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Review Article

The effect of antiplatelet drugs on the management of cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading global cause of mortality, necessitating innovative strategies for prevention, diagnosis, and treatment. Antiplatelet drugs play a vital role in mitigating adverse atherothrombotic events by inhibiting platelet aggregation, crucial for managing conditions such as myocardial infarction, ischemic stroke, and peripheral artery disease. Platelets, essential for haemostasis, also contribute to thrombus formation in vascular injury and disease. Their activation is triggered by stimuli like collagen, thrombin, and adenosine diphosphate (ADP). Antiplatelet drugs target these pathways to prevent arterial thrombosis. Key classes of antiplatelet agents include cyclooxygenase inhibitors, P2Y12 receptor antagonists, glycoprotein IIb/IIIa inhibitors, and phosphodiesterase inhibitors. Aspirin, a COX-1 inhibitor, irreversibly blocks thromboxane A2 production, effectively reducing recurrent cardiovascular events, though its role in primary prevention is tempered by bleeding risks. P2Y12 inhibitors, such as clopidogrel, prasugrel, and ticagrelor, suppress ADP-mediated platelet activation, with newer agents providing consistent efficacy but higher bleeding risk. Dual antiplatelet therapy, combining aspirin and a P2Y12 inhibitor, is the standard for acute coronary syndrome and post-PCI management. Challenges, including bleeding and resistance, underscore the need for personalized approaches using pharmacogenomics. Ongoing research aims to develop safer, targeted therapies, including thrombin receptor blockers and novel combination regimens.

Keywords: Atherosclerosis, Ticagrelor, Aspirin, Clopidogrel, MI, Thrombosis

INTRODUCTION

Cardiovascular diseases (CVDs) encompass a diverse group of conditions affecting the heart and vascular system, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease. These conditions collectively account for a significant proportion of global mortality and disability. Atherothrombosis, characterized by the formation of a thrombus at the site of an atherosclerotic plaque rupture, is the fundamental pathological mechanism underlying many CVDs.

Platelet activation, a critical event in this process, makes antiplatelet therapy a cornerstone of CVD management. Antiplatelet drugs have transformed the therapeutic landscape of CVDs by effectively reducing thrombotic complications and improving clinical outcomes. Their widespread use spans primary and secondary prevention of cardiovascular events, acute coronary syndromes (ACS), and post-percutaneous coronary intervention (PCI) care.

This review aims to provide a comprehensive overview of antiplatelet agents, examining their mechanisms of action, clinical applications, and the challenges associated with their use. Special attention is given to the comparative efficacy of monotherapy versus combination regimens, as well as emerging advances in the field that hold promise for optimizing CVD management. Statistical analyses from pivotal clinical trials further underline the importance of antiplatelet therapy. For instance, the ESPS-2 trial

showed that aspirin and dipyridamole combination therapy reduced stroke recurrence by 37%, outperforming either agent alone.[1] Dual antiplatelet therapy (DAPT) has been particularly transformative; the CURE trial highlighted a 20% reduction in cardiovascular events with aspirin plus clopidogrel.[2] The PLATO trial revealed a 22% mortality reduction with ticagrelor-based DAPT compared to clopidogrel.[3] The choice between single-agent therapy and combination regimens often depends on the clinical context, patient risk profile, and genetic factors. Emerging data advocate for integrating pharmacogenomic testing to personalize therapy further, ensuring optimal efficacy and safety for patients with diverse genetic backgrounds.

MECHANISM OF ACTION OF ANTIPLATELET DRUGS

Platelets are indispensable for hemostasis but play a pathological role in thrombus formation under diseased conditions. The activation of platelets involves a sequence of events: adhesion to the vascular endothelium, activation by agonists like thrombin and adenosine diphosphate (ADP), and aggregation facilitated by glycoprotein (GP) IIb/IIIa receptors. Antiplatelet drugs intervene at various points in this cascade to prevent thrombus formation.

SPECIFIC MODES OF ACTION BY DRUG CLASS

Cyclooxygenase inhibitors

Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1), suppressing thromboxane A2 synthesis, a potent inducer of platelet aggregation. This action effectively reduces platelet activity for the lifespan of the platelet, approximately 7–10 days.

P2Y12 *receptor antagonists*

These agents block the ADP receptor on platelets, thereby preventing activation and subsequent aggregation. Examples include:

Clopidogrel

A prodrug requiring hepatic activation, it binds irreversibly to P2Y12 receptors.

