity, and the biological response to reperfusion.

Primary PCI has transformed STEMI care by restoring epicardial patency more reliably than fibrinolysis. Stenting reduces acute recoil and reocclusion compared with balloon angioplasty alone, although procedural success does not guarantee myocardial reperfusion [15,23]. An open epicardial artery may coexist with extensive downstream obstruction. This distinction between vessel patency and tissue perfusion is central to understanding why thrombus burden and no-reflow remain clinically relevant even in the modern PCI era.

3. Intracoronary Thrombus Burden: Assessment and Consequences

Angiographic thrombus burden reflects the visible quantity of thrombotic material at the culprit lesion. The Thrombolysis in Myocardial Infarction (TIMI) framework established standardized angiographic assessment of coronary flow and supported subsequent thrombus grading systems [21]. In practice, thrombus may appear as an intraluminal filling defect, contrast staining, an abrupt cutoff, or total occlusion. A vessel with absent initial antegrade flow can obscure the true burden; reassessment after wiring or limited flow restoration may therefore reclassify the lesion more accurately.

High thrombus burden is not merely an imaging descriptor. It identifies a technically demanding lesion and a biologically active thrombotic state. During PCI, balloon inflation, aspiration, or stent deployment can fragment the clot and plaque contents. Distal migration of this material occludes arterioles and capillaries, releases vasoconstrictors, activates platelets and leukocytes, and aggravates endothelial injury. Large thrombus volume may also interfere with stent expansion and apposition, leaving residual material that contributes to later ischemic complications.

Clinical observations consistently connect high thrombus burden with intraprocedural no-reflow [24]. Its prognostic implications may persist beyond hospital discharge: patients with extensive thrombus have shown higher risks of reinfarction, stent thrombosis, heart failure, and mortality [4,26]. Thrombus burden should nevertheless be interpreted within the wider clinical context because ischemic delay, culprit-vessel territory, initial flow, infarct size, hemodynamic status, and treatment all influence outcome.

Mechanical reduction of thrombus initially appeared to offer a direct solution. The REMEDIA trial showed improved indices of myocardial reperfusion with manual aspiration in primary or rescue angioplasty [25]. Larger randomized evidence subsequently demonstrated that routine manual thrombectomy did not improve major clinical outcomes and raised concern about stroke, arguing against indiscriminate use [17]. This experience is instructive for biomarker research: identifying a high-risk phenotype does not automatically prove that one procedure will improve its prognosis. A TyG-based association with thrombus burden must therefore be distinguished from evidence supporting a specific TyG-guided intervention.

4. No-Reflow as a Failure of Tissue Reperfusion

No-reflow describes inadequate myocardial perfusion after epicardial obstruction has been relieved in the absence of a flow-limiting residual stenosis, dissection, spasm, or mechanical complication. Angiographic manifestations include reduced final TIMI flow and impaired myocardial blush, while electrocardiographic ST-segment resolution and cardiac magnetic resonance imaging offer complementary information about tissue-level reperfusion and microvascular obstruction. These methods assess related but nonidentical phenomena, which partly explains the variable incidence reported across studies [5,28].

The underlying injury is multifactorial. Prolonged ischemia damages endothelial cells and causes capillary swelling, loss of vasodilator capacity, increased permeability, and interstitial edema. Reperfusion introduces oxygen into vulnerable tissue, generating oxidative stress and activating inflammatory and cell-death pathways [18]. Neutrophils, platelets, fibrin, microthrombi, and plaque debris physically obstruct the microcirculation, while vasoconstrictor release and reduced nitric oxide further restrict flow. In severe injury, capillary integrity may be lost and intramyocardial hemorrhage may occur.

