DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

AMIODARONE MONITORING PROTOCOL

- Amiodarone is for initiation by the consultant or specialist only. Duration of treatment should be specified.

- Patients should be reviewed 6 monthly by their GP and monitored carefully for adverse effects of amiodarone therapy, particularly pulmonary toxicity and arrhythmias. U&E, TFT & LFT should also be monitored 6 monthly.

- Due to the long half-life of amiodarone, clinical problems (e.g. hyperthyroidism, photosensitivity) may occur/ persist for up to a year after stopping the drug. TFT should be monitored for up to 12months after discontinuation.

- Healthcare professionals should have a low threshold for suspecting amiodarone induced pulmonary toxicity (new/worsened cough or shortness of breath)– the patient should be referred to a specialist and carefully investigated.

- If optic neuropathy/ neuritis is suspected, refer urgently to ophthalmologist and discuss with patient's cardiologist.

- Amiodarone interacts with many other drugs – anyone prescribing medication for a patient taking amiodarone is responsible for checking for interactions.

- Due to increased risk of adverse effects over time, it is sensible to ask from time to time whether amiodarone is still indicated and whether the dose can be reduced. See appendix 3.

Document update	**Date of update**

Abbreviations

ALT	Alanine transaminase
CCF	Congestive cardiac failure
CXR	Chest X-ray
DLCO	Diffusing capacity of lung for carbon monoxide
ECG	Electrocardiogram
H&E	History & examination
HRCT	High resolution computed tomography
INR	International normalised ration
LFT	Liver function tests
MHRA	Medicines and Healthcare Products Regulatory Agency
PFT	Pulmonary function tests
T3	Liothyronine sodium
T4	Levothyroxine sodium
TSH	Thyroid stimulating hormone
TFT	Thyroid function tests
U&E	Urea and electrolytes

CONTENTS

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1. INTRODUCTION

Amiodarone is a class III antiarrhythmic drug (Vaughn-Williams classification) that reduces the incidence of arrhythmias by increasing the duration and refractory period of the cardiac action potential prolonging the QT interval. It also slows heart rate and cardiac action potential conduction through inhibition of beta receptors and ion channels in a similar manner to antiarrhythmic drugs from classes IA, II and IV.

Amiodarone can be used to treat many different types of arrhythmia but serious side effects, including fatal pulmonary toxicity, restrict its use clinically. It is therefore reserved for the treatment of severe rhythm disorder not responding to other therapies or when other treatments cannot be used.

Indications may include:

- Tachyarrhythmias associated with Wolff-Parkinson-White syndrome.
- Atrial flutter and fibrillation when other drugs cannot be used. (See local guidance for non-valvular AF)
- Tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias. Ventricular fibrillation; when other drugs cannot be used.

Initiation/ dosage

Only a cardiologist/specialist should initiate treatment with oral Amiodarone and duration of treatment should be specified. Primary care is responsible for the ongoing monitoring of patients prescribed Amiodarone. Oral loading dose 200mg 3 times daily for 1 week, reduced to 200mg twice daily for a further week; maintenance usually 200mg daily or the minimum required to control the arrhythmia.

These guidelines detail the monitoring of Amiodarone in primary care. Use in conjunction with local Management of non-valvular Atrial Fibrillation guidance.

2. PRIMARY CARE RESPONSIBILITIES

- Confirm indication and duration for prescribing amiodarone with the patient's cardiologist/ specialist if not already documented in patient's notes.
- Complete 6 monthly reviews of patients taking amiodarone, enquiring specifically about adverse effects and considering possible interacting drugs (see sections 4&5). Patients should be counselled to report side effects from amiodarone treatment.
- Check TFT, LFT, U&E, and if applicable digoxin level 6 monthly. See algorithms 5.1 and 5.2 for the management of abnormal results.
- If the patient has symptoms of pulmonary toxicity (new/worsened cough or shortness of breath), perform prompt ECG and CXR to exclude alternative diagnoses. If pulmonary toxicity remains a possibility, refer urgently to the initiating cardiologist/specialist or to a respiratory physician for confirmation of diagnosis and consideration of alternative anti-arrhythmics. Acute admission may be required. Early investigation with HRCT chest scan is important.
- If the patient reports new onset/worsening visual disturbances perform eye examination, make urgent Ophthalmology referral to exclude optic neuropathy and discuss alternative anti-arrhythmics with initiating cardiologist/specialist.
- If the patient presents with proarrhythmia, stop amiodarone and arrange urgent specialist appointment. Acute admission may be required.
- If bradycardia is detected, check for symptoms and arrange an ECG urgently if HR <50 or symptoms are present. If the patient has syncope or second or third degree heart block,

admission is advised. Mild sinus bradycardia is common but if the patient has symptoms such as increased breathlessness or presyncope which you feel may be due to this, please discuss with the specialist or arrange review