Prasugrel

Similar to clopidogrel but with more consistent platelet inhibition and reduced inter-patient variability.

Ticagrelor

A reversible, direct-acting antagonist that offers faster onset and offset of action compared to clopidogrel.

Glycoprotein IIb/IIIa inhibitors

Abciximab, eptifibatide, and tirofiban block the final common pathway of platelet aggregation by inhibiting fibrinogen from binding to GP IIb/IIIa receptors.

These agents are highly effective but typically reserved for high-risk procedures or refractory cases due to bleeding risks.

Phosphodiesterase inhibitors

Dipyridamole and cilostazol inhibit phosphodiesterase enzymes, leading to increased intracellular cAMP levels and reduced platelet activation. Cilostazol also has vasodilatory effects, making it beneficial in peripheral artery disease.

COMPARISON BETWEEN SAPT AND DAPT

Acute coronary syndrome (ACS):

DAPT

Superior in reducing major adverse cardiovascular events (MACE), particularly in the first year post-ACS.

SAPT

Recommended after completing the DAPT course for long-term secondary prevention.

Percutaneous coronary intervention

DAPT

Standard therapy to prevent stent thrombosis. The DAPT trial showed benefits of prolonged DAPT in high-risk patients but highlighted increased bleeding risks. 4

SAPT

Aspirin monotherapy can be considered in low-risk patients post-DAPT.

Stroke prevention

CHANCE Study

DAPT (aspirin+clopidogrel) within 21 days of a minor stroke reduced stroke recurrence by 32% compared to aspirin alone ($p<0.001$). Prolonged DAPT increases bleeding risk, favouring SAPT for maintenance therapy.[5,6]

Peripheral artery disease

CAPRIE trial

Clopidogrel showed marginally better outcomes than aspirin (RRR: 8.7%, p=0.043) in preventing vascular events

MDPI

Combination therapies are not typically used unless there is a high risk of thrombotic events.

Clinical recommendations

SAPT

Long-term therapy for stable CVD or after completing DAPT.

DAPT

Essential for high-risk settings like ACS, PCI, or recent stroke/TIA, with therapy duration tailored to bleeding risk.

ADRs OF THERAPY

Bleeding risks

Major bleeding events

Dual antiplatelet therapy (DAPT) increases bleeding risk significantly, with an annual major bleeding incidence of 1–3%.

Study data

The PLATO trial (ticagrelor vs. clopidogrel) reported major bleeding in 11.6% of patients on ticagrelor vs. 11.2% on clopidogrel.7,8

Gastrointestinal bleeding

Aspirin and P2Y12 inhibitors contribute heavily, especially without protective proton pump inhibitors (PPIs).

Incidence

Approximately 0.5–1.0% per year in low-risk patients, with higher rates in older adults and those with prior ulcers.

Intracranial haemorrhage

Risk is increased, particularly with aspirin, with a 0.2% annual rate.[9–11]

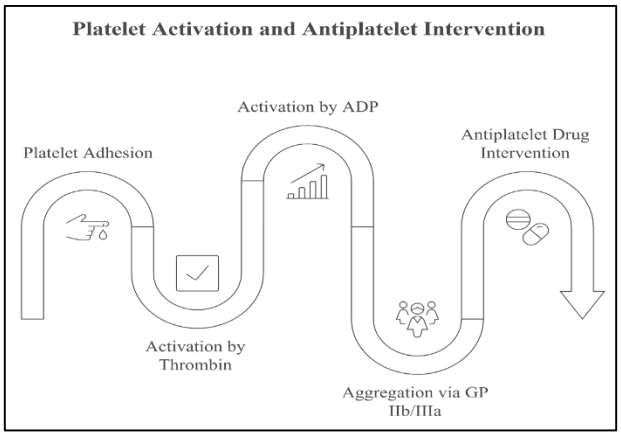

Figure 1: Mode of action of antiplatelet.

