

Aspirin resistance in stable angina patients with type 2 diabetes mellitus: Clinical and hemostatic determinants

Imankulova Djamshida Abdurakhmonovna *

Republican specialized scientific practical medical center of therapy and medical rehabilitation, Tashkent, Uzbekistan.

World Journal of Advanced Pharmaceutical and Life Sciences, 2026, 10(02), 001-010

Publication history: Received on 10 February 2026; revised on 24 March 2026; accepted on 27 March 2026

Article DOI: <https://doi.org/10.53346/wjapls.2026.10.2.0012>

Abstract

Background: Aspirin remains a cornerstone of secondary prevention in patients with stable angina; however, a substantial proportion of patients with type 2 diabetes mellitus (T2DM) exhibit reduced responsiveness to aspirin therapy. This phenomenon, commonly referred to as aspirin resistance or aspirin hyporesponsiveness, is associated with persistent platelet activation, impaired primary hemostasis control, and increased residual ischemic risk. In patients with stable coronary artery disease and T2DM, the problem is particularly relevant because diabetes promotes a prothrombotic milieu through platelet hyperreactivity, endothelial dysfunction, oxidative stress, chronic inflammation, and altered blood rheology.

Objective: To review current evidence on the clinical and hemostatic determinants of aspirin resistance in patients with stable angina and T2DM, with particular emphasis on mechanisms of primary hemostatic dysfunction, laboratory assessment, and therapeutic implications.

Main body: This review analyzes the pathophysiological basis of impaired aspirin response in T2DM, including enhanced platelet turnover, increased thromboxane-dependent and thromboxane-independent platelet activation, metabolic dysregulation, and inflammatory signaling. Special attention is given to hemostatic determinants such as platelet aggregation abnormalities, erythrocyte aggregation, coagulation disturbances, and endothelial dysfunction, all of which may contribute to reduced antiplatelet efficacy. Clinical factors including poor glycemic control, obesity, hypertension, dyslipidemia, chronic kidney disease, and treatment-related variables are also examined. The review further summarizes current laboratory methods for assessing aspirin responsiveness and discusses their strengths and limitations in routine clinical practice.

Conclusion: Aspirin resistance in stable angina patients with T2DM is a multifactorial clinical and biological phenomenon reflecting the complex interaction between cardiometabolic abnormalities and hemostatic dysregulation. Better recognition of its determinants may improve risk stratification and support more individualized antiplatelet strategies in this high-risk population.

Keywords: Aspirin resistance; Aspirin hyporesponsiveness; Stable angina; Type 2 diabetes mellitus; Platelet aggregation; Primary hemostasis; Erythrocyte aggregation; Antiplatelet therapy; Chronic coronary syndrome; Thrombosis

1. Introduction

Stable ischemic heart disease, currently conceptualized within the broader framework of chronic coronary syndromes (CCS) or chronic coronary disease (CCD), remains a major contributor to global cardiovascular morbidity and mortality.

* Corresponding author: Imankulova Djamshida Abdurakhmonovna

Contemporary guidelines emphasize that CCS represents not a benign or static phase of coronary artery disease, but a dynamic condition characterized by persistent ischemic risk, recurrent symptoms, progressive atherosclerotic burden, and ongoing vascular dysfunction [1,2]. This clinical burden is magnified by the worldwide expansion of type 2 diabetes mellitus (T2DM), which continues to rise at an alarming pace. The 11th edition of the International Diabetes Federation Diabetes Atlas estimated that 11.11% of adults worldwide were living with diabetes in 2024, with a further increase projected by 2050, underscoring diabetes as one of the fastest-growing global cardiometabolic threats [3]. In parallel, the 2023 ESC Guidelines on cardiovascular disease in patients with diabetes reaffirm that diabetes substantially amplifies the risk of atherosclerotic cardiovascular disease, heart failure, renal dysfunction, and premature death, thereby placing patients with concomitant CCS and T2DM among the most vulnerable populations in contemporary cardiology [4].

Aspirin remains a cornerstone of long-term antithrombotic therapy in patients with established obstructive chronic coronary disease. Current CCS recommendations generally support single antiplatelet therapy with aspirin or clopidogrel for long-term secondary prevention, with intensified antithrombotic regimens reserved for selected patients at high ischemic risk and acceptable bleeding risk [1,5]. However, even under guideline-directed aspirin therapy, a considerable residual thrombotic risk persists, especially in individuals with T2DM, diffuse atherosclerosis, prior revascularization, chronic kidney disease, obesity, or chronic inflammatory activation [1,4,5]. This persistent risk reflects the multifactorial nature of thrombosis in chronic coronary disease, where platelet activation, thromboxane generation, endothelial dysfunction, coagulation abnormalities, and adverse hemorheological changes may continue despite apparently adequate pharmacologic cyclooxygenase-1 inhibition [1,5,6]. Thus, the clinical question is no longer whether aspirin is useful in secondary prevention, but why its benefit is heterogeneous and why some high-risk patients remain thrombosis-prone despite continuous treatment.

