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A review on advances in antiplatelet therapy for cardiovascular diseases

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Abstract
Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with atherothrombosis as the central pathological mechanism driving coronary artery disease, ischemic stroke, and peripheral arterial disease [1]. Antiplatelet therapy is pivotal in preventing and treating these conditions by targeting platelet adhesion, activation, and aggregation [2]. Aspirin, the earliest and most widely used antiplatelet agent, irreversibly inhibits cyclooxygenase-1, thereby reducing thromboxane A2-mediated platelet activation; however, its benefits are often offset by gastrointestinal toxicity and bleeding risk [3]. The development of P2Y12 receptor inhibitors, such as clopidogrel, prasugrel, and ticagrelor, has revolutionized treatment, particularly in dual antiplatelet therapy (DAPT) following acute coronary syndromes and percutaneous coronary intervention [4]. Additional classes, including glycoprotein IIb/IIIa inhibitors, PAR-1 antagonists, and phosphodiesterase inhibitors, further broaden therapeutic options, though bleeding remains the major limitation [5]. Recent advances emphasize individualized therapy, incorporating genetic testing, platelet function assays, and escalation/de-escalation strategies to balance ischemic protection against hemorrhagic risk. Future perspectives focus on precision medicine, novel targets such as GPVI and PAR-4 receptors, and integration of digital health tools to optimize therapy. This review discusses the pathophysiology, treatment, current strategies, recent advances, and future directions in antiplatelet therapy for Cardiovascular diseases (CVDs) [6].

Keywords: Antiplatelet therapy, cardiovascular diseases, atherothrombosis, dual antiplatelet therapy (DAPT)

Introduction
Cardiovascular diseases (CVDs), including coronary artery disease (CAD), cerebrovascular events, and peripheral arterial disease, remain the leading causes of morbidity and mortality worldwide. Atherothrombosis, the underlying pathology in most of these conditions, is driven by platelet activation and aggregation at the site of vascular injury. Antiplatelet therapy has thus emerged as a cornerstone combination with the prophylaxis and therapy of cardiovascular events. Since the 1980s, aspirin, a cyclooxygenase (COX) inhibitor, has been extensively used for cardiovascular prophylaxis. Its role in reducing thrombotic events is well established, but its utility is sometimes limited by gastrointestinal side effects and bleeding risk [7].

The introduction of P2Y12 receptor inhibitors, such as clopidogrel, prasugrel, and ticagrelor, has significantly expanded the armamentarium of antiplatelet agents. These adenosine diphosphate (ADP) receptor antagonists also serve as alternatives in aspirin-intolerant individuals but also enable more potent platelet inhibition when used in combination with aspirin, a strategy known as dual antiplatelet therapy (DAPT) [8]. While DAPT has proven highly effective in reducing recurrent ischemic events especially following acute coronary syndrome (ACS) and percutaneous coronary interventions (PCI) the increased bleeding risk associated with enhanced platelet inhibition remains a major concern. Though adjunctive therapies like proton pump inhibitors can mitigate gastrointestinal bleeding, they offer limited protection against bleeding at other sites.

As a result, considerable research has focused on optimizing DAPT regimens to strike a balance between minimizing thrombotic risk and avoiding unnecessary bleeding. This has

led to a more nuanced understanding of the ideal duration and combinations of antiplatelet therapies tailored to individual patient profiles [9]. Contemporary guidelines now support personalized strategies, including escalation and de-escalation protocols based on ischemic and bleeding risk scores. Furthermore, the management of patients requiring both antiplatelet and oral anticoagulant therapy such as those with atrial fibrillation undergoing PCI has become a complex yet critical aspect of cardiovascular care.

In recent years, advances in precision medicine and pharmacogenomics have begun to influence antiplatelet therapy. Genetic testing for drug responsiveness, platelet function assays, and risk stratification tools are increasingly explored to guide individualized treatment decisions. forbye, Novel antiplatelet agents targeting specific platelet pathways are currently under investigation. These include inhibitors of glycoprotein VI, protease-activated receptors (PAR), and thromboxane receptors, aiming to retain antithrombotic efficacy while preserving normal hemostasis and reducing bleeding complications.

Despite the progress made, challenges persist. Residual high on-treatment platelet reactivity (HTPR) remains a concern in certain patient populations, highlighting the need for improved monitoring and alternative therapies [10]. Additionally, managing antiplatelet therapy in special clinical situations such as above surgical procedures or during active bleeding requires careful consideration and evolving protocols.

This review aims to synthesize the latest evidence on antiplatelet therapy, covering mechanisms of action, clinical applications, current guideline recommendations, and emerging agents. It further explores strategies for individualized protection and the future directions of antiplatelet therapy in the era of precision cardiovascular medicine [11].

