

NORTHERN NETWORK OF CARDIAC CARE GUIDELINES FOR THE DETECTION AND MANAGEMENT OF ATRIAL FIBRILLATION (AF)

**These notes should be read in conjunction with
the summary algorithms**

July 2007

CONTENTS

- 1. Introduction**
 - 1.1 Who are the guidelines intended for
 - 1.2 Classification of AF

- 2. Detection, diagnosis and investigation**
 - 2.1 Detection of AF
 - 2.2 Investigation

- 3. Management**
 - 3.1 Management of patients with newly detected AF
 - 3.1.1 Initial assessment
 - 3.1.2 Rate control
 - 3.1.3 Rate control versus rhythm control strategy
 - 3.1.4 Cardioversion
 - 3.1.4.1 Elective electrical cardioversion (AF > 48 hours)
 - 3.1.4.2 Electrical cardioversion with concomitant anti-arrhythmic drugs
 - 3.1.4.5 Transoesophageal echocardiography guided cardioversion
 - 3.1.5 Drug treatment for rhythm control
 - 3.2 Paroxysmal AF
 - 3.2.1 Detection and diagnosis of PAF
 - 3.2.2 Management of PAF
 - 3.3 Monitoring of anti-arrhythmic drugs used to manage AF

- 4. Thrombo-embolic and stroke prophylaxis**
 - 4.1 Risk stratification for thrombo-embolism / stroke and prophylaxis
 - 4.2 Initiation and management of warfarin treatment
 - 4.2.1 Initiation of warfarin
 - 4.2.2 Review of patients treated with warfarin
 - 4.2.3 Factors for which the INR clinic staff should inform the GP/supervising consultant
 - 4.2.4 Self monitoring of warfarin treatment
 - 4.3 Anti-thrombotic therapy in patients with AF and acute stroke
 - 4.4 Anti-thrombotic therapy in patients with AF and acute TIA
 - 4.5 Anti-thrombotic therapy following a stroke or TIA

- 5. Acute onset atrial fibrillation, and management of AF in patients presenting as emergency admissions**
 - 5.1 Management of patients within 48 hours of onset of AF who are not haemodynamically unstable
 - 5.2 Patients > 48 hours of onset, or onset unknown

- 6. Indications for non-pharmacological therapeutic interventions**
 - 6.1 AF catheter ablation with pulmonary vein isolation
 - 6.2 Pacemaker implantation and AV node ablation
 - 6.3 Ablation for other electrophysiological disorders
 - 6.4 Arrhythmia surgery for AF

- 7. Indications for referral**
 - 7.1 Referral by primary care to secondary care
 - 7.2 Referral by secondary care to tertiary care

7.3 Referral by primary care to tertiary care

7.4 Referral to stroke / TIA services

8. Follow up

APPENDICES

Appendix A: Warfarin and NSAIDs

Appendix B: Membership of the group and declared conflicts of interest

MANAGEMENT ALGORITHMS

Algorithm 1: Patients with suspected / confirmed AF

Algorithm 2: Rhythm control in persistent AF

Algorithm 3: Patients with paroxysmal atrial fibrillation (PAF)

Algorithm 4: Thrombo-embolic and stroke risk algorithm

Algorithm 5: Starting warfarin in AF - slow loading regimen

Algorithm 6: Acute onset AF (within 48 hours) in stable patients presenting as emergency admissions

Algorithm 7: AF of non recent onset (or onset unknown) in patients presenting as emergency admissions

Algorithm 8: Follow up

1. INTRODUCTION

These guidelines have been developed locally to help guide in the management of patients with atrial fibrillation (AF). The recommendations are consistent with those made in the NICE AF guidelines, and include additional information to aid in interpretation and implementation.

The recommendations are confined to those with AF and these guidelines are not intended for patients with atrial flutter (with the exception of when the recommendations coincide). These guidelines do not include management of patients with complex congenital heart disease or those with AF early after cardiac surgery.

It is assumed that patients with contra-indications will be identified and excluded (refer to the BNF)

1.1 Who are the guidelines intended for

These guidelines are intended for all clinicians in primary, secondary and tertiary care who diagnose and manage patients with AF in emergency and elective care.

The guideline has two parts; a number of algorithms and a set of supporting notes containing background information.

The algorithms are intended as everyday reminders. The notes contain additional information and clinicians are encouraged to be familiar with these and use them to refer to for further clarification of management in individual patients as needed.

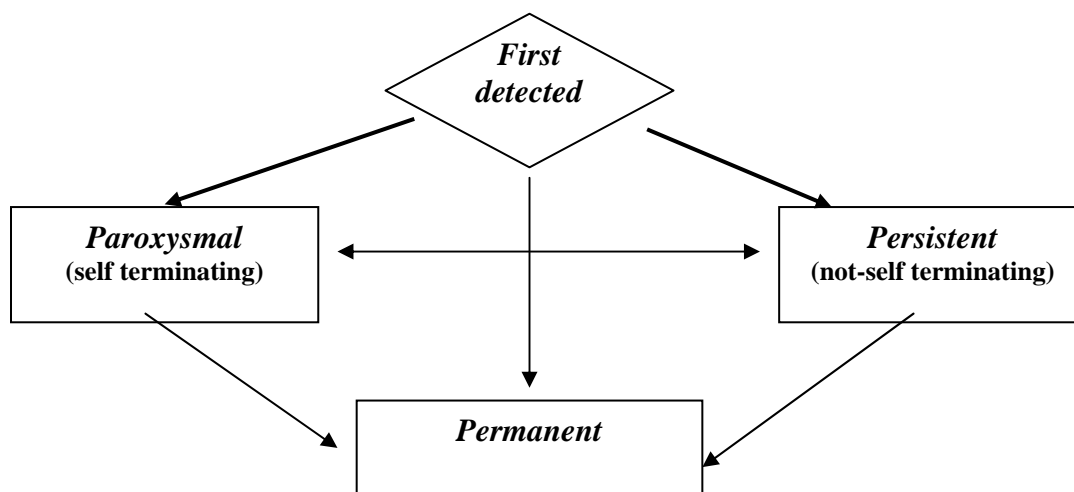
1.2 Classification of AF

| Terminology | Clinical features | Pattern |
|--|--|----------------------|
| Initial event (first detected episode) | Symptomatic Asymptomatic (first detected) Onset unknown (first detected) | May or may not recur |
| Paroxysmal | Spontaneous termination < 7 days and most often < 48 hours | Recurrent |
| Persistent | Not self terminating Lasting > 7 days or prior cardioversion | Recurrent |
| Permanent ('Accepted') | Not terminated Terminated but relapsed No cardioversion attempted | Established |

Recurrent is defined as when a patient experiences 2 or more episodes. These episodes may be paroxysmal when they terminate spontaneously, by consensus within 7 days, or persistent if they require electrical or pharmacological cardioversion.

Permanent AF is long standing AF (defined as more than a 1 year) and is not successfully terminated by cardioversion, or when cardioversion is not attempted.

Patients may progress from paroxysmal to persistent, and from persistent to permanent. Despite the term, patients with permanent AF may return to sinus rhythm, for example following an underlying disease process (eg thyroid disease) which is successfully treated, or a procedure which modifies the electrophysiological properties of the heart.



2. DETECTION, DIAGNOSIS AND INVESTIGATION

2.1 Detection of AF

Atrial fibrillation should be considered in patients presenting with any of the following symptoms;

- Breathlessness / dyspnoea
- Palpitations
- Syncope / dizziness
- Chest discomfort
- Stroke / TIA
- Heart failure

In patients with a pre-existing diagnosis of for example heart failure, any deterioration in symptoms should prompt an assessment to exclude the onset of atrial fibrillation. Manual pulse palpation should be performed for a minimum of 20 seconds, and a 12 lead ECG recorded¹ if any irregularity is detected.

Patients may develop atrial fibrillation and be asymptomatic. Pulse palpation should be performed as part of the annual review during chronic disease management in patients with the following chronic conditions;

- Hypertension
- Diabetes
- Coronary heart disease
- Cerebrovascular disease
- Peripheral arterial disease
- Heart failure (6 monthly review)

¹ A 12 lead ECG may be indicated for other reasons in patients presenting with these symptoms, even in the presence of a regular pulse

It was also agreed that it was good practice to perform manual pulse palpation each time a blood pressure is measured in patients aged ≥ 65 years.

In all patients pulse palpation should be for a minimum of 20 seconds (in patients over 65 years for the detection of AF, NPV 99% for any irregularity, 98% for frequent or continuous irregularities, 97% for continuous irregularity).

- A 12 lead ECG should be recorded in all patients, whether symptomatic or asymptomatic, in whom AF is suspected because an irregular pulse has been detected.

If AF is suspected, even if the pulse is not found to be clearly irregular, a 12 lead ECG should still be performed and a 12 lead ECG is always required in cases of suspected atrial flutter when the pulse may be regular.

2.2 Investigation

2.2.1 12 lead ECG

A 12 lead ECG is required for diagnosis. ECGs should be recorded to a high standard. It is recommended that those performing ECGs are trained, with regular updates, to fulfil the national competency standards for ECG recording. Most ECG machines have the facility for interpretation by computer software. This may aid interpretation, and the following performance has been reported; sensitivity of 87.3%, specificity 99.1%, a PPV of 89.5% and a NPV of 98.8% for diagnosing AF. However, this is not a substitute for clinical interpretation, both for diagnosis of the rhythm and any other abnormalities. Even following training, non specialists may make errors in interpretation and if there are any doubts about the interpretation of an ECG, an opinion of a cardiologist should be obtained².

2.2.2 Haematology / biochemistry

The following should be performed in all patients with a new diagnosis of AF

- Full blood count
- Clotting (if anti-coagulation being considered)
- Electrolytes and renal function
- Liver function tests
- Thyroid function tests
- Glucose

2.2.3 Radiology

A chest X ray should be performed if there is a clinical suspicion of an abnormality from the history and clinical examination

2.2.4 Transthoracic echocardiography (TTE)

It was agreed to adopt the recommendations made in the NICE AF guideline.

A TTE is recommended in the following patients;

- for whom a baseline echocardiogram is important for long-term management, such

² A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. FDR Hobbs, et al. HTA 2005;volume 9:number 40

- as younger patients
- for whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered
- in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or a heart murmur) that influences their subsequent management (for example, choice of anti-arrhythmic drug)
- in whom refinement of clinical risk stratification for anti-thrombotic therapy is needed

TTE should not be routinely performed;

- solely for the purpose of further stroke risk stratification in patients with AF for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria.

3. MANAGEMENT

3.1 Management of patients with newly detected AF

In all patients with newly detected AF, a management plan should include the following;

- Initial assessment to determine if emergency admission is appropriate (acutely unwell, haemodynamically unstable, other co-morbidity requiring admission, eligible for early cardioversion)
- Identify and manage any precipitating causes
- Achieve adequate rate control
- Discuss and initiate appropriate thrombo-embolic prophylaxis (see section 4)
- Identify whether a rate control strategy or a rhythm control strategy is appropriate
- Consider need for referral
- Arrange appropriate follow up, and finalise the diagnosis of paroxysmal, persistent or permanent AF.

3.1.1 Initial assessment

An initial assessment should be made to determine if patients require emergency admission. Emergency admission should be considered in those with unstable symptoms, or those in whom other co-morbidity requires in-patient management.

