

Deciding on a combination of anticoagulant and antiplatelet drugs

Patients being treated for atrial fibrillation may develop cardiovascular disease before or after the onset of their heart rhythm problem, and may require a combination of antiplatelet and anticoagulant drugs. This article describes the evidence for the combinations used to treat acute coronary syndrome in patients with atrial fibrillation.

Cardiovascular disease is one of the commonest conditions which benefit from antithrombotic therapy. There is now undisputed evidence for the place of anticoagulant therapy in reducing systemic thrombotic events and for the place of antiplatelet therapy in preventing arterial ischaemic events. In this context, it is not uncommon to find a patient who may require both antiplatelet and anticoagulant agents which clearly will have benefits but can cause unacceptable bleeding risks. This review provides the current evidence for a safe and effective strategy for treating these patients.

A patient on long-term anticoagulation who develops acute coronary syndrome

In the first scenario, a patient who is already on an anticoagulant for atrial fibrillation develops acute coronary ischaemia and is managed medically (i.e. without angioplasty). Should this patient be managed with anticoagulation, antiplatelet therapy or a combination? A meta-analysis in 2007 looked at the benefits of giving aspirin to patients on long-term oral anticoagulation (Dentali et al, 2007). It concluded that the addition of aspirin does not reduce the risk of arterial thromboembolism including myocardial infarction and stroke in patients with atrial fibrillation and/or stable coronary artery disease. However, the study did show that patients on combined therapy, compared to oral anticoagulation alone, were 1.5 times more likely to have a major bleed. This analysis did not apply to patients who required medical therapy following an acute myocardial infarction.

The randomized controlled trial, WARIS-II compared high intensity or moderate intensity warfarin plus low dose aspirin to aspirin alone following myocardial infar-

tion. This found the combination to be more effective for the prevention of non-fatal re-infarction and thromboembolic stroke (Hurlen et al, 2002). Major bleeding episodes were not more frequent among the warfarin groups. However, the incidence of minor bleeding episodes was higher in the combination group as would be expected. Another randomized controlled trial (the ASPECT-2 study) came to a similar conclusion. In this trial, patients with acute coronary syndrome were randomized to high-intensity (international normalized ratio (INR) 3.0–4.0) or moderate-intensity (INR 2.0–2.5) oral anticoagulation plus aspirin, or aspirin alone (Van Es et al, 2002). Anticoagulant treatment, either alone or in combination with aspirin, was associated with a significant reduction of mortality or cardiovascular events after 12 months, albeit with a higher risk of major bleeding (Van Es et al, 2002).

So what may be concluded regarding treatment of these patients? Current guidelines state that oral anticoagulants should not be interrupted in patients with atrial fibrillation suffering from an acute coronary syndrome (Lip et al, 2014), but that antiplatelet therapy should be added to carefully controlled anticoagulation (Figure 1). This is based on the fact that the relative risk of thrombosis is much higher than the increased risk of bleeding in these patients (Lip et al, 2010). Dual therapy is necessary with the anticoagulant and one antiplatelet agent (Faxon et al, 2011). Based on a registry analysis in patients who were continuing on dual therapy, the combination of warfarin and clopidogrel or aspirin was as effective as triple therapy in reducing myocardial infarction and recurrent coronary events with much reduced bleeding rates (Lamberts et al, 2013).

A patient on long-term anticoagulation who needs coronary stenting

Percutaneous coronary intervention with stents is increasingly being considered for patients with stable angina or acute coronary syndrome. In this setting, a period of antiplatelet therapy (aspirin and/or clopidogrel) is mandatory to reduce the risk of potentially fatal stent thrombosis until such a time as the metal struts have endothelialized. However, the choice and duration

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of antiplatelet regimen is complex and depends on multiple factors including stent type, coronary anatomy and clinical setting (Lip et al, 2014). In particular, the risk of stent thrombosis is higher following placement of coronary stents for acute coronary syndrome than for stable angina.

