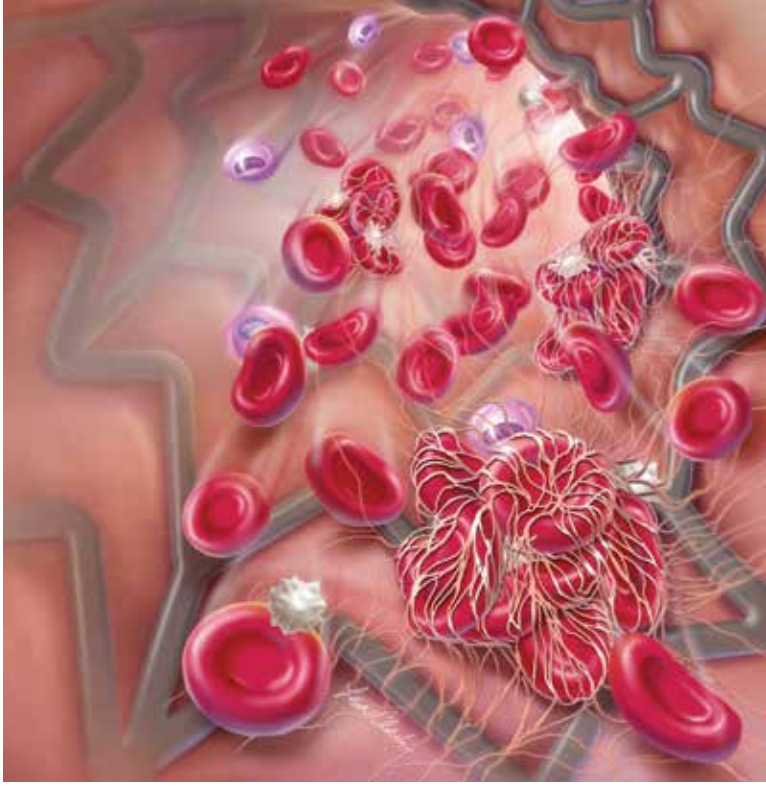
Duration of dual antiplatelet therapy after ACS

A moving target



ADAM J. NELSON BMedSc, MB BS
MATTHEW I. WORTHLEY MB BS, PhD, FRACP

Secondary prevention with dual antiplatelet therapy (DAPT) is recommended for most patients after acute coronary syndrome. The optimal duration of DAPT (ranging from 14 days to more than 12 months) is influenced by factors such as the nature of the index cardiac event, extent and complexity of angiographic disease and stenting procedure, and balance of long-term ischaemic versus bleeding risk.

Acute coronary syndrome (ACS) remains the major cause of morbidity and mortality in Australia, costing more than $5 billion to our healthcare system in 2010.[1] The greatest risk factor for ACS is a previous ACS, and almost one-third of the financial impost of all ACS is driven by repeat events.[1] Secondary prevention through lifestyle changes and pharmacotherapy remains pivotal to reducing the burden of ACS on patients and our healthcare system.

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Dr Nelson is an Advanced Trainee in the Department of Cardiology, Royal Adelaide Hospital; Clinical Lecturer in the Discipline of Medicine, University of Adelaide; and Research Fellow in the South Australian Health and Medical Research Institute, Adelaide. Associate Professor Worthley is an Interventional Cardiologist in the Department of Cardiology, Royal Adelaide Hospital; Associate Professor in the Discipline of Medicine, University of Adelaide; and Research Fellow in the South Australian Health and Medical Research Institute, Adelaide, SA.

Understanding the risks and benefits of prolonged administration of medication is extremely important in any setting but particularly so in the case of blood-thinning agents. This article focuses on the evolution of prescribing habits for dual antiplatelet therapy (DAPT) as the basis for deciding the duration of DAPT in patients who have experienced ACS.