Other patients who should be considered for emergency admission are those in whom the onset of AF is clearly within the last 48 hours (and who have not had other paroxysms within the last month) and in whom very early cardioversion would be considered (thus avoiding the need for prolonged anti-coagulation). For example, younger patients with structurally normal hearts and PAF with infrequent symptoms (first symptom within the last month), other patients with new onset AF in whom early cardioversion would be considered (see section 5)

3.1.2 Rate control

Aim for a heart rate < 100 per minute at rest, and < 130 per minute during moderate activity (this can be assessed during clinic review eg walk up the corridor, walk upstairs). Recommendations for drug therapy are made in the NICE AF guidelines. In patients who require drugs for rate control;

- Standard beta blockers or rate limiting calcium channel blockers are preferred initial monotherapy in all patients.
- Digoxin should only be considered as monotherapy in predominantly sedentary patient

- If adequate rate control is not achieved with monotherapy, beta blockers or rate limiting calcium channel blockers may be combined with digoxin.

The combination of a beta blocker and diltiazem is not included in the NICE AF guidelines, but there was a consensus that this may be used in some patients, but only when initiated and stabilised in specialist care. *Treatment with the combination of verapamil and a beta blocker must be avoided.*

All patients having treatment initiated for rate control should be reassessed for response, at a minimum after a week, or earlier if symptomatic (some require reassessment the following day).

Choice of agent

Standard beta blocker; atenolol (25-50mg od, possibly 100mg od) or bisoprolol 5-10mg od) first line. Metoprolol 25-50mg bd or tds, possibly 100mg bd) if an agent with a shorter duration of action is preferred.

Rate limiting calcium channel blockers; diltiazem XL (120mg, 180mg, 360mg od), verapamil SR (120mg – 240mg od).

Patients may already be treated with a non-rate limiting calcium channel blocker for another condition eg hypertension. These patients may be switched to a rate limiting calcium channel blocker for rate control providing there are no contra-indications, for example heart failure and left ventricular systolic dysfunction.

3.1.3 Rate control versus rhythm control strategy

Patients with persistent AF may be managed in the longer term with a rate control strategy or a rhythm control strategy. Those managed with a rate control strategy who have been in AF for at least a year can be defined as being in permanent AF.

The two options of rate vs rhythm control should not be regarded as mutually exclusive. Before agreeing which to adopt any co-morbidities which might indicate one approach rather than the other should be taken into account and the potential advantages and disadvantages of each strategy should be explained to the patient.

A rate control strategy is the usually the preferred option in the following patients who remain in AF;

- Patients aged over 65 years
- Patients with coronary artery disease
- Patients with contra-indications to anti-arrhythmic drugs
- Patients unsuitable for cardioversion, including those with;
 - contra-indications to anti-coagulation
 - structural heart disease (eg left atrium > 5.5cm, mitral stenosis) that precludes long term maintenance of sinus rhythm
 - a long duration of AF (usually > 12 months)
 - a history of multiple failed attempts at cardioversion and or relapses, even with concomitant use of anti-arrhythmic drugs or non pharmacological approaches
 - an ongoing, but reversible cause for AF (eg thyrotoxicosis) until this is corrected

A rhythm control strategy is usually the preferred option in the following patients who remain in AF;

- Patients who are symptomatic despite adequate rate control
- Younger patients
- Patients presenting for the first time with lone AF
- Patients with AF secondary to a treated/corrected precipitant
- Patients with congestive heart failure

Patients who present early (within 48 hours) who may be considered for very early cardioversion should be referred as an emergency, thus avoiding the need for a prolonged period of anti-coagulation before and after cardioversion. This includes younger patients not known to have structural heart disease (eg no prior cardiac symptoms, no murmurs), those with infrequent episodes of AF (these patients require appropriate education to present early), providing no other acute and on-going co-morbidity has precipitated the onset of AF.

In older people with co-morbidities such as hypertension, diabetes, coronary disease, cardioversion is not associated with a major difference in mortality and major cardiac events compared to rate control. In patients with other irreversible conditions and no reversible causes, the chances of being in sinus rhythm at 1 year was estimated locally as about 25%. Cardioversion is unlikely to lead to the warfarin being stopped, and electrical cardioversion requires a general anaesthetic.

3.1.4 Cardioversion

Cardioversion may be either pharmacological, electrical or electrical cardioversion with concomitant drug therapy.

- The advantages of these should be discussed with the patient before initiating treatment
- If the onset of AF has been within the previous 48 hours, either pharmacological or electrical cardioversion may be used
- In those with prolonged AF (onset > 48 hours), electrical cardioversion is the preferred option

If anti-arrhythmic drugs are being used for pharmacological cardioversion, the choice of agent is determined by whether patients have structural heart disease (includes ischaemic heart disease, hypertension with significant LVH, cardiomyopathy, including HCM, left ventricular dysfunction)

- In patients without structural heart disease, a Class 1c drug (such as flecainide or propafenone) should be the drug of choice.
- In the presence of structural heart disease, amiodarone should be the drug of choice.

Continuous in-patient ECG monitoring is required in all those having acute pharmacological cardioversion for the first time, although some, following specialist assessment and trial of treatment may be managed with a 'pill in the pocket' strategy for subsequent episodes.

3.1.4.1 Elective electrical cardioversion (AF > 48 hours)

- Patients must be adequately anti-coagulated for a minimum of 4 weeks, INR target 2.5, range 2-3, prior to cardioversion.
- The INR monitoring service should be notified of the plan to cardiovert. Local arrangements will vary, and local agreement is needed to determine how this can be best achieved. In some cases direct written communication may be needed, but

noting the plan to cardiovert in the yellow warfarin book, or on the INR service referral form may be alternatives.

- After cardioversion anti-coagulation should be continued for a minimum of 4 weeks. In those with a high risk of recurrence (eg history of AF for longer than 12 months, mitral valve disease, LV dysfunction, enlarged left atrium, or a history of AF recurrence) or with a high thrombo-embolic risk, more prolonged anti-coagulation should be considered.
- After successful cardioversion, digoxin should be routinely stopped unless a plan has been made to continue this for other indications such as symptomatic management for heart failure and LV dysfunction. Beta blockers and rate limiting calcium channel blockers should be continued providing there are no contra-indications.
- Patients should be followed up in secondary care 4 weeks after cardioversion, when a further management plan should be made, including thrombo-embolic prophylaxis. If warfarin is not continued long term, most patients will be switched to aspirin.
- If a long term management plan can be made when patients are seen 4 weeks after cardioversion, patients may be discharged to primary care for on-going management. These patients should be seen in primary care after 6 months for clinical assessment and an ECG to confirm sinus rhythm.
- In some patients the long term management plan may be made after a longer period of observation. These patients will be seen in secondary care after 6 months, or more frequently if there is a clinical indication to do so.
- Patients who have a recurrence of symptoms after successful cardioversion, should be advised to seek further medical attention early.
- Patients who have a recurrence of AF, following successful cardioversion, require reassessment and revision of the long term management plan.

It is anticipated that each individual hospital undertaking electrical cardioversion will have an operational policy for performing the procedure.

3.1.4.2 Electrical cardioversion with concomitant anti-arrhythmic drugs

In patients undergoing elective electrical cardioversion in whom there is heightened concern about successfully restoring sinus rhythm (such as previous failure to cardiovert or early recurrence of AF), concomitant treatment with amiodarone or sotalol (progressively titrated from 80mg bd up to 240mg bd) should be given for at least 4 weeks prior to cardioversion.

In practice, there was a consensus that many cardiologists would use amiodarone in preference and continue treatment for 3 to 6 months after the procedure. In each case, an individual management plan should be made in secondary care, including duration of anti-arrhythmic drug treatment and follow up surveillance.

3.1.4.5 Transoesophageal echocardiography guided cardioversion

- Can be used in patients with AF for more than 48 hours and in whom early elective cardioversion is indicated.
- Both TOE guided cardioversion and conventional cardioversion should be considered equally effective
- A TOE guided cardioversion strategy should be considered;
 - where experienced staff and appropriate facilities are available, and
 - where a minimal period of precardioversion anticoagulation is indicated due to patient choice or bleeding risks.
- All patients with AF > 48 hours who undergo a TOE guided cardioversion require therapeutic anti-coagulation for a minimum of 4 weeks after the procedure

3.1.5 Drug treatment for rhythm control

An anti-arrhythmic drug is not required to maintain sinus rhythm after successful cardioversion in patients with a clear precipitant for AF (eg chest infection, other pyrexial illness) which has been corrected, providing there are no risk factors for recurrence.

In patients with persistent AF who require anti-arrhythmic drugs to maintain sinus rhythm and who have structural heart disease (includes ischaemic heart disease, hypertension with significant LVH, cardiomyopathy, including HCM, left ventricular dysfunction)

- Initial treatment should be with a standard beta blocker
- If a standard beta blocker is ineffective, contra-indicated or not tolerated amiodarone should be used

In patients with persistent AF who require anti-arrhythmic drugs to maintain sinus rhythm and who do not have structural heart disease

- Initial treatment should be with a standard beta blocker
- If a standard beta blocker is ineffective, contra-indicated or not tolerated;
 - a class Ic agent or
 - sotalol (progressively titrated from 80mg bd up to 240mg bd) should be used
- Where other drug classes are ineffective, contra-indicated or not tolerated amiodarone should be used

Other pharmacological agents

There is some evidence that other drug therapy, for example ACE inhibitors, angiotensin II receptor blockers may have a beneficial effect in maintaining sinus rhythm. At the present time these are not recommended routinely in all patients, but may be recommended for this indication in secondary / tertiary care for some patients being managed with a rhythm control strategy.

3.2 Paroxysmal AF

A diagnosis of PAF is made when patients have recurrent episodes of AF which last less than or equal to 7 days (most often less than 48 hours). Those with a first episode of AF without any recurrence are diagnosed as having had a first episode of AF.

In all patients with suspected and confirmed PAF, a management plan should include the following;

- Appropriate assessment to confirm the diagnosis
- Identify and manage any precipitants
- Discuss and agree with the patient an appropriate management strategy
- Discuss and initiate appropriate thrombo-embolic prophylaxis (see section 4)
- Consider need for referral
- Arrange appropriate follow up

3.2.1 Detection and diagnosis of PAF

An accurate diagnosis of PAF is needed with ECG documentation of AF. An accurate history is important in making a diagnosis. Some patients may also have suspected sick sinus syndrome from the history although this requires ECG confirmation. No symptoms

are specific for sick sinus syndrome, but patients may present with lightheadedness, pre-syncope or syncope for example.

In some the episode of AF may be captured during a standard 12 lead ECG, but most patients will require further investigation;

- Ambulatory 24 hour ECG recording should be used in those with symptomatic and or asymptomatic episodes less than 24 hours apart.
- An event recorder ECG should be used in those with symptomatic episodes more than 24 hours apart

Baseline investigations are required as for all patients with AF. Those with PAF are managed with a rhythm control strategy (with or without drugs) and thus fulfill the criteria for an echocardiograph.

3.2.2 Management of PAF

Where patients have infrequent symptoms, or where there are clear precipitants (eg alcohol, caffeine), a no drug treatment strategy or a pill in the pocket strategy should be considered and discussed with the patient. A pill in the pocket strategy may be considered in those who;

- have no history of left ventricular dysfunction, valvular or ischaemic heart disease; and
- have a history of infrequent symptomatic episodes of PAF, and
- have a systolic blood pressure greater than 100mmHg and a resting heart rate above 70 beats per minute; and
- are able to understand how to, and when to, take the medication; and
- have been assessed and treated for a pill in the pocket strategy in secondary care

Patients requiring regular prophylactic treatment

In patients with symptomatic paroxysms (with or without structural heart disease), treatment with a standard beta blocker should be the initial treatment option.

