

The management of antiplatelet therapy in acute coronary syndrome patients with thrombocytopenia: a clinical conundrum

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Dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y₁₂ receptor antagonist is a fundamental component of acute coronary syndrome (ACS) management, with longstanding endorsements by both the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) and the European Society of Cardiology (ESC).^{1,2} Dual antiplatelet therapy reduces the risk of both stent thrombosis and spontaneous ischaemic events, at the cost of an increased bleeding risk.^{3,4} The management of antiplatelet therapy in ACS patients with thrombocytopenia poses a particular challenge for physicians, as they are at higher risk of both bleeding and, paradoxically, ischaemic events.⁵ Unfortunately, there are currently no guideline recommendations or consensus reports to guide clinicians on the management of this cohort. In this setting, we examine the evidence to date and provide our opinion on future directions and management strategies for this group (Figure 1).

Including the excluded

The reported prevalence and incidence of thrombocytopenia among patients with ACS has varied depending on the definition and the nature of the study. Observational evidence suggests that baseline thrombocytopenia, defined as a platelet count of $<150 \times 10^9/L$, is present in approximately 5% of ACS patients,^{6,7} whereas incident thrombocytopenia can be expected in 13% of patients.⁶ Incident thrombocytopenia can be seen more frequently in patients who are older or have diabetes, renal insufficiency, heart failure, or prior cardiovascular disease.⁶

Despite making up a substantial proportion of ACS patients in clinical practice, these patients have been excluded or under-represented in important clinical trials evaluating antiplatelet therapies in ACS

patients. Patients with thrombocytopenia were excluded from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38,⁸ the PLATelet inhibition and patient Outcomes (PLATO) trial,⁹ the Cangrelor versus standard therapy to achieve optimal Management of Platelet Inhibition (CHAMPION) PHOENIX trial,¹⁰ and represented only 0.8% of the participants in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.¹¹

Prognostic implications

The presence of thrombocytopenia in ACS patients predicts significantly worse outcomes.^{6,7} Yadav *et al.* examined the implication of baseline thrombocytopenia on clinical outcomes in 10 603 patients who underwent percutaneous coronary intervention (PCI) for non-ST-elevation ACS (NSTEMI-ACS) or ST-elevation myocardial infarction (STEMI) pooled from two large-scale randomized trials.⁷ In multivariable analysis, the presence of thrombocytopenia at baseline was an independent predictor of mortality at 1 year [hazard ratio (HR), 1.74; 95% confidence interval (CI), 1.12–2.69; $P = 0.01$], ischaemic target lesion revascularization (HR, 1.37; 95% CI: 1.04–1.81; $P = 0.03$), and major adverse cardiac events (HR, 1.39; 95% CI: 1.09–1.79; $P = 0.009$).⁷ The authors found no association between baseline thrombocytopenia and major or minor bleeding rates at 30 days, however, they noted that their cohort of patients only included patients with mild thrombocytopenia (platelet count of $100 \times 10^9/L$ – $150 \times 10^9/L$).

