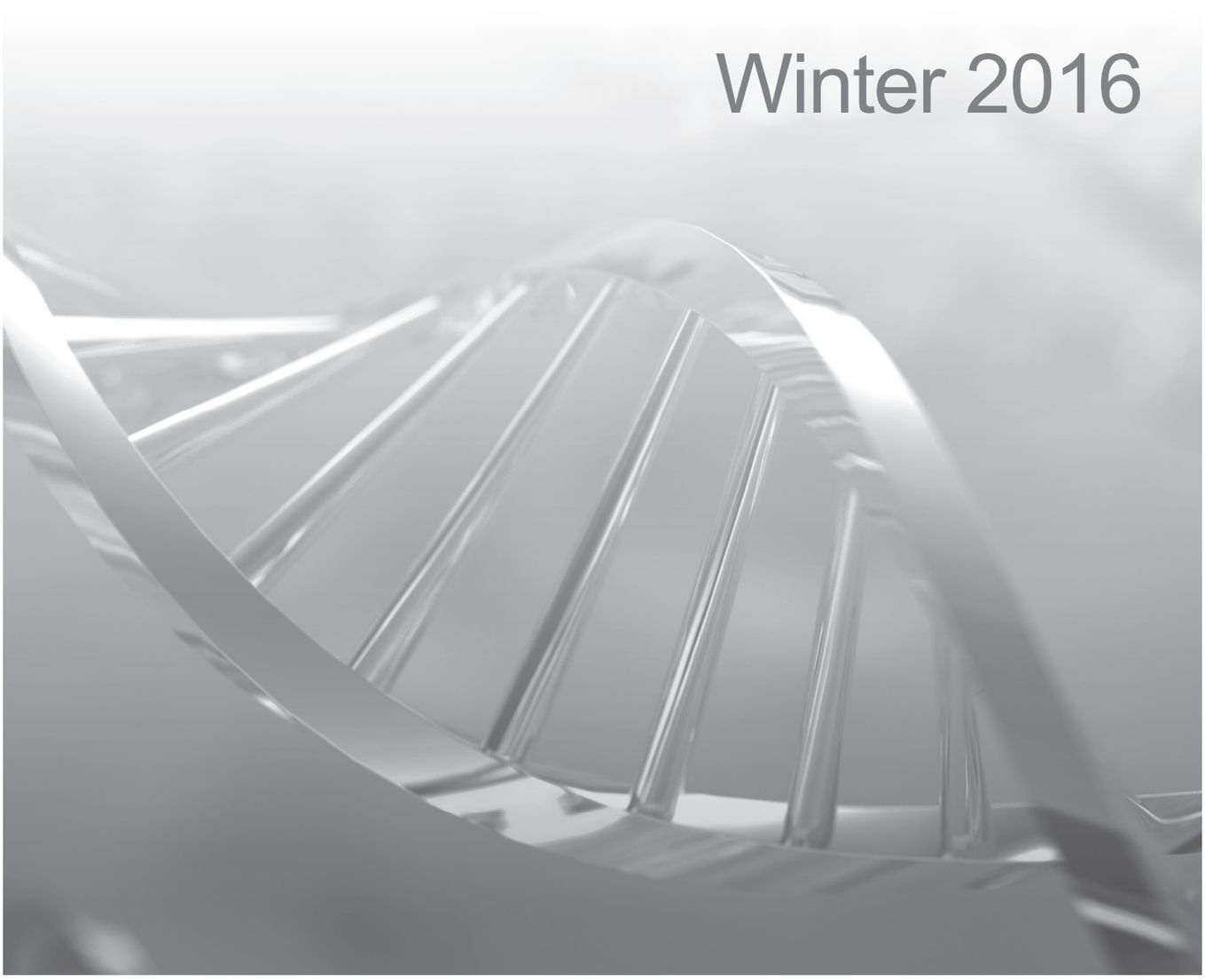
GP-Update
Red Whale

The GP Update Handbook

Winter 2016



Abbreviations used in the GP Update Handbook

We try to avoid using abbreviations except where they are universally recognised (MI, COPD). The only exceptions to this are the abbreviations of some of the journals we use:

Ann. Int. Med.	Annals of Internal Medicine
Arch. Int. Med.	Archives of Internal Medicine
BJGP	British Journal of General Practice
BMJ	British Medical Journal
DTB	Drugs and Therapeutics Bulletin
JAMA	Journal of the American Medical Association
MeReC	National Prescribing Centre Bulletins *(not exactly an abbreviation!)*
NEJM	New England Journal of Medicine
NICE	National Institute for Health and Clinical Excellence
SIGN	Scottish Intercollegiate Guidelines Network

Statistical abbreviations are listed in the statistics chapter.

A note on Cochrane references

Cochrane reviews are referenced as: Cochrane 2005;CD002946. Go to www.cochrane.org (NOT cochrane.co.uk!) and type the 'article number' without the date (e.g. CD002946) into the search engine.

At the end of each section in the Handbook you will find a summary box, which include the key take home messages, some ideas to help you apply your learning and some useful websites.

	This icon occurs where we list **Take home messages**
	This icon occurs where we list possible ideas for **CPD actions**
	This icon occurs where we list **Useful websites**
	This icon shows where you can add your own **Notes**

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Welcome to the GP Update Handbook

GP Update is very pleased to offer this series of one-day courses in Australia. We have a proven track record in delivering high quality education for primary care clinicians in the UK, with around half of all British GPs attending our courses every year.

For this series of courses, we have been working with local partners to adapt our resources to the Australian context. We are well aware that, in the current climate, new evidence is constantly emerging resulting in frequent guideline change: as a result, it can be difficult for even the most dedicated of GPs to keep up. However, help is at hand as we have done the legwork for you by trawling through the journals to bring you up to speed on the latest issues, literature, research and guidelines in Australian general practice. Everything that you will learn on our fun and entertaining courses (plus more!) is covered in this Handbook, so that you can reinforce your learning and reference the relevant information when you need it. We hope that this will prove to be a valuable resource in helping you to deliver the best care for your patients.