Within this context, aspirin resistance—more precisely described in many contemporary sources as aspirin hyporesponsiveness, incomplete thromboxane suppression, or high on-aspirin platelet reactivity—retains substantial clinical relevance [6–8]. Although the term “aspirin resistance” is methodologically and biologically heterogeneous, and some studies have challenged its uniform definition, the phenomenon continues to describe an important subgroup of patients in whom laboratory or biochemical markers suggest insufficient antiplatelet effect during aspirin therapy [6,7]. The American Diabetes Association has acknowledged that aspirin resistance has been described in diabetes using *ex vivo* and *in vitro* methods, even though the degree and mechanisms of impairment may vary between assays and populations [8]. More recent studies and reviews indicate that diabetes is associated with enhanced thromboxane biosynthesis, increased platelet turnover, systemic inflammation, obesity-related metabolic stress, and higher on-treatment platelet reactivity, all of which may attenuate aspirin responsiveness and worsen cardiovascular prognosis [6,7,9]. Therefore, aspirin resistance remains clinically important not merely as a laboratory curiosity, but as a potential marker of residual atherothrombotic risk and a possible target for more individualized secondary prevention strategies.

The special relevance of primary hemostasis in diabetic coronary disease deserves particular emphasis. T2DM induces a prothrombotic state through several converging pathways, including chronic hyperglycemia, insulin resistance, oxidative stress, non-enzymatic glycation of platelet and vascular proteins, endothelial nitric oxide deficiency, and low-grade inflammation [4,9,10]. These alterations reprogram platelet phenotype toward heightened adhesion, activation, secretion, and aggregation, while also interacting with erythrocytes, leukocytes, fibrinogen, and the vascular wall [9,10]. In this setting, primary hemostasis is not limited to platelet aggregation alone; it encompasses the broader interplay between platelets, erythrocyte aggregation, blood viscosity, shear-dependent interactions, and endothelial surface reactivity. This is particularly relevant in stable angina, where recurrent ischemia often develops on the background of chronic plaque burden, impaired microvascular perfusion, and persistent hemorheological abnormalities rather than overt plaque rupture alone. Accordingly, diabetic abnormalities of primary hemostasis may help explain why some patients with stable angina exhibit persistent ischemic symptoms, adverse laboratory platelet profiles, and attenuated benefit from standard-dose aspirin despite the absence of an acute coronary event [4,9,10]. Focusing specifically on stable angina rather than acute coronary syndromes (ACS) is scientifically and clinically justified. In ACS, thrombus formation is dominated by acute plaque disruption, intense systemic and local inflammatory activation, procedural factors, and routine use of dual antiplatelet therapy with aspirin plus a P2Y₁₂ inhibitor, which can obscure the isolated contribution of aspirin responsiveness [11]. By contrast, patients with stable angina represent a more suitable model for studying aspirin effect in the chronic phase of coronary disease, where aspirin often remains the principal long-term antiplatelet agent and where residual thrombogenicity may reflect enduring patient-specific biological determinants rather than the transient pathobiology of an acute event [1,5,11]. Moreover, stable coronary disease in T2DM is highly heterogeneous, spanning obstructive epicardial atherosclerosis, diffuse multivessel disease, endothelial dysfunction, and coronary microvascular impairment; all of these phenotypes may modulate platelet behavior and aspirin response in different ways [1,2,4]. For these reasons, the stable angina population offers a particularly informative setting in which to examine the clinical and hemostatic determinants of aspirin hyporesponsiveness.

The purpose of this review is to summarize current evidence on aspirin resistance in patients with stable angina and type 2 diabetes mellitus, with special emphasis on its clinical predictors, primary hemostatic mechanisms, laboratory assessment, and implications for individualized antiplatelet management.

2. Clinical Definitions and Terminology

The terminology used to describe an inadequate response to aspirin remains heterogeneous and is one of the major reasons for variation in the reported prevalence and interpretation of this phenomenon across studies. In contemporary cardiovascular literature, the traditional term “aspirin resistance” is increasingly considered too broad, because it may include several biologically distinct conditions, such as true pharmacodynamic nonresponse, poor adherence, reduced bioavailability, assay-related variability, and continued platelet activation through non-cyclooxygenase-dependent pathways [12–14]. For this reason, many recent authors prefer the more precise expressions aspirin hyporesponsiveness, incomplete aspirin response, or high on-aspirin platelet reactivity, particularly when laboratory testing is used to characterize persistent platelet activity during aspirin treatment [12,13].

In its classical sense, aspirin resistance refers to the failure of aspirin to produce its expected antiplatelet effect or to prevent recurrent atherothrombotic events despite regular administration [12,13]. However, this definition requires careful interpretation. A recurrent ischemic event during aspirin therapy does not necessarily indicate true biological resistance, since cardiovascular events may develop through multiple mechanisms that are only partially dependent on platelet cyclooxygenase-1 activity. Likewise, an abnormal platelet function test does not automatically prove true resistance, because laboratory results may be influenced by the assay used, the timing of blood sampling, the formulation of aspirin, the dosing interval, and patient adherence [12,14]. Thus, in current scientific usage, “aspirin resistance” is best regarded as a general descriptive term rather than a uniform mechanistic diagnosis.

