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Antiplatelet Therapy In Coronary Artery Disease: A Review Of Efficacy And Safety

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ABSTRACT

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, this necessitates effective strategies for preventing thrombotic complications. Antiplatelet therapy contributes greatly to reducing the risk of major adverse cardiovascular events (MACE) by inhibiting platelet aggregation and preventing arterial thrombosis. Among the most widely used agents are aspirin and P2Y12 inhibitors such as clopidogrel, prasugrel, and ticagrelor. While these drugs have demonstrated efficacy in secondary prevention, variations in patient response due to genetic polymorphisms, particularly in CYP2C19 metabolism, have raised concerns about treatment efficacy and safety. Additionally, the risk of bleeding remains a significant limitation of potent antiplatelet therapy, necessitating a balance between thrombotic protection and hemorrhagic complications. Recent advancements in genotype-guided therapy, novel antiplatelet agents, and machine learning-driven risk prediction models hold promise for enhancing personalized treatment approaches. Ongoing research aims to refine antiplatelet strategies to optimize outcomes while minimizing adverse effects. Future investigations should focus on validating precision medicine approaches, improving risk stratification, and developing safer, more effective therapeutic alternatives.

Keywords and phrases: Coronary Artery Disease, Antiplatelet Therapy, Thrombotic Events, Aspirin, Clopidogrel, P2Y12 Inhibitors, CYP2C19 Polymorphisms, Bleeding Risk, Personalized Medicine, Novel Antiplatelet Agents.

INTRODUCTION

Coronary artery disease (CAD) also known as ischemic heart disease (IHD), remains the leading cause of morbidity and mortality globally and in the United States. It arises from the accumulation of atherosclerotic plaque within the arterial walls, which restricts blood flow and reduces oxygen supply to the heart muscle, ultimately contributing to significant cardiovascular complications and highlighting the need for prevention and effective management strategies (Rai et al., 2024). A 2023 report from the World Heart Federation (WHF) revealed that global deaths from cardiovascular disease (CVD) surged from 12.1 million in 1990 to 20.5 million in 2021, making it the leading cause of death worldwide, with

80% of these fatalities concentrated in low- and middle-income countries (LMICs) (World Heart Federation, 2023). Coronary artery disease (CAD), responsible for 17.8 million deaths annually and costing over $200 billion in U.S. healthcare expenses each year (Jonathan et al., 2023). A recent report by Venessa (2024) indicates that 18.2 million adults, or 6.7% of the U.S. population aged 20 and older, suffer from coronary artery disease, while approximately six million Americans are living with heart failure—a number that is steadily rising due to the aging demographic. Given its widespread impact, optimizing therapeutic strategies, including antiplatelet therapy, is essential to reducing ischemic complications and improving patient outcomes.

CAD is driven by atherosclerosis, a progressive inflammatory condition characterized by lipid deposition, endothelial dysfunction, and plaque formation in coronary arteries. Among adults in the United States, atherosclerotic cardiovascular disease (ASCVD) affects 18.3 million individuals, representing 8.0% of the population (Alexa et al., 2020). When atherosclerotic plaques rupture, platelet activation leads to thrombus formation via the glycoprotein (GP) IIb/IIIa receptor pathway, which can result in acute coronary syndromes (ACS) (Asada et al, 2020). The high risk of recurrent events highlights the necessity of effective antiplatelet strategies to prevent arterial thrombosis.

Platelet inhibition contributes to the prevention of thrombotic events in both ACS and post-percutaneous coronary intervention (PCI) settings. Over 600,000 PCI procedures are performed annually in the U.S. (Kataruka et al., 2022), with stent thrombosis occurring in about 0.5% of cases despite optimal therapy (Agosti, 2022). The landmark CURE trial (2021) demonstrated that dual antiplatelet therapy (DAPT) with aspirin and clopidogrel reduced the incidence of MI and stroke by 20% in ACS patients compared to aspirin alone (Alexander et al., 2023). The PLATO trial (Wallentin et al., 2009) found that ticagrelor reduced cardiovascular death, MI, or stroke by 16% compared to clopidogrel. Similarly, the TRITON-TIMI 38 trial (Wiviott et al., 2007) reported a 19% lower rate of ischemic events with prasugrel compared to clopidogrel, though at the cost of increased major bleeding (2.4% vs. 1.8%). These findings highlight the importance of balancing ischemic protection with bleeding risk when selecting an antiplatelet regimen.

This review aims to evaluate the efficacy and safety of major antiplatelet agents which include aspirin, clopidogrel, and newer P2Y12 inhibitors (ticagrelor, prasugrel), in the management of CAD. It will compare monotherapy versus dual therapy strategies, analyze bleeding risks and drug resistance, and discuss optimal treatment selection based on contemporary clinical evidence and guidelines from organizations such as the American College of Cardiology (ACC) and the European Society of Cardiology (ESC).