ACS and antiplatelet agents

The emerging focus on reperfusion therapy mandates the subclassification of patients with ACS by the presenting ECG. However, irrespective of whether a patient presents with ST segment elevation or non-ST segment elevation, and with a myocardial infarction or unstable angina pectoris, the pathology is the same.[2] Although recent evidence has suggested the new concept of 'plaque erosion' as a contributor to ACS, the major pathology involves local inflammation, 'vulnerable' plaque, vasoconstriction and platelet-rich thrombus. It is therefore logical that, in the context of coronary artery disease, antiplatelet agents have been the mainstay of therapy.

Aspirin has improved outcomes in patients presenting with ACS for over three decades and continues to be the cornerstone of antithrombotic therapy.[3,4] Despite aspirin use, however, rates of repeat atherothrombotic events remained unacceptably high, driving the development of more potent antiplatelet agents. A focus on the adenosine diphosphate (ADP) receptor-mediated pathway of platelet aggregation led to the evaluation of $P2Y_{12}$ receptor blockers as antithrombotic therapy. Although the first-in-class $P2Y_{12}$ receptor antagonist ticlopidine was effective, it had an unacceptable side effect profile.[5] This led to the development of a second $P2Y_{12}$ receptor antagonist clopidogrel.

The birth of DAPT: clopidogrel

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial was a landmark study showing improved outcomes

in an ACS cohort treated with aspirin and clopidogrel compared with aspirin alone.[6] This finding was independent of management strategy and remained if the patient was treated medically or with a stent, or even following bypass surgery, although the benefit in the bypass cohort appeared early, with no added benefit apparent following discharge.[7] The findings of this study supported continuing DAPT for at least 12 months after ACS.

Duration of DAPT: drug-eluting stent era

The application of balloon angioplasty in the 1980s to treat angiographic stenosis, although revolutionary, resulted in early recoil and restenosis in as many as 50% of patients. The introduction of bare metal stents in the mid-1990s solved the early recoil problem through scaffolding of the epicardial vessel; however, neointimal hyperplasia led to in-stent restenosis in up to 30% of patients. First-generation drug-eluting stents with their antiproliferative coating were widely adopted in 2003, following early results demonstrating restenosis rates of less than 5% and a far reduced need for revascularisation. However, meta-analysis data presented only a few years later showed increased rates of stent thrombosis, presumably secondary to impaired 're-endothelialisation' of the drug-coated stent struts.[8] Although the validity of these data has since been questioned, the uncertainty about the duration of DAPT persisted, with a preference remaining for longer duration DAPT given the significant mortality associated with acute stent thrombosis.[9]

Reassuringly, modern second-generation drug-eluting stents (introduced from 2008) have addressed the stent thrombosis issue by incorporating more 'biocompatible' or even 'bioresorbable' polymers, which adhere the antiproliferative agent to the stent, meaning they are no more thrombotic than their bare metal counterparts.[10] Furthermore, there is evolving evidence for the safety and noninferiority of shorter duration DAPT in patients undergoing elective percutaneous coronary intervention for stable ischaemic heart disease (IHD), specifically as little as one month for patients with bare metal stents and three months for those with newer generation drug-eluting stents.[11,12] Nevertheless, the preference for longer duration DAPT in patients treated with first-generation drug-eluting stents continues to drive longer periods of administration in patients undergoing all types of percutaneous coronary intervention.

Unacceptable major adverse cardiac events: more potent agents

Recurrent ischaemic events in patients receiving antiplatelet therapy have driven the development of newer, more potent antiplatelet agents.[13] The Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON) and Platelet Inhibition and Patient Outcomes (PLATO) trials recently showed that prasugrel and ticagrelor, respectively, are more efficacious than clopidogrel in high-risk ACS patients.[14,15]

Prasugrel is a thienopyridine agent, like clopidogrel, but has only a single-step metabolism. This ameliorates the problem of genetic polymorphisms seen among patients treated with clopidogrel, whereby some were deemed 'resistant'. Although prasugrel is efficacious in ACS patients, it was shown to be of benefit only in those undergoing percutaneous coronary intervention rather than medical management alone.[16] Furthermore, it was deemed less safe in specific subgroups, including the elderly (age over 75 years), leaner individuals (weight less than 60 kg) and those with comorbid renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2) or a history of intracranial haemorrhage.