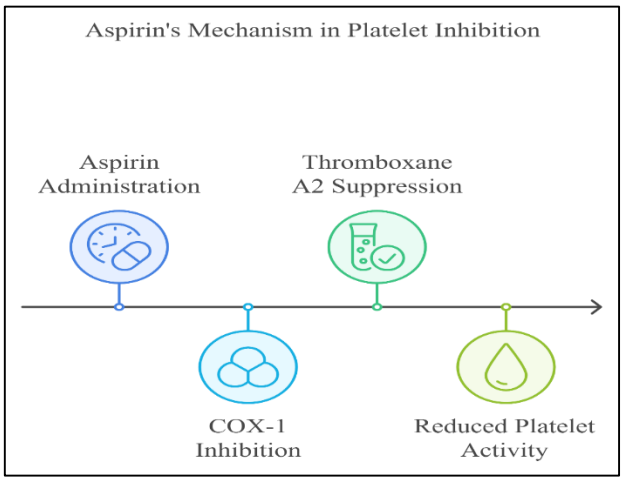

Figure 2: MOA of aspirin

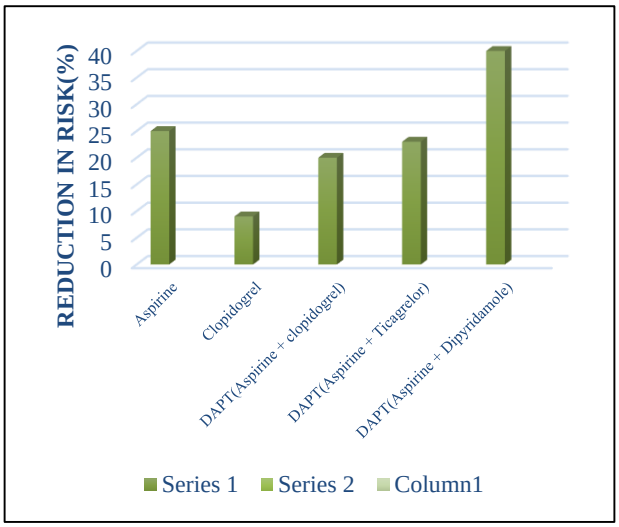

Figure 3: Reduction in Risk of MI.

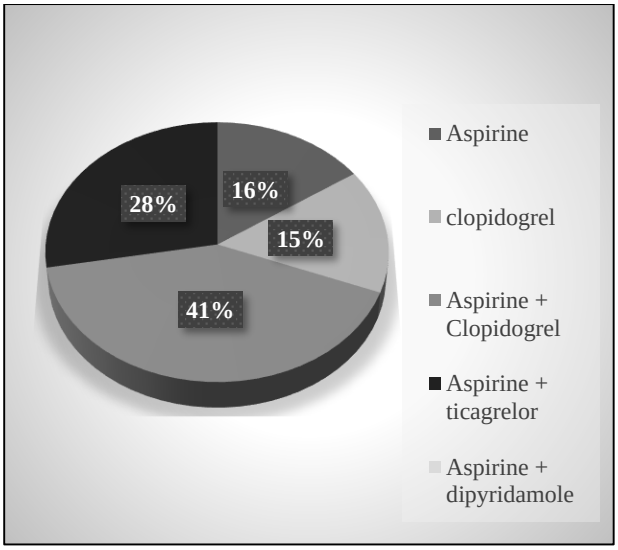

Figure 4: Annual bleeding risk.

Thrombocytopenia

Mechanism

Drugs like abciximab cause immune-mediated platelet destruction, observed in 1–2% of users.

Clinical data

Trials like the REPLACE-2 study noted thrombocytopenia in 0.5–2.0% of patients on glycoprotein IIb/IIIa inhibitors.

Allergic and hypersensitivity reactions

Aspirin-exacerbated respiratory disease

Affects 10% of asthmatic patients on aspirin.

Severe reactions

Clopidogrel-related hypersensitivity dermatitis (e.g., rash or itching) occurs in up to 6% of patients.

Drug resistance and reduced efficacy

Clopidogrel resistance

Caused by CYP2C19 polymorphisms, affecting up to 44% of patients. Leads to increased cardiovascular event recurrence.

Management

Alternatives like ticagrelor or prasugrel are often preferred.

Non-bleeding ADRs

Liver toxicity

Rarely associated with ticlopidine, requiring liver enzyme monitoring.

Hematologic ADRs:

Ticlopidine can cause neutropenia in 0.8–2.1% of patients.

Mortality and ADR correlation

Long-term DAPT Risks

The DAPT trial found that while prolonged therapy reduced ischemic events, it increased moderate-to-severe bleeding by 2.5% and resulted in higher mortality in those with severe bleeding.

