Atrial fibrillation (AF) is the commonest cardiac arrhythmia worldwide, occurring in 1-2% of the general population. It is a disease of increasing age: the estimated prevalence is 4-7% in those aged 65-74 years of age, increasing to 14-19% in those aged >85 years. AF is associated with increased mortality and morbidity, including stroke and other thromboembolic events, cardiovascular disease (CVD) and reduced quality of life. Moreover, studies have shown that stroke due to AF is more severe, leading to greater mortality and disability, increased lengths of hospital stay and greater requirements for long-term institutional care, compared with strokes due to other causes.

A recent Irish study using data from TILDA (the Irish longitudinal study on ageing) reported a prevalence of 3.2% of ECG-documented AF in the cohort (ranging from 0.8% in the 50-59 years age group to 10.8% of those aged >80 years) of whom approximately 40% were unaware that they had an arrhythmia. In the 65-70 year age group this lack of awareness of diagnosis rose to over 60%. Estimated demographic changes are expected to increase future costs of stroke in Ireland by >50% from 2007-2021, therefore active management of AF is an important public health measure that may help offset some of these projected costs. This, the second of two bulletins, will outline the management of non-valvular AF in current practice.

**RISK FACTORS FOR ATRIAL FIBRILLATION**

The mechanisms underlying AF are multifactorial and challenging to pinpoint on an individual case basis. Age is the strongest determinant of AF with a life-time risk estimated at 25% for a 40-year old person. A familial component of AF is also well established, especially in the case of young-onset AF; having an affected parent doubles an individual’s risk. The presence of cardiovascular disease such as hypertension or heart failure may also induce AF probably due to remodelling. In addition, there are many known extrinsic factors involved in the development of AF including cigarette smoking, chronic alcohol consumption (dose-related effect), use of illicit drugs such as marijuana and cocaine, and obesity (associated with sleep apnoea, hypertension and atrial dilatation).

**CLASSIFICATION AND DIAGNOSIS OF ATRIAL FIBRILLATION**

AF is characterised by chaotic contraction of the atrium. Table 1 outlines the internationally-agreed classification system for types of AF that may be identified in an individual patient.

**Table 1: Classification of Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Type of AF</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>&gt;2 episodes of AF that each terminate spontaneously within 7 days</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>Continuous AF that is sustained beyond 7 days</td>
</tr>
<tr>
<td>Longstanding persistent AF</td>
<td>Continuous AF of &gt;12 months’ duration</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>Sustained AF where a decision not to restore sinus rhythm has been made</td>
</tr>
</tbody>
</table>

The method of presentation depends on the type of AF. Patients may present with palpitations or with signs of acute disease such as acute heart failure or stroke in association with previously undiagnosed AF. However, many patients with AF are asymptomatic, although a thorough medical history may uncover symptoms potentially related to arrhythmia, especially in the case of paroxysmal AF. The most cost-effective method for the detection of AF in primary care is by opportunistic screening of people aged ≥65 years by pulse palpation. If an irregular pulse is found, a 12-lead ECG will clarify the diagnosis in the majority of patients and may also identify structural heart disease. Where paroxysmal AF is suspected, longer ECG monitoring periods (at least 24 hours) should be used. The National Cardiovascular Strategy has recommended the establishment of an AF screening programme in Ireland for people aged 65 years and over.

**MANAGEMENT OF ATRIAL FIBRILLATION**

AF is associated with increased rates of death, stroke and other thromboembolic events, heart failure and hospitalisations, reduced quality of life, reduced exercise capacity and left ventricular dysfunction. Management includes prevention of AF-related thromboembolic events, rhythm and/or rate control, adequate therapy of concomitant cardiac disease and relief of concomitant symptoms.

**PREVENTION OF AF-RELATED THROMBOEMBOLIC EVENTS**

There are 2 main types of anti-thrombotic therapies (ATT) that have been used in the prevention of AF-related thromboembolic events: oral anticoagulants and anti-platelet therapies.

**Oral Anticoagulants (OACs).** The Vitamin K antagonist, warfarin, has been the principal OAC for many years. A meta-analysis of ATT trials reported a relative risk reduction of 64% with warfarin therapy compared with placebo in the primary prevention of non-valvular AF-related thromboembolism. It was shown to be significantly more effective than aspirin, the most frequently used anti-platelet therapy which had a relative risk reduction of 22% versus placebo. Studies have shown that the beneficial effect of warfarin on reducing ischaemic stroke increases with increasing age, while benefit decreases for aspirin as patients get older.