- See section 5 for the management of common and serious side effects. If any other abnormalities are detected or other adverse effects are suspected, the case should be discussed with a specialist for consideration of dose reduction or stopping amiodarone. A specialist appointment may be required.

3. MONITORING REQUIREMENTS

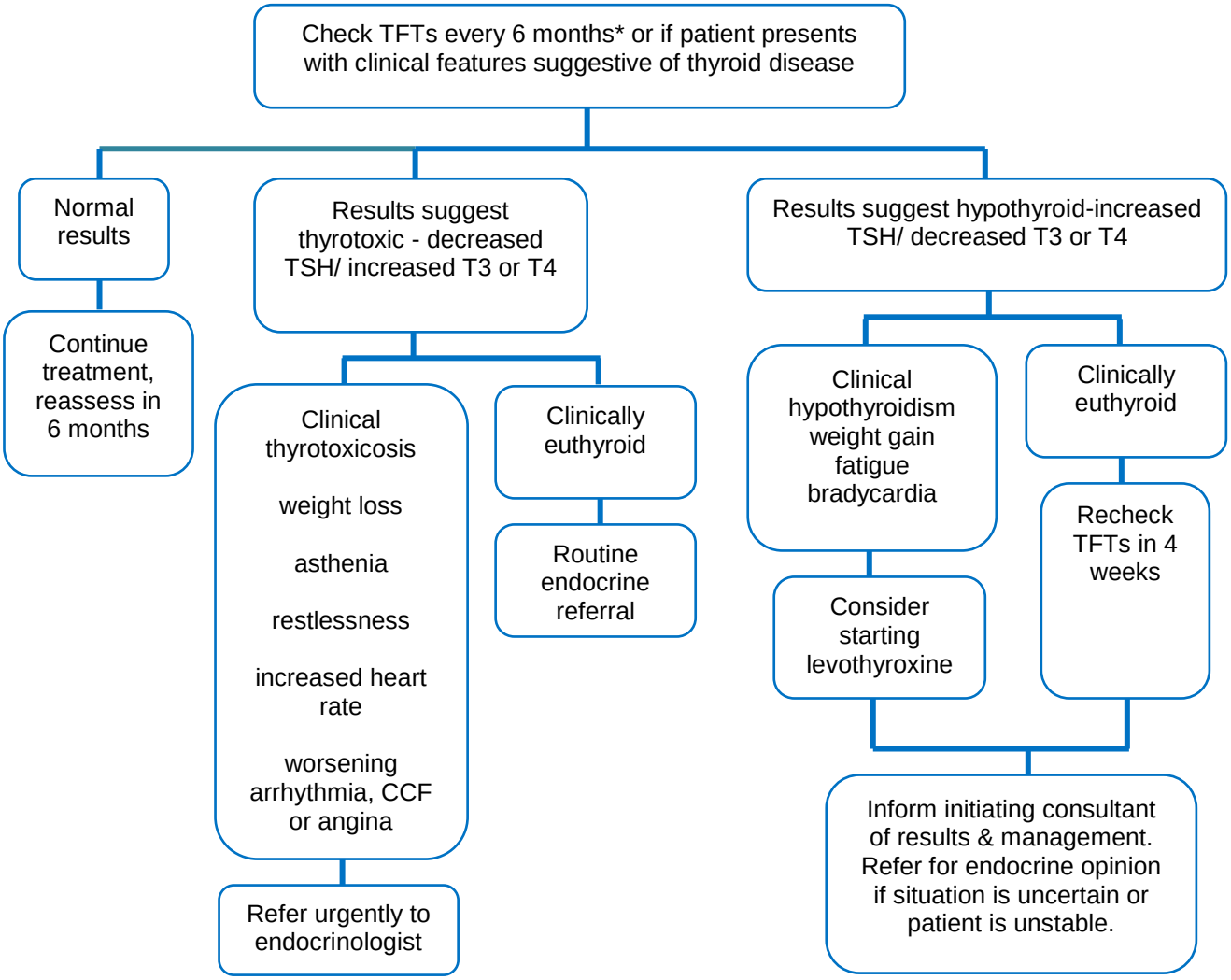
Monitoring at baseline and during initiation is the responsibility of secondary care. Consultants will make an assessment and amend other medications to minimise the risk of bradycardia or other adverse effects as appropriate. Further monitoring is the responsibility of primary care. See table below