Combination therapy complications

Dual/triple therapy

Combining antiplatelets with anticoagulants (e.g., warfarin) can raise bleeding risks up to 15%, as seen in the WOEST trial.

Key considerations

Risk stratification

Use scoring systems like HAS-BLED or DAPT scores to balance bleeding and thrombotic risks.

Preventative measures

Routine co-prescription of PPIs for GI protection. Genetic testing for clopidogrel metabolism (CYP2C19 variants).

Monitoring

Regular platelet counts and liver enzyme checks.

The future of antiplatelet therapy lies in integrating advanced pharmacogenomics and precision medicine approaches. Genetic profiling can enhance the selection of antiplatelet agents, ensuring maximum efficacy with minimal adverse effects. Emerging therapies that target multiple pathways of platelet activation, such as combination regimens integrating anticoagulants, hold potential for improving outcomes in complex cardiovascular conditions. Furthermore, ongoing research into thrombin receptor antagonists, reversible P2Y12 inhibitors, and agents with more targeted mechanisms will likely expand the therapeutic arsenal.

Table 1: Outcomes of antiplatelet therapy.

Disease/condition	Study	Antiplatelet therapy	Outcome	Statistical data
Coronary artery disease (CAD)	Plato	Ticagrelor vs. Clopidogrel	Reduced composite outcome of CV death, MI, or stroke.	Ticagrelor: 9.8% vs. Clopidogrel: 11.7% (HR: 0.84, p<0.001).
Acute coronary syndrome (ACS)	Triton-timi	Prasugrel vs. Clopidogrel	Significant reduction in ischemic events but increased bleeding risk.	Ischemic events: 9.9% vs. 12.1% (HR: 0.81, p<0.001).
Stroke prevention	Chance	Aspirin + Clopidogrel	Reduced risk of recurrent stroke compared to aspirin alone.	Stroke recurrence: 8.2% vs. 11.7% (HR: 0.68, p<0.001).
Peripheral artery disease (PAD)	Caprie	Clopidogrel vs. Aspirin	Clopidogrel showed marginally better outcomes than aspirin in vascular events prevention.	Relative risk reduction: 8.7% (p=0.043).
Diabetes & primary prevention	Ascend	Aspirin vs. Placebo	Modest reduction in vascular events, but increased bleeding risk.	Vascular events: 8.5% vs. 9.6%; Major bleeding: 4.1% vs. 3.2% (p<0.001).
TAVI	Popular tavi	Aspirin alone vs. Aspirin + Clopidogrel	Aspirin monotherapy associated with fewer bleeding events compared to DAPT.	Bleeding: 15.1% vs. 24.9% (HR: 0.57, p<0.001).
COVID-19 Thrombosis	Remap-cap	Aspirin	Studied impact on thrombotic complications in severe COVID-19 patients.	No significant reduction in mortality; bleeding risks not statistically significant.

Digital health tools, including AI-driven risk stratification and real-time monitoring of therapy adherence and side effects, could revolutionize clinical practice. By combining these technological advancements with innovative drug development, the field of antiplatelet therapy is well-positioned to meet the evolving needs of cardiovascular care.

CONCLUSION

Antiplatelet therapy has significantly improved the management and outcomes of cardiovascular diseases (CVDs), particularly in conditions such as myocardial infarction, ischemic stroke, and peripheral arterial disease. By targeting key mechanisms of platelet activation and aggregation, these medications effectively reduce thrombotic risks and enhance patient survival rates.

The effectiveness of cyclooxygenase inhibitors like aspirin, P2Y12 receptor antagonists such as clopidogrel, prasugrel, and ticagrelor, and glycoprotein IIb/IIIa inhibitors like abciximab has been extensively validated in clinical trials. The role of dual antiplatelet therapy (DAPT) in acute coronary syndrome (ACS) and post-percutaneous coronary intervention (PCI) management underscores its importance in preventing major adverse cardiovascular events. Despite these advances, challenges such as bleeding risks and inter-patient variability in drug response necessitate careful therapeutic strategies tailored to individual patient profiles. Pharmacogenomic insights are paving the way for personalized medicine, addressing issues such as clopidogrel resistance and optimizing drug efficacy. Additionally, novel antiplatelet agents, including thrombin receptor antagonists and reversible P2Y12 inhibitors, show promise in further reducing thrombotic complications while minimizing bleeding risks.

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