Atrial fibrillation and concomitant CAD

An individualised approach to combined antithrombotic therapy

LOUISE SEGAN MB BS(Hons)
JOHN AMERENA MB BS, FRACP, FCSANZ

An individualised approach to antithrombotic management should be adopted in patients with atrial fibrillation and concomitant coronary artery disease with consideration to both bleeding and thrombotic risk.

Current guidelines on atrial fibrillation (AF) suggest an individualised antithrombotic strategy based on assessment of thrombotic and bleeding risks.[1] Patients with a high risk of stroke invariably have a high risk of major bleeding, although the net clinical benefit usually favours stroke prevention.[1]

Stroke risk assessment: CHA_2DS_2-VASc score

International guidelines strongly recommend initiating anticoagulation in patients with nonvalvular AF and a CHA_2DS_2-VASc score of 2 or greater, where the adjusted annual stroke rate is more than 2%. The guidelines also recommend considering anticoagulation in patients with a CHA_2DS_2-VASc score of 1 (annual stroke rate of 1.3%) provided there are no major contraindications to anticoagulation (Tables 1 and 2).[2]

Recent studies suggest female gender is a stroke risk modifier rather than an overall or specific risk factor.[3] This concept is reflected in the current Cardiac Society of Australia and New Zealand and National Heart Foundation guideline, which advocates the use of a genderless CHA_2DS_2-VA score.[1,4]

Key points

- **One in five patients receiving long-term anticoagulation have coronary artery disease.**
- **These patients present a unique challenge in balancing the risks and benefits of combined anticoagulant and antiplatelet therapies.**
- **The efficacy and safety of combination antiplatelet and anticoagulant therapies have been assessed recently in several trials.**
- **An individualised approach to antithrombotic management should be adopted in patients with dual indications, typically those with pre-existing nonvalvular atrial fibrillation presenting with an acute coronary syndrome, with consideration to both bleeding and thrombotic risks.**

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Dr Segan is a Cardiology Registrar at Barwon Health, Geelong.
Associate Professor Amerena is Director of the Barwon Health Cardiology Research; and Associate Professor in Medicine at Deakin University, Geelong, Vic.

Table 1. CHA_2DS_2-VASc risk criteria

Risk factor	Points*
Congestive heart failure	1
Hypertension	1
Age >75 years	2
Diabetes	1
Stroke, transient ischaemic attack, thromboembolism	2
Vascular disease (acute myocardial infarction, peripheral vascular disease)	1
Age 65 to 74 years	1
Sex category – female gender	1

* Maximum score is 9

Bleeding risk: HAS-BLED score

Bleeding risk assessment is far more challenging and variable. The HAS-BLED score is a commonly used risk assessment tool, traditionally applied to stratify bleeding risk in patients receiving warfarin (Table 3).[5] A score of 3 or greater indicates a high one-year bleeding risk on anticoagulation, sufficient to warrant greater caution and regular clinical review (Table 4).[5,6] This score does not encompass all clinically relevant factors such as known arterial venous malformations, aneurysms or history of peptic ulcer disease

Table 3. HAS-BLED risk criteria[5]

HAS-BLED risk factor	Points*
Hypertension	1
Abnormal renal and/or liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency	1
Labile international normalised ratio	1
Elderly (age >65 years)	1
Drugs and/or alcohol (1 point each)	1 or 2

* Maximum score is 9

Table 2. Annual thromboembolic risk according to CHA_2DS_2-VASc score[3]

Score	Stroke rate (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

(with or without prior bleeding). In these cases, an individualised approach and specialist opinion may be warranted. Moreover, the HAS-BLED score has not been validated in patients receiving the new oral anticoagulants such as apixaban, rivaroxaban and dabigatran.[6]

AF and concomitant CAD

Almost 20% of patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention have AF requiring long-term anticoagulation.[7] Patients with an indication for long-term anticoagulation and who have concomitant CAD present a unique challenge in balancing the risks and benefits of combined anticoagulant and antiplatelet therapies (Tables 2 and 4). Typically, this challenge arises when patients who are receiving oral anticoagulation present with an acute coronary syndrome and proceed to coronary angiography with or without percutaneous coronary intervention. Classification of antiplatelet and anticoagulant agents by mechanism and drug class is shown in the Box.

