East Sussex Hospitals NHS Trust
Hastings
East Kent Hospitals NHS Trust

DEPARTMENT OF CARDIOLOGY

[redacted]
Kings Drive
Eastbourne
East Sussex
BN21 2UD

Tel: 01323 417400
Website: www.esht.nhs.uk
Direct Dial:
Fax: [redacted]

ANS/pjm

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Ms Nicole Reid
NICE
Level 1A
City Tower
Piccadilly Plaza
MANCHESTER M1 4BD

Dear Ms Reid

Re: NICE Technology Appraisal of Dronedarone for the treatment of atrial fibrillation

I have been asked by [redacted] of HRUK to both represent HRUK on the NICE Appraisal Committee for Dronedarone and to collate the response of HRUK members to the preliminary decision of the NICE Committee appraising Dronedarone.

I have had e-mail or written responses from 27 members of HRUK and had verbal discussions with approximately 10 more HRUK members, as well as Physician and Cardiology colleagues.

The response below is taking into account most, if not all, the comments made by professional colleagues. The majority of the report is based on the 2 most comprehensive responses from [redacted] (BHF [redacted] at St George's University of London) who is also [redacted] of the European Society of Cardiology Guidelines for Atrial Fibrillation Development Group, previous [redacted] of the NICE Guideline Development Group for Atrial Fibrillation and [redacted] of the Arrhythmia Alliance as well as [redacted] at CTC Liverpool (an interventional Electrophysiologist undertaking complex ablation of atrial fibrillation among other arrhythmias as well as being an HRUK [redacted]). I am the [redacted] to the NICE Committee representing HRUK and a [redacted] of the NICE Guideline Development Committee on Atrial Fibrillation. Many of the Cardiologists whose responses I have also collated are widely published in the diagnosis and treatment of atrial fibrillation as are [redacted].

Every response has suggested that the Technology Appraisal Committee's preliminary decision is flawed for several reasons and should be reversed. The reasons are outlined below.

The most frequent comments are: "we note that restricted approval for the drug has been granted in both the United States and Canada following exhaustive review by National Committees" and "no anti-arrhythmic drug has been approved for atrial fibrillation therapy for 20 years and there is a paucity of drugs in our current pharmacological arsenal to treat this extremely common complaint". The comments will be expanded below to include the commonly quoted fact that the only truly efficacious drug we currently have available is Amiodarone and this is not tolerated by a large minority of patients in the short-term and a majority of patients in the long-term due to a very adverse side-effect profile that would not allow the drug to be approved by the NICE Technology Appraisal Committee if the drug was assessed in a similar way to Dronedarone.

Finally, much of the therapeutic efficacy of Dronedarone described by the appraisal Committee for the suppression of atrial fibrillation is based on trials with potentially flawed monitoring techniques and reliance on patient symptomatology and ignores a major effect of Dronedarone which is the rate control of AF which is actually mandated in patients over the age of 65 by the NICE Guideline for the Treatment of Atrial Fibrillation. I will allude to this further below.

Drug Comparators used in the NICE Assessment

The key drug comparator in the NICE Assessment is Amiodarone but this drug is used as a last resort in almost all patients with atrial fibrillation. This is in spite of the fact that it is unquestionably the most efficacious drug currently approved for use in atrial fibrillation. This is due to its extremely wide and varied adverse event profile. This is outlined in a recent randomised study using Amiodarone in Atrial Fibrillation published in JAMA 2008. Due to its adverse event profile the authors attempted intermittent use of the drug comparing it to continuous use and demonstrated no advantages with the same adverse event profile. This showed that almost 25% of patients in both arms of the trial experienced significant adverse events. This is also corroborated by the CIDS study when Amiodarone was used for life threatening arrhythmias. Long-term follow-up in a single centre cohort of 60 patients randomised to Amiodarone treatment showed that over 80% of patients suffered significant side-effects, with cessation of Amiodarone required in 50% of patients after 5.6 years.

