INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Antithrombotic Therapy After Acute Coronary Syndrome: Balancing Ischaemic Protection and Bleeding Risk

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ARTICLE INFO

Published: 20 Nov 2026

Keywords:
Acute coronary syndrome, Antithrombotic therapy, Dual antiplatelet therapy, P2Y12 inhibitors, Bleeding risk, Percutaneous coronary intervention

DOI:
10.5281/zenodo.24394566

ABSTRACT

Antithrombotic therapy is central to preventing recurrent ischaemic events after acute coronary syndrome (ACS), yet it also increases bleeding, which is itself associated with adverse outcomes. This review summarises the mechanisms of coronary thrombosis, the pharmacology of antiplatelet and anticoagulant agents, and the evidence guiding the duration and intensity of dual antiplatelet therapy (DAPT). Twelve months of DAPT remains the default for most patients without high bleeding risk. In selected, clinically stable patients after percutaneous coronary intervention (PCI), shortened DAPT followed by P2Y12-inhibitor monotherapy reduced bleeding without an increase in ischaemic events in several randomised trials. However, immediate aspirin withdrawal after PCI did not show non-inferiority for ischaemic outcomes in NEO-MINDSET, with the excess events concentrated in the first month. Bleeding-risk tools, including the Academic Research Consortium high-bleeding-risk criteria and the PRECISE-DAPT score, together with patient characteristics, should inform treatment duration, particularly in older adults, patients with chronic kidney disease and those requiring oral anticoagulation. Evidence from Indian populations remains limited. Individualised treatment, reassessed as clinical circumstances change, offers the best balance between ischaemic protection and bleeding risk.

INTRODUCTION

Acute coronary syndrome (ACS) usually follows rupture or erosion of an atherosclerotic plaque, leading to platelet activation and thrombus formation. Antithrombotic treatment reduces recurrent myocardial infarction, stent thrombosis and cardiovascular death. Its benefit, however, must be weighed against bleeding, which can force treatment interruption and is itself associated with adverse outcomes[1,2].

Management has therefore moved away from uniform, prolonged platelet inhibition. Contemporary decisions take into account the clinical presentation, revascularisation strategy, ischaemic risk, bleeding risk

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

and the patient's ability to continue treatment. This review summarises the mechanisms of thrombosis and the principal antithrombotic therapies used after ACS, with emphasis on the duration of dual antiplatelet therapy (DAPT) and its individualisation.

2. MECHANISMS OF THROMBOSIS AND RISK ASSESSMENT

In type 1 ACS, plaque rupture or erosion exposes thrombogenic material to circulating blood. Platelets adhere and become activated, releasing mediators that include thromboxane A2 and adenosine diphosphate (ADP). These recruit further platelets, which aggregate through glycoprotein IIb/IIIa receptors. Activation of tissue factor also generates thrombin, which converts fibrinogen to fibrin and stabilises the thrombus. Aspirin, P2Y12 inhibitors and anticoagulants interrupt different stages of this process[3].

Ischaemic risk is increased by recurrent myocardial infarction, diabetes with multivessel disease, previous stent thrombosis and complex PCI. Bleeding risk rises with advanced age, renal impairment, anaemia, previous bleeding and the need for oral anticoagulation. Some characteristics, particularly chronic kidney disease (CKD), increase both risks and make treatment selection difficult[1,2].

The Global Registry of Acute Coronary Events (GRACE) score estimates prognosis and can help guide invasive management, but it is not a bleeding-prediction tool[1,2]. The Academic Research Consortium high-bleeding-risk (ARC-HBR) definition identifies high bleeding risk by the presence of at least one major or two minor criteria. The PRECISE-DAPT score incorporates age, creatinine clearance, haemoglobin, white-cell count and previous bleeding; a score of 25 or more indicates high bleeding risk. These instruments support clinical assessment but should not replace individual judgement.Their performance in diverse populations, including Indian patients, requires further evaluation[4,5] (Table 1).