Table 4. Annual bleeding risk from anticoagulation[5]

Score	One-year bleeding risk (%)
0	0.9
1	3.4
2	4.1
3	5.8
4	8.9
5	9.1
6–9	Insufficient data

Historically, guideline recommendations in patients with dual indications (usually nonvalvular AF and an acute coronary syndrome) promoted triple therapy using warfarin and dual antiplatelet therapy (aspirin and a P2Y12 inhibitor).[8] More recently, several pivotal trials, including PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicentre Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) and AUGUSTUS trial (Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention), evaluated the risks and benefits of combined antithrombotic therapies (Table 5).[9-11] These and other earlier clinical trials demonstrated a reduction in bleeding events with nonvitamin K oral anticoagulants (apixaban, rivaroxaban and dabigatran), and similar thrombotic events compared with warfarin therapy.[12-14]

There is a rationale to temporarily combine an oral anticoagulant with two antiplatelet agents in patients with AF following an acute coronary syndrome with or without intervention. This is particularly relevant in the first 30 days after the event if the bleeding risk is not prohibitive, as the risk of recurrent ischaemia and stent thrombosis is highest during this period.[15]

The current Australian recommendations regarding antithrombotic therapies are derived from the 2018 Cardiac Society of Australia and New Zealand guidelines (Figure).[1,7,8]

- The duration of triple therapy (aspirin, P2Y12 inhibitor and an oral anticoagulant) should be as short as possible to mitigate bleeding risk while providing adequate antithrombotic cover during the initial high thrombotic risk period following an acute coronary syndrome and/or stenting. Triple therapy is typically prescribed for one month, followed by a single antiplatelet (usually clopidogrel) and oral anticoagulant (apixaban, rivaroxaban or dabigatran) for up to 12 months.
- In cases where dual antiplatelet therapy is required in combination with an oral anticoagulant, the recommended initial antiplatelet strategy is aspirin 100 mg daily and clopidogrel 75 mg daily.
- Clopidogrel is the preferred second antiplatelet agent over ticagrelor and prasugrel in the short term following an acute coronary syndrome or coronary stenting, as it has been more extensively studied.
- Patients with nonvalvular AF requiring long-term anticoagulation for stroke prevention who also warrant short-term dual antiplatelet therapy should be prescribed a nonvitamin K antagonist oral anticoagulants rather than warfarin in the absence of contraindications (creatinine clearance <25–30 mL/min or valvular AF).
- In cases of nonvalvular AF where an oral anticoagulant is used for stroke prevention, discontinuation of antiplatelet therapy should be considered 12 months following stent implantation or acute coronary syndrome or both, with continuation of oral anticoagulation as monotherapy.
- Proton pump inhibitors reduce gastrointestinal bleeding in high-risk patients taking aspirin, therefore the risk of gastrointestinal bleeding in patients on triple therapy may be reduced by concomitant administration of proton pump inhibitors. However, the recent changes to PBS prescribing may limit the dose and availability of this agent in the absence of an appropriate clinical indication, including gastroeosophageal reflux disease, scleroderma oesophagus or Zollinger-Ellison syndrome.

Finally, a collaborative, patient-centred approach is fundamental in establishing effective communication between healthcare providers to ensure continuity of care at the critical point of transition from the hospital environment back into the community. It is integral that communication from the

Classification of antiplatelet and anticoagulation therapies

Antiplatelets

- Inhibit platelet aggregation
- Prevent arterial thrombotic events (stroke, acute myocardial infarction, vascular events)
- Antiplatelet drugs
  - aspirin
  - clopidogrel
  - ticagrelor
  - prasugrel

Anticoagulants

- Prevent coagulation
- Prevent venous thrombotic events
- Anticoagulant drugs
  - vitamin K oral anticoagulant: warfarin
  - nonvitamin K oral anticoagulants: apixaban, rivaroxaban, dabigatran

Table 5. Comparison of bleeding and thrombotic events in patients receiving combination antiplatelet and anticoagulant therapies

Study	Year	Study design	Outcome
PIONEER AF-PCI[9]	2016	Randomised control trial 1. Rivaroxaban 15 mg + P2Y12 inhibitor* 2. Rivaroxaban 2.5 mg twice daily + DAPT† 3. Warfarin + DAPT†	↓ Bleeding with NOAC ⟷ Thrombotic events across groups
RE-DUAL PCI[10]	2017	Randomised control trial 1. Triple therapy (warfarin, aspirin, P2Y12 inhibitor*) 2. Dabigatran 150 mg twice daily + P2Y12 inhibitor* 3. Dabigatran 110 mg twice daily + P2Y12 inhibitor*	↓ Nonmajor bleeding in dabigatran groups ⟷ Thrombotic events across groups
AUGUSTUS[11]	2019	Randomised control trial 1. Apixaban + P2Y12 inhibitor* 2. Apixaban + DAPT† 3. Warfarin + P2Y12 inhibitor* 4. Warfarin + DAPT†	↓ Bleeding rates in apixaban groups ⟷ Thrombotic events across groups

* P2Y12 inhibitors include clopidogrel or ticagrelor.

† DAPT includes aspirin in combination with a P2Y12 inhibitor (usually clopidogrel).

