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Insulin resistance biomarkers and risk stratification after percutaneous coronary intervention in patients with type 2 diabetes mellitus: a narrative review

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Abstract

Patients with type 2 diabetes mellitus (T2DM) undergoing percutaneous coronary intervention (PCI) remain at disproportionately high risk of major adverse cardiovascular events (MACE), repeat revascularization, and in-stent restenosis (ISR) compared with non-diabetic patients, despite advances in stent technology and antiplatelet therapy. Insulin resistance (IR) is a central pathophysiological driver of this excess risk, promoting endothelial dysfunction, vascular smooth muscle cell proliferation, and accelerated neointimal growth. Because direct measurement of IR is impractical in routine practice, several simple, laboratory-derived surrogate indices have been investigated for post-PCI risk stratification in T2DM. Of these, the triglyceride-glucose (TyG) index has accumulated the most consistent evidence, with multiple cohort studies and meta-analyses demonstrating an independent, graded association between elevated TyG values and MACE, mortality, ISR, and recurrent revascularization after PCI in diabetic populations. TyG also improves discrimination when added to established risk scores such as GRACE, and outperforms alternative markers such as the triglyceride-to-HDL-cholesterol ratio and METS-IR in this setting. Complementary inflammatory and metabolomic biomarkers add prognostic information that IR markers alone do not capture. This review summarizes the pathophysiological rationale linking

IR to adverse PCI outcomes in T2DM, synthesizes the current evidence for IR-derived and complementary biomarkers, discusses methodological limitations, and outlines their potential role in post-PCI risk stratification, while highlighting the need for prospective, standardized, multi-ethnic validation before clinical adoption.

Keywords

Percutaneous coronary intervention; type 2 diabetes mellitus; insulin resistance; triglyceride-glucose index; risk stratification; in-stent restenosis.

Introduction

Diabetes mellitus is one of the most consistent predictors of adverse outcomes after PCI: a meta-analysis of nearly 140,000 patients found significantly higher in-hospital mortality, MACE, and stent thrombosis in T2DM versus non-diabetic patients undergoing PCI [1], an excess risk that persists in the drug-eluting stent era and is compounded by glycemic control status and insulin treatment requirement [2]. Traditional risk markers—HbA1c, fasting glucose, lipid fractions—only partially capture the metabolic derangement driving this risk. Insulin resistance (IR) is a more proximate pathophysiological substrate, and several inexpensive, routinely available biomarkers have been proposed as IR surrogates for cardiovascular risk stratification. This review focuses on IR-based biomarkers—principally the triglyceride-glucose (TyG) index, but also HOMA-IR, the triglyceride-to-HDL-cholesterol (TG/HDL-C) ratio, and the metabolic score for insulin resistance (METS-IR)—for risk stratification after PCI in T2DM, and extends to complementary inflammatory and metabolomic markers, integration with clinical risk scores, and methodological limitations constraining clinical translation.

Pathophysiological rationale: insulin resistance and vascular injury after PCI

IR disrupts vascular signaling in ways that predispose to both atherogenesis and impaired healing after stenting. Physiologically, insulin acts via the PI3K/Akt pathway to stimulate endothelial nitric oxide synthase and vasodilation, while a parallel MAPK

pathway mediates growth-promoting, pro-inflammatory effects. In insulin-resistant states, PI3K/Akt signaling is selectively impaired while MAPK signaling is preserved or amplified by compensatory hyperinsulinemia, shifting the balance toward vasoconstriction, inflammation, and vascular smooth muscle cell proliferation [3,4].

This selective pathway resistance underlies the endothelial dysfunction of diabetes and prediabetic IR states, reducing nitric oxide bioavailability and increasing oxidative stress, inflammatory cytokine expression, and leukocyte adhesion [3,5]. In PCI, the same mechanisms drive neointimal hyperplasia and in-stent restenosis: unchecked smooth muscle proliferation/migration and impaired re-endothelialization are amplified under IR and hyperinsulinemia [4], providing a mechanistic basis for expecting IR biomarkers—independent of a formal diabetes diagnosis—to track with adverse outcomes after stenting. Endothelial dysfunction and IR are mechanistically intertwined rather than sequential, so combining a metabolic IR index with a vascular-injury biomarker could in principle capture more prognostic variance than either alone, though this combination has not yet been tested in PCI cohorts.

