A GUIDE TO

deprescribing

phn TASMANIA
An Australian Government Initiative

primary health TASMANIA

CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

ANTICOAGULANTS

KEY POINTS

An initial 3 months of anticoagulation is usually indicated for acute VTE. After this, the decision of whether or not to continue anticoagulation indefinitely is made on a case-by-case basis considering the likelihood of recurrence and the patient's bleeding risk. Extended anticoagulation (beyond 3 months) should be considered in patients with PE or proximal DVT which are unprovoked, or provoked by a non-surgical transient or persistent risk factor, especially among males. The favourable efficacy and safety of low-intensity rivaroxaban and apixaban has expanded the indications for indefinite therapy for VTE.

Oral anticoagulant therapy is the cornerstone of stroke prevention in patients with AF. However, in patients at high risk of intracranial haemorrhage with anticoagulation, other strategies, such as left atrial appendage closure, might be an alternative. Aspirin is not recommended as an alternative.

No anticoagulant is without risk and ongoing re-assessment of the benefits of therapy versus the risk of bleeding is essential. In patients who require long-term anticoagulation, yearly re-assessment and discussion regarding the risks and benefits are critical.

CONTEXT

This guide considers the discontinuation of anticoagulants, when used for their principal long-term indications (following venous thromboembolism and for ischaemic stroke prevention in chronic non-valvular atrial fibrillation).

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduced frequency of thromboembolic event	**Increased Benefit** • High risk of DVT relapse (unprovoked VTE, pulmonary embolus, proximal DVT, antiphospholipid antibody syndrome, male) • High risk of AF related stroke	**Decreased Benefits** • Low risk of recurrence of clotting • Ongoing thrombophilia (e.g. Factor V Leiden)
Main Harms Bleeding	**Reduced Harm** • Concurrent PPI (reduced risk of GI bleeding) • Good INR control if on warfarin • Appropirate DOAC dose for renal clearance	**Increased Harms** • Frail, elderly or increased risk of falls • Poorly controlled hypertension • Concurrent antiplatelet agents (often antiplatelets should be deprescribed) • Renal or liver impairment • Anaemia or history of bleeding

RECOMMENDED DEPRESCRIBING STRATEGY

Although existing prediction scores for major bleeding have not yet been validated in prospective VTE studies, the following risk factors might independently predict the long-term risk of major bleeding: advanced age (e.g. >65 years), concomitant antiplatelet therapy, chronic renal impairment (creatinine clearance <50 mL/min), anaemia, and history of bleeding.[1] The presence of 2 or more of these risk factors is probably associated with a high (>2-3% annually) risk of major bleeding. It has been recommended that patients at high risk of major bleeding should discontinue long-term anticoagulation for VTE.[1]

While there are guidelines regarding the continued use of anticoagulant therapy in patients with VTE or AF, the decision to deprescribe anticoagulants needs to be individualised and consider potential benefits and harms and patient preferences. Doctors and patients should engage in shared decision making and discuss adherence, beliefs, values, risks and benefits.

BACKGROUND

VTE

Venous thromboembolism (VTE), comprising both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular condition. It affects approximately 10 million people every year worldwide (1-2 cases per 1000 population), which rises exponentially with age.[1-3] The lifetime prevalence is greater than 5%,[3,4] with more than one-half of patients with acute VTE aged over 70 years.[5] It presents with not only a high mortality, but also a high morbidity and recurrence rate.[2]

Approximately 20% of all VTE events are classified as 'provoked' because of recent immobilisation, trauma, surgery, or hospitalisation. An additional 30% of VTE events are associated with cancer, while the remaining 50% are considered 'unprovoked'.[6]

The length of treatment with anticoagulation after a VTE has been a controversial topic and depends on a number of factors. Therapy is usually continued for 3 months and there is evidence that the stoppage of anticoagulants before this time significantly increases the risk of recurrent VTE.[2,3] Whether to extend or discontinue therapy after 3 months should be decided on a case by case basis, evaluating the risk for increased bleeding against the risk of recurrent clotting.[2,6]

AF

Atrial fibrillation (AF) is the most common arrhythmia detected in clinical practice.[7,8] The prevalence of AF in Australia is 2-4% and increasing, with a predominance in older people (approximately 10% of the general population aged ≥80 years have AF). This is likely to be an underestimation because it does not include silent AF; paroxysmal AF, in particular, often remains undiagnosed. The estimated lifetime risk of developing AF is 25%. Most cases of AF in Australia are nonvalvular.[7,8]

AF is associated with a significant increase in the long-term risk of stroke (by 2 to 5-fold), heart failure, impaired quality of life and all-cause mortality. Approximately one-quarter of ischaemic strokes are due to AF, and AF-related strokes tend to be especially severe and disabling. The burden of disease appears to be increasing with a higher prevalence and rates of AF-related hospital admissions.[7,8]

Clinicians often need to make decisions to start, continue or stop oral anticoagulation and these decisions can be challenging in patients with non-valvular AF.[9] A disabling stroke is a disaster for the patient and their family, as is a disabling or fatal bleed. Perhaps unsurprisingly, there is ample evidence of both under- and over-treatment of patients with AF.[9] In a recent US study of over 15,000 nursing home residents with AF and advanced dementia, it was found that one-third remained on anticoagulation in the last 6 months of life.[10]

Currently, direct oral anticoagulants (DOACs; dabigatran, rivaroxaban and apixaban) are recommended over warfarin therapy in the management of VTE[3,4] and non-valvular AF. Warfarin remains recommended in patients with valvular AF.[7-9]