In patients with PAF and no structural heart disease

- If a standard beta blocker does not achieve symptomatic suppression;
 - a class Ic agent (such as flecainide or propafenone) or
 - sotalol (progressively titrated from 80mg bd up to 240mg bd) should be used
- If a standard beta blocker, a class Ic agent or sotalol do not achieve symptomatic suppression;
 - amiodarone or
 - referral for non-pharmacological intervention should be considered

In patients with PAF and coronary heart disease

- If a standard beta blocker does not achieve symptomatic suppression;
 - Sotalol should be used
- If a standard beta blocker or sotalol do not achieve symptomatic suppression;
 - amiodarone or
 - referral for non-pharmacological intervention should be considered

In patients with PAF and poor left ventricular function

- Where standard beta blockers are given as part of the routine management strategy and adequately suppresses paroxysms, no further treatment for paroxysms is needed
- If a standard beta blocker does not achieve symptomatic suppression;
 - amiodarone or
 - referral for non-pharmacological intervention should be considered

In patients with documented PAF, treatment with a beta blocker may be initiated in primary care, but anti-arrhythmic drugs (including sotalol) require referral to secondary care for initiation and stabilization.

Other pharmacological agents

There is some evidence that other drug therapy, for example ACE inhibitors, angiotensin II receptor blockers may have a beneficial effect in maintaining sinus rhythm. At the present time these are not recommended routinely in all patients, but may be recommended for this indication in secondary / tertiary care for some patients with PAF.

3.3 Monitoring of anti-arrhythmic drugs used to manage AF

- Anti-arrhythmic drugs used to treat patients with AF should be initiated and stabilised in secondary / tertiary care.
- Stable patients treated with some agents may be discharged for on-going monitoring to primary care, with appropriate agreement. Details of specific monitoring requirements once stable are given below.
- If an anti-arrhythmic drug is being used for any other indication other than to maintain sinus rhythm (eg amiodarone may in be used for rate control in selected patients) this should be made clear when the patient is discharged to primary care and should be recorded in the GP records.
- In some patients drugs may be prescribed in primary care, but monitoring undertaken in secondary / tertiary care, or shared between primary and secondary / tertiary care (with explicit written arrangements).

Patients treated with the following drugs may be discharged to primary care

(GPs should let the consultant cardiologist / physician know if they are not agreeable to the patient being discharged for monitoring and management in primary care)

| Drug | Biochemical monitoring | Frequency of ECG recording, and specific components to be analysed | Clinical review | Other monitoring |
|-------------|--|--|--|---|
| Amiodarone | 6 monthly thyroid function and liver function tests U&E as indicated for any co-prescribed treatment (eg ACE inhibitors, diuretics, risk of hypokalaemia) | Annually and with any change in symptoms, including syncope, presyncope (suggestive of torsade de pointe or bradycardia). ¹ Analysed for heart rate, PR interval and corrected QT interval | At least annually. Review of current rhythm; if the rhythm is AF and the indications for amiodarone are to maintain sinus rhythm, the patient requires further assessment as to the appropriateness of continuing amiodarone | PFT with transfer factor, and CXR at baseline before initiation and if new respiratory symptoms develop eg cough, breathlessness on treatment Ophthalmological assessment at baseline <i>only</i> if underlying abnormality present / suspected (adverse effects include optic neuritis) which will influence decision to treat with amiodarone. ² If visual symptoms develop whilst treated with amiodarone; 1. Refer to an optometrist. 2. Provide the optometrist with instructions to refer to ophthalmology if (a) in his / her opinion the symptoms derive from amiodarone verticillata, or (b) examination reveals any other unrelated pathology where he /she would normally refer |
| Sotalol | U&E as indicated for any co-prescribed treatment (eg | Annually and with any change in symptoms, including | At least annually. Review of current rhythm; if the rhythm is AF, the patient | |

| | | | | |
|--|--|--|---|--|
| | ACE inhibitors, diuretics, risk of hypokalaemia) | syncope, presyncope (suggestive of torsade de pointe or bradycardia). ¹ Analysed for heart rate, PR interval and corrected QT interval | requires further assessment as to the appropriateness of continuing sotalol | |
| <p>¹ If corrected QT interval is ≥ 500 milliseconds, check for any symptoms which may suggest torsade de pointe; discuss with / refer back to a cardiologist If corrected QT interval is prolonged (> 440 milliseconds in men, > 460 milliseconds in women), but less than 500 milliseconds, as a new finding since the last ECG, review other drugs prescribed and stop any that prolong the QT interval if possible. Repeat the ECG within 4 weeks. Marked bradycardia (< 50 beats per minute), or prolongation of the PR interval/ development of higher degrees of block compared to previous ECG; discuss with / refer back to a cardiologist.</p> <p>² As advised by Consultant Ophthalmologists, The Newcastle upon Tyne Hospitals NHS Foundation Trust</p> | | | | |

Other anti-arrhythmic drugs used in patients with AF

Patients treated with the following drugs may be discharged to primary care, following a clear agreement from a consultant cardiologist that this is appropriate and the GP agrees to accept responsibility.

| Drug | Biochemical monitoring required | Frequency of ECG recording, and specific components to be analysed | Clinical review |
|---|---|---|--|
| Class 1c agent (flecainide / propafenone) | U&E as indicated for any co-prescribed treatment (eg ACE inhibitors, diuretics, risk of hypokalaemia) | Annually and with any change in symptoms, including syncope, presyncope (suggestive of torsade de pointe or bradycardia). Analysed for heart rate, PR interval, QRS duration and corrected QT interval | At least annually. Monitor for other conditions in which appropriateness of treatment with a class 1c agent needs review eg heart failure, ischaemic heart disease Review of current rhythm; if the rhythm is AF, the patient requires further assessment as to the appropriateness of continuing a class 1c agent |

4. THROMBO-EMBOLIC AND STROKE PROPHYLAXIS

All patients with AF (including PAF, persistent AF and permanent AF) require appropriate management to reduce the risk of thrombo-embolism and stroke. The decision of the need for anti-thrombotic treatment in patients with PAF should be based on appropriate risk stratification, as for permanent AF, and not the frequency or duration of paroxysms (symptomatic or asymptomatic).

Patients may be treated with warfarin or aspirin. The choice of agent is determined by the level of individual patient risk of thrombo-embolism and stroke, and bleeding risk, and their individual wishes.

4.1 Risk stratification for thrombo-embolism / stroke and prophylaxis

The NICE AF guidelines identified the following as independent risk factors for thrombo-embolism and stroke, based on the evidence;

- Previous stroke or TIA
- Being elderly (aged over 75)
- Structural heart disease
- Hypertension
- Previous MI

The evidence for diabetes as an independent risk factor was not convincing, but was included in the NICE AF guideline as an important indicator of increased stroke risk in the general AF population.

Left ventricular dysfunction demonstrated by echocardiograph is a known risk factor for stroke, and this may confound previous MI being an independent risk factor for stroke. The NICE AF guidelines also included heart failure as a risk factor although acknowledge the evidence for this was inconclusive.

Athero-thrombotic vascular disease is a clinical spectrum which includes coronary disease and peripheral arterial disease, and contributes to stroke risk. Complex aortic plaque on TOE is a stroke risk factor and ischaemic stroke in AF may be associated with carotid disease. The NICE AF guidelines incorporate vascular disease into the risk stratification model.

The NICE AF guidelines do not include some co-morbidities as stratifying patients to having a high thrombo-embolic risk, but it was recognized that patients with some co-morbidities were excluded from, or under-represented in the trials. The local guideline group agreed to include that patients with thyrotoxicosis and those in AF with a permanent pacemaker should be managed as having a high thrombo-embolic risk.

There are a number of tools available to aid assessment of thrombo-embolic risk. There was a consensus in the group to adopt the recommendations in the NICE AF guidelines which risk stratify patients into high, medium and low risk groups based on clinical risk factors. In some patients who are risk stratified to a moderate risk group, the risk may be further refined by an echocardiograph, but an echocardiograph is not required for routine assessment. The NICE risk algorithm is a revised algorithm based on a model which has been optimized for use in a UK population. This was based on a modification of the AF

investigators' algorithm³.

The risk algorithm (algorithm 4) should be used in patients with AF to assess their risk of stroke and thrombo-embolism, and appropriate thrombo-embolic prophylaxis given.

In patients with AF warfarin reduced the risk of stroke by 68%⁴, and aspirin by 21%⁵. The estimates below can be used when discussing the pros and cons of different anti-thrombotic treatments with patients.

Risk of stroke in patients with AF, stratified by risk, with and without anti-thrombotic prophylaxis. Values are percentages per patient per year³

| Risk | No prophylaxis | Aspirin | Warfarin |
|---|----------------|---------|----------|
| High | | | |
| Previous stroke or TIA | 12% | 10% | 4-5% |
| Age ≥ 75 years with other clinical risk factors* | 8% | 4-5% | 1-2% |
| Moderate** | | | |
| Age < 65 years with other clinical risk factors* | | | |
| Age 65-74 | 4% | 1-2% | 1-2% |
| Age ≥ 75 years with no clinical risk factors* | | | |
| Low | | | |
| Age < 65 years with no clinical risk factors | 1% | <1% | <1% |
| * Such as diabetes and hypertension ** The figures for stroke risk in this group are those quoted in the BMJ publication. However, stroke risk factors are cumulative and in patients with a number of risk factors the stroke risk with aspirin is likely to be greater than that with warfarin. The highest risk of stroke (annual risk 12%) is in people with previous TIA or stroke. Warfarin is more effective in absolute terms as secondary prophylaxis than as primary prophylaxis, and also seems more effective than aspirin. In addition to a history of thromboembolism, other independent risk factors for thromboembolism are increasing age (especially age > 75 years), diabetes, and history of hypertension. | | | |

Other factors will also influence the final choice of agent.

In addition to risk stratification it was accepted that patients preferences should be considered as some patients will still decline anticoagulation treatment for a variety of reasons. These include:

- the inconvenience of dosing adjustments and regular blood tests to monitor INR levels
- dietary restrictions
- the risk of minor and major bleeding, and
- under-appreciation or lack of knowledge regarding the risk of stroke, or poor adherence to the treatment regimen.

³ Lip GYH, Lowe GDO . Antithrombotic treatment for atrial fibrillation. BMJ 1996;312:45-49

⁴ Laupacis A, Boysen G, Connolly S et al. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Archives of Internal Medicine*. 1994;154:1449–1457

⁵ Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomised trials. *Arch Intern Med* 1997; 157: 1237-40.

The annual risk of major bleeding in patients treated with warfarin is 1-2%. This risk is increased with co-morbidity. The NICE guidelines have identified that particular attention should be paid to patients who;

- are over 75 years of age
- are taking antiplatelet drugs (such as aspirin or clopidogrel) or non-steroidal anti-inflammatory drugs
- are on multiple other drug treatments (polypharmacy)
- have uncontrolled hypertension
- have a history of bleeding (for example, peptic ulcer or cerebral haemorrhage)
- have a history of poorly controlled anticoagulation therapy.

There was discussion within the guideline group about the co-administration of NSAIDs and warfarin. The consensus in the group was that routinely this should be avoided, although it was acknowledged there may be some selected patients who may be treated with the combination (eg some patients may be treated with warfarin and aspirin for secondary prevention after MI if the bleeding risk is low). This should only be following a comprehensive assessment of the patient with careful consideration of the risks and benefits, and discussion with the patient. It is anticipated that such decisions would be made in secondary care/tertiary care and require appropriate communication to primary care.