Ticagrelor is a first-in-class compound that directly and reversibly inhibits the same $P2Y_{12}$ receptor as clopidogrel but has superior (and quicker) platelet inhibition. Ticagrelor has become the agent of choice for patients with high-risk, undifferentiated ACS, in whom it has greater efficacy than clopidogrel regardless of invasive or medical management strategy. Given ticagrelor's adenosine-mediated activity, it is relatively contraindicated in patients with asthma, other bronchospastic airways disease or high-degree atrioventricular block. Ticagrelor may also be less appropriate in patients whose compliance is a concern, as it requires twice-daily dosing.

Most guidelines on treatment of patients with ACS currently recommend treatment with aspirin in addition to a $P2Y_{12}$ inhibitor for 12 months after the ACS, allowing individual clinicians to prescribe ticagrelor, prasugrel or clopidogrel.[11,17]

Why is bleeding important?

Inherent in the use of more potent platelet inhibitors is a degree of obligate bleeding, and although ischaemic events are significantly reduced, the overall success of these agents is attenuated by safety concerns. Bleeding is now recognised as an independent predictor of mortality and in some studies is potentially more potent than ischaemic endpoints.[18] Mechanisms for the relation of bleeding with mortality obviously include bleeding-related death but may also involve the requirement to cease antiplatelet therapy, the development of heart failure, lowering of the ischaemic threshold or harms associated from the requisite transfusions.

Although the prevention of major adverse cardiac events remains the forefront of antiplatelet therapy, recognising bleeding risk, detecting blood loss early and mitigating factors that contribute to blood loss are all crucial to the net benefit of ongoing DAPT. We recommend that any of the following events should prompt GPs to discuss the duration of DAPT with the patient's treating cardiologist:

- a diagnosis of anaemia
- a comorbid indication for oral anticoagulation
- more than 'nuisance' bleeding
- worsening renal function.

The more the merrier: what is the optimal duration of DAPT?

With over one-third of all cases of ACS being repeat events, and over half of these resulting in death, the DAPT and PEGASUS studies both investigated prolonged DAPT in high-risk patients.[1,19,20] The DAPT study randomly allocated patients who had received DAPT for 12 months to a further 18 months of DAPT or to ongoing medical management and showed a significant halving of further myocardial events with further DAPT (2.1% vs 4.1%). This was, however, at a significant cost of moderate to severe bleeding events (e.g. haemodynamic compromise or transfusion requirement, nonfatal), with an increase in absolute