SECTION 1: MECHANISMS OF PLATELET INHIBITION IN CAD

1.1 Platelet Activation and Aggregation in Atherosclerosis

Coronary artery disease (CAD) is primarily driven by atherosclerosis, a chronic inflammatory condition characterized by lipid accumulation and endothelial dysfunction. This condition is responsible for nearly 50% of deaths in Western societies and is a leading cause of atherosclerotic cardiovascular disease (ASCVD), which manifests as heart attacks, strokes, and peripheral arterial disease (Pahwa & Jialal, 2023). Atherosclerosis develops due to the accumulation of low-density and remnant lipoproteins in areas of disturbed blood flow, triggering chronic vascular inflammation. When an atherosclerotic plaque ruptures, subendothelial collagen and von Willebrand factor (vWF) are exposed, leading to platelet adhesion via distinct receptor pathways. Glycoprotein (GP) Ib-IX-V interacts with vWF, while collagen binds to GP VI,

initiating platelet activation. This activation leads to the release of pro-thrombotic mediators such as thromboxane A2 (TXA2), adenosine diphosphate (ADP), and serotonin, which further amplify platelet aggregation through the GP IIb/IIIa receptor complex. The resulting thrombus formation can cause complete arterial occlusion, leading to acute coronary syndromes (ACS), including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina. Notably, coronary thrombus formation is a major cause of sudden cardiac death and can occur regardless of the degree of stenosis, even in individuals previously considered asymptomatic (Adnan et al., 2022). Beyond their role in thrombosis, platelets are increasingly recognized as key modulators of the immune system. Leela et al. (2024) suggest that antiplatelet therapy may influence post-treatment outcomes not only by reducing thrombotic events but also by modulating immune responses. This has opened avenues for potential applications of antiplatelet agents in chronic inflammatory and infectious diseases, underscoring the need for further investigation into their broader therapeutic effects. Understanding these mechanisms allows clinicians to optimize antiplatelet strategies to prevent thrombotic events while considering emerging insights into the immunological functions of platelets.

1.2 Cyclooxygenase (COX) Inhibition by Aspirin

Aspirin (acetylsalicylic acid) exerts its antiplatelet effect by irreversibly acetylating a serine residue in the active site of cyclooxygenase-1 (COX-1), thereby inhibiting thromboxane A2 (TXA2) synthesis. Since platelets lack a nucleus and cannot synthesize new COX-1 enzymes, this inhibition persists for the platelet's lifespan, approximately 8 to 10 days. TXA2 is a potent platelet activator and vasoconstrictor, making its inhibition a key mechanism in reducing platelet aggregation and arterial thrombosis risk. Studies have established aspirin's role in managing acute coronary syndrome and preventing cardiovascular events (Qureshi & Dua, 2024; Yang et al., 2025). The Antithrombotic Trialists' Collaboration (2002) found that aspirin therapy reduced the risk of serious vascular events—including myocardial infarction (MI), stroke, and vascular death—by 25% in high-risk patients. Additionally, a meta-analysis reported by GP Notebook (2021) confirmed that low-dose aspirin (75–150 mg daily) is as effective as higher doses for long-term prevention in patients with cardiovascular disease. However, aspirin use is associated with an increased risk of major bleeding, particularly gastrointestinal hemorrhage, necessitating careful patient selection and risk assessment (Mahady et al., 2021).

1.3 P2Y12 Receptor Inhibition by Thienopyridines (Clopidogrel, Prasugrel) and Ticagrelor

P2Y12 inhibitors block ADP-mediated activation of platelets, preventing sustained platelet aggregation. Marcin et al. (2024) explain that inhibiting the P2Y12 receptor decreases the expression of the glycoprotein IIb/IIIa complex, which plays a critical role as the final common pathway in platelet aggregation. These agents differ in their pharmacokinetics and efficacy:

Clopidogrel, a prodrug requiring hepatic activation via CYP2C19, exhibits variable efficacy due to genetic polymorphisms affecting metabolism. Clopidogrel (Plavix) is an antiplatelet medication used to lower the risk of myocardial infarction (MI) and stroke in individuals with acute coronary syndrome (ACS) or atherosclerotic vascular disease, as well as in combination with aspirin for patients undergoing percutaneous coronary interventions (PCI), like stent placement (Dean & Kane, 2022). Its efficacy relies on its conversion to an active metabolite by the CYP2C19 enzyme, and individuals with the CYP2C19 poor metabolizer (PM) phenotype, characterized by two loss-of-function

gene copies, exhibit reduced enzyme activity, leading to a diminished antiplatelet effect. The CAPRIE trial (1996) found clopidogrel superior to aspirin in reducing ischemic events by 8.7% in high-risk patients, though the benefit was modest.