In 2014, GP Update set up a social enterprise, Primary Care International (PCI), to extend its reach outside of the UK. Revenue from GP Update courses delivered in settings such as Australia will be used to support PCI's operational costs as it develops projects in low and middle income countries. These projects include health worker training on non-communicable diseases in refugee camps and other humanitarian settings, as well as partnering with African organisations to test new approaches to primary care through a Healthcare Innovation Programme. If you would like to subscribe to the GP Update Online Handbook and related CPD activities (UK version), please contact mail@pci-360.com. Each subscription will support PCI's project work internationally. To find out more about PCI, visit www.pci-360.com.

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CATEGORY 2

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Atrial fibrillation

You notice Mrs Jones (85y) is in AF. What do you do?

AF statistics

- *Prevalence is 5.35% in people aged ≥55y, although in the over 85s it is nearer 18% (MJA 2015; 202 (1):32).*
- *AF increases stroke risk 5-fold compared to people without AF (European Heart Journal 2012, 33:2719)).*

Definitions

Lone AF: those <65y with no other risk factors (so no structural or ischaemic heart disease, etc.).

Paroxysmal AF: AF which terminates spontaneously within 7 days of onset (often within 48h of onset). It may recur frequently or rarely.

Persistent AF: AF which is present continuously for 7 days or more OR terminated by cardioversion (mainly a term used by cardiologists rather than GPs).

Permanent AF: AF which can't be terminated by cardioversion OR a decision has been made not to attempt cardioversion. Most of our patients will be in this latter group.

Cardioversion: remember this may be chemical (using drugs) or electrical.

Valvular and non-valvular AF: Western Australian guidelines (we don't have any current national ones!) state that people with known or suspected valvular AF (mitral valve disease, prosthetic valve, valve repair) should all be prescribed antithrombotic therapy unless contraindicated (Department of Health, Western Australia, 2014, Quick reference guide: Atrial fibrillation information for the health practitioner). People with non-valvular AF should have their stroke risk assessed using CHA_2DS_2Vasc before considering anticoagulation.

Known unknowns

NICE in the UK highlight the fact that in AF we still don't know:

- Whether referring to a specialist is beneficial?
- What is the best risk stratification tool for stroke prevention? To assess bleeding risk?
- What is the best antithrombotic agent?

However, we do have some guidance from the National Prescribing Service (NPS) that we can use whilst this is being explored.

NICE, NPS and WA Department of Health guidance on AF

In 2014 NICE updated their guidance on AF. I've included it here as we don't have any recent Australian national guidelines on the management of AF. However, I've also supplemented it with information from the NPS, Therapeutic Guidelines (TG), an MJA article and WA Department of Health. If there is any disagreement between these references I've indicated it in the text. Here is a summary of the guidance.

- **Aspirin is no longer recommended. Anticoagulation is the treatment of choice to reduce strokes.**
- **The majority with AF should be offered rate control. Rhythm control is first line therapy in only a minority.** Examples of when you might consider rhythm control in the Australian guidance include acute onset, symptomatic AF and patients with severe symptoms or compromised haemodynamic state.
- **Use CHA_2DS_2Vasc score in preference to $CHADS_2$ to assess stroke risk.**
- **Use HASBLED in all to assess bleeding risk.**
- **Stratify stroke risk for paraoxysmal AF and flutter in the same way you would permanent AF.**
- **There is increased use of left atrial appendage occlusion (explained later) for those who do not respond to conventional therapies.**

'Screening' NICE 2014, CG180

- Do NOT screen for AF: that is, don't do population screening in asymptomatic patients. However, watch this space. Some health professionals are advocating for a national approach to AF screening given its increasing prevalence (MJAInsight, 19/1/15)
- Opportunistic case finding is advocated: look for AF (by taking the pulse) in those presenting with:
  - Breathlessness
  - Palpitations
  - Syncope/dizziness
  - Chest discomfort
  - Stroke/TIA.
- An irregular pulse has good sensitivity and specificity especially in the over 75s.
- If a pulse is regular, the chance of AF is very small (negative predictive value around 99%).

Diagnosis and investigations

Diagnosis and investigations

Based on NICE (2014, CG180), MJA (2013, 199(9):592), Department of Health, Western Australia (2014, Quick reference guide: Atrial fibrillation information for the health practitioner).

Look for AF by OPPORTUNISTIC CASE FINDING

- Take the **pulse** in those with symptoms suggestive of AF:
  - Breathlessness
  - Palpitations
  - Syncope/dizziness
  - Chest discomfort
  - Stroke/TIA
- Do NOT screen asymptomatic populations (evidence shows no benefit)

AF may also be detected as an incidental finding on clinical examination

↓

Record a 12-lead ECG

If paroxysmal AF is suspected: Holter monitor or event recorder

↓

ECG confirms AF or flutter

Patient education	Stroke prevention/bleeding risk assessment	Rate/rhythm control	Bloods? Echo? Referral?
Ensure patient has up to date information on AF including: Cause, effects, possible complications, management (rate/rhythm control, stroke prevention) and support networks. See Useful websites box for some useful patient sites.	**Assess stroke risk using CHA_2DS_2Vasc** (preferred to $CHADS_2$) **AND** **Assess bleeding risk using HASBLED.**	**Rate control is treatment of choice for majority.** Rhythm control may be indicated if: • Unacceptable arrhythmia-related symptoms • 1st presentation with non-valvular AF • AF secondary to treated/correctable precipitant, e.g. infection • Intolerance to rate controlling drugs • Congestive heart failure • Younger people (<65y)	**Bloods**: NICE do not recommend any blood tests. However, most GPs would do FBE, UEC and thyroid function as a minimum **Echo**: NICE recommend not to routinely order an echo but the MJA article does (see below) **Referral to specialist**: NICE state that routine referral is not needed. Referral should occur if patient is haemodynamically unstable or treatment doesn't control symptoms. However, the MJA article states that all patients should be considered for referral given the increasing therapeutic options available – but it was written by four cardiologists!