A more rigorous concept is laboratory aspirin resistance, often referred to as high on-aspirin platelet reactivity. This term describes the persistence of measurable platelet activity despite aspirin exposure, as demonstrated by platelet function or biochemical testing [12,13]. Depending on the methodology, this may be reflected by persistent aggregation in response to arachidonic acid or other agonists, inadequate suppression of thromboxane generation, or abnormal results in point-of-care platelet function assays [12,13]. Importantly, high on-aspirin platelet reactivity is an assay-based phenotype and should not be interpreted as proof of a single underlying mechanism. This distinction is especially important in patients with type 2 diabetes mellitus, in whom chronic inflammation, hyperglycemia, oxidative stress, obesity, and accelerated platelet turnover may sustain increased platelet reactivity even under aspirin therapy [12,15].

The term clinical aspirin resistance is sometimes used to describe the occurrence of myocardial infarction, stroke, unstable angina, or other ischemic events despite aspirin treatment [13]. Although clinically intuitive, this concept is less specific than laboratory resistance. Clinical treatment failure may result from progression of atherosclerosis, endothelial dysfunction, activation of coagulation pathways, plaque instability, or other non-platelet mechanisms, and therefore should not be considered synonymous with biochemical or functional nonresponse to aspirin [13]. For this reason, separating laboratory evidence of insufficient platelet inhibition from adverse clinical outcomes is essential for accurate interpretation of the literature.

An equally important concept is pseudo-resistance, which refers to an apparently inadequate aspirin effect that is not caused by true pharmacodynamic failure. The most common explanation is poor adherence, which remains a frequent and underestimated cause of abnormal aspirin-response testing [14]. Another major contributor is the use of enteric-coated aspirin, which may delay or reduce absorption and lead to lower or more variable systemic bioavailability compared with plain aspirin [16,17]. This issue appears particularly relevant in patients with obesity and diabetes, in whom absorption kinetics may be less predictable [16]. In addition, drug interactions, especially with certain nonsteroidal anti-inflammatory drugs, may competitively interfere with aspirin binding to platelet cyclooxygenase-1 and create the false appearance of reduced responsiveness [12]. In such situations, abnormal platelet testing reflects insufficient effective exposure rather than true biological resistance.

It is also useful to distinguish aspirin resistance from aspirin treatment failure. Aspirin resistance is primarily a pharmacodynamic or laboratory concept related to incomplete inhibition of platelet thromboxane-dependent activity, whereas treatment failure is a broader clinical concept referring to the inability of aspirin-based therapy to prevent an ischemic event [12,13]. The latter may occur even when platelet cyclooxygenase-1 is adequately inhibited, because chronic coronary disease and diabetes are characterized by multiple overlapping prothrombotic mechanisms. Therefore, these terms should not be used interchangeably in scientific writing.

For the purposes of this review, the term aspirin resistance will be used in its broad conventional sense, while preference will be given to more specific terminology whenever possible. Laboratory aspirin resistance or high on-aspirin platelet reactivity will denote persistent platelet activity demonstrated during aspirin therapy; clinical aspirin resistance will refer to ischemic events occurring despite treatment, without implying definite pharmacologic nonresponse; and pseudo-resistance will indicate apparent nonresponse caused by poor adherence, impaired absorption, enteric coating, drug interactions, or analytical artifact. Such terminology provides a more precise and clinically meaningful framework for understanding aspirin responsiveness in stable angina patients with type 2 diabetes mellitus [12–14,16].

3. Why Type 2 Diabetes Mellitus Promotes Reduced Aspirin Responsiveness

Type 2 diabetes mellitus (T2DM) is characterized by a complex prothrombotic phenotype in which platelet hyperreactivity, endothelial dysfunction, oxidative stress, chronic low-grade inflammation, and altered thrombopoiesis act synergistically to reduce the effectiveness of aspirin-mediated platelet inhibition [18–21]. In patients with chronic coronary disease, these abnormalities are especially relevant because aspirin targets only one major pathway of platelet activation, namely cyclooxygenase-1-dependent thromboxane A₂ synthesis, whereas diabetes amplifies several parallel activation mechanisms that may persist despite aspirin therapy [18,20,22]. As a result, patients with T2DM more often exhibit high on-aspirin platelet reactivity, incomplete thromboxane suppression, and greater residual ischemic risk than individuals without diabetes (figure 1) [18,19,21].

3.1. Platelet abnormalities in T2DM

Platelets in T2DM display a baseline phenotype of increased activation and enhanced responsiveness to multiple agonists. Contemporary evidence indicates that diabetic platelets are more readily activated, show greater surface expression of pro-adhesive and pro-aggregatory molecules, and demonstrate amplified aggregation responses under both resting and stimulated conditions [18,21,23]. This hyperreactive phenotype is driven by metabolic stress, mitochondrial dysfunction, calcium dysregulation, and persistent interaction with an abnormal vascular environment. Importantly, because aspirin selectively inhibits thromboxane-dependent signaling, it may not fully suppress platelet activation when non-thromboxane pathways are simultaneously upregulated in diabetes [18,20,23]. A key feature of diabetic platelet dysfunction is **enhanced thromboxane generation**. T2DM is associated with increased thromboxane biosynthesis and higher residual thromboxane activity, which may reflect incomplete aspirin suppression, increased extra-platelet thromboxane formation, or accelerated production of newly released platelets that have not yet been acetylated by aspirin [18,20,24]. This mechanism is particularly important because thromboxane A₂ is a potent mediator of vasoconstriction and platelet recruitment; persistent thromboxane activity therefore reduces the net antiplatelet effect of standard once-daily aspirin regimens [18,24].