The combination of warfarin and clopidogrel is associated with an increased risk of bleeding and there is no indication for this combination for thrombo-embolic prophylaxis in patients with AF. It may be recommended in selected patients, for example after coronary artery stenting, and any such decisions should be clearly documented, including the duration of therapy.

Further information about the bleeding risk in patients treated with warfarin and NSAID is available in appendix 1.

Both the anti-thrombotic benefits and potential bleeding risks of long term anti-coagulation should be explained to, and discussed with the patient.

There was no consensus by the guideline group to recommend a single dose of aspirin, and patients being treated with aspirin may be treated with aspirin 75-300mg od. It was agreed however, that enteric coated aspirin should be avoided as this may not be as effective as non enteric coated preparations⁶. If patients develop dyspepsia, management should be in line with dyspepsia guidelines. Aspirin should be taken with food, and in those treated with aspirin 300mg od, the dose reduced to 75mg od. If appropriate, treatment with aspirin and a PPI should be considered.

Clopidogrel is not licensed for thrombo-embolic prophylaxis in patients with AF, and there is no evidence base for this indication. Patients with contra-indications to aspirin, for example those who are truly allergic to aspirin, should be considered for warfarin. However, if the risk of bleeding with warfarin is high, or the patient does not wish warfarin, clopidogrel treatment could be considered following an appropriate discussion and explanation to the patient.

⁶ Cox et al. Stroke 2006;37:2153-2158

Dipyridamole is not recommended for thrombo-embolic prophylaxis in patients with AF, although may be used for secondary prevention of ischaemic stroke in line with other local stroke guidelines and the NICE TAG.

4. 2 Initiation and management of warfarin treatment

4.2.1 Initiation of warfarin

Warfarin should be initiated following baseline assessment and appropriate management of any co-morbidities. In the majority of patients slow initiation will be appropriate (see algorithm 5).

Clinicians who are initiating warfarin should provide the patient with a yellow warfarin book, and complete the anti-coagulation clinic referral form which has been adopted across all localities. The indications for warfarin should be included and duration of therapy noted. If the duration of therapy is uncertain, a review date for this decision to be updated should be noted. The clinical notes should also record the decision to initiate warfarin and the target INR.

Patients should receive appropriate information and education about warfarin, including the need to avoid taking over the counter drugs which may interact.

In most patients warfarin treatment will be initiated in a dose of 1mg daily, although in selected patients, warfarin treatment may be initiated in a dose of 2mg od (eg younger patients, not taking drugs which may interact, maintenance dose during any previous warfarin treatment > 2mg od).

When warfarin is being initiated with a slow loading regimen, aspirin should be administered at the onset and stopped when the INR is 1.8 or higher. This information should be included in the yellow warfarin book and on the anti-coagulation clinic referral form. Anti-coagulation clinic staff may remind patients to stop taking aspirin at the appropriate time, but are not responsible for making the initial management plan to do so.

A more rapid onset of anti-coagulation may be indicated in selected patients (it is envisaged that these patients will generally have been assessed in specialist care), and this may be routine for some anti-coagulation services. Arrangements for appropriate monitoring should be made with the local anti-coagulation clinic, or by individual arrangements within specialist services / GP practices.

In patients being loaded more rapidly, earlier and more frequent INR checks are required initially and there may be a higher risk of over anti-coagulation.

Prescriptions for warfarin should only be issued after the yellow book is reviewed and or it is confirmed that the patient is having regular INR monitoring.

4.2.2 Review of patients treated with warfarin

Patients should be routinely reviewed 2 months after starting warfarin and thereafter at least annually, when patients should be assessed for the following;

- Frequent falls (4+ in the last year)
- Polypharmacy (4+ drugs), but recognised that in some patients the benefits of warfarin will still outweigh the risks eg patients with heart failure have a high thrombo-embolic risk and are usually taking more than 4 agents

- Problems with compliance. Unstable INRs and frequent warfarin dose changes may indicate compliance problems.
- Concerns that cognitive impairment is causing problems with taking medication. Recognised that some patients with cognitive impairment are still able to take warfarin, some have carer support.
- Uncontrolled hypertension
- Any new bleeding events (it is expected that these will be identified at the time of the bleed, but still to be included in the annual review)
- Any new drugs which interact, including OTC drugs (refer to the BNF)
- Excess alcohol which is effecting INR control

Patients who are identified as being, or possibly being, at increased risk of bleeding complications during treatment with warfarin should be further assessed by the GP / hospital consultant. These patients require reassessment for the pros and cons of treatment with warfarin.

4.2.3 Factors for which the INR clinic staff should inform the GP/supervising consultant

In addition, in some patients there are factors which may indicate problems with compliance / drug interactions / other issues such as variable alcohol intake which should trigger the anti-coagulation clinic staff to inform the GP or supervising consultant;

- Failure to attend the INR clinic on 3 consecutive occasions
- Unstable INRs visit to visit
- Frequent dose changes in the last 3 months

4.2.4 Self monitoring of warfarin treatment

Self monitoring may be preferred by some patients and may be considered providing;

- The equipment for self monitoring is available and regularly checked via a quality control programme
- The patient is physically and cognitively able to perform the self monitoring test, or if not, a designated carer is able to do so
- An adequate supportive educational programme is in place to train patients and or carers
- The patients ability to self manage is regularly reviewed

It is recommended that clinicians check availability within their own local areas.

4.3 Anti-thrombotic therapy in patients with AF and acute stroke

In all patients with AF who have had an acute stroke, any uncontrolled hypertension should be appropriately managed before anti-thrombotic therapy is started.

In patients with AF and an acute stroke;

- All patients should have a CT or MRI as early as possible to exclude cerebral haemorrhage. Refer to local stroke guidelines for choice of scanning mode
- In the presence of haemorrhage, anticoagulation and anti-platelet therapy should not be given
- In the absence of haemorrhage, the timing of initiation of anticoagulation is dependent on the size of cerebral infarction;

- in many patients this will be after 2 weeks
- in selected patients with a small cerebral infarction, anticoagulation may be considered earlier
- in the presence of a large cerebral infarction, initiation of anti-coagulation should be delayed.

4.4 Anti-thrombotic therapy in patients with AF and acute TIA

- All patients should have a CT or MRI as early as possible to exclude recent cerebral haemorrhage
- Refer to local guidelines for management of TIA, for management prior to the scan. Some patients with a TIA may have had a cerebral haemorrhage, and require investigation to exclude this before anti-coagulation is initiated. Local TIA guidelines should be referred to, to guide treatment with regards to any anti-platelet therapy (from discussion by the guideline group, this may vary between localities)
- In the absence of cerebral infarction or haemorrhage, anticoagulation therapy should begin as soon as possible

4.5 Anti-thrombotic therapy following a stroke or TIA

Patients with AF who are either post stroke, or have had a TIA;

- Should have been appropriately assessed to exclude a previous cerebral haemorrhage
- In the absence of a previous cerebral haemorrhage, warfarin should be administered.
- Patients with a previous cerebral haemorrhage or sub-arachnoid haemorrhage require a full assessment of the risks and benefits of anti-thrombotic treatment. Risk of thrombo-embolism, the circumstances of the cerebral haemorrhage and risk of recurrence, and patients wishes need to be taken into account

5. ACUTE ONSET ATRIAL FIBRILLATION, AND MANAGEMENT OF AF IN PATIENTS PRESENTING AS EMERGENCY ADMISSIONS

- In patients with life threatening deterioration in haemodynamic stability following the onset of AF, emergency electrical cardioversion should be performed, irrespective of the duration of the AF.
- In patients with non life-threatening haemodynamic instability following the onset of AF
 - electrical cardioversion should be performed
 - where there is a delay in organizing electrical cardioversion, intravenous amiodarone should be used
- For those with known Wolff-Parkinson-White syndrome;
 - flecainide may be used as an alternative for attempting pharmacological cardioversion
 - atrioventricular node blocking drugs (such as beta blockers, rate limiting calcium channel blockers, digoxin) should not be used

5.1 Management of patients within 48 hours of onset of AF who are not haemodynamically unstable

Management is summarized in algorithm 6.

- In those with non-cardiac co-morbidity possibly precipitating AF and who are haemodynamically stable, treatment of the underlying condition, rate control and thrombo-embolic prophylaxis is the main focus of treatment.
- In those without non cardiac co-morbidity precipitating AF, patients should be considered for cardioversion providing an acute cardiac event is ruled out.
- Any patient being considered for cardioversion should have had an appropriate clinical assessment.
- Electrical cardioversion is an alternative to pharmacological cardioversion or may be used if pharmacological cardioversion fails to achieve sinus rhythm.
- Patients undergoing cardioversion should be anticoagulated with heparin (5000 units IV heparin at start, with dose adjustment for body weight if needed, with on-going treatment with subcutaneous low molecular heparin).
- All patients being considered for cardioversion should be discussed with senior medical staff. This will vary between Trusts and should be agreed locally. It is anticipated that in Trusts with a cardiologist on call, this will be with a cardiologist. In Trusts without a cardiologist available, this will be with the responsible consultant physician.

5.2 Patients > 48 hours of onset, or onset unknown

Management is summarized in algorithm 7.

Patients who are acutely ill (these patients will require in-patient management) and in whom a tachycardia is expected, should have the underlying condition treated, with reassessment of the heart rate and consideration for additional rate control as appropriate. Those not acutely unwell should be managed as for all stable patients presenting with AF (algorithm 1).

6. INDICATIONS FOR NON-PHARMACOLOGICAL THERAPEUTIC INTERVENTIONS

These include;

- AF ablation with pulmonary vein isolation
- Pacemaker implantation and AV node ablation
- Arrhythmia surgery at the same time as other cardiac surgery such as mitral valve surgery
- Intervention for other arrhythmias when AF develops eg Wolff Parkinson White syndrome

6.1 AF catheter ablation with pulmonary vein isolation

- Catheter ablation of AF is a relatively new and arduous procedure taking about 4 hours, and requires appropriate facilities and skilled staff.
- The procedure needs to be consolidated by a second intervention in about 50% of cases
- Long-term outcome relates to the patient's 'AF-burden' prior to the procedure, those with a lower burden have a greater chance of success (eg: paroxysmal 'lone' AF > persistent 'lone' AF > permanent AF with heart disease)

- AF ablation should be considered in patients managed with a rhythm control strategy in whom pharmacological therapy is not achieving control of the arrhythmia and or is not tolerated.
- There is balance between a reasonable trial of pharmacological therapy before considering ablation and not waiting too long until the burden of AF is such that the procedure is less likely to be successful
- Patients most likely to benefit (long term sinus rhythm likely in about 70%) have;
 - Structurally normal heart ('lone AF')
 - Paroxysmal AF with episodes lasting < 12 hrs
 - Highly symptomatic during episodes, despite optimum medical therapy
 - Co-morbidity compatible with arduous procedure
 - Appreciate potential for serious adverse effects
- Patients less likely to benefit and to have a higher risk of complications (long term sinus rhythm in < 50%)
 - Structural heart disease (eg DCM, HCM, LVH, CHD)
 - Persistent AF (eg prior history of DC cardioversion)
 - Lower level symptoms or 'keen to be on less drugs'
 - Co-morbidity (+) (eg contraindication to anti-coagulation)
 - Increasing frailty (age or comorbidity)
- Patients who do not achieve long term sinus rhythm need to be managed with appropriate thrombo-embolic prophylaxis

6.2 Pacemaker implantation and AV node ablation

This is an alternative to AF ablation. The AV node is ablated and the patient has permanent ventricular pacing. This controls symptoms well but may have long term deleterious effects on ventricular function. In some patients biventricular pacing rather than right ventricular pacing alone may be considered. Patients need to continue appropriate thrombo-embolic prophylaxis.