Distal embolization provides a direct connection between culprit-lesion thrombus and microvascular failure. It does not act alone, however. The same amount of embolized material may produce different consequences depending on ischemic duration, baseline microvascular health, diabetes, inflammatory activity, collateral circulation, and reperfusion injury. Coronary microvascular dysfunction is therefore both a substrate and a consequence of STEMI [19]. Endothelial dysfunction reduces nitric oxide bioavailability, favors vasoconstriction and leukocyte adhesion, and weakens the antiplatelet properties of the vascular surface [29]. Myocardial necrosis further evokes an inflammatory response that is necessary for healing but can intensify edema and early microvascular damage when excessive [30].

No-reflow is more than an angiographic inconvenience. It is associated with larger infarct size, lower recovery of left ventricular systolic function, adverse remodeling, heart failure, ventricular arrhythmias, cardiogenic shock, and mortality [6,27]. Reported predictors include advanced age, delayed reperfusion, diabetes or hyperglycemia, anterior infarction, high inflammatory indices, low initial flow, and high thrombus burden [7,16,28]. Their predictive accuracy remains incomplete, creating interest in biomarkers that capture upstream biological susceptibility.

5. The TyG Index as a Practical Metabolic Marker

Insulin resistance denotes reduced responsiveness of insulin-sensitive tissues to the metabolic actions of insulin. It develops well before overt diabetes in many individuals and is closely related to visceral adiposity, hypertriglyceridemia, ectopic lipid accumulation, hypertension, and chronic low-grade inflammation. Although the hyperinsulinemic–euglycemic clamp is the reference technique, it is labor-intensive and unsuitable for emergency or large-scale clinical use. The homeostasis model assessment of insulin resistance is more practical but requires fasting insulin, which is neither standardized nor routinely obtained during acute STEMI care [32].

The TyG index is calculated as:

TyG index = ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2]

Its original validation demonstrated a relationship with insulin sensitivity measured using the clamp technique [9]. Because triglycerides and glucose are inexpensive and widely available, TyG can be derived without an additional specialized assay. This simplicity has encouraged its evaluation across diabetes, metabolic syndrome, atherosclerosis, and cardiovascular disease [31].

Several studies link higher TyG values with atherosclerotic disease. The index has been associated with symptomatic coronary artery disease in secondary-care populations [20], carotid atherosclerosis [34], progression of coronary artery calcification [37], and broader macrovascular and microvascular injury [38]. Longitudinal observations also suggest that TyG can identify people at increased risk of cardiovascular events [33]. These associations are biologically credible but do not make TyG a direct measure of atherosclerotic plaque or coronary thrombosis. It is a composite metabolic marker influenced by its two components and by the circumstances under which they are measured.

Interpretation in acute myocardial infarction needs particular caution. Stress hormones, catecholamine release, inflammation, recent food intake, and treatment can alter glucose and triglyceride concentrations. Acute hyperglycemia may reflect both chronic metabolic dysfunction and the physiological severity of infarction. A value calculated from nonfasting or early emergency samples may therefore not be equivalent to one derived after a standardized fast. Furthermore, the TyG index can be elevated in people without diabetes and may add information beyond diagnostic categories, but its incremental value over admission glucose, glycated hemoglobin, lipid measures, and established risk models must be shown rather than assumed.

Other lipid-based ratios have also been related to cardiovascular risk, including the triglyceride-to-high-density-lipoprotein cholesterol ratio [36]. These markers should not be treated as interchangeable. Their formulas represent different metabolic relationships, and an association reported for one index cannot be transferred automatically to another.

6. Why a Higher TyG Index Could Accompany Thrombus Burden and No-Reflow

6.1 Endothelial dysfunction

Healthy endothelium regulates vascular tone and opposes thrombosis through nitric oxide and other mediators. Insulin normally supports endothelial nitric oxide production, whereas insulin resistance selectively impairs this pathway while leaving mitogenic and vasoconstrictor signaling relatively preserved. Oxidative stress further consumes nitric oxide and promotes endothelial activation [29,39]. The vascular surface consequently becomes more adhesive to platelets and leukocytes, less vasodilatory, and less resistant to thrombosis. In STEMI, this chronic vulnerability is superimposed on acute ischemic endothelial injury.