EFFICACY

VTE

Anticoagulation is indicated in most cases of VTE to reduce the extension of DVT and risk of fatal PE, and morbidity from recurrent VTE, post-thrombotic syndrome and pulmonary hypertension.[3] The post-thrombotic syndrome is a spectrum of signs and symptoms of chronic venous insufficiency, ranging from mild ankle swelling to debilitating venous claudication or leg ulcers. Moderate-to-severe post-thrombotic syndrome occurs in 20-35% of patients with DVT.[1]

Acute PE has a mortality rate of close to 25% in haemodynamically unstable patients and approximately 1.5% in haemodynamically stable patients.[11] Although PE-related death rates are declining, approximately 20% of patients with PE die within 1 year of diagnosis, albeit mostly due to comorbidities (e.g. cancer) rather than recurrent PE.[1]

The DOACs and warfarin are equally effective, with the DOACs having a strong trend to less bleeding. They also have the advantage of having few food and drug interactions, and do not require laboratory coagulation monitoring.[3,5] The oral factor Xa inhibitors (e.g. apixaban, rivaroxaban) are preferred to dabigatran or warfarin to treat proximal DVT and PE because they do not require parenteral anticoagulation for initiation,[4] and are now the preferred option for most adults with acute VTE.[3] Pooled analyses of randomised trials in acute VTE treatment indicate that in patients aged over 75 years, DOACs, when compared with warfarin, are associated with a large reduction in major bleeding and fewer VTE recurrences.[5] Direct comparisons between the DOACs are lacking for VTE.

Anticoagulation is required for at least 3 months for proximal DVT and PE. A shorter duration (e.g. 4-6 weeks) is associated with higher rates of recurrence.[2,3]

AF

Anticoagulation with warfarin reduces the risk of ischaemic stroke by around 64% and of mortality by 30% when used in patients with non-valvular AF.[5,7-9] Randomised clinical trials have shown that DOACs are as good as or better than warfarin in reducing stroke and systemic embolism, and that overall bleeding rates are less or similar to warfarin. Of note, the risk of intracranial haemorrhage is significantly reduced with DOACs compared with warfarin. DOACs also have minimal drug and food interactions, and do not need coagulation monitoring, so are much easier to use.[6] Aspirin is no longer recommended for stroke prevention in AF, largely due to significantly reduced efficacy compared to anticoagulation.[7-9]

While the DOACs have overall better or similar efficacy and safety when used in patients with non-valvular AF for stroke prevention compared with warfarin, the absolute (vs. relative) risk reductions are modest, so the number needed to treat (NNT) to prevent stroke, and to reduce intracranial haemorrhage and mortality is in the hundreds relative to warfarin e.g. approximately 130 patients with AF need to be treated with apixaban, rather than warfarin, for 2 years to prevent one death from any cause.[8]

ADVERSE EFFECTS

VTE

The estimated risk for major bleeding while receiving anticoagulation therapy following VTE is approximately 1% to 2% over 6 months, based on prospective clinical trial data.[11]

In patients with VTE receiving extended anticoagulation, major bleeding events occur at an annual rate of approximately 1-3%,[1] but is less in patients who complete 6 months of oral anticoagulants without bleeding.[1,4] As opposed to the situation of stroke prevention in AF, because anticoagulant-related major bleeds are nearly 3-times more likely to be fatal than recurrent VTE (11% vs 4%), consideration of the risk of major bleeding becomes critically important when deciding the duration of anticoagulation in VTE.[1] Assessing when the bleeding risk outweighs the benefit of anticoagulation may be difficult and is often subjective. Importantly, among patients in whom recent therapeutic anticoagulation has been prescribed with no bleeding, the subsequent risk of major bleeding is relatively low (0.8-1.6% per year), particularly with low-intensity (i.e. reduced-dose) DOACs, and similar to those not on anticoagulants.[4]

AF

About 2-3% of patients taking anticoagulants for stroke prophylaxis in non-valvular AF experience a major bleed per year (approximately 1.9-3.6% for DOACs and 3.1-4.2% for warfarin), and about half of these events are gastrointestinal (GI) bleeds.[12] DOACs have a slightly reduced overall major bleeding risk relative to warfarin (with the difference being more pronounced in countries and centres with lower time in the INR therapeutic range for warfarin), but a greater incidence of GI bleeding (increased by about 25%) and a significantly reduced (approximately halved) risk of intracranial haemorrhage.[8,9]

The HAS-BLED score (discussed later) was developed to determine the risk of bleeding (Table 3). Scores range from 0 to 9. Scores ≥3 indicate a high risk of bleeding, and the need for cautious management and regular review of the patient. However, it is not intended that HAS-BLED scoring is used to deny anticoagulant therapy in AF, but instead to allow the clinician to identify risk factors for bleeding and to correct those that are modifiable.[13]

Warfarin is implicated in many pharmacokinetic and pharmacodynamic interactions. There are far fewer such interactions for the DOACs, especially of a pharmacokinetic nature, and those that do exist usually involve combined inhibition of P-glycoprotein and CYP3A4 enzymes. Polypharmacy (> 5 drugs) is a known risk factor for adverse events with any type of oral anticoagulant. In the ARISTOTLE trial, three-quarters of patients were exposed to polypharmacy; this subgroup had increased comorbidities, more interacting drugs, increased mortality, and higher rates of both thromboembolic and bleeding complications.[14] The risk of major bleeding for patients using 6 or more concomitant drugs was significantly higher than for those using up to 5 drugs (using 0-5 drugs as reference group; 6-8 drugs: adjusted hazard ratio 1.24 (95% confidence interval (CI) 1.04 to 1.49)). Although rates of major bleeding were consistently lower with apixaban than with warfarin, the magnitude of benefit with apixaban decreased with the increasing number of concomitant drug treatments.[14]