	Baseline	Loading	Monitoring frequency
History & examination	♦		Continue Annually
adverse effects	♦	♦	Continue every 6 months [1]
Heart rate & ECG	♦	♦	Continue Annually [2]
TFTs	♦		Continue every 6 months and for up to 12 months after discontinuation [3]
U&Es	♦		Continue every 6 months
LFTs	♦	♦	Continue every 6 months
Digoxin level (if applicable)	♦	♦	Assess serum digoxin levels if dose increased or toxicity is suspected.
INR (if applicable)	♦	♦	More frequent monitoring of INR both during and after amiodarone treatment (initially weekly for first 7 weeks) (see p7&9 under local warfarin guideline)
CXR	♦	Also if any suspected pulmonary toxicity	
PFTs inc DLCO	♦	Also if any suspected pulmonary toxicity	
Eye examination		Assess if new or worsening visual symptoms occur.	

Adapted from UKMI. Suggestions for Drug Monitoring in Adults in Primary Care. https://www.sps.nhs.uk [6/11/2018]

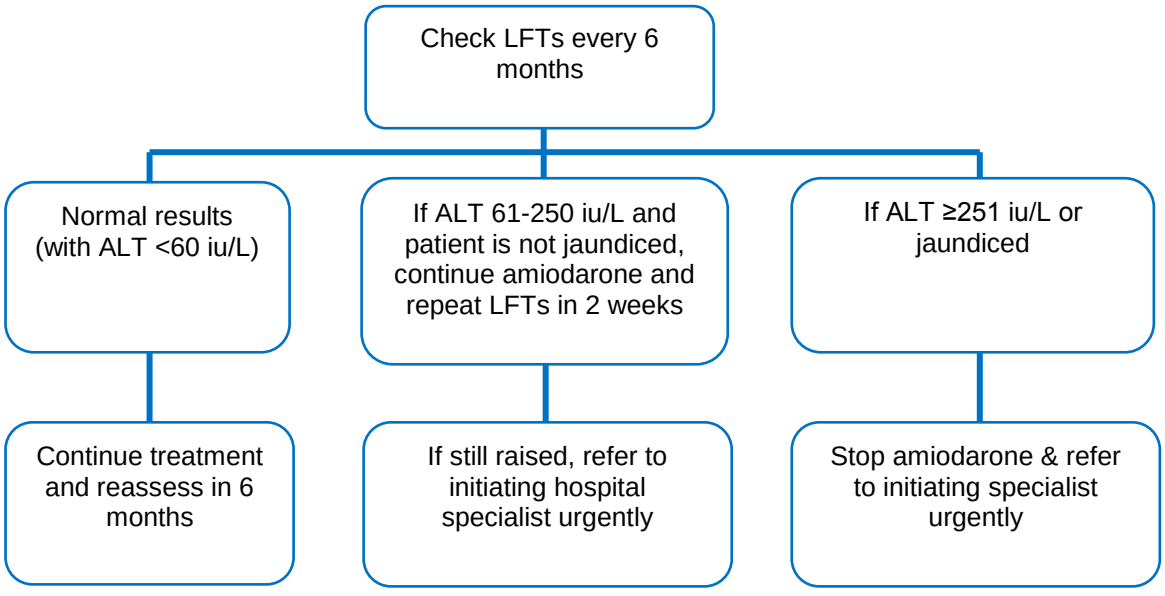
1. At each review visit ask about breathlessness and non-productive cough, related to possible pulmonary toxicity
2. ECG is valuable e.g. for detecting transition from PAF to permanent AF which may occur 'silently'. See also appendix 3.
3. An increase of up to 40% above the baseline T4 is a normal effect of amiodarone. This occurs approximately 2 months after initiation and does not require discontinuation if there is no clinical or further biological evidence (TSH) of thyroid disease. If TFTs are borderline repeat test in 6 weeks. In the event of thyrotoxosis seek the urgent advice of an endocrinologist.