An important aspect of treatment with warfarin is the need to ensure that the patient achieves and maintains an optimal INR (international normalised ratio). The optimal INR range for stroke prevention in AF with warfarin is 2.0 – 3.0 with the...
recommendation that patients should achieve a **TTR of >70%** (time in the therapeutic range). However problems with warfarin therapy include the high inter- and intra-individual variation in INRs and significant drug, food and alcohol interactions; in order to achieve optimal control, regular monitoring is required which has time and cost implications. Therefore, real-life studies suggest that some patients may achieve optimal TTR for less than 50% of the time, which offsets the potential benefits of warfarin in the prevention of stroke.7

Anticoagulation management has been improved in recent years by use of **self-monitoring and point-of-care testing** which results in improved TTR targets. A recent Irish study showed a median TTR of 74% in patients who were self-testing compared with a median TTR of 58.6% for those attending an anticoagulation management service. Pharmacogenetics of warfarin are also better understood and may aid in optimising warfarin dosing in the future; however such testing is not readily available.22 In recent years, OACs with new modes of action have been developed. Dabigatran is a direct thrombin inhibitor, while rivaroxaban and apixaban are direct Factor Xa inhibitors. The pharmacology of these individual agents is described in detail in the **NMIC companion bulletin** (NMIC 2012; Vol 18: 6).19 The clinical studies relating to use of the new OACs (NOACs) in non-valvular AF are outlined in Table 2. Each NOAC was compared with warfarin in individual large randomised controlled, non-inferiority “pivotal” trials in patients with non-valvular AF at increased risk of stroke. A further trial compared apixaban with aspirin in patients who were unsuitable for warfarin therapy.23

**Table 2: Pivotal trials for NOACs in patients with atrial fibrillation at increased risk of stroke**

<table>
<thead>
<tr>
<th>Drug / study</th>
<th>Dosage Regimen</th>
<th>Efficacy Results</th>
<th>Safety Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY</strong> study: n=18,213 (mean age 71 years) at moderate risk* of stroke. Follow-up was mean 2.0 years.</td>
<td>Apixaban 150mg or 110mg twice daily (randomly assigned to either dose) vs. dose-adjusted warfarin.</td>
<td>Dabigatran 110mg was non-inferior [and 150mg dose was superior] to warfarin in prevention of stroke or systemic embolism.</td>
<td>Compared with warfarin, rates of ICH + haemorrhagic stroke significantly ↓ with dabigatran while rate of major GI bleeding was significantly ↑ with dabigatran 150mg dosage. Non-significant ↑ in rate of MI with dabigatran compared with warfarin.</td>
<td>Patients with severe renal dysfunction (CrCl&lt;30ml/min) and active liver disease were excluded from trial.</td>
</tr>
<tr>
<td><strong>ROCKET AF</strong> study: n=14,264, (median age 73 years) at high risk** of stroke. Follow-up was mean 1.9 years.</td>
<td>Rivaroxaban 20 mg daily vs. dose-adjusted warfarin. [Dosage ↓ to 15mg daily for patients with CrCl of 30-49ml/min]</td>
<td>Rivaroxaban was non-inferior to warfarin in prevention of stroke or systemic embolism.</td>
<td>Compared with warfarin, rates of ICH + haemorrhagic stroke significantly ↓ with rivaroxaban while rate of major GI bleeding was significantly ↑ with rivaroxaban compared with warfarin. Rate of MI was similar in both groups.</td>
<td>Patients with severe renal dysfunction (CrCl&lt;30ml/min) were excluded from trial.</td>
</tr>
<tr>
<td><strong>ARISTOTLE</strong> study: n=18,201 (median age 70 years) at moderate risk* of stroke. Follow-up was mean 1.8 years.</td>
<td>Apixaban 5 mg twice daily vs. dose-adjusted warfarin. [Dosage ↓ to 2.5 mg twice daily for patients with serum creatinine &gt;133 µmol/l, age &gt;80 years or low body weight (&lt;60kg)]</td>
<td>Apixaban was superior to warfarin in prevention of composite endpoint of stroke or systemic embolism.</td>
<td>Compared with warfarin, the rates of major bleeding, haemorrhagic stroke and death were significantly less with apixaban. The rates of GI haemorrhage and MI were similar in both groups.</td>
<td>Patients with severe renal dysfunction (serum creatinine &gt;221 µmol/l; calculated CrCl &lt;25ml/min) were excluded from trial.</td>
</tr>
<tr>
<td><strong>AVERROES</strong> study: n=5,599, (median age 70 years) at moderate risk*** of stroke. Follow-up was mean 1.3 years.</td>
<td>Apixaban 5 mg twice daily vs. aspirin (81-324mg daily). [Dosage ↓ to 2.5 mg twice daily as in ARISTOTLE study]</td>
<td>Apixaban was superior to aspirin in prevention of stroke or systemic embolism. [Study stopped early because of favourable results]</td>
<td>No significant difference in rates of major bleeding, haemorrhagic stroke, ICH or death between the treatment groups.</td>
<td>Exclusion criteria for renal dysfunction were similar to the ARISTOTLE study.</td>
</tr>
</tbody>
</table>

**RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy)**

**ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)**

**ARISTOTLE (Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation)**

**AVERROES (Apixaban Versus Aspirin to Reduce the Risk of Stroke)**

CHADS2 score: 1.0; CHA2DS2-VASc score: 2.0; **CHADS2** score: 3.5; **CHADS2-VASc** score: 4.0; NICE CHADS2 (2001): NICE CHA2DS2-VASc (2012); **CHADS2** score: 2.1; **CHADS2-VASc** score: 3.5

**Anti-platelet therapies.** Aspirin at doses of 75-300mg has been reported to reduce the risk of stroke versus placebo (22% relative risk reduction versus placebo). However, as noted previously, aspirin is significantly less effective than warfarin and the anti-atherothrombotic effect appears to lessen with age, while the risk of major bleeding with aspirin is at least equivalent to warfarin in elderly populations. More recently, the AVERROES study (Table 2) showed that apixaban significantly reduced the rate of stroke or systemic embolism compared with aspirin; no statistically significant differences in the rates of death, major bleeding or haemorrhagic stroke between the treatment groups were noted. Therefore aspirin monotherapy is no longer recommended for prevention of AF-related thromboembolic events. The addition of clopidogrel 75mg to aspirin further reduces the risk of stroke compared with aspirin alone but is associated with increased risk of bleeding; therefore the combination is not recommended as first-line ATT for this patient group. However, it may be useful in patients for whom OAC therapy is not suitable.

**EVALUATING THE NEED FOR THROMBOPROPHYLAXIS IN CLINICAL PRACTICE**

Not all patients with AF have a similar risk of thromboembolism. Several scales have been developed to estimate the risk and assess the need for ATT on an individual basis. The simplest scoring system is the **CHADS2** (0-6 score) which calculates stroke risk on the basis of **existing CVD disease, diabetes mellitus, age and prior stroke** / **TIA** into high (>2), moderate (1-2) and low risk (0). However, it is now recognised that the risks associated with AF change over time with age and medical status, which may not be captured in the CHADS2 score. Therefore an updated scoring system (CHADS2-VASc) was developed which takes into account **additional risk factors including female gender, vascular disease, and age 65-74 years** (Table 3).
The CHA\textsubscript{2}-DS\textsubscript{2}-VASc scoring system is more inclusive of common stroke risk factors and has been validated in numerous studies, which have confirmed its ability to identify truly low risk patients who could be managed with no ATT as well as to predict stroke and thromboembolism in higher risk patients (Table 4).\textsuperscript{28,29} In addition, this scale provides clearer guidance for those patients with a previous CHADS\textsubscript{2} score of 0-1; in a recent study it was possible to reclassify 26% of patients with a CHADS\textsubscript{2} score of 1 to a low annual risk of stroke / systemic embolus of 1% i.e. truly “low risk” not requiring ATT.\textsuperscript{30}

However, many of the risk factors associated with AF-related thromboembolic events are also associated with an increased risk of bleeding with ATT.\textsuperscript{31} Therefore an evaluation of the risk of bleeding consequences should also be undertaken in the individual patient prior to ATT. Several bleeding risk scores are available; the HAS-BLED (see Table 5)\textsuperscript{8,12} and HEMORR\textsubscript{H}AGES (see Table 6)\textsuperscript{32} scoring systems.