Prasugrel provides more potent and consistent platelet inhibition than clopidogrel. The TRITON-TIMI 38 trial (Wiviott et al., 2007) demonstrated reduction in ischemic events with prasugrel versus clopidogrel, but at the cost of increased major bleeding. Prasugrel, a thienopyridine and irreversible ADP P2Y12 receptor antagonist, is a prodrug metabolized by the hepatic CYP system into active and inactive forms, offering antiplatelet effects throughout the lifespan of platelets and is used to treat acute coronary syndrome in patients undergoing percutaneous intervention (Sampat & Wadhwa, 2023). Compared to clopidogrel, prasugrel's active thiolactone metabolite offers a faster onset of action, more consistent bioavailability, and fewer drug-drug interactions involving the CYP450 enzyme system, enhancing its effectiveness in certain scenarios (Dhulab, 2023). Prasugrel is used to lower the risk of heart attack or other serious cardiovascular issues by preventing platelet aggregation, particularly in individuals with a history of heart attack, acute coronary syndrome (ACS), or those with a stent, and may be prescribed for other conditions as determined by a healthcare provider (VanWert, 2023).

Ticagrelor, a direct-acting, reversible P2Y12 inhibitor, does not require hepatic activation and provides faster, more potent platelet inhibition. The PLATO trial (Wallentin et al., 2009) found ticagrelor superior to clopidogrel, reducing cardiovascular death, MI, or stroke, though it was associated with a higher risk of dyspnea. Ticagrelor, an oral antiplatelet medication often combined with low-dose aspirin, is prescribed to reduce the risk of myocardial infarction and stroke in patients with acute coronary syndromes, though it has been associated with rare hypersensitivity reactions and mild liver injury (LiverTox, 2020).

1.4 Glycoprotein IIb/IIIa Inhibitors (Abciximab, Tirofiban, Eptifibatide) and Their Role

Glycoprotein IIb/IIIa inhibitors (GPIs) are potent antiplatelet agents that block the final common pathway of platelet aggregation by preventing fibrinogen binding to GP IIb/IIIa receptors (Tunmala & Rai, 2023). These agents are primarily used in high-risk PCI cases:

Abciximab, a monoclonal antibody, provides long-lasting inhibition but carries a higher risk of thrombocytopenia. According to Rikken et al. (2023), abciximab-associated thrombocytopenia, primarily caused by preformed or delayed antibody responses, occurs most commonly and carries an increased risk upon readministration. Abciximab has the highest affinity for the GP IIb/IIIa receptor among antiplatelet drugs, binding rapidly despite its short plasma half-life of 10–30 minutes (Dhulab, 2023). While platelet function typically recovers within 48 hours after infusion, its high receptor affinity can result in residual activity persisting for up to 15 days.

Tirofiban and eptifibatide, small-molecule inhibitors, offer short-acting and reversible platelet inhibition. Clinical trials such as EPIC (1994) and ESPRIT (2000) have shown that GPIs reduce periprocedural thrombotic complications but increase bleeding risk, limiting their routine use outside of PCI. Eptifibatide is a cyclic heptapeptide with a lysine-glycine-aspartate (KGD) sequence similar to the integrin antagonist barbourin in snake venom, exhibiting a rapid onset of action with dose-dependent receptor occupancy and platelet inhibition (Dhulab, 2023). Eptifibatide functions as a glycoprotein IIb/IIIa inhibitor, effectively disrupting multiple pathways involved in platelet activation and aggregation, making it a valuable agent in preventing thrombotic cardiovascular events (Tonin, G., & Klen, 2023). Tirofiban is a synthetic, nonpeptide small molecule that mimics the arginine-glycine-aspartate (RGD) sequence to reversibly inhibit the GP IIb/IIIa receptor, with platelet inhibition occurring within five minutes and returning to normal in 4–8 hours (Dhulab, 2023). Its

metabolism is influenced by renal function, as 65% of the drug is excreted by the kidneys, and while it has a faster onset of action than abciximab, its lower affinity for the GP IIb/IIIa receptor results in a shorter duration of effect.

SECTION 2: COMPARATIVE EFFICACY OF ANTIPLATELET AGENTS

2.1 Aspirin as the Foundation of Antiplatelet Therapy

Aspirin remains the cornerstone of antiplatelet therapy due to its well-established efficacy in reducing cardiovascular events. By irreversibly inhibiting cyclooxygenase-1 (COX-1), aspirin prevents thromboxane A2 (TXA2) synthesis, thereby suppressing platelet aggregation. Thromboxanes, produced by platelets to promote clot formation, vasoconstriction, and platelet aggregation, are derived from polyunsaturated fatty acids via cyclooxygenase, with the active but unstable thromboxane A2 (TXA2) rapidly hydrolyzing into the inactive thromboxane B2 (TXB2) within 30 seconds (Trapali, 2024). Dhulab (2023) highlighted that aspirin, at low doses, irreversibly acetylates cyclooxygenase-1 (COX-1), preventing the synthesis of platelet-derived thromboxane A2 (TXA2), while at higher doses, it also inhibits COX-2, contributing to its anti-inflammatory effects. The Antithrombotic Trialists' Collaboration meta-analysis found that long-term aspirin therapy reduced the relative risk of major vascular events by approximately 25% in high-risk patients (Baigent et al., 2009). Despite being the gold-standard antiplatelet therapy, aspirin has faced a growing phenomenon known as aspirin resistance, where its effectiveness in inhibiting platelet aggregation is diminished in certain individuals. Khan et al. (2022) described aspirin resistance through two broad definitions: clinically defined resistance, where the standard dose fails to prevent recurrent cardiovascular events, and laboratory-defined resistance, where aspirin does not produce the expected effects on platelet function tests, such as prolonged bleeding time, reduced thromboxane A2 synthesis, or inhibited platelet aggregation. Aspirin resistance can also be classified into pharmacokinetic resistance, which results from insufficient aspirin concentration due to poor absorption, increased degradation, or high platelet turnover, and pharmacodynamic resistance, where genetic polymorphisms in the COX-1 enzyme or structural platelet changes prevent aspirin from effectively inhibiting COX-1 and reducing platelet aggregation, with recent studies identifying a COX-1 polymorphism and the multidrug resistance protein 4 (MRP4) as potential contributors.