The other drug comparators were Sotalol and Flecainide. It is felt by some HRUK clinicians that the increased mortality risks with both these drugs was not adequately clarified by the NICE appraisal documentation as these drugs have been demonstrated to increase mortality, (Sotalol due to polymorphic ventricular tachycardia, with a reported risk as high as 6%. Flecainide has also been shown to increase mortality and pro-arrhythmia both with polymorphic ventricular tachycardia and also producing 1:1 conduction in atrial flutter. This has also been described with Propafenone, another 1c agent).

It has also been pointed out that as atrial fibrillation prevalence is so high, it is often managed by non-arrhythmologists in the UK, and these clinicians are much more reluctant to use 1c agents due to their adverse events profile cutting the pharmacological armamentarium available to most patients in the NHS. It is also pointed out by several clinicians that as atrial fibrillation is a disease of the elderly and in patients with significant heart disease, large numbers of such patients are unable to take 1c agents or Sotalol and in such patients the side-effect profile of Dronedarone would allow the use of this drug when no others were available. There was one described episode of Torsades (polymorphic VT) with Dronedarone and, in my opinion, there is a negligible risk of Torsades with Dronedarone therapy.

Has all relevant evidence been reviewed?

Several clinicians have commented that whilst relevant evidence regarding Dronedarone has been carefully evaluated by the Committee, the efficacy and side-effect profile of other anti-arrhythmic agents used in the suppression of atrial fibrillation have not been adequately assessed and that the development programme and modelling of the use of Dronedarone has not been sufficiently acknowledged; specifically it has not been made clear regarding the relative efficacy of Dronedarone in rate control therapy of atrial fibrillation as opposed to its use in the suppression of atrial fibrillation (rhythm control) which is the main focus of the appraisal document.

Clinical effectiveness and cost effectiveness

It is unanimous that there are flaws in the assessment of both clinical and cost effectiveness of Dronedarone due to the way trial data has been interpreted. It is not, however, unanimous how the trial data should be interpreted with regard to cost effectiveness.

It is my opinion, and that of some respondents, that the Committee is correct in its assumption that the efficacy of Dronedarone in rhythm control of atrial fibrillation is similar to that of Sotalol and the 1C agents Propafenone and Flecainide and significantly less effective than Amiodarone. As stated previously, all respondents agree that Dronedarone is a far safer drug to use than 1c agents, Sotalol or Amiodarone. Professor Camm, who is the Chairman of the ESC Guidelines Committee for atrial fibrillation and was a member of the NICE Guideline Development Group for atrial fibrillation, confirms that Amiodarone will be placed as the drug of last resort due to its unacceptable adverse side-effect profile. The European guideline which is evidence based and the NICE guideline when it is updated (assuming that Dronedarone can be used), will place the drug as 1 of 4 choices for use after initial treatment with beta-blockade. The other drugs are Flecainide, Propafenone and Sotalol all of which will be placed before Amiodarone. Professor Camm confirms that ESC advice will be that "which drug is used before Amiodarone depends on whether anti-arrhythmic efficacy, cost efficacy or safety is the overriding consideration". All HRUK members are convinced that Dronedarone is the safest of all these anti-arrhythmic drugs and should therefore be part of the drug treatment of atrial fibrillation for both rhythm and rate control.

With regard to rhythm control, if Dronedarone is not effective and patients suffer multiple recurrences of their AF induced symptoms, the drug will be stopped, as suppression of symptoms by suppression of the arrhythmia is the aim of this therapeutic intervention. Very few patients would remain on Dronedarone if there is therapeutic failure and costs will therefore be limited. This is not taken into account in any of the cost efficacy studies reviewed. Alternative treatment for such patients would be the use of other anti-arrhythmic drugs, cardioversion with drugs, or catheter ablation with Amiodarone used only as the last resort.

There is some evidence from EURIDIS and ADONIS to suggest that Dronedarone may be effective after failure of 1c agents, Sotalol and other beta-blockers but not Amiodarone.