Warfarin and DOACs cross the placenta and can be associated with adverse pregnancy outcomes. Thus, pregnant women should be treated with LMWH.[1,15] However, both warfarin and LMWHs are considered safe to use during breastfeeding, whereas DOACs are not recommended pending further evidence of safety.[1,15]

FACTORS TO CONSIDER

DVT/PE

The appropriate duration of initial anticoagulant therapy for DVT and PE is influenced by the location of the thrombosis, presence or absence of provoking factors, the patient's risk factors for recurrence of VTE or bleeding, and patient preference.[1-4,6,16-19] Distal DVT is confined to veins distal to the popliteal vein, and has a lower risk of extension and of development of PE than proximal DVT.[3,16] There are limited clinical trials of anticoagulant duration for distal DVT, with discordant results. Some suggest 6 weeks to 3 months of anticoagulation is needed, while others question the need for anticoagulation at all.[3] A common practice is to treat with therapeutic anticoagulation for 6 weeks to 3 months for symptomatic patients with a low bleeding risk and isolated distal DVT, as reflected in the Australian guidelines.[3,4] If the bleeding risk is considered high, surveillance ultrasound (at least 2 ultrasounds over 2 weeks) is a reasonable alternative. If ultrasound shows an extension of the DVT, anticoagulation should be commenced.[3]

The current guidelines recommend classifying the risks of recurrence, and suggest anticoagulation therapy of limited duration (3 months) for low-risk patients, including patients with VTE provoked by major transient risk factors such as major surgery, and anticoagulation therapy of extended duration (sometimes indefinite) for high-risk patients, including those with active cancer, previous VTE, antiphospholipid antibody syndrome or certain rare thrombophilias (antithrombin deficiency, protein C or S deficiency).[1,3,4,16,17] The most common thrombophilias e.g. heterozygous factor V Leiden and prothrombin gene mutations, have little effect on recurrence rates and do not guide the duration of anticoagulation.[3,16]

If the VTE was related to a major transient risk factor, such as major surgery or trauma, the risk of recurrence after initial anticoagulation is low at 1%-3% within 5-10 years (**Table 1**).[4,18] This is the basis for recommending time-limited treatment in such cases (**Figure 1** and **Table 2**), as well as in most cases involving a minor transient risk factor such as travel or minor surgery, although some patients in this group could be considered for extended therapy.[18]

In a meta-analysis of 18 studies involving 7515 patients with a first unprovoked VTE event who had completed at least 3 months of treatment, the risk of recurrent VTE after discontinuing anticoagulation was 10% in the first year, 16% at 2 years, 25% at five years, and 36% at 10 years, with 4% of the recurrent events resulting in death.[20]

In many cases there is an intermediate risk of recurrence[3] and extended anticoagulation therapy (sometimes indefinite) for such patients has been a matter of active debate.[2,6,17,18] Management of extended duration anticoagulation for VTE is less well defined than in AF.[21] The results of trials of extended anticoagulation with low-intensity DOACs (e.g. rivaroxaban 10 mg once daily or apixaban 2·5 mg twice daily) compared with placebo have somewhat simplified decision-making in this dilemma. These studies demonstrate a

low recurrence among patients receiving low-intensity DOAC treatment, without a significant increase in major haemorrhage.[3,17] Continuing anticoagulation beyond 3-6 months of treatment results in a reduction of 80% or more in recurrent VTE compared with placebo.[1] Strong consideration should therefore be given to indefinite low-intensity anticoagulation with DOACs for patients at intermediate risk of recurrence (e.g. non-surgical or unprovoked VTE).[2,3,11] Patient preference is important in this scenario.[3,6,16,17]

Patients who are taking extended anticoagulant therapy should be periodically re-assessed (e.g. at least annually or when their clinical condition changes), taking into account both risk of recurrent VTE and bleeding.[6,11,16]

Cancer and its treatment are associated with a 4- to 7-fold increase in risk of VTE and a higher rate of VTE recurrence.[11,17,22-25] It is estimated that around 15% of patients with cancer will experience VTE.[22,25] Thromboembolic complications are the second-leading cause of death in cancer out-patients.[23] Among patients with active cancer, the annual incidence of first VTE varies with cancer type (e.g. 3% for breast cancers, 4-7% for colon and prostate cancers, 10-12% for lung, stomach, ovary, and brain cancers, and 15% for pancreatic cancer).[1] In addition, patients with active cancer have a higher risk of bleeding, creating difficulty in achieving a good risk-benefit balance with anticoagulant therapy.[11,22,24,25] In the absence of evidence for prolonged prophylaxis, recent international guidelines suggest using primary thromboprophylaxis in only those patients with cancer considered at high risk for thrombosis and receiving systemic anti-cancer therapy, for up to 6 months after the start of chemotherapy.[22,25] Low-molecular-weight heparin (LMWH) was previously the preferred anticoagulant option, but based on clinical trial evidence, the DOACs are now being more commonly recommended by guidelines,[22,25] based on their improved efficacy, greater convenience, and lower costs.