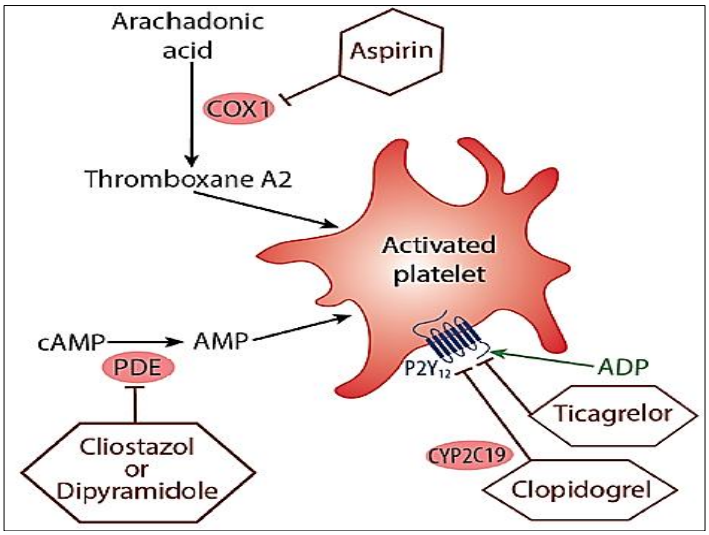

Fig 1: Antiplatelet Therapies After Ischemic Stroke

Pathophysiology of Atherothrombosis In Cardiovascular Disease

Endothelial Dysfunction

The endothelium plays a crucial role in continuous vascular homeostasis by regulating vascular tone, inhibiting platelet aggregation, and preventing leukocyte adhesion. In the presence of cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, obesity, and hyperlipidemia, the endothelium undergoes functional variation. This dysfunction is characterized by reduced bioavailability of nitric oxide (NO) and prostacyclin, both potent vasodilators and platelet agglutination inhibitors. At the same time, there is increased production of endothelin-1 and expression of adhesion molecules, promoting vasoconstriction, leukocyte infiltration, and platelet adhesion [12].

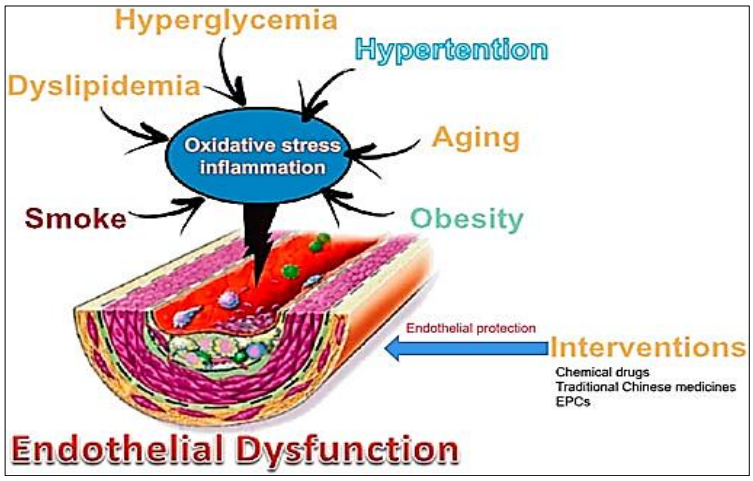

Fig 2: Endothelial Dysfunction

Atherosclerotic Plaque Development

Endothelial dysfunction facilitates the entry of low-density lipoprotein (LDL) particles into the arterial intima. These lipoproteins undergo oxidative modification and trigger an inflammatory response. Monocytes migrate into the vessel wall, differentiate into macrophages, and engulf oxidized LDL, transforming into foam cells. The accumulation of foam cells produces fatty streaks, the earliest visible sign of atherosclerosis. Over time, smooth muscle cells proliferate and secrete extracellular matrix proteins, forming a fibrous cap. The plaque consists of a lipid-rich necrotic core, foam cells, inflammatory cells, and a fibrous covering. Persistent inflammation and enzymatic degradation weaken the fibrous cap, making the plaque vulnerable to rupture [13].