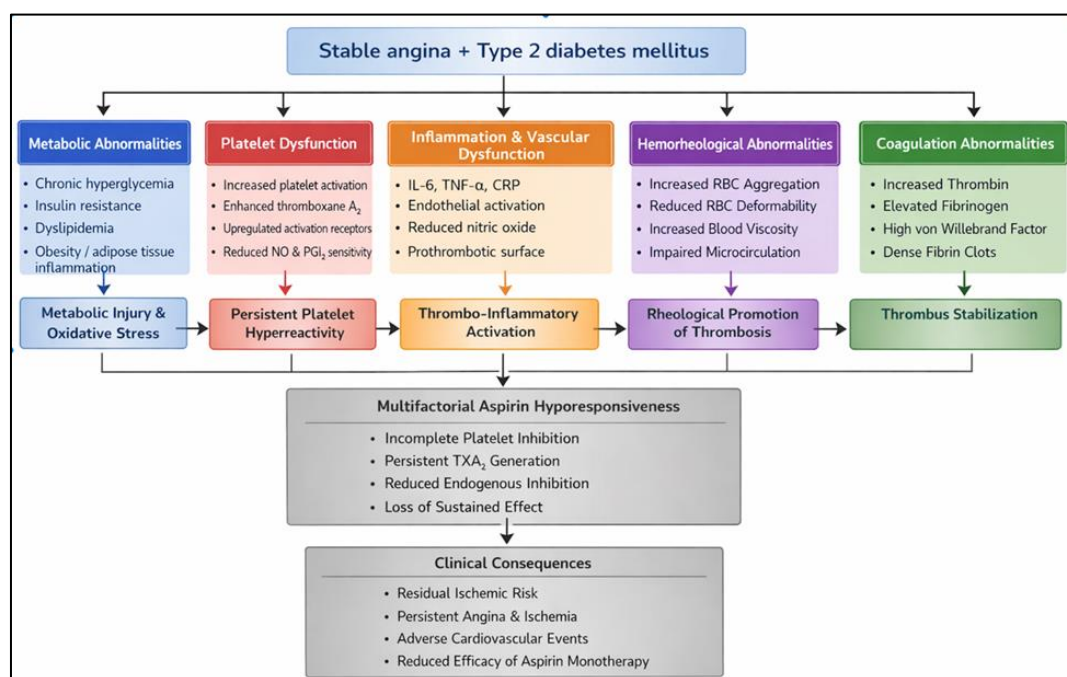


Figure 1 Pathological model of aspirin resistance in stable angina and type 2 diabetes mellitus

Diabetic platelets also exhibit increased expression of activation receptors and adhesion-related molecules, including glycoprotein IIb/IIIa, P-selectin, glycoprotein Ib, and other receptor systems involved in platelet adhesion and aggregation [18,21,23]. Upregulation of these receptors facilitates platelet interaction with fibrinogen, von Willebrand factor, leukocytes, and the injured endothelium, thereby amplifying thrombus propagation even when cyclooxygenase-1 is inhibited [18,23]. In addition, diabetic platelets show reduced sensitivity to endogenous inhibitory pathways, including nitric oxide- and prostacyclin-mediated signaling, which normally restrain platelet activation [19,21]. This impaired response to physiologic inhibition further shifts the balance toward sustained platelet reactivity and may help explain why aspirin monotherapy is less effective in some patients with T2DM.

3.2. Hyperglycemia and glycation-mediated mechanisms

Chronic hyperglycemia is a central driver of reduced aspirin responsiveness in T2DM. Persistent elevation of glucose promotes non-enzymatic glycation of platelet proteins, membrane receptors, and circulating hemostatic proteins, altering platelet structure and function in ways that favor activation and aggregation [19,21,25]. Glycation may modify platelet membrane fluidity, receptor behavior, and intracellular signaling efficiency, thereby lowering the threshold for activation and making platelets less responsive to pharmacologic inhibition. Hyperglycemia is also associated with increased osmotic and metabolic stress within platelets, which contributes to calcium mobilization and enhanced secretion of prothrombotic mediators [19,21].

In parallel, hyperglycemia contributes substantially to endothelial dysfunction, which is a major determinant of platelet activation in diabetes. The diabetic endothelium produces less nitric oxide and prostacyclin, while expressing more adhesion molecules and proinflammatory mediators, thereby creating a vascular surface that is more thrombogenic and less capable of suppressing platelet reactivity [20,21,25]. Since aspirin does not correct endothelial dysfunction directly, persistent endothelial injury may sustain platelet activation even when thromboxane synthesis is partially inhibited. This is particularly relevant in stable angina, where chronic endothelial impairment and microvascular dysfunction often coexist with epicardial atherosclerosis [20,21].

Another major mechanism is oxidative stress. Hyperglycemia increases reactive oxygen species generation through mitochondrial dysfunction, activation of protein kinase C pathways, and advanced glycation end-product signaling [19,21,25]. Oxidative stress enhances platelet activation, impairs nitric oxide bioavailability, promotes endothelial injury, and may increase thromboxane-related signaling. Under these conditions, aspirin's inhibitory effect may be functionally attenuated because pro-oxidative and proinflammatory mechanisms continue to drive platelet aggregation through alternative routes [19,25].