Type of VTE	Recurrence rate at one year after stopping anticoagulation	Recurrence rate at 5 years after stopping anticoagulation
First VTE provoked by major surgery or major trauma	1%	3%
First VTE provoked by transient risk factor (non-surgical) e.g. long-distance air travel, hospitalisation for medical illness, oestrogen use	5%	15%
Provoked VTE with persistent risk factors (e.g., active cancer, inflammatory bowel disease, antiphospholipid antibody syndrome)	15%	45%
First unprovoked distal DVT	5%	15%
First unprovoked proximal DVT or PE	10%	30%
Second episode of unprovoked VTE	15%	45%

Table 1: Recurrence rates without anticoagulant therapy, after an initial anticoagulant course of 3-6 months[4]

Distal DVT caused by a major provoking factor that is no longer present (e.g. major surgery, hospitalisation with immobilisation, oestrogen therapy, and pregnancy and the postpartum period): treat for 6 weeks
Distal DVT that has been unprovoked or with persisting risk factors: treat for 3 months
Proximal DVT or PE caused by major surgery or trauma that is no longer present: treat for 3 months
Proximal DVT or PE that is unprovoked or associated with a transient (non-surgical) risk factor: treat for 3-6 months
For DVT or PE that is provoked by active cancer: treat for at least 6 months
For patients continuing with extended anticoagulation, either therapeutic or low-intensity DOAC is preferred over warfarin in the absence of contraindications
Aspirin should be avoided unless anticoagulation cannot be used

Table 2: Thrombosis and Haemostasis Society of Australia and New Zealand guidelines: evidence-based recommendations for the management of VTE[4]

AF

Anticoagulation is only recommended when the net clinical benefit of ischaemic stroke reduction outweighs the potential harm from serious bleeding, particularly intracranial haemorrhage.[7-9,26] There are many stroke and bleeding risk factors, and the more common and validated factors have been used to formulate risk stratification tools to aid decision-making about anticoagulant use. Even though risk stratification schemes in non-valvular AF are plentiful, few have been incorporated into standard guidelines, mainly due to lack of adequate validation.[27] Of the available scores the CHA_2DS_2-VASc score is simple to use, widely known, and accepted in clinical practice. Most international guidelines have adopted the potentially cumbersome practice of selecting different CHA_2DS_2-VASc thresholds for males and females when recommending anticoagulation. In contrast, the Australian guidelines recommend removing female sex as a factor (CHA_2DS_2-VA score) and provide one consistent recommendation for both sexes (**Table 3**).[7-9] It is argued that female sex alone or in the presence of one additional risk factor does not confer sufficiently or consistently increased risk.[8]

Oral anticoagulation to prevent stroke and systemic embolism is currently recommended in patients with non-valvular AF whose CHA_2DS_2-VA score is 2 or more, unless there are contraindications to anticoagulation.[7-9] Oral anticoagulation should be considered in patients with non-valvular AF whose CHA_2DS_2-VA score is 1, and is not recommended in patients whose CHA_2DS_2-VA score is 0.[7-9]

While oral anticoagulant therapy is recommended if the CHA_2DS_2-VA score is 2 or greater, it should be appreciated that the risk of stroke is much higher when the CHA_2DS_2-VA score is, for example, 6 (approximately 7.5% in 12 months) compared with a CHA_2DS_2-VA score of 2 (approximately 2% in 12 months) (**Table 4**). This translates to a NNT with anticoagulation of approximately 75 for a CHA_2DS_2-VA score of 2, versus only 20 with a CHA_2DS_2-VA score of 6, to prevent one stroke in 12 months.

It is acknowledged that the current risk calculators are subject to limitations.[21] They are over-simplistic and binary in terms of how factors are weighted in the calculations. However, co-morbidities associated with thromboembolic risk represent a range and do not equally contribute to stroke risk. Additionally, duration and frequency of AF episodes are not taken into consideration, which may have an impact on thromboembolic risk. Finally, the models do not consider bleeding risk, so a comprehensive risk-benefit decision requires a separate bleeding risk assessment.[21]

Another risk stratification tool, the GARFIELD-AF web-based risk score (https://af.garfieldregistry.org/garfield-af-risk-calculator), was developed for the prediction of all-cause mortality, ischaemic stroke/systemic embolism and haemorrhagic stroke/major bleeding.[29,30] It was derived from 39,898 patients in the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF), a global, prospective, observational study of individuals with newly-diagnosed AF. Recent external validation studies have indicated that the GARFIELD-AF model was similar or potentially superior to CHA_2DS_2-VASc in predicting ischaemic stroke/systemic embolism and comparable with standard tools (e.g. HAS-BLED) for predicting major bleeding.[31-34] An advantage of the tool is the incorporation of other medical conditions e.g. dementia and chronic kidney disease. This helps place the patient's AF and risk of stroke in context when deciding on the use of anticoagulation, especially in older patients. Not surprisingly, the GARFIELD-AF model performs significantly better than the CHA_2DS_2-VASc score for predicting all-cause mortality.[29]

Patients with AF at high risk of stroke are also generally at high risk of major bleeding.[8] The bleeding risk can be estimated using the HAS-BLED score. Although higher bleeding risk scores can be used to alert the patient and the doctor, a high HAS-BLED score, on its own, is not sufficient reason to withhold anticoagulants in AF.[7-9,26] The net benefit to the patient (at high risk of stroke) almost always favours stroke prevention with anticoagulation over the risk of major bleeding. In a recent longitudinal study using Taiwanese nationwide health insurance data, for patients with AF whose HAS-BLED scores had increased to ≥3, the continuation of anticoagulant therapy (which occurred in the majority of patients) was associated with better clinical outcomes (significantly lower risk of ischaemic stroke, major bleeding and all-cause mortality).[26]