6.3 Ablation for other electrophysiological disorders

All patients with Wolff- Parkinson – White syndrome who develop AF should be considered for ablation of the accessory pathway

6.4 Arrhythmia surgery for AF

- Surgical AF ablation should be considered in all patients with AF, when cardiac surgery is indicated for management of the mitral valve disease.
- For patients who have been in persistent AF and remain symptomatic or who have AF in the context of structural heart disease, an epicardial, off-pump approach to is more likely to yield higher overall success rates after a single procedure than a single catheter ablation procedure.

7. INDICATIONS FOR REFERRAL

7.1 Referral by primary care to secondary care

The following patients should be considered for referral for further cardiological assessment;

- Patients with an uncertain diagnosis

- Patients who remain symptomatic despite adequate rate control or in whom rate control cannot be achieved
- If rhythm control in patients with persistent AF is being considered, or drug therapy in PAF
- For consideration of cardioversion. If patients develop recurrent AF after a previous cardioversion some time in the past, patients should be managed according to the recommendations for consideration of rate vs rhythm control
- Patients with valve disease who develop AF
- Patients with heart failure who develop AF
- Younger patients with AF, for example under the age of 60 years

7.2 Referral by secondary care to tertiary care

Patients being considered for non-pharmacological intervention should be considered for referral to tertiary care for further cardiological assessment.

Patients being referred should have had all the standard recommended investigations, and in addition the following should accompany the referral letter;

- Standard 12 lead ECGs recorded in sinus rhythm and AF
- A full transthoracic echo report, including details of left and right atrial size.
- A 24 hour tape

7.3 Referral by primary care to tertiary care

- If a previous management plan from secondary care is that patients who fail treatment / develop recurrence is that they are referred to tertiary care.
- Patients with Wolff-Parkinson-White syndrome who present with AF.

It is anticipated that these patients will have been admitted as an emergency to their DGH and treated and referred to tertiary care, but if not, and subsequently present to their GP with a previous episode of AF and are found to have WPW, referral may be made direct to tertiary care.

7.4 Referral to stroke / TIA services

- Patients with recent stroke or TIA should be referred in line with local stroke/TIA guidelines
- Patients with a previous stroke or TIA not previously investigated to exclude a cerebral haemorrhage should be considered for referral prior to anti-coagulation
- Patients with a previous intracerebral haemorrhage / SAH should be considered for referral for an assessment of the risks and benefits of thrombo-embolic prophylaxis

8. FOLLOW UP

This is summarized in algorithm 8.

All patients with AF require appropriate follow up. Many patients will be under review in primary care for other conditions, for example hypertension, diabetes, vascular disease, and review of their AF management can be incorporated into their existing arrangements. Stable patients should be considered for annual review, with appropriate education to present earlier if symptoms change. There may some who require more frequent assessment eg those treated with amiodarone require 6 monthly biochemical monitoring, and in some other co-morbidity will be an indication for more frequent review. Some, for

example those treated with some anti-arrhythmic drugs will have a review of their AF management in secondary care.

Patient review should include;

- Clinical status
- Review of thrombo-embolic risk and prophylaxis
- Monitoring of drug treatment, especially
 - Warfarin
 - Anti-arrhythmic drugs
- Patient information and education

APPENDIX A

Warfarin and NSAIDs

Battistella et al [1] conducted a case-control analysis involving 98,821 elderly patients treated continuously with warfarin for a total of 65,064 patient years (mean age at entry 77 years). This showed that the use of non-selective NSAIDs, celecoxib or rofecoxib all approximately doubled the risk of hospitalisation for upper gastro- intestinal haemorrhage. See table 1.

Table 1 Association between hospitalisation for upper gastrointestinal haemorrhage among elderly warfarin users and exposure to potentially interacting drugs in the preceding 90 days

| Drug Taken | No. | | Odds Ratio (95% Confidence Interval) | |
|--|--------------------------|-----------------------|---|---------------------------|
| | Case Patients (n=361) | Controls (n=1,437) | Univariate Analysis | Multivariate Analysis* |
| NSAID | 24 | 337 | 2.3 (1.8-3.2) | 1.9 (1.4-3.7) |
| Celecoxib | 22 | 339 | 1.9 (1.4-2.4) | 1.7 (1.2-3.6) |
| Rofecoxib | 25 | 336 | 2.6 (2.0-3.7) | 2.4 (1.7-3.6) |
| Ocular antibiotics | 17 | 344 | 1.1 (0.9-1.5) | 0.9 (0.7-1.3) |
| Multivariate analysis adjusts for other potential interacting medications, a history of gastrointestinal bleeding in the previous 3 years, other co-morbidities, the use of other gastro toxic medications and the use of anti-ulcer agents. | | | | |

Flaker et al [2] assessed the risk and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation involved in the SPORTIF III and IV randomised trials of anticoagulation with warfarin or ximelogatran involving 7,329 patients (average treatment exposure 16.5 months).

The dose of oral aspirin was <100mg / day in the patients given aspirin. The results showed that the addition of aspirin to warfarin was not associated with any increase in benefit (stroke reduction), but was associated with an increased risk of bleeding. See table 2.

Table 2 – Bleeding rates per patient year of follow-up

| | Ximelogatran (n = 3,120) | Ximelogatran + aspirin (n = 531) | P |
|-------------|--------------------------|----------------------------------|-------|
| Major bleed | 1.9% (78) | 2.0% (14) | 0.83 |
| Minor bleed | 31.45% (1,013) | 39.4% (202) | <0.01 |
| | Warfarin (n = 3,172) | Warfarin + aspirin (n = 481) | |
| Major bleed | 2.3% (100) | 3.9% (25) | 0.01 |
| Minor bleed | 36.8% (1,199) | 62.8% (251) | <0.01 |

Penning-van Beest et al conducted a retrospective cohort study involving 19,935 new users (aged 40 to 80) of the coumarin anticoagulants phenocoumon and acencoumarol) in Holland, to identify co-medications that were associated with an increased risk of bleeding when started more than two weeks after initiation of anticoagulation. Treatment with antibiotics and NSAIDs were both associated with an increase in bleeding requiring hospitalisation. See table 3.

Table 3 – Incidence rates and relative risks of bleeding requiring hospitalisation associated with the start of potentially interactive drugs during anticoagulant therapy with coumarins

| Potentially interactive drug | Number of bleedings | Number of patient years on combined use | Incidence rate per 100 patient years | RR (95% CI), crude | RR (95% CI), adjusted |
|-------------------------------------|----------------------------|--|---|---------------------------|------------------------------|
| Antibacterial drugs | | | | | |
| Doxycycline | 6 | 139.6 | 4.3 | 4.2 (1.9-9.5) | 4.2 (1.9-9.5) |
| Amoxicillin + clavulanic acid | 6 | 81.5 | 7.4 | 7.2 (3.2-16.2) | 7.0 (3.1-15.8) |
| Sulfamethoxazole + trimethoprim | 3 | 44.1 | 6.8 | 6.6 (2.1-20.8) | 6.2 (2.0-19.5) |
| Norfloxacin | 3 | 44.8 | 6.7 | 6.5 (2.1-20.4) | 5.9 (1.9-18.6) |
| NSAIDs | | | | | |
| Diclofenac | 8 | 295.8 | 2.7 | 2.6 (1.3-5.4) | 2.6 (1.3-5.2) |
| Ibuprofen | 5 | 211.2 | 2.4 | 2.3 (1.0-5.6) | 2.2 (0.9-5.4) |
| Naproxen | 9 | 131.8 | 6.8 | 6.7 (3.4-13.0) | 6.5 (3.3-12.7) |
| Omeprazole | 1 | 171.2 | 0.6 | 0.6 (0.1-4.1) | 0.6 (0.1-4.0) |
| Salicylates, antithrombotic | 3 | 103.8 | 2.9 | 2.8 (0.9-8.8) | 3.0 (1.0-9.4) |
| Tramadol | 3 | 84.9 | 3.5 | 3.4 (1.1-10.8) | 3.3 (1.1-10.4) |

In a retrospective conduct study of Tennessee Medicaid enrollees aged 65 and older (103,954 subjects, 209,066 person-years of follow up, including 2,203 persons years of current anticoagulant use) Shorr et al found that the use of a combination of anticoagulant and NSAIDs was associated with a 12.7 fold increase in the risk of haemorrhagic peptic ulcer disease compared with non users of either anticoagulant or NSAIDs.

Table 4 – Risk of hospitalisation for haemorrhagic ulcer disease

| Treatment | Relative risk of hospitalisation for haemorrhagic peptic ulcer disease | 95% CI | Comment |
|-----------------------------|---|---------------|---|
| Oral Anticoagulants | 2.2 | 1.6 to 3.1 | Adjusted incidence 10.2 per 1000 person years |
| Oral Anticoagulant + NSAIDs | 12.7 | 6.3 to 25.7 | |

In a study by Zobair et al the incidence of upper gastrointestinal bleeding in patients given coronary artery stents and treated with aspirin plus anticoagulants was compared with 109 angioplasty patients without stents treated with aspirin alone.

Upper gastrointestinal bleeding occurred in 28 of the 138 patients treated with aspirin + anticoagulants (rate = 20.3%, 95 CI, 13.3 to 26.7%) compared with 0% in the aspirin group.

The mean time to the occurrence of upper gastrointestinal bleeding was 2.5 days after initiation of the combination therapy. The dose of aspirin used in this study was 325mg/day.

References

1. Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of Upper Gastrointestinal Haemorrhage in Warfarin Users Treated With Nonselective NSAIDs or COX-2 Inhibitors. *Arch Int Med* 2005;165:189-192.
2. Flaker GC, Griuber M, Connolly SJ, Goldman S, Chaparro S, Vahanian A, Halinen MO, Horrow JL and Halperin JL. Risk and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: An exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (Sportif) Trials. *Am Heart J* 2006;152:967-973
3. Penning- van Beest F, Erkens J, Petersen KU, Rudolf KH, Herings Ron. Main communications associated with major bleeding during anticoagulant therapy with coumarins. *Eur J Clin Pharmacol* 2005;61:439-444.
4. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for haemorrhagic peptic ulcer disease. *Arch Int Med* 1993;153:1665-1670.
5. Younossi MZ, Strum BW, Schatz RA, Teirstein PS, Cloutier DA, Spinks TJ. Effect of combined Anticoagulation and Low Dose Aspirin Treatment on Upper Gastrointestinal Bleeding. *Dig Dis Sci* 1997;42:79-82.