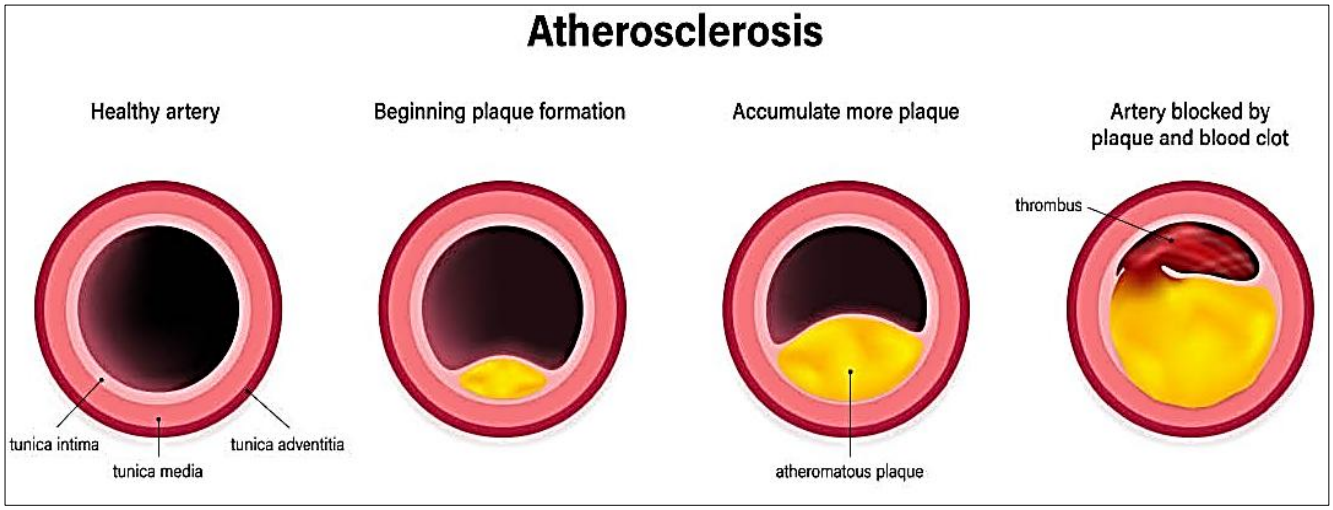

Fig 3: Stages of Atherosclerosis

Plaque Rupture and Thrombogenic Exposure:

The critical clinical events in atherothrombosis often occur when a plaque ruptures or erodes. A thin fibrous cap, especially one infiltrated by macrophages, is highly prone to rupture. When rupture or erosion happens, the subendothelial matrix including collagen, tissue factor, and von Willebrand factor (VWF) is exposed to circulating blood. These structures are highly thrombogenic and rapidly initiate platelet adhesion and activation. Even plaques that do not cause significant arterial narrowing may trigger acute thrombotic occlusion when ruptured, highlighting atherothrombosis's unpredictable and dangerous nature.

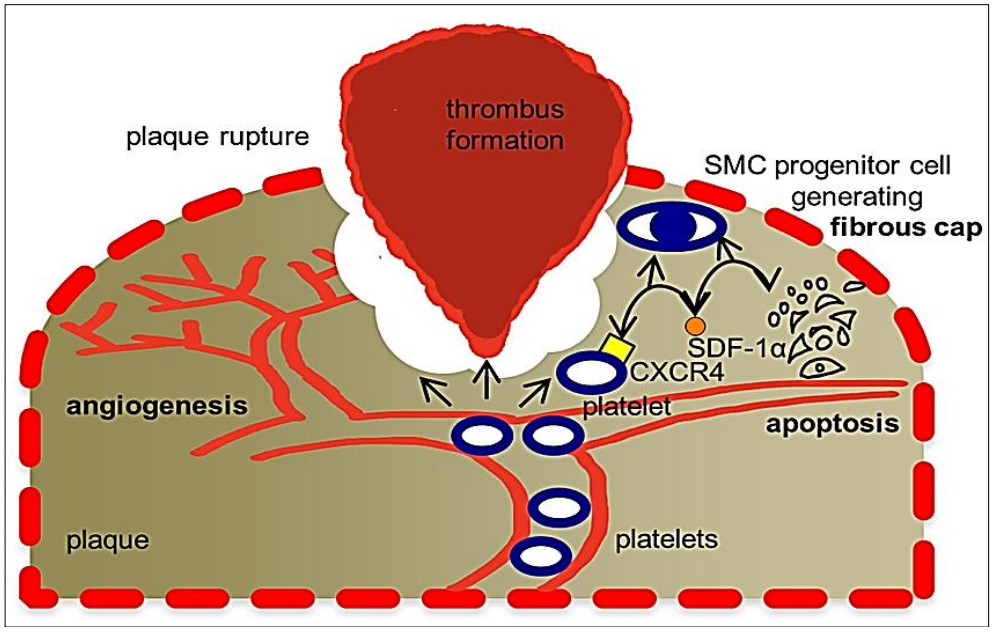

Fig 4: Plaque rupture

Platelet Adhesion

Following plaque disruption, circulating platelets are recruited to the site of injury. Adherence is moderate by interactions between platelet surface glycoproteins and exposed subendothelial proteins. Specifically, the GPIb-IX-V complex sticks to von Willebrand factor anchored on exposed collagen, while GPVI and integrin α2β1 directly bind to collagen. This initial adhesion secures platelets to the vascular wall, even under high shear stress conditions such as those in coronary arteries. This step is crucial in initiating thrombus formation and represents the first phase of platelet involvement in atherothrombosis [14].

