

PROPOSAL FOR THE INCLUSION OF
AMIODARONE AS AN ANTI-ARRHYTHMIC AND/OR FOR THE
TREATMENT OF CHRONIC HEART FAILURE

IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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WHO Model List Application, June, 2008

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1. Summary statement of the proposal for inclusion

Based on a well-established efficacy of amiodarone in the management of various heart rhythm disorders it is proposed to include amiodarone in in the subsection 12.2 *Antiarrhythmic medicines* of the WHO List of Essential Medicines (EML) for both the acute and chronic treatment of supraventricular and ventricular arrhythmias (EML 15, revised March 2007) available at the URL:

http://www.who.int/medicines/publications/08_ENGLISH_indexFINAL_EML15.pdf (last accessed 27 June 2008). Use of amiodarone for arrhythmias is recommended provided that Thyroid Stimulating Hormone (TSH) test is fully available for periodic monitoring of thyroid function (amiodarone could be even harmful for patients, in the absence of a periodic TSH monitoring).

On the contrary, based on the lack of evidence supporting the efficacy of amiodarone for the treatment of *heart failure* (HF), we do not recommend the inclusion of amiodarone in the WHO EML for the treatment of HF.

The proposal is based on the evidence and considerations described below.

2. Name of the focal point in WHO submitting or supporting the application

Dr. Suzanne Hill (WHO-HQ PAR/MPS) was consulted in the development of this application.

3. Name of the organization(s) consulted and/or supporting the application

CEVEAS, NHS Centre for the Evaluation of the Effectiveness of Health Care, WHO Collaborating Centre for Evidence Based Research Synthesis and Guideline Development in Reproductive Health, Modena, Italy.

4. International Nonproprietary Name (INN, generic name) of the medicine

The International Nonproprietary Name Modified (INN) of the medicine is: Amiodarone Hydrochloride.

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

- Amiodarone Hydrochloride HCl Tablets 100, 200, 400mg
- Amiodarone Hydrochloride Injection, 50 mg/ml, 3 ml

6. International availability - sources, if possible manufacturers (Appendix A)

A comprehensive listing of amiodarone manufacturers is given in the Appendix A.

Generic amiodarone is registered in many countries both in the developed and developing world. The choice will depend on price and availability at local (national) level.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

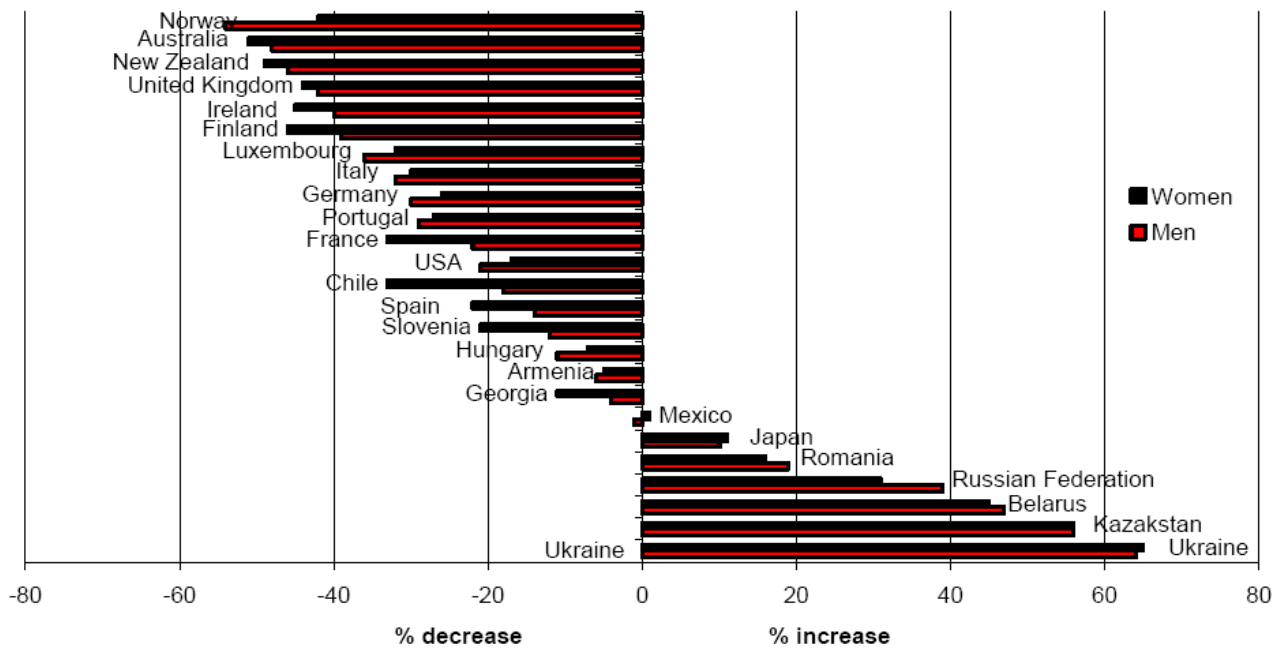
Listing is requested on the Model List of Essential Medicines as an individual medicine, to be included in the subsection 12.2 *Antiarrhythmic medicines* of the WHO EML.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)

As stated in the 2003 WHO document on prevention of cardiovascular disease, “non-communicable disease accounts for a large and increasing burden of disease worldwide”. (WHO 2003). Cardiovascular disease (CVD) is the most important single cause of non-communicable disease, accounting in 2001 for 29% of all

deaths and 10% of the global disease burden. Although the incidence of CVD has been decreasing over the last 20 years in many high-income populations, its incidence in low and middle-income populations has been rising steadily, due to ageing of the population and to better control of communicable disease and malnutrition, so that approximately three-quarters of global deaths from CVD now occur in those populations (Figure 1). This is especially true in sub-Saharan Africa, India, China and Russia. World-wide, deaths from CVD exceed those caused by cancer, infectious disease and trauma, constituting a deadly epidemic. It is predicted that in the next two decades there will be tripling of ischemic heart disease and stroke mortality in Latin America, the Middle East and sub-Saharan Africa (Callow 2006).

Changes in death rates from coronary heart disease, men and women aged 35 to 74, between 1990 and 2000, selected countries



Notes: ICD codes 410-414 (8th and 9th Revision), I20-I25 (10th revision). Age-standardised using the European standard population. **Sources:** World Health Organization (2004) www3.who.int/whosis

According to Gaziano, CVD is the leading cause of death in all developing regions, with the exception of sub-Saharan Africa; nonetheless, in this region, it is the first cause of death among those over the age of 30 (Gaziano 2005).

Furthermore, the proportion of all deaths due to cardiovascular causes in developing countries, estimated at about 25% in 1990, will increase to more than 40% in 2020 (Murray 1996). Several examples support this trend: in China the number of deaths attributed to circulatory diseases has doubled during the past two decades, with the higher increase among reasonably young people (35 to 54 years of age); in India the prevalence of coronary heart disease has increased from 6-8% to about 10% among people 35 to 64 years of age over the past 40 years, whereas the mortality associated to stroke among subjects 15 to 59 years of age is three to eight times as high in Tanzania as in UK. Stroke is currently the main CVD in China, South-east Asia, and sub-Saharan Africa, whereas coronary heart disease predominates in Latin America, the Middle East, and urban India (Reddy 2004).

There is a worrying increase in the prevalence of cardiovascular risk factors in developing countries, with marked gender differences. Smoking prevalence is 50% in adult males while it is 9% in adult female (Mackay 2002). Obesity is reported to be more prevalent among women in Brazil, Egypt, South Africa and Seychelles (Nishida 2005). Women from developing countries have higher blood pressure than women from developed countries; they also show higher blood pressure than their male counterpart (WHO 2005). Although the prevalence of diabetes is lower in developing countries, they have shown the greatest increase in diabetes. The prevalence is highest in the Eastern Mediterranean and Middle East (7%), South and Central America (5.6%), Western Pacific (3%) and Africa (2.4%). The prevalence is higher among women than among men in Latin America and in the Western Pacific (International Diabetes Federation 2003).

Developing countries display a set of specific risk factors for CVDs like acute respiratory infections (36% of all HF's in children in Nigeria), severe anaemia (28%), and congenital heart disease (25%) (Omokhodion 2005). Among adults rheumatic heart disease remains a major risk factor in Africa and Asia, especially in the young. Hypertension is an important cause of cardiovascular morbidity in the African and African-American population. Chagas' disease is still a cause of HF and cardiac arrhythmias in South America. (Mendez 2001).

Several conditions, like hypertension, valvular disease, coronary artery disease, ischemic heart diseases and diabetes, are often associated with both cardiac arrhythmias and HF. Furthermore arrhythmias and HF are inextricably linked: patients with either disorder are at substantially increased risk of developing the other, and when combined, they determine a substantially worse prognosis than either alone (Heist 2006).

Cardiac Arrhythmias

Among cardiac arrhythmias, atrial fibrillation is the most common and is an established risk factor for stroke and premature death. The lifetime risk for developing atrial fibrillation is approximately 25% in the general population (Heist 2006). The estimated prevalence of atrial fibrillation is 0.4% to 1% in the general population and it increases sharply with age (Fuster 2006): the prevalence at 55 years is 0.1% and reaches 9.0% in the elderly over 80 years of age (Feinberg 1995).

It has been estimated that 2.3 million people in United States and 6 million in the European Union have paroxysmal or persistent atrial fibrillation (Kannel 2008). Based on studies conducted in western countries atrial fibrillation is 1.5 times more frequent among men than among women (Benjamin 1994). Moreover atrial fibrillation is less common among African-American than Caucasian patients with HF (Fuster 2006).

Mortality rate is 25% higher among people with atrial fibrillation than among matched control. Mortality rate differences according to sex are variably detected in different studies. In Scotland one year case fatality rate was 12% in men with atrial fibrillation while it was 16% in women (Stewart 2001).

Ventricular tachycardia and ventricular fibrillation are the most common causes of out-of-hospital cardiac arrest, accounting for approximately three quarters of cases (Kokolis 2006). The epidemiology of ventricular arrhythmias spans a range of risk factors and clinical conditions, ranging from premature ventricular complexes and nonsustained ventricular tachycardia in normal subjects to sudden cardiac death due to ventricular tachyarrhythmias in patients with and without structural heart disease.

The geographical incidence of sudden cardiac death varies as a function of coronary heart disease prevalence in different regions. Estimates for the United States range from less than 200,000 to more than 450,000 sudden cardiac deaths annually, with the most widely used estimates in the range of 300,000 to 350,000 sudden cardiac deaths annually (Fuster 2006).

Post-myocardial infarction arrhythmias

Patients with acute myocardial infarction are at risk for arrhythmias and sudden cardiac death, and have higher rates of all-cause mortality in comparison with the general population (Solomon 2005).

Ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, are life-threatening complications of myocardial infarction. The reported incidence of post-myocardial infarction ventricular fibrillation varies from 2.1% to 12.4%, depending on the population and duration of observation (Carruth 1982), while the occurrence of post-myocardial infarction ventricular tachycardia ranges from 1% to 9.9%. The incidence of both ventricular fibrillation and ventricular tachycardia in the same population has been reported to be 1.9% to 10.2% (Henkel 2006).

Atrial fibrillation is a relatively common complication of acute myocardial infarction; it is present in 10-15% of myocardial infarctions and it is generally thought to be a marker of adverse prognosis. "Whether these worse outcomes are directly related to the development of atrial fibrillation or whether the development of atrial fibrillation is serving as a marker for greater myocardial dysfunction is unclear" (Campbell 2008).

Heart Failure

HF is a condition with high mortality rates, contributing to millions of hospitalizations annually and resulting in mortality rates after initial diagnosis that approach or exceed those of many malignancies.

Based on studies conducted in western countries the lifetime risk of developing chronic HF is about 20% for both men and women (Lloyd-Jones 2001). Data on HF prevalence in developed countries range from 2% in USA and Europe (Davies 2001) to more than 6% in Australia (Abhayaratna 2006). It was estimated that once HF has developed the median survival time is 1.7 years for men and 3.2 years for women (Ho 1993). More recently, five year mortality has been getting close to 50% for both sexes; mortality rates for HF have declined in men and only marginally in women over the past 20 years (Roger 2004).

Epidemiological burden in the developing countries

Epidemiological data from developing countries on HF and atrial fibrillation are rare but it is estimated that low and middle income countries contribute about 80% of global CVD-related deaths and 87% of CVD-related disabilities (Callow 2006).

CHF is estimated to have a case-fatality rate of 24% among Nigerian children (Omokhodion 2005).

Economical burden

Data from both the United States and UK show that atrial fibrillation is a costly public health problem. Many factors contribute to the high cost of atrial fibrillation with hospitalizations constituting the major contributor (52%), followed by drugs (23%), consultations (9%), further investigations (8%), loss of work (6%), and paramedical procedures (2%).

Globally, the annual cost per patient has been estimated being close to €3000 and, considering the prevalence of atrial fibrillation, the total societal burden is huge, about €13.5 billion in the European Union alone (Fuster 2006). With respect to HF, in European Union it is considered to be responsible for a greater percentage of healthcare costs than HIV or cancer, being 2–2.5% of the total healthcare budget (Remme 2005).

In the United States, the annual direct expenditure of healthcare dollars for symptom management of HF has been estimated to be \$20 billion to \$56 billion (Galbreath 2004); moreover it is the leading cause of hospitalization in patients over 65 years of age, accounting for more than \$3.6 billion only in this population (Maisel 2003).

9. Treatment details

Pharmacodynamics and pharmacokinetics

Amiodarone is a class III antiarrhythmic agent approved for the treatment of refractory life threatening ventricular arrhythmias and additionally used for the treatment of atrial and/or ventricular arrhythmias. Amiodarone is structurally similar to thyroxine. It is both an antiarrhythmic and a potent vasodilator. The antiarrhythmic effect of amiodarone it is not completely known but it may be due to at least two major properties: a prolongation of the myocardial cell-action potential duration and refractory period and a non competitive α - and β - adrenergic inhibition (Brunton 2005).

Peak concentrations are rapidly achieved using *intravenous amiodarone* and serum concentrations decline to 10% of peak values within 30 to 45 minutes after the end of the infusion. Desethylamiodarone is the major active metabolite of amiodarone in humans.

Oral amiodarone has a bioavailability of approximately 50%. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly it takes 1 to 3 weeks, even with loading doses. Food increases the rate and extent of absorption of amiodarone.

Amiodarone is a highly lipophilic compound with a large volume of distribution; the drug and even more its metabolite desethylamiodarone extensively accumulate in adipose tissue and highly perfused organs, such as liver, lung and spleen. This causes a delayed onset of action (2 to 3 days) and a long elimination half-life (up to 6 months). As a result, the therapy with amiodarone may be associated with frequent adverse events requiring a careful monitoring.

Amiodarone crosses the placenta in pregnant women and is excreted in varying amounts in breast milk. Its use should therefore be avoided in women who are pregnant or breast-feeding.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or desethylamiodarone in urine.

Amiodarone is metabolized by the cytochrome P450 enzyme group, specifically CYP3A4 and CYP2C8. Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit CYP3A4 may decrease the metabolism and increase serum concentrations of amiodarone. Examples include protease inhibitors, histamine H2 antagonists and grapefruit juice. Amiodarone may also suppress certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6 and CYP3A4. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes. Examples include: cyclosporine, HMG-CoA reductase inhibitors, cardiac glycosides, other antiarrhythmic drugs such as quinidine, procainamide, disopyramide and phenytoin, antihypertensives such as beta-blockers or calcium channel antagonists, anticoagulants and antibiotics such as rifampin.

Interactions with warfarin and digoxin are the most clinically relevant.

Potential of warfarin-type anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3 to 4 days, the dose of the anticoagulant should be reduced by one-third to one-third, and prothrombin time should be monitored closely.

In patients receiving digoxin therapy, administration of oral amiodarone regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. On initiation of oral amiodarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued. If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity.

Finally, though no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been recommended during chronic treatment with amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

9.1 Indications for use

Amiodarone is used in the treatment of most tachyarrhythmias, including atrial fibrillation, atrial flutter, supraventricular tachycardias of whatever origin (including those associated with pre-excitation), ventricular tachycardia and ventricular fibrillation. Furthermore, it can be used for both cardioversion and heart rate control.

The following indications are reported as available from the British National Formulary (BNF) and the Food and Drug Administration (FDA).

Amiodarone, the approved FDA indications for use:

Intravenous amiodarone

- initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation
- hemodynamically unstable ventricular tachycardia in patients refractory to other therapy
- treatment of patients with ventricular tachycardia or ventricular fibrillation for whom oral amiodarone is indicated, but who are unable to take oral medications.

Oral amiodarone, because of the life-threatening side effects and the substantial management difficulties associated with its use, should be considered only in case of no response to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated for:

- treatment of recurrent ventricular fibrillation
- recurrent hemodynamically unstable angina,

FDA recommends that, because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with amiodarone should be carried out in hospital (<http://www.fda.gov/cder/info/healthcare.htm>).

Amiodarone, the approved BNF indications for use:

- treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated;
- paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation;
- tachyarrhythmias associated with Wolff-Parkinson-White syndrome.

Amiodarone may be given by intravenous infusion as well as by mouth and it should be initiated only under hospital or specialist supervision, though it has the advantage of causing little or no myocardial depression. Unlike oral amiodarone, intravenous amiodarone may act relatively rapidly and intravenous injections may be used in cardiopulmonary resuscitation for ventricular fibrillation or pulseless tachycardia unresponsive to other interventions.

Other use in selected developing countries

Chagas' disease affects 1.8 to 2.5 million patients in Central and South America. Chronic Chagas' complications may include heart rhythm abnormalities causing sudden death and dilatative cardiomyopathy. Amiodarone is widely used to treat heart rhythm disorders in patients affected by Chagas' heart disease and poorly tolerated arrhythmias refractory to other treatments. Moreover, a recent study found that amiodarone would also have intrinsic direct activity against *Trypanosoma Cruzi* acting synergistically with the antifungal agent posaconazole (Benaim 2006).

Unlabelled use

Amiodarone has shown effectiveness for sinus rhythm conversion of atrial fibrillation and maintenance of sinus rhythm. It also appears to be useful in treating supraventricular tachycardia.

9.2 Dosage regimens

Tablets 100, 200, 400 mg

Vials and amps 50 mg/ml, 3 ml

FDA dosage recommendations:

Intravenous amiodarone: the recommended starting dose is about 1000 mg over the first 24 hours of therapy. After the first 24 hours, the maintenance infusion rate of 0.5 mg/min. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression. Patients whose arrhythmias have been suppressed by amiodarone injection may be switched to oral amiodarone. The optimal dose for changing from intravenous to oral administration of amiodarone will depend on the dose of intravenous amiodarone already administered, as well as the bioavailability of oral amiodarone.

Oral amiodarone: loading dose is usually 400 to 800 mg/day; a uniform, optimal dosage schedule for administration of amiodarone has not been determined. When adequate arrhythmia control is achieved, or if side effects become prominent, amiodarone dose should be reduced to the maintenance dose, usually of 200-400 mg/day. Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect.

The lowest effective dose should be used to prevent the occurrence of side effects.

BNF dosage recommendations:

Intravenous amiodarone: by infusion via central venous catheter, initially 5 mg/kg over 20–120 minutes with ECG monitoring; subsequent infusion given if necessary according to response up to maximum of 1200 mg in 24 hours.

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation: intravenous injection of amiodarone 300 mg or 5 mg/kg (from a prefilled syringe *or* diluted in 20 mL glucose 5%) should be considered after adrenaline to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. If ventricular fibrillation persists, an additional dose of amiodarone 150 mg (or 2.5 mg/kg) can be given.

Oral amiodarone: 200 mg 3 times daily for 1 week reduced to 200 mg twice a day for a further week; maintenance, usually 200 mg daily or the minimum required to control the arrhythmia.

9.3 Duration of therapy

Amiodarone injection should be used for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but amiodarone injection may be safely administered for longer periods if necessary. There has been limited experience in patients receiving amiodarone injection for longer than 3 weeks.

Prolonged treatment (years) with oral amiodarone can be indicated for maintenance of sinus rhythm in atrial fibrillation.

9.4 Reference to existing WHO and other clinical guidelines

At the moment there are no guidelines produced by WHO on the use of amiodarone. Appendix B provides a detailed comparison among available guidelines produced by other international agencies and scientific societies on the following topics:

Atrial fibrillation and amiodarone (Appendix B1)

- Snow V, Weiss KB, LeFevre M, McNamara R, Bass E, Green LA, Michl K, Owens DK, Susman J, Allen DI, Mottur-Pilson C. Management of newly detected atrial fibrillation: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med* 2003 Dec 16;139(12):1009-17.
- Canadian Cardiovascular Society. Atrial Fibrillation. Consensus Conference 2004
- New Zealand Guidelines Group. New Zealand Cardiovascular Guidelines Handbook: Developed for Primary Care Practitioners. June 2005
- New Zealand Guidelines Group (NZGG). The management of people with atrial fibrillation and flutter. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2005 May.
- Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey J-Y, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:e149–246.
- National Collaborating Centre for Chronic Conditions. Atrial fibrillation. National clinical guideline for management in primary and secondary care. London (UK): Royal College of Physicians; 2006.
- Institute for Clinical Systems Improvement. Health Care Guideline: Atrial Fibrillation. February 2007.

Other arrhythmias and amiodarone (Appendix B2)

- ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. Bethesda (MD): American College of Cardiology Foundation; 2002.
- Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias. A

report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Bethesda (MD): American College of Cardiology Foundation; 2003.

- American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest* 2005 Aug;128(2 Suppl):1S-64S.
- Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:e247– e346.
- National Institute for Health and Clinical Excellence. Implantable cardioverter defibrillators for arrhythmias. Review of Technology Appraisal 11. January 2006.
- Scottish Intercollegiate Guidelines Network (SIGN). Cardiac arrhythmias in coronary heart disease. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2007 Feb.
- Proyecto ISS – ASCOFAME. Guías de práctica clínica basadas en la evidencia. Arritmias ventriculares. Colombia.1997
- Proyecto ISS – ASCOFAME. Guías de práctica clínica basadas en la evidencia. Arritmias supraventriculares. Colombia.1997

Chronic heart failure, other heart disorders and amiodarone (Appendix B3)

- The National Heart Foundation of New Zealand. A guideline for the management of heart failure – health professional guide. December 2001
- Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED, Vogel RA, Abrams J, Bates ER, Brodie BR, Danias PG, Gregoratos G, Hlatky MA, Hochman JS, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Eur Heart J* 2003 Nov;24(21):1965-91.
- Veterans Health Administration, Department of Veterans Affairs. The pharmacologic management of chronic heart failure. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2003 Aug.
- National Collaborating Centre for Chronic Conditions. Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care. London: National Institute for Clinical Excellence (NICE); 2003.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site.
- Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: full text (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Sophia Antipolis (FR): European Society of Cardiology (ESC); 2005.
- JMO Arnold, P Liu, C Demers, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Can J Cardiol* 2006;22(1):23-45.
- National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand, Chronic Heart Failure Guidelines Expert Writing Panel. Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Sydney (Australia): National Heart Foundation of Australia; 2006 Nov.

- Heart Failure Society of America. HFSA 2006 Comprehensive Heart Failure Practice Guideline. www.hfsa.org. 2006
- Institute for Clinical Systems Improvement. Health Care Guideline: Heart Failure in Adults. August 2006.
- Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic heart failure. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2007 Feb.
- The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Guidelines on the management of valvular heart disease. European Heart Journal (2007) 28, 230–268
- Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of CVD. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2007 Feb.

Amiodarone and management of toxicity (Appendix B4)

- AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002 Nov-Dec;8(6):457-69.
- National Academy of Clinical Biochemistry (NACB). NACB: laboratory support for the diagnosis and monitoring of thyroid disease. Washington (DC): National Academy of Clinical Biochemistry (NACB); 2002.
- American Academy of Ophthalmology Refractive Errors Panel. Refractive errors. San Francisco (CA): American Academy of Ophthalmology; 2002.
- Clinical Practice Guideline Working Group. Clinical Practice Guideline: Investigation and Management of Primary Thyroid Dysfunction. 2007 Update

9.5 Need for special diagnostic or treatment facilities and skills

Patients treated with amiodarone should be followed regularly to assess ongoing need for amiodarone, efficacy of the drug, appropriateness of dosage, adverse events, and potential drug interactions (Siddoway 2003).

The New Zealand Guidelines Group document on the management of people with atrial fibrillation and flutter (NZGG 2005a) warns that because of amiodarone's non-cardiac effects, several precautions should be considered. Safety measures to be followed can be listed according to their clinical relevance as follows:

- progressive reduction of dosage to the minimum effective dosage (where possible)
- intensified INR monitoring at the commencement of therapy, and with any dosage adjustments (amiodarone increases the INR in people on warfarin).
- basal and subsequent regular monitoring of thyroid and liver function, at least every 6-months
- baseline lung function testing, including single breath diffusing capacity, repeated if there is a clinical suspicion of pulmonary toxicity (people with increasing breathlessness should be promptly referred for evaluation)
- protection against photosensitivity, e.g., liberal use of sunblock, wide-brimmed hat, long sleeves
- ophthalmologic assessment if there is any concern about background ocular disease, at least as a baseline, with follow-up as clinically indicated

10. Summary of comparative effectiveness in a variety of clinical settings

Based on primary and secondary studies retrieved and according to major recommendations from evidence based guidelines consulted, amiodarone appear to be effective in the treatment of arrhythmic disorders both in terms of reduced morbidity and mortality.

Relevant primary studies are summarized below in Table 1a and Table 1b.

Table 1a. Relevant RCTs on amiodarone in Heart Failure (HF) – Studies' description				
Trial/Setting	Study Design	Participants	Interventions	Outcomes
GESICA, 1994 Argentina	Open RCT	HF patients N=516 Males=79.3% Age=58.5	Amiodarone 300 mg/d vs placebo	24 months total mortality; sudden death or death due to HF; hospital admission due to HF
CHF-STAT, 1995 USA	Double-blind RCT	HF patients N=674 Males=99.1% Age=65.0±8.5	Amiodarone (800 mg/d for 14 days, then 400 mg/d for 50 weeks, then 300 mg/d) vs placebo	54 months total mortality; sudden death from cardiac causes; left ventricular ejection fraction
CHF-STAT substudy, 1996 USA	Double-blind RCT	HF patients N=674 Males=99.1% Age=65.0±8.5	Amiodarone (800 mg/d for 14 days, then 400 mg/d for 50 weeks, then 300 mg/d) vs placebo	Left ventricular function; hospitalization for HF; combination of hospitalization and cardiac mortality
CHF-STAT substudy, 1998 USA	Double-blind RCT	Patients with HF and atrial fibrillation N=103 Age=67±7	Amiodarone (800 mg/d for 14 days, then 400 mg/d for 50 weeks, then 300 mg/d) vs placebo	Rate control; conversion to sinus rhythm; general survival
SCD-HeFT, 2005 USA	Double-blind RCT	HF patients N=2521 Males=77% Age=60.4	Conventional therapy plus implantable cardioverter defibrillator (ICD) vs conventional therapy plus amiodarone vs conventional therapy plus placebo	60 months death from any cause
COMET, 2007 Denmark	Double-blind RCT	HF patients receiving Beta-blockers N=3029 Males=84.6% Age=63.6±10.6	Amiodarone (N=364) vs no Amiodarone (N=2665)	58 months all cause mortality, sudden death, death due to circulatory failure

Table 1b. Main RCTs evaluating amiodarone in patients with Heart Failure (HF) – Study results			
Study	Results	Benefits	Harms
GESICA, 1994 Argentina	Total mortality: 33.5% (Amiodarone) vs 44.4% (Placebo)[p=0.024], ARR=7.9%, NNT=12.6; Sudden death: 12.5% (Amiodarone) vs 15.2% (Placebo)[p=0.16], ARR=2.9%, NNT=34.5; Death due to CHF: 16.9% (Amiodarone) vs 20.3% (Placebo)[p=0.16], ARR=3.4%, NNT=29.4; Mortality and hospitalization for CHF: 45.8% (Amiodarone) vs 58.2% (Placebo) [p=0.0024], ARR=12.4, NNT=8.1	Decrease in total mortality and combined mortality-hospitalization for CHF.	Amiodarone-related adverse events in 6.1% of the patients. No information on adverse events in placebo group

Table 1b. Main RCTs evaluating amiodarone in patients with Heart Failure (HF) – Study results			
Study	Results	Benefits	Harms
CHF-STAT, 1995 USA	Total mortality: 42% (Amiodarone) vs 39% (Placebo)[p=0.6]; Sudden death: 15% (Amiodarone) vs 19% (Placebo) [p=0.43]; Left ventricular ejection fraction: 35.4±11.5% (Amiodarone) vs 29.8±12.2% (Placebo) [p<0.001]	Increase in left ventricular ejection fraction.	Higher therapy discontinuation because of adverse events in amiodarone group compared to placebo (27% versus 23%). Significant increase of overall severe adverse events in amiodarone group compared to placebo (18.2% versus 10.9%, p=0.008)
CHF-STAT substudy, 1996 USA	Increase in left ventricular function: 8.8±10.1% (Amiodarone) vs 1.9±9.4% (Placebo) [p<0.001]. Hospitalization for HF: 11.1% (Amiodarone) vs 13.6% (Placebo)[p=0.14]. Hospitalization and cardiac mortality: RR=0.82 [p=0.08]	Increase in left ventricular function; decrease in combined hospitalization-cardiac mortality.	No information on adverse events
CHF-STAT substudy, 1998 USA	Rate control: the patient randomized to amiodarone demonstrated significant reduction in ventricular rate [p=0.001]; Conversion to sinus rhythm: 31.4% (Amiodarone) vs 7.7% (Placebo) [p=0.002]; General survival: no significant difference in survival of patients with AF at baseline between the drug groups [p=0.83]	Reduction in ventricular rate and better conversion to sinus rhythm.	No information on amiodarone-related adverse events
SCD-HeFT, 2005 USA	Death from any cause: 28.9% (ICD) vs 34.0% (Amiodarone) vs 36.1% (Control); Amiodarone vs Control: 1.06 HR [p=0.53]; ICD vs Control: 0.77 HR [p=0.007] NYHA class III CHF (30% population): 44% increase in the risk of death among patients receiving amiodarone compared with Control (HR=1.44)	No proven benefits of amiodarone associated to conventional therapy compared with placebo associated to conventional therapy.	Increased mortality among patients with NYHA class III CHF who received amiodarone compared with control. Significant increased hypothyroidism and tremor in amiodarone group compared to control.
COMET, 2007 Denmark	All cause mortality NYHA II: 38.7% (Amiodarone) vs 26.2% (no Amiodarone), HR=1.60 [p<0.001]; All cause mortality NYHA III: 58.9% (Amiodarone) vs 43.3% (no Amiodarone), HR=1.30 [p<0.001]; Sudden death: HR=1.07 [p=0.6]; Increased mortality due to circulatory failure with amiodarone: HR=1.89 [p<0.001]	No proven benefits of amiodarone compared with placebo.	Increased all cause mortality and circulatory failure death with amiodarone compared with placebo. No information on amiodarone-related adverse events.