Glyn Trueman

Formulary Pharmacist, The Newcastle upon Tyne Hospitals NHS Foundation Trust

APPENDIX B

Membership of the group

Dr Jane Skinner, Consultant Community Cardiologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust (local guideline development group lead)

Anne-Marie Bailey, Pharmaceutical Advisor, Gateshead PCT

Paul Barbieri, Pharmaceutical advisor, South Tyneside Hospital

Prof David Barer, Consultant in Stroke Medicine, Gateshead Hospitals

Dr John Barker, Consultant Cardiologist, Gateshead Hospitals

Dr John Baxter, Consultant in Elderly Care, City Hospitals Sunderland

Dr David Beaumont, Consultant in Elderly Care, Gateshead Hospitals

Dr Rajesh Bhalla, GP with Specialist interest in Cardiology, South Tyneside PCT

Mandy Bowler Senior Nurse/Business Manager – Planned Care, South Of Tyne PCT

Dr John Bourke, Consultant Cardiologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust

David Cook, Lead Clinical Pharmacist, Northumbria Healthcare NHS Foundation Trust

Dr Bill Cunningham, GP, Northumberland Care Trust

Dr Michelle Davis Consultant in Stroke Medicine, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Mo Dewar, Consultant Haematologist, Northumbria Healthcare NHS Foundation Trust

Dr Coin Doig Consultant Cardiologist, North Tyneside Hospital

Dr Clive Edwards, Pharmaceutical Advisor, North Tyneside PCT

Lisa English, Community Cardiology, North Tyneside PCT

Dr Martyn Farrer, Consultant Cardiologist, City Hospitals Sunderland

Neil Gammack Clinical Service Manager, Pharmacy Gateshead Hospitals

Prof Chris Gray, Consultant in Stroke Medicine, City Hospitals Sunderland

Dr Iain Gilmour, GP, Sunderland TPCT

Dr Alex Hendrick, Consultant Haematologist, Gateshead Hospitals

Dr Annette Naylor, Consultant Haematologist, City Hospitals Sunderland

Zahra Irannejad, Pharmaceutical Advisor, Newcastle PCT

Dr Patrick Kesteven, Consultant Haematologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Margaret King, Community Cardiac Care, Newcastle PCT

Dr Stephen Kirk, GP, Gateshead PCT

Dr Mike Lavender, Consultant in Public Health Medicine, Northumberland Care Trust

Dr Stephen Lord, Consultant Cardiologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Greg Moorhouse, Pharmaceutical Advisor, Sunderland TPCT

Dr Abdul Nasser, Consultant Cardiologist, South Tyneside Hospital

Dr Fummi Nixon GP with Special interests, South Tyneside

Roger Owen, Cardiology Nurse Practitioner (RACPC), Gateshead Hospitals

Dr Steve Parry, Consultant in Elderly Care Medicine, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Kate Price, Service Improvement Facilitator, Northern Network of Cardiac Care

Dr Craig Runnett, Consultant Cardiologist, Wansbeck Hospital

Dr Mike Scott, GP, Newcastle PCT

Dr Jon Scott, Consultant Stroke Physician, South Tyneside Hospital

Nadeem Shah, Pharmaceutical Advisor, Northumberland Care Trust

Dr Caroline Sprake, GP, North Tyneside PCT

Ian Storer, Cardiology Specialist Nurse, South Tyneside PCT

Dr Mark Sudlow, Consultant in Elderly Care Medicine, North Tyneside Hospital

Glyn Trueman, Formulary Pharmacist, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr John Waddell, GP, Northumberland Care Trust

Alice Whincup, Northumberland Care Trust

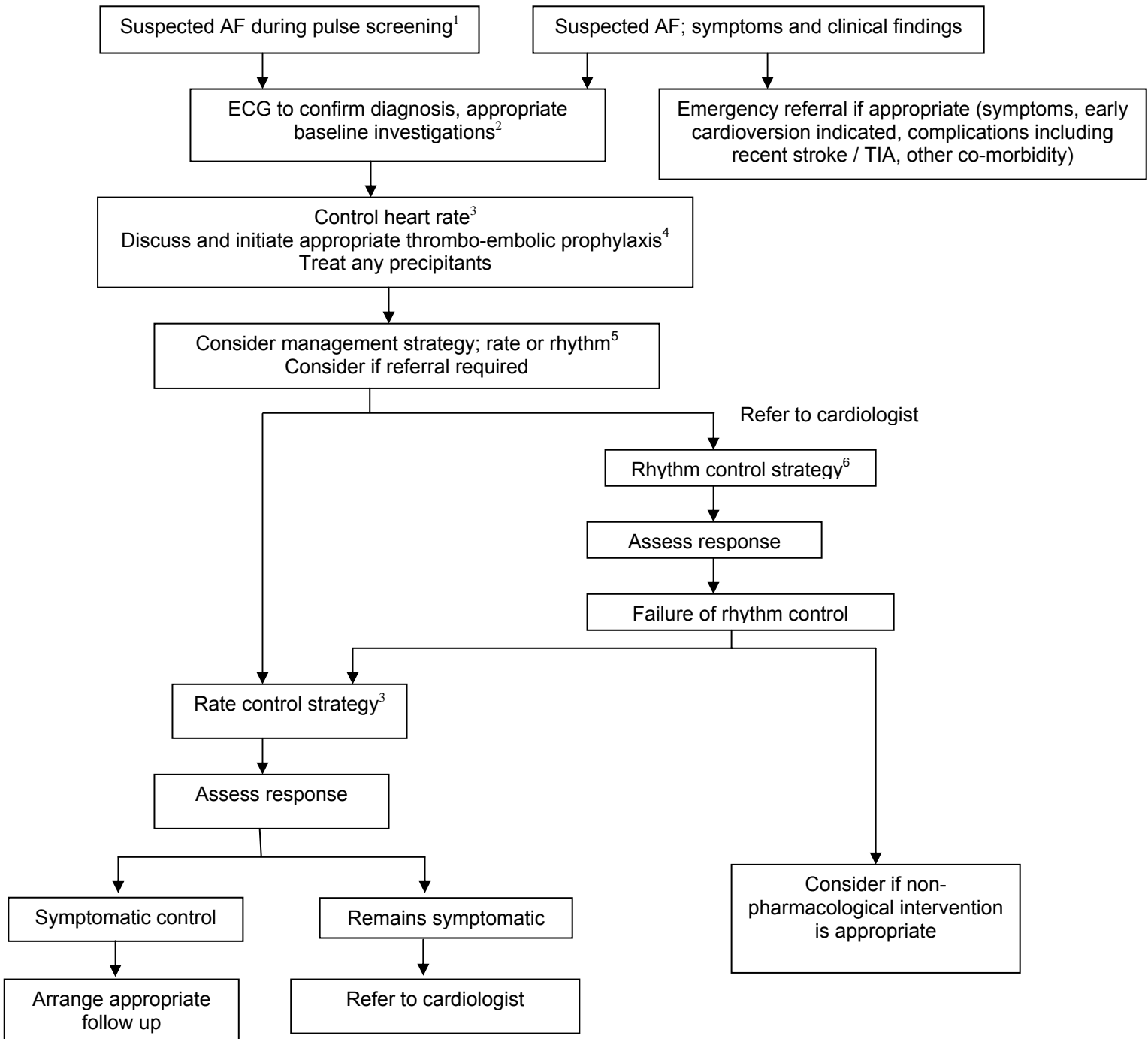
Declared conflicts of interest

None declared

Review date

June 2010, or earlier if new evidence makes this appropriate

Algorithm 1: Patients with suspected / confirmed AF



Notes

¹ For example, during annual review in patients with hypertension, diabetes, CHD, cerebro-vascular disease, PAD

² Baseline investigations; full blood count, clotting (prior to anti-coagulation), electrolytes and renal function, liver function, thyroid function, glucose. Chest X ray if clinical suspicion of abnormality, transthoracic echo if indicated (see notes)

³ Drugs for rate control

- Standard beta blockers or rate limiting CCB preferred monotherapy
- Digoxin monotherapy only in sedentary patients
- Beta blockers or rate limiting CCB may be combined with digoxin to optimise rate control

⁴ Thromboembolic prophylaxis; refer to section 4, algorithm 4

⁵ Rate control preferred in;

- Patients aged over 65 years
- Patients with coronary artery disease
- Patients with contra-indications to anti-arrhythmic drugs
- Patients unsuitable for cardioversion

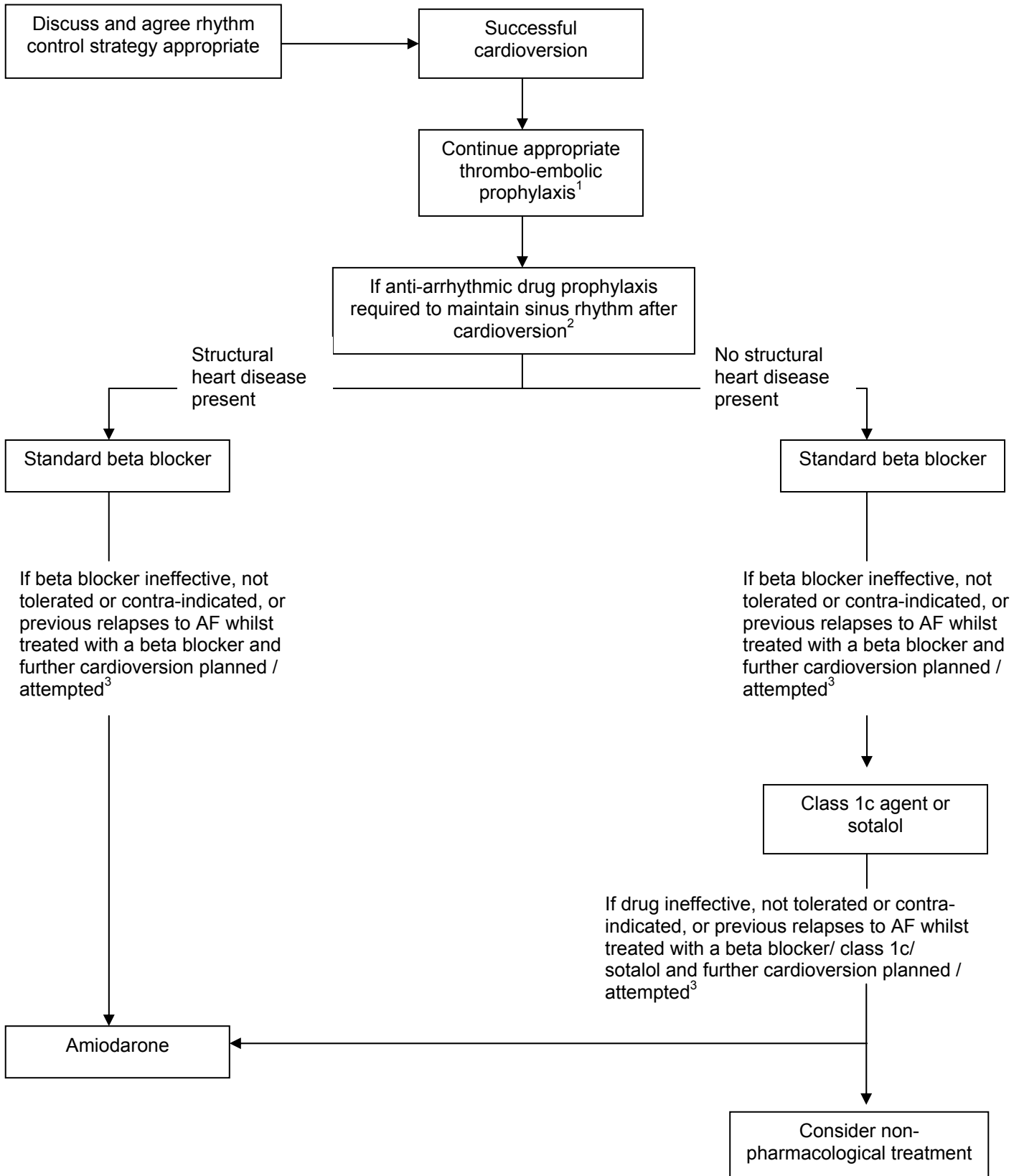
⁵ Rhythm control preferred in;