2.2 Clopidogrel: The Standard P2Y12 Inhibitor

Clopidogrel, a thienopyridine P2Y12 receptor inhibitor, has been a mainstay in dual antiplatelet therapy (DAPT) when combined with aspirin. Dual antiplatelet therapy (DAPT) combines aspirin with a P2Y12 receptor inhibitor for adenosine diphosphate (ADP), enhancing platelet inhibition to effectively reduce the risk of thrombotic events in patients with cardiovascular conditions (Alagna et al., 2023). Khan et al. (2022) noted clopidogrel as a widely used antiplatelet therapy for patients with peripheral artery disease (PAD) and carotid artery stenosis (CAS), functioning by irreversibly binding to the $P2Y_{12}$ receptor to inhibit ADP-induced platelet activation and aggregation. The CAPRIE trial previously demonstrated that long-term clopidogrel administration was more effective than aspirin in reducing adverse cardiovascular events, including myocardial infarction (MI), cerebrovascular accident (CVA), and cardiovascular-related death. Approximately 15% of clopidogrel undergoes metabolism by cytochrome P450 (CYP450) isoenzymes through a two-step process to form its active metabolite, while the remaining absorbed drug is converted by hepatic carboxylesterase 1 into an inactive molecule (Dhulab, 2023). The active metabolite irreversibly binds to the G-coupled $P2Y_{12}$ receptor on platelets, preventing ADP binding and subsequent platelet activation; however, its reliance on CYP450 metabolism predisposes clopidogrel to

drug-drug interactions, with genetic polymorphisms and CYP2C19 inhibitors, such as proton pump inhibitors, contributing to variable patient responses.

However, clopidogrel's effectiveness relies on its activation by the cytochrome P450 2C19 (CYP2C19) enzyme, but individuals with two loss-of-function copies of the CYP2C19 gene, known as CYP2C19 poor metabolizers (PM), exhibit significantly reduced enzyme activity, resulting in a diminished antiplatelet effect due to the inability to activate the drug properly (Dean & Kane, 2022). This pharmacogenetic limitation has prompted the development of more potent P2Y12 inhibitors.

2.3 Newer P2Y12 Inhibitors: Prasugrel and Ticagrelor

Prasugrel and ticagrelor are newer-generation P2Y12 inhibitors designed to overcome clopidogrel's limitations. Prasugrel, a third-generation thienopyridine similar to clopidogrel, undergoes more efficient metabolism, resulting in faster and more potent platelet inhibition, with its active thiolactone metabolite offering a rapid onset of action, more reliable bioavailability, and fewer CYP450-related drug interactions. (Dhulab, 2023). . The TRITON-TIMI 38 trial found that prasugrel reduced ischemic events by 19% compared to clopidogrel (9.9% vs. 12.1%, $p<0.001$), but at the cost of increased major bleeding (2.4% vs. 1.8%) (Wiviott et al., 2007). Consequently, Sampat & Wadhwa et al. (2023) noted that prasugrel is contraindicated in patients with hypersensitivity to the drug or its components, a history of transient ischemic attack or stroke, or any active pathological bleeding, and its use is generally not recommended in individuals over 75 due to an increased bleeding risk. Caution is necessary in patients with moderate to severe renal or hepatic impairment, a history of gastrointestinal bleeding or ulcers, recent surgery or trauma, and when used alongside medications like abrocitinib, which can significantly elevate bleeding risk, necessitating thorough medication reconciliation.

Ticagrelor, a direct-acting reversible P2Y12 inhibitor, provides even greater platelet inhibition without requiring metabolic activation. The THEMIS trial by Khan et al. (2022) showed that ticagrelor, when combined with aspirin, was significantly more effective in preventing adverse cardiovascular events than aspirin alone. Noting a research where ticagrelor has a markedly lower resistance rate (0–3%) compared to clopidogrel, with one study indicating that all aspirin-resistant patients remained responsive to ticagrelor, highlighting its potential as an alternative antiplatelet therapy. Ticagrelor binds reversibly to the ADP receptor, resulting in a bioavailability of 36% and variable efficacy based on plasma concentration (Dhulab, 2023). It does not require metabolic activation since it is not a prodrug, but its metabolite is equally effective at inhibiting the P2Y12 receptor, and its metabolism by CYP3A4 and CYP3A5 can be affected by co-administered drugs, including digoxin, which requires careful monitoring. The PLATO trial demonstrated that ticagrelor reduced the composite outcome of cardiovascular death, MI, or stroke compared to clopidogrel (Wallentin et al., 2009: Dean & Kane, 2022). Unlike prasugrel, ticagrelor was not associated with increased major bleeding overall, although it did increase non-CABG-related bleeding (Varma et al., 2021). A notable side effect of ticagrelor is dyspnea, attributed to its adenosine-mediated effects (Dominick et al., 2023).