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Guidelines were searched through the following sources (data last search August 30, 2007):

1. Guidelines databases:

National Guideline Clearinghouse (search strategy):

Arrhyth* OR "Atrial Fibrillation" [Disease/Condition] → 45 records retrieved

Amiodarone [free text] → 44 records retrieved

NLM Guideline Finder (search strategy):

Specialist Libraries/Cardiovascular Diseases/Conditions/Arrhythmia → 49 records retrieved

2. Network or Agency websites

Guidelines International Network (GIN)

Through the list of international agencies → 2 records retrieved

National Institute for Health and Clinical Excellence (NICE)

the database were checked through the “browse” function: guidance by topic/cardiovascular → 9 records retrieved

Scottish Intercollegiate Guidelines Network (SIGN)

the database were checked through the “browse” function: published guidelines by topic / CHD and Stroke → 3 records retrieved

New Zealand Guidelines Group

the database were checked through the “browse” function: Guidelines and Reports / List by therapeutic category / Cardiovascular → 3 records retrieved

CMA Infobase

the database were checked through the “search” function with the term: Arrhythmia [MESH] OR Amiodarone [free text] → 15 records retrieved

Australian Government National Health and Medical Research Council

the database were checked through the “browse” function: Publications by Category / Conditions and diseases / Cardiovascular → 0 records retrieved

After checking for duplicates, the search strategy identified 63 reports as potentially eligible for this document. Based on title assessment 31 reference were excluded. Therefore **32 guidelines** were included in the revision (see Appendix B).

PubMed were also searched for relevant RCTs that might not have been included in guidelines (last search August 21, 2007 – see Appendix C). The search strategy identified **32 records**.

10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)

Evidence supporting the use of amiodarone in a variety of clinical conditions are reported below. For each clinical condition (atrial fibrillation, other arrhythmias, myocardial infarction, HF) recommendations are first presented as stated in available guidelines and subsequently the evidence base (single RCT) are summarized.

Amiodarone in the treatment of atrial fibrillation***Recommendations from available guidelines (Appendix B)***

The guidelines on atrial fibrillation developed in New Zealand and United States (NZGG 2005a, Fuster 2006, ICSI 2007) agree on the following recommendations:

- amiodarone is the first choice as antiarrhythmic agents for maintenance of sinus rhythm when impaired left ventricular function, ischemic heart disease, chronic HF are present;
- amiodarone may be a first choice as pre-treatment to enhance the success of direct-current cardioversion and prevent recurrent atrial fibrillation;
- amiodarone may be the first choice for the management of patients with atrial fibrillation and acute myocardial infarction, in order to slow a rapid ventricular response in patients with impaired left ventricular function.

In addition ACC/AHA/ESC guideline suggests to use amiodarone to treat atrial fibrillation in post-myocardial infarction patients who are not candidates for sotalol or dofetilide, in patients with congestive HF and left ventricular dysfunction who are not candidates for dofetilide, in patients with significant left ventricular hypertrophy, and in antiarrhythmic drug-refractory symptomatic patients as a medical alternative to catheter ablation (Fuster 2006).

According to NICE guideline amiodarone should be considered only when digoxin, beta-blockers and calcium channel blockers are ineffective, contraindicated (i.e bronchospasm, HF) or not tolerated (NICE 2006).

The NZGG guideline affirms that pharmacological cardioversion with amiodarone is an alternative option to electrical cardioversion, either in the acute setting (atrial fibrillation and flutter duration <48 hours) or in the context of adequately anticoagulated patients with atrial fibrillation and flutter (NZGG 2005a). In particular

it affirms that: “as a general rule, as with choice of antiarrhythmic agents in general, the choice of drug for an individual depends more on clinical factors than speed of onset. If there is significant heart disease (eg, past myocardial infarction, coronary disease, poor left ventricular function) amiodarone is the agent of choice, and disopyramide, flecainamide and propafenone should be avoided. In practice, as people present acutely and such information is not easily available, a conservative approach using either amiodarone or rate control is often chosen”.

AAFP/ACP guideline at the contrary concludes that there are no definitive data on the efficacy of electrical over pharmacologic conversion of atrial fibrillation (Snow 2003).

Evidence from available trials (Appendix C)

The Canadian Trial of Atrial Fibrillation showed that amiodarone was more effective than propafenone or sotalol in preventing atrial fibrillation recurrences. After a follow-up of 16 months, 35% of the patients who received amiodarone and 63% of those treated with sotalol or propafenone had a recurrence of atrial fibrillation ($p < 0.001$), with an absolute risk reduction of 27.5% with amiodarone and NNT of 3.6. However, discontinuation rates due to adverse effects were higher in patients treated with amiodarone (18% versus 11%) (Roy 2000).

A sub-study of the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) showed that amiodarone was more effective at one year than either sotalol or class I agents for maintenance of sinus rhythm, with an absolute benefit increase respectively of 22% and 39% (AFFIRM investigators 2003).

The Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial confirmed these data, finding that amiodarone was superior both to sotalol and placebo in preventing recurrences of atrial fibrillation, with a recurrence rate at 1 year respectively of 48%, 68% (NNT=5) and 87% (NNT=2.5) (Singh 2005).

A meta-analysis concluded that amiodarone, when compared with class I drugs, significantly reduces mortality rate (OR, 0.39; $P = .009$; NNT=17), while it has no effect on mortality when compared with placebo. The authors pointed out that the effect on mortality of amiodarone compared with class I drugs was mainly due to the weight of the AFFIRM sub-study 2003 and persisted in sensitivity analysis. The meta-analysis also demonstrated that amiodarone reduces recurrences of atrial fibrillation significantly more than class I drugs and sotalol, with a risk reduction respectively of 26.5% and 20.7% (Lafuente 2006).

The AFFIRM study (AFFIRM investigators 2002) demonstrated no significant differences in stroke, quality of life or mortality with rhythm-control therapy versus rate-control: the mortality at five years was 23.8% with rhythm-control therapy and 21.3% with rate-control therapy; more patients were hospitalized and more adverse drug effects occurred in the rhythm-control group than in the rate-control group.

Rate control should be the recommended strategy for the majority of people with atrial fibrillation and flutter: amiodarone slows ventricular rate in atrial fibrillation, even when sinus rhythm is not restored, but it is not appropriate first-line therapy for chronic rate control (Vassallo 2007).

In a meta-analysis of 21 RCTs, amiodarone was found to be widely effective for cardioversion of atrial fibrillation: RR 4.3 (95% CI: 2.76-6.77) for achieving sinus rhythm in trials with mean atrial fibrillation duration of greater than 48 hours; RR 1.4 (95% CI: 1.25-1.57) in trials with atrial fibrillation of 48 hours or less. The NNT was 4 (95%CI: 3-14) for both groups (Letelier 2003).

Flecainamide and propafenone result in more rapid cardioversion than amiodarone (Kochiadakis 1998).

Amiodarone in the treatment of other arrhythmias

Recommendations from available guidelines (Appendix B)

The guidelines on arrhythmias developed by ACC/AHA/ESC and SIGN (Fuster 2006; SIGN 2007a) agree on the following recommendations with respect to intravenous amiodarone use:

- intravenous amiodarone may be the first choice in the acute management of hemodynamically stable and regular tachycardia with wide QRS complex of unknown origin in patients with poor left ventricular function;

- intravenous amiodarone should be the preferred antiarrhythmic drug for attempting a stable rhythm after further defibrillations for victims with ventricular tachyarrhythmic mechanisms of cardiac arrest, when recurrences occur after a maximally defibrillating shock;
- intravenous amiodarone is reasonable in patients with sustained monomorphic ventricular tachycardia that is hemodynamically unstable, refractory to conversion with countershock, or recurrent despite procainamide or other agents;
- intravenous amiodarone may be the first choice for treating repetitive monomorphic ventricular tachycardia in the context of coronary disease and idiopathic ventricular tachycardia;
- revascularization and beta blockade followed by intravenous of amiodarone are recommended for patients with recurrent or incessant polymorphic ventricular tachycardia due to acute myocardial ischemia;
- intravenous amiodarone is the first choice for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence.

They also support the following recommendations regarding oral amiodarone use:

- oral amiodarone may be considered for patients with a history of sustained ventricular tachycardia or ventricular fibrillation in patients with non-ischemic dilated cardiomyopathy;
- oral amiodarone prophylaxis may be the drug of choice for treatment in patients with hypertrophic cardiomyopathy with a history of sustained ventricular tachycardia and/or ventricular fibrillation when an implantable cardioverter defibrillator is not feasible;
- oral amiodarone therapy may be the first drug choice for treatment in patients with arrhythmogenic right ventricular cardiomyopathy with a history of sustained ventricular tachycardia and/or ventricular fibrillation when an implantable cardioverter defibrillator is not feasible;
- oral amiodarone may be the first pharmacological adjuncts to implantable cardioverter defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and non-sustained) in otherwise optimally treated patients with HF;
- oral amiodarone therapy may be the first drug choice as pharmacological alternatives to implantable cardioverter defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and non-sustained) in optimally treated patients with HF for whom implantable cardioverter defibrillator therapy is not feasible.

ACC/AHA/ESC 2006 guideline recommends to use beta blockers as first-line therapy in patient with ventricular arrhythmias, but if this therapy at full therapeutic dose is not effective, then it recommends trying amiodarone with monitoring for adverse effects during administration (Fuster 2006).

Evidence from available trials (Appendix C)

Amiodarone is approved by the FDA for the treatment of life-threatening, recurrent ventricular arrhythmias, such as ventricular fibrillation or ventricular tachycardia associated with hemodynamic instability. However, the overall long-term survival benefit from amiodarone is controversial.

In a meta-analysis of 13 RCTs amiodarone compared to placebo reduced overall mortality (OR: 0.87; 95%CI: 0.78 to 0.99), and arrhythmic death (OR: 0.71; 95%CI: 0.59 to 0.85); however, most studies were small sized and presented significant differences among recruited populations (Connolly 1999).

The SCD-HeFT trial showed no survival benefit from amiodarone compared with placebo with a HR 1.06 (p=0.53) (Bardy 2005).

Three randomized trials have assessed effectiveness of amiodarone in preventing sudden cardiac deaths: AVID trial (AAVV 1997), CASH trial (Kuck 2000) and CIDS trial (Connolly 2000). The trials comparing implantable cardioverter defibrillators with amiodarone or other antiarrhythmic drugs, have demonstrated, though just AVID significantly, that implantable cardioverter defibrillators was superior to amiodarone in improving survival and preventing sudden cardiac death in patients resuscitated from near-fatal ventricular arrhythmias: death rate decreased rate was 39%±20% at one year of follow up, 27%±21% at two years of follow up and 31%±21% at three years of follow up (AAVV 1997).

Two prospective double blind studies evaluated intravenous amiodarone for shock-resistant arrest due to ventricular tachycardia or ventricular fibrillation in individuals experiencing out-of-hospital cardiac arrest (Kudenchuk 1999; Dorian 2002). The first trial assessed the efficacy of amiodarone, measured as chance to survive to be admitted to the hospital, in patients with out-of-hospital cardiac arrest who had not been resuscitated after three or more precordial shocks. 504 patients were randomly treated with intravenous amiodarone or placebo. The study demonstrated an absolute increase in survival to admission to the hospital in the amiodarone group as compared with the placebo group of 9.4% (95%CI: 0.9 to 17.9), adjusted OR 1.6 (95% CI: 1.1 to 2.4; $p=0.02$).

NNT 11 (95% CI: 6 to 111) (Kudenchuk 1999). The second trial evaluated amiodarone compared with lidocaine for shock-resistant ventricular fibrillation. The study found that intravenous amiodarone was more effective than lidocaine for out-of-hospital ventricular fibrillation resistant to shocks and epinephrine, with an absolute increase in the survival to admission to hospital of 10.8% (95%CI: 2.9 to 18.7), adjusted OR 2.49 (95%CI: 1.28 to 4.85) and NNT 9 (95%CI: 5 to 34) (Dorian 2002). In both trials survival after hospital discharge did not differ between treatment groups.

Amiodarone after Acute Myocardial Infarction

Recommendations from available guidelines (Appendix B)

Patients with post-myocardial infarction are at risk for arrhythmias and sudden cardiac death, and have higher rates of all-cause mortality than the general population (Thomas 2008).

The guidelines reviewed generally agreed that intravenous administration of amiodarone may be the first choice for the management of patients with atrial fibrillation and acute myocardial infarction, in order to slow a rapid ventricular response in patients with impaired left ventricular function (Canadian Cardiovascular Society Guidelines on Atrial Fibrillation 2004; Fuster 2006). Furthermore, though a rate control strategy with beta blockers, when feasible, would be preferable in ischemic syndromes, “intravenous and oral amiodarone are useful for rate control especially when other rate control agents are relatively or absolutely contraindicated such as with bronchospasm or HF and are also useful for rhythm control” (Canadian Cardiovascular Society Guidelines on Atrial Fibrillation 2004).

ACC/AHA/ESC 2006 guideline affirms that amiodarone should not be used routinely after myocardial infarction; however, possibly in combination with beta blockers, it can be useful for patients with left ventricular dysfunction due to prior myocardial infarction and symptoms due to ventricular tachycardia unresponsive to beta blocking agents and for patients who cannot or refuse to have an implantable cardioverter defibrillator (Fuster 2006).

Evidence from available trials (Appendix C)

The role of amiodarone in patients with normal left ventricular function following myocardial infarction is very limited. Although randomized trials, assessing the effect of amiodarone treatment after myocardial infarction, have demonstrated a consistent trend toward reduction in arrhythmic deaths, no benefit emerged in all-cause mortality when empiric amiodarone was initiated early after myocardial infarction. Below we summarize three relevant studies on the use of amiodarone in post-myocardial infarction patients.

The Basel Antiarrhythmic Study of Infarct Survival (BASIS) demonstrated a significant reduction in total mortality with amiodarone compared with placebo in survivors of myocardial infarction, with an absolute risk reduction of 8.1% and NNT of 12.3; however, patients underwent follow-up for only 1 year and beta-blockers use was limited (Burkart 1990).

The European Myocardial Infarct Amiodarone Trial (EMIAT) assessed the survival of patients post-myocardial infarction and impaired left ventricular ejection fraction (LVEF < 40%) treated with amiodarone or placebo during a follow up period of 21 months. The study showed an absolute risk reduction in arrhythmic death of 2.3% (95% CI: 0 to 4.6), NNT 44 (NS), risk reduction 35% (95% CI 0–58, $p=0.05$). However there were no differences in all-cause deaths, respectively 13.9% with amiodarone and 13.7% with placebo, nor in cardiac deaths, respectively 11.4% with amiodarone and 12% with placebo. In addition 111 patients in the amiodarone group (14.9%) and 57 patients in the placebo group (7.7%) discontinued the therapy because of occurring adverse events ($p<0.0001$). Similarly, the overall incidence of severe adverse

events was significantly higher in the amiodarone compared to placebo (respectively 20.9% and 14.8%, $p=0.002$), with a significant increase of clinical hypothyroidism and skin disorders in patients receiving amiodarone and a higher incidence of bradycardia and other arrhythmias in the placebo group (Julian 1997).

Similarly to EMIAT, the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), assessing the effect of amiodarone or placebo among survivors of myocardial infarction, found that amiodarone reduces the cumulative risk of a composite outcome (arrhythmic death or resuscitated ventricular fibrillation): RR 48.5% (95%CI: 4.5 to 72.2) but it has no effect on arrhythmic deaths considered alone, nor on cardiac death and no on all-cause mortality (95%CI not significant for all these outcomes). The therapy was discontinued in 159 patients in the amiodarone group (26.2%) and in 82 patients in the placebo group (13.7%) because of the occurrence of adverse events ($p<0.0005$). Patients receiving amiodarone had a significant higher incidence of pulmonary, hypothyroid and neurological events while there was a significant increase of proarrhythmias and other ventricular tachyarrhythmias among patients treated with placebo (Cairns 1997).

Amiodarone in the treatment of heart failure

Recommendations from available guidelines (Appendix B)

The consulted guidelines (Hunt 2005; Swedberg 2005; Heart Failure Society of America 2006; Institute for Clinical Systems Improvement 2006; SIGN 2007b) agree on the following statement:

- Amiodarone should neither be considered nor justified as part of the routine treatment of patients with HF.

American (Hunt 2005; Heart Failure Society of America 2006; Institute for Clinical Systems Improvement 2006) and European (Swedberg 2005, SIGN 2007b) agree that amiodarone should neither be considered nor justified as part of the routine treatment of patients with HF; however, according to ACC/AHA guideline (Hunt 2005), it would remain “the agent most likely to be safe and effective when antiarrhythmic therapy is necessary to prevent recurrent atrial fibrillation or symptomatic ventricular arrhythmias”.

The ACC/AHA/ESC guideline on the management of atrial fibrillation affirms that amiodarone is the drug of choice for pharmacological maintenance of sinus rhythm in patients with symptomatic atrial fibrillation or flutter plus significant left ventricular disease and/or HF (Blomstrom 2006).

The other guideline produced by ACC/AHA/ESC on the management of ventricular arrhythmias and prevention of sudden cardiac death, affirms that amiodarone may be the drug of choice as pharmacological alternatives to implantable cardioverter defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias in optimally treated patients with HF for whom implantable cardioverter defibrillator therapy is not feasible; furthermore it may be the first pharmacological adjuncts to implantable cardioverter defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias in otherwise optimally treated patients with HF (Zipes 2006).

Evidence from available trials (Appendix C)

Patients with chronic HF can die suddenly and unpredictably from arrhythmia. However, the risk-benefit ratio of amiodarone in patients with chronic HF is complex and not definitively clear. Several studies have evaluated the role of amiodarone in survival of patients with chronic HF (Table 1a, Table 1b).

The GESICA (Grupo de Estudio de la Sobrenda en la Insuficiencia Cardiaca en Argentina) study was a randomized trial of prophylactic amiodarone compared with no additional treatment in 516 patients with CHF. It showed a significant reduction in overall mortality with amiodarone (33.5% versus 41.4%, ARR=7.9%, NNT=12.6), a reduction in sudden death (12.3% versus 15.2%, ARR=2.9%, NNT=34.5) and death due to progressive chronic HF (16.9% versus 20.3, ARR=3.4%, NNT=29.4) and decrease in both mortality and hospitalization for chronic HF, (45.8% versus 58.2%) (Doval 1994). However, it is important to notice that, at the time, the standard regimen for chronic HF did not include β -blockers. In this study amiodarone-related adverse events compared to placebo were not adequately studied.

The Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT), a double-blind study of 674 patients, evaluated the overall mortality in patients with congestive HF receiving amiodarone or placebo after a median follow-up of 45 months; amiodarone had no significant effect on survival: the overall

actuarial survival at two years was 69.4% (95%CI: 64.2% to 74.6%) with amiodarone and 70.8% (95%CI: 65.7% to 75.9%) with placebo. During the study period 274 deaths were registered: 131 (39%) in the amiodarone group and 145 (42%) in the placebo group. The study medication was discontinued in 90 patients in the amiodarone group (27%) and in 78 patients in the placebo group (23%) because of the occurrence of adverse events, with no significant difference between the two groups. Moreover, patients receiving amiodarone had a significant increase in overall severe adverse events compared to placebo (18.2% versus 10.9%, $p=0.008$). (Singh 1995).

In a CHF-STAT sub-study amiodarone therapy determined a substantial increase in left ventricular ejection fraction in patients with chronic HF (a 33% relative increase over baseline at each time point in the amiodarone group) but it was not associated with greater clinical improvement, lesser diuretics requirements or fewer hospitalizations for HF; a trend toward a reduction in the combined end point of hospitalizations and cardiac deaths which was significant in patients with non-ischemic etiology (RR: 0.56; 95%CI: 0.3 to 0.87) and absent in the ischemic group (RR: 0.95; 95%CI: 0.73 to 1.24) (Massie, 1996).

Another subanalysis of CHF-STAT, assessing the effect of amiodarone compared with placebo on morbidity and mortality in patients with atrial fibrillation and HF, found that amiodarone had a significant potential in spontaneously converting patients in atrial fibrillation to sinus rhythm (absolute benefit increase of 23.7%; 95%CI: 8.9% to 38.5%; NNT 4; 95%CI: 3 to 11) and in preventing the development of new-onset atrial fibrillation: absolute risk reduction of new onset atrial fibrillation: 4.3% (95%CI: 0.1% to 8.4%) and NNT 23 (95%CI: 12 to 670). Overall there was no significant difference in survival of patients with AF receiving amiodarone or placebo (P value = 0.83) (Deedwania 1998).

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), a randomized trial including 2521 patients, assessed the effect of conventional therapy and amiodarone (845 subjects), conventional therapy and placebo (847 subjects) and conventional therapy and implantable cardioverter defibrillator (829 subjects) in patients with HF during a period of at least two years. The study demonstrated that amiodarone did not reduce the risk of death from any cause (HR: 1.06, 95%CI: 0.86 to 1.30), while implantable cardioverter defibrillator therapy reduced overall mortality by 23% (HR: 0.77, 95%CI: 0.62 to 0.96). Amiodarone was discontinued in 269 patients (32%) while placebo was discontinued in 189 patients (22%), with a significant difference between the two groups ($p<0.001$). A significant increase in the complications rate was observed in the amiodarone group, as compared with the placebo group at last follow up visit: in amiodarone group hypothyroidism was present in 6% of patients ($p<0.001$) and tremor in 4% ($p=0.02$). Furthermore, a SCD-HeFT subgroup analysis showed a 44% relative increase in the risk of death among patients with NYHA class III receiving amiodarone compared with those in the placebo group (HR: 1.44; 95%CI: 1.05 to 1.97) (Bardy 2005).

Similarly, another study, analyzing the association between amiodarone therapy and mortality in the Carvedilol or Metoprolol European Trial (COMET) and including 3029 patients, concluded that treatment with beta-blockers and amiodarone compared with treatment with only beta-blockers was associated with an increased risk of death (HR: 1.5; 95%CI: 1.2 to 1.7) in multivariable analysis. The increased risk of death was due to an increase of the circulatory failure in amiodarone group (HR: 2.4; 95%CI: 1.9 to 3.1), while sudden death did not differ (Torp-Pedersen, 2007).

A meta-analysis of ten randomised trials of amiodarone in chronic HF, including many of the trials above described, found that amiodarone significantly reduces mortality rate (absolute reduction 21%; 95%CI: 8% to 23%) but it also significantly increases frequency of side effects (OR: 2.29; 95%CI: 1.97 to 2.66) (Piepoli 1998).

Dronedronarone, a new antiarrhythmic drug similar to amiodarone for electrophysiological properties but not containing iodine and therefore not inducing iodine-related adverse reactions, was recently evaluated in a placebo-controlled trial in patients with severe HF and left ventricular systolic dysfunction. The RCT however was prematurely stopped because after enrolling 627 patients (310 in the dronedronarone group and 317 in the placebo group) an excess of deaths was registered in the intervention group. At two months of follow up 37 deaths happened: 25 deaths (8.1%) in dronedronarone group and 12 deaths (3.8%) in placebo group (HR: 2.13; 95%CI: 1.07 to 4.25). The excess of deaths was associated with a significant worsening of HF in dronedronarone group (Køber 2008).

Conclusions

Amiodarone should not be part of the routine treatment of patients with HF.

Amiodarone could play a relevant role in the treatment of arrhythmic disorders as antiarrhythmic agent for maintenance of sinus rhythm, particularly when impaired left ventricular function, acute coronary artery disease and chronic HF are present, and for sustained ventricular tachyarrhythmias associated with structural or functional heart disease who are not candidates for an implantable cardioverter defibrillator; in both cases, because of its risk/benefit profile, amiodarone requires a careful and periodic monitoring of the adverse events, with particular attention to thyroid function.

11. Summary of comparative evidence on safety

A summary of most common adverse events related to amiodarone use, their incidence and monitoring system required is reported below in Table 2.

Table 2. Type, incidence and monitoring of amiodarone-induced main adverse events*				
System	Adverse Event	Incidence	Baseline Tests	Follow-up
Cardiac	Bradycardia	5%	ECG (at baseline and during loading dose)	Yearly
	Prolonged QT Interval	In most patients		
	Torsades de pointes	<1%		
Dermatologic	Blue Discoloration	<10%	Physical examination	As needed for signs or symptoms
	Photosensitivity	25-75%		
Endocrine	Hypothyroidism	20%	TSH and TPOAb. FT4 and FT3 if TSH is abnormal	TSH every 6 months
	Hyperthyroidism	3-20%		
Gastroenteric	Nausea, anorexia and constipation	30%		
Hepatic	AST or ALT level greater than 2 times normal	15-30%	AST and ALT	AST and ALT every 6 months
	Hepatitis and cirrhosis	<3%		
Neurologic	Ataxia, paresthesias, peripheral polyneuropathy, sleep disturbance, impaired memory and tremor	3-30%	Physical examination	As needed for signs or symptoms
Ophthalmologic	Photophobia, visual blurring, and microdeposits	>90%	Eye examination	As needed for signs or symptoms
	Optic Neuropathy	<1%		
	Halo vision, especially at night	<5%		
Pulmonary	Pulmonary Toxicity (cough, fever, dyspnea)	2%	Pulmonary function tests (spirometry, lung volume determination, and diffusing capacity measurement tests)	As needed for signs or symptoms
			Chest radiography	Yearly

*Table based on Goldschlager 2007, Zimetbaum 2007, Siddoway 2003

11.1 Estimate of total patient exposure to date

Amiodarone has been used in the past decades by hundreds of thousands of patients in various settings and for a wide variety of clinical indications. This has involved both developed and developing countries. Amiodarone is one of the most frequently prescribed specific antiarrhythmic drugs in the United States (Al-Khatib 2003), but it is also widely used in Chagas disease's heart involvement, a particular indication affecting more than 2 million people in Latin America.

Its risk-benefit profile is quite well-established and requires a careful monitoring of thyroid function to be prescribed and to have a favourable risk-benefit ratio.

11.2 Description of adverse effects/reactions

Amiodarone is a highly lipophilic compound with a large volume of distribution; this causes a delayed onset of action (2 to 3 days) and a long elimination half-life (up to 6 months). As a result, there is a substantial lag between initiation, modification, or discontinuation of amiodarone and a change in its activity.

Amiodarone is metabolized in the liver, without any clinically significant renal metabolism. Amiodarone crosses the placenta in pregnant women and is excreted in varying amounts in breast milk. Its use should therefore be avoided in women who are pregnant or breast-feeding.

Labelled contraindications to the use of amiodarone include severe sinus-node dysfunction and advanced conduction disease. The drug should also be used cautiously in patients with severe lung disease (Zimetbaum, 2007).

Chronic amiodarone administration may have side effects including thyroid disease, hepatic dysfunction, lung disease (fibrosis), neurologic dysfunction, bradycardia, photosensitivity, phlebitis, *torsades de pointes*.

Adverse effects are common, with prevalence as high as 15% in the first year of use and 50% during long-term use, indicating a cumulative effect with chronic use. Furthermore, because of the gap between the use of amiodarone and the effect it produces, it may take more than 6 months before an adverse drug effect is reversed. Many adverse effects are manageable and the need to discontinue amiodarone therapy due to serious adverse reactions is relatively low, occurring in less than 20% of patients (Goldschlager, 2007; Singh 2005).

As mentioned, adverse effects increase with time of exposure and they are partly dose-related. Some adverse effects (neurological and gastrointestinal tract toxicity) are clearly dose-related, and they frequently occur in the first phases of amiodarone loading. Visual changes are generally, but not always, dose-related. Serious long-term toxicity, especially pulmonary and, less frequently, hepatic toxicity, appears to be in part dose-related.

A baseline assessment and a safety meticulous follow-up is central to the care of patients taking amiodarone. Early assessment and intervention is required when an adverse effect is suspected.

Effects on thyroid function

Amiodarone therapy can induce the development of thyroid dysfunction (hypo- or hyperthyroidism). It can determine various forms of thyroid dysfunction ranging from elevated serum thyroxine (T4) levels and low triiodothyronine (T3) levels in euthyroid patients to overt hypothyroidism or hyperthyroidism. The primary cause of the thyroid dysfunction is its large iodine load (a 200-mg standard daily dose provides about 300 times the usual daily iodine intake) that can cause either hypothyroidism or hyperthyroidism. Hyperthyroidism can also be caused by a thyroiditis that is iodine-independent, and known as type 2 hyperthyroidism.