Table 1: Risk Assessment Tools Used After Acute Coronary Syndrome

Tool	Purpose and components	Interpretation
GRACE score	Estimates prognosis in ACS and helps guide invasive management	Not a bleeding-prediction tool[1,2]
ARC-HBR definition	Consensus definition of high bleeding risk in patients undergoing PCI	At least one major or two minor criteria indicates high bleeding risk[4]
PRECISE-DAPT score	Age, creatinine clearance, haemoglobin, white-cell count and previous bleeding	Score of 25 or more indicates high bleeding risk[5]

ACS, acute coronary syndrome; ARC-HBR, Academic Research Consortium high bleeding risk; DAPT, dual antiplatelet therapy; GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention. These tools support, but do not replace, clinical judgement.

3. ANTIPLATELET AND ANTICOAGULANT THERAPY

Aspirin irreversibly inhibits cyclooxygenase-1 and reduces thromboxane A2 production. It remains a foundation of ACS treatment, generally at a maintenance dose of 75–100 mg daily. P2Y12 inhibitors reduce ADP-mediated platelet activation. Clopidogrel is a prodrug whose activation depends partly on CYP2C19, producing a variable response. Prasugrel provides potent and consistent inhibition but increases bleeding and is contraindicated after previous stroke or transient ischaemic attack. Ticagrelor acts directly and reversibly and is given twice daily; dyspnoea and ventricular pauses are recognised adverse effects[1,2] (Table 2).

Table 2: Antiplatelet Agents Used After Acute Coronary Syndrome

Agent	Mechanism	Key clinical points
Aspirin	Irreversible inhibition of cyclooxygenase-1; reduced thromboxane A2 production	Generally given at a maintenance dose of 75–100 mg daily

Agent	Mechanism	Key clinical points
Clopidogrel	Prodrug; activation depends partly on CYP2C19	Variable response; important when bleeding risk is high, potent agents are unsuitable or oral anticoagulation is required
Prasugrel	Potent and consistent P2Y12 inhibition	Increases bleeding; contraindicated after previous stroke or transient ischaemic attack
Ticagrelor	Direct, reversible P2Y12 inhibition	Given twice daily; dyspnoea and ventricular pauses are recognised adverse effects

ADP, adenosine diphosphate. P2Y12 inhibitors reduce ADP-mediated platelet activation. Content summarised from the guidelines cited[1,2].

For patients with ACS undergoing PCI, prasugrel or ticagrelor is generally preferred to clopidogrel when there is no contraindication and bleeding risk is acceptable. In the PLATO trial, ticagrelor reduced the composite of cardiovascular death, myocardial infarction or stroke compared with clopidogrel, although non-coronary artery bypass grafting (non-CABG) major bleeding was increased[6]. TRITON-TIMI 38 found fewer ischaemic events with prasugrel than with clopidogrel in patients scheduled for PCI, but major and fatal bleeding were more frequent[7]. ISAR-REACT 5 reported fewer ischaemic events with a prasugrel-based strategy than with ticagrelor, while major bleeding was similar; its open-label design and the differing treatment strategies should be considered when interpreting this result[8]. Clopidogrel remains important when bleeding risk is high, when potent agents are unsuitable, or when oral anticoagulation is also required.

Unfractionated heparin is commonly used during PCI, and enoxaparin is an alternative in selected settings. Fondaparinux may be used in conservatively managed non-ST-elevation ACS, but unfractionated heparin is required during PCI to reduce the risk of catheter thrombosis. Bivalirudin is an option in selected patients. Anticoagulant choice and dose should take account of renal function, body weight and bleeding risk[1,2].

4. DAPT DURATION AND DE-ESCALATION

Twelve months of DAPT with aspirin and a P2Y12 inhibitor remains the usual starting strategy after ACS for patients who are not at high bleeding risk[1,2]. Longer treatment may be considered when ischaemic risk remains high and bleeding risk is low, but the decision should be revisited rather than continued automatically.