SECTION 3: DUAL ANTIPLATELET THERAPY (DAPT) VS. MONOTHERAPY

3.1 Rationale for DAPT in ACS and PCI

Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, is the cornerstone of secondary prevention in patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI) (Alagna et al., 2023). The primary rationale for DAPT is to reduce the risk of thrombotic events, particularly stent thrombosis,

which is associated with significant morbidity and mortality. Aspirin provides irreversible inhibition of cyclooxygenase-1 (COX-1), thereby reducing thromboxane A2-mediated platelet activation, while P2Y12 inhibitors such as clopidogrel, prasugrel, and ticagrelor block ADP-induced platelet aggregation, offering complementary antithrombotic effects. The combination has demonstrated superiority over aspirin monotherapy in preventing major adverse cardiovascular events (MACE), particularly in high-risk patient populations. Liu et al. (2023) demonstrated that in patients with CAD, clopidogrel use further reduced the risk of MACCE, MI, stroke, and BARC major bleeding compared to aspirin, supporting its preference over aspirin for long-term antiplatelet monotherapy in preventing ischemic events.

3.2 Optimal Duration of DAPT

The duration of DAPT remains a subject of ongoing research, with studies evaluating the balance between ischemic protection and bleeding risk. Park (2022) highlighted that advancements in drug-eluting stents (DES) have significantly reduced ischemic event rates, paving the way for de-escalation antiplatelet strategies, particularly in high bleeding risk (HBR) patients, who constitute approximately 40% of those undergoing PCI. Various de-escalation approaches, including P2Y12 inhibitor monotherapy after short-term DAPT, dose reduction of potent P2Y12 inhibitors, and switching to clopidogrel, have consistently demonstrated lower bleeding rates with comparable ischemic event outcomes, though HBR patients remain underrepresented in clinical trials. As outlined in the American College of Cardiology/American Heart Association (class IIb) guidelines, dual antiplatelet therapy (DAPT) may be shortened to 3 months for individuals with stable ischemic heart disease (SIHD) and to 6 months for those with acute coronary syndrome (ACS) if they have a high bleeding risk, suffer severe bleeding (such as after major intracranial surgery), or exhibit significant visible bleeding (Brenden et al., 2025). Mankerious et al. (2023) conducted a sensitivity analysis comparing 3-month and 12-month dual antiplatelet therapy (DAPT) in high bleeding risk (HBR) patients. The analysis revealed that the 3-month DAPT strategy was linked to a significantly higher risk of ischemic stroke (OR 2.37, 95% CI 1.15–4.87; $p = 0.02$, $I2 = 0\%$), while offering a reduction in major bleeding events and similar overall ischemic outcomes. However, certain subsets showed an elevated risk of ischemic stroke and myocardial infarction (MI) within one year of follow-up.

According to Furtado et al. (2020), the PEGASUS-TIMI 54 study demonstrated that long-term dual antiplatelet therapy (DAPT) with aspirin and ticagrelor significantly reduces thrombotic events and major adverse cardiovascular events (MACE) in patients with prior myocardial infarction (MI), regardless of prior coronary stenting, supporting its use in high-risk patients to prevent atherothrombotic events.

Similarly, Han et al. (2023) found that prolonged dual antiplatelet therapy (DAPT) might not provide sufficient benefit to acute coronary syndrome (ACS) patients within 12–18 months after the initial percutaneous coronary intervention (PCI), as the increased risk of significant bleeding events outweighs the potential advantages. However, Kinlay et al. (2023) concluded that discontinuing dual antiplatelet therapy (DAPT) after 9 months reduces long-term risks of ischemic and bleeding events, aligning with updated guidelines recommending shorter DAPT durations following PCI with second-generation drug-eluting stents. These findings highlight the need for individualized therapy based on patient-specific thrombotic and hemorrhagic risk factors.