Higher HAS-BLED scores might be used to alert the clinician to a greater need to attend to any modifiable bleeding risk factors.[8,26] For instance, the individual components of the score (such as uncontrolled hypertension, excessive alcohol intake or concomitant antiplatelet drugs), attention to falls prevention measures or addition of a proton pump inhibitor can be targeted to reduce potential risks.[9]

REGULAR REASSESSMENT AND A PATIENT-CENTRED APPROACH

Importantly, the patient's risk of either ischaemic stroke or bleeding is not a static 'one off' assessment.[26] Both change over time with aging and incident risk factors require regular re-assessment; annual review is recommended to ensure that risk is adequately characterised to guide oral anticoagulant therapy.[6,8,35]

The regular re-assessments require shared decision making with the patient after discussing the risks and benefits of the treatment strategy.[7-9] An exclusive focus on the CHA_2DS_2-VA score (and therefore the risk of ischaemic stroke) has flaws, particularly in elderly patients with co-morbidities where there are "competing risks" (likelihood of death from other causes). As mentioned above, the GARFIELD-AF web-based risk score[29] (https://af.garfieldregistry.org/garfield-af-risk-calculator) may be more useful in providing a broader view of overall mortality risk in elderly individuals.

While AF is largely a disease of the elderly, old individuals, particularly older frail adults, have been under-represented in most randomised controlled trials of anticoagulation for stroke prevention in non-valvular AF. Instead, guidance for the use of anticoagulants in the elderly has typically relied on data from large cohort studies and registries.[36] Age is a strong and independent risk factor for both ischaemic stroke and bleeding in patients with AF. Oral anticoagulation is generally associated with a net clinical benefit in elderly patients despite their elevated bleeding risk,[37] and guidelines recommend anticoagulation for all patients aged 75 years and older with non-valvular AF.[8,38]

However, aging also increases the risk of anticoagulant-associated bleeding complications and the risk of death from other causes (e.g. cancer or dementia), thereby limiting the likelihood of actualised benefit or harm from AF and anticoagulation.[38] Examining a large cohort of almost 15,000 patients aged 75 years and older with AF using a simulation model, Shah et al. estimated the net clinical benefit of anticoagulation by age.[38] They found that the net clinical benefit of anticoagulant use decreases with age beyond 75 years, and for the typical patient provides minimal benefit after age 87 years with warfarin and 92 years when using apixaban. Competing risks (death from other causes) have an important influence on this declining net clinical benefit.[38]

In contrast, in a very large observational cohort of very elderly (≥90 years of age) patients with AF from the Taiwanese nationwide health insurance database, it was found that AF was still associated with an increased risk of ischaemic stroke in this age group, antiplatelet agents showed no significant benefit, warfarin use was associated with a lower risk of ischaemic stroke, with no difference in

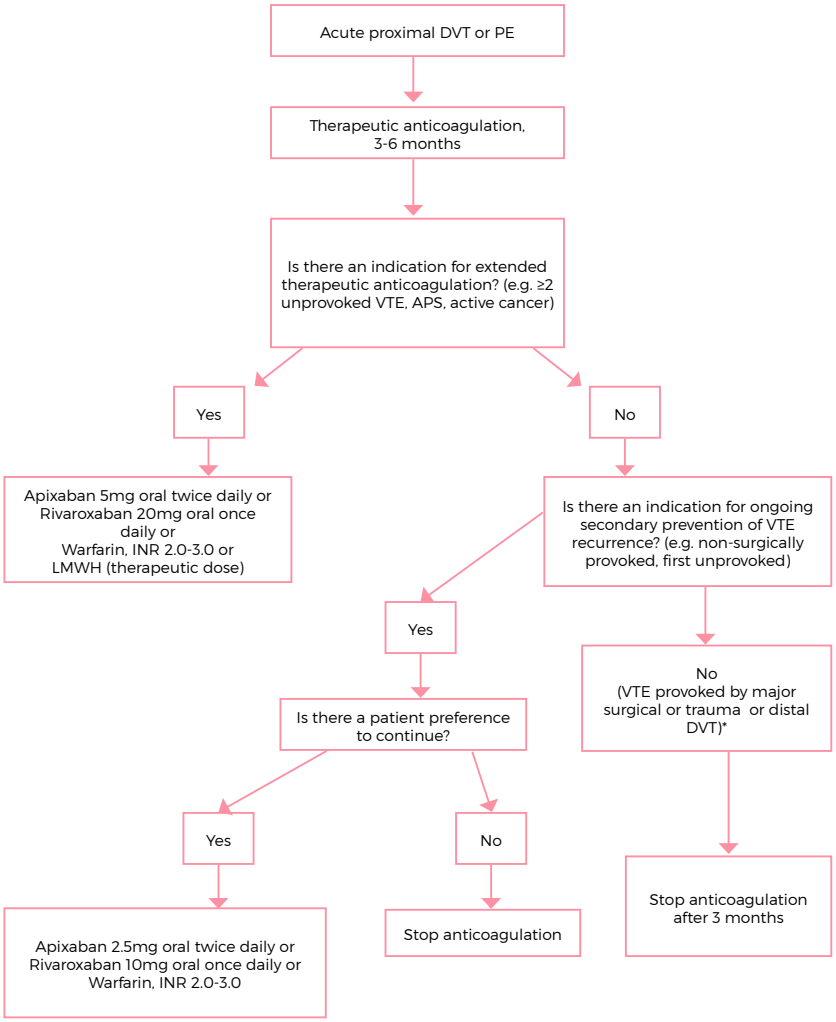

Figure 1: Recommended duration of anticoagulation for VTE[4]