- Patients who are symptomatic despite adequate rate control
- Younger patients
- Patients presenting for the first time with lone AF
- Patients with AF secondary to a treated/corrected precipitant
- Patients with congestive heart failure

⁶ Refer to Algorithm 2 rhythm control in persistent AF or Algorithm 3 Patients with paroxysmal AF

All patients require appropriate follow up and review; clinical status, ensure appropriate thrombo-embolic prophylaxis, drug monitoring

Algorithm 2: Rhythm control in persistent AF



Notes

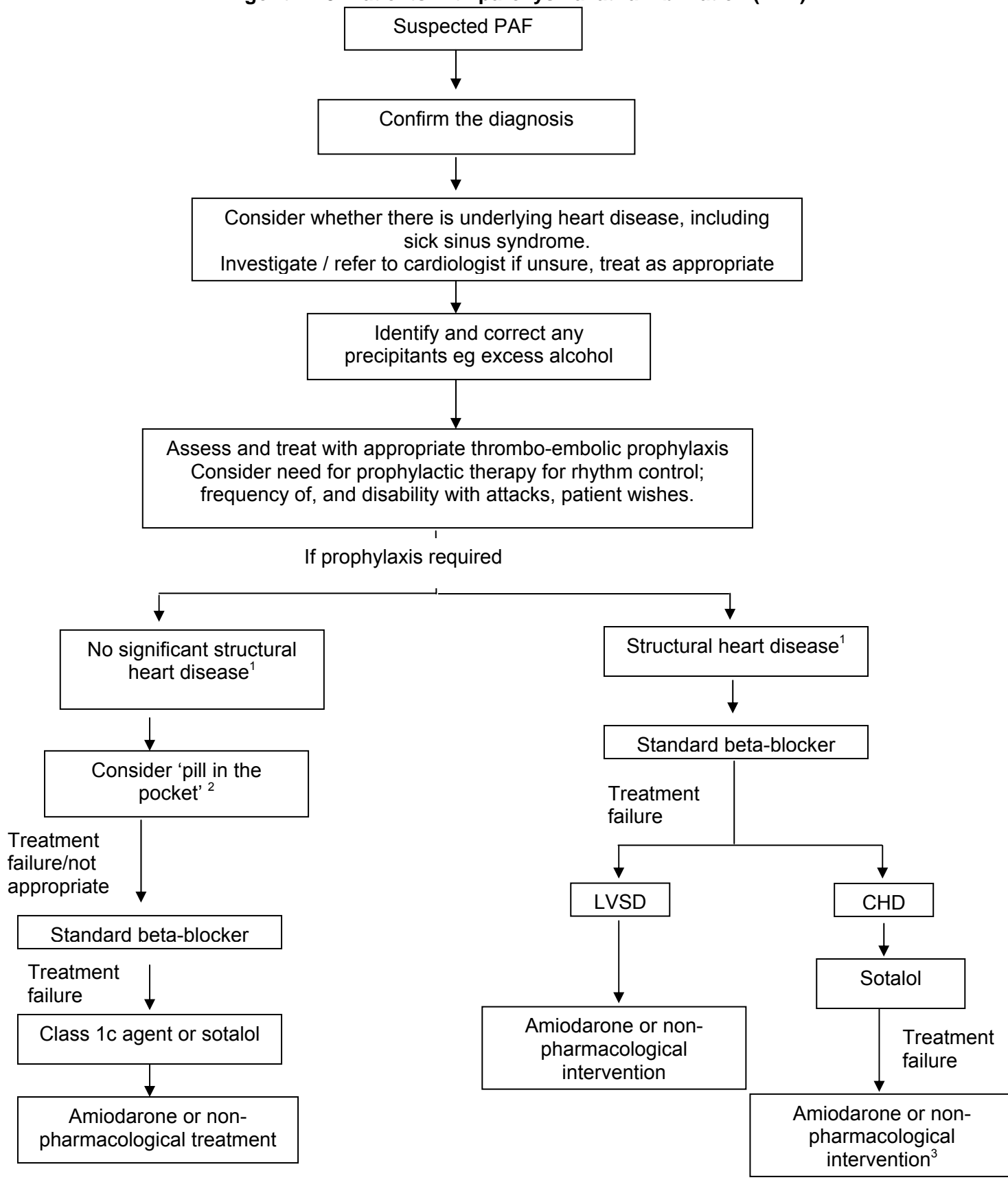
¹ Based on thrombo-embolic / stroke risk algorithm 4

² Anti-arrhythmic drugs are not indicated to maintain sinus rhythm in patients with a reversible, corrected precipitant for AF

³ Patients who relapse back into AF, require full re-evaluation for a rate control vs rhythm control strategy

All patients require appropriate follow up and review; clinical status, ensure appropriate thrombo-embolic prophylaxis, drug monitoring

Algorithm 3: Patients with paroxysmal atrial fibrillation (PAF)



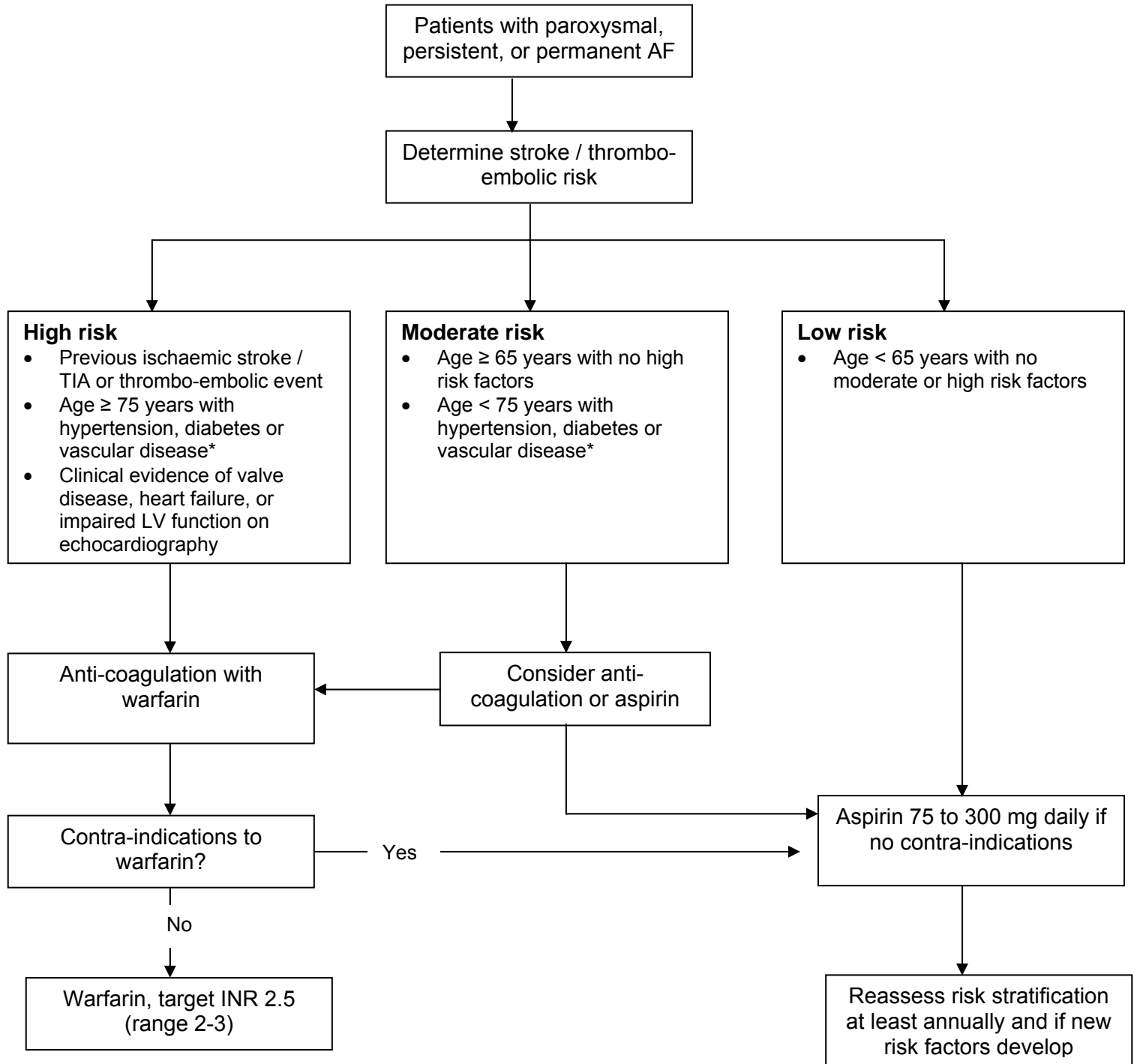
¹ Structural heart disease includes CHD, LVSD, valvular heart disease.

² Patients being considered for 'pill in the pocket' require appropriate assessment, and have systolic BP > 100mmHg, heart rate > 70bpm, and are able to understand how and when to take medication.

³ Non pharmacological intervention particularly in those with 'lone AF'

All patients require appropriate follow up and review; clinical status, ensure appropriate thrombo-embolic prophylaxis, drug monitoring