Echo

Guidelines currently provide conflicting advice with regard to whether echocardiograms should be ordered for all patients presenting with AF. The MJA article recommends that echos should be routinely performed to look for structural disease, whilst the DoH WA guidance recommends them for people with symptomatic AF, known or suspected heart disease or cardiac risk factors.

NICE advises do NOT routinely do an echo if the decision to initiate anticoagulation has already been made on clinical grounds (this will be the case for most of our patients). However, they say that an echo should be done if:

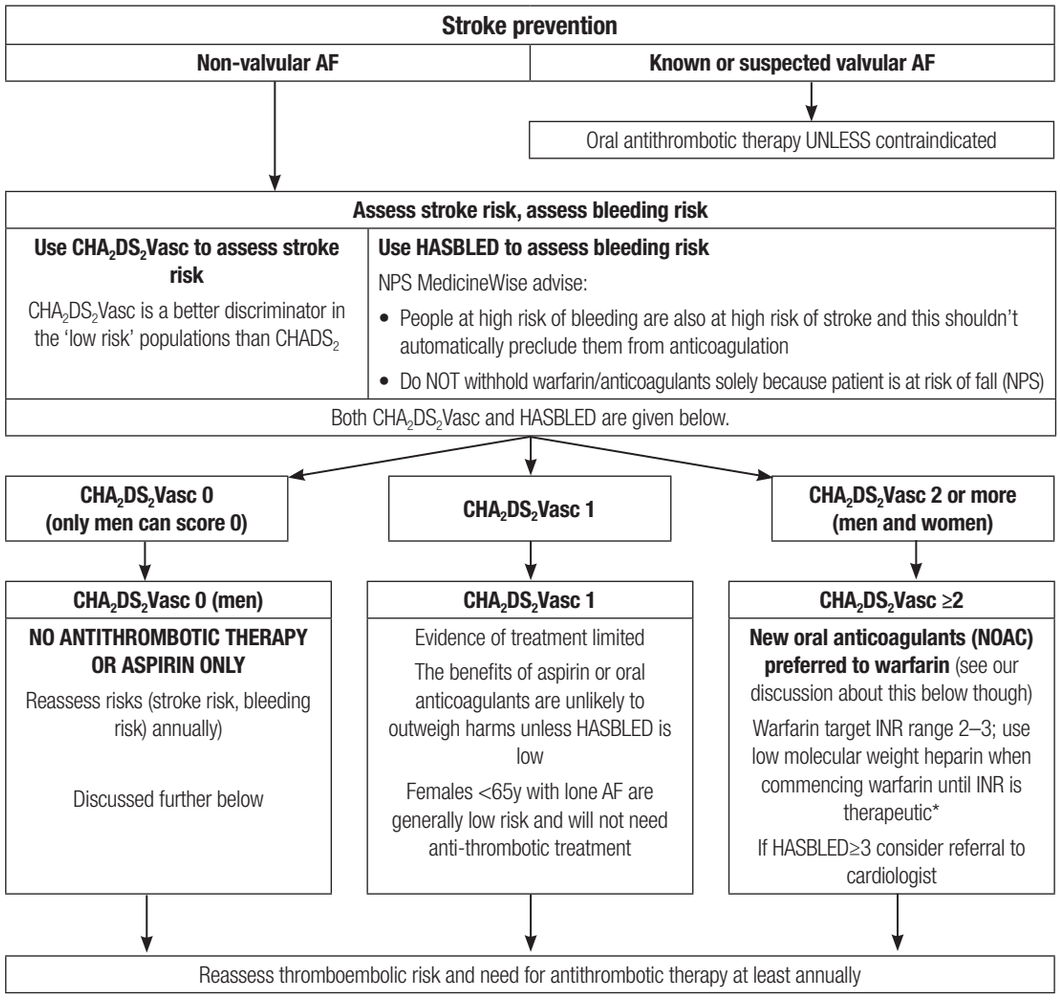
- Suspected underlying structural or functional heart disease (e.g. murmur, heart failure).
- Cardioversion planned (echo can indicate likelihood of success).
- Better stroke risk stratification for antithrombotic therapy is needed (for example, high risk of stroke but also high risk of bleeding).

A trans-oesophageal echo maybe used in specific situations but this would be a cardiologist's decision. .

As the guidance differs, clinician's should use their individual discretion in regards to deciding whether to order an echo or not.

Stroke and bleeding risk stratification

Stroke and bleeding risk stratification Department of Health, Western Australia, 2014



*See Therapeutic Guidelines, NPS and section below for further information as LMWH is not always required when commencing warfarin.

This guidance continues a few pages on after a discussion of the above guidance.

Women and AF

A Swedish cohort study has shown that women are at slightly higher risk of stroke when in AF than men, after adjusting for other risk factors (about 1.1–1.2× higher risk) (BMJ 2012;344:e3522). However, although CHA_2DS_2Vasc score gives women an extra point, NICE then ignores this by setting a higher threshold for anticoagulation in women – in effect NOT weighting being female as a risk factor!

CHA_2DS_2Vasc score

The CHA_2DS_2Vasc stratifies stroke risk.

- Score 2 or more (men and women): offer anticoagulants.
- Score 1 in men only: consider anticoagulants.
- Score 1 in women only: consider no antithrombotics.
- Score 0 (men): no antithrombotics.

Letter	Risk factor	CHA_2DS_2Vasc: maximum = 9
C	**C**ongestive cardiac failure/left ventricular dysfunction	1
H	**H**ypertension	1
A	**A**ge ≥75y	2
D	**D**iabetes	1
S	Previous **S**troke/TIA/thromboembolism	2
V	**Vasc**ular disease (MI, PAD, aortic plaques)	1
A	**A**ge 65–74y	1
Sc	**S**ex **c**ategory (female)	1
Note: maximum score is 9 since age may contribute 0, 1 or 2 points		

Why is CHA_2DS_2Vasc preferred to $CHADS_2$?