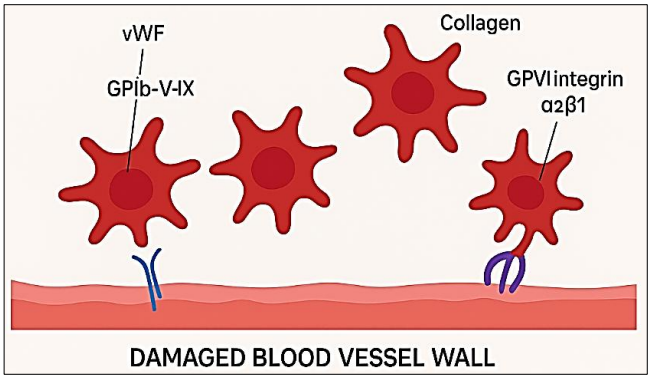

Fig 5: Platelet Adhesion

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Platelet Activation

Adherent platelets undergo profound biochemical and morphological changes. They become activated and release mediators such as adenosine diphosphate (ADP), thromboxane A2 (TXA2), serotonin (5-HT), and platelet-activating factor (PAF) from their dense granules. These mediators act on platelet receptors P2Y1, P2Y12, TP, and 5-HT2A to recruit and activate additional platelets. Platelets also express negatively charged phospholipids on their surface, which serve as a catalytic platform for coagulation factor complexes. Importantly, thrombin, caused by tissue factor-driven activation of the coagulation cascade, is the most potent platelet activator. Thrombin acts through protease-activated receptors (PAR-1 and PAR-4), inducing strong platelet aggregation and fibrin generation [15].

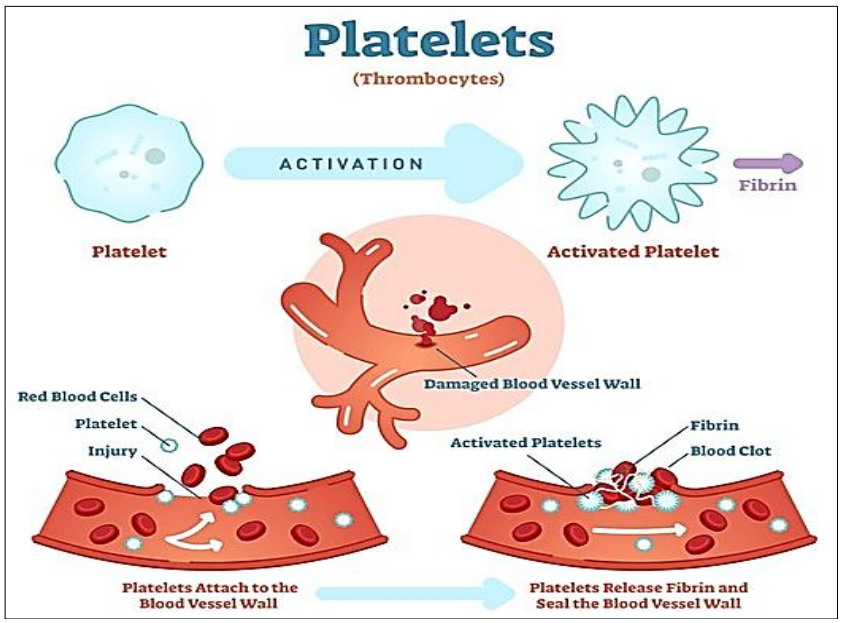

Fig 6: Platelet Activation

Platelet Aggregation

Once activated, platelets transform and express the GP IIb/IIIa (αIIbβ3) integrin receptor in its high-affinity conformation. This receptor binds fibrinogen and von Willebrand factor, cross-linking adjacent platelets and stabilizing the extended platelet mass. The aggregation process creates a platelet-rich plug at the site of vascular injury. Another adhesion molecules, such as junctional adhesion molecule-A (JAM-A), ephrin ligands, and P-selectin glycoprotein ligand-1 (PSGL-1), further stabilize platelet-platelet interactions.