3.3. Insulin resistance and platelet signaling

Insulin resistance is another major factor linking T2DM to aspirin hyporesponsiveness. Under physiologic conditions, insulin exerts anti-aggregatory effects on platelets by enhancing nitric oxide signaling, modulating cyclic nucleotide pathways, and reducing platelet responsiveness to agonists [21,26]. In insulin-resistant states, these protective effects are blunted, resulting in a loss of insulin-mediated restraint on platelet activation. Consequently, platelets become more reactive and more prone to aggregate in response to subthreshold stimuli [21,26].

At the intracellular level, insulin resistance is associated with amplified platelet signaling, including enhanced calcium flux, increased activation of mitogen-activated protein kinases, phosphoinositide 3-kinase-related disturbances, and greater sensitivity to ADP- and collagen-mediated pathways [21,26]. These abnormalities reinforce thromboxane-independent mechanisms of platelet activation and help explain why aspirin, despite effective cyclooxygenase-1 blockade in some patients, does not fully normalize platelet behavior in T2DM. Thus, insulin resistance not only promotes platelet hyperactivity directly but also broadens the spectrum of signaling pathways that remain active during aspirin therapy [21,26].

3.4. Inflammation and diabetic vascular milieu

T2DM is accompanied by chronic low-grade inflammation, which substantially contributes to reduced aspirin responsiveness. Increased circulating levels of proinflammatory cytokines, including interleukin-6, tumor necrosis factor- α , and other mediators of innate immune activation, stimulate platelet production, platelet priming, endothelial activation, and coagulation pathway engagement [19,20,27]. Inflammatory signaling can also enhance megakaryopoiesis and increase the release of young, highly reactive platelets into the circulation, thereby reducing the duration of aspirin's effective action [19,27].

The diabetic vascular milieu is characterized by persistent endothelial activation, with increased expression of adhesion molecules, tissue factor-related activity, leukocyte recruitment, and reduced antithrombotic surface function [20,25,27]. In this environment, platelets are continuously exposed to activating stimuli, while the vessel wall becomes less capable of counterbalancing thrombosis. The net result is a prothrombotic shift, in which platelet activation, coagulation activation, impaired fibrinolysis, and inflammatory amplification mutually reinforce one another [20,27]. Under such conditions, aspirin acts on only one part of a broader thrombo-inflammatory network, making incomplete clinical or laboratory responsiveness more likely.

3.5. Accelerated platelet turnover

Accelerated platelet turnover is one of the most important mechanisms explaining reduced aspirin responsiveness in diabetes. Aspirin irreversibly acetylates cyclooxygenase-1 only in circulating platelets present at the time of dosing. When thrombopoiesis is increased, newly released platelets enter the circulation between doses without prior exposure to aspirin, restoring thromboxane-producing capacity before the next tablet is taken [18,24,28]. This mechanism is particularly relevant in T2DM, where inflammation, obesity, metabolic stress, and vascular injury promote increased platelet production and turnover [18,21,28].

These newly formed platelets are often identified as immature or reticulated platelets, which are larger, more RNA-rich, and more functionally reactive than mature platelets [28,29]. Elevated immature platelet fraction has been associated with higher platelet reactivity and weaker response to antiplatelet therapy in several cardiovascular settings [28,29]. In diabetes, an increased proportion of immature platelets may contribute to the loss of sustained aspirin effect between doses, especially with once-daily low-dose regimens [18,24,28]. This concept has renewed interest in tailored aspirin dosing schedules and in broader strategies to address the diabetic prothrombotic phenotype beyond cyclooxygenase-1 inhibition alone [18,24].

Taken together, T2DM promotes reduced aspirin responsiveness through a multifactorial interaction of platelet hyperactivation, enhanced thromboxane generation, glycation-mediated cellular dysfunction, oxidative stress, insulin resistance, inflammation, endothelial injury, and accelerated platelet renewal. These interrelated mechanisms help explain why aspirin hypo-responsiveness is more common in diabetic patients with stable coronary disease and why this population remains exposed to substantial residual thrombotic risk despite standard antiplatelet therapy [18-21,24].

4. Hemostatic Determinants of Aspirin Resistance

Aspirin resistance in stable angina patients with type 2 diabetes mellitus is not determined solely by incomplete cyclooxygenase-1 inhibition, but by a broader disturbance of hemostatic balance in which platelet hyperreactivity, abnormal erythrocyte rheology, enhanced thrombin generation, endothelial dysfunction, and biomarker-defined thrombo-inflammatory activation interact to sustain residual thrombogenicity [30-33]. In this setting, aspirin acts on only one component of a complex network, and its apparent insufficiency often reflects the persistence of parallel mechanisms of platelet recruitment, clot propagation, and impaired endogenous antithrombotic control [30,31].

4.1. Platelet function abnormalities

The most direct hemostatic determinant of aspirin resistance is persistent platelet hyperreactivity. In diabetic coronary disease, platelets show increased spontaneous activation, exaggerated aggregation in response to adenosine diphosphate, collagen, and thrombin-related agonists, and incomplete suppression of arachidonic acid-dependent pathways in a subset of patients receiving aspirin [30,31,34]. Although aspirin effectively suppresses platelet thromboxane A₂ generation in many individuals, diabetic platelets may continue to aggregate through non-thromboxane mechanisms, including amplified ADP signaling, enhanced surface expression of glycoprotein IIb/IIIa and P-selectin, and increased responsiveness to inflammatory and shear-dependent stimuli [30,31,34]. Thus, platelet function abnormalities form the central biological substrate of high on-aspirin platelet reactivity.