### Table 5: HAS-BLED scoring system* for risk of bleeding\textsuperscript{8,12}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal / liver function</td>
<td>1/1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly</td>
<td>1</td>
</tr>
<tr>
<td>Drugs / alcohol</td>
<td>1/1</td>
</tr>
</tbody>
</table>

* low risk <3; high risk ≥3

Each scoring system has been evaluated in several independent cohorts.\textsuperscript{32} The HEMORR\textsubscript{H}AGES score has the advantage of including the risk of falls. The HAS-BLED score has shown a significant predictive performance for ICH\textsuperscript{8} and, in addition, highlights risk factors that can be actively managed to reduce the bleeding risk (such as use of NSAIDs or uncontrolled hypertension).\textsuperscript{2}

A high bleeding risk score (see Tables 5 and 6) does not necessarily constitute a contraindication to the use of OACs but rather will indicate the need for careful monitoring and education of the patient.\textsuperscript{12}

### RHYTHM / RATE CONTROL IN ATRIAL FIBRILLATION

There has been much debate over which is the best strategy for managing AF in terms of rhythm versus rate management. Studies comparing outcomes of rhythm vs. rate control strategies in AF patients found no difference in the incidence of mortality or stroke between the groups.\textsuperscript{9} Therefore the choice depends on individual patient factors. Figure 1 outlines guidance for choosing rhythm versus rate management first in AF.

### Figure 1: Rhythm versus Rate Control in patients with non-valvular AF\textsuperscript{2,8}

#### Rhythm control first for patients:
- Symptomatic
- Younger (< 65 years old)
- Presenting for first time with lone AF
- Secondary to treated or corrected precipitant (e.g. thyroid disease)
- With congestive heart failure
- Patients who may be considered for catheter ablation

#### Rate control first for patients:
- > 65 years old
- With coronary artery disease
- With contraindications to anti-arrhythmic drugs
- Unsuitable for cardioversion

Rhythm control by way of cardioversion is usually undertaken in a hospital setting and may consist of pharmacological cardioversion (PCV) and/or electrical cardioversion (ECV); a recent international survey showed that the preference for PCV or ECV varies between countries.\textsuperscript{23} Pharmacological agents include the anti-arrhythmic agents flecainide, vernakalant or amiodarone, depending on whether there is no, moderate or severe structural heart disease present respectively.\textsuperscript{2,8,34-36} Patients must undergo adequate anticoagulation before cardioversion is undertaken: anticoagulation (for 3 weeks) is mandatory for AF of > 48 hours / unknown duration. In emergency situations, patients should be heparinised.\textsuperscript{2} Follow-up consists of appropriate thromboprophylaxis (even if in sinus rhythm) for at least 4 weeks and ß-blocker therapy (unless in bradycardia). Patients should be evaluated at 1 and 6 months to see if sinus rhythm is maintained. If AF has recurred, patients should be re-evaluated to see if further rhythm control is warranted; otherwise they should be considered for rate control and need for ATT.\textsuperscript{9} Patients with paroxysmal or persistent AF who have achieved sinus rhythm may be treated with dronedarone to maintain sinus rhythm.\textsuperscript{2} Because of its safety profile, including multiple drug interactions, it should only be initiated and monitored in the specialist setting, after alternative treatments have been considered.\textsuperscript{35} It is contraindicated in heart failure, and in combination with dabigatran.\textsuperscript{37} It must not be used in patients with permanent AF because of an increased risk of mortality and morbidity.\textsuperscript{27,38}
Great care is needed when switching from PCV medications to dronedarone. If AF recurs while on dronedarone, or any rhythm-controlling agent, consideration should be given to its discontinuation and the patient re-evaluated.8,34-37

**Rate control.** As well as being evaluated for ATT, patients undergoing rate control therapy should be treated with a β-blocker or rate-limiting calcium antagonist (e.g. verapamil or diltiazem) in order to achieve a target resting heart rate of <100bpm and an exercise heart rate of <110bpm.8 Some patients achieve these targets without the need for any pharmacological treatment. Amiodarone is also effective in this main setting but because of its extra cardiac toxicity profile it should only be used if the above rate-control measures are ineffective.9 If amiodarone was used in the acute setting for rhythm control, it should be discontinued if the patient develops permanent AF.4 Current guidelines recommend that digoxin should only be added if inadequate rate control is achieved with the above drugs. Digoxin should only be considered as monotherapy in predominantly sedentary patients as it does not control the increased heart rate that may occur with exercise.8