The frequency of thyroid dysfunction is about 14-18% of treated patients, with the highest prevalence among women and those with antithyroid antibodies (AACE, 2002; NACB, 2002). Amiodarone-induced hypothyroidism frequency registered in iodine-sufficient regions is 20% (Pearce 2003) but it is more common among populations with pre-existing autoimmune thyroid disease and sufficient iodine intake, such as in the United States: one study comparing an iodine-sufficient area of Massachusetts and an iodine-deficient area of Italy found rates of amiodarone-induced hypothyroidism, as defined by elevated TSH levels and low or low-normal thyroxine level, to be 22% in Massachusetts and 5% in Italy (Martino 1984). Other risk factors for amiodarone-induced hypothyroidism include female sex and the presence of antithyroid

antibodies (Martino 1994). Antithyroid peroxidase antibodies are more common among white compared with black and Mexican-American individuals; 14.3%, 5.3%, and 10.9 %, respectively (Melmed 1981). Amiodarone-induced thyrotoxicosis is far more prevalent in iodine-deficient regions (Licata, 1997). Hyperthyroidism occurs in 3% of patients in areas where dietary iodine is sufficient but it occurs in up to 20% of patients in iodine-deficient areas (Zimetbaum, 2007). Type I amiodarone-induced thyrotoxicosis is defined as synthesis and release of excessive thyroid hormone; it is iodine-induced, and it is more likely to occur in patients with preexisting subclinical thyroid disorders, especially nodular goiter. Type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis that causes the release of preformed thyroid hormone from the damaged thyroid gland. Distinguishing between the two forms of amiodarone induced thyrotoxicosis is difficult, especially since some patients have both types.

Monitoring and recommendations

The NACB guidelines on laboratory support for the diagnosis and monitoring of thyroid disease, developed recommendations for monitoring patients starting amiodarone, identifying three main steps:

- Pre-treatment. Thorough physical thyroid examination together with baseline TSH and TPOAb. FT4 and free triiodothyronine (FT3) tests are only necessary if TSH is abnormal. Positive TPOAb is a risk factor for the development of thyroid dysfunction during treatment.
- First 6 months. Abnormal tests may occur in the first six months after initiating therapy. TSH may be discordant with thyroid hormone levels (high TSH/highT4/low T3). TSH usually normalizes with long-term therapy if patients remain euthyroid.
- Long-term follow-up. Monitor thyroid status every 6 months with TSH or sooner based on clinical findings. Serum TSH is the most reliable indicator of thyroid status during therapy.

Hypothyroidism is easily managed with levothyroxine and generally is not cause for discontinuing amiodarone.

Type I amiodarone-induced thyrotoxicosis is best treated with high doses of antithyroid drugs (methimazole or propylthiouracil), sometimes with the addition of potassium perchlorate to prevent further uptake of iodine by the thyroid; the recommended treatment of Type II amiodarone-induced thyrotoxicosis requires glucocorticoids and/or beta-blockers if cardiac status allows. When hyperthyroidism is severe, surgery with pre-treatment with iopanoic may be considered (Pearce 2003).

In general, the management of hyperthyroidism requires the assistance of an experienced endocrinologist and may require discontinuation of amiodarone therapy (NACB 2002); the decision to discontinue amiodarone is made balancing cardiac needs of the patient and clinical evidence of thyroid dysfunction.

Pulmonary toxicity

Pulmonary toxicity is one of the most serious complications of amiodarone use and it may result from direct drug-induced phospholipidosis or immune-mediated hypersensitivity (Pollak 1999). It occurs in about 2% of patients and it is more common in older patients and with higher doses of therapy. Amiodarone pulmonary toxicity can occur with higher dose regimens as well as with low dose therapy (Vorperian 1997); it may have both early and late presentation. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, there was a slightly increased incidence of pulmonary toxicity in patients with pre-existing pulmonary disease, but mortality from pulmonary causes and overall mortality were not higher among these patients than among those without pre-existing pulmonary disease (Olshansky 2005). The most common clinical presentation of amiodarone pulmonary toxicity is acute or sub-acute cough and progressive dyspnea, with associated interstitial infiltrates on chest radiographs and reduced diffusing capacity on pulmonary function tests with evidence of restriction. A much less common presentation is adult respiratory distress syndrome (Siddoway 2003).

Monitoring and recommendations

Screening pulmonary function tests and chest radiography should be performed at baseline, and chest radiography should be performed yearly. Pulmonary function tests (spirometry, lung volume determination, and diffusing capacity measurement) should be repeated if symptoms develop.

The management of acute pulmonary toxicity involves discontinuation of therapy, supportive management, and, in extreme cases, corticosteroid administration.

Ophthalmologic events

Corneal microdeposits are seen in almost all patients receiving long-term amiodarone therapy and are rarely clinically significant (Pollak 1999). Optic neuropathy has been reported in less than 1% of treated patients, but it may be a result of associated medical conditions rather than an effect of amiodarone (Zimetbaum 2007).

Monitoring and recommendations

Ophthalmologic examinations are recommended at baseline only for patients with pre-existing abnormalities. They should also be performed as needed in any patient who would note changes in visual acuity or peripheral vision. Corneal microdeposits seldom affect vision and rarely necessitate discontinuation of the drug (Siddoway 2003). Otherwise, the potential severity of optic neuropathy may warrant discontinuation of amiodarone therapy if the condition is suspected.

Dermatologic events

Dermatologic side effects of amiodarone use include photosensitivity (25-75% of treated patients), with susceptibility to sunburn, particularly in patients with a fair complexion (Goldschlager 2007). A grey-bluish skin discoloration may be seen in less than 10% of patients who take large doses of amiodarone for long periods.

Monitoring and recommendations

A physical examination at baseline and as needed for signs and symptoms should be recommended. Avoidance of direct exposure to the sun and use of sunscreen can diminish dermatologic events. The bluish skin discoloration resolves over several months after amiodarone is discontinued.

Gastrointestinal events and Hepatic toxicity

Gastrointestinal events include nausea, anorexia and constipation and they occur in 30% of patients treated with amiodarone. Hepatic toxicity, manifested by elevation of liver transaminase levels (more than two times the upper limit of the normal range), is a rare complication of amiodarone therapy when the drug is used in low doses and for short periods.

Monitoring and recommendations

Gastrointestinal events often are dosage related and usually improve when the dosage is reduced. Liver-function tests should be measured at baseline and every 6 months thereafter. Hepatic toxicity can generally be reversed by discontinuing the drug but can result in cirrhosis if unheeded

Neurologic events

Neurologic side effects, which occur in up to 30% of patients, can include ataxia, tremor, peripheral polyneuropathy, insomnia, and impaired memory (Goldschlager 2007; Zimetbaum 2007). These effects are often dose-related and occur more often in elderly patients than in younger patients.

Monitoring and recommendations

A physical examination at baseline should be recommended. Amiodarone should be discontinued or reduced in dosage when signs and symptoms appear.

Cardiac events

The most frequent cardiovascular events are bradycardia and heart block (1 to 3% of treated patients); they are often dose-related and occur more frequently in elderly patients. Prolongation of the QT interval is seen in most of the patients but it is associated with a very low incidence of *torsades de pointes* (<0.5% of treated patients) as compared with other drugs that prolong the QT interval (e.g., sotalol and dofetilide) (Zimetbaum 2007). Intravenously administered amiodarone causes bradycardia and heart block in 5% of patients and hypotension in 16% (Siddoway 2003).

Monitoring and recommendations

An ECG at baseline and during loading dose is recommended together with a yearly follow-up. If bradycardia and heart block occur, infusion of amiodarone should be discontinued or the rate of infusion should be reduced.

Adverse Events and Costs

According to a review on the use of amiodarone in atrial fibrillation (Zimetbaum 2007), the initial screening tests performed before treatment begins (chest radiography and tests of pulmonary, thyroid, and liver function) would cost approximately \$250, with a similar expense annually to screen for adverse effects. A controlled trial conducted in 2002 (Lumer 2002) found that the costs for 1 year of maintenance therapy with amiodarone for atrial fibrillation would be lower than therapy with sotalol and propafenone; furthermore, even if based on not statistically significant data, the cost of treating side effects of low dose amiodarone would be lower than the savings it generates in atrial fibrillation related costs.

11.3 Identification of variation in safety due to health systems and patient factors

Amiodarone-induced thyrotoxicosis and world iodine deficiency

As mentioned previously, people living in iodine-deficient areas are at mayor risk of developing amiodarone-induced thyrotoxicosis, particularly difficult to manage and considerably risky; about 31% (1900,9 million) of the world population is estimated to have insufficient iodine intakes, with the most affected WHO regions being South-East Asia, Africa and Europe (WHO 2007)

The Canadian Network for sustained Elimination of Iodine Deficiency has assigned top priority in 2005-2010 to supporting India, Pakistan and Bangladesh towards the elimination of iodine deficiency. However, there are other iodine-deficient countries, in particular Afghanistan, Angola, Bolivia, China, Egypt, Ethiopia, Ghana, Guatemala, Haiti, Indonesia, Niger, The Philipines, Russia, Senegal, Sudan, Ukraine, and Vietnam.

Amiodarone-induced thyroid dysfunctions and Chagas' disease

A greater care should be provided also towards patients with Chagas' disease taking amiodarone to control life-threatening arrhythmias; Chagas' disease, in fact, causes autonomic disfunctions that may mask clinical manifestations of thyroid disease and, moreover, it has an epidemiologic superposition with iodine-deficient areas in Central and South America that may contribute to a high prevalence of underlying thyroid abnormalities, such as nodular goiter (Silva 2004).

Amiodarone in pregnant patients

Amiodarone is not well-studied in pregnant patients. Amiodarone crosses the placental barrier and it can cause fetal hypothyroidism, growth retardation, and prematurity. Given the drug's complex pharmacokinetics, effects on thyroid metabolism and significant end-organ toxicity, the drug should not be used in pregnant patients unless no other option exists (Goldschlager 2007).

Amiodarone in pediatric patients

Intravenous amiodarone in children is not well studied and may be associated with a high incidence of adverse events. In a trial, assessing the use of intravenous amiodarone for tachyarrhythmias in 61 children, adverse events were common (87%) and drug withdrawals occurred in 16% of cases. There were 5 deaths in the 30-day follow-up period (2 possibly related to the drug) (Saul 2005).

However, some tachyarrhythmias in children, as transient tachyarrhythmias after congenital heart disease surgery and tachyarrhythmias that cause cardiomyopathy, require rapid control as they may be lethal. Amiodarone is often the antiarrhythmic drug of choice in these settings. Arrhythmias in pediatric patients may change or resolve with time, making long-term amiodarone therapy unnecessary. If the tachyarrhythmias persist, ablation is a possibility (Goldschlager 2007).

Drug-drug interactions

Amiodarone inhibits liver metabolism through several cytochrome P450 pathways and therefore interacts with many other drugs, as previously mentioned in this document (9. Treatment details, Pharmacodynamics and pharmacokinetics). Interactions with warfarin and digoxin are the most clinically important ones.

Amiodarone reduces warfarin clearance and can lead to sudden and significant increases in the Prothrombin Time (PT) and International Normalized Ratio (INR) (Sanoski 2002). "The peak effects of interaction occur approximately seven weeks after initiation of therapy" (Siddoway 2003). Digoxin levels may double after coadministration with amiodarone (Freitag 1995). This increase occurs because of the inhibition of digoxin secretion from renal tubules (Yamreudeewong 2003). The digoxin dosage should be reduced by 50 percent when amiodarone therapy is started and plasma levels of digoxin should be monitored closely.

11.4 Summary of comparative safety against comparators

Not applicable since amiodarone is a unique antiarrhythmic drug.

12. Summary of available data on comparative costs and cost-effectiveness

Costs associated with amiodarone therapy include both costs of the drug and costs linked to the monitoring test to be executed while in therapy with amiodarone. An estimate of costs is summarized below in Table 3.

	Annual Costs \$
Amiodarone (200 mg/day)	16-19
Annual screening for adverse events (thyroid and liver function, ECG, chest radiography)	250
- TSH	20-30

12.1 Range of cost of the proposed medicine

We used the *International Drug Price Indicator Guide*, published by Management Sciences for Health (MSH), to obtain present prices of Amiodarone (International Drug Price Indicator Guide). The estimate for oral therapy with amiodarone (200 mg/day) is 0.0519 \$ per tablet (median price) and 0.0432 \$ per tablet (lowest price). The cost for intravenous amiodarone is 0.4567/ml and 0.2758/ml (respectively median and lowest prices). Considering a DDD of 200 mg, the annual cost of amiodarone would range between \$16-19 per person. The MSH Drug Price Indicator Guide catalogues prices of medicines achieved through tender agreements between selected national governments and generic firms. MSH cautions, however, that these tender agreements may not represent an “international” price (WHO, 2006).

Costs associated with Amiodarone therapy

As previously mentioned, amiodarone is associated to a wide range of adverse events and chronic treatment with amiodarone requires both baseline examination and therapy-long follow-up of patients.

According to a review on the use of amiodarone in atrial fibrillation (Zimetbaum 2007), the initial screening tests performed before treatment begins (chest radiography and tests of pulmonary, thyroid, and liver function) would cost approximately \$250, with a similar expense annually to screen for adverse effects. In particular, chronic therapy with amiodarone can not leave out of consideration the monitoring of thyroid function through the TSH test, to perform twice a year at the cost of about \$10-15 per test.

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

It is complex to estimate the total burden of the costs related to therapy with amiodarone, particularly considering the difficulty in applying costs estimations carried out in countries (western developed countries) that are not the target of this document. Furthermore, it is difficult to have a reliable esteem of the expenses associated to the monitoring and follow up of patients treated with amiodarone in the context of a developing country.

An indirect evidence of economic advantages of amiodarone could be derived from clear evidences of the positive effect of amiodarone on mortality and morbidity.

According to a meta-analysis assessing trials on amiodarone in preventing sudden cardiac death, amiodarone therapy would reduce total mortality by between 10% (placebo-controlled trials only) and 19% (all trials) in patients at moderate to high risk of sudden cardiac death (Sim 1997).

Amiodarone would have also a positive impact on the control of atrial fibrillation; globally, the annual cost per patient with AF has been estimated being close to €3000 (ACC/AHA/ESC 2006), more than half due to frequent hospitalizations.

A meta-analysis performed in 2003 (Chevalier 2003) demonstrated that amiodarone efficacy for cardioversion of AF was superior to placebo and similar to propafenone, while the sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) found that amiodarone was equally efficacious to sotalol in converting AF but superior for maintaining sinus rhythm (Singh 2005). A controlled trial conducted in 2002 (Lumer 2002) showed that the costs for 1 year of maintenance therapy with amiodarone for atrial fibrillation would be lower than therapy with sotalol and propafenone; furthermore, even if based on not statistically significant data, the study claimed that the cost of treating side effects of low dose amiodarone would be lower than the savings it generates in atrial fibrillation related costs.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Amiodarone was originally developed and launched in Europe in the 1960's as a coronary artery vasodilator and was subsequently discovered to possess antiarrhythmic properties. Reports of amiodarone's antiarrhythmic efficacy after intravenous and oral administration were published in the 1970's. Oral amiodarone was first licensed in the UK as an anti-arrhythmic drug in 1980 (in Italy in 1984) and in USA at the end of 1985.

In 2002, the Amiodarone patent expired and many generics came to market (see Appendix A).

Summary of regulatory approval in the US is provided below.

In United States:

Amiodarone HCl oral

FDA approval date: December 27, 1985

Amiodarone HCl injection

FDA approval date: August 3, 1995

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

British Pharmacopoeia: Yes (British National Formulary 54)

European Pharmacopoeia: Yes (Version 5.5)

Chinese Pharmacopoeia: Yes

United States Pharmacopoeia: No

15. Proposed (new/adapted) text for the WHO Model Formulary

Description

Amiodarone is a class III antiarrhythmic agent approved for the treatment of refractory life threatening ventricular arrhythmias and additionally used for the treatment of atrial and/or ventricular arrhythmias. Amiodarone is structurally similar to thyroxine. It is both an antiarrhythmic and a potent vasodilator. The antiarrhythmic effect of amiodarone it is not completely known but it may be due to at least two major properties: a prolongation of the myocardial cell-action potential duration and refractory period and a non competitive α - and β - adrenergic inhibition

How Supplied

Tablets 100, 200, 400mg

Vials and amps 50 mg/ml, 3 ml

Use

Amiodarone should not be used for routine treatment of patients with HF. Amiodarone can be used in the treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated. It may be used for

paroxysmal supraventricular, ventricular and nodal tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It may also be used for tachyarrhythmias associated with Wolff-Parkinson-White syndrome. In Latin America it is widely prescribed to treat the cardiac disorders of Chagas' disease.

It should be initiated only under hospital or specialist supervision. Unlike oral amiodarone, intravenous Amiodarone may act relatively rapidly.

Intravenous injection of amiodarone may be used in cardiopulmonary resuscitation for ventricular fibrillation or pulseless tachycardia unresponsive to other interventions.

Contraindications

Amiodarone is contraindicated in severe sinus-node dysfunction (except in cardiac arrest), causing marked sinus bradycardia, sino-atrial heart-block unless pacemaker-fitted, avoid in severe conduction disturbances or sinus node disease; goiter and thyroid hyperfunction; iodine sensitivity; avoid intravenous use in severe respiratory failure, circulatory collapse, severe arterial hypotension; avoid bolus injection in congestive HF or cardiomyopathy.

Amiodarone is contraindicated in patients with a known hypersensitivity to the drug or to any of its components, including iodine; in pregnancy and lactation; in neonates.

Adverse Effects

Adverse effects are common with amiodarone; many are dose-related and reversible with reduction in dose. Some effects, such as gastrointestinal disturbances, are transient; others affecting the lungs, thyroid, liver, heart, eyes and SNC are potentially more serious.

The main adverse effects are:

- gastrointestinal (nausea, vomiting, taste disturbances)
- cardiovascular (e.g. bradycardia) (see Precautions);
- pulmonary toxicity including pneumonitis and fibrosis;
- tremor, sleep disorders;
- hypothyroidism, hyperthyroidism;
- reversible corneal microdeposits;
- phototoxicity, persistent slate-grey skin discoloration.

Less commonly: onset or worsening of arrhythmia, conduction disturbances, peripheral neuropathy and myopathy (usually reversible on withdrawal).

Very rarely: chronic liver disease including cirrhosis, sinus arrest, bronchospasm (in patients with severe respiratory failure), ataxia, benign intracranial hypertension, headache, vertigo, epididymo-orchitis, impotence, haemolytic or aplastic anaemia, thrombocytopenia, rash (including exfoliative dermatitis), hypersensitivity including vasculitis, alopecia, impaired vision due to optic neuritis or optic neuropathy (including blindness), anaphylaxis on rapid injection, also hypotension, respiratory distress syndrome, sweating, and hot flushes.

It should also be underscored that Amiodarone has a well-known established toxicity that can be severe and that should then be carefully monitored. Here below is reported a FDA warning letter which summarises some of the most relevant Amiodarone toxicities.

Life-threatening arrhythmias (reported warning FDA 2005):

Amiodarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Potential fatal toxicities:

Amiodarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Amiodarone, but is usually mild and evidenced only by abnormal liver

enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Amiodarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2 to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2 to 5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Amiodarone than with many other agents used in this population, the effects are prolonged when they occur. Even in patients at high risk of arrhythmic death, in whom the toxicity of Amiodarone is an acceptable risk, Amiodarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first. The difficulty of using Amiodarone effectively and safely itself poses a significant risk to patients.

Pulmonary disorders

In patients treated with oral amiodarone, with or without initial I.V. therapy, have been reported pulmonary infiltrates and/or mass on X-ray, pulmonary alveolar hemorrhage, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death.

Cardiac effects

Amiodarone can cause serious exacerbation of the presenting arrhythmia

Liver toxicity

Amiodarone induced elevation of liver enzyme concentrations (also above 2 – 3 times the upper limit of normal) and in most cases are asymptomatic. It should be discontinued if the abnormalities in liver function are persistent or severe, or if the patient develops clinical signs of liver disease. The liver-function tests are required before treatment and then every 6 months

Ophthalmologic effects

Corneal microdeposits (reversible on withdrawal of treatment) occur in nearly all patients taking amiodarone, usually develop within the first month of starting the therapy; these rarely interfere with vision, but drivers may be dazzled by headlights at night.

Thyroid effects

Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism may occur. Clinical assessment is necessary to rule out thyroid hyperplasia but also alone is unreliable, and laboratory tests should be performed before treatment (TSH and anti-TPO antibodies) and every 6 months during treatment (fT3 fT4 TSH).

Precautions (summarized from MICROMEDEX ® and BNF)

Monitoring: chest x-ray required before treatment; hypokalaemia (measure serum-potassium concentration) before treatment; monitor thyroid function at baseline and periodically during therapy, particularly in the elderly and in any patients with a history of thyroid dysfunction; regular ophthalmic examination; liver-function tests before treatment and then every 6 months; ECG monitoring and resuscitation facilities must be available during intravenous use;

Evidence or history of thyroid disorders;

Severe bradycardia, sino-atrial block, AV block or other severe conduction disorders (unless the patient has a pacemaker), severe hypotension, or severe respiratory failure and conduction disturbances in excessive dosage;

Heart failure;

Porphyria, because it has been shown to be porphyrinogenic in in-vitro systems;

Elderly;

Intravenous use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) or severe hepatocellular toxicity (monitor transaminases closely);

Patients with moderate or severe renal impairment, because the urinary excretion is not a major route for the elimination of amiodarone or its metabolites, some have nevertheless advised caution for the possibility of iodine accumulation.

Drug Interactions

There are a number of important drug interactions with Amiodarone and some of these interactions are related to the inhibition of cytochrome P450.

Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped.

Amiodarone is metabolised by the cytochrome P450, isoenzyme CYP3A4, and interactions may occur with inhibitors of this enzyme, such as HIV-protease inhibitors, cimetidine and grapefruit juice. Enzyme inducers such as rifampicin and phenytoin may reduce amiodarone levels. In addition, amiodarone is an inhibitor of some cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6, resulting in higher plasma concentrations of other drugs metabolised by these enzymes. Examples of these include ciclosporin, clonazepam, digoxin, flecainide, phenytoin, simvastatin and warfarin.

Main interactions: agalsidase beta, antiarrhythmics (quinidine, procainamide, disopyramide and phenytoin), antihypertensives (e.g. β -receptor blocking agents as propranolol or calcium channel antagonists as verapamil and diltiazem), antibacterials (e.g. fluoroquinolones, rifampicin), antiepileptics, antivirals (atazanavir, nelfinavir, ritonavir), grapefruit juice (plasma concentration of amiodarone increased by grapefruit juice), histamine H₂-antagonists (e.g. cimetidine).

Amiodarone should be used with caution with drugs liable to induce bradycardia, such as beta blockers or non dihydropyridin calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, for example phenothiazine antipsychotics, tricyclic antidepressants, halofantrine, and terfenadine, should be avoided.

Amiodarone injection has been reported to be incompatible with aminophylline, flucloxacillin, heparin, and sodium bicarbonate. Further studies reported incompatibility with ampicillin/sulbactam sodium, ceftazidime sodium, digoxin, furosemide, imipenem/cilastatin sodium, magnesium sulfate, piperacillin sodium, piperacillin/tazobactam sodium, potassium phosphate, and sodium phosphate.

The manufacturers states that it is incompatible with sodium chloride solutions.

Pediatric Use

Safety and efficacy of Amiodarone have not been studied in paediatric patients.

Geriatric Use

Clinical studies did not include a large number of patients 65 years of age and older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pregnancy Use

The uncertainty effect of the iodine contained in amiodarone load on the fetus has largely limited the use of amiodarone in pregnancy, since iodine freely crosses the placenta and may cause thyroid disorders in the fetus.

In general amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.

Dosage and Administration

By mouth, 200 mg 3 times daily for 1 week reduced to 200mg twice daily for a further week; maintenance, usually 200 mg daily or the minimum required to control the arrhythmia

By intravenous infusion via central venous catheter, initially 5 mg/kg over 20–120 minutes with ECG monitoring; subsequent infusion given if necessary according to response up to max. 1.2 g in 24 hours

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation: Intravenous injection of Amiodarone 300 mg or 5 mg/kg (from a prefilled syringe or diluted in 20 mL Glucose 5%) should be considered after adrenaline to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. If ventricular fibrillation persists, an additional dose of amiodarone 150 mg (or 2.5 mg/kg) can be given.

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Appendix A

L: AMIODARONUM
 I: AMIODARONE
 D: AMIODARON
 F: AMIODARONE
 S: AMIODARONA
 Coronary vasodilator
 ATC: C01BD01
 CAS-Nr.: 0001951-25-3
 OS: Amiodarone (BAN, DCF, DCIT, USAN)
 IS: SKF 33134-A

Trades name (manufacturer, country)

Amiodarona Fabra (Fabra: AR)
 Amiodarona L.CH. (Chile: CL)
 Amiodarona Merck (Merck Genericos: PT)
 Amiodarona MK (MK: CO)
 Amiokordin (Krka: HR, SI)
 Aratac (Alphapharm: SG)
 Cardiogesic (LAM: DO)
 Cordarone (inj.) (Lek: HR)
 Cordarone (inj.) (Sanofi-Synthelabo: SI)
 ratio-Amiodarone (Ratiopharm: CA)
 Ritmocardyl (Sanofi Winthrop: AR)

HYDROCHLORIDE:

Adenosin Item (Sanofi Synthelabo: DK)
 Aldarone (Cadila: IN)
 Amicordin (Sanofi Synthelabo: PL)
 Amiobal (Pharmedica: BR)
 Amiocar (Klonal: AR)
 Amiocordin (Krka: PL)
 Amiodacore (CTS: IL)
 Amiodarex (Sanofi Synthelabo: DE)
 Amiodaron "Orifarm" (Sanofi Synthelabo: DK)
 Amiodaron 1A Pharma (1A: DE)
 Amiodaron AL (Aliud: DE)
 Amiodaron AZU (Azupharma: DE)
 Amiodaron beta (betapharm: DE)
 Amiodaron Ebewe (Ebewe: AT)
 Amiodaron Heumann (Heumann: DE)
 Amiodaron Lindo (Lindopharm: DE)
 Amiodaron Sanofi (Sanofi Synthelabo: DE)
 Amiodaron Stada (Stadapharm: DE)
 Amiodaron-Mepha (Mepha: CH)
 Amiodaron-ratiopharm (Ratiopharm: DE)
 Amiodarona Clorhidrato (Biosano: CL)
 Amiodarona Clorhidrato (Sanderson: CL)
 Amiodarona HCL (Mintlab: CL)
 Amiodarona Larjan (Veinfar: AR)
 Amiodarona (Chemopharma: CL)
 Amiodarona (Labormed Pharma: RO)
 Amiodarona (Lakor: CO)
 Amiodarona (Medipharma: AR)
 Amiodarona (Promedic: RO)
 Amiodarona (Rider: CL)
 Amiodarone EG (Eurogenerics: BE)

Amiodarone GNR (GNR: IT)
 Amiodarone HCl (Bedford: US)
 Amiodarone-Rivo (Rivopharm: RO)
 Amiodarone (Alpharma (Vet): GB)
 Amiodarone (APS: GB)
 Amiodarone (Aurum: GB)
 Amiodarone (Eurogenerics: LU)
 Amiodarone (Faulding: CA)
 Amiodarone (Generics: GB)
 Amiodarone (Hillcross: GB)
 Amiodarone (Ivax: GB)
 Amiodarone (Sabex: CA)
 Amiodarone (Sterwin: GB)
 Amiodaron (Balkanpharma: BG)
 Amiodaron (Farmagon: NO)
 Amiodaron (Zdravlje: YU)
 Amiodar (Sigma-Tau: IT)
 Amiodex (EMS: BR)
 Amiodura (Merck dura: DE)
 Amiod (1A: DE)
 Amiogamma (Worwag: DE)
 Amiohexal (Hexal: DE)
 Amiohexal (Salutas Fahlberg: CZ)
 Amiokordin (Krka: CZ, HU, RO)
 Amiorit (Synthesis: CO)
 Ancaron (Taisho: JP)
 Ancoron (Libbs: BR)
 Angoten (Microsules: AR)
 Aratac (Alphapharm: AU)
 Aratac (Merck: TH)
 Aratac (Pacific: NZ)
 Arycor (Sanofi-Synthelabo: CO)
 Atlansil (pharma Investi: CL)
 Atlansil (Roemmers: AR)
 Atlansil (sanofi Synthelabo: BR)
 Braxan (Armstrong: MX)
 Cardilor (Grace: ET)
 Cardilor (Pharmacie Tropicale: MU)
 Cardilor (Pharmanova: ZW)
 Cardilor (Remedica: BH, CY, JO, OM, RO, SD, YE)
 Cardilor (Siho Trading: SD)
 Cardilor (Twokay: KE)
 Cloridrato de Amiodarona (Biosintetica: BR)