The only major randomized controlled trial in this setting is the WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial which compared dual therapy (warfarin plus clopidogrel) to triple therapy (warfarin plus aspirin and clopidogrel) in 573 patients (Dewilde et al, 2013). The aim of the trial was to identify any differences in any bleeding events within 1 year of follow up. Unsurprisingly, it demonstrated that dual therapy was associated with fewer bleeding complications; however, dual therapy did not lead to an increase in the rate of thrombotic events, including stent thrombosis. Interestingly, a significant reduction in mortality at 12 months was also observed with dual therapy. The drawbacks of this study are its smaller size (making it difficult to achieve statistical significance) and the fact that stent insertion was done electively in three-quarters of the patients (Lip et al, 2014), as angioplasty in the acute setting may be a risk factor for stent thrombosis (Dewilde et al, 2013). Moreover, the difference in bleeding was mostly driven by minor bleeding complications, e.g. skin haematoma.

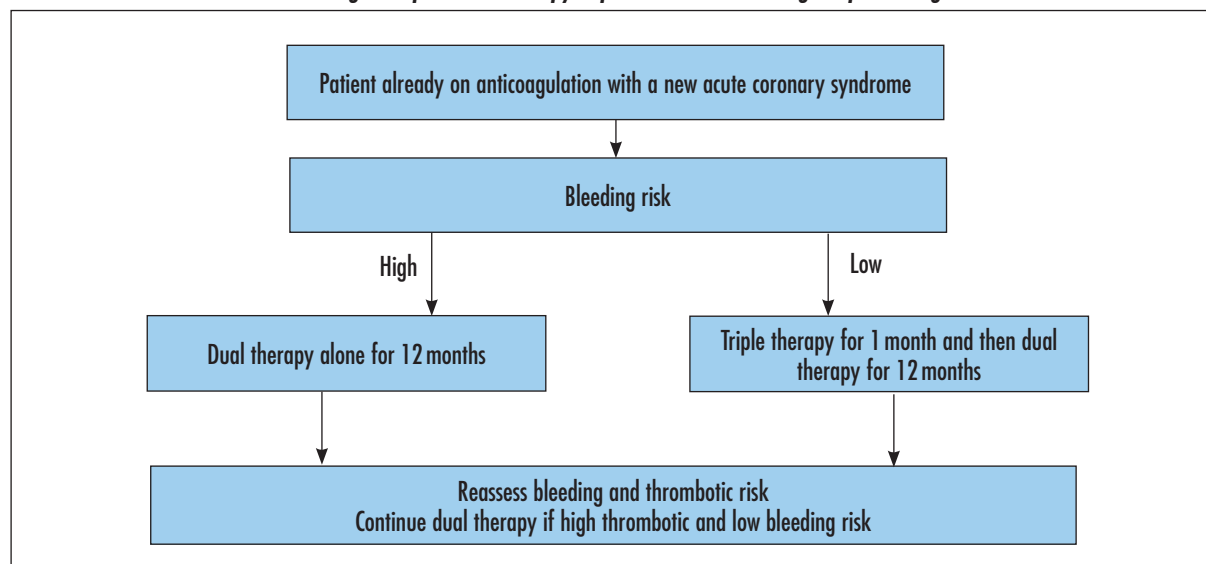
Dual or triple therapy?

The North American guidelines recommend triple therapy with aspirin, clopidogrel and oral anticoagulant agents for all patients already receiving anticoagulation for atrial fibrillation or mechanical valves who undergo percutane-

ous coronary intervention and stenting (Faxon et al, 2011). The risk of stent thrombosis and/or recurrent cardiac events is diminished 12 months after a stent insertion or acute coronary syndrome, so one of the antiplatelet agents should be discontinued, and anticoagulation continued indefinitely (January et al, 2014). The new European consensus recommends triple therapy as ideal (Lip et al, 2014). However, it takes into account bleeding risk and therefore recommends a more individualized approach. Both American and European guidelines used to suggest the preferential use of bare metal stents rather than drug-eluting stents. However, the 2014 European guidelines took into account multiple recent sources of data suggesting that newer generation everolimus-eluting stents actually have lower rates of stent thrombosis than other drug-eluting stents and even lower than bare metal stents (Lip et al, 2014). Where appropriate, bare metal stents or one of the newer drug-eluting stents with lower thrombotic risk should be preferred to minimize the duration of triple therapy (January et al, 2014; Lip et al, 2014). This recommendation is based on the fact that the risk of bleeding increases with prolonged therapy, from four-fold at 6 months to eight-fold at 12 months (January et al, 2014; Lip et al, 2014).

