Oral anticoagulation for atrial fibrillation

Appropriate Care Guide

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Key messages

1. Offer anticoagulation to patients with atrial fibrillation (AF) and a modified CHA2DS2-VASc score of 2 or more.

2. Choose warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC), based on patient, drug and disease factors.
   - Warfarin and NOACs are comparable in preventing AF-related stroke and systemic embolism. NOACs are also known as direct oral anticoagulants (DOACs).
   - Warfarin is the only drug with proven safety and efficacy in patients with AF and mechanical heart valves or moderate to severe mitral stenosis.
   - Use NOACs only in patients with creatinine clearance 30 mL/min or more (using Cockcroft-Gault formula).

3. Review oral anticoagulation at least annually and when patients' clinical circumstances change.

4. Use antiplatelet agents selectively based on risk stratification when anticoagulation is contraindicated. Antiplatelet agents are inferior to anticoagulants for preventing AF-related strokes.

Preventable strokes in atrial fibrillation

The prevalence of atrial fibrillation (AF) increases as the population ages. AF increases the risk of stroke by 3 to 5 times\(^1,2\) and in Singapore, about 17% of strokes occurred in patients with AF.\(^3\)

Although oral anticoagulation (OAC) has been shown to be beneficial in patients with AF, many remain inadequately anticoagulated. In Asia, 1 in 2 patients requiring OAC is not on therapy and for those who are on warfarin, 59% have international normalised ratios (INRs) below the therapeutic range.\(^4\) Ensuring adequate anticoagulation is important as it can reduce the risk of AF-related strokes in Singapore. A holistic approach should also be taken to decide the appropriate OAC therapy; advanced age alone is not a contraindication to anticoagulation.\(^5\)
Estimating stroke risk

CHA$_2$DS$_2$VASc score

To decide if OAC is clinically indicated, assessment of patients’ stroke risk is required. The CHA$_2$DS$_2$VASc score was developed to estimate stroke risk in patients with AF. A higher score signifies a higher stroke risk.

Modified CHA$_2$DS$_2$VASc score

In the absence of other risk factors, female gender alone may not increase stroke risk. There seems to be no benefit from anticoagulating patients with CHA$_2$DS$_2$VASc score = 0 for males and CHA$_2$DS$_2$VASc score = 1 for females. Recent guidelines have also disregarded gender when deciding if a patient requires anticoagulation. The modified CHA$_2$DS$_2$VASc (mCHA$_2$DS$_2$VASc) is used in this Appropriate Care Guide, where gender does not contribute to the score.

Assessing and addressing bleeding risk

It is important to assess and address bleeding risk throughout the full duration of anticoagulation. Annual major bleeding risks in patients on anticoagulation range from 3.1 to 3.4% for warfarin and 2.1 to 3.6% for NOACs. Most of these were gastrointestinal bleeds and less frequently, intracranial haemorrhages.

Generally, bleeding risk scores, such as HAS-BLED, poorly predict major bleeding events. However, they are useful in identifying risk factors that may be modifiable such as:

- concomitant drugs which may predispose to bleeding, such as NSAIDs and antiplatelet agents
- excessive alcohol consumption (≥ 8 units per week)
- poorly-controlled blood pressure
- less than 6 in 10 INRs within the therapeutic range for warfarin.

Table 1. HAS-BLED score

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong> Hypertension (systolic blood pressure &gt; 160 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> Abnormal renal function: Dialysis, renal transplant, serum creatinine &gt; 200 micromol/L</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver function: Cirrhosis or Bilirubin &gt; 2x Normal or AST or ALT or ALP &gt; 3x Normal</td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong> Stroke (history of)</td>
<td>1</td>
</tr>
<tr>
<td><strong>B</strong> Bleeding (history or predisposition to bleeding)</td>
<td>1</td>
</tr>
<tr>
<td><strong>L</strong> Labile INRs (unstable or high INRs or &lt; 6 in 10 INRs were within the therapeutic range)</td>
<td>1</td>
</tr>
<tr>
<td><strong>E</strong> Elderly (age &gt; 65 years)</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong> Drugs (e.g. antiplatelet agents or NSAIDs)</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol (≥ 8 units per week)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maximum score 9

High stroke risk

A CHA$_2$DS$_2$VASc score of 2 is associated with a stroke risk of 2 to 3 strokes per 100 patients per year, while a score of 6 is associated with a stroke risk of 6 to 10 strokes per 100 patients per year.9,10

Bleeding risk scores

Bleeding risk scores should not be used to withhold anticoagulation. Instead, make every effort to reduce bleeding risk.

High bleeding risk

A HAS-BLED score of ≥ 3 indicates high bleeding risk, with ≥ 4 bleeds per 100 patients per year. Monitor these patients more frequently, and take steps to reduce their bleeding risks.
Selecting an oral anticoagulant

The choice of oral anticoagulant is based on patient factors such as bleeding risks, age, comorbidities, renal and liver function, concomitant drugs, drug tolerability, cost and individual preferences.