3.1 Thyroid function test algorithm



* and for up to 12months after discontinuation of amiodarone as hyperthyroidism may occur up to several month after discontinuation.

3.2 Liver function test algorithm



4. DRUG INTERACTIONS

Amiodarone inhibits metabolism through several cytochrome P450 pathways, causing interactions with many commonly used drugs. Due to the long half-life of amiodarone, the onset of drug interactions may be slow after initiating amiodarone, and interactions may be observed for several months after discontinuation of amiodarone.

Concomitant use with amiodarone *contraindicated*	
Anti-arrhythmics	Class Ia anti-arrhythmic drugs eg.**, Disopyramide** and Class III anti-arrhythmic drugs eg. **Sotalol,** prolong the QT interval therefore increase the risk of torsades de pointes.
Antibacterial drugs	**Parental erythromycin, moxifloxacin, co-trimoxazole** and **pentamidine** injection prolong the QT interval.
Antidepressants	**Lithium** and tricyclics eg. **Doxepin, amitriptyline** prolong the QT interval. Manufacturer of **citalopram** and **escitalopram** states concomitant use of class III antiarrhythmics (amiodarone) that prolong the QT interval is contraindicated.
Anti-psychotics	**Chlorpromazine, fluphenazine, pimozide, haloperidol, amisulpiride** and prolong the QT interval.
Antihistamines	and **mizolastine** prolong the QT interval
Anti-malarias	**Quinine, mefloquine, chloroquine,** prolong the QT interval
Concomitant use with amiodarone *not recommended* or should be *avoided*	
Antivirals	*Avoid* combination therapy containing simeprevir and sofosbuvir due to risk of severe bradycardia and heart block; unless other antiarrhythmics cannot be given MHRA, 2015
Beta-blocker	Potentiation of negative chronotropic properties and conduction slowing effects may occur. Concomitant administration is *not recommended*
Calcium channel inhibitors	Rate lowering calcium channel inhibitors eg. **Diltiazem, verapamil** potentiate negative chronotropic properties and conduction slowing effects may occur. Concomitant administration is *not recommended*
Fluoroquinolone	eg. **levofloxacin,** may prolong QT interval. Concomitant use of amiodarone should be *avoided.*
Grapefruit & grapefruit juice	Inhibit cytochrome P450 3A4 and may increase the plasma concentration of amiodarone therefore should be *avoided*.
Laxatives (stimulant)	Stimulant laxatives eg. **Bisacodyl, senna** may cause hypokalaemia and increase the risk of torsades de pointes. Concomitant administration is *not recommended*
Concomitant use with amiodarone are *cautioned*	
Anticoagulants	**Warfarin** clearance is reduced. This can lead to sudden and pronounced increase in INR. Interaction reaches its peak in 6-7 weeks. Decrease warfarin dose by 33-50% and monitor the INR weekly, tailoring the warfarin dose to the INR target. Amiodarone increases the exposure to **dabigatran** thus increase the risk of bleeding. Adjust the dosage of dabigatran according to manufacturers' advice (note dose may be different for different clinical indications).
Cardiac Glycosides	Plasma level of **Digoxin** approximately doubles over weeks after commencement of amiodarone. Halve digoxin dose and monitor digoxin level if applicable.
Ciclosporin	Plasma level of ciclosporin increased when used with amiodarone. A reduction in the dose of ciclosporin may be necessary.
Drugs may cause hypokalaemia/ hypomagnesaemia	Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia: and/or hypomagnesaemia e.g. **diuretics**, **systemic corticosteroids**, **tetracosactrin**, **IV amphotericin, aminophylline, theophylline**
Lipid-regulating	Increased incidence of myopathy with **Simvastatin** (do not exceed 20mg per day.)
Phenytoin	Plasma level of phenytoin increased with amiodarone. Phenytoin dosage should be reduced in signs of overdosage and plasma levels may be measured.