The triglyceride-glucose index as a surrogate marker of insulin resistance

The TyG index, calculated as the natural logarithm of [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2], has been validated against the hyperinsulinemic-euglycemic clamp as a simple, inexpensive, non-insulin-based surrogate for IR, and has become the most extensively studied IR biomarker in cardiovascular risk stratification, including in T2DM patients undergoing PCI.

TyG index and MACE/mortality after PCI in T2DM

In 776 patients with T2DM and acute coronary syndrome (ACS) undergoing PCI, TyG was independently associated with a composite of mortality, stroke, myocardial infarction, and unplanned revascularization, with more than double the hazard in the highest versus lowest tertile [6]. This has been widely replicated, and a 2024 meta-analysis confirmed the MACE association holds similarly across diabetic and non-

diabetic subgroups, suggesting TyG-captured IR operates as a continuous risk factor across the glycemic spectrum, even though absolute risk remains highest in T2DM [11].

TyG index, in-stent restenosis, and repeat revascularization

TyG also shows a dose-response relationship with ISR and repeat revascularization. In ACS patients receiving drug-eluting stents, ISR prevalence rose stepwise across TyG tertiles, with each one-unit increase independently associated with higher ISR odds after adjustment [7]. In chronic coronary syndrome patients followed for a median of five years, TyG independently predicted repeat revascularization/ISR with a linear dose-response [8]. In T2DM specifically, recurrent revascularization was driven mainly by lesion progression rather than classic ISR, yet TyG remained an independent predictor and improved model discrimination [9].

Combining the TyG index with established clinical risk scores

Because the GRACE score is already embedded in ACS pathways, several studies tested whether TyG adds information on top of it. In 899 T2DM/ACS patients undergoing PCI, TyG and GRACE were each independent predictors of long-term MACE, and a combined TyG-GRACE model outperformed either alone [13]. In 515 non-ST-elevation ACS patients, adding TyG to GRACE improved the 2-year AUC from 0.798 to 0.849 with substantial net reclassification, contributing more predictive value than HbA1c, fasting glucose, triglycerides, or LDL-C individually [14]. This supports using TyG as an adjunct that sharpens discrimination within existing risk scores, rather than a replacement for them.

Comparative performance of non-insulin-based insulin resistance indices

Because several IR surrogates are calculable from routine lipid and glucose panels, direct comparisons are clinically relevant. In 9,514 patients undergoing complex PCI, only TyG remained independently associated with cardiovascular events after multivariable adjustment; neither TG/HDL-C nor METS-IR reached significance, and only TyG meaningfully improved model discrimination [10]. This may reflect TyG's

integration of both hypertriglyceridemia and hyperglycemia—two mechanistically linked abnormalities more pronounced in T2DM—whereas TG/HDL-C and METS-IR weight adiposity more heavily and may be less specific to the glucotoxic and lipotoxic pathways implicated in post-PCI vascular injury.

Insulin-based indices and microvascular correlates

HOMA-IR, calculated from fasting glucose and insulin, is the most widely used insulin-based IR index and has been linked to impaired coronary microvascular function after PCI. TyG itself has similarly been associated with coronary microvascular dysfunction and no-reflow phenomenon in T2DM patients with STEMI undergoing primary PCI, extending its relevance beyond epicardial restenosis to microvascular injury [12]. HOMA-IR's main limitations for routine use are the need for a standardized insulin assay, considerable inter-laboratory variability, and confounding by exogenous insulin therapy—common among T2DM patients presenting for PCI—more than any demonstrated inferiority in prognostic accuracy.

Beyond insulin resistance: complementary and emerging biomarkers

IR indices capture metabolic risk but do not fully account for the inflammatory and metabolomic dimensions of post-PCI prognosis in T2DM. Untargeted metabolomic profiling in a nested case-control T2DM-PCI cohort identified a six-metabolite signature centered on NAD+ metabolism that distinguished one-year MACE, with external validation in an independent cohort of 301 patients and functional experiments in high-glucose-cultured vascular smooth muscle cells supporting a mechanistic role [15]. In a prospective cohort of 2,755 T2DM patients on dual antiplatelet therapy after PCI, the high-sensitivity C-reactive protein-to-albumin ratio (CAR), a simple inflammatory index, was independently associated with 5-year all-cause and cardiac mortality [16]. Because inflammation and IR are mechanistically linked but only partially overlapping drivers of risk, a multi-biomarker approach combining metabolic, inflammatory, and

metabolomic indices appears more promising than reliance on any single index in isolation.