APS = antiphospholipid syndrome. DVT = deep vein thrombosis. INR = international normalised ratio. LMWH = low-molecular-weight-heparin. PE = pulmonary embolism. † Warfarin is preferred in APS. ‡ For distal DVT without persisting risk, anticoagulation can stop after 6 weeks.

intracranial haemorrhage risk compared with non-warfarin treatment, and DOACs were associated with a lower risk of intracranial haemorrhage compared with warfarin.[36] The authors concluded that oral anticoagulants may still be considered as thromboprophylaxis for very elderly patients with AF, with DOACs being the more favourable choice.[36]

In a recent meta-analysis including 22 studies enrolling over 440,000 patients ≥75 years, indirect comparisons between the DOACs showed no significant differences for risk of stroke/systemic embolism, but significant differences in risk of major bleeding; apixaban was associated with a significantly lower risk of major bleeding compared with both dabigatran and rivaroxaban, while there was no significant difference between dabigatran and rivaroxaban.[39]

While patients with a high risk of falling have increased risk of intracranial haemorrhage, they also have a high risk of ischaemic stroke, and will generally benefit from anticoagulant therapy. Modelling has indicated that older people would have to fall almost 300 times a year for the risk of traumatic intracranial haemorrhage among patients on warfarin to outweigh the benefits.[8]

Oral anticoagulation for those with chronic kidney disease is complicated by at least 2 main factors.[9] The DOACs are renally excreted and therefore need dose adjustment in these patients and are not recommended in severe renal failure. While this is an evolving area,[40] at present warfarin is the only choice of oral anticoagulant for those with creatinine clearance less than 15 mL/minute or on dialysis. However, there are no reliable randomised controlled trial data that show warfarin is beneficial for stroke prevention in these patients. In addition, renal failure is associated with an increased risk of bleeding.[9]

IN FAVOUR OF DEPRESCRIBING

Serious adverse effects (e.g. intracranial haemorrhage) can be life-threatening. The threat of bleeding can also have a psychological impact on patients.[5]

There is the potential to eliminate the risks associated with drug interactions, particularly involving warfarin.

Adherence to oral anticoagulants is often sub-optimal and dosing errors are not uncommon.

Deprescribing anticoagulants will reduce the cost and inconvenience of taking drugs and, in the case of warfarin, avoid regular pathology tests.

Unstable anticoagulation (as reflected in the INR) with warfarin may be more hazardous than AF; the availability of the DOACs is clearly an advantage in this context.

There may be other management options to reduce the risk of ischaemic stroke – in particular, the potential surgical option of left atrial appendage occlusion. This approach is based on the left atrial appendage being the major site of thromboembolism in non-valvular AF (over 90% of cases). A multitude of new devices have been developed for left atrial appendage occlusion over the past decade and evidence is now quickly building that it is a safe, effective and feasible alternative to systemic anticoagulation in patients with non-valvular AF, to prevent thromboembolic events while mitigating bleeding complications and adherence issues.[41-43] Insertion of an occluder requires a period of antiplatelet or anticoagulant treatment post-deployment. In selected patients, left atrial appendage closure is comparable to oral anticoagulation for prevention of stroke with additional reduction in bleeding events, as well as cardiovascular and overall mortality. Current guidelines recommend left atrial appendage closure only for patients with AF at high risk for thromboembolism, who are unable to tolerate treatment with DOACs.[8,41,42]

AGAINST DEPRESCRIBING

There is a lack of high-quality data, with little evidence that can be used to guide well-supported recommendations around when and how to start thinking about discontinuing anticoagulation.

Studies have generally indicated that patients with AF would rather have a bleed than a stroke; stroke risk reduction and a moderate increase in bleeding risk are perceived as the most important attributes of anticoagulation treatment.[9,44] While doctors typically put more weight on bleeding risks, patients with AF are willing to accept higher bleeding risks for significant stroke risk reductions, and prefer easy-to-administer treatments (i.e. once-daily dosing, no food/drug interactions, and no need for frequent blood tests).[9,44]

Most adverse events, especially minor bleeds, should not lead to permanent oral anticoagulant discontinuation. In cases of major GI or intracranial bleeds, it is preferable to restart oral anticoagulant therapy after resolution of the bleeding episode and when the stroke risk is believed to exceed the risk of further bleeding.[8,45]

There are educational and other strategies (e.g. appropriate dosage reduction of DOACs with kidney impairment) that can maximise the benefit to harm ratio of taking oral anticoagulant therapy in non-valvular AF (e.g. **Table 5**).[8]