Corbionax (Irex: FR)
 Cordarex (Sanofi Synthelabo: DE)
 Cordarone X (Sanofi Synthelabo: GB)
 Cordarone X (Sanofi Torrent: IN)
 Cordarone (Euromedica: NO)
 Cordarone (Farmagon: NO)
 Cordarone (Krka: CZ, PL, RU)
 Cordarone (Labaz: RO)
 Cordarone (Mason: HK)
 Cordarone (Orifarm: NO, SE)
 Cordarone (Paranova: NO)
 Cordarone (Sanofi: AE, BH, CR, CY, DO, EC, EG, GT, HN, JO, KW, LB, NI, OM, PA, QA, SA, SG, SV, TR)
 Cordarone (Sanofi Synthelabo: AU, CL, DK, FI, FR, GB, NZ, PL, PT, RO, RU)
 Cordarone (Sanofi Winthrop: IE, LU, MX)
 Cordarone (Sanofi-Synthelabo: CO, CZ, ID, IT, NO, SE, SI, TH)
 Cordarone (Sanofi-Synthelabo: BE, CH, HU)
 Cordarone (Sigma: NO)
 Cordarone (Wyeth: CA, US)
 Cornaron (TAD: DE)
 Coronovo (Labinca: AR)
 Escodarone (Streuli: CH)
 Eurythmic (Troikka: IN)
 Gen-Amiodarone (Genpharm: CA)
 Hexarone (Hexal: ZA)
 Kandarone (Darya-Varia: ID)
 Miocard (Millet Roux: BR)
 Miocoron (Cristalia: BR)
 Miodaron (Biosintetica: BR)
 Miodar (Osmopharm: DO)
 Miodrone (Alter: PT)
 Mioritmin (Helcor: RO)
 Miotenk (Biotenk: AR)
 MTW-Amiodaron (MTW: DE)
 Novo-Amiodarone (Novopharm: CA)
 Opacorden (Polpharma: PL, RU)
 Pacerone (Upsher-Smith: US)
 Procor (Unipharm: IL)
 Rhoxal-amiodarone (Rhoxalpharma: CA)
 Ritmocardyl (Bago: CL)
 Ritmocardyl (Sanofi Winthrop: AR)
 Sedacoron (Sanofi Winthrop: AR)
 Sedacoron (Edewe: AT, CZ, RO, RU, YU)
 Sedacoron (Health Care: HK)
 Tachydaron (AWD.pharma: DE)
 Tiaryt (Fahrenheit: ID)
 Trangorex (Sanofi Synthelabo: ES)
 Uro-Septra (Biosintetica: BR)

Legend

AD = Andorra
 AE = United Arab Emirates
 AF = Afghanistan
 AG = Antigua and Barbuda
 AI = Anguilla
 AL = Albania
 AM = Armenia
 AN = Netherlands Antilles
 AO = Angola
 AQ = Antarctica
 AR = Argentina
 AS = American Samoa
 AT = Austria
 AU = Australia
 AW = Aruba
 AZ = Azerbaijan
 BA = Bosnia and Herzegovina
 BB = Barbados
 BD = Bangladesh
 BE = Belgium
 BF = Burkina Faso
 BG = Bulgaria
 BH = Baharain
 BI = Burundi
 BJ = Benin
 BM = Bermuda
 BN = Brunei Darussalam
 BO = Bolivia
 BR = Brazil
 BS = Bahamas
 BT = Bhutan
 BV = Bouvet Island
 BW = Botswana
 BY = Belarus
 BZ = Belize
 CA = Canada
 CC = Cocos (Keeling) Islands
 CF = Central African Republic
 CG = Congo
 CH = Switzerland
 CI = Cote D'Ivoire (Ivory Coast)
 CK = Cook Islands
 CL = Chile
 CM = Cameroon
 CN = China
 CO = Colombia
 CR = Costa Rica
 CU = Cuba
 CV = Cape Verde
 CX = Christmas Island
 CY = Cyprus
 CZ = Czech Republic
 DE = Germany
 DJ = Djibouti
 DK = Denmark
 DM = Dominica
 DO = Dominican Republic
 DZ = Algeria

EC = Ecuador	KW = Kuwait
EE = Estonia	KY = Cayman Islands
EG = Egypt	KZ = Kazakhstan
EH = Western Sahara	LA = Laos
ER = Eritrea	LB = Lebanon
ES = Spain	LC = Saint Lucia
ET = Ethiopia	LI = Liechtenstein
FI = Finland	LK = Sri Lanka
FJ = Fiji	LR = Liberia
FK = Falkland Islands (Malvinas)	LS = Lesotho
FM = Micronesia	LT = Lithuania
FO = Faroe Islands	LU = Luxembourg
FR = France	LV = Latvia
FX = France, Metropolitan	LY = Libya
GA = Gabon	MA = Morocco
GB = United Kingdom	MC = Monaco
GD = Grenada	MD = Moldova
GE = Georgia	MG = Madagascar
GF = French Guiana	MH = Marshall Islands
GH = Ghana	MK = Macedonia
GI = Gibraltar	ML = Mali
GL = Greenland	MM = Myanmar
GM = Gambia	MN = Mongolia
GN = Guinea	MO = Macau
GP = Guadeloupe	MP = Northern Mariana Islands
GQ = Equatorial Guinea	MQ = Martinique
GR = Greece	MR = Mauritania
GS = S. Georgia and S. Sandwich Is	MS = Montserrat
GT = Guatemala	MT = Malta
GU = Guam	MU = Mauritius
GW = Guinea-Bissau	MV = Maldives
GY = Guyana	MW = Malawi
HK = Hong Kong	MX = Mexico
HM = Heard and MacDonal Islands	MY = Malaysia
HN = Honduras	MZ = Mozambique
HR = Croatia (Hrvatska)	NA = Namibia
HT = Haiti	NC = New Caledonia
HU = Hungary	NE = Niger
ID = Indonesia	NF = Norfolk Island
IE = Ireland	NG = Nigeria
IL = Israel	NI = Nicaragua
IN = India	NL = Netherland
IO = British Indian Ocean Territor	NO = Norway
IQ = Iraq	NP = Nepal
IR = Iran	NR = Nauru
IS = Iceland	NT = Neutral Zone
IT = Italy	NU = Niue
JM = Jamaica	NZ = New Zealand (Aotearoa)
JO = Jordan	OM = Oman
JP = Japan	PA = Panama
KE = Kenya	PE = Peru
KG = Kyrgyzstan	PF = French Polynesia
KH = Cambogia	PG = Papua New Guinea
KI = Kiribati	PH = Philippines
KM = Comoros	PK = Pakistan
KN = Saint Kitts and Nevis	PL = Poland
KP = Korea (North)	PM = St. Pierre and Miquelon
KR = Korea (South)	PN = Pitcairn

PR = Puerto Rico
PT = Portugal
PW = Palau
PY = Paraguay
QA = Qatar
RE = Reunion
RO = Romania
RU = Russian Federation
RW = Rwanda
SA = Saudi Arabia
SC = Seychelles
SD = Sudan
SE = Sweden
SG = Singapore
SH = St. Helena
SI = Slovenia
SJ = Svalbard and Jan Mayen Island
SK = Slovak Republic
SL = Sierra Leone
SM = San Marino
SN = Senegal
SO = Somalia
SR = Suriname
ST = Sao Tome and Principe
SV = El Salvador
SY = Syria
SZ = Swaziland
Sb = Solomon Island
TC = Turks and Caicos Island
TD = Chad
TF = French Southern Territories
TG = Togo
TH = Thailand
TJ = Tajikistan
TK = Tokelau
TM = Turkmenistan
TN = Tunisia
TO = Tonga
TP = East Timor
TR = Turkey
TT = Trinidad and Tobago
TV = Tuvalu
TW = Taiwan
TZ = Tanzania
UA = Ukraine
UG = Uganda
UM = US Minor Outlying Islands
US = United States
UY = Uruguay
UZ = Uzbekistan
VA = Vatican City State (Holy See)
VC = Saint Vincent and the Grenadines
VE = Venezuela
VG = Virgin Islands (British)
VI = Virgin Islands (U.S.)
VN = Viet Nam
VU = Vanuatu
WF = Wallis and Futuna Islands
WS = Samoa
YE = Yemen
YT = Mayotte
YU = Yugoslavia
ZA = South Africa
ZM = Zambia
ZR = Zaire
ZW = Zimbabwe

Appendix B1**Evidence Tables – Guidelines Atrial Fibrillation and Amiodarone – September, 6th 2007**

References:

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- Document 16: New Zealand Guidelines Group (NZGG). The management of people with atrial fibrillation and flutter. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2005 May.
- Document 17: Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey J-Y, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:e149–246.
- Document 19: National Collaborating Centre for Chronic Conditions. Atrial fibrillation. National clinical guideline for management in primary and secondary care. London (UK): Royal College of Physicians; 2006.
- Document 25: Institute for Clinical Systems Improvement. Health Care Guideline: Atrial Fibrillation. February 2007.

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
06	Management of Newly Detected Atrial Fibrillation	AAFP/ACP - 2003	<p><u>Recommendation 1</u>: Rate control with chronic anticoagulation is the recommended strategy for the majority of patients with atrial fibrillation. Rhythm control has not been shown to be superior to rate control (with chronic anticoagulation) in reducing morbidity and mortality and may be inferior in some patient subgroups to rate control. Rhythm control is appropriate when based on other special considerations, such as patient symptoms, exercise tolerance, and patient preference. Grade: 2A</p> <p><u>Recommendation 2</u>: Patients with atrial fibrillation should receive chronic anticoagulation with adjusted-dose warfarin, unless they are at low risk of stroke or have a specific contraindication to the use of warfarin (thrombocytopenia, recent trauma or surgery, alcoholism). Grade: 1A</p> <p><u>Recommendation 3</u>: For patients with atrial fibrillation, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil (drugs listed alphabetically by class). Digoxin is only effective for rate control at rest and therefore should only be used as a second-line agent for rate control in atrial fibrillation. Grade: 1B</p> <p><u>Recommendation 4</u>: For those patients who elect to undergo acute cardioversion to achieve sinus rhythm in atrial fibrillation, both direct-current cardioversion (Grade: 1C) and pharmacological conversion (Grade: 2A) are appropriate options.</p> <p><u>Recommendation 5</u>: Both transesophageal echocardiography with short-term prior anticoagulation followed by early acute cardioversion (in the absence of intracardiac thrombus) with postcardioversion anticoagulation versus delayed cardioversion with</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
11	Atrial fibrillation	Canadian Cardiovascular Society - 2004	<p>pre- and postanticoagulation are appropriate management strategies for those patients who elect to undergo cardioversion. Grade: 2A</p> <p><u>Recommendation 6:</u> Most patients converted to sinus rhythm from atrial fibrillation should not be placed on rhythm maintenance therapy since the risks outweigh the benefits. In a selected group of patients whose quality of life is compromised by atrial fibrillation, the recommended pharmacologic agents for rhythm maintenance are amiodarone, disopyramide, propafenone, and sotalol (drugs listed in alphabetical order). The choice of agent predominantly depends on specific risk of side effects based on patient characteristics. Grade: 2A</p> <p><u>Conversion of Atrial Fibrillation</u></p> <p><u>Class I:</u></p> <ol style="list-style-type: none"> 1. Electrical or pharmacologic conversion should be considered in patients with AF who are hemodynamically stable (Level of Evidence: C) 2. Immediate conversion to sinus rhythm is recommended in patients with AF who are hemodynamically unstable. Electrical cardioversion is more effective and is preferred over pharmacologic conversion in these patients. (Level of Evidence: C) <p><u>Class IIA:</u></p> <ol style="list-style-type: none"> 1. Rate-control with anticoagulation therapy alone is acceptable while awaiting spontaneous conversion in patients with AF of less than 48 hours duration. (Level of Evidence: B) 2. Pharmacological agents may be used to accelerate conversion of AF in patients with AF of less than 48 hours duration. (Level of Evidence: B). See table 1 for specific drug recommendations. 3. Antiarrhythmic drugs may be used to pre-treat patients before electrical cardioversion (to decrease early recurrence of AF and to enhance cardioversion efficacy). (Level of Evidence: B) <p><u>Table 1 - Recommended Drugs for Conversion of Atrial Fibrillation</u></p> <p><u>Class I</u></p> <p>Ibutilide (Level of Evidence: A)</p> <p>Flecainide (Level of Evidence: A)</p> <p>Procainamide (Level of Evidence: B)</p> <p>Propafenone (Level of Evidence: A)</p> <p><u>Class IIA</u></p> <p>Chronic Oral Amiodarone (Level of Evidence: B)</p> <p><u>Class III</u></p> <p>Sotalol (Level of Evidence: B)</p> <p><u>Class IIB</u></p> <ol style="list-style-type: none"> 1. Blockade of the angiotensin-renin system may be considered in combination with amiodarone before electrical cardioversion in order to decrease the recurrence rate of AF (Level of evidence: B)

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p><u>Maintenance of Sinus Rhythm in Patients with AF</u></p> <p><u>Class I</u></p> <p>1. Oral antiarrhythmic drugs may be used in patients with recurrent AF in whom long-term maintenance of sinus rhythm is desired and in whom a reversible cause of AF is not identified. (Level of Evidence: B)</p> <p>2. The choice of an antiarrhythmic drug should be based on the safety profile of the different agents, taking in account the clinical characteristics of the patient. (Level of Evidence: B) Recommendations regarding specific agents are listed in <u>table 2</u>.</p> <p><u>Class IIA</u></p> <p>1. In patients without risk factors for proarrhythmia, antiarrhythmic drugs may be initiated as outpatients. (Level of Evidence: B)</p> <p>2. In patients with structural heart disease (including those with LV dysfunction) amiodarone may be initiated as outpatients. (Level of Evidence: B)</p> <p>3. An AV nodal blocking agent is recommended in patients treated with a class 1C antiarrhythmic drug. (Level of Evidence: B)</p> <p><u>Class IIB</u></p> <p>1. Patients treated with sotalol or dofetilide should be reassessed if QTc exceeds 480 msec. (Level of Evidence: C)</p> <p><u>Class III</u></p> <p>1. Sotalol should not be used for rate-control alone in patients with permanent atrial fibrillation. (Level of Evidence: C)</p> <p><u>Table 2 - Chronic Antiarrhythmic Drug Selection</u></p> <p>1. Patients with Structurally Normal Hearts</p> <p>First Choices: Propafenone Flecainide Sotalol*</p> <p>Second Choice: Amiodarone</p> <p>Alternative Choices: Disopyramide Dofetilide**</p> <p>2. Patients with Structurally Abnormal Hearts</p> <p>A. CAD with normal ventricular function</p> <p>First Choice: Sotalol*</p> <p>Second Choice: Amiodarone</p> <p>Additional Choices: Dofetilide** Propafenone</p> <p>B. Left Ventricular Dysfunction (with or without CHF)</p> <p>First Choice: Amiodarone</p> <p>Second Choice: Dofetilide**</p> <p>C. Hypertension with LVH</p> <p>First Choices: Sotalol Amiodarone Propafenone</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>Flecainide * contraindicated in females > 65 years of age taking diuretics ** Dofetilide is available in Canada through Health Canada's special access program</p> <p>Toxicity of Antiarrhythmic Drugs Amiodarone Photosensitivity Bradycardia GI upset Thyroid dysfunction Phlebitis Hepatic toxicity Neuropathy Pulmonary toxicity Torsades de pointes (rare)</p> <p><u>Recommendations for the Prevention and Treatment of Atrial Fibrillation following Cardiac Surgery:</u></p> <p><u>Class I</u> 1. Patients who have been receiving a beta-blocker prior to cardiac surgery should have that therapy continued through the operative period in the absence of the development of a new contraindication. (Level of Evidence: A) 2. Temporary ventricular epicardial pacing electrode wires should be placed at the time of cardiac surgery to allow backup pacing as necessary. (Level of Evidence: C) 3. Post-operative atrial fibrillation with a rapid ventricular response rate should be treated with a beta-blocker, a non-dihydropyridine calcium antagonist, or amiodarone to establish ventricular rate control. In the absence of a specific contraindication, the order of choice is as listed. (Level of Evidence: B)</p> <p><u>Class IIa</u> 1. Patients who have not been receiving a beta-blocker prior to cardiac surgery should be considered for prophylactic therapy to prevent post-operative atrial fibrillation with a beta-blocker or amiodarone (Level of Evidence A) or with atrial pacing or magnesium. (Level of Evidence B) 2. Post-operative atrial fibrillation may be appropriately treated with either a ventricular response rate-control strategy or a rhythm-control strategy. (Level of Evidence: A) 3. Consideration should be given to anticoagulation if post-operative atrial fibrillation persists for more than 48 hours. (Level of Evidence: C) 4. When anticoagulation therapy, rate-control therapy, and/or rhythm control therapy has been prescribed for post-operative atrial fibrillation, formal reconsideration of the ongoing need for such therapy should be undertaken six to eight weeks later. (Level of Evidence: B)</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p><u>Reccomendations for management of AF in patients with hypertrophic cardiomyopathy</u></p> <p><u>Class I</u></p> <p>1. Anticoagulate patients with paroxysmal, persistent, or permanent atrial fibrillation with warfarin (INR 2 to 3). (Level of Evidence: B)</p> <p><u>Class IIa</u></p> <p>1. Strategies to maintain sinus rhythm are generally preferred over rate control. (Level of Evidence: C)</p> <p>2. Amiodarone is generally the preferred antiarrhythmic agent for maintenance of sinus rhythm (Level of Evidence: C)</p> <p><u>Reccomendations for management of AF in the Wolff-Parkinson-White syndrome</u></p> <p><u>Class I</u></p> <p>1. Catheter ablation of the accessory pathway is recommended in symptomatic patients with AF. (Level of Evidence: B)</p> <p>2. Operative ablation of the accessory pathway is indicated in patients with problematic or life-threatening AF where catheter ablation is not feasible. (Level of Evidence: B)</p> <p>3. Antiarrhythmic therapy with amiodarone, sotalol, disopyramide, flecainide, propafenone, quinidine or procainamide is recommended when corrective ablation is not feasible. (Level of Evidence: C)</p> <p>4. Immediate electrical cardioversion is recommended where AF occurs with a rapid ventricular response and hypotension. (Level of Evidence: B)</p> <p>5. Intravenous procainamide or ibutilide is recommended in AF with predominantly preexcited complexes when the patient is hemodynamically stable. (Level of Evidence: C)</p> <p>6. Verapamil, diltiazem or beta blockers are indicated for rate control when AF occurs without preexcitation. (Level of Evidence: C)</p> <p><u>Class III</u></p> <p>Intravenous beta-blocking agents are not generally useful and digitalis, diltiazem, or verapamil are contra-indicated in patients with a rapid ventricular response related to preexcitation. (Level of evidence: B)</p> <p><u>Reccomendations for management of AF in pregnancy</u></p> <p><u>Class I</u></p> <p>1 Control the rate of ventricular response with digoxin, a beta-blocker, or a calcium channel antagonist. (Level of Evidence: C)</p> <p>2. Perform electrical cardioversion in patients who become unstable due to AF. (Level of Evidence: C)</p> <p>3. Administer antithrombotic therapy (anticoagulant or aspirin) throughout pregnancy in all patients with persistent or paroxysmal AF. (Level of Evidence: C)</p> <p>4. In patients at risk of thrombo-embolism, administer heparin during the first trimester and after 36 weeks gestation. Unfractionated heparin may be administered by intravenous infusion or by twice a day subcutaneous injection (dose adjusted to maintain an activated partial thromboplastin time 2-3 times control value). Alternately, low molecular weight heparin can be utilized (dose adjustment guided by anti Xa levels). (Level of Evidence: C)</p> <p>5. Administer warfarin or heparin during the second trimester to patients with AF and at high thromboembolic risk. (Level of Evidence: C)</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p><u>Class IIa</u> 1. For symptomatic patients or those with poorly tolerated AF, pharmacologic or electrical cardioversion may be considered. (Level of Evidence: C)</p> <p><u>RECCOMENDATIONS FOR MANAGEMENT OF ATRIAL ARRHYTHMIAS IN PATIENTS WITH CONGENITAL HEART DISEASE</u> <u>Recommendatios for Cardioversion of AT</u></p> <p><u>Class I</u> 1. Immediately perform electrical cardioversion in patients with AT who are hemodynamically unstable. (Level of Evidence: C)</p> <p><u>Class IIa</u> 1. Electrical cardioversion for the early restoration of sinus rhythm is advisable in patients with newly diagnosed AT after appropriate anticoagulation. For those patients with pacemakers, cardioversion may also be accomplished by overdrive pace termination of atrial tachycardia. (Level of Evidence: C) All patients with congenital heart disease and atrial tachycardia should be managed as patients with atrial fibrillation and structural heart disease with respect to anticoagulation. (Level of Evidence: C) 3. In addition, all patients with complex heart lesions require a transoesophageal echocardiogram before elective cardioversion if no prior anticoagulation or if anticoagulation is subtherapeutic, independent of arrhythmia duration. (A complex heart lesion in this setting is defined as one with excessive atrial enlargement (in particular right atrial enlargement) and scarring , sluggish blood flow and predisposition to atrial thrombus formation even in sinus rhythm, often accompanied by systemic ventricular dysfunction and /or right to left shunting– as such, it most commonly applies to the patient post-Fontan operation but can also be encountered in other clinical situations such as Ebstein’s anomaly). (Level of Evidence: C) 4. Strategies to maintain sinus rhythm are generally preferred over rate control. (Level of Evidence: C)</p> <p><u>Class IIb</u> 1. Pharmacological cardioversion of AT may be considered in patients who are hemodynamically stable and who have a controlled ventricular rate. (Level of Evidence: C)</p> <p><u>Recommendations For Pharmacologic Therapy To Maintain Sinus Rhythm</u></p> <p><u>Class I</u> 1. Patients placed on antiarrhythmic drugs require periodic ambulatory monitoring to identify pro-arrhythmia, in particular, bradycardia. (Level of evidence: C)</p> <p><u>Class IIa</u> 2. Class III drugs (amiodarone and sotalol) are generally the preferred antiarrhythmic agents for the maintenance of sinus rhythm. (Level of Evidence: C)</p> <p><u>Class IIb</u> 1. If a Class Ic drug is to be used for preventing recurrence of AT, the concomitant administration of drugs to modify AV node conduction is advised. Consideration should be given to commencing antiarrhythmic drug therapy under ECG monitoring in hospital.</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p><u>Recommendations For Heart Rate Control</u></p> <p><u>Class I</u></p> <p>1. Patients with persistent or permanent AT should have heart rate control assessed at rest and with exercise. 2. Administer beta-blockers or calcium channel blockers to slow the ventricular response rate in patients with persistent or permanent AT with rapid ventricular response not requiring immediate electrical cardioversion. (Level of Evidence: C)</p> <p><u>Class IIa</u></p> <p>1. Adjunctive therapy with digoxin may be utilized to control the ventricular rate. Use of digoxin alone is not recommended. (Level of Evidence: C)</p> <p><u>Recommendations For Longterm Antithrombotic Management In Patients With Congenital Heart Disease And AT</u></p> <p><u>Class I</u></p> <p>1. Anticoagulation with adjusted dose warfarin is advised in patients with complex high risk lesions who have had an episode of AT. (Level of Evidence: C)</p> <p><u>Class IIa</u></p> <p>1. Anticoagulation with adjusted dose warfarin should be considered in all other patients with congenital heart disease and recurrent episodes of AT. (Level of Evidence: C)</p> <p><u>Class IIb</u></p> <p>1. The usefulness of anticoagulation or aspirin in patients with congenital heart disease who have minimal residual lesions and who have experienced a single episode of AT is uncertain. The decision to initiate anticoagulation with adjusted dose warfarin should then be based on conventional risk factors (see Chapter 12). (Level of Evidence: C)</p> <p><u>Recommendations For The Nonpharmacologic Management Of Patients With Congenital Heart Disease And AT</u></p> <p><u>Class I</u></p> <p>1. Cardiac pacing should be considered in patients with sinus node or AV node conduction disorders when pharmacologic management causes symptomatic or hemodynamically relevant bradycardia. (Level of Evidence: C)</p> <p>2. Ablation therapy directed at the arrhythmia substrate is beneficial and should be considered in selected patients with recurrent episodes of AT in whom there is a reasonable expectation of success. (Level of Evidence: C)</p> <p><u>Class IIa</u></p> <p>1. Ablation therapy directed at the arrhythmia substrate can be useful and may be considered in patients with recurrent AT following the Fontan operation. (Level of Evidence: C)</p> <p><u>Recommendations For Surgery In Patients With Congenital Heart Disease And Recurrent AT</u></p> <p><u>Class I</u></p> <p>1. All patients presenting with AT require full clinical assessment and investigation to evaluate for anatomically correctable abnormalities. (Level of Evidence: C)</p> <p>2. Concomitant atrial arrhythmia surgery is recommended in patients with symptomatic, recurrent AT who will be undergoing an operative procedure to correct anatomic abnormalities. (Level of Evidence: C)</p> <p><u>Class IIa</u></p> <p>1. Arrhythmia mapping and surgery as a primary indication for surgery is reasonable and may be considered in patients with arrhythmias refractory to medical and ablation therapy without a co-existing anatomic/haemodynamic indication for surgery. (Level</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>of Evidence: C)</p> <p><u>ATRIAL FIBRILLATION AND FLUTTER IN THE PAEDIATRIC PATIENT WITHOUT CONGENITAL HEART DISEASE</u> <u>RECOMMENDATIONS</u></p> <p><u>Acute management</u></p> <p><u>Class I</u></p> <ol style="list-style-type: none"> 1. Perform electrical cardioversion if there is severe haemodynamic compromise. 2. Unless otherwise contraindicated, anticoagulate with heparin for urgent cardioversion in patients in whom the duration of arrhythmia is > 48 hours or is uncertain. 3. Administer beta blockers, calcium blockers and, less frequently, digoxin to achieve acute rate control. Intravenous calcium channel blockers should be avoided in infants who are more susceptible to their negative inotropic effects. 4. Consider transoesophageal atrial pacing, which has been shown to be particularly effective in terminating neonatal atrial flutter. 5. In patients not on anticoagulation or subtherapeutically anticoagulated, perform transoesophageal echocardiography before cardioversion if arrhythmia has been present for > 48 hours or is of uncertain duration. 6. In stable patients with duration of AF > 48 hours or of uncertain duration in whom a decision has been made to attempt cardioversion, optimize rate control and anticoagulate to an INR of 2.0 – 3.0 for 3 weeks prior to cardioversion. <p><u>Class IIa</u></p> <ol style="list-style-type: none"> 1. Transoesophageal echocardiography is recommended in individuals in whom it is considered that the transthoracic echocardiogram has not provided sufficient imaging quality to rule out thrombus. <p><u>Chronic management</u></p> <p><u>Class IIa</u></p> <ol style="list-style-type: none"> 1. Consider drugs with class IC and class III actions as preferred agents for prevention of recurrence of atrial arrhythmias. AV Node blockade should be considered as adjunctive therapy when using IC drugs. 2. Consider radiofrequency ablation of recurrent atrial flutter. 3. Antithrombotic therapy with aspirin, if not contraindicated, may be considered in young patients with recurrent episodes who are considered low risk for stroke. <p>Investigation</p> <p><u>Class I</u></p> <ol style="list-style-type: none"> 1. Echocardiography to rule out cardiomyopathy and/or structural heart disease is recommended in patients with newly-presenting atrial flutter and fibrillation. 2. Holter monitoring and exercise testing should be performed in young patients with chronic atrial arrhythmia because of the increased occurrence of one-to-one conduction. <p>All recommendations Level of evidence: C.</p> <p><u>Recommendations for the Management of Atrial Fibrillation in the Emergency Department:</u></p> <p><u>Class I</u></p> <ol style="list-style-type: none"> 1. In stable patients with duration of AF > 48 hours or of uncertain duration in whom a decision has been made to attempt

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>cardioversion, optimize rate control and anticoagulate to an INR of 2.0 – 3.0 for 3 weeks prior to cardioversion. (Level of Evidence: C)</p> <p>2. In patients with AF of duration > 48 hours or of uncertain duration who are highly symptomatic after efforts to achieve adequate rate control, transesophageal echo to exclude atrial thrombus can be considered prior to cardioversion. (Level of Evidence: B)</p> <p>3. Select a strategy of rate control or rhythm control based on symptoms and clinical variables (see text. Level of Evidence: B)</p> <p>4. When a decision is made to cardiovert patients with AF < 48 hours, synchronized DC cardioversion or pharmacological cardioversion may be utilized. See chapter 3. (Level of Evidence: C)</p> <p>5. When DC cardioversion is chosen, use biphasic waveform when available to increase success and reduce cardioversion energy. (Level of Evidence: B)</p> <p>6. After acute conversion of an episode of atrial fibrillation or atrial flutter, long-term antithrombotic therapy should be prescribed based on thromboembolic risk and bleeding risk from antithrombotic therapy (see Chapter 12) (Level of Evidence: A)</p> <p>7. In patients with AF and pre-excitation, perform urgent cardioversion if hemodynamically unstable. If stable, consider using Class 1 (e.g. procainamide) or Class 3 (e.g. ibutilide) antiarrhythmic agents. (Level of Evidence: C)</p> <p>8. Hospital admission can be limited to highly symptomatic patients, those with structural heart disease, those who have had an embolic event or those at high risk for thromboembolism, and those with failure of rate control in the emergency department. (Level of Evidence: C)</p> <p><u>Class IIa</u></p> <p>1. Anticoagulation should be considered for most patients presenting to the ER with AF with either unfractionated heparin or low molecular weight heparin. Exceptions include those already on warfarin with an INR > 2.0 or those in whom the short term risk of bleeding on anticoagulant therapy is believed to exceed the risk of thromboembolism. (Level of Evidence: C)</p> <p>2. After conversion to sinus rhythm has been achieved, decide whether antiarrhythmic drug therapy is indicated based on the estimated probability of recurrence and the symptoms during AF. (Level of Evidence: C)</p> <p><u>Class III</u></p> <p>1. Do not administer digoxin, calcium channel blocking agents or beta-blocking agents alone to patients with pre-excitation during AF. (Level of Evidence: B)</p> <p>3. Do not administer adenosine to attempt rate control or cardioversion during AF. (Level of Evidence: B)</p> <p><u>Recommendations for Management of Patients with Atrial Fibrillation and Acute Myocardial Infarction:</u></p> <p><u>Class I</u></p> <p>1) Use electrical cardioversion for patients requiring urgent restoration of sinus rhythm for hemodynamic reasons. (Level of Evidence: C)</p> <p>2) Administer beta-blockers to slow a rapid ventricular response in patients without contraindication to beta-blockers. Diltiazem may be used as an alternative. These agents may be given orally or intravenously, depending on the urgency. (Level of Evidence: C)</p> <p>3) Administer intravenous digitalis or amiodarone to slow a rapid ventricular response in patients with impaired LV function. (Level of Evidence: C)</p> <p>4) Administer heparin for patients with AF and acute MI, unless contraindicated. (Level of Evidence: C)</p> <p><u>Class III</u></p> <p>1) Do not administer type IC antiarrhythmic drugs in patients with AF in the setting of acute MI. (Level of Evidence: C)</p>