**SPECIALIST INTERVENTION THERAPIES IN ATRIAL FIBRILLATION**

Ablation therapy (most commonly catheter ablation therapy) is used in specialist settings for selected patients in order to restore sinus rhythm and/or improve quality of life. It is particularly suitable for patients with symptomatic AF refractory to, or intolerant of, prior PCV.9 To date, there is limited evidence that ablation improves prognosis but trials are ongoing.9 Patients must have adequate ATT cover and patients may require long-term OAC post-procedure depending on the outcome and existing risk factors for stroke.2

Left atrial appendage (LAA) closure: The LAA is considered the main (but not the only) site of thrombus formation inducing AF-related stroke. Procedures such as occlusion / closure of the LAA orifice or excision of the LAA may be undertaken in specialist settings for selected AF patients with a high stroke risk.7 ATT cover is also required with these procedures.

**MANAGEMENT OF ATRIAL FIBRILLATION IN PRACTICE**

Figure 2 summarises the current guidance for the management of non-valvular AF in clinical practice.2,8,12,39-41 In addition to rhythm and/or rate management, concomitant cardiovascular disease should be actively managed: many of these conditions are known to be independent risk factors for stroke and, in addition, optimal control reduces the risk of cardiac remodelling which may worsen AF.7,42 OAC therapy is the mainstay of thromboprophylaxis for patients who are judged to be at risk of AF-related stroke. A patient with aCHA2.DS2-VASc score of ≥2 should be considered for OAC (Figure 2); the exception is a patient with lone AF <65 years (including females) who is judged to be truly low risk, who does not require thromboprophylaxis.12 Individual circumstances, including renal function and risk of bleeding (using a scoring system appropriate to the patient’s risk factors) should be taken into account when deciding on the type of OAC.2,12 Education is important: patients should be informed that all OACs are associated with a risk of bleeding.13,16-19 For patients who are taking warfarin, the potential risks and benefits of switching to a NOAC should be considered in light of their level of INR and TTR.39-41 For patients currently well-controlled on warfarin, automatic switching to a NOAC is not routinely recommended.2,41 Similarly, warfarin may be preferable for patients with poor renal function.12 However a patient who has difficulty maintaining a therapeutic INR, but is otherwise adherent, may benefit from changing treatment to a NOAC.2,41

Prescribers should be aware that clinical experience with the NOACs is still limited, therefore care, vigilance and further information on their effectiveness in clinical practice are needed.2 Renal function must be reviewed regularly and creatinine clearance should be estimated at least annually (see companion bulletin: NMIC 2012; Vol 18: 6).19 In addition, the risk of AF-related stroke (and therapy-related bleeding) changes over time, therefore patients should be re-evaluated regularly regarding their need for OAC therapy.12

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**Figure 2: Treatment Algorithm for Non-Valvular Atrial Fibrillation**8,10,12

Confirm diagnosis of non-valvular atrial fibrillation (AF) ↓

Rhythm and/or rate therapy as appropriate ↓

Management of concomitant CVD ↓

**NO**

Is patient <65 years and lone AF (including females)? ↓

Assess risk of stroke using the CHA2.DS2-VASc scoring system ↓

0 ↓

1 ↓

≥2 ↓

Consider chronic OAC ↓

Chronic OAC recommended ↓

Assess bleeding risk (HAS-BLED\HEMORR.HAGES scoring system) ↓

(Consider patient circumstances, including renal function, ability to comply with therapy and preferences) ↓

No ATT ↓

OAC = anticoagulant therapy; ATT= anti-thrombotic therapy

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In Ireland, approval for individual patient reimbursement for a NOAC must be obtained from the HSE through the Primary Care Reimbursement Service. Applications forms are available online at: [http://www.sspcrs.ie/libr/html/OralAnticoagulantIndividualReimbursementApplication.pdf](http://www.sspcrs.ie/libr/html/OralAnticoagulantIndividualReimbursementApplication.pdf)

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List of references available on request. Date of preparation: February 2013

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.
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