CHA_2DS_2VASc is a better discriminator than $CHADS_2$ in the 'low risk' populations – that is, it helps separate those who will benefit from anticoagulation from those who won't.

Do note that most of the trials showing this have recruited patients from hospital settings (or mixed hospital and primary care settings).

HASBLED score

The HASBLED score identifies those at high risk of bleeding (score ≥3).

Letter	HASBLED Criteria: score 3 or more suggests high risk	Points: maximum = 9
H	**H**ypertension (SBP >160)	1
A	**A**bnormal renal function (on dialysis/transplant/Cr>200) and/or **A**bnormal liver function (defined as chronic hepatic disease (e.g. cirrhosis) or abnormal LFTs (e.g. bilirubin >2× upper limit of normal, AST/ALT/ALP >3× upper limit normal)	1 point for any renal abnormalities 1 point for any liver abnormalities
S	**S**troke	1
B	**B**leeding (PMH of bleeding problems/anaemia/bleeding tendency)	1
L	**L**abile INRs (unstable INRs or INRs frequently not in therapeutic range)	1 Score 0 if never had warfarin
E	**E**lderly (age >65y)	1
D	**D**rugs (e.g. on aspirin/NSAIDs) or alcohol abuse (1 point each)	1 or 2

For those who like to play around with numbers, the SPARC tool allows you to look at risks and benefits of different treatments based on different CHA_2DS_2Vasc and HASBLED scores (www.sparctool.com). Do note that it does include some treatments not used in Australia.

What about aspirin?

The WA Department of Health guidelines advise that aspirin may be considered for those with a CHA_2DS_2Vasc score of 0 or 1 whilst the NPS doesn't recommend aspirin for people with a CHA_2DS_2Vasc score ≥1 unless anticoagulation is contraindicated. Let's look at what other international guidelines are saying.

The UK NICE guidelines do not recommend the use of aspirin at all. Compared to placebo, NICE found no benefit from aspirin in terms of:

- All-cause mortality.
- Ischaemic strokes.
- Systemic emboli.
- Major bleeding.

When aspirin is compared with anticoagulants, there is clear benefit from anticoagulation in terms of:

- All-cause mortality.
- Ischaemic stroke.

However, the 2014 American Guidelines DO offer aspirin alone as an option in those with a CHA_2DS_2Vasc of 1 (other options for a score of 1 are anticoagulation or nothing) (JACC 2014;64:2246).

The 2010 European AF guidelines DO offer aspirin alone as an option for treating AF, but never as a preferred treatment. If the CHA_2DS_2Vasc score is 1, anticoagulation is preferred but aspirin is an option. If the CHA_2DS_2Vasc score is 0, no treatment is preferred, but aspirin is offered as an option (Eur Heart J 2010;31:2369 and 2012 update).

What about clopidogrel?

Clopidogrel alone

Australian, American and European guidance do not recommend the use of clopidogrel as monotherapy in AF (Therapeutic Guidelines, 2012, Eur Heart J 2010;31:2369 (and 2012 update) and JACC 2014;64:2246).

Clopidogrel and aspirin together

Therapeutic Guidelines do NOT recommend using aspirin with clopidogrel. They concluded there WAS evidence of benefit (compared to aspirin alone), and they acknowledged that some people would benefit from this treatment. However, the only group they would recommend it for would be those in whom all other forms of anticoagulation were contraindicated or not tolerated, and that in this group the bleeding risk was likely to be high (57% increase in major bleeds compared to those taking aspirin alone). *I think that what Therapeutic Guidelines are saying is that they recognise some people would benefit but this is a decision to be made on an individual patient basis (probably by a cardiologist, not a GP) rather than in a guideline.*

The 2010 European AF guidelines do recommend aspirin + clopidogrel as options for treating AF, for those unsuitable for anticoagulation (Eur Heart J 2010;31:2369 and 2012 update).

The US guidance does NOT recommend clopidogrel with aspirin in AF (JACC 2014;64:2246).

What does all this mean in practice?

I think that the take home message here is that anticoagulation is significantly better than antiplatelet therapy in AF.

However, there may be people who can't use warfarin and, on specialist advice and ensuring the patient understands this is a second best option, it may be appropriate to use aspirin or clopidogrel, or both, in this small group of people.

What is the benefit from anticoagulation?

Compared with placebo, NICE found anticoagulants (basically this means warfarin):

- Reduce all-cause mortality: 22 fewer/1000 treated (NICE give no time frames: probably 1y).
- Reduce ischaemic stroke: 37 fewer/1000 treated.
- Didn't increase risk of significant bleeds: 2 fewer to 24 more/1000 treated.

Do note that although these pooled data suggest no increased bleeding risk overall, individual trials do show an increased bleeding risk with anticoagulants:

- The Birmingham AF trial gave a bleeding risk in the order of 1.5%/y for a significant bleed (Lancet 2007;370:493). This was a population that included some people who had already been on warfarin for years, and so were likely to have selected themselves out as being 'lower' risk by definition.
- The NOAC trials showed the risk of a significant bleed for warfarin (and the NOACs) was around 3.3–3.6%/year (data for dabigatran, NEJM 2011;363:1875).

Warfarin in older people

NPS (MedicineWise News, Feb 2013) reminds us that:

- For most, the benefit of anticoagulation outweighs the risks.
- We should NOT withhold warfarin solely because the person is at risk of having a fall.

Clinicians can be reluctant to use warfarin in older people, often because an overemphasis on the harms and an under-appreciation of the benefits. So here are some data that should challenge you about the use of warfarin in older people.