Persistent thromboxane-related activity also remains highly relevant. Recent analyses in diabetes have shown that heightened thromboxane biosynthesis is associated with a more thrombogenic phenotype and may identify patients in whom aspirin-mediated suppression is incomplete or insufficiently sustained over the full dosing interval [31,35]. This is particularly important in stable angina, where chronic platelet activation rather than acute plaque rupture predominates, and where low-grade but continuous thromboxane generation may contribute to recurrent ischemic symptoms and long-term event risk [31,35].

4.2. Erythrocyte aggregation and hemorheology

Erythrocyte aggregation and altered hemorheology are increasingly recognized as underappreciated determinants of thrombotic risk in diabetes and coronary disease. Red blood cells influence platelet behavior through rheological margination, shear-dependent transport toward the vessel wall, release of ADP and ATP, redox signaling, and provision of procoagulant membrane surfaces under pathologic conditions [32,36]. Increased erythrocyte aggregation raises blood viscosity, worsens microcirculatory flow, and facilitates closer interaction between platelets and the endothelium, thereby amplifying thrombogenic conditions in which aspirin alone may be insufficient [32,36].

This mechanism is especially relevant in patients with stable angina and T2DM, because diabetes promotes both red cell deformability abnormalities and enhanced erythrocyte aggregation, contributing to impaired tissue perfusion and a pro-adhesive intravascular milieu [32,36]. From a hemostatic perspective, erythrocyte aggregation should not be regarded as merely a viscosity marker; rather, it may actively modulate platelet recruitment and thrombus growth, particularly in stenotic coronary vessels and the diabetic microcirculation. Accordingly, erythrocyte aggregation may represent an important adjunctive determinant of apparent aspirin hyporesponsiveness when platelet inhibition is assessed in isolation [32,36].

4.3. Coagulation abnormalities

Aspirin resistance is also influenced by abnormalities in secondary hemostasis and fibrin clot architecture. In diabetes, elevated fibrinogen levels, increased thrombin generation, enhanced tissue factor activity, and reduced fibrinolytic efficiency contribute to formation of denser, less permeable fibrin networks that are more resistant to lysis [33,37]. These coagulation abnormalities can sustain residual thrombogenicity even when platelet cyclooxygenase-1 is inhibited, thereby creating a clinical picture in which aspirin appears less effective because downstream clot stabilization remains pronounced [33,37]. Particular attention should be paid to von Willebrand factor (vWF), which links endothelial injury to platelet adhesion under high-shear conditions. Recent work in stable coronary artery disease has shown that vWF-related parameters and vWF-mediated platelet adhesion are altered in CAD, supporting the view that high-shear platelet tethering and endothelial perturbation contribute to thrombotic propensity beyond classic aggregation assays [38]. Elevated vWF, together with increased fibrinogen and clot density, may therefore define a hemostatic phenotype in which aspirin-treated patients remain at increased risk because platelet adhesion and fibrin-rich thrombus propagation persist despite suppression of thromboxane-mediated amplification [33,38].

4.4. Endothelial dysfunction and platelet–vessel wall interaction

Endothelial dysfunction is a major upstream determinant of aspirin resistance. The healthy endothelium restrains thrombosis through release of nitric oxide, prostacyclin, and ectonucleotidases that suppress platelet activation and limit leukocyte–platelet adhesion. In diabetes and chronic coronary disease, this protective function is impaired, resulting in reduced nitric oxide bioavailability, increased oxidative stress, enhanced expression of adhesion molecules, and a more thrombogenic vascular surface [31,39]. Under these conditions, aspirin may inhibit one platelet activation pathway, yet the endothelium continues to deliver pro-adhesive and pro-inflammatory signals that favor platelet activation, especially under arterial shear [31,39].

The platelet–vessel wall interaction is therefore central to understanding why some patients exhibit persistent platelet reactivity on aspirin. Endothelial activation increases local vWF release, favors platelet rolling and adhesion, and enhances cross-talk between platelets, leukocytes, and the coagulation system. This is particularly important in diabetic stable angina, where chronic endothelial dysfunction and microvascular impairment can maintain low-grade ischemia and thrombo-inflammatory activity in the absence of acute plaque rupture [31,38,39].

4.5. Inflammatory and metabolic biomarkers linked to aspirin resistance

A growing body of evidence suggests that inflammatory and metabolic biomarkers are closely linked to aspirin resistance. In diabetic patients, higher body mass index, poor glycemic control, systemic inflammation, and oxidative stress have been associated with attenuated aspirin efficacy and a greater prevalence of biochemical aspirin resistance [31,40]. Markers such as HbA1c, C-reactive protein, interleukin-6, tumor necrosis factor- α , fibrinogen, uric acid, and indices of renal dysfunction likely reflect an integrated thrombo-inflammatory burden rather than isolated metabolic disturbance [31,40].