DIONYSIS is a small trial with, in my opinion, an unsatisfactory composite endpoint which suggested there was no significant difference between Dronedarone and Amiodarone. This endpoint, however, fails to hide the fact that Amiodarone was significantly more effective in arrhythmia suppression than Dronedarone although it was associated with more side-effects.

This trial is also flawed in that it has a relatively short follow-up which will tend to minimise the long-term adverse effects of Amiodarone. In my opinion, a better constructed, larger trial with more appropriate endpoints and longer follow-up could be undertaken comparing Amiodarone and Dronedarone. It would better demonstrate relative efficacy of these 2 drugs in AF suppression and a similar trial should be undertaken for rate control in more elderly patients. In my opinion, there is no data to support the use of Dronedarone after failure of Amiodarone to suppress atrial fibrillation unless the reason for cessation of Amiodarone is due to adverse side-effects.

The pivotal trial described appropriately in the appraisal document is ATHENA. This trial is the only investigation of an anti-arrhythmic drug in patients with multiple cardiac risk factors and recurrent atrial fibrillation. In my opinion, the trial does not adequately delineate the amount or severity of atrial fibrillation and could be construed as a mild heart failure trial with multiple risk factors, but it is unequivocal that the primary endpoint of all cause mortality or cardiovascular hospitalisation was significantly reduced in patients treated with Dronedarone with hazard ratio of 0.76. This was largely driven by reduced cardiovascular hospitalisation and this is not adequately acknowledged by the NICE appraisal Committee. This reduction in hospitalisation will accrue a significant cost saving which alone should reduce the QALY to under £20,000.00. It is also unequivocal that all cause mortality was numerically reduced by the drug and this is not adequately acknowledged. It is true that cardiovascular mortality showed no significant reduction with Dronedarone and it has been argued that this is because of multiple other causes of death due to the elderly population that was recruited into the trial and who would be treated with the drug in the everyday clinical setting. The all cause mortality reduction between 3% and 7% should also reduce the QALY to under £20,000.00. It also not adequately acknowledged that 1c agents and Sotalol are contra-indicated in the majority of patients included in the trial because of i) heart failure (Sotalol relatively contra-indicated, Flecainide and Propafenone contra-indicated); ii) ischaemic heart disease (Flecainide and Propafenone contra-indicated). Overall, Electrophysiologists point out that there is no comparable trial data with Amiodarone which would also be expected to have a beneficial effect in the ATHENA patient group with only meta-analyses quoted by the appraisal Committee which are of limited value and do not support the use of Amiodarone in this situation.

It is also clear from the ATHENA data that in long-term follow-up with significant exposure to Dronedarone there is unequivocally no increase in mortality with this drug and no significant adverse side-effects in the long-term. (There are side-effects with commencement of Dronedarone namely diarrhoea but the number of patients having to stop the drug because of this is extremely small).

All respondents agree that it must be acknowledged that Dronedarone is the only anti AF drug that has been shown to reduce cardiovascular outcomes in an AF population with increased risk of cardiovascular events.

[redacted] points out that the hospitalisation endpoint has been required by regulatory authorities rather than the absence of symptoms and documented episodes of atrial fibrillation and Dronedarone is the only drug that has been investigated in this way with a positive result. Dofetilide has been assessed in the DIAMOND trial in patients with atrial fibrillation and heart failure and did reduce hospitalisations but this drug has not been made available in the United Kingdom and has a much more adverse side-effect profile than Dronedarone. Finally, HRUK clinicians have pointed out that even with Amiodarone as the

drug of last resort to be used in atrial fibrillation, many patients have specific contra-indications to the drug and many

have had the drug previously and developed serious side-effects requiring a cessation of the medication. In these patients only Dronedarone is available for AF rhythm control.

Are the provisional recommendations regarding the use of Dronedarone in the NHS appropriate and justifiable?

All respondents find it difficult to accept the recommendation that "Dronedarone is not recommended for treatment of atrial fibrillation". As stated above, this is the only drug proven to reduce serious cardiovascular outcomes and hospitalisation in patients with multiple cardiovascular risk and atrial fibrillation and all HRUK members agree that it appears to the safest anti-arrhythmic that has been developed.