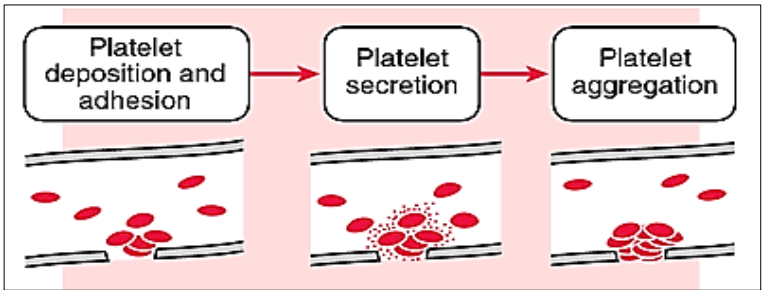

Fig 7: Platelet Aggregation

Coagulation Cascade and Thrombus Formation

The activated platelet surface accelerates the coagulation cascade by providing a negatively charged phospholipid surface that facilitates assembly of enzyme complexes. Tissue factor, introduced from the ruptured plaque, activates the extrinsic pathway, leading to large-scale thrombin generation. Thrombin converts soluble fibrinogen into insoluble fibrin strands that braid through the platelet plug, creating a stable thrombus. Thrombin also provides positive feedback by further activating platelets, perpetuating thrombus growth. The final result is the formation of an occlusive thrombus that may obstruct blood flow, produce acute myocardial infarction, ischemic stroke, or peripheral arterial ischemia [16].

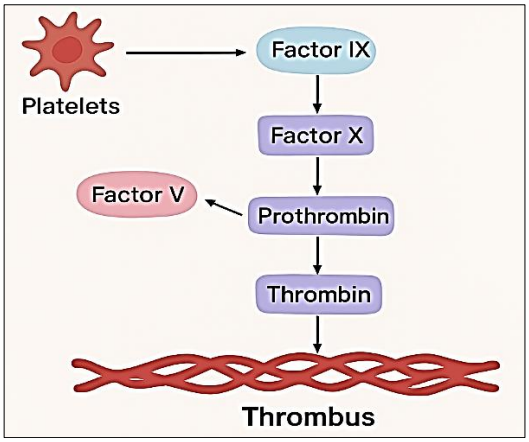

Fig 8: Coagulation Cascade and Thrombus Formation:

Clinical Implications: Understanding the pathophysiology of atherothrombosis has guided the development of targeted therapies. Aspirin inhibits cyclooxygenase-1 (COX-1), blocking thromboxane A2 synthesis and reducing platelet activation. P2Y12 receptor antagonists such as clopidogrel, prasugrel, and ticagrelor inhibit ADP-mediated platelet aggregation. GP IIb/IIIa inhibitors block the final standard procedure of platelet aggregation, while PAR-1 antagonists inhibit thrombin-mediated platelet activation. These therapies directly target key steps in the thrombotic cascade and remain the cornerstone of cardiovascular prevention and treatment [17].