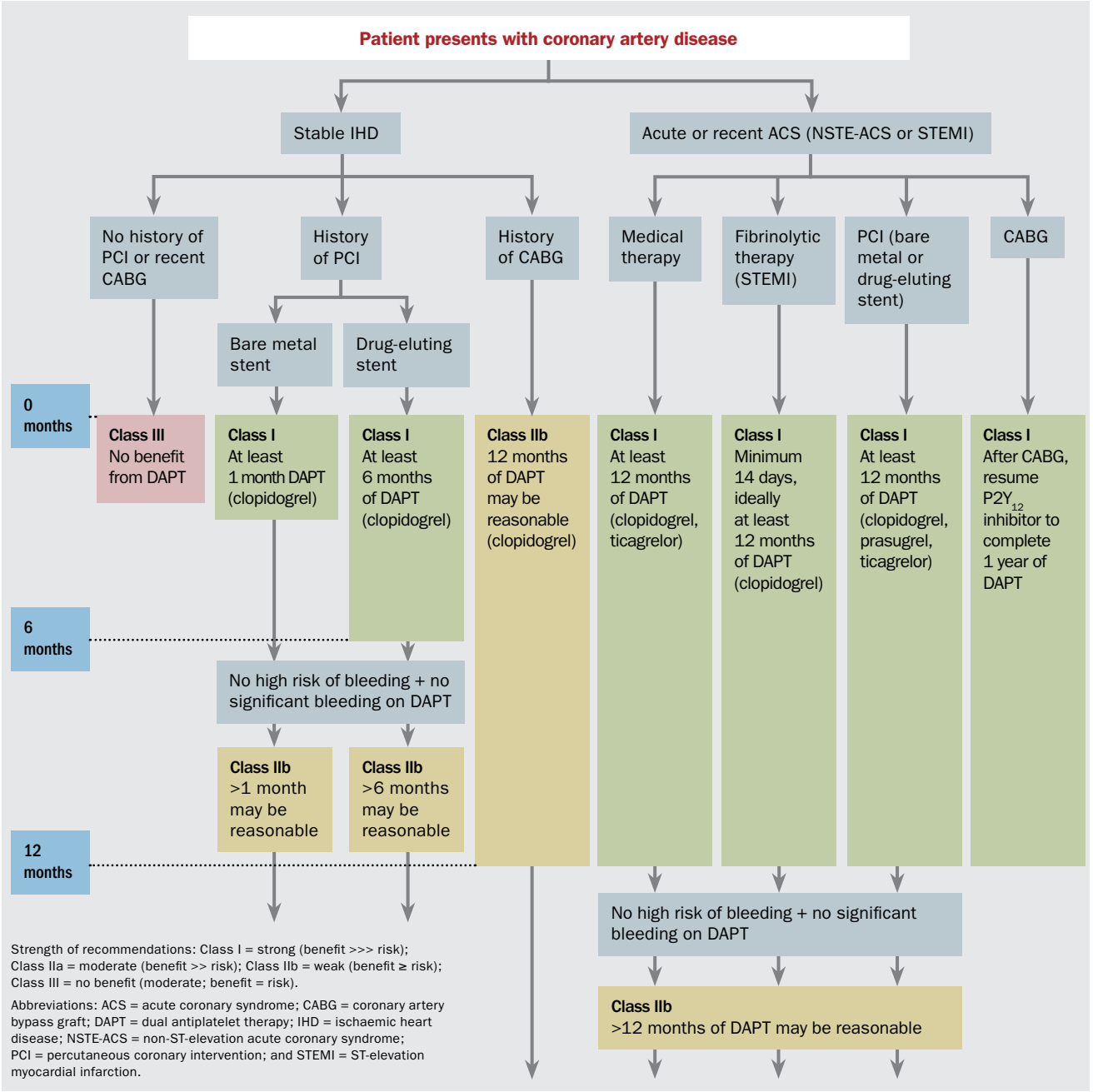

Figure 1. Master treatment algorithm for duration of DAPT in patients with either unstable or stable ischaemic heart disease.*[11]

* Developed by the American College of Cardiology and American Heart Association.