CHA_2DS_2-VA	SCORE	HAS-BLED	SCORE
Congestive heart failure	1	**H**ypertension (systolic blood pressure >160 mm Hg)	1
Hypertension, whether or not blood pressure is currently elevated	1	**A**bnormal renal and liver function (1 point each)	1 or 2
Age ≥75 years old	2	**S**troke	1
Diabetes mellitus	1	**B**leeding tendency/ predisposition	1
Stroke/transient ischaemic attack/thromboembolism	2	**L**abile INRs (if on warfarin)	1
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1	**E**lderly (age >65 years old)	1
Age 65–74 years old	1	**D**rugs or alcohol (1 point each) • concomitant use of antiplatelets/NSAIDs • ≥8 alcohol drinks/week	1 or 2
Maximum score	9	Maximum score	9

CHA_2DS_2-VA score = 0: oral anticoagulant or antiplatelet not recommended
CHA_2DS_2-VA score = 1: consider oral anticoagulant
CHA_2DS_2-VA score ≥ 2: oral anticoagulant recommended

Table 3: Scoring systems for assessing the risk of ischaemic stroke (CHA_2DS_2-VA) and bleeding (HAS-BLED) in patients with non-valvular AF

CHA2DS2-VA	Annual Risk of Stroke	
	Male	Female
0	0.6	0.6
1	1	1
2	2	2.3
3	3	3
4	5.3	6.7
5	6.6	9.3
6 or more	7.3	8.4

Table 4: One Year Risk of Ischaemic Stroke or Systemic Embolism in Patients with AF according to Sex and CHA_2DS_2-VA Score[28]

Domains		Rationale	Examples
A	Adherence assessment and counselling	Potentially preventable thrombosis can occur if DOACs are not administered correctly	Review medication adherence
			Reinforce importance of taking DOAC as prescribed
			Remind patients to take rivaroxaban (15 mg and 20 mg tablets) with food for optimal bioavailability
			Plan for interruption and resumption of DOACs for elective procedures associated with a bleeding risk
			Avoid interruption for very-low-bleeding-risk procedures
B	Bleeding risk assessment	Bleeding can be potentially avoided if risk factors are recognised and managed	Avoid concomitant aspirin (if not indicated), NSAIDs, and excessive alcohol consumption
		In those with a bleeding event, potential bleeding or thrombosis could be prevented by ensuring appropriate interruption and resumption of DOACs	Assess BP and treat hypertension to minimise risk of intracranial haemorrhage
			Assess for dosing error and prescribe the appropriate dose
C	CrCl (Renal function)	Potentially preventable bleeding can occur, because DOACs are cleared renally	If renal function deteriorates, then DOACs may need to be dose adjusted, discontinued, or switched to warfarin
D	Drug interactions	Potentially preventable thrombosis or bleeding can occur if DOACs are taken with P-glycoprotein or CYP450 inducers or inhibitors	Check for concomitant medications for clinically significant interactions

Table 5: Suggested follow-up checklist for patients taking a DOAC[5,46]

DISCONTINUATION SYNDROMES

None described.

REFERENCES

1. Khan F, Tritschler T, Kahn SR, et al. Venous thromboembolism. Lancet 2021;398(10294):64-77.
2. Alexander P, Visagan S, Issa R, et al. Current trends in the duration of anticoagulant therapy for venous thromboembolism: a systematic review. Cureus 2021;13(10):e18992.
3. Stevens H, Tran H, Gibbs H. Venous thromboembolism: current management. Aust Prescr 2019;42:123-6.
4. Tran HA, Gibbs H, Merriman E, et al. New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. Med J Aust 2019;210:227-35.
5. Chan NC, Eikelboom JW. How I manage anticoagulant therapy in older individuals with atrial fibrillation or venous thromboembolism. Blood 2019;133:2269-78.
6. Serhal M, Barnes GD. Venous thromboembolism: A clinician update. Vascular Medicine. 2019;24:122-131.
7. McCallum CJ, Raja DC, Pathak RK. Atrial fibrillation: an update on management. Aust Prescr 2019;42:186-91.
8. 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. Heart Lung Circ 2018;27:1209-66.
9. Lindley RI. Balancing the benefits and harms of oral anticoagulation in non-valvular atrial fibrillation. Aust Prescr 2021;44:49-52.
10. Ouellet GM, Fried TR, Gilstrap LG, et al. Anticoagulant use for atrial fibrillation among persons with advanced dementia at the end of life. JAMA Intern Med 2021;181:1121-1123.
11. Pribish AM, Secemsky EA, Schmaier AA. Venous thromboembolism for the practicing cardiologist. Cardiol Clin 2021;39:551-66.
12. Rohla M, Weiss TW, Pecen L, et al. Risk factors for thromboembolic and bleeding events in anticoagulated patients with atrial fibrillation: the prospective, multicentre observational PREvention oF thromboembolic events - European Registry in Atrial Fibrillation (PREFER in AF). BMJ Open 2019;9:e022478.
13. Tideman PA, Tirimacco R, John AS, Roberts GW. How to manage warfarin therapy. Aust Prescr 2015;38:44-8.
14. Jaspers Focks J, Brouwer MA, Wojdyla DM, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. BMJ 2016;353:i2868.
15. Scheres LJJ, Bistervels IM, Middeldorp S. Everything the clinician needs to know about evidence-based anticoagulation in pregnancy. Blood Rev 2019;33:82-97.
16. Anticoagulant therapy for proximal deep vein thrombosis and pulmonary embolism [published 2018]. In Therapeutic Guidelines: Cardiovascular, version 7 [digital]. Melbourne: Therapeutic Guidelines Limited; 2022 Mar.
17. Yamashita Y, Morimoto T, Kimura T. Venous thromboembolism: Recent advancement and future perspective. J Cardiol 2022;79:79-89.
18. Ellis MH, Avnery O. Decision-making in the management of venous thromboembolism. Am J Med 2021;134:317-25.
19. Nair S, Garza N, George M, et al. Treatment of acute venous thromboembolism. Med Clin North Am 2020;104:631-46.
20. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ 2019;366:l4363
21. Pallazola VA, Kapoor RK, Kapoor K, et al. Anticoagulation risk assessment for patients with non-valvular atrial fibrillation and venous thromboembolism: A clinical review. Vascular Medicine. 2019;24:141-152.
22. Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. Nat Rev Dis Primers 2022;8(1):11.
23. Langer F. A one-fits-all approach to cancer-associated thrombosis - Are we there yet? Trends Cardiovasc Med 2022 doi: 10.1016/j.tcm.2022.02.011