Algorithm 4: Thrombo-embolic and stroke risk algorithm

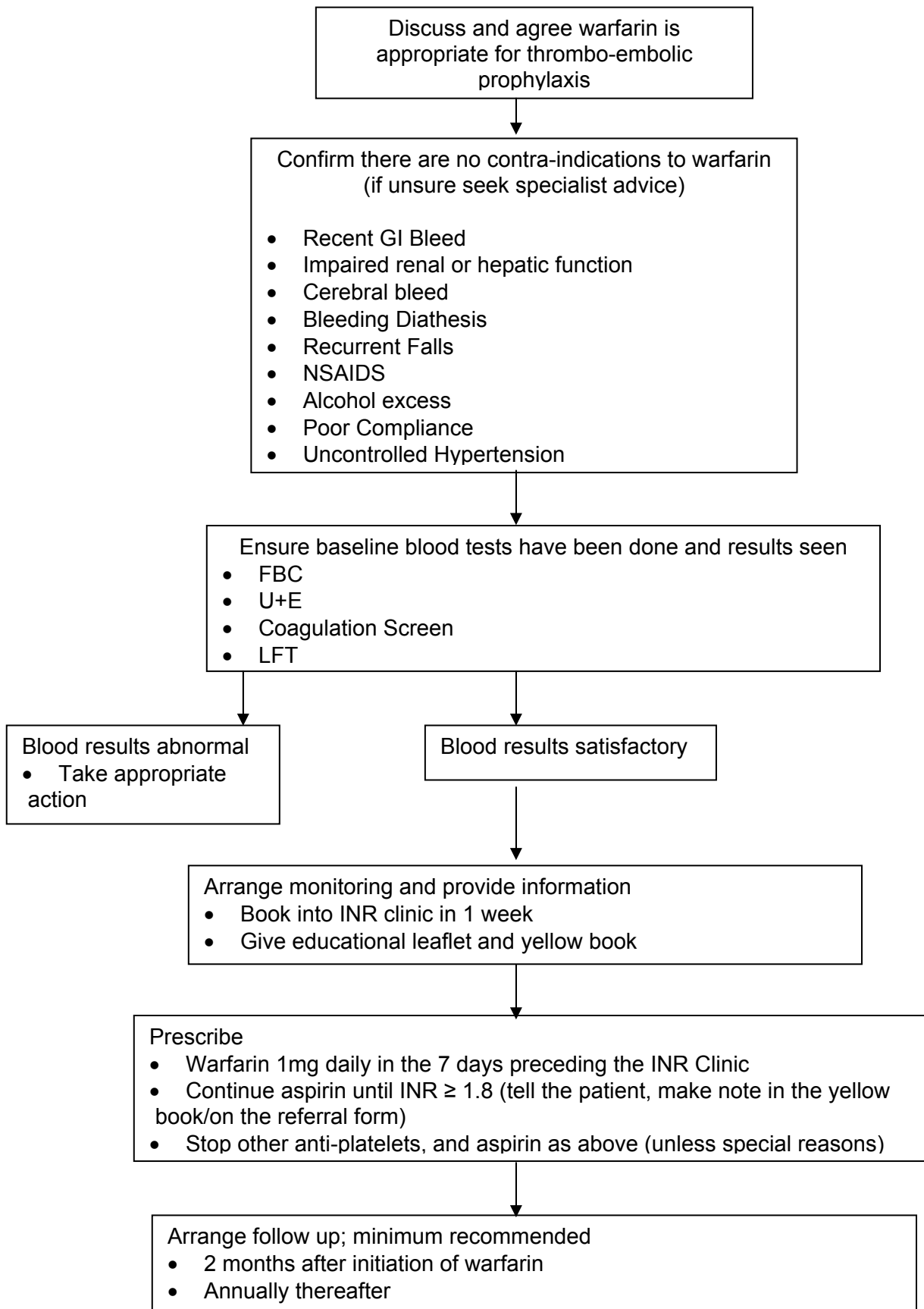


Notes

- Risk factors are not mutually exclusive, and are additive to each other to produce a composite risk. This is particularly important to consider in those falling into the moderate risk group.
- Treatment needs to be decided on an individual basis, balancing the risks and benefits of warfarin versus aspirin.
- In patients with two or moderate risk factors, warfarin may be preferred in such patients as risk factors are cumulative. Echocardiography to assess left atrial size and LV function may help in some uncertain cases
- The local guideline group also recommended that some other patients be treated as high risk, including those with thyrotoxicosis, permanent pacemaker

* Coronary artery disease or peripheral arterial disease

Algorithm 5: Starting warfarin in AF - slow loading regimen

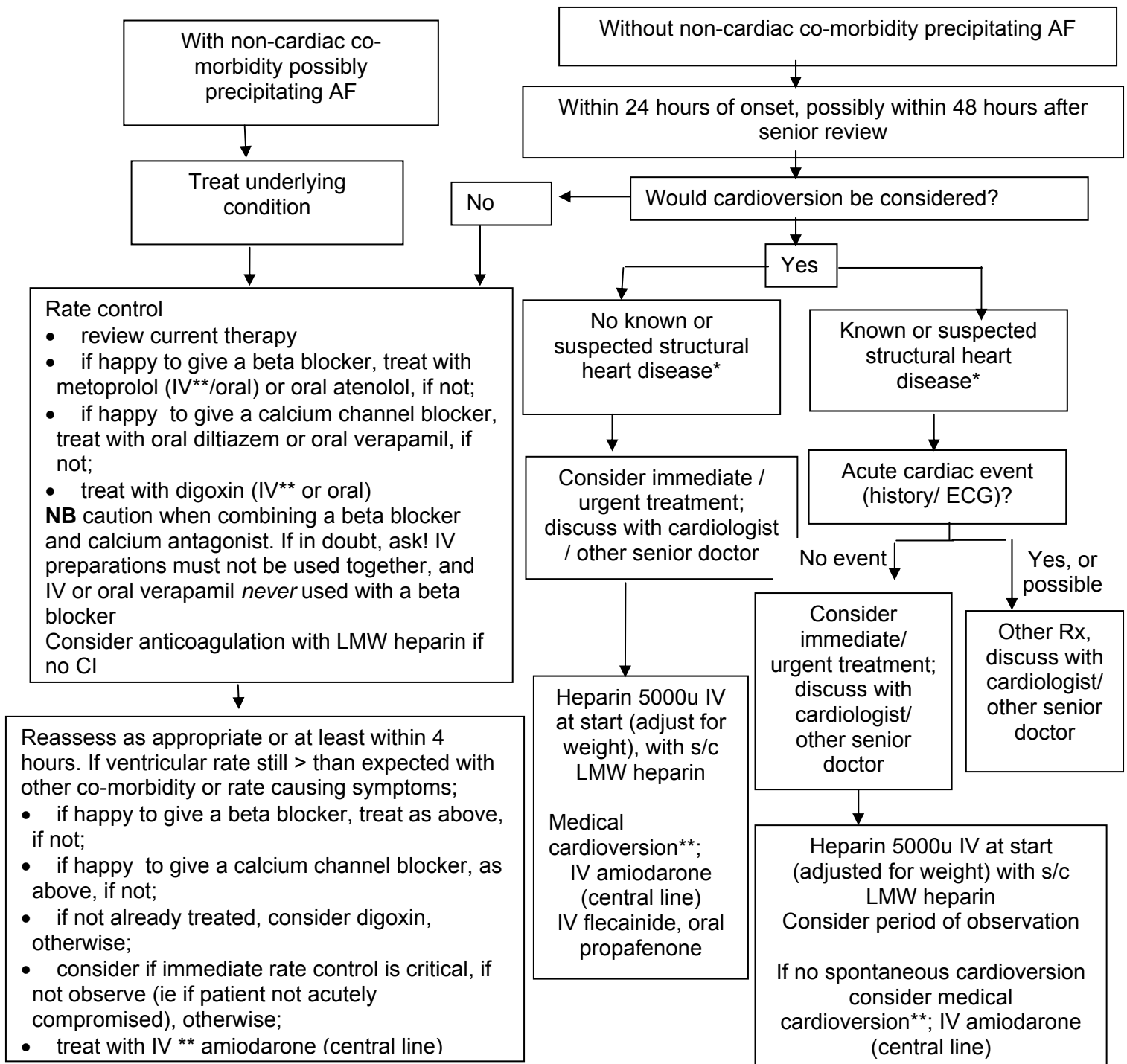


Notes

Target INR range should be 2 – 3 (target 2.5) for patients with atrial fibrillation. If individual circumstance suggests an alternative range may be required please discuss with specialist care

Algorithm 6: Acute onset AF (within 48 hours) in stable patients presenting as emergency admissions

The time of onset of the episode of AF must be clear from the history. The following therapy should **only** be used if it is certain that the onset of AF is within the last 24 to 48 hours and there have not been frequent paroxysms in the last month. If in doubt, treat as for 'AF of non recent onset'.



Notes

* eg ischaemic heart disease, hypertension with possible or definite LVH, cardiomyopathy, including HCM.

** with continuous supervised ECG monitoring eg on CCU/ cardiology ward telemetry under cardiologist care (or as arranged locally).

Anti-arrhythmic drugs are listed in alphabetical order not in the order of suggested use. Semi-elective electrical cardio-version might also be considered in these patients in preference to drugs (discuss with cardiologist)

Providing there are no contra-indications, calcium channel blockers are preferred in COPD

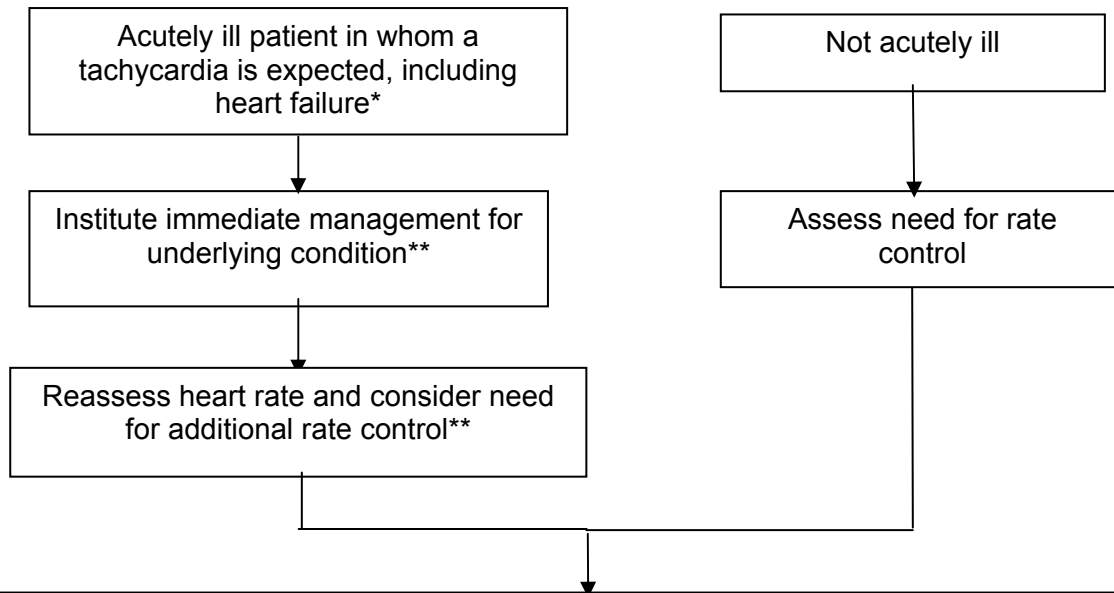
Emergency electrical cardioversion will be required in those with life-threatening deterioration in haemodynamic stability (see notes).

Patients being considered for early, semi elective cardioversion should be discussed with a senior doctor first. In hospitals with a cardiologist on call this will be with the cardiologist, in hospitals without a cardiologist available this will be with the supervising consultant physician

All patients require an on-going management plan

Algorithm 7: AF of non recent onset (or onset unknown) in patients presenting as emergency admissions

The initial aim of management is rate control and to address thrombo-embolic prophylaxis. Some patients may be known to have AF and already be taking treatment. This needs to be taken into account when considering the addition of further treatment.



Rate control

- if happy to give a beta blocker, treat with metoprolol (IV^{***}/oral) or oral atenolol, if not;
- if happy to give a calcium channel blocker, treat with oral diltiazem or oral verapamil, if not;
- treat with digoxin (IV^{***} or oral)

NB caution when combining a beta blocker and calcium antagonist. If in doubt, ask for senior medical help! IV preparations must not be used together and IV or oral verapamil *never* used with a beta blocker

Consider anticoagulation if no contraindications, otherwise aspirin

LMW heparin *or* if not acutely unwell consider warfarin (slow loading may be used in patients without very high thrombo-embolic risk, in whom early discharge is planned and who are being managed as an out-patient)

Reassess as appropriate or at least within 4 hours. If ventricular rate still > than expected with other co-morbidity or rate causing symptoms;

- if happy to give a beta blocker, treat as above, if not;
- if happy to give a calcium channel blocker, as above, if not;
- if not already treated, consider digoxin, otherwise;
- consider if immediate rate control is critical, if not observe (ie if patient not acutely compromised), otherwise;
- treat with IV ^{***} amiodarone (central line)

Notes

* Heart failure may be secondary to uncontrolled atrial fibrillation, or may be secondary to some other mechanism eg left ventricular systolic dysfunction.

** In practice these will tend to be done very much at the same time

*** With continuous supervised ECG monitoring eg on CCU/ cardiology ward telemetry under cardiologist care Providing there are no contra-indications, calcium channel blockers are preferred in COPD Slow loading warfarin; 1mg daily (2mg in selected patients) with INR in 1 week; see algorithm 5

Patients with life threatening acute haemodynamic instability due to AF require emergency electrical cardioversion (see notes)

Algorithm 8: Follow up