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Ref	Argument	Agency - Year	Recommendations
14	Cardiovascular Guidelines Handbook: Developed for Primary Care Practitioners: Atrial Fibrillation	NZGG - 2005	<p><u>Atrial Flutter – Similarities and Differences - RECOMMENDATIONS</u></p> <p>...</p> <p><u>Electrical Cardioversion of Atrial Flutter</u></p> <p>...</p> <p><u>Therapies for the Prevention of Stroke and Other Vascular Events in Atrial Fibrillation and Flutter</u></p> <p>...</p> <p>This document reports a short synthesis of the recommendations from the guidelines “The Management of People with Atrial Fibrillation and Flutter”, reported below (doc 16)</p>
16	The Management of People with Atrial Fibrillation and Flutter	NZGG - 2005	<p>All people with atrial fibrillation (AF) or atrial flutter (AFL) require thromboembolic risk assessment, irrespective of their current rhythm. The majority of people with AF/AFL require anticoagulation to reduce their risk of stroke. A</p> <p>Rate control is the recommended strategy for the majority of people with AF/AFL. A</p> <p>People who have significant haemodynamic compromise or have rate-related angina, myocardial ischaemia or acute pulmonary oedema, as a result of rapid AF/AFL, should be cardioverted immediately, where possible. This is also an effective and rapid means of achieving rate control in such people. C</p> <p>Electrical cardioversion is the treatment of choice for people with pre-excited AF (WPW syndrome) with any haemodynamic compromise. C</p> <p>People with unacceptable arrhythmia-related symptoms should be considered for a rhythm-control approach. C</p> <p>...</p> <p>Rate control is the recommended strategy for the majority of people with atrial fibrillation (AF) or atrial flutter (AFL). A</p> <p>People who have significant haemodynamic compromise or rate-related angina, myocardial ischaemia or acute pulmonary oedema, as a result of rapid AF/AFL, should be cardioverted immediately, where possible. C</p> <p>Consider atrioventricular (AV) nodal ablation plus ventricular pacing when rate control has not been achieved by pharmacological means. B</p> <p>In the non-acute situation:</p> <ul style="list-style-type: none"> • beta-blockers (particularly atenolol, carvedilol, metoprolol, nadolol and propranolol), verapamil, diltiazem and digoxin are effective rate-control agents, although digoxin is not effective during exercise. A • a combination of rate-control agents is sometimes required to achieve adequate rate control, but the combination of beta-blockers with verapamil should be used with considerable caution. C

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			<p>Beta-blockers are contraindicated in people with asthma, and should be introduced slowly in people with heart failure or hypotension. A</p> <p>Beta-blockers, calcium channel blockers (diltiazem, verapamil) and digoxin are contraindicated in people with Wolff-Parkinson-White (WPW) syndrome and especially in those with pre-excited AF. C</p> <p>Digoxin is the rate-control agent of first choice in people with heart failure. B</p> <p>Sotalol should NOT be used solely for rate control because it is associated with a higher incidence of life-threatening ventricular arrhythmias (particularly torsades de pointes). B</p> <p>Amiodarone can be considered when rate control has not been achieved with combinations of the usual rate-control agents. C</p> <p>Consideration should be given to the prescription of rate-control agents, specifically to reduce symptom severity, on an 'as required' basis for selected people with paroxysmal AF (PAF), so that they can initiate treatment at, or soon after, the onset of AF symptoms. C</p> <p>GOOD PRACTICE POINT</p> <p>Addition of amiodarone, propafenone or verapamil to digoxin may lead to elevated serum digoxin levels. The dose of digoxin may therefore need to be reduced, and digoxin levels checked.</p>

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Ref	Argument	Agency - Year	Recommendations																								
			<p>Table 7.1: Choice of a rate-control agent</p> <table border="1"> <thead> <tr> <th>Comorbidity</th> <th>First-line</th> <th>Second-line</th> <th>Less effective or desirable</th> </tr> </thead> <tbody> <tr> <td>No heart disease</td> <td>Beta-blockers* OR Calcium channel blockers†</td> <td></td> <td>Digoxin‡ (can be first-line in people unlikely to be active)</td> </tr> <tr> <td>Hypertension</td> <td>Beta-blockers* OR Calcium channel blockers†</td> <td></td> <td>Digoxin‡</td> </tr> <tr> <td>Ischaemic heart disease</td> <td>Beta-blockers*</td> <td>Calcium-channel blockers† OR Digoxin‡</td> <td>Ablation + pacing</td> </tr> <tr> <td>Congestive heart failure</td> <td>Digoxin in overt heart failure Carvedilol or metoprolol in stable heart failure</td> <td>Beta-blockers* (excluding carvedilol and metoprolol) OR Diltiazem</td> <td>Amiodarone Ablation and pacing should be considered</td> </tr> <tr> <td>Chronic obstructive pulmonary disease</td> <td>Calcium channel blockers†</td> <td>Beta-blockers* (if there is no reversible bronchospasm)</td> <td>Digoxin‡</td> </tr> </tbody> </table> <p>* excluding sotalol † diltiazem or verapamil ‡ as monotherapy (can be used in combination with other rate-control agents)</p> <p>Adapted from: Boriani G, Biffi M, Diemberger I, et al.¹⁸⁴</p>	Comorbidity	First-line	Second-line	Less effective or desirable	No heart disease	Beta-blockers* OR Calcium channel blockers†		Digoxin‡ (can be first-line in people unlikely to be active)	Hypertension	Beta-blockers* OR Calcium channel blockers†		Digoxin‡	Ischaemic heart disease	Beta-blockers*	Calcium-channel blockers† OR Digoxin‡	Ablation + pacing	Congestive heart failure	Digoxin in overt heart failure Carvedilol or metoprolol in stable heart failure	Beta-blockers* (excluding carvedilol and metoprolol) OR Diltiazem	Amiodarone Ablation and pacing should be considered	Chronic obstructive pulmonary disease	Calcium channel blockers†	Beta-blockers* (if there is no reversible bronchospasm)	Digoxin‡
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Ref	Argument	Agency - Year	Recommendations																			
			Amiodarone	400 to 800 mg/day for 1 week	1 to 3 wk	200 mg/day	Photosensitivity and other skin reactions, pulmonary toxicity, polyneuropathy, gastrointestinal upset, bradycardia, hepatic toxicity, thyroid dysfunction, torsades de pointes (rare)	Although there is fairly good evidence of efficacy, this is an agent of last resort in this indication, due to its long-term toxicity														
<p>In acutely symptomatic people with rapid AF/AFL, consider use of the following IV rate-control agents, which have been proven to be effective in haemodynamically stable people:</p> <ul style="list-style-type: none"> • esmolol (very short-acting), metoprolol, propranolol, diltiazem or verapamil. A • amiodarone or digoxin. B <p>Note: Atenolol IV is not currently available in New Zealand. The choice of medication should be individualised.</p> <p>Special caution is required in the setting of symptomatic rapid AF/AFL with hypotension, overt heart failure, or both. Metoprolol, propranolol and verapamil may exacerbate these conditions. Prompt electrical cardioversion is recommended. Until this is available, IV digoxin is the agent of first choice, although cautious use of IV diltiazem or esmolol are other options. B</p> <p>Table 7.3: Intravenous pharmacological agents for acute control of ventricular rate in AF/AFL</p> <table border="1"> <thead> <tr> <th>Drug</th> <th>Commonly used loading dose (IV)</th> <th>Onset of action</th> <th>Commonly-used maintenance dose (IV)</th> <th>Adverse effects</th> <th>Limitations</th> <th>Commonly-used oral maintenance dose for long-term rate control</th> </tr> </thead> <tbody> <tr> <td>Amiodarone</td> <td>5 mg/kg over 20 min</td> <td>Variable (10 min to 4 hours)</td> <td>50 mg/hour infusion</td> <td>Hypotension, back pain, heart block, phlebitis</td> <td>N/A</td> <td>100 to 200 mg/day</td> </tr> </tbody> </table>									Drug	Commonly used loading dose (IV)	Onset of action	Commonly-used maintenance dose (IV)	Adverse effects	Limitations	Commonly-used oral maintenance dose for long-term rate control	Amiodarone	5 mg/kg over 20 min	Variable (10 min to 4 hours)	50 mg/hour infusion	Hypotension, back pain, heart block, phlebitis	N/A	100 to 200 mg/day
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Ref	Argument	Agency - Year	Recommendations
			<p>...</p> <p>People who have significant haemodynamic compromise or have rate-related angina, myocardial ischaemia or acute pulmonary oedema, as a result of rapid AF/AFL, should be cardioverted immediately where possible. C</p> <p>Electrical cardioversion is the treatment of choice for people with pre-excited AF (WPW syndrome) with any haemodynamic compromise. If the person is stable and pre-excitation is intermittent or rates are slower, pharmacological cardioversion can be considered, but atrioventricular (AV) nodal blockers (beta-blockers, non-dihydropyridine calcium channel blockers and digoxin) must be avoided. C</p> <p>People with unacceptable arrhythmia-related symptoms should be considered for a rhythm-control approach. C</p> <p>If a rhythm control strategy is chosen for people who are not anticoagulated, they should be cardioverted within 48 hours of onset. If they cannot be cardioverted within 48 hours of onset, then they should have either:</p> <ul style="list-style-type: none"> • a therapeutic INR (2.0 to 3.0, target 2.5) for at least 3 weeks, OR • a transoesophageal echocardiogram to exclude atrial thrombi before cardioversion. B <p>Prior to receiving cardioversion therapy, either electrical or pharmacological, a person should have normal electrolyte levels and no suggestion of digoxin toxicity. C</p> <p>Electrical cardioversion should not be performed in people with contraindications to sedatives or anaesthetics. C</p> <p>Electrical cardioversion is marginally more effective than pharmacological cardioversion. C</p> <p>In New Zealand, people in need of immediate conversion to normal sinus rhythm should receive electrical cardioversion treatment, unless they have any contraindications to sedation or anaesthesia. This is because the antiarrhythmic agents capable of very fast conversion (ibutilide, dofetilide, procainamide) are not available in New Zealand. Second-choice drug therapies are IV (and/or oral) propafenone or flecainide, while third-choice therapy is IV (and/or oral) amiodarone (in terms of the time taken to achieve cardioversion). C</p> <p>Electrical and pharmacological methods of cardioversion should be considered equivalent in terms of thromboembolic risk. C</p> <p>Pharmacological cardioversion is an alternative option to electrical cardioversion. A</p> <p>Consider amiodarone (eg, 400 mg/day) pretreatment (3 to 4 weeks) for people with persistent AF who are awaiting an elective electrical cardioversion procedure, as long as they have already received at least 3 weeks of therapeutic warfarin. B</p> <p>People in whom electrical cardioversion has failed may be given pretreatment with oral amiodarone before further electrical cardioversion is attempted, as long as they have already received at least 3 weeks of therapeutic warfarin. B</p> <p>There is insufficient evidence to recommend the addition of verapamil, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II inhibitors as pretreatment regimens prior to electrical cardioversion. I</p> <p>Pharmacological cardioversion should be considered equivalent to electrical cardioversion in terms of thromboembolic risks. C</p> <p>When a rhythm-control strategy has been chosen, in most cases pharmacological cardioversion is an alternative option to electrical cardioversion, either in the acute setting (AF/AFL duration <48 hours, or longer if no atrial thrombi on TOE), or if the person with AF/AFL is adequately anticoagulated. A</p>

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Ref	Argument	Agency - Year	Recommendations
			<p>Consider the following agents for pharmacological cardioversion:</p> <ul style="list-style-type: none"> • amiodarone (IV or oral) • flecainide (IV or oral) • propafenone (IV or oral). <p>Note: The pharmacological agents capable of very rapid cardioversion (dofetilide, ibutilide and procainamide) are not currently available in New Zealand. A</p> <p>Flecainide or propafenone therapy usually results in more rapid cardioversion than amiodarone therapy, but should be avoided if there is clinical suspicion of structural heart disease (eg, past myocardial infarction, coronary disease, left ventricular dysfunction (LVD), severe left ventricular hypertrophy LVH), when amiodarone is the preferred agent for pharmacological cardioversion. A</p> <p>Sotalol is not recommended for cardioversion because it is ineffective in this setting. A</p> <p>There is insufficient evidence of efficacy for disopyramide for cardioversion of AF/AFL. I</p> <p>Consider oral amiodarone therapy for 3 to 4 weeks for cardioversion of people with persistent AF/AFL, as long as they have received at least 3 weeks of therapeutic warfarin. Note: This is sometimes considered after failure of electrical cardioversion. A</p> <p>People undergoing pharmacological cardioversion should have normal electrolyte levels and no suggestion of digoxin toxicity. C</p>

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Ref	Argument	Agency - Year	Recommendations																						
			<p>Table 8.2: Recommended doses of drugs that are effective for pharmacological cardioversion of atrial fibrillation and atrial flutter and are available in New Zealand</p> <table border="1"> <thead> <tr> <th rowspan="2">Drug*</th> <th rowspan="2">Route</th> <th rowspan="2">Commonly used dosages†</th> <th colspan="2">Approximate time to conversion</th> <th rowspan="2">Adverse effects</th> </tr> <tr> <th>AF <48 hours</th> <th>AF ≥48 hours‡</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Amiodarone</td> <td>IV + oral</td> <td>5 mg/kg bolus then 15 mg/kg/day infusion plus oral 600 mg/day for 1 week, then 400 mg/day for 1 week then 200 mg/day (or less)</td> <td>7 (+/- 5) hours²⁰⁸</td> <td>47 to 80% in one month^{278,279,282}</td> <td rowspan="3">Hypotension (related to infusion rate), bradycardia, QT prolongation, torsades de pointes (rare), gastrointestinal upset (oral), phlebitis (IV), tremor With long-term amiodarone treatment: pulmonary toxicity, skin reactions, polyneuropathy, hepatic toxicity, thyroid dysfunction</td> </tr> <tr> <td>High-dose IV</td> <td>125 mg/hour (maximum total dose 3g)</td> <td>92% within 24 hours²⁰⁹</td> <td>>50% of patients within 8 hours²⁷²</td> </tr> <tr> <td>Oral</td> <td>200 to 400 mg/day OR 30 mg/kg single dose²⁰⁷</td> <td>7.9 hours²⁰⁷</td> <td>47% in 24 hours; 63% at 48 hours²⁷¹</td> </tr> </tbody> </table> <p>Amiodarone, disopyramide, flecainide, propafenone and sotalol are recommended for the pharmacological maintenance of sinus rhythm. A</p> <p>The choice of antiarrhythmic agent for maintenance of sinus rhythm should be made on the basis of safety considerations, such as contraindications in certain subgroups, and the potential for cardiac and non-cardiac side effects. C</p> <p>Amiodarone is more effective for maintenance of sinus rhythm than other agents, but has a higher risk of long-term serious side effects. It is the drug of choice for pharmacological maintenance of sinus rhythm, for people with AF/AFL plus significant LVD and/or CHF. Note: Dofetilide also has proven efficacy, but is not available in New Zealand. A</p> <p>The following drugs are either ineffective or have insufficient evidence of efficacy for maintenance of sinus rhythm:</p> <ul style="list-style-type: none"> • ‘conventional’ beta-blockers (all beta-blockers except for sotalol) 	Drug*	Route	Commonly used dosages†	Approximate time to conversion		Adverse effects	AF <48 hours	AF ≥48 hours‡	Amiodarone	IV + oral	5 mg/kg bolus then 15 mg/kg/day infusion plus oral 600 mg/day for 1 week, then 400 mg/day for 1 week then 200 mg/day (or less)	7 (+/- 5) hours ²⁰⁸	47 to 80% in one month ^{278,279,282}	Hypotension (related to infusion rate), bradycardia, QT prolongation, torsades de pointes (rare), gastrointestinal upset (oral), phlebitis (IV), tremor With long-term amiodarone treatment: pulmonary toxicity, skin reactions, polyneuropathy, hepatic toxicity, thyroid dysfunction	High-dose IV	125 mg/hour (maximum total dose 3g)	92% within 24 hours ²⁰⁹	>50% of patients within 8 hours ²⁷²	Oral	200 to 400 mg/day OR 30 mg/kg single dose ²⁰⁷	7.9 hours ²⁰⁷	47% in 24 hours; 63% at 48 hours ²⁷¹
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Ref	Argument	Agency - Year	Recommendations
			<ul style="list-style-type: none"> • ACE inhibitors • digoxin • calcium channel blockers (diltiazem, verapamil) • azimilide, moricizine, procainamide (not available in New Zealand). I <p>A nonpharmacological approach to the maintenance of sinus rhythm (eg, surgical or catheter ablation, or implantable pacemaker) may be justified in selected people with AF/AFL (see Section 8.2.3, Nonpharmacological maintenance of sinus rhythm). B</p> <p>GOOD PRACTICE POINTS</p> <p>People should be informed of the risks associated with antiarrhythmic agents, including proarrhythmia, which may occur at any time, as well as the serious adverse effects that may occur with long-term treatment, particularly with amiodarone</p>

Arrhythmias: Atrial Fibrillation

Ref	Argument	Agency - Year	Recommendations
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Table 8.3: Choice of antiarrhythmic agent for maintenance of sinus rhythm

Comorbidities	Amiodarone†	Disopyramide	Flecainide	Propafenone	Sotalol
No comorbidities	Not as first-line	✓	✓	✓	✓
Asthma	Use with care	✓	✓	Use with care	AVOID
Bradycardia (without pacemaker)	Use with care	Use with care	Use with care	Use with care	Use with care
Hypertension with significant LVH (≥ 1.4 cm)	✓	AVOID	AVOID	AVOID	AVOID
Impaired LV function	✓	AVOID	AVOID	AVOID	AVOID
CHF	✓	AVOID	AVOID	AVOID	AVOID
Ischaemic heart disease or past myocardial infarction	✓	AVOID	AVOID	AVOID	✓
Thyroid disease	AVOID or consult with endocrinologist	✓	✓	✓	✓
Long QT syndrome, family history of long QT syndrome, concern about long QT*	AVOID	AVOID	✓‡	✓‡	AVOID

* Avoid quinidine, procainamide, dofetilide and ibutilide in long QT syndromes.

† Amiodarone is more effective than other agents and has the advantage of being able to be used in people with CHF and poor LV function. It should only be used first-line in people with CHF, poor LV function, severe LVH or in refractory AF as pretreatment prior to electrical cardioversion.

‡ Antiarrhythmic agents in general are best avoided in people with a long QT interval. However, if an antiarrhythmic agent is absolutely required, flecainide and propafenone are least likely to cause problems.

Table 8.4: Typical doses and adverse effects of antiarrhythmic drugs used to maintain sinus rhythm in people with atrial fibrillation or atrial flutter

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Ref	Argument	Agency - Year	Recommendations
17	Management of Patients With Atrial Fibrillation	ACC/AHA/ES C - 2006	<p><u>Pharmacological Rate Control During Atrial Fibrillation</u></p> <p><u>RECOMMENDATIONS</u></p> <p>Class I</p> <ol style="list-style-type: none"> 1. Measurement of the heart rate at rest and control of the rate using pharmacological agents (either a beta blocker or nondihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent AF. (Level of Evidence: B) 2. In the absence of preexcitation, intravenous administration of beta blockers (esmolol, metoprolol, or propranolol) or nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended to slow the ventricular response to AF in the acute setting, exercising caution in patients with hypotension or HF. (Level of Evidence: B) 3. Intravenous administration of digoxin or amiodarone is recommended to control the heart rate in patients with AF and HF who do not have an accessory pathway. (Level of Evidence: B) 4. In patients who experience symptoms related to AF during activity, the adequacy of heart rate control should be assessed during exercise, adjusting pharmacological treatment as necessary to keep the rate in the physiological range. (Level of Evidence: C) 5. Digoxin is effective following oral administration to control the heart rate at rest in patients with AF and is indicated for patients with HF, LV dysfunction, or for sedentary individuals. (Level of Evidence: C) <p>Class IIa</p> <ol style="list-style-type: none"> 1. A combination of digoxin and either a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise in patients with AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia. (Level of Evidence: B) 2. It is reasonable to use ablation of the AV node or accessory pathway to control heart rate when pharmacological therapy is insufficient or associated with side effects. (Level of Evidence: B) 3. Intravenous amiodarone can be useful to control the heart rate in patients with AF when other measures are unsuccessful or contraindicated. (Level of Evidence: C) 4. When electrical cardioversion is not necessary in patients with AF and an accessory pathway, intravenous procainamide or ibutilide is a reasonable alternative. (Level of Evidence: C) <p>Class IIb</p> <ol style="list-style-type: none"> 1. When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF using a beta blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate. (Level of Evidence: C) 2. Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway. (Level of Evidence: B) 3. When the rate cannot be controlled with pharmacological agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate. (Level of Evidence: C) <p>Class III</p> <ol style="list-style-type: none"> 1. Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF. (Level of Evidence: B) 2. Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in

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Ref	Argument	Agency - Year	Recommendations																																																						
			<p>patients with AF. (Level of Evidence: C)</p> <p>3. In patients with decompensated HF and AF, intravenous administration of a nondihydropyridine calcium channel antagonist may exacerbate hemodynamic compromise and is not recommended. (Level of Evidence: C)</p> <p>4. Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with AF and a preexcitation syndrome may paradoxically accelerate the ventricular response and is not recommended. (Level of Evidence: C)</p> <p>TABLE 10. Intravenous and Orally Administered Pharmacological Agents for Heart Rate Control in Patients With Atrial Fibrillation</p> <table border="1"> <thead> <tr> <th>Drug</th> <th>Class/LOE Recommendation</th> <th>Loading Dose</th> <th>Onset</th> <th>Maintenance Dose</th> <th>Major Side Effects</th> </tr> </thead> <tbody> <tr> <td colspan="6">ACUTE SETTING</td> </tr> <tr> <td colspan="6"><i>Heart rate control in patients with heart failure and without accessory pathway</i></td> </tr> <tr> <td>Digoxin</td> <td>Class I, LOE B</td> <td>0.25 mg IV each 2 h, up to 1.5 mg</td> <td>60 min or more[§]</td> <td>0.125 to 0.375 mg daily IV or orally</td> <td>Digitalis toxicity, HB, ↓ HR</td> </tr> <tr> <td>Amiodarone†</td> <td>Class IIa, LOE C</td> <td>150 mg over 10 min</td> <td>Days</td> <td>0.5 to 1 mg/min IV</td> <td>↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia</td> </tr> <tr> <td colspan="6">NON-ACUTE SETTING and CHRONIC MAINTENANCE THERAPY¶</td> </tr> <tr> <td colspan="6"><i>Heart rate control in patients with heart failure and without accessory pathway</i></td> </tr> <tr> <td>Digoxin</td> <td>Class I, LOE C</td> <td>0.5 mg by mouth daily</td> <td>2 days</td> <td>0.125 to 0.375 mg daily, orally</td> <td>Digitalis toxicity, HB, ↓ HR</td> </tr> <tr> <td>Amiodarone†</td> <td>Class IIb, LOE C</td> <td>800 mg daily for 1 wk, orally 600 mg daily for 1 wk, orally 400 mg daily for 4 to 6 wk, orally</td> <td>1 to 3 wk</td> <td>200 mg daily, orally</td> <td>↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia</td> </tr> </tbody> </table> <p>*Onset is variable and some effect occurs earlier.</p> <p>†Only representative members of the type of beta-adrenergic antagonist drugs are included in the table, but other, similar agents could be used for this indication in appropriate doses. Beta blockers are grouped in an order preceding the alphabetical listing of drugs.</p> <p>‡Amiodarone can be useful to control the heart rate in patients with atrial fibrillation (AF) when other measures are unsuccessful or contraindicated.</p> <p><u>Cardioversion of Atrial Fibrillation</u></p> <p><u>RECOMMENDATIONS</u></p> <p><u>Recommendations for Pharmacological Cardioversion of Atrial Fibrillation</u></p> <p>Class I</p> <p>Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. (Level of Evidence: A)</p>	Drug	Class/LOE Recommendation	Loading Dose	Onset	Maintenance Dose	Major Side Effects	ACUTE SETTING						<i>Heart rate control in patients with heart failure and without accessory pathway</i>						Digoxin	Class I, LOE B	0.25 mg IV each 2 h, up to 1.5 mg	60 min or more [§]	0.125 to 0.375 mg daily IV or orally	Digitalis toxicity, HB, ↓ HR	Amiodarone†	Class IIa, LOE C	150 mg over 10 min	Days	0.5 to 1 mg/min IV	↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia	NON-ACUTE SETTING and CHRONIC MAINTENANCE THERAPY¶						<i>Heart rate control in patients with heart failure and without accessory pathway</i>						Digoxin	Class I, LOE C	0.5 mg by mouth daily	2 days	0.125 to 0.375 mg daily, orally	Digitalis toxicity, HB, ↓ HR	Amiodarone†	Class IIb, LOE C	800 mg daily for 1 wk, orally 600 mg daily for 1 wk, orally 400 mg daily for 4 to 6 wk, orally	1 to 3 wk	200 mg daily, orally	↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia
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			<p>Class IIa</p> <ol style="list-style-type: none"> 1. Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF. (Level of Evidence: A) 2. A single oral bolus dose of propafenone or flecainide (“pill-in-the-pocket”) can be administered to terminate persistent AF outside the hospital once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundlebranch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs. (Level of Evidence: C) 3. Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary. (Level of Evidence: C) <p>Class IIb</p> <p>Administration of quinidine or procainamide might be considered for pharmacological cardioversion of AF, but the usefulness of these agents is not well established. (Level of Evidence: C)</p> <p>Class III</p> <ol style="list-style-type: none"> 1. Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended. (Level of Evidence: A) 2. Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of AF to sinus rhythm. (Level of Evidence: B) <p>TABLE 16. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of Up to 7-d Duration</p> <table border="1"> <thead> <tr> <th>Drug*</th> <th>Route of Administration</th> <th>Class of Recommendation</th> <th>Level of Evidence</th> <th>References</th> </tr> </thead> <tbody> <tr> <td colspan="5">Agents with proven efficacy</td> </tr> <tr> <td>Dofetilide</td> <td>Oral</td> <td>I</td> <td>A</td> <td>498–503</td> </tr> <tr> <td>Flecainide</td> <td>Oral or intravenous</td> <td>I</td> <td>A</td> <td>489–491, 493, 504–509</td> </tr> <tr> <td>Ibutilide</td> <td>Intravenous</td> <td>I</td> <td>A</td> <td>510–515</td> </tr> <tr> <td>Propafenone</td> <td>Oral or intravenous</td> <td>I</td> <td>A</td> <td>491, 494, 495, 505, 509, 516–526, 557</td> </tr> <tr> <td>Amiodarone</td> <td>Oral or intravenous</td> <td>IIa</td> <td>A</td> <td>496, 504, 516, 527–534</td> </tr> </tbody> </table> <p>TABLE 17. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation Present for More Than 7 d</p> <table border="1"> <thead> <tr> <th>Drug*</th> <th>Route of Administration</th> <th>Recommendation Class</th> <th>Level of Evidence</th> <th>References</th> </tr> </thead> <tbody> <tr> <td colspan="5">Agents with proven efficacy</td> </tr> <tr> <td>Dofetilide</td> <td>Oral</td> <td>I</td> <td>A</td> <td>498–503</td> </tr> <tr> <td>Amiodarone</td> <td>Oral or intravenous</td> <td>IIa</td> <td>A</td> <td>496, 504, 516, 527–534</td> </tr> <tr> <td>Ibutilide</td> <td>Intravenous</td> <td>IIa</td> <td>A</td> <td>510–515</td> </tr> </tbody> </table>	Drug*	Route of Administration	Class of Recommendation	Level of Evidence	References	Agents with proven efficacy					Dofetilide	Oral	I	A	498–503	Flecainide	Oral or intravenous	I	A	489–491, 493, 504–509	Ibutilide	Intravenous	I	A	510–515	Propafenone	Oral or intravenous	I	A	491, 494, 495, 505, 509, 516–526, 557	Amiodarone	Oral or intravenous	IIa	A	496, 504, 516, 527–534	Drug*	Route of Administration	Recommendation Class	Level of Evidence	References	Agents with proven efficacy					Dofetilide	Oral	I	A	498–503	Amiodarone	Oral or intravenous	IIa	A	496, 504, 516, 527–534	Ibutilide	Intravenous	IIa	A	510–515
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			<p>TABLE 18. Recommended Doses of Drugs Proven Effective for Pharmacological Cardioversion of Atrial Fibrillation</p> <table border="1"> <thead> <tr> <th>Drug*</th> <th>Route of Administration</th> <th>Dosage†</th> <th>Potential Adverse Effects</th> <th>References</th> </tr> </thead> <tbody> <tr> <td>Amiodarone</td> <td>Oral</td> <td>Inpatient: 1.2 to 1.8 g per day in divided dose until 10 g total, then 200 to 400 mg per day maintenance or 30 mg/kg as single dose Outpatient: 600 to 800 mg per day divided dose until 10 g total, then 200 to 400 mg per day maintenance</td> <td>Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)</td> <td>496, 504, 516, 527–534, 537, 545</td> </tr> <tr> <td></td> <td>Intravenous/oral</td> <td>5 to 7 mg/kg over 30 to 60 min, then 1.2 to 1.8 g per day continuous IV or in divided oral doses until 10 g total, then 200 to 400 mg per day maintenance</td> <td></td> <td></td> </tr> </tbody> </table> <p><u>Direct-Current Cardioversion of Atrial Fibrillation and Flutter</u> <u>RECOMMENDATIONS</u></p> <p>Class I</p> <ol style="list-style-type: none"> 1. When a rapid ventricular response does not respond promptly to pharmacological measures for patients with AF with ongoing myocardial ischemia, symptomatic hypotension, angina, or HF, immediate R-wave synchronized direct-current cardioversion is recommended. (Level of Evidence: C) 2. Immediate direct-current cardioversion is recommended for patients with AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs. (Level of Evidence: B) 3. Cardioversion is recommended in patients without hemodynamic instability when symptoms of AF are unacceptable to the patient. In case of early relapse of AF after cardioversion, repeated direct-current cardioversion attempts may be made following administration of antiarrhythmic medication. (Level of Evidence: C) <p>Class IIa</p> <ol style="list-style-type: none"> 1. Direct-current cardioversion can be useful to restore sinus rhythm as part of a long-term management strategy for patients with AF. (Level of Evidence: B) 2. Patient preference is a reasonable consideration in the selection of infrequently repeated cardioversions for the management of symptomatic or recurrent AF. (Level of Evidence: C) <p>Class III</p> <ol style="list-style-type: none"> 1. Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF after multiple cardioversion procedures despite prophylactic antiarrhythmic drug therapy. (Level of Evidence: C) 	Drug*	Route of Administration	Dosage†	Potential Adverse Effects	References	Amiodarone	Oral	Inpatient: 1.2 to 1.8 g per day in divided dose until 10 g total, then 200 to 400 mg per day maintenance or 30 mg/kg as single dose Outpatient: 600 to 800 mg per day divided dose until 10 g total, then 200 to 400 mg per day maintenance	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)	496, 504, 516, 527–534, 537, 545		Intravenous/oral	5 to 7 mg/kg over 30 to 60 min, then 1.2 to 1.8 g per day continuous IV or in divided oral doses until 10 g total, then 200 to 400 mg per day maintenance		
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			<p>2. Electrical cardioversion is contraindicated in patients with digitalis toxicity or hypokalemia. (Level of Evidence: C)</p> <p><u>Pharmacological Enhancement of Direct-Current Cardioversion</u></p> <p><u>RECOMMENDATIONS</u></p> <p>Class IIa</p> <p>1. Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent atrial fibrillation. (Level of Evidence: B)</p> <p>2. In patients who relapse to AF after successful cardioversion, it can be useful to repeat the procedure following prophylactic administration of antiarrhythmic medication. (Level of Evidence: C)</p> <p>Class IIb</p> <p>1. For patients with persistent AF, administration of beta blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain. (Level of Evidence: C)</p> <p>2. Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF. (Level of Evidence: C)</p> <p>3. Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient. (Level of Evidence: C)</p> <p><u>Maintenance of Sinus Rhythm</u></p> <p><u>RECOMMENDATIONS</u></p> <p>Class I</p> <p>Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (Level of Evidence: C)</p> <p>Class IIa</p> <p>1. Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. (Level of Evidence: C)</p> <p>2. Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. (Level of Evidence: C)</p> <p>Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. (Level of Evidence: C)</p> <p>4. In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. (Level of Evidence: B)</p> <p>5. Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with class III drug-related proarrhythmia are not present. (Level of Evidence: C)</p> <p>6. Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement. (Level of Evidence: C)</p> <p>Class III</p>