- **Don't overestimate the risk of bleeding in older people:** in the primary care UK-based BAFTA trial, where all participants were 75y or older (mean age 81y), **the rate of haemorrhage in the aspirin and warfarin groups were very similar** (approx. 1.5%/y). Now, some of these patients had already been on warfarin before the start of the trial (thus showing they were relatively 'safe' on warfarin), and those with obvious contraindications to warfarin were excluded from the trial, but nevertheless this was a UK-based primary care study, of patients with AF just like yours and mine (Lancet 2007;370:493).
- **Don't underestimate the benefits of warfarin in terms of stroke prevention:** a reduction in mortality of 22 fewer deaths/1000 treated and 37 fewer strokes/1000 treated (NICE 2014, CG180).
- **Don't overestimate the risks of harms from falls.** In a study in 1999 (old, but we don't think it has been repeated) researchers looked at those with a $CHADS_2$ score of 2–3 (average annual stroke risk around 5%) and showed that they would need to fall 295 times for the risk of falls to outweigh the benefits of warfarin (Arch Intern Med 1999;159:677).

Warfarin: assessing time in therapeutic range

Aim for a time in therapeutic range (TTR) of more than 65%.

Most computer dosing systems calculate TTR automatically. For manual dosing it is the proportion of tests in the correct range. TTR should be calculated over a 6m period, excluding the initial 6w of treatment.

Poor control is shown by (in last 6m):

- TTR of 65% or less.
- 1 INR higher than 8.
- 2 INRs higher than 5.
- 2 INRs less than 1.5.

If poor control on warfarin, consider factors that may contribute to this:

- Cognitive function.
- Compliance.
- Drug interactions or co-morbidities.
- Lifestyle factors including alcohol and diet.

If poor control and this can't be improved:

- Review stroke and bleeding risk and consider:
  - Left atrial appendage occlusion (see below)
  - NOAC, but beware! See 'Caution in poor compliers' below.

A scoring tool (SAMe-TT2R2) has been proposed as a way of assessing who will do well with warfarin and who won't (Chest 2013;144:1555). This has not yet been widely tested, so I won't cover it here.

Warfarin WITH antiplatelets?

Do NOT use warfarin and an antiplatelet to reduce stroke risk in AF.

However, some people will need warfarin for their stroke prevention but have also had an MI and so should be on aspirin/clopidogrel for secondary prevention of cardiovascular disease. Let's look at what the UK guidelines say about this. In these situations the NICE guidance on secondary prevention post-MI is clear: if both agents are needed, balance risks with benefits, and unless there is a high risk of bleeding, warfarin and aspirin, or warfarin and clopidogrel can be used together. The newer antiplatelets (prasugrel, ticagrelor) should NOT be used. The NICE AF guidance says that the NOACs should not be used in this context either (lack of evidence for these combinations) (NICE 2013, CG127). (For those of you who may have seen the NICE guidance on acute coronary syndrome with raised biomarkers, some patients MAY be discharged from hospital on rivaroxaban and aspirin +/– clopidogrel, but that is a completely different scenario to AF and would be a hospital initiated decision (NICE 2015, TA335).) However, there is no specific guidance in the Australian guidelines, so it might be worth talking to your local cardiologist.

What role for NOACs?

The advice about which agent should be used for anticoagulation in AF is mixed. Whilst Therapeutic Guidelines and NPS recommend warfarin as a first-line agent, the more recently released WA guidelines state that NOACs are the preferred agents (NPS MedicineWise News, Feb 2013; Department of Health, Western Australia, 2014, Quick reference guide: Atrial fibrillation information for the health practitioner; Therapeutic Guidelines, 2012). Let's weigh up the evidence for this.

NOACs: the evidence in AF

Here I will look at the evidence on NOACs in AF, mainly from a Lancet review, with evidence from other sources to complement this (Lancet 2015;386:303). There is more on NOACs, particularly the practicalities of their use, in the NOACs article elsewhere in this Cardiovascular chapter.

- NOACs are easy to use because they need no monitoring.
- There are relatively few food and drug interactions compared with warfarin.
- Renal excretion means that there is concern about use in renal impairment (see the NOACs article for more detail).
- There have been no head-to-head trials of the NOACs so you can't say that any one is 'better' than another.
- Onset of action is fast (2–3h) and half-life is around 12h (longer in renal impairment).
    - The short half-life means that one missed dose matters, and also makes NOACs unsuitable if compliance is erratic because the anticoagulation effect will also be erratic.
    - The short half-life means they clear relatively rapidly from the system, however, in the event of significant bleeding, there are no antidotes yet available (trials are underway). To reverse a NOAC, activated charcoal may be given orally to reduce absorption (if NOAC taken within previous 2h), or specialist blood products may be used (prothrombin complex concentrate, activated factor VII) although guidance on use and evidence of effectiveness is lacking.

Benefits of NOACs: stroke prevention in AF

- **In large clinical trials NOACs had lower all-cause mortality than warfarin.**
- **NOACs are at least as good as warfarin at preventing strokes in AF.**
    - In the AF trials some of the data suggested the NOACs may be better than warfarin (NNT 100–333/y – that is, you have to treat between 100 and 333 people for a year with a NOAC instead of warfarin to prevent one extra stroke). However, because in some trials the time in the therapeutic range in those on warfarin was significantly below that achieved in the UK, the NNT may well be higher (making the relative benefit over warfarin smaller) (Rocket AF trial, NEJM 2011;365:883).