3.3 Monotherapy Approaches

Recent trials have investigated whether monotherapy with either aspirin or a P2Y12 inhibitor could provide sufficient protection while minimizing bleeding risk. According to Jacobsen et al. (2020), while early trials on aspirin use in CCS suggested potential benefits, none of the six post-MI trials in the ATT meta-analyses consistently showed statistically significant reductions in primary endpoints, rendering their individual findings inconclusive for aspirin's role in secondary prevention. Aspirin monotherapy has traditionally been the standard for long-term secondary prevention, but its efficacy may be limited in patients with high thrombotic risk or aspirin resistance. Overall, studies indicate that transitioning from short dual antiplatelet therapy (DAPT) to P2Y12 inhibitor monotherapy reduces bleeding complications without significantly raising ischemic risks compared to standard DAPT, while limited evidence suggests that clopidogrel monotherapy offers superior net benefits, fewer ischemic events, and reduced bleeding compared to aspirin monotherapy (Greco et al., 2022). Gragnano et al. emphasize that P2Y12 inhibitor monotherapy, compared to aspirin monotherapy in patients with coronary artery disease (CAD), significantly lowers risks of cardiovascular death, myocardial infarction, and stroke, primarily due to reduced myocardial infarction rates and noncardiovascular adverse events (NACE). While major bleeding rates were similar, P2Y12 inhibitor monotherapy demonstrated lower risks of gastrointestinal bleeding and hemorrhagic stroke, suggesting that it may be a preferable option for long-term secondary prevention in CAD patients based on current randomized evidence. P2Y12 inhibitor monotherapy, particularly with ticagrelor, has emerged as a potential alternative. The TWILIGHT trial demonstrated that in high-risk PCI patients, transitioning to ticagrelor monotherapy after three months of DAPT significantly reduced major bleeding without increasing ischemic events. Nicolas et al. (2020) demonstrated that transitioning high-risk patients from dual antiplatelet therapy with ticagrelor and aspirin to ticagrelor monotherapy at 3 months post-percutaneous coronary intervention significantly reduced bleeding risks without raising the likelihood of death, myocardial infarction (MI), or stroke. These findings suggest that selected patients may benefit from P2Y12 inhibitor monotherapy, although further research is needed to define optimal patient selection criteria.

SECTION 4: SAFETY CONCERNS AND EMERGING ISSUES

4.1 Bleeding Risks Associated with Antiplatelet Therapy

The most critical safety concern associated with antiplatelet therapy is the risk of major bleeding, which includes intracranial hemorrhage and gastrointestinal (GI) bleeding. Data from the PLATO trial from Wallentin et al. (2009) research indicated that the overall major bleeding rate was 11.6% for ticagrelor and 11.2% for clopidogrel (P=0.43), indicating no statistically significant difference between the two drugs. Similarly, TIMI-defined major bleeding occurred at comparable rates (7.9% vs. 7.7%, P=0.57). However, non-CABG-related major bleeding was slightly higher in the ticagrelor group (4.5% vs. 3.8%, P=0.03), as was TIMI-defined non-CABG major bleeding (2.8% vs. 2.2%, P=0.03). While intracranial bleeding was numerically higher with ticagrelor (0.3% vs. 0.2%, P=0.06), fatal intracranial bleeding showed a significant increase (0.1% vs. 0.01%, P=0.02). Notably, ticagrelor was associated with fewer fatal bleeds from other causes compared to clopidogrel (0.1% vs. 0.3%, P=0.03), highlighting a nuanced safety profile. The research points that ticagrelor had similar overall major bleeding rates to clopidogrel, with higher non-CABG-related bleeding but lower fatal bleeding from non-intracranial causes (Wallentin et al., 2009). A recent study by Ma, Ying et al. (2022) found that while ticagrelor increased the risk of any bleeding, PLATO major bleeding, and dyspnea compared to clopidogrel in East Asian patients with acute coronary syndrome, it significantly lowered the risk of stent thrombosis.

Similarly, the conclusion from Mankerious et al. (2023) research aligns with the general findings of the DAPT trial in terms of bleeding risk and ischemic outcomes. The DAPT trial reported that extending dual antiplatelet therapy (DAPT) beyond 12 months increased the risk of major bleeding while reducing stent thrombosis and myocardial infarction. In contrast, Mankerious et al. (2023) found that short-term DAPT (≤12 months) reduced major bleeding events while maintaining similar ischemic outcomes, though with a higher risk of ischemic stroke and a trend toward increased MI in some subsets. The balance between thrombosis prevention and bleeding risk is particularly challenging in high-risk populations, including elderly patients, those with chronic kidney disease, and individuals with prior bleeding history. The TWILIGHT trial demonstrated that ticagrelor monotherapy after three months of DAPT significantly reduced major bleeding events (HR 0.49, 95% CI 0.33–0.74) without increasing ischemic events, suggesting a potential strategy to mitigate bleeding risks in high-risk patients. Nicolas et al. (2020) supports the notion that transitioning from dual antiplatelet therapy (DAPT) to ticagrelor monotherapy at three months post-PCI reduces bleeding risk (HR 0.56; 95% CI [0.45–0.68]; $p<0.001$) without increasing the risk of ischemic events (HR 0.99; 95% CI [0.78–1.25]). This aligns with findings from Mankerious et al. (2023), which also indicated a reduction in major bleeding events with shorter DAPT durations while maintaining similar ischemic outcomes. However, Mankerious et al. noted a higher risk of ischemic stroke and MI in certain subsets, a nuance not explicitly addressed in Nicolas et al.'s findings.