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Ref	Argument	Agency - Year	Recommendations
			<p>1. Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent. (Level of Evidence: A)</p> <p>2. Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. (Level of Evidence: C)</p>

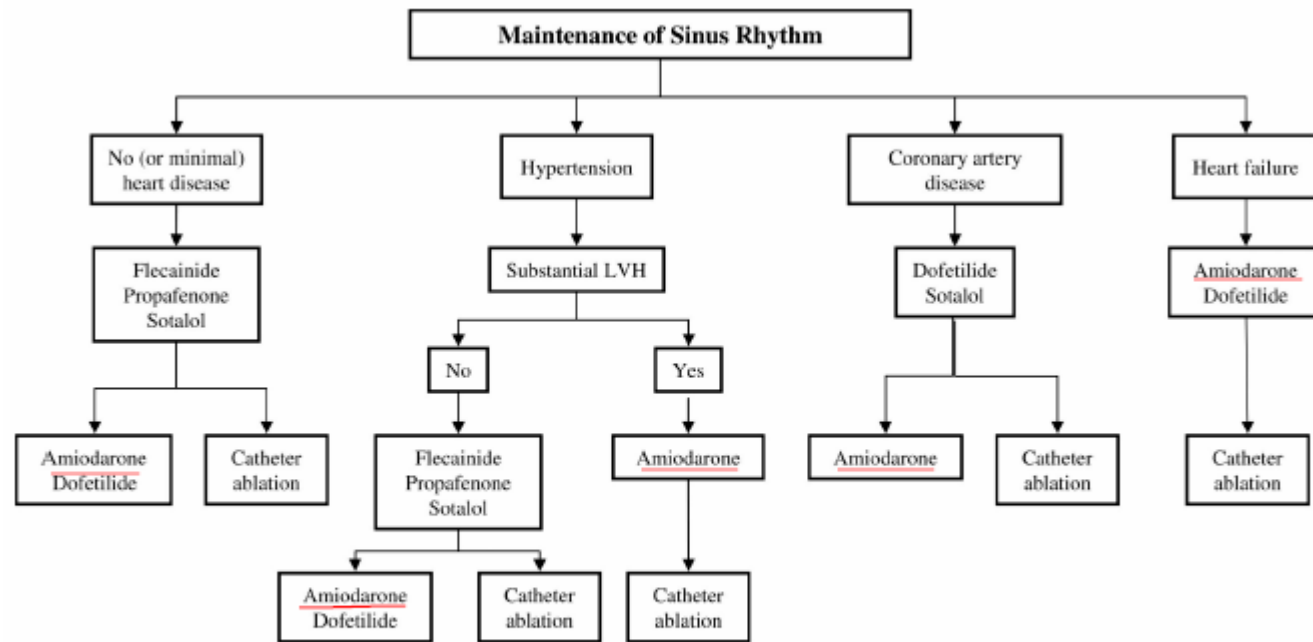


Figure 15. Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. See Section 8.3.3.3 for details. LVH indicates left ventricular hypertrophy.

TABLE 20. Typical Doses of Drugs Used to Maintain Sinus Rhythm in Patients With Atrial Fibrillation*

Drug†	Daily Dosage	Potential Adverse Effects
Amiodarone‡	100 to 400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications

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Ref	Argument	Agency - Year	Recommendations										
			<p>TABLE 23. Pharmacological Treatment Before Cardioversion in Patients With Persistent AF: Effectiveness of Various Antiarrhythmic Drugs on Acute and Subacute Outcome of Transthoracic DC Shock</p> <table border="1"> <thead> <tr> <th>Efficacy</th> <th>Enhance Conversion by DC Shock and Prevent IRAF*</th> <th>Suppress SRAF and Maintenance Therapy Class</th> <th>Recommendation Class</th> <th>Level of Evidence</th> </tr> </thead> <tbody> <tr> <td>Known</td> <td>Amiodarone Flecainide Ibutilide Propafenone Quinidine Sotalol</td> <td>All drugs in recommendation class I (except ibutilide) plus beta blockers</td> <td>I</td> <td>B</td> </tr> </tbody> </table> <p><u>Postoperative AF</u> <u>RECOMMENDATIONS</u></p> <p>Class I</p> <ol style="list-style-type: none"> 1. Unless contraindicated, treatment with an oral beta blocker to prevent postoperative AF is recommended for patients undergoing cardiac surgery. (Level of Evidence: A) 2. Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF. (Level of Evidence: B) <p>Class IIa</p> <ol style="list-style-type: none"> 1. Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF. (Level of Evidence: A) 2. It is reasonable to restore sinus rhythm by pharmacological cardioversion with ibutilide or directcurrent cardioversion in patients who develop postoperative AF as advised for nonsurgical patients. (Level of Evidence: B) 3. It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF. (Level of Evidence: B) 4. It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as recommended for nonsurgical patients. (Level of Evidence: B) <p>Class IIb</p> <p>Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. (Level of Evidence: B)</p>	Efficacy	Enhance Conversion by DC Shock and Prevent IRAF*	Suppress SRAF and Maintenance Therapy Class	Recommendation Class	Level of Evidence	Known	Amiodarone Flecainide Ibutilide Propafenone Quinidine Sotalol	All drugs in recommendation class I (except ibutilide) plus beta blockers	I	B
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Ref	Argument	Agency - Year	Recommendations
			<p><u>Acute Myocardial Infarction</u></p> <p><u>RECOMMENDATIONS</u></p> <p>Class I</p> <ol style="list-style-type: none"> 1. Direct-current cardioversion is recommended for patients with severe hemodynamic compromise or intractable ischemia, or when adequate rate control cannot be achieved with pharmacological agents in patients with acute MI and AF. (Level of Evidence: C) 2. Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF and improve LV function in patients with acute MI. (Level of Evidence: C) 3. Intravenous beta blockers and nondihydropyridine calcium antagonists are recommended to slow a rapid ventricular response to AF in patients with acute MI who do not display clinical LV dysfunction, bronchospasm, or AV block. (Level of Evidence: C) 4. For patients with AF and acute MI, administration of unfractionated heparin by either continuous intravenous infusion or intermittent subcutaneous injection is recommended in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 to 2.0 times the control value, unless contraindications to anticoagulation exist. (Level of Evidence: C) <p>Class IIa</p> <p>Intravenous administration of digitalis is reasonable to slow a rapid ventricular response and improve LV function in patients with acute MI and AF associated with severe LV dysfunction and HF. (Level of Evidence: C)</p> <p>Class III</p> <p>The administration of class IC antiarrhythmic drugs is not recommended in patients with AF in the setting of acute MI. (Level of Evidence: C)</p> <p><u>Wolff-Parkinson-White (WPW) Preexcitation Syndromes</u></p> <p><u>RECOMMENDATIONS</u></p> <p>Class I</p> <ol style="list-style-type: none"> 1. Catheter ablation of the accessory pathway is recommended in symptomatic patients with AF who have WPW syndrome, particularly those with syncope due to rapid heart rate or those with a short bypass tract refractory period. (Level of Evidence: B) 2. Immediate direct-current cardioversion is recommended to prevent ventricular fibrillation in patients with a short anterograde bypass tract refractory period in whom AF occurs with a rapid ventricular response associated with hemodynamic instability. (Level of Evidence: B) 3. Intravenous procainamide or ibutilide is recommended to restore sinus rhythm in patients with WPW in whom AF occurs without hemodynamic instability in association with a wide QRS complex on the ECG (greater than or equal to 120-ms duration) or with a rapid preexcited ventricular response. (Level of Evidence: C) <p>Class IIa</p> <p>Intravenous flecainide or direct-current cardioversion is reasonable when very rapid ventricular rates occur in patients with AF involving conduction over an accessory pathway. (Level of Evidence: B)</p> <p>Class IIb</p> <p>It may be reasonable to administer intravenous quinidine, procainamide, disopyramide, ibutilide, or amiodarone to hemodynamically stable patients with AF involving conduction over an accessory pathway. (Level of Evidence: B)</p> <p>Class III</p>

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Ref	Argument	Agency - Year	Recommendations
			<p>Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists is not recommended in patients with WPW syndrome who have preexcited ventricular activation during AF. (Level of Evidence: B)</p> <p><u>Hyperthyroidism</u> <u>RECOMMENDATIONS</u> Class I</p> <ol style="list-style-type: none"> 1. Administration of a beta blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated. (Level of Evidence: B) 2. In circumstances when a beta blocker cannot be used, administration of a nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis. (Level of Evidence: B) 3. In patients with AF associated with thyrotoxicosis, oral anticoagulation (INR 2.0 to 3.0) is recommended to prevent thromboembolism, as recommended for AF patients with other risk factors for stroke. (Level of Evidence: C) 4. Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism. (Level of Evidence: C) <p><u>Pregnancy</u> <u>RECOMMENDATIONS</u> Class I</p> <ol style="list-style-type: none"> 1. Digoxin, a beta blocker, or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response in pregnant patients with AF. (Level of Evidence: C) 2. Direct-current cardioversion is recommended in pregnant patients who become hemodynamically unstable due to AF. (Level of Evidence: C) 3. Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (except those with lone AF and/or low thromboembolic risk). Therapy (anticoagulant or aspirin) should be chosen according to the stage of pregnancy. (Level of Evidence: C) <p>Class IIb</p> <ol style="list-style-type: none"> 1. Administration of heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism. Unfractionated heparin may be administered either by continuous intravenous infusion in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value or by intermittent subcutaneous injection in a dose of 10 000 to 20 000 units every 12 h, adjusted to prolong the mid-interval (6 h after injection) activated partial thromboplastin time to 1.5 times control. (Level of Evidence: B) 2. Despite the limited data available, subcutaneous administration of low-molecular-weight heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism. (Level of Evidence: C) 3. Administration of an oral anticoagulant may be considered during the second trimester for pregnant patients with AF at high thromboembolic risk. (Level of Evidence: C) 4. Administration of quinidine or procainamide may be considered to achieve pharmacological cardioversion in hemodynamically

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Ref	Argument	Agency - Year	Recommendations
19	Atrial fibrillation	NICE - 2006	<p>stable patients who develop AF during pregnancy. (Level of Evidence: C)</p> <p><u>Hypertrophic Cardiomyopathy</u> <u>RECOMMENDATIONS</u></p> <p>Class I Oral anticoagulation (INR 2.0 to 3.0) is recommended in patients with hypertrophic cardiomyopathy who develop AF, as for other patients at high risk of thromboembolism. (Level of Evidence: B)</p> <p>Class IIa Antiarrhythmic medications can be useful to prevent recurrent AF in patients with hypertrophic cardiomyopathy. Available data are insufficient to recommend one agent over another in this situation, but (a) disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist or (b) amiodarone alone is generally preferred. (Level of Evidence: C)</p> <p><u>Cardioversion</u> <u>Electrical versus pharmacological cardioversion</u> In patients with AF without haemodynamic instability for whom cardioversion is indicated: <ul style="list-style-type: none"> • the advantages and disadvantages of both pharmacological and electrical cardioversion should be discussed with patients before initiating treatment D(GPP) • where AF onset was within 48 hours previously, either pharmacological or electrical cardioversion should be performed B • for those with more prolonged AF (onset more than 48 hours previously) electrical cardioversion should be the preferred initial treatment option. D(GPP) <u>Pharmacological cardioversion</u> In patients with persistent AF, where the decision to perform pharmacological cardioversion using an intravenous antiarrhythmic agent has been made: <ul style="list-style-type: none"> • in the absence of structural heart disease, a Class 1c drug (such as flecainide or propafenone) should be the drug of choice B • in the presence of structural heart disease (Coronary artery disease or left ventricular dysfunction), amiodarone should be the drug of choice. D(GPP) <u>Electrical cardioversion with concomitant antiarrhythmic drugs</u> When patients with AF are to undergo elective electrical cardioversion and there is cause for heightened concern about successfully restoring sinus rhythm (such as previous failure to cardiovert or early recurrence of AF), concomitant amiodarone or sotalol should be given for at least 4 weeks before the cardioversion. B</p> <p><u>Transoesophageal echocardiography-guided cardioversion</u> In patients with AF of greater than 48 hours' duration, in whom elective cardioversion is indicated: <ul style="list-style-type: none"> • both TOE-guided cardioversion and conventional cardioversion should be considered equally effective B • a TOE-guided cardioversion strategy should be considered: <ul style="list-style-type: none"> – where experienced staff and appropriate facilities are available D(GPP), and – where a minimal period of precardioversion anticoagulation is indicated due to patient choice or bleeding risks. C <u>Treatment for persistent AF</u> <u>Rate-control versus rhythm-control</u></p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>As some patients with persistent AF will satisfy criteria for either an initial rate-control or rhythm-control strategy (for example, age over 65 but also symptomatic): D(GPP)</p> <ul style="list-style-type: none"> • the indications for each option should not be regarded as mutually exclusive and the potential advantages and disadvantages of each strategy should be explained to patients before agreeing which to adopt • any comorbidities that might indicate one approach rather than the other should be taken into account • irrespective of whether a rate-control or a rhythm-control strategy is adopted in patients with persistent AF, appropriate antithrombotic therapy should be used. <p><u>A rate-control strategy</u> should be the preferred initial option in the following patients with persistent AF:</p> <ul style="list-style-type: none"> • over 65 B • with coronary artery disease B • with contraindications to antiarrhythmic drugs D(GPP) • unsuitable for cardioversion D(GPP) • without congestive heart failure. B <p><u>A rhythm-control strategy</u> should be the preferred initial option in the following patients with persistent AF:</p> <ul style="list-style-type: none"> • those who are symptomatic D(GPP) • younger patients C • those presenting for the first time with lone AF D(GPP) • those with AF secondary to a treated/corrected precipitant D(GPP) • those with congestive heart failure. C <p><u>Rhythm-control for persistent AF</u></p> <p>An antiarrhythmic drug is not required to maintain sinus rhythm in patients with persistent AF in whom a precipitant (such as chest infection or fever) has been corrected and cardioversion has been performed successfully, providing there are no risk factors for recurrence. D(GPP)</p> <p>In patients with persistent AF who require antiarrhythmic drugs to maintain sinus rhythm and who have structural heart disease:</p> <ul style="list-style-type: none"> • a standard beta-blocker should be the initial treatment option D(GPP) <p>Patients unsuitable for cardioversion include those with:</p> <ul style="list-style-type: none"> • contraindications to anticoagulation • structural heart disease (e.g. large left atrium >5.5 cm, 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 antiarrhythmic drugs or non-pharmacological approaches • an ongoing but reversible cause of atrial fibrillation (e.g. thyrotoxicosis). 6 Coronary artery disease or left ventricular dysfunction. • where a standard beta-blocker is ineffective, contraindicated or not tolerated amiodarone should be used. A <p>In patients with persistent AF who require antiarrhythmic drugs to maintain sinus rhythm and who do not have structural heart disease:</p> <ul style="list-style-type: none"> • a standard beta-blocker should be the initial treatment option D(GPP) • where a standard beta-blocker is ineffective, contraindicated or not tolerated – a Class Ic agent C or – sotalol D(GPP) should be

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>given</p> <ul style="list-style-type: none"> • where other drug classes are ineffective, contraindicated or not tolerated amiodarone should be administered. B <p><u>Antithrombotic therapy for persistent AF</u></p> <p>.....</p> <p><u>Rate-control for permanent AF</u></p> <p>In patients with permanent AF, who need treatment for rate-control:</p> <ul style="list-style-type: none"> • beta-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in all patients A • digoxin should only be considered as monotherapy in predominantly sedentary patients. D(GPP) <p>Factors indicating a high risk of AF recurrence include:</p> <ul style="list-style-type: none"> • a history of failed attempts at cardioversion • structural heart disease (mitral valve disease, left ventricular dysfunction or an enlarged left atrium) • a prolonged history of AF (>12 months) • previous recurrences of AF. <p>In patients with permanent AF, where monotherapy is inadequate: B</p> <ul style="list-style-type: none"> • to control the heart rate only during normal activities, beta-blockers or rate-limiting calcium antagonists should be given with digoxin • to control the heart rate during both normal activities and exercise, rate-limiting calcium antagonists should be given with digoxin. <p><u>Antithrombotic therapy for permanent AF</u></p> <p>In patients with permanent AF a risk–benefit assessment should be performed and discussed with the patient to inform the decision whether or not to give antithrombotic therapy. D(GPP)</p> <p>In patients with permanent AF where antithrombotic therapy is given to prevent strokes and/or thromboembolism (see section 1.8.6):</p> <ul style="list-style-type: none"> • adjusted-dose warfarin should be given as the most effective treatment A • adjusted-dose warfarin should reach a target INR of 2.5 (range 2.0 to 3.0) A • where warfarin is not appropriate, aspirin should be given at 75 to 300 mg/day B • where warfarin is appropriate, aspirin should not be coadministered with warfarin purely as thromboprophylaxis, as it provides no additional benefit. B <p><u>Treatment for paroxysmal AF</u></p> <p><u>Rhythm-control for paroxysmal AF</u></p> <p>Where patients have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a ‘no drug treatment’ strategy or a ‘pill-in-the-pocket’ strategy should be considered and discussed with the patient. D(GPP)</p> <p>In patients with symptomatic paroxysms (with or without structural heart disease¹², including coronary artery disease) a standard beta-blocker should be the initial treatment option. D(GPP)</p> <p>In patients with paroxysmal AF and no structural heart disease:</p> <ul style="list-style-type: none"> • where symptomatic suppression is not achieved with standard beta-blockers, either – a Class Ic agent (such as flecainide or propafenone) D(GPP) or – sotalol D(GPP) should be given • where symptomatic suppression is not achieved with standard beta-blockers, Class Ic agents or sotalol, either – amiodarone B or

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>– referral for non-pharmacological intervention (see section 1.9.3) A should be considered.</p> <p>In patients with paroxysmal AF and coronary artery disease:</p> <ul style="list-style-type: none"> • where standard beta-blockers do not achieve symptomatic suppression, sotalol should be given D(GPP) • where neither standard beta-blockers nor sotalol achieve symptomatic suppression, either – amiodarone B or – referral for non-pharmacological intervention A should be considered. <p>In patients with paroxysmal AF with poor left ventricular function:</p> <ul style="list-style-type: none"> • where standard beta-blockers are given as part of the routine management strategy and adequately suppress paroxysms, no further treatment for paroxysms is needed D(GPP) • where standard beta-blockers do not adequately suppress paroxysms, either – amiodarone B or – referral for non-pharmacological intervention (see section 1.9.3) A should be considered. <p>Patients on long-term medication for paroxysmal AF should be kept under review to assess the need for continued treatment and the development of any adverse effects. D(GPP)</p> <p><u>Treatment strategy for paroxysmal AF</u></p> <p>In patients with paroxysmal AF, a ‘pill-in-the-pocket’ strategy should be considered in those who: C</p> <ul style="list-style-type: none"> • have no history of left ventricular dysfunction, or valvular or ischaemic heart disease; and • have a history of infrequent symptomatic episodes of paroxysmal AF; and • have a systolic blood pressure greater than 100 mmHg and a resting heart rate above 70 bpm; and • are able to understand how to, and when to, take the medication. <p><u>Antithrombotic therapy for paroxysmal AF</u></p> <p>....</p> <p><u>Treatment for acute-onset AF</u></p> <p><u>Acute AF in haemodynamically unstable patients</u></p> <p>In patients with a life-threatening deterioration in haemodynamic stability following the onset of AF, emergency electrical cardioversion should be performed, irrespective of the duration of the AF. D</p> <p>In patients with non-life-threatening haemodynamic instability following the onset of AF:</p> <ul style="list-style-type: none"> • electrical cardioversion should be performed D • where there is a delay in organising electrical cardioversion, intravenous amiodarone should be used D • for those with known Wolff–Parkinson–White syndrome: D(GPP) – flecainide may be used as an alternative for attempting pharmacological cardioversion – atrioventricular node-blocking agents (such as diltiazem, verapamil or digoxin) should not be used. <p>In patients with known permanent AF where haemodynamic instability is caused mainly by a poorly controlled ventricular rate, a pharmacological rate-control strategy should be used. D</p> <p>Where urgent pharmacological rate-control is indicated, intravenous treatment should be with one of the following: D</p> <ul style="list-style-type: none"> • beta-blockers or rate-limiting calcium antagonists • amiodarone, where beta-blockers or calcium antagonists are contraindicated or ineffective.

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
25	Atrial fibrillation	ICSI - 2007	<p><u>Antithrombotic therapy for acute-onset AF</u> <u>Post-operative AF</u> <u>Drug prophylaxis for post-operative AF</u> In patients undergoing cardiothoracic surgery:</p> <ul style="list-style-type: none"> • the risk of post-operative AF should be reduced by the administration of one of the following: <ul style="list-style-type: none"> – amiodarone A – a beta-blocker A – sotalol A – a rate-limiting calcium antagonist B • digoxin should not be used. B <p>In patients undergoing cardiac surgery on pre-existing beta-blocker therapy, this treatment should be continued unless contraindications develop (such as post-operative bradycardia or hypotension). A Unless contraindicated, a rhythm-control strategy should be the initial management option for the treatment of post-operative AF following cardiothoracic surgery. C Unless contraindicated, post-operative AF following non-cardiothoracic surgery should be managed as for acute-onset AF with any other precipitant. D(GPP) In the prophylaxis and management of post-operative AF, the appropriate use of antithrombotic therapy and correction of identifiable precipitants (such as electrolyte imbalance or hypoxia) is recommended. D(GPP) <u>Antithrombotic therapy [.....]</u></p> <p><u>First Detected Episode Duration Known > 48 Hours or Duration Unknown</u> Key Points:</p> <ul style="list-style-type: none"> • Anticoagulation with warfarin (INR greater than or equal to 2.0 for three weeks) is recommended before electrical or pharmacologic cardioversion back to sinus rhythm. An alternative is TEE-guided cardioversion without the traditional pre-cardioversion anticoagulation, although this cannot be routinely recommended. • TEE-guided cardioversion without traditional pre-cardioversion anticoagulation cannot be routinely recommended. • Amiodarone is the most effective antiarrhythmic drug for maintenance of normal sinus rhythm. However, it also is associated with the highest potential for non-cardiac toxicity, and absolutely requires regular scheduled medical follow-ups. • ACE-inhibitors and angiotensin receptor blockers (ARBs) have an emerging role as adjunctive medical therapies to antiarrhythmic drugs for maintenance of normal sinus rhythm. <p><u>Maintenance of Sinus Rhythm Following Conversion</u> Several antiarrhythmic drugs have been demonstrated to improve sinus rhythm maintenance following cardioversion, including amiodarone, propafenone, disopyramide, sotalol, flecainide, dofetilide and quinidine (McNamara, 2003). Amiodarone has been shown to be the single most effective agent of the lot, although it also contributes the most to non-cardiac drug-related toxicity (Roy, 2000). When administered at 800 mg per day for two weeks prior to elective cardioversion, amiodarone chemically converts</p>

Arrhythmias: Atrial Fibrillation			
Ref	Argument	Agency - Year	Recommendations
			<p>one-fifth of patients with persistent AF, and when continued for eight weeks at 200 mg per day, doubled the number of patients in normal sinus rhythm at that time (Channer, 2004). Both the ACE inhibitor, enalapril, and angiotensin receptor blocker, irbesartan, have been demonstrated to enhance the maintenance of normal sinus rhythm after cardioversion when added to amiodarone (Ueng, 2003; Madrid, 2002). A meta-analysis of studies using this class of compounds has added further credence to these initial observations (Healey, 2005). Supporting evidence is of class: A</p> <p>Amiodarone is a first-line agent for patient with decompensated heart failure. Amiodarone has side effects including thyroid disease, hepatic dysfunction, lung disease, neurologic dysfunction and bradycardia and should be reserved for patients with coronary artery disease with heart failure, moderate to severe systolic dysfunction, or hypertension with significant left ventricle hypertrophy. Supporting evidence is of class: A</p> <p><u>Consultation for Treatment Options</u> Key Points:</p> <ul style="list-style-type: none"> • Patients with recurrent atrial fibrillation should be reassessed for symptoms during A Fib, side effects to treatment and review of past therapeutic results to plan future therapy. • Antiarrhythmic agents used for A Fib suppression are chosen based on risk of proarrhythmia related to underlying heart disease and potential side effects. Drugs should be used in adequate doses with the reduction of the frequency and severity of symptomatic A Fib episodes as the primary treatment goal. • Cardiac pacing may allow the use of antiarrhythmic drugs that are contraindicated due to bradycardia and also may provide definitive rate control when coupled with His ablation in patients with poorly controlled ventricular response. <p>Isthmus-dependent A Flutter can be readily controlled with radiofrequency ablation.</p> <ul style="list-style-type: none"> • Catheter-based and surgically based pulmonary vein isolation procedures show great promise in the suppression of A Fib, with better outcomes expected as techniques and experience develop. <p>Intermittent Cardioversion</p> <ul style="list-style-type: none"> • Intermittent electrical or chemical cardioversion may be considered for: infrequent recurrences, hemodynamic instability (see Annotation #6, "Hemodynamic Stabilization"), or failure of an antiarrhythmic agent. • Evaluate for potentially reversible causes. • Assess for chronic anticoagulation. • Future treatment option: implantable atrial defibrillator. <p><u>Antiarrhythmics</u> Antiarrhythmic agents should be individualized for the patient's anticipated proarrhythmia risks, based on underlying cardiac conditions and other comorbidities while attempting to minimize organ toxicity. Optimal antiarrhythmic drug therapy should be effective in reducing symptoms, preventing recurrent A Fib and should have a low incidence of toxicity and proarrhythmia. In A Fib patients without structural or organic heart disease, as demonstrated by echocardiography, exercise testing with nuclear scintigraphy or by coronary angiography, Propafenone and Flecainide are drugs of first choice. Low dose Amiodarone and Dofetilide are alternatives.</p> <p>In A Fib patients with structural heart disease including coronary artery disease, but with no evidence of heart failure, Sotalol and</p>