Harms: bleeding risk (in the AF trials)

- **All three NOACs have bleeding risks roughly equivalent to warfarin (about 3.3–3.6%/y) although NOACs result in fewer intracranial bleeds but more gastrointestinal bleeds**. Do note that GI bleeding is the commonest source of unwanted bleeding in those on anticoagulation (NEJM 2011;363:1875).
- However, in two large 'real world' studies comparing dabigatran, rivaroxaban and warfarin:
    - **There were no significant differences between the 3 drugs in terms of bleeding risk, once they adjusted for known risk factors** (age, NSAID use, etc.). However, because the bleeding rate was low the confidence intervals were wide – there could be up to twice as many bleeds in the rivaroxaban group compared with the warfarin group and a 0.5-fold (50%) increased risk of bleeding in the dabigatran group compared with the warfarin users (BMJ 2015;350:h1585).
    - **NOACs seemed to have a higher risk of bleeding than warfarin in older people, and over the age of about 76y, warfarin had a lower bleeding risk than the NOACs** (do note in this study the higher dose of dabigatran was used, whereas the lower would be recommended in the UK in older people because of reduced renal clearance) (BMJ 2015;350:h1857).
    - **These 'real world' trials suggest the GI bleeding risk of dabigatran, rivaroxaban and warfarin are similar, although this may not be true in older populations, where warfarin may be safer.**
    - **The editorial accompanying both these articles wonders if some kind of monitoring (drug plasma concentrations) may be beneficial, to help stratify those at increased risk of bleeding with the NOACs, particularly in the elderly. *This would rather negate one of the big benefits of the NOACs!* (BMJ 2015;350:h1679).**

Heparin: what role in AF?

Heparin is mentioned in the AF guidance, but in the context of people developing new AF, for example, post-operatively or in the context of fast AF with significant compromise, when heparin is recommended until a decision is made about long term anticoagulation. It doesn't have a role in primary care management of AF.

Left atrial appendage occlusion

The left atrial appendage is the embryological remnant of the left atrium and is a little blind-ending passage/sac off the left atrium. Unlike the rest of the atria, its surface is crenelated, not smooth, and unlike the right atrial appendage it has a relatively narrow opening. All this increases the risk of stasis and thrombus formation, and in AF it is thought to be a major source of thrombus. Left atrial appendage occlusion involves closing the left atrial appendage using a catheter, and can be done in the catheter lab on relatively frail individuals because it does not require a general anaesthetic. Once closed, although the atria continues to fibrillate the risk of thrombus is low, so anticoagulation/antithrombotics are not indicated. However, do not refer everyone for this because it is a relatively new procedure (the trials showing benefit quoted by NICE had under 1000 people in them).

NICE recommend left atrial appendage occlusion as a second line therapy in AF or paroxysmal AF when:

- **Anticoagulation is contraindicated.**
- **Other treatments have failed.**

Left atrial appendage occlusion is available in Australia and information about the procedure is available on the AF Association Australia website (www.atrialfibrillation-au.org).

Rate or rhythm control in atrial fibrillation?

Rate or rhythm control in AF? WA Dept of Health, 2014 and Therapeutic Guidelines, 2012

The bottom line is: rate control for most people!

Rate or rhythm control?

- **New onset non-valvular AF** (new onset isn't defined; think about identifying people with a good story for recent onset, e.g. I suddenly got these dreadful palpitations)?
- **AF with reversible cause?**
- **Heart failure?**
- **Unacceptable arrhythmia related symptoms?**

NO / **YES**

Rate control (the vast majority)

Use beta blockers or rate-slowing calcium channel blockers:

- Atenolol 25–100mg od OR
- Metoprolol tartrate 25–100mg bd OR
- Diltiazem controlled release 180–360mg od OR
- Verapamil sustained release 160–480mg od

Digoxin can be considered for elderly sedentary patients or in those with AF and heart failure where other drugs may be contraindicated or require slower titration.

Rhythm control (a minority)

Refer for cardioversion

Electrical cardioversion often preferred. If AF>48h or uncertain duration and patient stable – anticoagulation for 3w prior and 4w post cardioversion. If patient unstable, urgent cardioversion is required +/– trans-oesophageal echo. Antithrombotic therapy is then based on stroke risk/risk AF recurrence/presence of thrombus.

Pharmacological cardioversion can be considered if AF is of short duration. Amiodarone, sotolol and flecainide may be prescribed by experts for this purpose, however amiodarone does not achieve cardioversion in the short to medium term.

After cardioversion – consider referral to cardiologist/electrophysiologist

Some people may require dual therapy to achieve rate control of their AF. This isn't addressed in the Australian guidelines, but NICE recommends two of either a beta blocker, diltiazem or digoxin and if this is ineffective, to refer for rhythm control or ablation.

NICE guidelines suggest to aim to keep the pulse rate under 100/min.

Why is rate control preferred over rhythm control?

There are no significant differences in outcomes between rate and rhythm control. This applies even in the presence of heart failure.

Rate control is simpler, more cost effective and may result in fewer admissions.

Do note that the sub-groups selected for rhythm control (new onset AF, AF with reversible cause and heart failure caused predominantly by AF) were decided on the basis of expert consensus, not because of evidence.

Why is digoxin third line?

There is limited RCT evidence for digoxin in AF! Increasingly it is recognised that although digoxin controls rate at rest, it tends to have much less impact when people are active.

An analysis of data of people on digoxin in one of the NOAC trials looked at the outcomes in those on digoxin versus those not on it (Lancet 2015;385:2363).

- **In those on digoxin there was an increase in all-cause mortality (approximately 1 extra death/100 patient years).**
- The excess deaths appeared to be, in part at least, due to vascular deaths and sudden death.
- These increased risks were the same whether or not people also had heart failure.

A meta-analysis of 9 trials of people with AF and 3 trials of those with AF and heart failure (and 7 studies of CHF) showed that digoxin increased the all-cause mortality.

- **In those with AF the hazard ratio was 1.3 (CI 1.2–1.4)**

Although there are some issues with this meta-analysis (mainly observational studies, not analysed at the individual patient data level), it was large (over 300 000 people) and the average length of follow-up was 2.6y (Eur Heart J 2015 doi:10.1093/eurheartj/ehv143).

- **A much larger meta-analysis found digoxin had no impact on mortality and slightly reduced the risk of hospital admission in those with heart failure, and those with heart failure and AF. They didn't have enough robust data to comment on digoxin use in those with AF alone** (BMJ 2015;351:h4451).