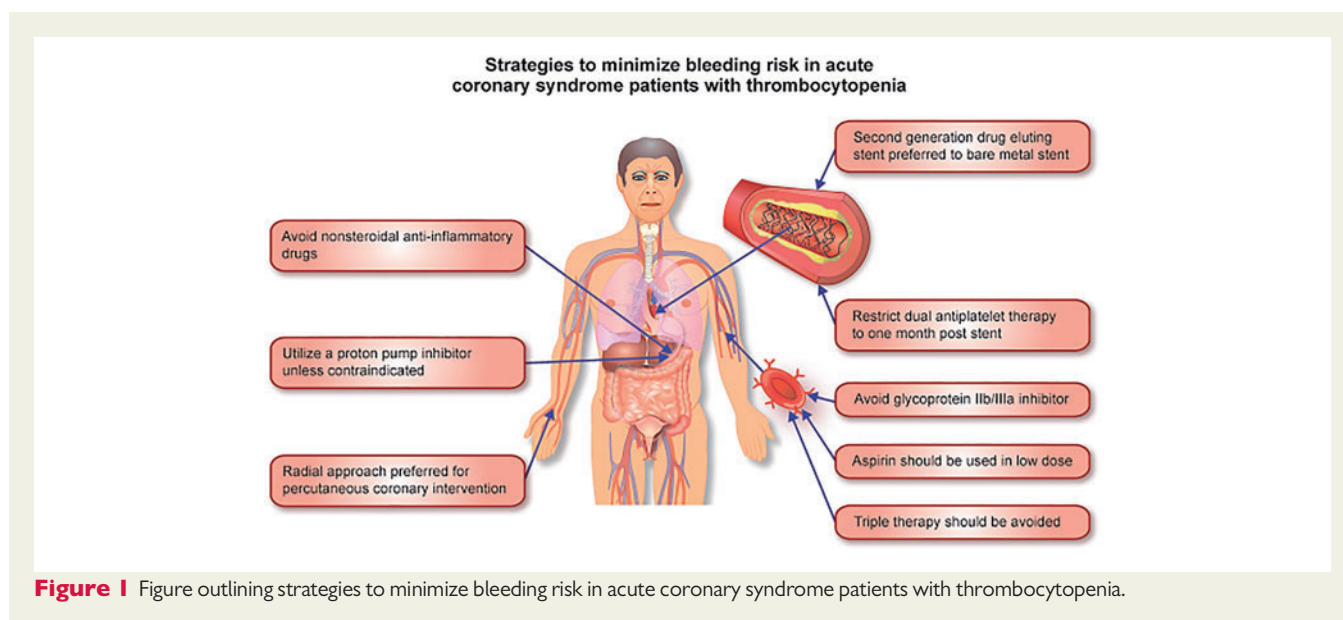
Wang *et al.*⁶ investigated the effect of incident thrombocytopenia on outcomes in 36 182 NSTEMI-ACS patients participating in the Can

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Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) quality improvement initiative. Risks of inpatient mortality and bleeding correlated directly with severity of thrombocytopenia and even mild thrombocytopenia (platelet nadir 100 to $149 \times 10^9/L$) was associated with increased risks of mortality [adjusted odds ratio (OR), 2.01; 95% CI: 1.69 to 2.38] and bleeding (adjusted OR, 3.76; 95% CI: 3.43 to 4.12). Every 10% decrease in platelet count was associated with increased mortality (adjusted ORs: 1.39, 95% CI: 1.33 to 1.46) and bleeding risk (adjusted OR: 1.89, 95% CI: 1.83 to 1.95). Ominously, approximately one in four patients who developed moderate/severe thrombocytopenia did not survive the hospitalization.⁶ The influence of the aetiology of thrombocytopenia on prognosis and treatment has not been well investigated and warrants exploration. Liver disease in particular is associated with coagulation disorders as well and therefore may carry even greater bleeding risk in the setting of thrombocytopenia.

The association of thrombocytopenia and increased ischaemic events remains poorly understood. It may reflect the presence of a greater degree of comorbidities that are unmeasured. Some authors have suggested that thrombocytopenia in ACS may reflect a greater burden of atherosclerosis predisposing to heightened platelet consumption, or reflect clinically significant thrombosis, and consequently, its presence should be viewed as a marker of disease severity.^{5,12}

Management strategies and future directions

Has this common and high-risk group of patients been neglected by the research community to date? This appears to be the case, with an absence of evidence to guide physicians on the management of this cohort leading to a sense of despair amongst clinicians, as summarized by Warkentin *et al.* in an editorial 'We know that

Table 1 Classification of thrombocytopenia

Classification	Platelet count
Mild	$<150 \times 10^9/L$ but $\geq 100 \times 10^9/L$
Moderate	$<100 \times 10^9/L$ but $\geq 50 \times 10^9/L$
Severe	$<50 \times 10^9/L$

Table 2 Strategies to minimize bleeding risk in patients with significant thrombocytopenia

- Avoid non-steroidal anti-inflammatory drugs
- Avoid glycoprotein IIb/IIIa inhibitors
- Utilize a proton pump inhibitor unless contraindicated
- Aspirin should be used in low-dose form
- If a patient is already receiving a long-term anticoagulation agent, triple therapy should be avoided
- If a patient is undergoing percutaneous coronary intervention:
 - Radial approach preferred to femoral approach
 - Restrict dual antiplatelet therapy to 1 month post-stent
 - Second generation drug-eluting stent preferred to bare-metal stent

thrombocytopenia is bad, but we do not think we can do anything about it'.¹² It is our belief that positive steps can be made and should begin with randomized clinical trials evaluating the safety and efficacy of various antiplatelet regimens in this cohort.