Arrhythmias: Atrial Fibrillation

Ref	Argument	Agency - Year	Recommendations																														
			<p>Dofetilide are drugs of first choice. Amiodarone and catheter ablation are reasonable alternatives.</p> <p>In A Fib patients with structural heart disease including coronary artery disease, but with evidence of heart failure, low-dose Amiodarone and Dofetilide are drugs of first choice.</p> <p>In patients with hypertension and evidence of significant left ventricle hypertrophy, Sotalol and Amiodarone are drugs of choice. Of note, low-dose Amiodarone has become a popular choice but still has side effects including thyroid disease, hepatic dysfunction, lung disease, neurologic dysfunction and bradycardia. Therefore, its use should be reserved for patients with structural heart disease/coronary artery disease with heart failure, moderate to severe systolic dysfunction and hypertension with significant left ventricle hypertrophy. For patients with antiarrhythmic drug therapy, monitoring for side effects such as proarrhythmia, bradycardia and other systemic side effects is essential.</p> <p>The following may guide in selection of antiarrhythmic agents:</p> <p>Table 6: Selection of Antiarrhythmic Agent by Type of Condition</p> <table border="1"> <thead> <tr> <th>Condition Type</th> <th>Normal</th> <th>Autonomic</th> <th>LVH/HCM</th> <th>MI/CAD</th> <th>DCM</th> </tr> </thead> <tbody> <tr> <td>Proarrhythmia Risk</td> <td>Low</td> <td>Low</td> <td>Moderate</td> <td>High</td> <td>High</td> </tr> <tr> <td>Choice 1</td> <td>Propafenone Flecainide</td> <td>Beta-blockers Calcium-blockers Disopyramide</td> <td>Propafenone Flecainide</td> <td>Amiodarone</td> <td>Dofetilide Amiodarone</td> </tr> <tr> <td>Choice 2</td> <td>Sotalol Dofetilide Disopyramide</td> <td>Sotalol</td> <td>Sotalol Amiodarone</td> <td>Sotalol Dofetilide</td> <td>Sotalol</td> </tr> <tr> <td>Never</td> <td>-----</td> <td>-----</td> <td>Quinidine</td> <td>Flecainide d-Sotalol</td> <td>Flecainide Disopyramide</td> </tr> </tbody> </table> <p>LVH = left ventricular hypertrophy HCM = hypertrophic cardiomyopathy DCM = dilated cardiomyopathy</p>	Condition Type	Normal	Autonomic	LVH/HCM	MI/CAD	DCM	Proarrhythmia Risk	Low	Low	Moderate	High	High	Choice 1	Propafenone Flecainide	Beta-blockers Calcium-blockers Disopyramide	Propafenone Flecainide	Amiodarone	Dofetilide Amiodarone	Choice 2	Sotalol Dofetilide Disopyramide	Sotalol	Sotalol Amiodarone	Sotalol Dofetilide	Sotalol	Never	-----	-----	Quinidine	Flecainide d-Sotalol	Flecainide Disopyramide
Condition Type	Normal	Autonomic	LVH/HCM	MI/CAD	DCM																												
Proarrhythmia Risk	Low	Low	Moderate	High	High																												
Choice 1	Propafenone Flecainide	Beta-blockers Calcium-blockers Disopyramide	Propafenone Flecainide	Amiodarone	Dofetilide Amiodarone																												
Choice 2	Sotalol Dofetilide Disopyramide	Sotalol	Sotalol Amiodarone	Sotalol Dofetilide	Sotalol																												
Never	-----	-----	Quinidine	Flecainide d-Sotalol	Flecainide Disopyramide																												

Arrhythmias: Atrial Fibrillation

Ref	Argument	Agency - Year	Recommendations
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Table 8: Comparison of Antiarrhythmic Agents to Maintain Sinus Rhythm

Scale of 1 - 5	Code for Average Costs	Cost Scale
1 = least effective / least likely	B = brand	\$ = < \$20
5 = most effective / most likely	G = generic	\$\$ = \$20 - \$50
		\$\$\$ = \$50 - \$100
		\$\$\$\$ = > \$100

	Quinidine	Procainamide	Disopyramide	Flecainide
Efficacy – Maintenance	2	2	2	3
Proarrhythmia	4	3	3	2
Duration of Inpatient Monitoring	2-3 days	Clinical discretion	Clinical discretion	Clinical discretion
Negative Inotropic Effects	2	2	5	4
Negative Chronotropic Effects	0	0	0	3
Non-Cardiac Side Effects	4	4	3	1
Average Monthly Cost	\$\$ (G) 325 mg every 8 hours	\$\$ (G) \$\$\$ (B) 500 mg SR every 6 hours	150 mg CR twice daily \$\$\$ (G) 200 mg CR twice daily \$\$\$\$ (B)	\$\$\$ (G) \$\$\$\$ (B) 100 mg twice daily
Added Concerns	GI intolerance Torsades	Drug-induced SLE Torsades especially with renal failure	Anticholinergic side effects, HF, inotropic	Proarrhythmia with CAD (CAST)

	Propafenone	Sotalol	Amiodarone	Dofetilide
Efficacy – Maintenance	2	3	4	3
Proarrhythmia	2	5	1	4*
Duration of Inpatient Monitoring	Clinical discretion	Clinical discretion	Clinical discretion	Minimum 3 days
Negative Inotropic Effects	4	4	1	1
Negative Chronotropic Effects	3	5	5	3
Non-Cardiac Side Effects	2	2	5	2
Average Monthly Drug Cost	\$\$\$\$ (B) \$\$\$\$ (G) 150 mg 3 times daily	\$\$\$\$ (B) \$\$\$ (G) 80 mg twice daily	\$\$\$\$ (B) \$\$ (G) 200 mg daily	\$\$\$\$ (B) 500 mcg twice daily
Added Concerns	Proarrhythmia with CAD	Torsades especially with renal failure Bradycardia	Systemic side effects	Torsades especially with renal failure Drug interactions

* Used per guidelines.

Information presented in this table represents a consensus statement based upon the clinical experience of ICSI Atrial Fibrillation guideline work group members.

Costs were current at the time the guideline was under revision. Practitioners should consult formularies utilized

Annex B2**Evidence Tables – Guidelines Other Arrhythmias and Amiodarone – September, 6th 2007**

References:

- Document 2: ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. Bethesda (MD): American College of Cardiology Foundation; 2002.
- Document 8: Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias. A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Bethesda (MD): American College of Cardiology Foundation; 2003.
- Document 12: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005 Aug;128(2 Suppl):1S-64S.
- Document 18: Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006;48:e247– e346.
- Document 24: National Institute for Health and Clinical Excellence. Implantable cardioverter defibrillators for arrhythmias. Review of Technology Appraisal 11. January 2006.
- Document 26: Scottish Intercollegiate Guidelines Network (SIGN). Cardiac arrhythmias in coronary heart disease. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2007 Feb.
- Document 31: Proyecto ISS – ASCOFAME. Guías de practica clinica basadas en la evidencia. Arritmias ventriculares. Colombia. Year?
- Document 32: Proyecto ISS – ASCOFAME. Guías de practica clinica basadas en la evidencia. Arritmias supraventriculares. Colombia. Year?

Arrhythmias: Other than AF

Ref	Argument	Agency - Year	Reccomendations				
08	Management of Patients With Supraventricular Arrhythmias	ACC/AHA/ESC - 2003	Recommendations for Acute Management of Hemodynamically Stable and Regular Tachycardia				
			ECG	Recommendation*	Classification	Level of Evidence	References
			Narrow QRS-complex tachycardia (SVT)	Vagal maneuvers	I	B	
				Adenosine	I	A	(4,69,90)
				Verapamil, diltiazem	I	A	(91)
				Beta blockers	IIb	C	(92,93)
				Amiodarone	IIb	C	(94)
				Digoxin	IIb	C	
			Wide QRS-complex tachycardia				
			•SVT and BBB	See above			
			•Pre-excited SVT/AF†	Flecainide‡	I	B	(95)
				Ibutilide‡	I	B	(96)
				Procainamide‡	I	B	
				DC cardioversion	I	C	
			•Wide QRS-complex tachycardia of unknown origin	Procainamide‡	I	B	(84,97)
				Sotalol‡	I	B	(85)
				Amiodarone	I	B	(25,86)
				DC cardioversion	I	B	(98)
				Lidocaine	IIb	B	(85,97)
				Adenosine§	IIb	C	(99)
				Beta blockers¶	III	C	(98)
				Verapamil**	III	B	(73)
			Wide QRS-complex tachycardia of unknown origin in patients with poor LV function	Amiodarone	I	B	(25,86)
				DC cardioversion, lidocaine	I	B	(98)
			The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.				

Recommendations for Long-Term Treatment of Patients With Recurrent AVNRT

Clinical Presentation	Recommendation	Class	Level of Evidence	References
Poorly tolerated AVNRT with hemodynamic intolerance	Catheter ablation	I	B	(189)
	Verapamil, diltiazem, beta blockers, sotalol, amiodarone	IIa	C	(189)
	Flecainide,* propafenone*	IIa	C	
Recurrent symptomatic AVNRT	Catheter ablation	I	B	(189)
	Verapamil	I	B	(203)
	Diltiazem, beta blockers	I	C	(192)
	Digoxin†	IIb	C	
Recurrent AVNRT unresponsive to beta blockade or calcium-channel blocker and patient not desiring RF ablation	Flecainide,* propafenone,* sotalol	IIa	B	(194,197-199,205,208)
	Amiodarone	IIb	C	(210)
AVNRT with infrequent or single episode in patients who desire complete control of arrhythmia	Catheter ablation	I	B	
Documented PSVT with only dual AV-nodal pathways or single echo beats demonstrated during electrophysiological study and no other identified cause of arrhythmia	Verapamil, diltiazem, beta blockers, flecainide,* propafenone*	I	C	
	Catheter ablation‡	I	B	
Infrequent, well-tolerated AVNRT	No therapy	I	C	(189)
	Vagal maneuvers	I	B	
	“Pill-in-the-pocket”	I	B	
	Verapamil, diltiazem, beta blockers	I	B	
	Catheter ablation	I	B	(227)

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

Recommendations for Treatment of Focal and Nonparoxysmal Junctional Tachycardia Syndromes

Clinical Presentation	Recommendation	Class	Level of Evidence	References
Focal junctional tachycardia	Beta blockers	IIa	C	
	Flecainide	IIa	C	(232)
	Propafenone*	IIa	C	(237)
	Sotalol*	IIa	C	(238)
	Amiodarone*	IIa	C	(239,240)
	Catheter ablation	IIa	C	(228,234-236)
Nonparoxysmal junctional tachycardia	Reverse digitalis toxicity	I	C	(242,243)
	Correct hypokalemia	I	C	
	Treat myocardial ischemia	I	C	(244)
	Beta blockers, calcium-channel blockers	IIa	C	(68,245)

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

Recommendations for Long-Term Therapy of Accessory Pathway–Mediated Arrhythmias

Arrhythmia	Recommendation	Class	Level of Evidence	References
WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Catheter ablation	I	B	(89,222,265,285)
	Flecainide, propafenone	IIa	C	(205,265-277)
	Sotalol, amiodarone, beta blockers	IIa	C	(278-282)
	Verapamil, diltiazem, digoxin	III	C	(283)
WPW syndrome (with AF and rapid-conduction or poorly tolerated AVRT)	Catheter ablation	I	B	(222,225, 284-290)
AVRT, poorly tolerated (no pre-excitation)	Catheter ablation	I	B	(222,225,284-290)
	Flecainide, propafenone	IIa	C	(205,265-277)
	Sotalol, amiodarone	IIa	C	(278-282)
	Beta blockers	IIb	C	(283)
	Verapamil, diltiazem, digoxin	III	C	(283)
Single or infrequent AVRT episode(s) (no pre-excitation)	None	I	C	
	Vagal maneuvers	I	B	
	'Pill-in-the-pocket'— verapamil, diltiazem, beta blockers	I	B	(211,212)
	Catheter ablation	IIa	B	(222,225,284-290)
	Sotalol, amiodarone	IIb	B	(278-282)
	Flecainide, propafenone	IIb	C	(205,265-277,283)
	Digoxin	III	C	
Pre-excitation, asymptomatic	None	I	C	
	Catheter ablation	IIa	B	(222,225,284-290)

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

AF indicates atrial fibrillation; AVRT, atrioventricular reciprocating tachycardia; WPW, Wolff-Parkinson-White.

Recommendations for Treatment of Focal Atrial Tachycardias*

Clinical Situation	Recommendation	Class	Level of Evidence	References
Acute treatment†				
A. Conversion				
Hemodynamically unstable patient	DC cardioversion	I	B	
Hemodynamically stable patient	Adenosine	IIa	C	(333,334)
	Beta blockers	IIa	C	(337,351)
	Verapamil, diltiazem	IIa	C	(295,339)
	Procainamide	IIa	C	
	Flecainide, propafenone	IIa	C	(335,336, 338,339)
	Amiodarone, sotalol	IIa	C	(209,303,336, 340-342)
B. Rate regulation (in absence of digitalis therapy)				
	Beta blockers	I	C	(337,351)
	Verapamil, diltiazem	I	C	(306)
	Digoxin	IIb	C	
Prophylactic therapy				
Recurrent symptomatic AT				
	Catheter ablation	I	B	(346)
	Beta blockers, calcium-channel blockers	I	C	
	Disopyramide‡	IIa	C	(342)
	Flecainide, propafenone‡	IIa	C	(335,336,339, 343,344)
	Sotalol, amiodarone	IIa	C	(209,303, 340,342)
Asymptomatic or symptomatic incessant ATs	Catheter ablation	I	B	
Nonsustained and asymptomatic	No therapy	I	C	
	Catheter ablation	III	C	

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

Recommendations for Acute Management of Atrial Flutter

Clinical Status/ Proposed Therapy	Recommendation*	Class	Level of Evidence	References
Poorly tolerated				
•Conversion	DC cardioversion	I	C	
•Rate control	Beta blockers	IIa	C	
	Verapamil, diltiazem	IIa	C	
	Digitalis†	IIb	C	
	Amiodarone	IIb	C	
Stable flutter				
•Conversion	Atrial or transesophageal pacing	I	A	(396-400)
	DC cardioversion	I	C	(391)
	Ibutilide‡	IIa	A	(383,384)
	Flecainide§	IIb	A	(387,388)
	Propafenone§	IIb	A	(387,388)
	Sotalol	IIb	C	(389,390)
	Procainamide§	IIb	A	(385)
	Amiodarone	IIb	C	(95,382)
•Rate control	Diltiazem, verapamil	I	A	(91,377-379)
	Beta blockers	I	C	(379)
	Digitalis†	IIb	C	(378)
	Amiodarone	IIb	C	(382)

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

Recommendations for Long-Term Management of Atrial Flutter

Clinical Status/ Proposed Therapy	Recommendation	Class	Level of Evidence	References
First episode and well-tolerated atrial flutter	Cardioversion alone	I	B	(391)
	Catheter ablation*	IIa	B	(427)
Recurrent and well-tolerated atrial flutter	Catheter ablation*	I	B	(424-426)
	Dofetilide	IIa	C	(406,407)
	Amiodarone, sotalol, flecainide,†‡ quinidine,†‡ propafenone,†‡ procainamide,†‡ disopyramide†‡	IIb	C	(95,405,408)
Poorly tolerated atrial flutter	Catheter ablation*	I	B	(424-426)
Atrial flutter appearing after use of class Ic agents or amiodarone for treatment of AF	Catheter ablation*	I	B	(431,432)
	Stop current drug and use another	IIa	C	
Symptomatic non-CTI-dependent flutter after failed antiarrhythmic drug therapy	Catheter ablation*	IIa	B	(450-452)

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

Recommendations for Treatment Strategies for Supraventricular Tachycardia During Pregnancy			
Treatment Strategy	Recommendation	Classification	Level of Evidence
Acute conversion of PSVT	Vagal maneuver	I	C
	Adenosine	I	C
	DC cardioversion	I	C
	Metoprolol, propranolol	IIa	C
	Verapamil	IIb	C
Prophylactic therapy	Digoxin	I	C
	Metoprolol*	I	B
	Propranolol*	IIa	B
	Sotalol,* flecainide†	IIa	C
	Procainamide	IIb	B
	Quinidine, propafenone,† verapamil	IIb	C
	Catheter ablation	IIb	C
	Atenolol‡	III	B
Amiodarone	III	C	

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

*Beta-blocking agents should not be taken in the first trimester, if possible.

18 Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

ACC/AHA/ESC - 2006

Management of Cardiac Arrest

Class I

1. After establishing the presence of definite, suspected, or impending cardiac arrest, the first priority should be activation of a response team capable of identifying the specific mechanism and carrying out prompt intervention. (Level of Evidence: B)
2. Cardiopulmonary resuscitation (CPR) should be implemented immediately after contacting a response team. (Level of Evidence: A)
3. In an out-of-hospital setting, if an AED is available, it should be applied immediately and shock therapy administered according to the algorithms contained in the documents on CPR (334,335) developed by the AHA in association with the International Liaison Committee on Resuscitation (ILCOR) and/or the European Resuscitation Council (ERC). (Level of Evidence: C)
4. For victims with ventricular tachyarrhythmic mechanisms of cardiac arrest, when recurrences occur after a maximally defibrillating shock (generally 360 J for monophasic defibrillators), intravenous **amiodarone** should be the preferred antiarrhythmic drug for attempting a stable rhythm after further defibrillations. **(Level of Evidence: B)**
5. For recurrent ventricular tachyarrhythmias or nontachyarrhythmic mechanisms of cardiac arrest, it is recommended to follow the algorithms contained in the documents on CPR (334,335) developed by the AHA in association with ILCOR and/or the ERC. (Level of Evidence: C)
6. Reversible causes and factors contributing to cardiac arrest should be managed during advanced life support, including management of hypoxia, electrolyte disturbances, mechanical factors, and volume depletion. (Level of Evidence: C)

Class IIa

For response times greater than or equal to 5 min, a brief (less than 90 to 180 s) period of CPR is reasonable prior to attempting

defibrillation. (Level of Evidence: B)

Class IIb

A single precordial thump may be considered by health care professional providers when responding to a witnessed cardiac arrest.

(Level of Evidence: C)

Sustained Monomorphic Ventricular Tachycardia

Recommendations

Class I

1. Wide-QRS tachycardia should be presumed to be VT if the diagnosis is unclear. (Level of Evidence: C)
2. Direct current cardioversion with appropriate sedation is recommended at any point in the treatment cascade in patients with suspected sustained monomorphic VT with hemodynamic compromise. (Level of Evidence: C)

Class IIa

1. Intravenous procainamide (or ajmaline in some European countries) is reasonable for initial treatment of patients with stable sustained monomorphic VT. (Level of Evidence: B)
2. Intravenous **amiodarone** is reasonable in patients with sustained monomorphic VT that is hemodynamically unstable, refractory to conversion with countershock, or recurrent despite procainamide or other agents. **(Level of Evidence: C)**
3. Transvenous catheter pace termination can be useful to treat patients with sustained monomorphic VT that is refractory to cardioversion or is frequently recurrent despite antiarrhythmic medication. (Level of Evidence: C)

Class IIb

Intravenous lidocaine might be reasonable for the initial treatment of patients with stable sustained monomorphic VT specifically associated with acute myocardial ischemia or infarction. (Level of Evidence: C)

Class III

Calcium channel blockers such as verapamil and diltiazem should not be used in patients to terminate wide-QRS-complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction. (Level of Evidence: C)

Repetitive Monomorphic Ventricular Tachycardia

Recommendations

Class IIa

Intravenous **amiodarone**, beta blockers, and intravenous procainamide (or sotalol or ajmaline in Europe) can be useful for treating repetitive monomorphic VT in the context of coronary disease (375) and idiopathic VT. (Level of Evidence: C)

Polymorphic VT

Recommendations

Class I

1. Direct current cardioversion with appropriate sedation as necessary is recommended for patients with sustained polymorphic VT with hemodynamic compromise and is reasonable at any point in the treatment cascade. (Level of Evidence: B)
2. Intravenous beta blockers are useful for patients with recurrent polymorphic VT, especially if ischemia is suspected or cannot be excluded. (Level of Evidence: B)
3. Intravenous loading with **amiodarone** is useful for patients with recurrent polymorphic VT in the absence of abnormal repolarization related to congenital or acquired LQTS. **(Level of Evidence: C)**
4. Urgent angiography with a view to revascularization should be considered for patients with polymorphic VT when myocardial ischemia cannot be excluded. (Level of Evidence: C)

Class IIb

Intravenous lidocaine may be reasonable for treatment of polymorphic VT specifically associated with acute myocardial ischemia or infarction. (Level of Evidence: C)

Incessant Ventricular TachycardiaRecommendations**Class I**

Revascularization and beta blockade followed by intravenous antiarrhythmic drugs such as procainamide or **amiodarone** are recommended for patients with recurrent or incessant polymorphic VT due to acute myocardial ischemia. (Level of Evidence: C)

Class IIa

Intravenous **amiodarone** or procainamide followed by VT ablation can be effective in the management of patients with frequently recurring or incessant monomorphic VT. (Level of Evidence: B)

Class IIIb

1. Intravenous **amiodarone** and intravenous beta blockers separately or together may be reasonable in patients with VT storm. (Level of Evidence: C)

2. Overdrive pacing or general anesthesia may be considered for patients with frequently recurring or incessant VT. (Level of Evidence: C)

3. Spinal cord modulation may be considered for some patients with frequently recurring or incessant VT. (Level of Evidence: C)

Left Ventricular Dysfunction Due to Prior Myocardial InfarctionRecommendations**Class I**

1. Aggressive attempts should be made to treat HF that may be present in some patients with LV dysfunction due to prior MI and ventricular tachyarrhythmias. (Level of Evidence: C)

2. Aggressive attempts should be made to treat myocardial ischemia that may be present in some patients with ventricular tachyarrhythmias. (Level of Evidence: C)

3. Coronary revascularization is indicated to reduce the risk of SCD in patients with VF when direct, clear evidence of acute myocardial ischemia is documented to immediately precede the onset of VF. (Level of Evidence: B)

4. If coronary revascularization cannot be carried out and there is evidence of prior MI and significant LV dysfunction, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy and those who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: A)

5. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: A)

6. The ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who present with hemodynamically unstable sustained VT, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: A)

Class IIa

1. Implantation of an ICD is reasonable in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I on chronic optimal medical therapy, and who have

- reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)
2. **Amiodarone**, often in combination with beta blockers, can be useful for patients with LV dysfunction due to prior MI and symptoms due to VT unresponsive to beta-adrenergic– blocking agents. **(Level of Evidence: B)**
 3. Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LV dysfunction due to prior MI unresponsive to beta-blocking agents. (Level of Evidence: C)
 4. Adjunctive therapies to the ICD, including catheter ablation or surgical resection, and pharmacological therapy with agents such as **amiodarone** or sotalol are reasonable to improve symptoms due to frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI. **(Level of Evidence: C)**
 5. **Amiodarone** is reasonable therapy to reduce symptoms due to recurrent hemodynamically stable VT for patients with LV dysfunction due to prior MI who cannot or refuse to have an ICD implanted. **(Level of Evidence: C)**
 6. Implantation is reasonable for treatment of recurrent ventricular tachycardia in patients post-MI with normal or near normal ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)

Class IIb

1. Curative catheter ablation or **amiodarone** may be considered in lieu of ICD therapy to improve symptoms in patients with LV dysfunction due to prior MI and recurrent hemodynamically stable VT whose LVEF is greater than 40%. **(Level of Evidence: B)**
2. **Amiodarone** may be reasonable therapy for patients with LV dysfunction due to prior MI with an ICD indication, as defined above, in patients who cannot or refuse to have an ICD implanted. **(Level of Evidence: C)**

Class III

1. Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. (Level of Evidence: B)
2. Class IC antiarrhythmic drugs in patients with a past history of MI should not be used. (Level of Evidence: A)

Dilated Cardiomyopathy (Nonischemic)

Recommendations

Class I

1. EP testing is useful to diagnose bundle-branch re-entrant tachycardia and to guide ablation in patients with nonischemic DCM. (Level of Evidence: C)
2. EP testing is useful for diagnostic evaluation in patients with nonischemic DCM with sustained palpitations, wide-QRS-complex tachycardia, presyncope, or syncope. (Level of Evidence: C)
3. An ICD should be implanted in patients with nonischemic DCM and significant LV dysfunction who have sustained VT or VF, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: A)
4. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic DCM who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)

Class IIa

1. ICD implantation can be beneficial for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)

2. ICD implantation can be effective for termination of sustained VT in patients with normal or near normal ventricular function and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)

Class IIb

1. **Amiodarone** may be considered for sustained VT or VF in patients with nonischemic DCM. (Level of Evidence: C)

2. Placement of an ICD might be considered in patients who have nonischemic DCM, LVEF of less than or equal to 30% to 35%, who are NYHA functional class I receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)

Hypertrophic Cardiomyopathy

Recommendations

Class I

ICD therapy should be used for treatment in patients with HCM who have sustained VT and/or VF and who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)

Class IIa

1. ICD implantation can be effective for primary prophylaxis against SCD in patients with HCM who have 1 or more major risk factor (see Table 7) for SCD and who are receiving chronic optimal medical therapy and in patients who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)

2. **Amiodarone** therapy can be effective for treatment in patients with HCM with a history of sustained VT and/or VF when an ICD is not feasible. (Level of Evidence: C)

Class IIb

1. EP testing may be considered for risk assessment for SCD in patients with HCM. (Level of Evidence: C)

Arrhythmogenic Right Ventricular Cardiomyopathy

Recommendations

Class I

ICD implantation is recommended for the prevention of SCD in patients with ARVC with documented sustained VT or VF who are receiving chronic optimal medical therapy and who have reasonable reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)

Class IIa

1. ICD implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, 1 or more affected family member with SCD, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)

2. **Amiodarone** or sotalol can be effective for treatment of sustained VT or VF in patients with ARVC when ICD implantation is not feasible. (Level of Evidence: C)

3. Ablation can be useful as adjunctive therapy in management of patients with ARVC with recurrent VT, despite optimal antiarrhythmic drug therapy. (Level of Evidence: C)

Class IIb

EP testing might be useful for risk assessment of SCD in patients with ARVC. (Level of Evidence: C)

HEART FAILURERecommendations

Class I

1. ICD therapy is recommended for secondary prevention of SCD in patients who survived VF or hemodynamically unstable VT, or VT with syncope and who have an LVEF less than or equal to 40%, who are receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: A)
2. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: A)
3. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)
4. **Amiodarone**, sotalol, and/or other beta blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with HF. (Level of Evidence: C)
5. **Amiodarone** is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. (Level of Evidence: B)

Class IIa

1. ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in SCD in patients with NYHA functional class III or IV, are receiving optimal medical therapy, in sinus rhythm with a QRS complex of at least 120 ms, and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)
2. ICD therapy is reasonable for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I, are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)
3. ICD therapy is reasonable in patients who have recurrent stable VT, a normal or near normal LVEF, and optimally treated HF and who have a reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: C)
4. Biventricular pacing in the absence of ICD therapy is reasonable for the prevention of SCD in patients with NYHA functional class III or IV HF, an LVEF less than or equal to 35%, and a QRS complex equal to or wider than 160 ms (or at least 120 ms in the presence of other evidence of ventricular dyssynchrony) who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)

Class IIb

1. **Amiodarone**, sotalol, and/or beta blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with HF for whom ICD therapy is not feasible. (Level of Evidence: C)
2. ICD therapy may be considered for primary prevention to reduce total mortality by a reduction in SCD in patients with

			nonischemic heart disease who have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)
31	Arritmias ventriculares	ASCOFAME – Colombia ??	<p><u>Extrasístoles ventriculares</u></p> <p>E. En caso de falla cardíaca el manejo va dirigido a mejorar la función ventricular y modular la respuesta neurohormonal. En caso de síntomas significativos por EV se considera el uso de betabloqueadores y, en caso de intolerancia, la amiodarona. No se deben usar antiarrítmicos de clase I</p> <p><u>Taquicardia ventricular sostenida</u></p> <p>Se hacen las siguientes recomendaciones:</p> <ol style="list-style-type: none"> 1. Cuando la taquiarritmia precipita hipotensión arterial, angina, falla cardíaca o síntomas de hipoperfusión cerebral, la cardioversión eléctrica sincronizada debe hacerse lo más pronto posible con carga de uno o dos joules/k; a veces la frecuencia ventricular es rápida y con complejos muy anchos, lo cual hace que la sincronización no sea posible. En estos casos se le aplica un impulso desfibrilatorio con 200 joules. A excepción de extrema urgencia y paciente inconsciente, se debe realizar sedación previa. 2. En pacientes hemodinámicamente estables puede ser manejada con fármacos. <p>3. Asociada al infarto agudo del miocardio se puede realizar uno de los siguientes tratamientos:</p> <ol style="list-style-type: none"> A. Lidocaína: dosis inicial IV de 1 - 1.5 mg/k, con dosis adicional; a los ocho minutos de 0.5 - 0.7 mg/kg - hasta una dosis de carga total de 3 mg/kg, seguido de una infusión de 2 a 4 mg/minuto. B. Procainamida: 10 - 15 mg/k administrados IV 20 - 30 mg/min., seguido por una infusión de uno a cuatro mg/minuto. C. Amiodarona: 150 mg intravenoso en 10 minutos seguido por una infusión de un mg/min., por seis horas e infusión de mantenimiento de 0.5 mg/min. D. Tosilato de bretilio 5 mg x kg peso e infusión de 1-3 mg/minuto. E. Cardioversión eléctrica sincronizada si falla el manejo farmacológico. <p>3. En pacientes con taquicardia ventricular fuera de la fase aguda del infarto, se usa procainamida y amiodarona IV</p> <p>4. La taquicardia ventricular pleomórfica en el infarto agudo del miocardio tiende a ser resistente a droga y conlleva a muy mal pronóstico. En estos casos se recomienda manejo agresivo de la isquemia miocárdica, con betabloqueador, balón de contrapulsación aórtico, revascularización con angioplastia o cirugía. La utilización de amiodarona puede ser útil; además optimizar el estado hemodinámico - hidroelectrolítico y ácido básico.</p> <p>5. Para pacientes con taquicardia ventricular sin cardiopatía isquémica, es preferible procainamida y amiodarona intravenosa.</p> <p>Prevención de recurrencia</p> <p>Después de la estabilización del paciente y conversión a ritmo sinusal, el manejo debe enfocarse a la profilaxis, problema más complejo que el manejo agudo de la taquiarritmia debido al gran riesgo de mortalidad de pacientes con taquicardia ventricular recurrente. Se hacen las siguientes recomendaciones:</p> <ol style="list-style-type: none"> 1. Tratar de corregir causas reversibles, optimizar el tratamiento de la cardiopatía de base, mejorar isquemia y mejorar la función ventricular. 2. Se justifica iniciar manejo en forma empírica con amiodarona o sotalol, dependiendo de la fracción de expulsión del ventrículo izquierdo. 3. El estudio electrofisiológico debe siempre ser considerado en el paciente con taquicardia ventricular recurrente.
32	Arritmias supraventriculares	ASCOFAME – Colombia ??	<p><u>Fibrilación auricular</u></p> <p>Se hacen las siguientes recomendaciones:</p> <ol style="list-style-type: none"> 1. Pacientes con episodio aislado con buena tolerancia hemodinámica, sin factores de riesgo ni cardiopatía estructural, la mayoría de ellos permanecen en ritmo sinusal después de la cardioversión e espontánea o inducida, por lo cual se recomienda no dar tratamiento

crónico.