4.2 Antiplatelet Drug Resistance

Aspirin Resistance: Causes and Impact on Clinical Outcomes

Khan et al. (2022) defined aspirin resistance in two ways: (1) "clinically defined aspirin resistance," where the standard aspirin dose fails to prevent recurrent cardiovascular events, and (2) "laboratory-defined aspirin resistance," where standard aspirin does not produce expected platelet function test outcomes, such as increased bleeding time, reduced thromboxane A2 (TxA2) synthesis, or inhibited platelet aggregation. Aspirin resistance, defined as the inability of aspirin to inhibit platelet thromboxane A2 production, depending on the definition and diagnostic methods used. This resistance may be attributed to genetic polymorphisms, increased platelet turnover, and drug interactions, particularly with nonsteroidal anti-inflammatory drugs (NSAIDs). Studies such as Gendeleka, G., & Gendeleka, (2022) suggest that aspirin resistance correlates with an increased risk of adverse cardiovascular events. Khan et al. (2022) reveal that one in four patients with vascular disease exhibits resistance to aspirin therapy, leading to a nearly fourfold increase in the risk of major adverse limb and cardiovascular events. While diagnostic strategies for aspirin resistance remain unvalidated, promising laboratory assays and emerging therapies like rivaroxaban, when combined with aspirin, have shown potential in improving outcomes for these patients.

Clopidogrel Resistance (CYP2C19 Polymorphisms)

Despite clopidogrel's overall efficacy, resistance is relatively common and occurs when there is no significant reduction in platelet function after therapy, resulting in High on-Treatment Platelet Reactivity (HTPR). HTPR, affecting an estimated 16–50% of clopidogrel-treated individuals, leaves platelet P2Y12 receptors responsive, increasing the risk of thrombotic events like stent thrombosis or recurrent acute coronary syndromes (Dean & Kane, 2022).

Clopidogrel resistance is largely attributed to polymorphisms in the CYP2C19 gene, which impair the hepatic bioactivation of the prodrug. The TRITON-TIMI 38 trial identified that carriers of the CYP2C19 loss-of-function allele had a 53% higher rate of cardiovascular events when treated with clopidogrel compared to non-carriers (Mega et al., 2009). Kayla et al. (2024) examined 567 Black patients undergoing PCI who were treated with clopidogrel and CYP2C19

genotyped, and found that those with intermediate and poor metabolizer phenotypes experienced significantly higher rates of major atherothrombotic events (35.1 vs 15.9 events per 100 person-years; adjusted HR, 2.00; P=0.008), while bleeding event rates remained low and comparable across the groups. These findings suggest that Black patients with reduced CYP2C19 function may benefit from genotype-guided antiplatelet strategies, such as using prasugrel or ticagrelor, instead of clopidogrel, warranting further prospective research in this population. This has led to growing interest in genotype-guided therapy. Pereira et al. (2021) examined the TAILOR-PCI trial and found that ticagrelor did not significantly reduce ischemic events compared to clopidogrel in CYP2C19 loss-of-function (LOF) carriers at 12 months, based on the trial's prespecified analysis and an expected 50% treatment effect. However, a Bayesian analysis by Parcha et al. (2021) suggested a potential reduction in major adverse cardiovascular events (MACE) with genotype-guided P2Y12 inhibitor therapy after PCI, although the primary analysis did not achieve statistical significance (RR 0.78, 95% CrI 0.55–1.07, probability of RR<1 = 94%). When integrating prior evidence, the probability of benefit increased, reinforcing the relevance of genotype-guided antiplatelet therapy. These findings contribute to the ongoing debate about the cost-effectiveness and clinical utility of routine genetic testing for patients requiring antiplatelet therapy.

Potential for Genotype-Guided Therapy

Given the impact of CYP2C19 polymorphisms on clopidogrel metabolism, genotype-guided therapy has been explored as a strategy to optimize antiplatelet treatment. Studies such as Naveen et al. (2021) found that the effectiveness of ticagrelor or prasugrel in reducing ischemic events, compared to clopidogrel, in patients with coronary artery disease (CAD) undergoing PCI largely depends on CYP2C19 loss-of-function carrier status. These findings highlight the importance of genetic testing before initiating P2Y12 inhibitor therapy. Yoon et al. (2020) found that CYP2C19 reduced-metabolizers achieve superior clinical outcomes when treated with prasugrel or ticagrelor compared to clopidogrel. Amber et al. (2022) reported that the POPular-Genetics trial demonstrated genotype-guided treatment to be non-inferior to the universal use of ticagrelor or prasugrel in terms of net adverse atherothrombotic or major bleeding events, while significantly lowering the risk of clinically significant bleeding events. However, despite promising data, routine genetic testing remains underutilized due to logistical barriers and the lack of universal consensus on clinical guidelines. Future research should aim to refine patient selection criteria and cost-effectiveness analyses to enhance the feasibility of genotype-guided strategies in clinical practice. Overall, while antiplatelet therapy remains a cornerstone of cardiovascular disease management, addressing safety concerns such as bleeding risks and drug resistance through individualized treatment approaches is essential to optimizing patient outcomes.