Generalizability, standardization, and methodological considerations

A key limitation is geographic and ethnic concentration: nearly all PCI-specific TyG studies discussed above—the founding T2DM-ACS-PCI cohort, the ISR and revascularization analyses, and the GRACE-combination studies—were conducted in Chinese populations [6-10,12-14]. A systematic review of TyG in general, non-procedural populations draws on a broader international base and confirms the cardiovascular/mortality association across countries and ethnicities [17], supporting biological plausibility outside East Asian cohorts, but direct validation of TyG-based risk stratification in T2DM patients undergoing PCI in European, North American, or other non-Asian populations remains sparse.

A second issue is the absence of an agreed TyG threshold for clinical decision-making: reported cut-points vary by endpoint, follow-up duration, and statistical method (tertile-based, median-split, or ROC-derived), complicating cross-study comparison. Most supporting studies are also retrospective, raising the usual concerns about residual confounding (medication adherence, diet, diabetes duration) and reverse causation common to observational biomarker-outcome studies.

Therapeutic implications: does targeting insulin resistance improve PCI outcomes?

If IR is mechanistically upstream of neointimal proliferation, insulin-sensitizing agents should reduce restenosis and MACE in T2DM, and trial evidence supports this. In the POPPS trial, 97 T2DM patients receiving bare-metal stents were randomized to pioglitazone or control; target lesion revascularization was lower with pioglitazone (12.5% vs. 29.8%), and intravascular ultrasound showed a smaller neointimal index, supporting a direct anti-proliferative rather than purely glycemic effect [18]. A subsequent meta-analysis confirmed that thiazolidinediones, particularly pioglitazone,

reduce ISR, target lesion revascularization, and MACE after PCI without increased cardiovascular risk [19].

SGLT2 inhibitors (SGLT2i), which lower glucose independently of insulin and show pleiotropic vascular effects, have drawn more recent attention. A meta-analysis of 8 observational studies (24,229 T2DM patients with myocardial infarction undergoing PCI) found SGLT2i use associated with lower all-cause mortality, cardiovascular mortality, MACE, heart-failure hospitalization, stroke, and acute kidney injury, though repeat revascularization did not differ significantly [20], suggesting SGLT2i act mainly through hemodynamic, myocardial, and renal mechanisms rather than a direct anti-restenotic effect—though this evidence remains observational.

Together, these data support IR as a modifiable therapeutic target after PCI in T2DM, not merely a prognostic marker. However, evidence is fragmented across agent classes, endpoints, and stent generations, and no trial has prospectively used TyG-defined risk strata to select patients for intensified insulin-sensitizing or SGLT2i therapy.

Future directions

Four priorities would advance this field: (1) prospective, multi-ethnic studies outside East Asia to test whether TyG-outcome associations and thresholds generalize across healthcare systems and diets; (2) combined biomarker panels integrating a metabolic index (TyG), an inflammatory marker (CAR), and potentially a metabolomic signature—biologically plausible given their partial mechanistic overlap, but empirically untested as a unified model; (3) a prospective trial randomizing TyG-defined high-risk T2DM patients to intensified pioglitazone, SGLT2i, or standard care, bridging the retrospective biomarker literature with the older, smaller pioglitazone restenosis trials; and (4) mechanistic imaging studies directly comparing SGLT2i's mortality/heart-failure benefit against pioglitazone's anti-proliferative effect, to clarify whether these agents act through overlapping or distinct vascular pathways.

Conclusion

Insulin resistance is a mechanistically plausible and empirically supported contributor to excess cardiovascular risk after PCI in T2DM, acting through impaired endothelial nitric oxide signaling, vascular smooth muscle proliferation, and disordered vascular healing. Among available surrogates, the TyG index has the strongest evidence base—independently associated with mortality, MACE, ISR, and repeat revascularization, outperforming TG/HDL-C and METS-IR, and improving discrimination when combined with GRACE—and can be calculated at no added cost from routine preprocedural labs, making it a practical adjunctive tool for identifying diabetic patients who may warrant closer follow-up or more intensive management. Complementary inflammatory and metabolomic markers capture additional prognostic information, pointing toward multi-biomarker models as a future direction. Trial data with pioglitazone and observational data with SGLT2 inhibitors indicate that IR is a modifiable target, not merely a passive marker. Nonetheless, the evidence remains predominantly observational, retrospective, geographically concentrated in East Asian cohorts, and without a consensus TyG threshold. Prospective, externally validated, and ideally interventional studies are needed before IR indices can be formally integrated into post-PCI risk stratification and treatment-selection algorithms in T2DM.

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