A comparative study of DAPT vs. aspirin or P2Y₁₂ inhibitor monotherapy in ACS patients with thrombocytopenia would be valuable. Sub-analysis of patients with varying degrees of thrombocytopenia would help determine the platelet count at which these regimens reach a 'tipping point', where the bleeding risk outweighs any ischaemic benefit. Of the P2Y₁₂ inhibitors, clopidogrel offers a lower

bleeding risk compared with ticagrelor or prasugrel,^{3,8} and accordingly would be the agent of choice in patients receiving DAPT in such a trial. An interesting alternative approach would involve utilizing an intravenous antiplatelet agent such as cangrelor in this cohort. Cangrelor has a plasma half-life of approximately 3–6 min and platelet function is restored within 1 h after cessation of the infusion. Therefore, such an agent may be advantageous in patients at higher risk of bleeding events. Indeed, in the CHAMPION PHOENIX trial, cangrelor significantly reduced the rate of ischaemic events (including stent

thrombosis) compared with clopidogrel, with no significant increase in severe bleeding or transfusions.¹⁰ However, patients with a platelet count of $<100 \times 10^9/L$ were excluded from this trial. As such, the bleeding risk associated with cangrelor might be significant if used in patients with platelets below this threshold. Nevertheless, an investigation of cangrelor in the inpatient setting as both monotherapy or as part of a combination regimen in this cohort might be worthwhile.

Thrombocytopenia can generally be classified as mild, moderate, or severe (Table 1). While a patient's risk of bleeding can increase

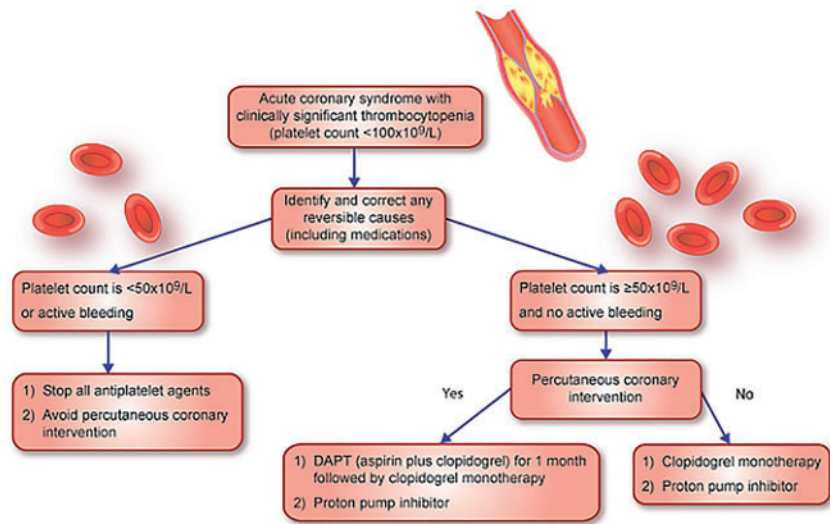


Figure 2 Figure outlining approach to acute coronary syndrome patients with thrombocytopenia.