It is the majority view that the Committee should therefore recommend that Dronedarone be used after a trial of beta-blockade for the suppression of symptomatic atrial fibrillation in patients with recurrent symptomatic AF episodes.

It is generally agreed that Dronedarone is as efficacious as Flecainide, Propafenone and Sotalol although there are no head-to-head trials of the drug with these approved medications although most believe that the side-effect profile is better with Dronedarone and it is therefore safer to use. Clinical academic opinion is unanimous that Amiodarone, the comparator drug required by European and American regulators is more efficacious than Dronedarone in suppression of AF (most people agree that Dronedarone is about half as efficacious in the short to medium-term) and all agree that this it is much safer to use Dronedarone than Amiodarone and the latter must remain the drug of last resort. All agree that Dronedarone should not be used in NYHA IV as per the Committee's recommendations based on good trial data. It should be acknowledged that Amiodarone has not been shown to reduce cardiovascular risk in studies such as AFFIRM and AF STAT unlike the data from ATHENA with Dronedarone.

Requirement for further trial data

I personally feel that the trial designs, whilst giving good information on safety and some clinical outcomes, do not give adequate information on relative efficacy of the drug and further investigation comparing Dronedarone and Amiodarone in appropriately powered randomised trials with adequate long-term follow-up should be undertaken. I think trials should be designed to assess comparative efficacy in AF rhythm control as well as AF rate control which could be the largest indication for the drug with evidence from ANDROMEDA, ATHENA, EURIDIS and ADONIS all pointing to Dronedarone's equivalence with Amiodarone with regard to rate control and this is not mentioned by the Appraisal Committee at all. It is interesting that Sanofi, the manufacturers, have also not mentioned the rate control aspect of the drug and there has been no modelling of the effect of Dronedarone on rate control. The reason for this is that it is an extremely difficult exercise.

Finally:

i) all respondents from HRUK were unanimous that Section 4.18 is incorrect in suggesting that there is no benefit from the use of Dronedarone over Amiodarone, 1c agents or Sotalol. The only major side-effect described with Dronedarone when used

at 400mgs-bd is that 9% of patients in ATHENA had diarrhoea lasting approximately 1 week due to receptor interaction in the large bowel. This responded to standard

dose Imodium. It should be noted that the placebo arm showed a 6% incidence of diarrhoea. There were no other significant side-effects.

ii) There is little mention of a significant risk reduction for stroke found in the ATHENA post-hoc analysis nor that patients with moderate heart failure (NYHA III) improved more than NYHA 1 & II. Even if the Appraisal Committee does not accept the pre-specified mortality endpoints of ATHENA and therefore the mixed treatment comparisons described by Professor Freemantle, the decrease in primary cardiovascular hospital admission rate with Dronedarone must be taken into account in the cost efficacy analysis.

The final general comment from the majority of Electrophysiologists is that there is not a large number or variety of pharmaco-therapies available in atrial fibrillation and this drug represents a new opportunity for a large number of patients with low risk for adverse events and no increase in mortality. It should, therefore, be approved for use in the NHS.

Kind regards

Yours sincerely

Dr A N Sulke DM FRCP FESC FACC
Consultant Cardiologist
HRUK Nominated Specialist Advisor to NICE Technology Appraisal Committee for Dronedarone