For patients at high bleeding risk, abbreviated DAPT is an important option. In MASTER DAPT, among selected high-bleeding-risk patients who had undergone PCI and remained suitable for randomisation, one month of DAPT followed by single antiplatelet therapy was non-inferior for net adverse clinical events and reduced bleeding compared with a longer regimen[9]. Other trials evaluated aspirin withdrawal with continuation of a P2Y12 inhibitor. In TWILIGHT, ticagrelor monotherapy after three months of DAPT reduced clinically relevant bleeding without an increase in ischaemic events[10]. TICO and ULTIMATE-DAPT also reported less bleeding with ticagrelor alone after an initial DAPT period, without a significant increase in major ischaemic outcomes[11,12]. These results support aspirin withdrawal in selected, clinically stable patients, but they do not establish that every patient, or every P2Y12 inhibitor, can be managed in the same way.

The timing of aspirin withdrawal is important. In NEO-MINDSET, early potent P2Y12-inhibitor monotherapy after PCI did not meet non-inferiority compared with standard DAPT, and the excess ischaemic risk was concentrated in the first month[13]. The early post-ACS period therefore remains particularly important for protection against stent thrombosis. De-escalation, such as switching from a potent P2Y12 inhibitor to clopidogrel or reducing drug intensity after the first month, may be considered in selected patients in line with guideline recommendations[1,2].

After DAPT, long-term single antiplatelet therapy is generally continued. The choice of agent should reflect the patient's clinical history, tolerance, bleeding risk and current guideline recommendations[1,2]. The principal trials discussed above are summarised in Table 3.

Table 3: Principal Randomised Trials Informing P2Y12-Inhibitor Selection and DAPT Duration After Acute Coronary Syndrome or PCI

Trial	Comparison	Principal finding
PLATO[6]	Ticagrelor vs clopidogrel in ACS	Fewer cardiovascular deaths, myocardial infarctions or strokes with ticagrelor; non-CABG major bleeding increased
TRITON-TIMI 38[7]	Prasugrel vs clopidogrel in ACS scheduled for PCI	Fewer ischaemic events with prasugrel; major and fatal bleeding more frequent
ISAR-REACT 5[8]	Ticagrelor vs prasugrel-based strategy in ACS	Fewer ischaemic events with the prasugrel-based strategy; major bleeding similar; open-label design
MASTER DAPT[9]	One month of DAPT then single antiplatelet therapy vs longer DAPT in high-bleeding-risk patients after PCI	Non-inferior for net adverse clinical events; reduced bleeding
TWILIGHT[10]	Ticagrelor monotherapy after three months of DAPT vs ticagrelor plus aspirin after PCI	Less clinically relevant bleeding without an increase in ischaemic events
TICO[11]	Ticagrelor monotherapy after an initial DAPT period vs ticagrelor plus aspirin in ACS	Less bleeding without a significant increase in major ischaemic outcomes
ULTIMATE-DAPT[12]	Ticagrelor alone vs ticagrelor plus aspirin from month 1 to month 12 after PCI in ACS	Less bleeding without a significant increase in major ischaemic outcomes
NEO-MINDSET[13]	Potent P2Y12-inhibitor monotherapy immediately after PCI vs standard DAPT in ACS	Non-inferiority not met for ischaemic outcomes; excess ischaemic risk concentrated in the first month

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

5. SPECIAL PATIENT GROUPS

Older adults and frail patients face substantial competing risks of ischaemia and bleeding. Age alone should not determine treatment, but frailty, low body weight, renal function, previous bleeding and drug tolerance should influence the choice and intensity of antiplatelet therapy. Clopidogrel or a reduced-intensity strategy may be reasonable when bleeding risk is prominent, provided that early protection after ACS is not compromised[1,2].

CKD increases both thrombotic and bleeding complications. Renal function should guide anticoagulant selection and dosing, and advanced kidney disease may support consideration of a shorter DAPT course. Evidence in patients with severe renal impairment or those receiving dialysis remains limited; treatment should be individualised with close monitoring[1,2,4].