6.2 Platelet hyperreactivity

Insulin-resistant states are associated with enhanced platelet activation, altered calcium handling,

oxidative stress, and reduced responsiveness to endogenous inhibitory signals. Platelets may therefore adhere and aggregate more readily after plaque disruption [8]. Hyperglycemia can also promote protein glycation, reactive oxygen species generation, and activation of platelet signaling, while triglyceride-rich lipoproteins contribute to an inflammatory and proatherogenic environment. Together, these effects offer a plausible explanation for the association between a higher TyG index and a larger culprit-lesion thrombus.

6.3 Coagulation and impaired fibrinolysis

Insulin resistance is accompanied by increased procoagulant activity and deficient fibrinolysis. Higher concentrations or activity of tissue factor, fibrinogen, and plasminogen activator inhibitor-1 favor formation and persistence of fibrin-rich clot. The resulting imbalance does not originate from the TyG index itself; rather, TyG may serve as an accessible signal of the metabolic environment in which this imbalance develops. Simple clinical approaches to identifying insulin-resistant individuals at elevated cardiovascular risk were proposed before TyG became widely adopted [40], underscoring the long-recognized link between metabolic dysfunction and thrombogenic risk.

6.4 Inflammation, plaque behavior, and oxidative stress

Metabolic dysfunction activates innate immune pathways and increases cytokines, adhesion molecules, and oxidative stress. These processes accelerate atherosclerosis, weaken endothelial homeostasis, and can influence plaque disruption and the magnitude of the thrombotic response [3,22]. During myocardial reperfusion, the same inflammatory and oxidative pathways worsen capillary permeability, edema, leukocyte plugging, and cellular injury [14,30]. Thus, an elevated TyG index may relate to both the upstream event—formation of a large thrombus—and the downstream event—failure of microvascular reperfusion.

6.5 Microvascular susceptibility

Chronic insulin resistance can impair small-vessel vasomotor function and promote structural microvascular damage. When acute STEMI occurs, the coronary microcirculation may have less reserve to tolerate ischemia, embolization, and reperfusion stress. Associations between TyG and measures of microvascular damage in other populations support this concept [38], although they cannot establish the mechanism within an infarct-related territory. The proposed pathway is therefore integrative: TyG reflects metabolic disturbance; metabolic disturbance promotes endothelial, inflammatory, platelet, coagulation, and microvascular abnormalities; these abnormalities increase susceptibility to thrombus accumulation and no-reflow.

7. Clinical Evidence in STEMI Undergoing Primary PCI

The most direct evidence comes from observational studies specifically examining angiographic outcomes. Köktürk et al. [10] evaluated patients with STEMI treated by primary PCI and reported higher TyG values among those with greater intracoronary thrombus burden. Multivariable analysis supported an independent association after adjustment for relevant covariates. This study moved the TyG concept beyond long-term cardiovascular risk and connected it to the culprit-lesion phenotype encountered during emergency intervention.

Zhang et al. [11] similarly examined the relationship between TyG and coronary no-reflow after primary PCI. A higher index was associated with impaired postprocedural flow, supporting the hypothesis that metabolic dysfunction contributes to microvascular reperfusion failure. The finding is coherent with evidence linking inflammatory and hematological abnormalities to no-reflow [7] and with the established contribution of high thrombus burden to distal embolization [24].

The two outcomes are related but should not be collapsed into one. Thrombus burden is principally a feature of the culprit lesion assessed before or during intervention. No-reflow is a postreperfusion manifestation arising from embolic, ischemic, inflammatory, endothelial, and microvascular processes. A higher TyG index could be associated with no-reflow partly through increased thrombus burden, but mediation has not been established. It may also mark baseline microvascular vulnerability or greater systemic inflammatory stress.