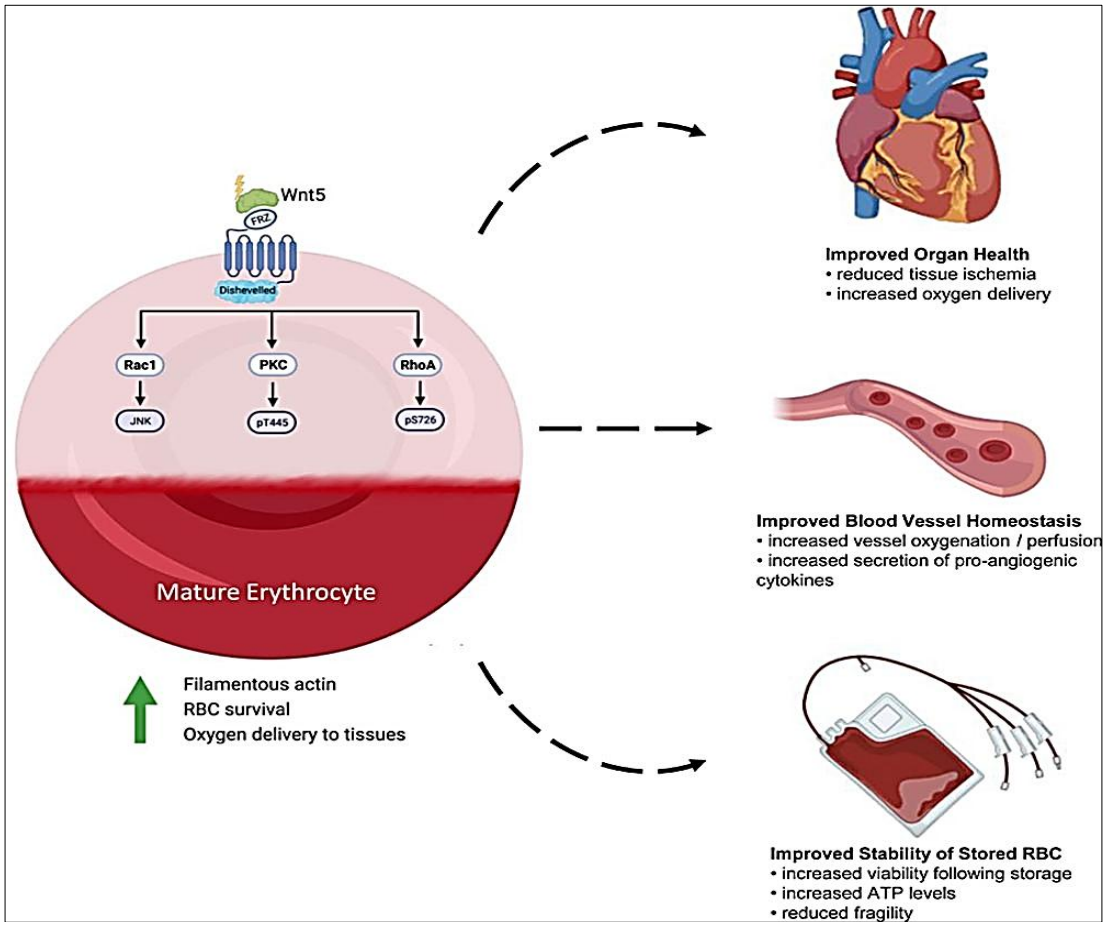

Fig 9: Clinical Implications

Drugs Used in Antiplatelet Therapy for Cardiovascular Diseases

Table 1: Classification of Antiplatelet Therapy for Cardiovascular Diseases

Class	Example	Mechanism of action	Route of administration	Clinical uses
Cyclooxygenase (COX-1) Inhibitor [18]	Aspirin	rreversibly inhibits COX-1 → ↓ Thromboxane A2 (TXA2) → ↓ platelet activation & aggregation	Oral, IV	Primary & secondary prevention of MI, stroke, PAD, after PCI
P2Y12 (ADP Receptor) Inhibitors [19]	Clopidogrel, Prasugrel, Ticagrelor	Block ADP binding to the P2Y12 receptor → inhibit platelet aggregation	Oral	ACS, post-stent placement (DAPT with aspirin)
Glycoprotein IIb/IIIa Inhibitors [20]	Abciximab	Blocks GP IIb/IIIa receptor → prevents fibrinogen cross-linking and platelet aggregation (final pathway)	IV	PCI, ACS (high-risk patients)
PAR-1 (Protease-Activated Receptor-1) Antagonist [21,22]	Vorapaxar	Inhibits thrombin-mediated platelet activation	Oral	Secondary prevention in patients with prior MI or PAD
Phosphodiesterase (PDE) Inhibitors [23]	Dipyridamole	Inhibits PDE → ↑ cAMP in platelets → ↓ platelet aggregation	Oral, IV	Stroke prevention (with aspirin)

Adverse Effects

1. Aspirin (Cox-1 Inhibitor)

- Gastrointestinal bleeding & ulceration (due to COX-1 inhibition → ↓ gastric mucosal protection).
- Dyspepsia, gastritis, nausea.
- Hypersensitivity reactions (asthma exacerbation in aspirin-sensitive patients) [24].

2. P2Y12 Receptor Inhibitors (Clopidogrel, Prasugrel, Ticagrelor, Cangrelor)

- Bleeding (major & minor) - most common adverse effect.
- Dyspnea (especially with ticagrelor, due to adenosine reuptake inhibition).
- Drug interactions & variable response (especially clopidogrel due to CYP2C19 metabolism) [25].

3. Glycoprotein IIb/IIIa Inhibitors (Abciximab, Eptifibatide, Tirofiban)

- Severe bleeding (GI, intracranial, vascular access site).
- Thrombocytopenia (immune-mediated, especially with Abciximab).
- Hypotension & allergic reactions (rare) [26].

4. PAR-1 Antagonist (Vorapaxar)

- Significant bleeding risk (especially intracranial hemorrhage).
- Contraindicated in patients with prior stroke, TIA, or intracranial haemorrhage [27].

5. PDE Inhibitors (Dipyridamole, Cilostazol)

- Headache, flushing, dizziness (vasodilation effect).
- Hypotension (with IV dipyridamole in stress testing).
- Contraindicated in heart failure (cilostazol - due to PDE-3 inhibition) [28].

Treatment Strategies in Antiplatelet Therapy

1. Lifestyle Modification

Non-pharmacological measures form the backbone of cardiovascular prevention. Quitting smoking, maintaining a balanced diet, exercising regularly, and achieving optimal blood pressure and glucose control improve endothelial function and decrease thrombosis risk. Lifestyle changes also enhance the effectiveness of drug therapy [29].