Bleeding with triple therapy can vary from 4.7% to 9.2% with most occurring in the first month of treatment (Orford et al, 2004; Khurram et al, 2006; Rogacka et al, 2008). This means that balancing the bleeding risk with thrombotic risk is crucial in this scenario. The MUSICA trial, a non-randomized registry trial, attempted to clarify this dilemma (Sambola et al, 2009). Three therapeutic regimens including triple therapy, dual therapy and dual antiplatelet without anticoagulation were compared. As would be expected, at 6 months, those on

Figure 1. Algorithm for the management of a patient already on anticoagulation presenting with a new acute coronary event. When dual therapy is chosen, this is with warfarin or a novel oral anticoagulant in conjunction with aspirin or clopidogrel (preferred). During combination therapy, close monitoring of anticoagulation with warfarin is recommended to avoid large fluctuations in international normalized ratio. The authors consider gastric protection therapy in patients who are taking antiplatelet agents.



triple therapy showed the greatest rate of bleeding events while no bleeding events occurred on those on dual antiplatelet therapy in patients with low thromboembolic risk. However, the dual antiplatelet therapy was also associated with no increased cardiovascular events, suggesting that triple therapy should be reserved for patients at moderate–high thromboembolic risk. Considering the small size and non-randomized nature of the trial, this conclusion should be looked at with caution. The MUSICA 2 trial will supplement this conclusion by focusing on patients with low–moderate risk of stroke (CHADS₂ ≤ 2) who are undergoing coronary stenting. This study will compare the efficacy of a combination of clopidogrel and high dose aspirin with that of triple therapy (clinicaltrials.gov NCT01141153).

A recent meta-analysis (D’Ascenzo et al, 2015) compared the efficacy of triple therapy with that of dual therapy (clopidogrel and oral anticoagulation). It concluded that dual therapy is non-inferior to triple therapy in terms of cardiac and neurological outcomes. However, the study includes limited data on patients admitted with acute coronary syndrome. The conclusions should, therefore, be judged with caution as patients with acute coronary syndrome are more thrombogenic.

Direct oral anticoagulants instead of warfarin?

Can the direct oral anticoagulants be used in place of warfarin? This issue has not been directly assessed in the big randomized trials comparing warfarin and direct oral anticoagulants in patients with atrial fibrillation, so the role of direct oral anticoagulants in secondary prevention after myocardial infarction is still uncertain. However, in these trials, some patients were already receiving antiplatelet therapy and were given lower direct oral anticoagulant doses to minimize the risk of bleeding, making analysis of the effectiveness of direct oral anticoagulants in preventing stroke or coronary events difficult. The most recent European Society of Cardiology guidelines recommend anticoagulation with warfarin (tight control; INR 2.0–2.5) or a direct oral anticoagulant and clopidogrel or aspirin (not a newer antiplatelet) for the first 12 months for a patient with atrial fibrilla-

tion and stable coronary artery disease and then monotherapy with the anticoagulant except if there is an extremely high thrombotic risk (e.g. recurrent myocardial infarctions and stents) (Lip et al, 2014). In all cases, it is wise to take into account the bleeding risk and the person’s wishes and discuss continuation of combination therapy beyond 1 year in those with low bleeding risk but high thrombotic risk.

Does adding aspirin benefit patients with atrial fibrillation on anticoagulation outside the setting of coronary artery disease?

Aspirin reduces the risk of stroke by 21% in the absence of antithrombotic therapy but vitamin K antagonists reduce the risk of ischaemic stroke by 68% in the absence of antithrombotic therapy or 52% in relation to aspirin (You et al, 2012). A meta-analysis of randomized controlled trials comparing combined therapy *vs* anticoagulant therapy alone included ten studies, totalling 4180 patients (Dentali et al, 2007). The risk of arterial thromboembolism was lower in patients receiving combination therapy than those having oral anticoagulation therapy alone. However, this advantage was limited to those patients with a mechanical heart valve and not those in atrial fibrillation or with coronary artery disease. In addition, there was no difference in all-cause mortality but major bleeding was higher in the combined group. This would suggest addition of an antiplatelet agent to anticoagulation will only benefit patients with a mechanical heart valve, especially if they had a systemic embolism despite therapeutic INR or ischaemic heart disease.