Evidence from broader coronary populations lends contextual support. Higher TyG has been associated

with symptomatic coronary disease [20,35], coronary calcification progression [37], and adverse cardiovascular risk [33]. These studies indicate that TyG captures a clinically relevant metabolic phenotype, but they do not directly validate its use for thrombus or no-reflow prediction in acute STEMI. Similarly, evidence concerning endothelial or microvascular damage [38] supports biological plausibility rather than a treatment threshold.

Several limitations temper interpretation. First, observational studies cannot exclude residual confounding. Diabetes, admission hyperglycemia, renal function, inflammatory burden, infarct location, ischemic time, initial TIMI flow, and antithrombotic treatment may influence both TyG and angiographic outcome. Second, single-center cohorts may not generalize across different populations or PCI systems. Third, data-driven cutoff values often perform better in the derivation sample than in external populations. Fourth, inconsistent definitions of high thrombus burden and no-reflow reduce comparability. Finally, the timing and fasting status of blood sampling are crucial but not always uniform.

The current literature therefore supports association and risk enrichment, not causation. It does not show that lowering TyG during the acute event prevents thrombus formation, nor that choosing aspiration, glycoprotein IIb/IIIa inhibition, intracoronary vasodilators, or another procedural strategy according to TyG improves clinical outcomes. This distinction is particularly important given the neutral clinical results of routine thrombectomy despite its intuitive mechanistic appeal [17].

8. Potential Clinical Role and Research Priorities

The practical appeal of TyG is clear. The required laboratory tests are inexpensive, familiar, and usually obtained during the early evaluation of acute coronary disease. If validated, TyG could be incorporated into a multivariable preprocedural model to identify patients who warrant heightened preparation for thrombus-related complications, careful assessment of microvascular reperfusion, and closer post-PCI surveillance. Its role would most plausibly be additive rather than solitary.

Routine implementation is premature for several reasons. There is no universally accepted STEMI-specific cutoff, and the meaning of a value depends on blood-sampling conditions. A fasting requirement may conflict with the emergency nature of primary PCI, while delaying reperfusion to obtain a standardized sample would be unacceptable. Studies should therefore distinguish an admission TyG index from a fasting TyG index measured later and determine which, if either, provides clinically useful discrimination.

Future investigations should use prospective, multicenter designs with prespecified sampling, core-laboratory angiographic assessment, and uniform definitions of thrombus burden and no-reflow. Models should adjust for established predictors and report calibration, discrimination, decision-curve performance, and net incremental value rather than statistical significance alone. External validation is essential. Serial measurements could clarify whether acute stress or chronic metabolic status drives the association, particularly when analyzed alongside glycated hemoglobin and prior diabetes status.

Mechanistic studies should determine whether the TyG–no-reflow relationship is mediated by thrombus burden, inflammatory activity, platelet reactivity, endothelial dysfunction, or pre-existing microvascular disease. Cardiac magnetic resonance endpoints, including microvascular obstruction and intramyocardial hemorrhage, would provide more sensitive tissue-level assessment than angiographic flow alone. Finally, randomized trials would be required before any treatment strategy could be recommended specifically on the basis of TyG risk classification.

9. Conclusion

The triglyceride–glucose index connects routinely measured metabolic variables with a pathophysiological network relevant to acute coronary thrombosis and myocardial reperfusion. Higher TyG values have been associated with greater intracoronary thrombus burden and no-reflow in patients with STEMI undergoing primary PCI. Endothelial dysfunction, platelet hyperreactivity, inflammation, oxidative stress, impaired fibrinolysis, and reduced microvascular reserve offer plausible explanations for these observations. The index is inexpensive and potentially useful for early risk enrichment, but the evidence remains observational and heterogeneous. TyG should currently be regarded as a promising

adjunctive marker rather than an established stand-alone predictor or a basis for selecting therapy. Standardized prospective validation and demonstration of incremental clinical utility are necessary before routine incorporation into STEMI care.

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