This list is not exhaustive; for full list and details of interactions please refer to BNF and SPC. For further information on drugs that affect QT see the Credible Meds website.

5. ADVERSE EFFECTS

Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system. Patients on long term treatment should be carefully supervised because these reactions may be delayed. **The minimum effective maintenance dose should be given because undesirable effects are usually dose related**. Because of long half-life of amiodarone, clinical problems may occur up to a year (e.g. photosensitivity) after stopping the drug (hyperthyroidism may occur up to several months after discontinuation).

Adverse effect	Frequency %	Diagnosis	Management
Suspected pulmonary toxicity (suggested by new or worsening cough and/or shortness of breath)	2 to 17 (common)	CXR and ECG to exclude alternative diagnoses.	If no clear cause for cough/SOB found, or if pulmonary toxicity is still a possibility, refer urgently to initiating cardiologist or respiratory physician. Specialist to request PFTs inc DLCO and HRCT chest scan
Hyperthyroidism	2 (common)	Free T4, TSH	See algorithm
Hypothyroidism	6 (common)	Free T4, TSH	See algorithm
Liver toxicity	1 (common)	LFT	See algorithm
Optic neuropathy	0.13 (very rare)	Ophthalmologic examination	If optic neuropathy/neuritis is suspected, refer urgently to ophthalmologist and discuss possibility of stopping amiodarone & prescribing alternative antiarrhythmic therapy with patient's cardiologist
Neurological symptoms (e.g. tremor, ataxia)	Common	History, examination	Reduce dose. Rarely (0.3%) peripheral neuropathy may occur in people on long- term amiodarone
Proarrhythmia	<1 (uncommon)	ECG	Stop amiodarone
Bradycardia	2-4 (common)	Examination, ECG	If severe, discuss with cardiologist whether to stop amiodarone or insert pacemaker
Nausea, anorexia	30 (very common)	History + examination	Commonly occur with loading doses- Reduce dosage
Corneal micro-deposits	>90 (very common)	Slit-lamp examination	None. Most patients on amiodarone develop this (reversible on withdrawal of treatment) which rarely interfere with vision but driver may be dazzled by headlights at night.
Photosensitivity	4-9 (very common)	History, examination	Shield from light and use a wide spectrum sunscreen during treatment and for several months after discontinuing amiodarone
Blue skin discolouration	<9 (very common)	Examination	Reduce dosage

Adapted from Siddoway LA. Amiodarone: guidelines for use and monitoring. American family physician. 2003 Dec 1;68(11):2189–96. ; UKMI Suggestions for Drug Monitoring in Adults in Primary Care. https://www.sps.nhs.uk

APPENDIX 1. AMIODARONE 6 MONTHLY MONITORING CHECKLIST

Patient Name:
DOB:
NHS/Hospital Number:

Indication:
Date Amiodarone Started:
Current Dose Amiodarone:

Tick when Completed	Health Checklist
	Regular Prescription Ordering Pattern Confirmed
	6 Monthly U&Es, LFTs and TFTs taken and results recorded in notes
	Heart Rate and Rhythm Assessment: HR…….beats per minute Currently in Sinus Rhythm/Atrial Fibrillation (delete as applicable)
	No symptoms of pulmonary toxicity (new/worsening cough or shortness of breath), proarrythmia (dizziness or fainting), bradycardia or photosensitivity
	Check for drugs <u>contraindicated</u> with amiodarone: Class Ia anti-arrhythmic drugs e.g., disopyramide Class III anti-arrhythmic drugs e.g. sotalol, Antibacterial: IV erythromycin, moxifloxacin, co-trimoxazole or pentamidine Anti-psychotics: Chlorpromazine, , fluphenazine, pimozide, haloperidol, amisulpiride Antidepressants: Lithium and Tricyclic antidepressants e.g. doxepin, maprotiline, amitriptyline; Citalopram and escitalopram Antihistamines e.g., mizolastine Anti-malarials e.g. quinine, mefloquine, chloroquine,
	Check for drugs <u>not recommended</u> or should be <u>avoided</u> with amiodarone: Antivirals: combination therapy containing simeprevir and sofosbuvir Beta Blockers Rate Limiting Calcium Channel Blockers (Diltiazem, Verapamil) Fluoroquinolone e.g. Levofloxacin Grapefruit & grapefruit juice Stimulant Laxative (e.g. bisacodyl, Senna)
	Check for drugs where concomitant use with amiodarone are <u>cautioned</u>: Anticoagulants: Warfarin (current dose regimen_____/ last INR____) , dabigatran Digoxin Ciclosporin Drugs that may cause hypokalaemia / hypomagnesaemia e.g. Diuretics. Systemic Corticosteroids, aminophylline, theophylline Lipid regulating drugs e.g. Simvastatin (if yes reduce dose to 20mg OD) Phenytoin
	Date of Last face to face Medication Review of all interacting medicines: Appointment for next full annual medication review:
	Results of Six Monthly Review recorded in patient notes