From a mechanistic standpoint, these biomarkers matter because they track the same biological processes that sustain high on-aspirin platelet reactivity: platelet priming, endothelial activation, thrombin generation, oxidative injury, and accelerated platelet turnover [30,31,35,40]. Therefore, aspirin resistance should be viewed not as a single laboratory

abnormality but as a multidimensional hemostatic phenotype, in which platelet function tests are most informative when interpreted together with rheological, coagulation, endothelial, inflammatory, and metabolic indicators [30–40].

5. Conclusion

Aspirin resistance in patients with stable angina and type 2 diabetes mellitus represents a clinically meaningful manifestation of residual thrombotic risk rather than an isolated laboratory phenomenon. In this population, reduced aspirin responsiveness develops on the background of a multifactorial prothrombotic state characterized by platelet hyperreactivity, enhanced thromboxane generation, impaired endogenous antiplatelet mechanisms, endothelial dysfunction, chronic inflammation, oxidative stress, abnormal erythrocyte aggregation, and activation of coagulation pathways. Diabetes therefore weakens the antiplatelet benefit of aspirin not only through cyclooxygenase-dependent mechanisms, but also through amplification of thromboxane-independent pathways that sustain platelet activation and thrombus formation despite treatment.

The reviewed evidence indicates that aspirin hyporesponsiveness in stable coronary disease should be interpreted within a broader hemostatic and cardiometabolic context. Platelet function abnormalities remain central, but they should be evaluated together with rheological, endothelial, inflammatory, and metabolic determinants. Such an integrated view is especially important in stable angina, where persistent ischemic risk is driven by chronic vascular dysfunction rather than the acute plaque-rupture biology that dominates acute coronary syndromes. In this setting, laboratory high on-aspirin platelet reactivity may identify patients with a particularly unfavorable thrombo-inflammatory phenotype.

From a practical standpoint, the concept of aspirin resistance should encourage more precise risk stratification, careful exclusion of pseudo-resistance, and individualized therapeutic decision-making. Optimization of adherence, aspirin formulation, dosing strategy, and control of glycemia, obesity, dyslipidemia, inflammation, and renal dysfunction may all contribute to improving antiplatelet efficacy. At the same time, future research should focus on standardized diagnostic criteria, multimarker assessment, and personalized antiplatelet approaches capable of addressing the complex biology of diabetic thrombosis. Overall, aspirin resistance in stable angina with type 2 diabetes mellitus should be regarded as a multidimensional hemostatic disorder with important implications for prognosis, monitoring, and precision cardiovascular prevention.

Compliance with ethical standards

Acknowledgments

The author thank to the Republican specialized scientific practical medical center of therapy and medical rehabilitation for the technical support.

References

- [1] Vrints CJM, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45(36):3415-3537.
- [2] Uzokov J., Alyavi B., Karimov B., Abdullaev A. Relationship between blood inflammation state and platelet aggregation rate in patients with atherosclerotic coronary artery disease after percutaneous coronary interventions. *Atherosclerosis*, 2023, 379, S174-S175.
- [3] Genitsaridi I, Duncan BB, Magliano DJ, et al. 11th edition of the IDF Diabetes Atlas: global, regional, and national diabetes prevalence estimates for 2024 and projections for 2050. *Lancet Diabetes Endocrinol*. 2025.
- [4] Minovarova C., Atakhodjaeva G., Uzokov, J. Prognostic role of adiponectin for the development of insulin resistance in patients with metabolic syndrome. *Eur J Clin Inv*, 2025, 55.
- [5] Canonico ME, Andreotti F, Capodanno D, et al. Long-term antithrombotic therapy in patients with chronic coronary syndrome: an updated review of current evidence. *Prog Cardiovasc Dis*. 2025.
- [6] Uzokov J., Alyavi B., Orzиеv D., Ubaydullaev S. Endothelial functional status in patients with hypertension and type 2 diabetes mellitus after COVID-19. *Journal of Hypertension*, 2023, 41(Suppl 3), e207.
- [7] Zhang F, et al. Clinical predictors of aspirin resistance in patients with type 2 diabetes: a systematic review and meta-analysis. *Rev Cardiovasc Med*. 2025;26(1).