Review the indication and choice of oral anticoagulant at least annually and when patients’ clinical circumstances change.

Warfarin

Warfarin is the only drug with proven safety and efficacy in patients with mechanical heart valves or moderate to severe mitral stenosis. The presence of either condition is associated with exceptionally high thromboembolic risks. Warfarin is the treatment of choice for these patients.

When patients on warfarin have INR levels which are not in therapeutic range, more frequent INR monitoring and dose adjustments are needed.

Table 2. Management of high INR without significant bleeding

<table>
<thead>
<tr>
<th>INR</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than therapeutic range but &lt; 4.5</td>
<td>Decrease or withhold dosage. Monitor INR more frequently if clinically indicated, and restart warfarin at a lower dose when INR is within therapeutic range.</td>
</tr>
<tr>
<td>4.5–9.0</td>
<td>Withhold warfarin and consider administering oral vitamin K at 1-3 mg. Recheck INR within 24–48 h. If within range, resume warfarin at a lower dose. If INR is still high, administer a second dose of oral vitamin K at 1–3 mg.</td>
</tr>
<tr>
<td>&gt; 9.0</td>
<td>Withhold warfarin and consider administering oral vitamin K at 3-5 mg. Recheck INR within 24–48 h. If within range, resume warfarin at a lower dose. If INR is still high, administer a second dose of vitamin K at 1–3 mg.</td>
</tr>
</tbody>
</table>

Caution:
1. Oral vitamin K is prepared from injection vitamin K.
2. The effect of vitamin K is usually seen after 24 h.
3. Too much vitamin K use can cause resistance towards warfarin upon restarting later.

Mild bleeding episodes can be managed in outpatient settings while severe bleeding episodes warrant hospitalisations. If reversal of anticoagulation is required, patients may be referred to specialists or the emergency department.

Shared decision-making

Counsel patients on the risks and benefits of anticoagulation. Discuss therapeutic options to help them make informed decisions about their treatment. This will facilitate management of potential complications and also encourage adherence.

INR monitoring

For patients initiated on warfarin, perform INR test:
• at baseline,
• weekly, until INR is within therapeutic range and
• at 8 to 12 weekly intervals once INR is stable.

Warfarin’s drawbacks

- Frequent drug-drug, drug-food or drug-herb interactions.
- A narrow therapeutic range.
- The need for at least 6 out of 10 INR readings to be within therapeutic range.
- A delayed onset and offset of anticoagulation which may necessitate bridging therapy.
Non-vitamin K antagonist oral anticoagulants (NOACs)

These drugs are also known as direct oral anticoagulants (DOACs) or target-specific oral anticoagulants (TSOACs). With the lack of head-to-head trials, there is insufficient evidence to recommend one NOAC over the others in terms of safety and efficacy.

NOACs are as effective as warfarin in reducing AF-related strokes and systemic embolisms. They are also associated with fewer intracranial haemorrhages (ICH) compared to warfarin (about 2 to 5 ICH events avoided for every 1,000 patients treated per year). However, they may be associated with increased gastrointestinal bleeding when compared to warfarin. Limited experience with reversal agents may make NOACs less preferable in patients with high bleeding risks.

Table 3. Using NOACs in valvular heart disease (VHD)

<table>
<thead>
<tr>
<th>VHD subgroup</th>
<th>Evidence</th>
<th>NOACs Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical heart valves or moderate to severe mitral stenosis</td>
<td>None</td>
<td>x</td>
</tr>
<tr>
<td>Bioprosthetic heart valves, tricuspid regurgitation or mild mitral stenosis</td>
<td>Limited22-24</td>
<td>Individualise</td>
</tr>
<tr>
<td>Aortic stenosis, aortic or mitral regurgitation</td>
<td>Yes25</td>
<td>✓</td>
</tr>
</tbody>
</table>

Coagulation tests are not useful in patients on NOACs, except in cases of severe bleeding or urgent surgery. INR is not specific for NOACs and a normal prothrombin time or activated prothrombin time does not rule out the presence of residual NOACs’ effects.

Diminished role of antiplatelet agents

Antiplatelet agents are inferior to anticoagulants in AF-related stroke prevention and are no longer recommended in recent guidelines.