Cc Professor Peter Clark – Chairman of NICE Appraisal Committee for Dronedarone

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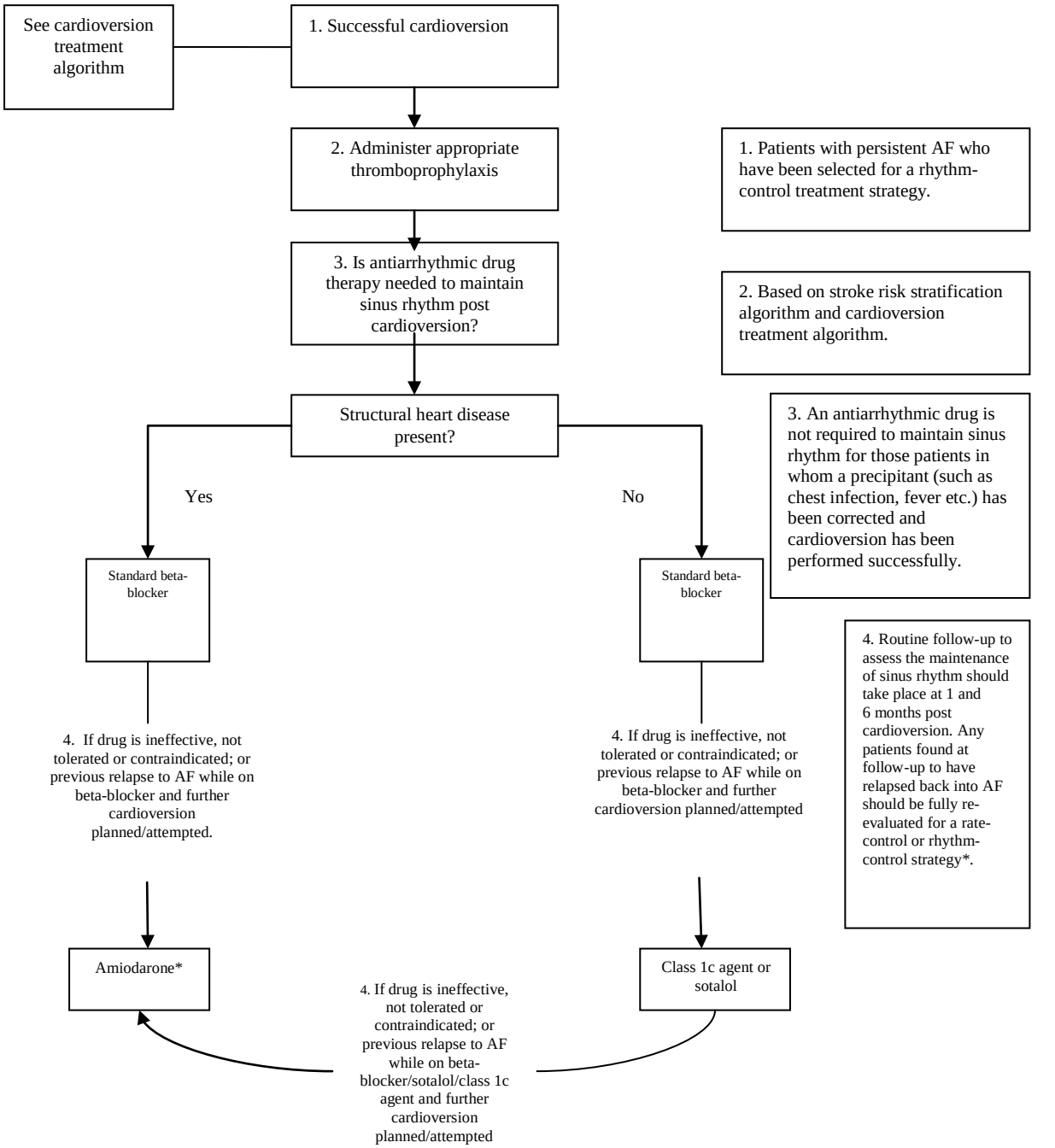
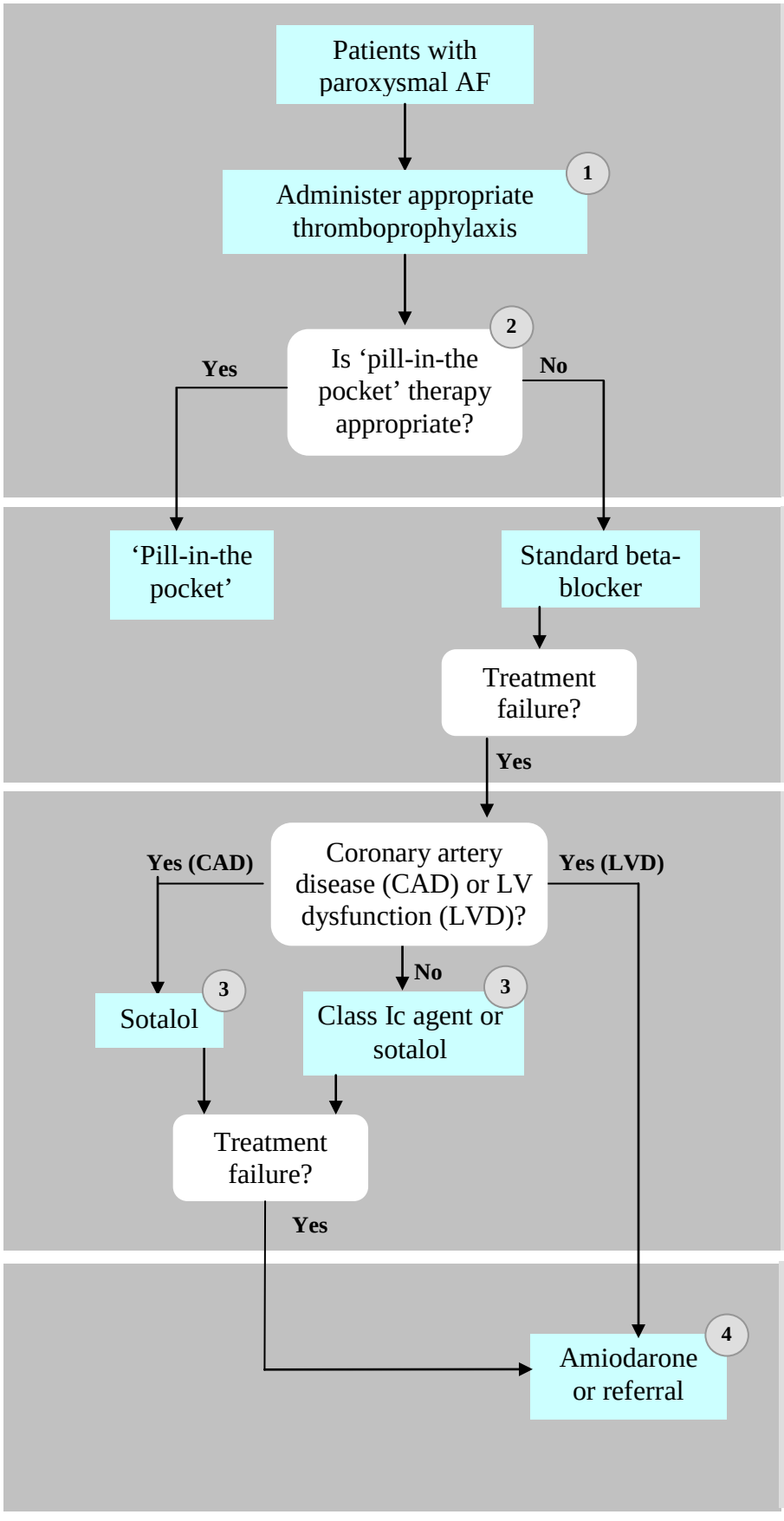
Appendix

Rhythm-control treatment algorithm for persistent AF



Rhythm-control treatment algorithm for paroxysmal AF



1. Based on stroke risk stratification algorithm.
2. Consider a 'pill-in-the-pocket' strategy for those who i) have no history of LV dysfunction, or valvular or ischaemic heart disease, ii) have a history of infrequent symptomatic episodes of paroxysmal AF, iii) have a systolic blood pressure > 100 mmHg and a resting heart rate above 70 bpm, iv) are able to understand how to, and when to, take the medication.
3. Sotalol to be progressively titrated from 80 mg twice daily up to 240 mg twice daily.
4. Referral for further specialist investigation should be considered, especially in those with lone AF or ECG evidence of an underlying electrophysiological disorder (e.g. WPW syndrome) or where pharmacological therapy has failed.