24. Giustozzi M, Franco L, Agnelli G, et al. Unmet clinical needs in the prevention and treatment of cancer-associated venous thromboembolism. Trends Cardiovasc Med 2022 doi: 10.1016/j.tcm.2022.02.003
25. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021;5:927-74.
26. Chao TF, Chan YH, Chiang CE, et al. Continuation or discontinuation of oral anticoagulants after HAS-BLED scores increase in patients with atrial fibrillation. Clin Res Cardiol 2022;111:23-33.
27. Samaras A, Doundoulakis I, Antza C, et al. Comparative analysis of risk stratification scores in atrial fibrillation. Curr Pharm Des 2021;27:1298-310.
28. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA_2DS_2-VA score rather than CHA_2DS_2-VASc? Circulation 2018;137:832-40.
29. Fox KAA, Lucas JE, Pieper KS, et al. GARFIELD-AF Investigators. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open 2017;7(12):e017157.
30. GARFIELD-AF risk calculator. Garfield-AF registry. Accessed March 25, 2022. https://af.garfieldregistry.org/garfield-af-risk-calculator
31. Fox KAA, Virdone S, Pieper KS, et al. GARFIELD-AF risk score for mortality, stroke, and bleeding within 2 years in patients with atrial fibrillation. Eur Heart J Qual Care Clin Outcomes 2022;8:214-27.
32. Dalgaard F, Pieper K, Verheugt F, et al. GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study. BMJ Open 2019;9(11):e033283.
33. Proietti M, Rivera-Caravaca JM, Esteve-Pastor MA, et al. Stroke and thromboembolism in warfarin-treated patients with atrial fibrillation: comparing the CHA_2DS_2-VASc and GARFIELD-AF risk scores. Thromb Haemost 2021;121:1107-14.
34. Gao X, Cai X, Yang Y, et al. Diagnostic accuracy of the HAS-BLED bleeding score in VKA- or DOAC-treated patients with atrial fibrillation: a systematic review and meta-analysis. Front Cardiovasc Med 2021;8:757087.
35. Bezabhe WM, Bereznicki LR, Radford J, et al. Stroke risk reassessment and oral anticoagulant initiation in primary care patients with atrial fibrillation: A ten-year follow-up. Eur J Clin Invest 2021;51:e13489.
36. Chao TF, Liu CJ, Lin YJ, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. Circulation 2018;138:37-47.
37. Rutherford O-CW, Jonasson C, Ghanima W, et al. Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation. Heart 2022;108:345-52.
38. Shah SJ, Singer DE, Fang MC, et al. Net clinical benefit of oral anticoagulation among older adults with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2019;12:e006212.
39. Silverio A, Di Maio M, Prota C, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta- analysis of 22 studies and 440 281 patients. Eur Heart J Cardiovasc Pharmacother 2021;7:f20-9.
40. Makani A, Saba S, Jain SK, et al. Safety and efficacy of direct oral anticoagulants versus warfarin in patients with chronic kidney disease and atrial fibrillation. Am J Cardiol 2020;125:210-14.
41. Narasimhan B, Aedma SK, Bhatia K, et al. Current practice and future prospects in left atrial appendage occlusion. Pacing Clin Electrophysiol 2021;44:1236-52.
42. Kleinecke C, Gloekler S, Meier B. Utilization of percutaneous left atrial appendage closure in patients with atrial fibrillation: an update on patient outcomes. Expert Rev Cardiovasc Ther 2020;18:517-30.
43. Escudero-Martinez I, Morales-Caba L, Segura T. Atrial fibrillation and stroke: A review and new insights. Trends Cardiovasc Med 2021 doi: 10.1016/j.tcm.2021.12.001
44. Wilke T, Bauer S, Mueller S, Kohlmann T, Bauersachs R. Patient preferences for oral anticoagulation therapy in atrial fibrillation: a systematic literature review. Patient 2017;10:17-37.
45. Cools F, Johnson D, Camm AJ, et al. Risks associated with discontinuation of oral anticoagulation in newly diagnosed patients with atrial fibrillation: Results from the GARFIELD-AF Registry. J Thromb Haemost 2021;19:2322-34.
46. Gladstone DJ, Geerts WH, Douketis J, et al. How to monitor patients receiving direct oral anticoagulants for stroke prevention in atrial fibrillation: a practice tool endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. Ann Intern Med 2015;163:382-5.

AUTHORSHIP

This guide was prepared for Primary Health Tasmania by Prof Greg Peterson and reviewed by the Deprescribing Project Advisory Group, Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania and Dr David Dunbabin, Geriatrician.

DEPRESCRIBING PROJECT ADVISORY GROUP

DECEMBER 2022