This study pooled all trials of those with AF or heart failure (many patients had both) that randomised people to digoxin v placebo (52 studies, 600 000 patients) from 1960 to 2014. They adjusted for known risk factors. Interestingly those with lower digoxin plasma concentration had some mortality benefit but those with higher plasma concentration levels (>0.9ng/ml) did have an increased risk of death (the therapeutic range is usually given as 0.8-2ng/ml).

The accompanying editorial pointed out that the trial also showed (BMJ 2015;351:h4662):

- Digoxin tends to be given to sicker patients (with whom you might expect to see higher mortality rates in, regardless of which drug you used).
- The RCTs showed the safety of digoxin, whereas the observational trials suggested (quite strongly) an increased mortality rate with digoxin. They argue that the Lancet and European Heart Journal studies involved observation data (at least in part) and this may have contributed to the findings.
- **The authors and editorial call for a large prospective trial so we really can understand the place for digoxin in heart failure and AF**

Rhythm control drugs: a reminder!

There are 4 main classes of anti-arrhythmics (from BNF 2014):

Class 1c: flecainide, propafenone. (Class 1a (disopyramide) drugs – rarely used in the UK.)

Class 2: beta-blockers (but not sotalol, see below).

Class 3: amiodarone, dronedarone, sotalol. NOTE: sotalol only has class 3 properties above 240mg/day. Below this dose (and most are on lower doses) it acts like a standard beta-blocker, but lengthens QT interval and for this reason it is not a primary care drug (NICE CKS on AF).

Class 4: rate limiting calcium channel blockers (verapamil, diltiazem), NOT the non-rate limiting calcium channel blockers (the dihydropyridines – amlodipine, nifedipine, etc.).

In primary care we would rarely be initiating rhythm control drugs except on the advice of secondary care.

REMINDER: verapamil should not be used with beta-blockers (risk of hypotension and asystole) (very occasionally used in combination by cardiologists if good myocardial function – but a definite no in primary care!).

Verapamil and diltiazem depress myocardial function and should not be used in heart failure.

Maintenance of sinus rhythm

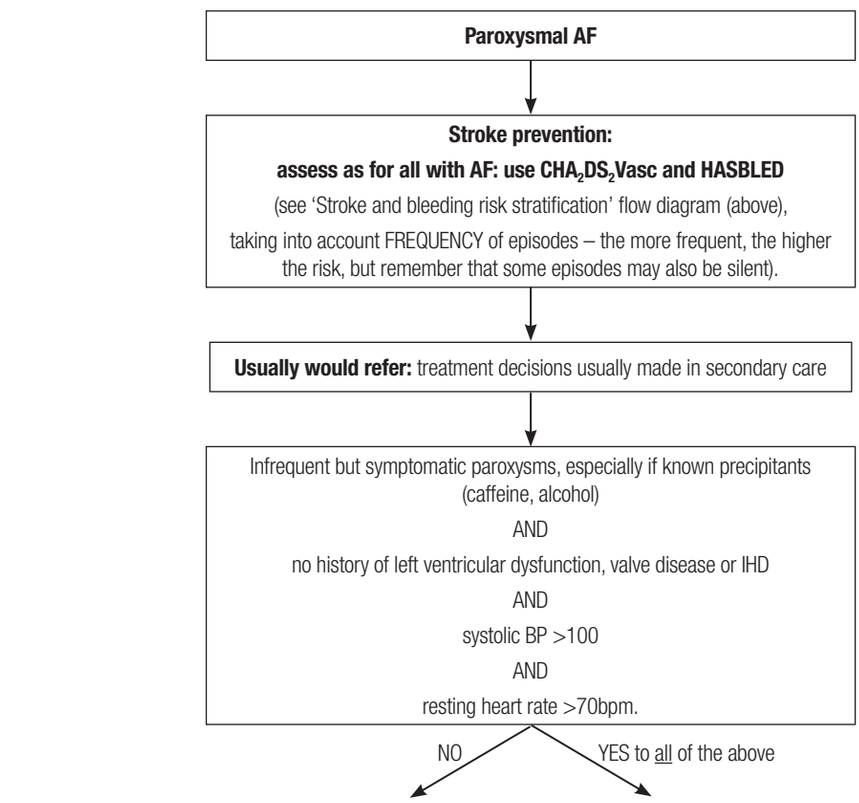
Drugs may be used long term to maintain someone in sinus rhythm after cardioversion. This would always be a cardiologist's decision. Here's what Therapeutic Guidelines have to say:

- Flecainide is recommended for people with normal left ventricular function and no coronary disease.
- Sotalol
    - Beware of sotalol use in those with renal impairment (BNF advises half doses if eGFR 30–60 and quarter doses if eGFR 10–30). Specialist advice is recommended.
    - Australian Medicines Handbook advises sotalol is contraindicated in prolonged QT interval as this is a potential side effect and can increase the risk of arrhythmia. They do not specifically state that a baseline ECG or ongoing monitoring is required although this is advised by the British National Formulary.
- Amiodarone may be used if left ventricular impairment or heart failure.

Paroxysmal AF

Therapeutic Guidelines remind us that paroxysmal AF confers a similar stroke risk to permanent atrial fibrillation, so assessment with CHA_2DS_2Vasc and HASBLED is important. Usually, these patients would be referred to a cardiologist for review and a management plan regarding rate and rhythm control. Below I've included the algorithm from the UK NICE guidelines (note that we don't use dronedarone in Australia) to provide an outline of the possible management strategies.

Management of paroxysmal AF



Long term rhythm control: to hold in sinus rhythm

(this will be the majority)

Use beta-blocker (not sotalol)

(unless contraindicated).