2. Aspirin Monotherapy

Aspirin is the oldest and most widely prescribed antiplatelet drug. By irreversibly inhibiting COX-1 and reducing thromboxane A2 synthesis, it decreases platelet aggregation. Low-dose aspirin (75-100 mg/day) is effective for secondary prevention of myocardial infarction and ischemic stroke. However, its sustained use is limited by gastrointestinal side effects and bleeding risk [30].

3. P2Y12 Receptor Inhibitors

Clopidogrel, prasugrel, ticagrelor, and cangrelor inhibit ADP-mediated platelet activation. They are often combined with aspirin as dual therapy in ACS and PCI patients [31]. Ticagrelor and prasugrel give more potent and consistent inhibition than clopidogrel but have a higher bleeding risk. Personalized selection is guided by patient profile and clinical setting [32].

4. Dual Antiplatelet Therapy (DAPT)

DAPT, usually aspirin plus a P2Y12 inhibitor, is the standard of care after ACS and stent implantation. It significantly reduces the risk of stent thrombosis and recurrent ischemic events. Guidelines recommend 6-12 months of therapy, with shorter courses for high bleeding risk patients and prolonged for those with high ischemic burden [33].

5. Triple Therapy (Antiplatelet + Anticoagulant)

In patients with atrial fibrillation who tolerate PCI, triple therapy combining oral anticoagulants with aspirin and a P2Y12 inhibitor may be used initially [34]. Because this increases bleeding risk, clinicians often shorten therapy duration and later switch to dual therapy (anticoagulant + single antiplatelet) [35].

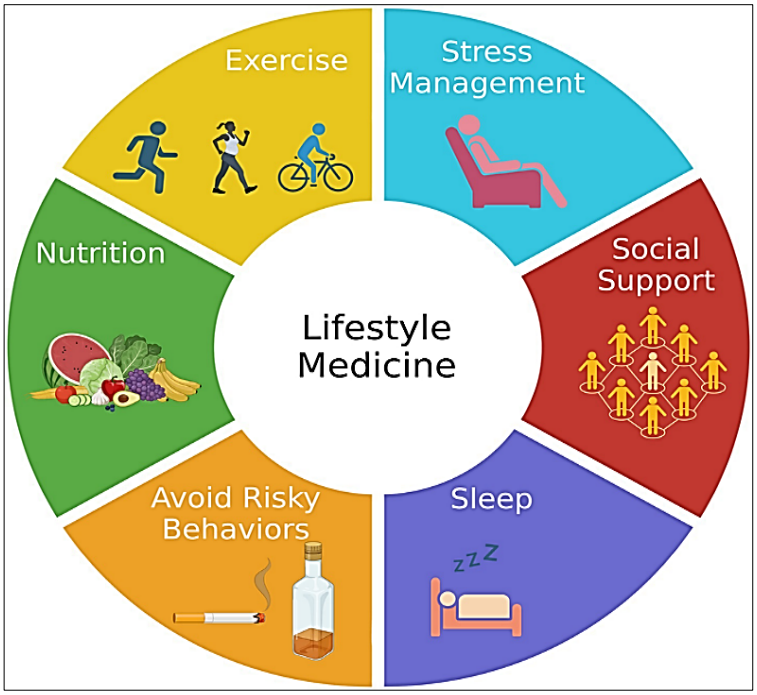

Fig 10: The components of lifestyle medicine

Challenges in Antiplatelet Therapy

1. Bleeding Risk

The most significant limitation of antiplatelet therapy is the risk of bleeding. While aspirin and P2Y12 inhibitors reduce ischemic events, they also increase gastrointestinal and intracranial outflow, especially in elderly patients and those with comorbidities such as peptic ulcer disease. More potent agents (prasugrel, ticagrelor) and dual antiplatelet therapy (DAPT) further raise bleeding risks, requiring careful selection of treatment duration and intensity [36].

2. Drug Resistance (Clopidogrel Resistance)

Clopidogrel shows a variable response because it requires metabolic activation by the CYP2C19 enzyme. Genetic polymorphisms in CYP2C19 can lead to poor metabolizer status, causing high on-treatment platelet reactivity (HTPR) and increased risk of stent thrombosis and recurrent ischemic events. This "clopidogrel resistance" remains a major clinical challenge, particularly in Asian populations where CYP2C19 loss-of-function alleles are more common [37].