Patients with atrial fibrillation or another indication for long-term oral anticoagulation require particular care because triple therapy increases bleeding. In AUGUSTUS, an apixaban-based strategy caused less bleeding than a vitamin K antagonist, and aspirin increased bleeding when added to an oral anticoagulant plus a P2Y12 inhibitor[14]. Current guidance therefore favours limiting triple therapy to the shortest appropriate period, followed by an oral anticoagulant plus clopidogrel in most suitable patients. The duration depends on coronary and embolic risks. A proton-pump inhibitor is appropriate when gastrointestinal bleeding risk is increased, and potent P2Y12 inhibitors are generally avoided as part of triple therapy[1,2].

6. PCI-RELATED CONSIDERATIONS AND BLEEDING MANAGEMENT

Bleeding risk is influenced by procedural practice as well as by drug selection. Radial access reduces access-site bleeding and vascular complications compared with femoral access and is recommended when feasible. In non-ST-elevation ACS, routine P2Y12 pre-treatment is generally avoided when early angiography is planned. During PCI, unfractionated heparin is commonly used, while glycoprotein IIb/IIIa inhibitors are usually reserved for selected bailout situations[1,2].

When bleeding occurs, clinicians should promptly assess its severity and the patient's haemodynamic status. Minor bleeding may be managed with local measures and a review of contributing medicines. Major bleeding may require resuscitation, endoscopic or surgical control, correction of reversible factors and temporary interruption of antithrombotic treatment. Gastroprotection should be considered in patients at increased gastrointestinal risk[1,2].

Reversal depends on the anticoagulant involved. Protamine reverses unfractionated heparin; specific reversal agents or prothrombin complex concentrate may be used for life-threatening bleeding associated with selected oral anticoagulants. No specific antidote is routinely available for P2Y12 inhibitors. Antithrombotic treatment should be restarted once haemostasis is secure, with timing and intensity determined by the bleeding site, its severity and the risk of thrombosis. Decisions after major bleeding, particularly intracranial haemorrhage or recent PCI, should involve the relevant specialist teams[1,2].

7. CURRENT EVIDENCE AND CONCLUSION

Current European and American guidelines retain 12 months of DAPT as the default for many patients without high bleeding risk, while supporting shorter regimens in selected patients[1,2]. Trials of ticagrelor monotherapy after an initial DAPT period show reduced bleeding in selected patients, whereas NEO-MINDSET cautions against routine aspirin withdrawal immediately after PCI[10–13]. Further research is needed to clarify the optimal single antiplatelet agent and the best strategies for patients with advanced kidney disease, frailty or medically managed ACS.

Evidence from Indian populations remains limited. The Kerala ACS Registry documented the presentation, management and outcomes of more than 25,000 ACS admissions and highlighted the need to improve the delivery of evidence-based care[15]. Differences in body weight, comorbidity, access to medicines and affordability may influence both bleeding and adherence. Prospective Indian registries and pragmatic multicentre studies are needed to validate risk tools and to inform locally appropriate treatment.

Antithrombotic therapy after ACS should not be regarded as a fixed regimen for every patient. Aspirin with a potent P2Y12 inhibitor remains an appropriate initial strategy for many, but treatment duration and intensity should be reassessed as the patient's condition evolves. Shorter DAPT and aspirin withdrawal can reduce bleeding in selected patients, while premature de-escalation may expose patients to early ischaemic events. The preferred strategy is one that balances both risks and can be followed consistently.

FUNDING

The authors received no external funding for the preparation of this review article.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest related to the publication of this review article.

AUTHOR CONTRIBUTIONS

Abinash K: Conceptualisation, literature search, manuscript preparation, drafting and critical revision.

Monica K: Literature review, critical evaluation and manuscript revision.

Manisha M: Scientific supervision, critical review and final approval.

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HOW TO CITE: Manisha. M., Abinash. K., Monica. K., Antithrombotic Therapy After Acute Coronary Syndrome: Balancing Ischaemic Protection and Bleeding Risk, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 3638-3643. https://doi.org/10.5281/zenodo.24394566