Appendix 2. Amiodarone Patient Advice

Many people take Amiodarone for a long period to maintain a regular heart rhythm without experiencing any problems.

However, unwanted effects can occur as a result of taking Amiodarone including:

- dizziness or fainting:
- unexplained dry cough and/or shortness of breath
- rapid weight loss
- new or worsening visual symptoms

If you experience any of the above symptoms while taking Amiodarone please make an appointment to see your GP.

You will require regular (every six months) blood tests to check your thyroid function during treatment with amiodarone and for up to 12 months after, due to potential adverse effects.

Protect your skin from sunlight
Keep out of direct sunlight while taking this medicine and for a few months after you have finished taking it. This is because your skin may become more sensitive to the sun. Use high factor, wide-spectrum sunscreen to protect against both long-wave ultraviolet and visible light, and/or wear a hat and clothes which cover your arms and legs.

Amiodarone can also affect the action of other medications taken for other medical conditions including:

Warfarin: Amiodarone increases the blood thinning effect of Warfarin. If you notice increased bruising, nose bleeds or difficulty stopping bleeding from cuts please make an appointment to see your GP immediately to adjust your dose of Warfarin.

Digoxin: Amiodarone increases the effect of Digoxin. Your GP will halve your dose of Digoxin when you start taking Amiodarone. If you notice any unexplained nausea or vomiting, loss of appetite or visual disturbances see your GP immediately, as the level of Digoxin in your blood could be too high.

Antidepressants: Certain medications such as Lithium and Amitriptyline can increase the risk of irregular electrical activity in the heart if taken together with Amiodarone.

Please inform your GP about any other medications you take when you first see them after starting Amiodarone.

Appendix 3. Guidelines for stopping long-term amiodarone treatment

Amiodarone is a very effective antiarrhythmic drug, often used in the treatment of paroxysmal atrial fibrillation (PAF) and ventricular tachycardia (VT). Unlike most other antiarrhythmics, it is safe in heart failure. Its use is limited by side-effects, some of them life-threatening. The risk of these side-effects increases with time and with dose. It seems sensible therefore to ask from time to time whether the drug is still indicated and whether the dose can be reduced. The following is a simple guide to establishing whether amiodarone should be continued at its present dose, or whether treatment can be reduced or withdrawn completely.

Step 1: Establish the original indication for amiodarone therapy

- paroxysmal atrial fibrillation (PAF)
- permanent AF
- ventricular tachycardia (VT)
- Wolff-Parkinson-White syndrome (WPW)
- palpitations of uncertain cause

Step 2: Review diagnosis & need for amiodarone in light of current status

PAF

The natural history of PAF is for it to become chronic at some stage (25% in 5 years). This may happen 'silently'. AF can be considered permanent when the patient has been shown to be in AF on two occasions and no longer reports symptoms of cardiac rhythm change. When a patient develops permanent AF the amiodarone should be stopped and heart rate controlled with beta blockers, calcium channel blockers or digoxin. The usual amiodarone dose in PAF is 200 mg od. If a patient has been very stable for a year or more this can be reduced to 100 mg.

Permanent AF

Very occasionally it is necessary to use amiodarone for rate control in permanent AF. As other rate control options (e.g. AV nodal ablation plus pacemaker insertion) could be considered, all patients on amiodarone for rate control should initially be under the care of a cardiologist. Once a patient has been stable for two years it is worth considering reducing or stopping amiodarone without necessarily referring back to hospital. The long terminal half-life of amiodarone means that it will take months before its effect on AV node conduction has gone completely.