Abbreviations: AUGUSTUS = Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention; DAPT = dual antiplatelet therapy; NOAC = nonvitamin K oral anticoagulant; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

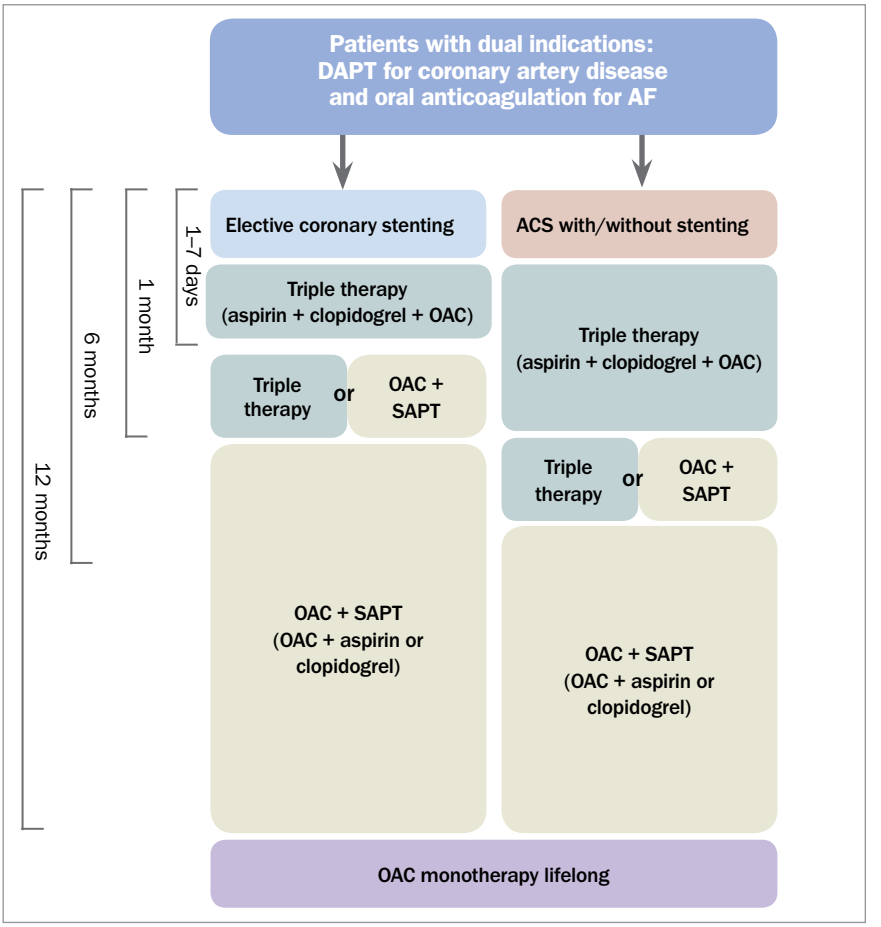

Figure. Proposed combined antiplatelet and anticoagulant strategy for patients with dual indications (coronary artery disease and atrial fibrillation) based on bleeding and thrombotic risk.

Adapted from Kirchhof P, et al. Eur Heart J 2016; 37: 2693-2962.[8]

Abbreviations: ACS = acute coronary syndrome; AF = atrial fibrillation; DAPT = dual antiplatelet therapy (aspirin and clopidogrel); OAC = oral anticoagulant; SAPT = single antiplatelet therapy (either aspirin or clopidogrel).

in-hospital treating team to primary care providers and other relevant community stakeholders outlines clear recommendations regarding dose and duration of combined antiplatelet and anticoagulant therapies in patients with dual indications.[1]

Conclusion

Patient care and individual clinical circumstances tend to change over time, highlighting the importance of integrated, co-ordinated care involving appropriate specialist follow up, regular clinical review and interval risk assessment and stratification to ensure safe prescribing of antiplatelet and anticoagulation therapies. Communication between healthcare providers and patients regarding treatment objectives, care plans and changes to patient management remains vital to maintaining the fine balance between addressing cardiovascular risk while minimising bleeding sequelae. CT

References

1. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ 2018; 27: 1209-1266.
2. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.
3. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GY. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA Score Rather than CHA2DS2-VASc? Circulation 2018; 137: 832-840.
4. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the rueo heart survey on atrial fibrillation. Chest 2018; 137: 263-272.
5. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2011; 57: 173-180.
6. Janardan J, Gibbs H. Combining anticoagulation and antiplatelet drugs in coronary artery disease. Aust Prescr 2018; 41: 111-115.
7. Brieger D, Amerena J, Attia JR, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Med J Aust 2018; 209: 356-362.
8. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893-2962.
9. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with AF undergoing PCI. N Engl J Med 2016; 375: 2423-2434.
10. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017; 377: 1513-1524.
11. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019; 380: 1509-1524.
12. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.
13. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-891.
14. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-992.
15. Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J 2014; 35: 3155-3179.

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