3. Variability in Patient Response

Beyond genetics, many factors affect variability in drug response. Age, body weight, diabetes, renal dysfunction, drug-drug interactions, and adherence issues all influence therapeutic effectiveness. For example, proton pump inhibitors (PPIs) may inhibit clopidogrel activation, and interactions with anticoagulants can raise bleeding risk. This variability complicates the use of standardized protocols for all patients [38].

Fig 11: Challenges in Antiplatelet Therapy

Recent Advances in Antiplatelet Therapy

1. Novel P2Y12 Inhibitors

Newer P2Y12 receptor inhibitors, including prasugrel and ticagrelor, have shown superior potency and faster onset compared with clopidogrel. These agents provide more consistent platelet inhibition and significantly rescue ischemic events in acute coronary syndrome (ACS) patients. Unlike clopidogrel, ticagrelor does not require metabolic activation, avoiding variability caused by CYP2C19 polymorphisms. However, their increased efficacy comes with a higher risk of bleeding, requiring careful patient selection [39].

2. Pharmacogenomic-Guided Therapy

Pharmacogenomics is reshaping antiplatelet therapy by allowing personalization of treatment. Genetic variations, especially in CYP2C19, impact clopidogrel metabolism and effectiveness. Testing for these polymorphisms enables

clinicians to identify non-responders and adjust therapy accordingly, often switching to ticagrelor or prasugrel. Similarly, platelet function testing is being explored as a tool to guide escalation or de-escalation strategies. These approaches highlight the growing role of precision medicine in optimizing efficacy while minimizing bleeding risk [40].

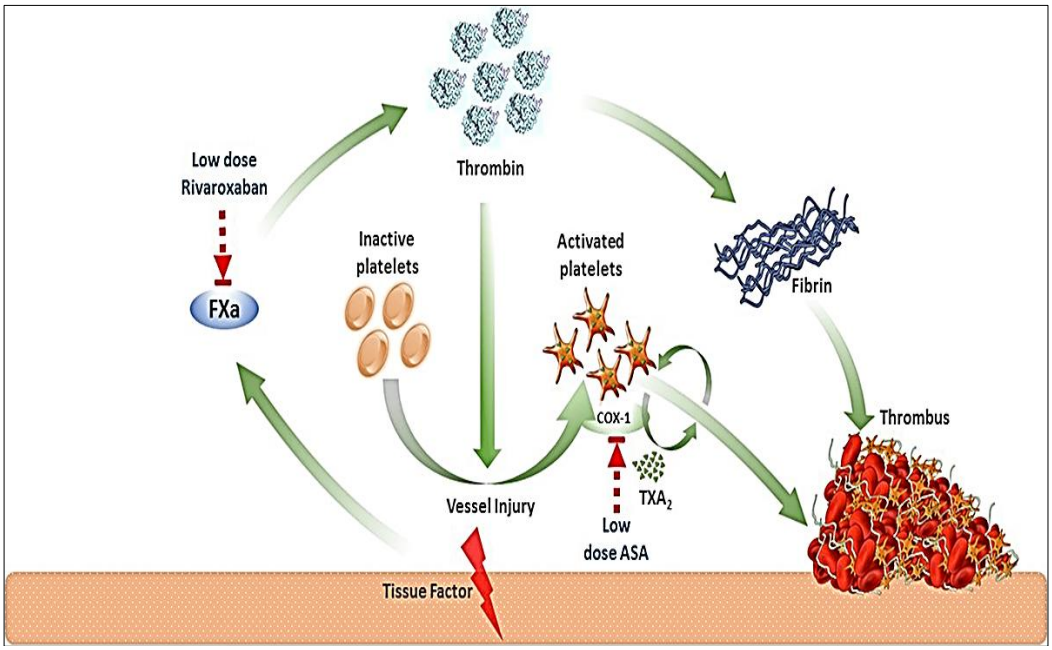

Fig 12: Advances in Antiplatelet Therapy

Future Perspectives

The future of antiplatelet therapy lies in precision medicine, where treatment will be tailored according to genetic, biochemical, and clinical profiles. Biomarker-based strategies, including platelet function assays, may soon guide dose adjustments and drug selection [41]. Novel agents with selective mechanisms that inhibit thrombosis but spare normal hemostasis are under development. Research into combination therapies that improve safety and efficacy is ongoing to provide more efficacious, individualized, and safer antiplatelet regimens [42].

Conclusion

Antiplatelet therapy has transformed the prevention and treatment of cardiovascular disease. While aspirin and P2Y12 inhibitors remain the principle of therapy, advances in novel agents and individualized approaches continue to refine treatment [43]. The greatest challenge remains balancing protection in case of thrombotic events with the risk of bleeding. Future strategies integrating pharmacogenomics, biomarkers, and new therapeutic targets are expected to provide safer and more effective patient-centered care [44, 45]

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