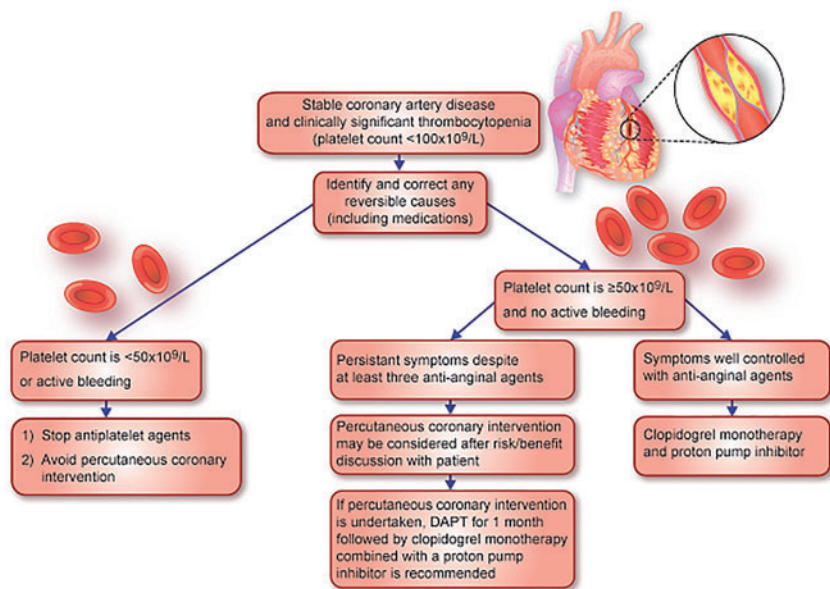


Figure 3 Figure outlining approach to stable coronary artery disease patients with thrombocytopenia.

even with mild thrombocytopenia,⁶ we believe a platelet count of $<100 \times 10^9/L$ is clinically relevant, and warrants proactive measures to reduce the risk of bleeding (Table 2). What approach could clinicians take until further randomized trial evidence is available? We believe initial management should begin with identification and correction of any reversible causes of thrombocytopenia. If suspected as the instigating factor, medications associated with the development of thrombocytopenia such as unfractionated heparin, glycoprotein IIb/IIIa inhibitors, furosemide, NSAIDs, and penicillin-based antibiotics should be discontinued.

It is our opinion that clopidogrel monotherapy should be administered to ACS patients with thrombocytopenia who are not undergoing PCI if their platelet count is $<100 \times 10^9/L$ but $\geq 50 \times 10^9/L$ and in the absence of bleeding (Figure 2). We suggest clopidogrel as opposed to aspirin monotherapy based on the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) randomized controlled trial. This trial demonstrated a statistically significant relative risk reduction in gastrointestinal bleeding with clopidogrel 75 mg as opposed to aspirin 325 mg (relative risk reduction of 31.8%, CI: 7.9–49.5, $P=0.012$).¹³ Due to their association with higher bleeding rates³, we propose prasugrel and ticagrelor be avoided in this cohort, though their study as monotherapy, particularly of ticagrelor with its twice daily dosing and reversible binding, would be of great interest. In patients with a platelet count $<50 \times 10^9/L$ or in the setting of active bleeding, we advise stopping all antiplatelet therapy and avoidance of PCI. The addition of a proton pump inhibitor would likely reduce the rates of gastrointestinal bleeding and would be advised.¹⁴ In ACS patients with thrombocytopenia undergoing PCI, second generation drug-eluting stents are preferable to bare-metal stents. While traditional teaching would advise the utility of bare-metal stents in patients at higher risk of bleeding, two recent randomized trials—Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) and Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS)—demonstrated superior outcomes with second generation drug-eluting stents compared with bare-metal stents in patients at high bleeding risk (including patients with thrombocytopenia) who may need a shorter duration of DAPT.^{15,16} Based on the limited data from these trials, we would recommend that stented patients with ACS who have a platelet count of $<100 \times 10^9/L$ but $\geq 50 \times 10^9/L$ receive DAPT with aspirin and clopidogrel for 1 month followed by a single antiplatelet agent thereafter.

Finally in patients with stable coronary artery disease, in the absence of evidence, we suggest stopping antiplatelet therapy and avoiding PCI in patients with a platelet count $<50 \times 10^9/L$. In thrombocytopenic patients with a platelet count $\geq 50 \times 10^9/L$ and $<100 \times 10^9/L$, we advise clopidogrel monotherapy and a proton pump inhibitor. If a patient's symptoms persist despite three antianginal agents at maximally tolerated doses, then PCI is reasonable after a risk/benefit discussion with the patient (Figure 3). If PCI is undertaken, we recommend a second generation drug-eluting stent in combination with DAPT with aspirin and clopidogrel for 1 month followed by clopidogrel thereafter, along with a proton pump inhibitor.

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