- [8] Ubaydullaev S., Alyavi A., Uzokov J. Endothelial functional status in patients with atherosclerotic coronary artery disease and type 2 diabetes mellitus after COVID-19. *Atherosclerosis*, 2023, 379, S155.
- [9] Patti G., Cavallari I., Andreotti F., Calabrò P., et al. Prevention of atherothrombotic events in patients with diabetes mellitus: from antithrombotic therapies to new-generation glucose-lowering drugs. *Nature reviews. Cardiology*, 2019,16(2), 113–130.
- [10] Su H, et al. The association between fibrinogen levels and severity of coronary artery disease in patients with type 2 diabetes mellitus. *Front Endocrinol*. 2023;14:1287855.
- [11] Rao SV, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes. *Circulation*. 2025.
- [12] Uzokov J., Alyavi B., Karimov B., Abdullaev A. Relationship between blood inflammation state and platelet aggregation rate in patients with atherosclerotic coronary artery disease after percutaneous coronary interventions. *Atherosclerosis*, 2023, 379, S174-S175.
- [13] Krishnan K, Mungee S, Khandelwal P. Antiplatelet resistance: a review of concepts, mechanisms, and management in ischemic stroke and transient ischemic attack. *Stroke Vasc Interv Neurol*. 2023;3:e000576.
- [14] Orziev D., Abdullaev A., Alyavi B., Uzokov J., Mukhitdinova O. Comparative efficacy of ticagrelor in patients with coronary artery disease and type 2 diabetes mellitus after percutaneous coronary interventions. *Eur J Clin Investig*, 2023, 53, 51.
- [15] Antiplatelet therapy and platelet activity testing for ischemic stroke and transient ischemic attack: current concepts and future directions. *Stroke Vasc Interv Neurol*. 2024.
- [16] Uzokov J., Alyavi B., Alyavi A., Payziev D. Coronary Artery Plaque Characteristics and Calcium Scoring in Patients With Type 2 Diabetes and Coronary Artery Disease. *J Nuclear Cardiol*, 2024, 38.
- [17] Silva DA, Webster GK, Bou-Chacra N, Löbenberg R. Opportunities to add clinical relevance to the dissolution test for enteric-coated aspirin products. *J Control Release*. 2020;328:240-249.
- [18] Orziev D., Alyavi B., Uzokov J., Rakhimova D., Abidova D., Muyassar M., Dildora N. Features of platelet induces in patients with atherosclerotic coronary artery disease. In European journal of clinical investigation, *Eur J Clin Invest*, 2022, 52.
- [19] Chen B, Liu Y, Zhang Y, et al. Factors associated with aspirin resistance in diabetic patients. *PLoS One*. 2025;20(9):e0332323.
- [20] Uzokov J., Alyavi B. A., Muminov S. H. K., Abdullaev A. X., Iskhakov S. A. Microvascular dysfunction in patients with non-obstructive coronary artery disease. *Eur Heart J.*, 46(Supplement_1), 2025, ehaf784-2165.
- [21] Safdar NZ, Malkani K, Bhandari S, et al. The cellular and protein arms of coagulation in diabetes. *Biomedicines*. 2023;11:3000.
- [22] Uzokov J., Alyavi B.A., Muminov S.K., Abdullaev A.X., Iskhakov S.A. Microvascular dysfunction in patients with non-obstructive coronary artery disease. *Eur Heart J.*, 2025, 46(Supplement_1), ehaf784-2165.
- [23] Greaves J, et al. Hyperactivity and pro-inflammatory functions of platelets in diabetes-associated vascular disease. *Front Biosci (Landmark Ed)*. 2025;30:26190.
- [24] Dillinger JG, Georges JL, Delarche N, et al. Twice-a-day administration of aspirin in patients with diabetes mellitus or aspirin resistance after acute coronary syndrome: rationale and design of the randomized ANDAMAN trial. *Am Heart J*. 2025;288:1-8.
- [25] Panfoli I, et al. Resveratrol as a potential platelet inhibitor in aspirin-resistant type 2 diabetes mellitus. *Life (Basel)*. 2025;15:1718.
- [26] Mohammadian K, et al. Insulin resistance and platelet hyperactivity. *Nutrients*. 2026;18:763.
- [27] Christodorescu RM, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: pathophysiological basis and clinical implications. *Eur Heart J*. 2023;44:4043-4140.
- [28] Tsankof A, et al. The role of immature platelet fraction and reticulated platelets in cardiovascular disease. *Biomedicines*. 2025;13:1462.
- [29] Cao Z, et al. Immature platelet fraction in cardiology. *Thromb Res*. 2025;245:109987.

- [30] Sharma N, Verma SK, Kalra S. Diabetic platelets: pathophysiology, clinical significance, and therapeutic perspectives. *Diabetes Ther.* 2025;16:1–22.
- [31] Chen B, Liu Y, Zhang Y, et al. Factors associated with aspirin resistance in diabetic patients: a metabolic and inflammatory profile analysis. *PLoS One.* 2025;20(9):e0332323.
- [32] Charansonney OL, et al. Erythrocyte aggregation kinetics for studying the vascular impact of red blood cells in cardiometabolic disease. *Int J Mol Sci.* 2025;26.
- [33] Zvetkova E, et al. Hematological and hemorheological parameters of blood and fibrin clot properties in type 2 diabetes mellitus. *Appl Sci.* 2024;14:4684.
- [34] Bańka P, et al. Platelet-related biomarkers and efficacy of antiplatelet therapy in cardiovascular disease. *Int J Mol Sci.* 2025;26:7083.
- [35] Petrucci G, et al. Thromboxane biosynthesis and future vascular events in diabetes. *Eur Heart J.* 2024;45:1355–1365.
- [36] Platelet–red blood cell interactions in thrombosis and cardiovascular disease. *Curr Opin Hematol.* 2025.
- [37] Grant PJ, et al. Coagulation and fibrinolysis in diabetes and cardiometabolic disease. *Diabetologia.* 2023.
- [38] Gabbasov Z, et al. Von Willebrand factor collagen-binding activity and VWF-mediated platelet adhesion in stable coronary artery disease. *Biomedicines.* 2024;12:2007.
- [39] Das D, et al. Endothelial dysfunction, platelet hyperactivity, and metabolic vascular injury: mechanistic links and therapeutic implications. *Front Nutr.* 2023;10:1221438.
- [40] Zhang F, et al. Clinical predictors of aspirin resistance in patients with type 2 diabetes mellitus: a systematic review. *Rev Cardiovasc Med.* 2025;26(1).