SECTION 5: FUTURE DIRECTIONS IN ANTIPLATELET THERAPY

5.1 Personalized Antiplatelet Therapy Based on Genetic Testing

Advancements in pharmacogenomics have led to increased interest in planning antiplatelet therapy based on genetic testing. CYP2C19 polymorphisms, particularly loss-of-function variants, significantly impact clopidogrel metabolism, contributing to treatment resistance and influencing patient outcomes (Sharma et al., 2024). Studies, including the TAILOR-PCI trial, have investigated the clinical utility of CYP2C19 genotyping in guiding P2Y12 inhibitor selection. While initial findings did not show a statistically significant reduction in ischemic events (Pereira et al., 2020), subsequent Bayesian analyses incorporating prior evidence suggested a higher probability of benefit (Parcha et al., 2021). Additionally, recent research has highlighted racial disparities in clopidogrel metabolism, particularly among Black

patients, further supporting the case for genotype-guided therapy in high-risk populations (Kayla et al., 2024). Despite these findings, routine genetic testing remains controversial due to cost-effectiveness concerns and the need for broader validation in real-world clinical settings.

5.2 Novel Antiplatelet Agents in Development

Ongoing drug development efforts aim to enhance platelet inhibition while minimizing bleeding risk. Emerging P2Y12 inhibitors, such as selatogrel and AZD1283, are being explored for their potential to provide more predictable pharmacokinetics and improved safety profiles compared to existing agents (Hajbabaie, 2022; Milluzzo et al., 2020). Also, Tantry et al. (2020) highlighted the potential of novel thrombin receptor antagonists, including vorapaxar analogs, to minimize thrombotic complications without notably increasing bleeding risks. Vorapaxar therapy was associated with a 10% reduction in cardiovascular death, myocardial infarction, stroke, urgent coronary revascularization, and moderate or severe bleeding, showcasing its promise in improving clinical outcomes. Recent clinical trials have also investigated combination therapies that balance potent platelet inhibition with protective mechanisms against hemorrhagic complications. A systematic review and meta-analysis found that a 1-month dual antiplatelet therapy (DAPT) followed by aspirin or a P2Y12 receptor inhibitor reduced major bleeding without increasing thrombotic risk compared to longer-term DAPT (Bajraktari et al., 2024). As these agents progress through clinical evaluation, their efficacy and safety will determine their potential role in future antiplatelet therapy strategies.

Role of AI and Machine Learning in Predicting Thrombotic Risk

Artificial intelligence (AI) and machine learning (ML) have increasingly been integrated into cardiovascular medicine, offering promising applications in thrombosis risk stratification and personalized antiplatelet therapy. Predictive models utilizing AI can analyze large-scale patient data, identifying high-risk individuals who may benefit from intensified therapy while minimizing overtreatment in low-risk groups. Al Raizah A and Alrizah (2025) emphasized that accurately predicting future venous thromboembolism (VTE) is crucial for balancing risks and benefits. This approach enables the identification of high-risk patients who would gain the most from pharmacological thromboprophylaxis. Machine learning algorithms have demonstrated superior accuracy in predicting major adverse cardiovascular events compared to traditional risk scores (Lakhani et al. 2025). Furthermore, AI-driven decision support systems can optimize antiplatelet selection by incorporating genetic, clinical, and procedural variables, improving individualized treatment approaches. Future research will focus on validating these models in prospective studies and integrating AI-driven decision-making into routine clinical practice. As antiplatelet therapy continues to evolve, the convergence of genetic insights, novel pharmacologic agents, and AI-driven risk prediction holds the potential to refine patient management strategies, ultimately improving cardiovascular outcomes while managing associated risks.

CONCLUSION

The continual change in antiplatelet therapy outlines the significance of optimizing treatment strategies to enhance both efficacy and safety. Major findings indicate that genetic polymorphisms, particularly CYP2C19 loss-of-function variants, contribute significantly in clopidogrel metabolism, impacting patient outcomes. Studies, including the TAILOR-PCI trial and Bayesian analyses, have suggested that genotype-guided therapy may offer potential benefits, although definitive evidence remains inconclusive. Also, short-duration dual antiplatelet therapy (DAPT) has demonstrated a reduction in

bleeding events without significantly increasing ischemic risk in high-risk patients undergoing percutaneous coronary intervention (PCI). These findings hold important implications for clinical practice. Personalized antiplatelet therapy based on genetic testing has the potential to refine treatment selection, particularly for populations with high rates of CYP2C19 polymorphisms. Emerging evidence also supports the transition from traditional DAPT regimens to monotherapy strategies in select patient cohorts to manage bleeding risks while maintaining protection against thrombotic events. Furthermore, novel antiplatelet agents and the integration of artificial intelligence in risk stratification may further individualize therapy, improving patient outcomes.

Future research should focus on large-scale, prospective trials to validate the clinical utility of genotype-guided antiplatelet therapy. Additionally, investigations into the long-term effects of novel agents and combination therapies are necessary to enhance safety and efficacy. As precision medicine advances, integrating genetic and machine-learning-driven approaches into routine practice may redefine antiplatelet management, ensuring optimal treatment strategies structured to individual patient profiles.

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