If beta-blockers don't work or are contraindicated the following may be used:

- Amidoarone (if heart failure/LV impairment).
- Sotalol, at doses that give class 3 antiarrhythmic effect, (care in renal failure or if low BMI).
- If structural heart disease: do NOT use class 1 antiarrhythmic such as flecainide or propafenone.
- There is almost no role for digoxin.

If the above fail/can't be used consider:

dronedarone or left atrial appendage occlusion.

Dronedarone is very definitely a secondary care drug! NICE set strict criteria for use in 2010 (NICE 2010, TA197).

The MHRA also highlighted concerns about the cardiovascular risks, concerns about hepatotoxicity and the risk of pulmonary fibrosis. Regular cardiac, renal and hepatic function monitoring is required (Drug Safety Update 2011;5:3).

Try 'pill in the pocket': to abort AF when it occurs

(this will be a minority)

The patient takes a one-off oral dose of an antiarrhythmic to abort the attack (e.g. flecainide).

Suitable for those on no or low maintenance doses of antiarrhythmic.

Aim is to abort the attack with a single dose of antiarrhythmic, without further treatment/admission.

Secondary care decision.

Evidence for 'pill in the pocket'?

A trial of 212 people with mild symptoms and <12 attacks/year of paroxysmal AF were given either flecainide or propafenone to self-administer during an attack (BMJ 2007;334:637):

The results showed:

- No reduction in the number of attacks.
- Statistically significant drops in rates of A&E visits (from 45.6/month to 4.9/month).
- Statistically significant reduction in hospital admissions (from 15/month to 1.6/month).

A significant benefit to patients and cost saving for the NHS.

Paroxysmal AF in cryptogenic stroke

Cryptogenic stroke is a stroke for which no cause is found on routine investigations. A small trial of 572 patients over the age of 55 who had had a cryptogenic stroke/TIA, randomised them to a 30d event recorder or a 24h event recorder (NEJM 2014;370:2467). This was to look for paroxysmal AF.

The 30d recorder picked up significantly more paroxysmal AF than the 24h recorder. By the end of the trial 19% in the 30d arm were on anticoagulants because of AF compared with 11% in the 24h arm. This difference is statistically significant. Perhaps we need to be looking harder for paroxysmal AF in those who have had a stroke or TIA of 'unknown' cause?

Fast AF

Obviously the treatment depends on how compromised an individual is. For us as GPs this is the critical assessment as admission is indicated in the presence of compromise. From a GP perspective all of these people need admission!

Pace and ablate

Used in permanent AF with on-going symptoms or high ventricular rate where other treatments have failed.

A pacemaker is fitted and the AV node ablated. This controls ventricular rhythm but the atria still fibrillate, so there is still a need for anticoagulation.

'Watch BP Home A' device for screening for AF

A new device has been approved by NICE to help screen for AF in those with hypertension (NICE 2012, MTG13). It is called Watch BP Home A (not the catchiest name for a device!) and I mention it here because it is available for purchase in Australia online. It is basically a blood pressure machine (it looks just like the electronic machines we all have on our desks) that also detects an irregular pulse. The device can be used in the surgery or lent to patients for home monitoring. The idea is that it screens for AF, thus reducing the burden of strokes from undiagnosed AF (although, as we mentioned above there is actually no evidence for screening for AF in asymptomatic populations as yet!).

- The machine is currently sold for around $220 – up to twice the cost of other BP machines.
- Everyone detected by the device as having an irregular pulse would need an ECG. For every 6 ECGs done, only 1 would actually have AF.
- NICE concluded that over the long-term the device would be cost-effective, particularly in the elderly population at higher risk of stroke (less evidence in the under 65s).
- NICE approved its use in the context of the diagnosis and management of hypertension, not for every patient you see.

Given the high sensitivity and specificity of pulse taking, I can't see the use for this in my daily practice.

Atrial fibrillation

- Population screening is not recommended. Opportunistic case finding is. Feel for an irregular pulse in those with breathlessness, palpitations, syncope/dizziness, chest discomfort or after a stroke/TIA.
- If AF is suspected do an ECG.
- If AF (or atrial flutter) confirmed, assess stroke risk using CHA_2DS_2Vasc and bleeding risk using HASBLED.
- CHA_2DS_2Vasc scores:
  - Score 2 or more (men and women): offer anticoagulants.
  - Score 1 in men only: consider anticoagulants.
  - Score 1 in women only: consider no antithrombotics.
  - Score 0 (men): no antithrombotics.
- Aspirin may be considered for people with a CHA_2DS_2Vasc score ≤1 depending on which guidelines you use. NPS doesn't recommend aspirin for people with a CHA_2DS_2Vasc score ≥1 unless anticoagulation is contraindicated because it is less effective in reducing all-cause mortality and ischaemic stroke.
- NOACs are an alternative to warfarin but have no antidote. They are not a good choice in poor compliers. See the article on NOACs for more information.
- Most with AF will be treated with rate control rather than rhythm control.
- Left atrial occlusion may be offered if anticoagulation is contraindicated or other treatments fail.
- In paroxysmal AF, a 'pill in the pocket' can be used for some, but others will need long-term rhythm control, usually with a beta-blocker. Don't forget anticoagulation often needed too!

Audit your use of thromboprophylaxis in line with the latest guidance. Focus particularly on those on aspirin: would warfarin be more appropriate? Or nothing?

For patients:

Heart Foundation:

http://heartfoundation.org.au/images/uploads/publications/Atrial-Fibrillation-information-sheet.pdf

Atrial Fibrillation Association:

www.atrialfibrillation-au.org/

Stroke Foundation patient information booklet on atrial fibrillation: https://strokefoundation.com.au/~/media/strokewebsite/resources/factsheets/eli0104_af-a5-patbroch_v9fa_onlinespreads1.ashx?la=en

For professionals:

NPS summary on Good anticoagulant practice www.nps.org.au/_data/assets/pdf_file/0018/222174/MedicinewisNews-Feb-2012-Warfarin-best-practice.pdf

My notes