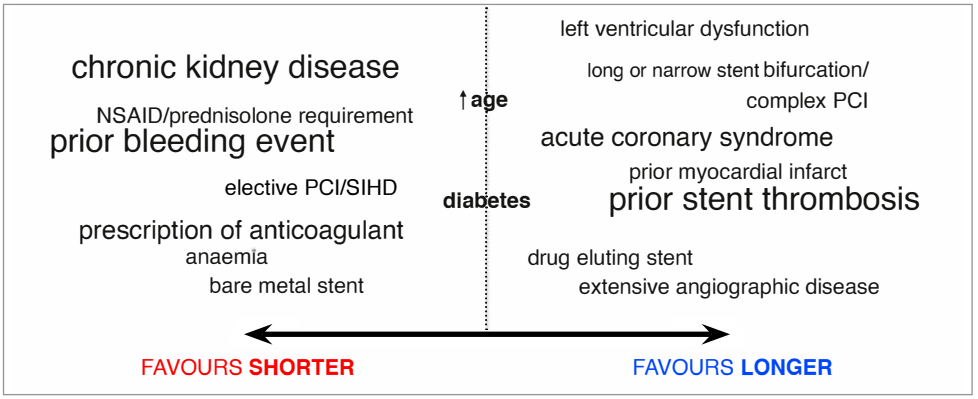

Figure 2. Factors associated with bleeding and thus favouring shorter DAPT versus factors associated with ischaemia or thrombosis and thus favouring longer duration DAPT. Diabetes and increasing age are associated with both bleeding and ischaemic risk.

Abbreviations: DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; SIHD = stable ischaemic heart disease.

risk of these bleeding events of 0.9%.[19] Patients with a prior myocardial infarction seemed to benefit more than those with stable IHD.

Longer duration DAPT was also supported in the PEGASUS study, in which high-risk patients between one and three years after a myocardial infarction were randomly allocated to ticagrelor or placebo in addition to aspirin.[20] A significant reduction in the primary endpoint (cardiovascular death, myocardial infarction or stroke) was seen in the DAPT arm, albeit at a small cost of bleeding. The benefit was greatest in the group that had ceased DAPT prior to enrolment for the shortest period of time.

These studies led to the recommendation in the recent guidelines of both the European Society of Cardiology and the American College of Cardiology that prolonged DAPT can be considered in patients with 'high ischaemic, low bleeding' risk.[11,17] Similarly, patients with 'low ischaemic, high bleeding' risk can be considered for shorter duration DAPT. As can be seen by the proposed guideline algorithm (Figure 1), the decision has become complex, with many factors needing to be considered.[11] These include the presenting nature of coronary disease (stable IHD or ACS), type of stent inserted and comorbidity profile (Figure 2). Which antiplatelet agents, in what doses and the relative contributions of each factor remain nebulous in the guidelines.

Although somewhat of a moving target, a 'DAPT score' is currently being evaluated and may be adopted in the future to help quantify the net clinical benefit of DAPT (ischaemic versus bleeding risk).[21] This score would be analogous to the CHA2DS2-VASc and HAS-BLED scores used to assess the risks versus benefits of anticoagulation in patients with atrial fibrillation.

PRACTICE POINTS

- In the ever-changing landscape of pharmacotherapy for acute coronary syndrome, the decision when to stop dual antiplatelet therapy (DAPT) has become increasingly complex.
- Recent evidence supports continuing DAPT for longer than 12 months in selected patients.
- The decision to stop or to continue DAPT needs to consider patient and disease variables, including the nature of the index cardiac event (stable versus unstable), the extent and complexity of angiographic disease and stenting procedure, and long-term ischaemic versus bleeding risk.
- With the current level of evidence and evolving heterogeneous guidelines, we recommend liaising closely with each patient's treating cardiologist to individualise decisions about ongoing antiplatelet therapy.

Conclusion

Contemporary antiplatelet agents probably provide maximal platelet inhibition with tolerable, safe bleeding in most patients for six to 12 months after ACS. However, the challenge remains to balance the competing risks of ischaemia versus bleeding. This is analogous to the decision regarding anticoagulation for patients with atrial fibrillation, where an assessment of benefit versus risk will be dynamic, particularly as many of the factors that influence the risks and benefits will change over time.

The ever-changing landscape of antiplatelet therapy has made it more difficult for primary care physicians to manage this increasingly complex issue. As outlined above, many evolving factors impact not only on the choice of antiplatelet agents but also on the duration of DAPT. Some practice points about DAPT are shown in the Box. Currently, with no simple way to quantify the risks versus benefits of antiplatelet therapy, we recommend a case-by-case individualised approach in consultation with the patient's usual cardiologist, until further studies can hopefully provide more guidance. MT

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A list of references is included in the website version of this article (www.medicinetoday.com.au).

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