Compared to antiplatelet agents, anticoagulants reduced the absolute risk of all strokes by 0.7 to 7% while increasing the absolute risk of major bleeding by 0.2%. When anticoagulation is contraindicated, the role of antiplatelet agents is unclear. Some studies showed that aspirin caused more harm compared with no treatment while others showed fewer and less severe strokes. Therefore, consider aspirin or clopidogrel only when anticoagulation is contraindicated in patients with mCHA2DS2VASc ≥ 2, especially for those with a history of ischaemic stroke or transient ischaemic attack.
## Table 4. Characteristics of oral anticoagulants (adapted from local product information leaflets)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Vitamin K antagonist</td>
<td>Direct thrombin inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>&gt; 95%</td>
<td>6.5%</td>
<td>80–100% when administered with food</td>
<td>~ 50%</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>72–96 h</td>
<td>0.5–2 h</td>
<td>2–4 h</td>
<td>3–4 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>12–14 h</td>
<td>5–13 h</td>
<td>12 h</td>
</tr>
<tr>
<td><strong>Routine coagulation monitoring</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Reversal agent(s)</strong></td>
<td>Vitamin K, fresh frozen plasma and prothrombin complex concentrates</td>
<td>Idarucizumab</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>~100% metabolised, negligible in urine</td>
<td>85% renal</td>
<td>67% renal, 33% faecal</td>
<td>27% renal, 73% faecal</td>
</tr>
<tr>
<td><strong>Drug interactions</strong>*</td>
<td>++++ Co-trimoxazole, fluconazole, metronidazole, amiodarone, rifampicin, carbamazepine, phenobarbitone, St John’s Wort</td>
<td>+++ Antifungals (e.g. azoles), macrolides (e.g. erythromycin), antituberculosis drugs (e.g. rifampicin), antiretrovirals and calcineurin inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cost†</strong></td>
<td>$–$$$$</td>
<td>$$$$</td>
<td>$$</td>
<td>$$$</td>
</tr>
<tr>
<td><strong>Dosing according to renal function, CrCl (mL/min)</strong></td>
<td>INR-adjusted</td>
<td>150 mg BD</td>
<td>20 mg daily</td>
<td>5 mg BD</td>
</tr>
<tr>
<td>&gt; 50</td>
<td></td>
<td>110 mg BD if patients have high risks of bleeding</td>
<td></td>
<td>2.5 mg BD if patients have ≥ 2 of the following:</td>
</tr>
<tr>
<td>30–50</td>
<td></td>
<td>15 mg daily</td>
<td></td>
<td>• age ≥ 80 years</td>
</tr>
<tr>
<td>&lt; 30</td>
<td></td>
<td>Patients were not included in pivotal trials</td>
<td></td>
<td>• body weight ≤ 60 kg</td>
</tr>
<tr>
<td><strong>Dosing in liver impairment</strong></td>
<td>INR-adjusted</td>
<td>Not recommended in severe liver disease</td>
<td></td>
<td>serum creatinine ≥ 133 micromol/L.</td>
</tr>
</tbody>
</table>

*List of drugs is not comprehensive. Please consult a pharmacist for information on drugs with interacting metabolic pathways, especially when patients are taking new concomitant drugs or supplements.

†Based on treatment costs (including INR monitoring for warfarin) to patients at public healthcare institutions. At the time of publication, rivaroxaban is the only NOAC listed on Medication Assistance Fund (MAF) and costs may vary over time.

‡As estimated by Cockcroft-Gault formula.
References


About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health (MOH). ACE develops evidence-based “Appropriate Care Guides” or ACGs to guide a specific area of clinical practice. ACGs are aimed at complementing MOH Clinical Practice Guidelines when these are available, by providing additions and updates as reflected in the evidence at the time of development, and incorporating cost-effectiveness considerations where relevant. The ACGs are not exhaustive of the subject matter. When using the ACGs, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional. This ACG will be reviewed 3 years after publication, or earlier, if new evidence emerges that requires substantive changes to the recommendations.

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Algorithm for oral anticoagulation in atrial fibrillation-related stroke prevention
(Refer to the ACG on “Oral anticoagulation for atrial fibrillation” for more information.)

**AF without mechanical heart valves or moderate to severe mitral stenosis**

**AF with mechanical heart valves or moderate to severe mitral stenosis**

**Estimate stroke risk based on mCHA2DS2VASc**

- **+1** Congestive heart failure
- **+1** Hypertension
- **+1** Diabetes mellitus
- **+2** Prior stroke or transient ischaemic attack
- **+1** Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)
- **+1** Age 65–74
- **+2** Age ≥ 75

*Gender (Sex Category) – Not counted*

**Determine treatment based on total score**

- **0**
  - No anticoagulants.
  - No antiplatelet agents.

- **1**
  - Consider anticoagulation as not all risk factors amount to the same risk.*
  - No antiplatelet agents.

- **≥ 2**
  - Offer warfarin or a NOAC if not contraindicated
  - Discuss and address bleeding risk factors.
  - Discuss treatment options.

**Factors favouring warfarin**
- Patients who can maintain at least 6 out of 10 INR readings within therapeutic range while on warfarin.
- Patients unable to tolerate side effects of NOACs e.g. epigastric discomfort.
- Patients with moderate to severe liver or renal impairment.
- Patients with clinically significant drug-drug interactions with NOACs as the gain or loss of effect cannot be routinely measured.

**Factors favouring NOACs**
- Patients with less than 6 out of 10 INR readings within therapeutic range (labile INR) while on warfarin.
- Patients with difficult access to INR monitoring, either due to venous access or laboratory access.
- Patients reluctant to have frequent INR monitoring.