VT

Patients with symptomatic VT should remain on amiodarone in the long term unless they develop significant side-effects. Patients with internal cardiac defibrillators (ICDs) are often also on amiodarone to reduce the frequency of shocks. Some patients are started on amiodarone for VT at the time of an acute illness. Any patient who has been completely well for two years with no suggestion of recurrent VT should be referred to a cardiologist for review of the long-term need for amiodarone.

WPW

Amiodarone is rarely used for WPW, unless an electrophysiologist has been unsuccessful in ablating an accessory pathway. Some WPW patients were started on amiodarone before the modern era of percutaneous treatments. Some are happy to stay on amiodarone but they should be given the opportunity to discuss definitive treatment with an electrophysiologist.

Palpitation

Patients should not be started on amiodarone unless there is a clearly defined electrophysiological diagnosis. If a patient was started on amiodarone because of suspicion of VT but has been stable for two years they should be reviewed by a cardiologist. If the indication was just palpitations then the amiodarone should be stopped.

Step 3: Stopping amiodarone

- Amiodarone can be stopped abruptly
- Amiodarone lingers longer after the drug is stopped. Plasma concentration falls by 50% in the first two weeks but it may then take a further 6 months before it is eliminated completely
- Ventricular rate control and AF: if resting heart rate is < 75 review in 2 weeks to consider increasing dose of other rate slowing drugs (NB the plasma level of digoxin will decrease upon withdrawal of amiodarone). If resting heart rate is >75 add in or increase beta blocker, digoxin, rate-limiting calcium channel blocker (e.g. start atenolol 25 mg or increase dose by same amount up to 100 mg). A further review of heart rate at 3 months after stopping amiodarone is sensible.
- Due to the long half-life of amiodarone, clinical problems (e.g. hyperthyroidism, photosensitivity) may occur/ persist for up to a year after stopping the drug. TFT should be monitored for up to 12months after discontinuation.
- Warfarin: the INR will decrease upon stopping amiodarone. In most cases it is sufficient to repeat the INR one week after stopping in the expectation that a dose increase will be necessary.

Appendix. 4 Consultant responsibilities

Initiating treatment with Amiodarone

Only a cardiologist/specialist should initiate treatment with oral Amiodarone.
The frequency of most adverse effects is related to the total amiodarone exposure; therefore the lowest effective dose should be used. The following should be done prior to commencement of treatment:

1. To complete, prior to initiation of treatment, or prior to hospital discharge if treatment initiated during an admission:
   - History and examination
   - ECG
   - CXR
   - Pulmonary Function Tests including DLCO (Diffusing capacity of the lung; the capacity of the lungs to transfer carbon monoxide (mL/min/mm Hg)
   - Thyroid Function Tests
   - Liver Function Tests
   - INR level if appropriate
   - Digoxin level if appropriate
2. Assess risk of bradycardia or side effects and amend other medications (e.g. beta-blocker, digoxin) to minimise the risk as appropriate.
3. Decrease the dose of warfarin/ other coumarin by 33-50%, if applicable.
4. Provide the patient with an information leaflet regarding their treatment with amiodarone. Advise the patient of the need to use sunscreen.
5. Monitor the patient during initiation (first 6 weeks) as clinically appropriate.
   - Inform patients that they should seek medical advice if they experience symptoms of dizziness.
   - If the patient is taking warfarin/other coumarin, check the INR at least weekly during the first 6 weeks of treatment and communicates with the GP appropriate INR monitoring has been undertaken.
   - Check LFTs and if applicable digoxin level 6 weeks after initiation.
   - Monitor the patient for signs and symptoms of adverse effects of amiodarone.
6. Titrate to the lowest effective dose of amiodarone.
7. Communicate the results of all the above investigations to the GP.
8. Discuss with the GP any queries they have regarding treatment with amiodarone, and review the patient promptly if the GP requests an appointment regarding the treatment with, or possible side effects of amiodarone. **If pulmonary toxicity is suspected, perform ECG, CXR, HRCT chest scan and PFTs including DLCO. If pulmonary toxicity remains the working diagnosis, stop amiodarone and consider treatment with corticosteroids.**
9. Promptly report any potential adverse effects to the CSM.