Conclusions

It is hoped that better risk stratification of thrombosis and bleeding risks in patients with atrial fibrillation leads to more appropriate and effective use of antithrombotic medications. However, with a concurrent increase in the use of antiplatelet therapies for acute coronary syndrome and particularly coronary stenting, it is likely that non-specialist physicians will frequently be faced with patients requiring combination therapies. The general approach, based on current guidelines, is that anticoagulation therapy should not be interrupted as the benefit in terms of stroke prevention greatly outweighs the increased bleeding risk. Dual therapy (anticoagulation plus either aspirin or clopidogrel) is the most likely regimen for patients with high bleeding risk who were treated conservatively following myocardial infarction. After stent insertion, triple therapy (anticoagulation, aspirin and clopidogrel) should be used, the duration of which should be balanced with the bleeding risk of the patient (*Figure 2*). In all cases, it is sensible to take a tailored approach, considering the balance of bleeding and thrombotic risks for individual patients. **BJHM**

Conflict of interest: none.

KEY POINTS

- Patients with atrial fibrillation and ischaemic cardiovascular disease may need a combination of antiplatelet and anticoagulant therapy.
- An assessment of bleeding and thrombotic risk should be undertaken in these patients regularly if they continue on combination therapy.
- In high thrombotic risk patients, triple therapy with two antiplatelet agents and an anticoagulant drug may be needed for a period of time and dual therapy after that.
- In those at high bleeding risk, the period of triple therapy should be shorter.

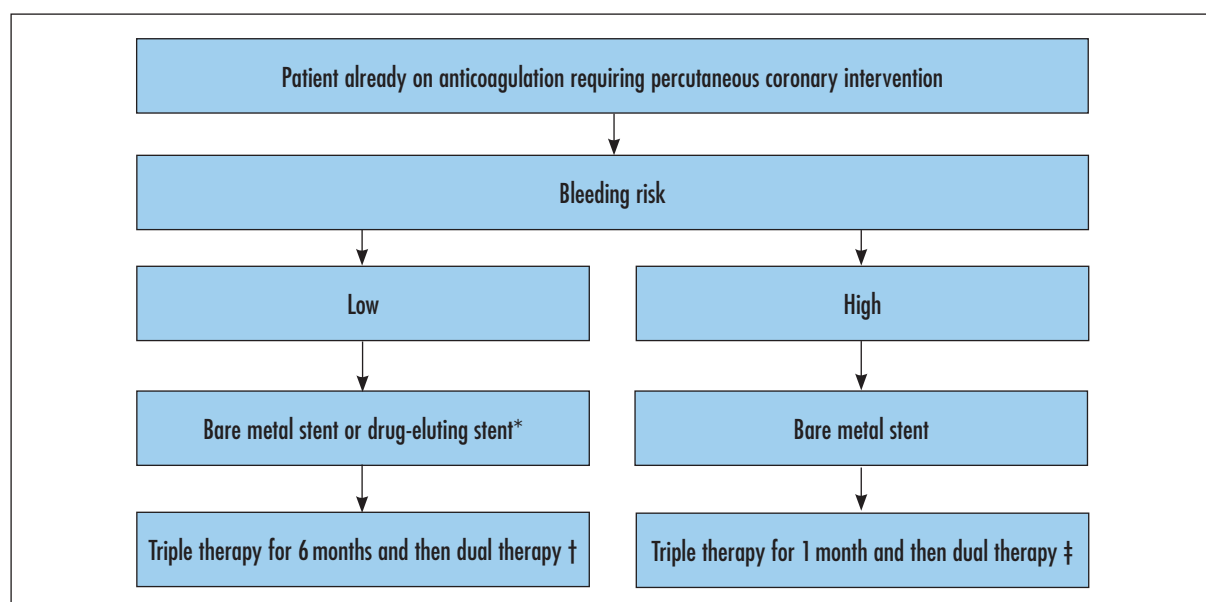


Figure 2. Algorithm for the management of a patient already on anticoagulation needing a percutaneous coronary intervention. This recommendation is primarily based on the latest European guidelines. When dual therapy is chosen, this is with warfarin or a novel oral anticoagulant in conjunction with aspirin or clopidogrel (preferred). During combination therapy, close monitoring of anticoagulation with warfarin is recommended to avoid large fluctuations in international normalized ratio. The authors consider gastric protection therapy in patients who are taking antiplatelet agents. The overall duration of combination therapy is 12 months. *New generation drug-eluting stents may be proffered over bare metal stents for patients with low bleeding risk. †If high risk of stent thrombosis, extend triple therapy beyond 6 months. ‡If low risk of stent thrombosis, give dual therapy for 12 months in selected patients.

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