2. En pacientes con disfunción sistólica del VI se deben evitar antiarrítmicos de clase I. La **amiodarona** es el fármaco preferido para revertir a ritmo sinusal; si no revierte se debe hacer el manejo corriente para insuficiencia cardíaca congestiva, con digital y anticoagulación indefinida.

3. Pacientes con cardiopatía isquémica con función sistólica conservada, la primera elección es el sotalol y la **amiodarona** como alternativa.

4. Pacientes sin cardiopatía estructural (incluyendo la presencia de hipertrofia ventricular izquierda leve) se puede utilizar propafenona, sotalol o **amiodarona**.

5. Pacientes con fibrilación auricular con conducción preferencial por una vía accesoria debe considerarse terapia ablativa. Están contraindicados verapamilo, diltiazem, digitálicos y betabloqueadores.

TAQUICARDIA AURICULAR ECTOPICA

Se hacen las siguientes recomendaciones:

1. En pacientes que no están tomando digitálicos se pueden administrar betabloqueadores y verapamilo o diltiazem para disminuir la frecuencia ventricular o para terminar la arritmia.

2. En caso de persistencia de la arritmia se puede adicionar propafenona, **amiodarona** o sotalol.

3. En pacientes que reciban digital debe sospecharse que ésta sea responsable de la arritmia. En estos casos lo prudente es retirar la droga y administrar potasio y/o magnesio. En caso de persistencia se pueden dar propranolol, fenitoína o lidocaína. Está contraindicada la cardioversión eléctrica. Si hay intoxicación digitálica la droga de elección son los anticuerpos antidigoxina (FAB).

4. En casos repetitivos la ablación con radiofrecuencia es el método ideal.

5. La mayoría de estos pacientes tienen cardiopatía estructural de base, por lo tanto hay que hacerles el diagnóstico con un ecocardiograma y el tratamiento para su enfermedad de base.

TAQUICARDIA SUPRAVENTRICULAR PAROXISTICA POR REENTRADA NODAL

se hacen las siguientes recomendaciones:

1. Las maniobras vagales son consideradas la primera línea terapéutica. Incluye el masaje al seno carotídeo, maniobras de Valsalva, Müeller, estimulación del reflejo nauseoso o exposición de la cara al agua fría (bolsas de hielo en el territorio del nervio trigémino). La taquicardia paroxística por reentrada nodal puede responder a las maniobras vagales con conversión abrupta a ritmo sinusal (o con previa disminución de la frecuencia ventricular) o no modificar la taquiarritmia. Las maniobras vagales son también de utilidad desde el punto de vista diagnóstico, porque pueden ayudar a diferenciar la reentrada nodal de otras arritmias auriculares "puras", como el flutter auricular, taquicardia auricular ectópica y hasta la fibrilación auricular con respuesta ventricular rápida (en donde es menos evidente la irregularidad RR). En estos casos las maniobras vagales disminuyen la respuesta ventricular sin lograr la conversión a ritmo sinusal, pero le permite al clínico una mejor identificación de la actividad auricular y mejor aproximación diagnóstica. Las maniobras vagales se realizan como intento terapéutico inicial y después de haber utilizado drogas.

2. La adenosina intravenosa (6 a 12 mg) administrada en forma rápida es la droga de elección. Su problema actual en el país es su poca disponibilidad y precio.

3. El verapamilo intravenoso (5 a 10 mg) en dosis fraccionada (2,5 mg cada cinco minutos) y alternando con maniobras vagales, es muy efectiva para terminar los episodios agudos.

4. Una alternativa es la utilización de betabloqueadores intravenosos. Tal vez el más utilizado es metoprolol (bolos de 2,5 mg cada cinco minutos hasta 10 ó 15 mg, o hasta que aparezcan efectos indeseables). En otros países esmolol es preferido por su corta

duración de acción. La disponibilidad en nuestro país es escasa.

5. Otra alternativa menos usada es la digitalización rápida, pero se tarda más en revertir a ritmo sinusal.

6. Si no convierte con lo anterior, se usa procainamida IV, 10 - 15 mg. kg/ peso o propafenona IV (1 mg X kg). **amiodarona** IV 5mg x kg/peso; también se puede usar sotalol IV.

7. Cardioversión eléctrica sincronizada, si se utiliza como terapia inicial con signos o síntomas de severo compromiso hemodinámico. El nivel de energía: 25 - 50 joules de descarga.

8. En caso de conseguir la conversión a ritmo sinusal no es necesaria la hospitalización del paciente.

Prevención de recurrencias

Se hacen las siguientes recomendaciones:

1. Episodios aislados (más de tres meses), con buena tolerancia hemodinámica, de breve duración, con terminación espontánea o inducidas por el paciente, no requieren de terapia a largo plazo.

2. Episodios frecuentes y/o aislados pero con compromiso hemodinámico (o sintomáticos), o de larga duración que necesitan siempre de manejo farmacológico para su terminación, se puede realizar ablación por radiofrecuencia, puesto que la relación costo-beneficio es muy importante. Además, tiene 98% de posibilidades de curación y las complicaciones son menores al 2%. Mientras se le realiza la ablación se puede manejar así: Verapamilo 240 mg/día, diltiazem 120 - 240 mg/día, propranolol 80 – 120 mg/día, metoprolol 50 - 100 mg/día, son algunos de los esquemas propuestos alternativos. Se pueden usar solos o combinados, dependiendo de la tolerancia individual.

3. En pacientes con episodios recurrentes sintomáticos o en aquellos que no deseen tomar drogas en forma indefinida o presenten efectos indeseables con ellas, debe considerarse la factibilidad de ablación con radiofrecuencia que es curativa y muy efectiva en estos casos. 4. En la actualidad, el manejo a largo plazo con quinidina, disopiramida, propafenona, **amiodarona** o sotalol no se justifica en estos casos. Debido a su potencial tóxico, antes de prescribirlos a largo plazo, debe considerarse la terapia ablativa.

Arrhythmias: particular aspects			
Ref	Argument	Agency - Year	Recommendations
02	Implantation of Cardiac Pacemakers and Antiarrhythmia Devices	ACC/AHA/NA SPE - 2002	Not specific recommendations concerning amiodarone
12	Postoperative Atrial Fibrillation After Cardiac Surgery	ACCP - 2005	<p><u>Pharmacologic Prophylaxis</u></p> <p>A number of antiarrhythmic drugs and classes of drugs have been found to demonstrate varying degrees of efficacy in preventing new-onset AF after cardiac surgery.</p> <ol style="list-style-type: none"> 1. In patients in whom prophylaxis against post-cardiac surgery AF is indicated, including those patients receiving long-term therapy with beta-blockers prior to surgery for whom therapy should be reinstated, the expert panel recommends the use of Vaughan-Williams class II beta-blockers (strength of recommendation, A; evidence grade, fair; net benefit, substantial). 2. Sotalol (Vaughan-Williams class III agent) therapy may be considered for postoperative AF prophylaxis but is associated with increased toxicity (strength of recommendation, B; evidence grade, good; net benefit, intermediate). 3. In individual patients for whom therapy with class II beta-blockers are contraindicated, therapy with amiodarone should be considered (strength of recommendation, B; evidence grade, good; net benefit, intermediate). 4. To prevent AF/AFL in patients following cardiac surgery, the expert panel recommends against the use of calcium channel antagonists (i.e., verapamil and diltiazem) (strength of recommendation, D; evidence grade, low; net benefit, none). 5. For the prevention of AF/AFL in patients following cardiac surgery, the expert panel recommends against routine treatment with magnesium (strength of recommendation, D; evidence grade, low; net benefit, none). 6. For reducing the incidence of post-surgical AF, the expert panel does not recommend digitalis for use as monotherapy (strength of recommendation, I; evidence grade, low; net benefit, none) <p><u>Pharmacologic Control of Rhythm</u></p> <p>Summary of Recommendations</p> <p>In patients who do not require emergent cardioversion, pharmacologic agents for control of postoperative AF and AFL are selected for use due to their efficacy in converting AF to normal sinus rhythm in the immediate postoperative period and in maintaining normal sinus rhythm postoperatively (see Table 4 in the chapter titled, "Pharmacologic Control of Rhythm" in the original guideline document). Antiarrhythmic drugs that are administered to maintain normal sinus rhythm are customarily continued for 4 to 6 weeks postoperatively. Because of a dearth of high-quality evidence regarding pharmacologic therapy for the maintenance of postoperative normal sinus rhythm after conversion of postoperative AF or AFL, recommendations for the pharmacologic maintenance of normal sinus rhythm postoperatively were extrapolated from recommendations for non-surgical patients with AF. In all instances, the choice of a drug or drugs to convert postoperative AF or AFL and subsequently to maintain normal sinus rhythm must be determined for each patient based on individual clinical characteristics. It is advisable to restore and maintain sinus rhythm for patients with postoperative AF or AFL that is complicated by significant symptoms or hemodynamic instability. Early cardioversion within 48 hours should be considered in patients with a contraindication to anticoagulation therapy. When these clinical conditions are absent, a strategy of rate control may be equivalent to one of rhythm control.</p>

Arrhythmias: particular aspects			
Ref	Argument	Agency - Year	Recommendations
			<p>Torsades de pointes and bradycardia are major complications of antiarrhythmic therapy. Patients should be monitored closely by continuous telemetry and should have access to a defibrillator when therapy with antiarrhythmic drugs is started during AF. Epicardial or transvenous pacing may be helpful to prevent torsades de pointes, pauses, or bradycardia.</p> <ol style="list-style-type: none"> 1. In patients with depressed left ventricular function in whom maintaining sinus rhythm is important, the expert panel recommends therapy with amiodarone (strength of recommendation, E/C; evidence grade, low; net benefit, intermediate). 2. In patients without heart failure, the expert panel recommends therapy with amiodarone, sotalol, or ibutilide, or, alternatively, class 1A agents for the conversion of AF following cardiac surgery (strength of recommendation, C [E/C for amiodarone]; evidence grade, low; net benefit, intermediate). 3. In patients with AF after cardiac surgery, the expert panel recommends 4 to 6 weeks of antiarrhythmic therapy (strength of recommendation, E/C; evidence grade, low; net benefit, small/weak). 4. In patients with AF following cardiac surgery, the expert panel cannot at this time recommend using flecainide, digoxin, or calcium channel blockers for the purpose of conversion to sinus rhythm (strength of recommendation, I; evidence grade, low; net benefit, none). 5. In patients with AF following cardiac surgery, the expert panel recommends against therapy with dofetilide and class 1C agents for conversion to sinus rhythm (strength of recommendation, D; evidence grade, low; net benefit, negative). <p><u>Pharmacologic Control of Ventricular Rate</u></p> <p>The pharmacologic management of the ventricular rate in postoperative AF or AFL patients with a rapid ventricular response is a problem that must frequently be addressed after cardiac surgery. A summary of the evidence grade, net benefit, and overall strength of the recommendations for pharmacologic agents is presented in the Table 2 in the chapter titled, "Pharmacologic Control of Ventricular Rate" in the original guideline document. The pharmacologic management of ventricular rate must be considered in the total context of the management of postoperative AF and AFL.</p> <ol style="list-style-type: none"> 1. In patients with postoperative AF and AFL who do not need urgent cardioversion and have no contraindication to anticoagulation therapy, therapy with beta-blockers is recommended as the first-line pharmacologic choice for ventricular rate control (Andrews et al., 1991; Balser et al., 1998; Maisel, Rawn, & Stevenson, 2001). This recommendation is based on a limited amount of evidence, but the recommendation is made in consideration of the hyperadrenergic state that typically exists after surgery and the effect of beta-blockers on adrenergic tone (strength of recommendation, B; evidence grade, low quality; net benefit, intermediate). 2. For patients with postoperative AF and AFL, the expert panel recommends the calcium channel blockers diltiazem and verapamil as second-line choices for ventricular rate control (strength of recommendation, B; evidence grade, low quality; net benefit, intermediate). 3. In the setting of postoperative AF or AFL, the expert panel does not consider amiodarone to be a first-line or first-alternative choice for ventricular rate control. While amiodarone may be used as an alternative to beta-blockers or calcium channel blockers, limited evidence suggests that excessive bradycardia or respiratory dysfunction (Ashrafian & Davey, 2001) may be side effects in some patients (strength of recommendation, I; evidence grade, low; net benefit, small/weak). 4. In the setting of postoperative AF or AFL, digoxin is not considered to be a first-line or first-alternative choice for

Arrhythmias: particular aspects			
Ref	Argument	Agency - Year	Recommendations
			<p>ventricular rate control. Although digoxin is widely used to treat postoperative AF and AFL, it has no effect on adrenergic tone and therefore may not be as efficacious for rate control in patients with AF or AFL. Limited evidence indicates that digoxin may not be more effective than diltiazem or amiodarone in controlling ventricular rate in patients with postoperative AF (strength of recommendation, I; evidence grade, low; net benefit, none).</p> <p>5. For the control of ventricular rate in patients with postoperative AF or AFL, the expert panel recommends against the use of any drugs that may be, or have been shown to be, proarrhythmic. While propafenone may be efficacious in controlling ventricular rate in patients with postoperative AF or AFL, it has a potential to cause bradycardia and should not be given to patients with coronary artery disease (Roy et al., 2000). Dofetilide is not considered to be efficacious and may be proarrhythmic (strength of recommendation, D; evidence grade, low quality; net benefit, negative).</p> <p>BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS</p> <p>POTENTIAL BENEFITS Appropriate management and prevention of postoperative atrial fibrillation (AF) and/or flutter (AFL) following cardiac surgery</p> <p>POTENTIAL HARMS</p> <ul style="list-style-type: none"> • Early anticoagulation therapy reduces the risk of stroke but carries the risk of bleeding and cardiac tamponade. • Sotalol and amiodarone are associated with potentially significant side effects. Sotalol therapy may result in life-threatening proarrhythmia, especially if prescribed for elderly patients with structural heart disease and with the concomitant use of diuretics in the setting of renal insufficiency. • Tables 2 and 3 of the chapter titled "Pharmacologic control of rhythm" in the original guideline document list the toxicities of drugs used for conversion of atrial fibrillation (AF) and drugs used for maintenance of sinus rhythm after conversion of AF, respectively.
24	Implantable cardioverter defibrillators for arrhythmias	NICE - 2006	Not specific recommendations concerning amiodarone
26	Cardiac arrhythmias in coronary heart disease	SIGN - 2007	<p><u>Arrhythmias Associated with Cardiac Arrest</u> Adjunctive Therapies in the Peri-Arrest Period</p> <p>D - Intravenous adrenaline/epinephrine should be used for the management of patients with refractory ventricular tachycardia/ventricular fibrillation (VT/VF).</p> <p>A - Intravenous amiodarone should be considered for the management of refractory VT/VF.</p> <p>D - Intravenous amiodarone, procainamide or sotalol should be used in the management of patients with haemodynamically stable VT.</p> <p>D - Patients with polymorphic VT should be treated with intravenous magnesium. QT interval prolonging drugs, if prescribed, should be withdrawn. If present, hypokalaemia should be corrected by potassium infusion and bradycardia by temporary pacing or isoprenaline infusion.</p>

Arrhythmias: particular aspects			
Ref	Argument	Agency - Year	Recommendations
			<p>D - Patients with cardiac arrest secondary to asystole or pulseless electrical activity should receive intravenous adrenaline/epinephrine.</p> <p>C - Atropine should be used in the treatment of patients with symptomatic bradycardia.</p> <p>D - Temporary transcutaneous pacing should be initiated quickly in patients not responding to atropine.</p> <p>D - When atropine or transcutaneous pacing is ineffective consider adrenaline/epinephrine, dopamine, isoprenaline or aminophylline infusions before transvenous pacing is instituted.</p> <p><u>Arrhythmias Associated with Acute Coronary Syndromes</u></p> <p><u>Atrial Fibrillation (AF)</u></p> <p>B - Class IC anti-arrhythmic drugs should not be used in patients with AF in the setting of acute myocardial infarction (MI).</p> <p>D - Patients with AF and haemodynamic compromise should have urgent synchronised direct current (DC) cardioversion or be considered for anti-arrhythmic and rate-limiting therapy using: Intravenous amiodarone or Digoxin, particularly in presence of severe left ventricular (LV) systolic dysfunction with heart failure.</p> <p>D - Patients with AF with a rapid ventricular response, without haemodynamic compromise but with continuing ischaemia should be treated with one of: Intravenous beta-blockade, in the absence of contraindications Intravenous verapamil where there are contraindications to beta blockade and there is no LV systolic dysfunction, Synchronised DC cardioversion</p> <p>D - Patients with AF without haemodynamic compromise or ischaemia should be treated with rate-limiting therapy, preferably a beta-blocker, and be considered for chemical cardioversion with amiodarone or DC cardioversion</p> <p><u>Arrhythmias Associated with Chronic Coronary Heart Disease/Left Ventricular Dysfunction</u></p> <p><u>Atrial Fibrillation</u></p> <p>A - Amiodarone or sotalol treatment should be considered where prevention of atrial fibrillation recurrence is required on symptomatic grounds.</p> <p>A - Rate control is the recommended strategy for management of patients with well tolerated atrial fibrillation.</p> <p>A - Ventricular rate in AF should be controlled with beta blockers, rate-limiting calcium channel blockers (<i>verapamil or diltiazem</i>), or digoxin.</p> <p>C - Digoxin does not control rate effectively during exercise and should be used as first line therapy only in people who are sedentary, or in overt heart failure.</p> <p>C - In some people a combination of drugs may be required to control heart rate in atrial fibrillation. Options include the addition of digoxin to either a beta blocker or a rate limiting calcium channel blocker.</p> <p>B - Ablation and pacing should be considered for patients with AF who remain severely symptomatic or have LV dysfunction in association with poor rate control or intolerance to rate control medication.</p> <p><u>Ventricular Arrhythmias</u></p> <p>C - Revascularisation should be considered in patients who have had sustained VT or VF.</p> <p>A - Patients with moderate to severe LV dysfunction (e.g., ejection fraction <0.35), in New York Heart Association (NYHA) class I-III at least one month after myocardial infarction should be considered for ICD therapy.</p>

Arrhythmias: particular aspects			
Ref	Argument	Agency - Year	Recommendations
			<p>B - Patients with spontaneous non-sustained ventricular tachycardia (<i>especially if sustained ventricular tachycardia is inducible</i>), severely impaired ejection fraction (<0.25) or prolonged QRS complex duration ($>120ms$) should be prioritised for ICD implantation.</p> <p>A - Patients meeting criteria for ICD implantation who have prolonged QRS duration ($>120ms$) and NYHA class III-IV symptoms should be considered for cardiac resynchronisation therapy + defibrillator (CRT-D) therapy.</p> <p>A - Patients surviving the following ventricular arrhythmias in the absence of acute ischaemia or treatable cause should be considered for ICD implantation:</p> <ul style="list-style-type: none"> • Cardiac arrest (<i>VT or VF</i>) • VT with syncope or haemodynamic compromise • VT without syncope if LVEF <0.35 (<i>not NYHA IV</i>) <p>A - Class 1 anti-arrhythmic drugs should not be used for treatment of premature ventricular beats or non-sustained VT in patients with previous MI.</p> <p>A - Long term beta-blockers are recommended for routine use in post-MI patients without contraindications.</p> <p>A - Amiodarone therapy is not recommended for post-MI patients or patients with congestive heart failure who do not have sustained ventricular arrhythmias or atrial fibrillation.</p> <p>B - Sotalol therapy is not recommended for post-MI patients who do not have sustained ventricular arrhythmias or atrial fibrillation.</p> <p>B - In patients who have recovered from an episode of sustained ventricular tachycardia (<i>with or without cardiac arrest</i>) who are not candidates for an ICD, amiodarone or sotalol should be considered.</p> <p>A - Calcium channel blocker therapy is not recommended for reduction in sudden death or all-cause mortality in post-MI patients</p> <p><u>Arrhythmias Associated with Coronary Artery Bypass Graft Surgery (CABG)</u></p> <p><u>Prophylactic Interventions</u></p> <p>A - Amiodarone may be used when prophylaxis for atrial fibrillation and ventricular arrhythmias is indicated following CABG surgery.</p> <p>A - Beta-blockers including sotalol may be used when prophylaxis for atrial fibrillation is indicated following CABG surgery.</p> <p>B - Verapamil and diltiazem may be used for prophylaxis of atrial fibrillation following CABG surgery.</p> <p>B - Digoxin should not be used for prophylaxis of atrial fibrillation following CABG surgery.</p> <p>C - Glucose-insulin-potassium regimens should not be used for prophylaxis of atrial fibrillation following CABG surgery.</p> <p>A - Magnesium may be used when prophylaxis for atrial fibrillation and ventricular arrhythmias is indicated following CABG surgery.</p> <p>A - The choice of anaesthetic agent or technique and analgesia should be based on factors other than atrial fibrillation prophylaxis.</p> <p>A - The choice of whether or not to use cardiopulmonary bypass should be based on factors other than atrial fibrillation prophylaxis.</p> <p>A - Atrial pacing may be used for prophylaxis of AF in patients who have atrial pacing wires placed for other indications.</p> <p>A - Bonded cardiopulmonary bypass circuits should not be used on the basis of AF prophylaxis alone.</p> <p>A - Defibrillators should not be routinely implanted in patients with a poor left ventricular ejection fraction at the time of coronary artery bypass graft surgery.</p> <p><u>Treatments for Atrial Fibrillation</u></p>

Arrhythmias: particular aspects			
Ref	Argument	Agency - Year	Recommendations
			<p>D - Patients with AF and haemodynamic compromise should have synchronized cardioversion.</p> <ul style="list-style-type: none"> • In the immediate postoperative period, patients with persistent AF without haemodynamic compromise should be treated with rate-limiting therapy. • Patients with persistent AF should be considered for elective synchronized cardioversion. <p><u>Treatments for Ventricular Arrhythmias</u></p> <p>D - Patients with VF or pulseless VT should be defibrillated immediately.</p> <ul style="list-style-type: none"> • Intravenous adrenaline/epinephrine should be used for the management of patients with refractory VT/VF. • Sternal reopening, internal heart massage and internal defibrillation should be considered in patients with refractory VT/VF. • Intravenous amiodarone should be considered for the management of patients with refractory VT/VF. <p>A - Biphasic defibrillation should be used to terminate ventricular fibrillation that occurs on declamping the aorta.</p> <p>BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS</p> <p>POTENTIAL BENEFITS Appropriate management of cardiac arrhythmias in coronary heart disease</p> <p>POTENTIAL HARMS Amiodarone use may be associated with serious non-cardiac side effects including pneumonitis, thyroid disorders, liver dysfunction, photosensitivity and warfarin interaction. These side effects are related to the dose and duration of exposure to the drug.</p> <p>Although use of atrial pacing avoids the potential side effects of pharmacological measures it carries an extremely small risk of tamponade and death. There are potential infection problems if wires cannot be completely removed.</p> <p>The combination of beta-blocker plus verapamil can cause severe bradycardia and should normally only be prescribed by cardiologists.</p>

Annex B3**Evidence Tables – Guidelines Chronic Heart Failure, other heart disorders and Amiodarone – September, 6th 2007**

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Heart Failure			
Ref	Argument	Agency - Year	Recommendations
01	Management of heart failure	National Heart Foundation of New Zealand - 2001	<p>Digoxin should be considered for all patients with heart failure who are in atrial fibrillation. (Strength of evidence = B) (...) Key Points (...) Additional agents such as low dose diltiazem or amiodarone may be required to control the exercise heart rate. If a betablocker is to be used for the treatment of heart failure then this may provide additional rate control</p> <p>Recommendation: In patients with AF anticoagulate with warfarin to prevent thromboembolism (INR 2.0-3.0). (<i>Strength of evidence = A</i>). Consider the need for cardioversion (will require specialist referral for cardioversion). Medical cardioversion may be achieved by amiodarone: 200mg tds for 2 weeks, 200mg bid for 2 weeks then 200mg daily (Strength of evidence = B). Anticoagulation with warfarin is required whether cardioversion is undertaken electrically or chemically. Cardioversion is recommended after 4 weeks if still in AF (success is much higher if the history of AF is less than 1 year or the left atrial diameter is less than 50mm) (Strength of evidence = C. Continue anticoagulation for a further 6-12 months while monitoring for recurrence. If AF persists consider long-term therapy with amiodarone. (Strength of evidence = C).</p>
09	The Pharmacologic Management of Heart Failure	Veterans Affairs - 2003	<p><u>Medications to avoid</u></p> <p>a) Anti-arrhythmic agents, other than β-adrenergic blockers, are not recommended to suppress asymptomatic ventricular arrhythmia or ectopy. Class I anti-arrhythmic agents have been shown to increase the risk of sudden death in patients with HF. Of the class III agents, treatment with amiodarone or dofetilide does not appear to increase the risk of death in patients with HF. Patients with ventricular arrhythmias should be referred to a cardiologist with expertise in electrophysiology for individualized treatment</p> <p>b) Most CCBs (except felodipine and amlodipine) should not be used in patients with systolic dysfunction (refer to 5.g above).</p> <p>c) Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided;^{1,2,28,29} alternative anti-inflammatory agents may be used (e.g., non-acetylated salicylates)</p>
10	Chronic Heart Failure	NICE - 2003	<p>Amiodarone: The decision to prescribe amiodarone should be made in consultation with a specialist. GPP The need to continue the prescription should be reviewed regularly. GPP Patients taking amiodarone should have a routine 6-monthly clinical review, including liver and thyroid function test, and including a review of side effects. GPP</p>
13	Diagnosis and Management of Chronic Heart Failure in the Adult	ACC/AHA - 2005	<p><u>Primary Prevention of Sudden Death [not specific explicit recommendations concerning amiodarone]:</u> ... Therefore, amiodarone should not be considered as part of the routine treatment of patients with HF, with or without frequent premature ventricular depolarizations or asymptomatic nonsustained VT; however, it remains the agent most likely to be safe and effective when antiarrhythmic therapy is necessary to prevent recurrent atrial fibrillation or symptomatic ventricular arrhythmias. Other pharmacological antiarrhythmic therapies, apart from beta-blockers, are rarely indicated in HF but may occasionally be used to suppress recurrent ICD shocks when amiodarone has been ineffective or discontinued owing to toxicity</p> <p><u>PATIENTS WITH HF WHO HAVE CONCOMITANT DISORDERS</u> <u>RECOMMENDATIONS</u> Class I 1. All other recommendations should apply to patients with concomitant disorders unless there are specific exceptions. (Level of</p>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
15	Diagnosis and treatment of chronic heart failure	ESC - 2005	<p>Evidence C)</p> <ol style="list-style-type: none"> Physicians should control systolic and diastolic hypertension and diabetes mellitus in patients with HF in accordance with recommended guidelines. (Level of Evidence: C) Physicians should use nitrates and beta-blockers for the treatment of angina in patients with HF. (Level of Evidence: B) Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina. (Level of Evidence: A) Physicians should prescribe anticoagulants in patients with HF who have paroxysmal or persistent atrial fibrillation or a previous thromboembolic event. (Level of Evidence: A) Physicians should control the ventricular response rate in patients with HF and atrial fibrillation with a beta-blocker (or amiodarone, if the beta-blocker is contraindicated or not tolerated). (Level of Evidence: A) Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina. (Level of Evidence: C) Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease. (Level of Evidence: B) <p>Class IIa</p> <ol style="list-style-type: none"> It is reasonable to prescribe digitalis to control the ventricular response rate in patients with HF and atrial fibrillation. (Level of Evidence: A) It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias. (Level of Evidence: C) <p>Class IIb</p> <ol style="list-style-type: none"> The usefulness of current strategies to restore and maintain sinus rhythm in patients with HF and atrial fibrillation is not well established. (Level of Evidence: C) The usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (Level of Evidence: B) The benefit of enhancing erythropoiesis in patients with HF and anemia is not established. (Level of Evidence: C) <p>Class III</p> <ol style="list-style-type: none"> Class I or III antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias. (Level of Evidence: A) The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular arrhythmias or to improve survival in patients with HF. (Level of Evidence: A) <p><u>Anti-arrhythmics</u></p> <p>Anti-arrhythmic drugs other than beta-blockers are generally not indicated in patients with CHF. In patients with atrial fibrillation (rarely flutter), non-sustained, or sustained ventricular tachycardia treatment with anti-arrhythmic agents may be indicated.</p> <p>Class I Anti-arrhythmics</p> <ul style="list-style-type: none"> Class I anti-arrhythmics should be avoided as they may provoke fatal ventricular arrhythmias, have an adverse haemodynamic effect, and reduce survival in heart failure (Class of recommendation III, level of evidence B) ("Preliminary report," 1989). <p>Class II Anti-arrhythmics</p>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
20	Conference recommendations on heart failure 2006: Diagnosis	Canadian Cardiovascular Society - 2006	<ul style="list-style-type: none"> Beta-blockers reduce sudden death in heart failure (Class of recommendation I, level of evidence A) (see also page 23 in the original guideline document) (López-Sendón et al., 2004). Beta-blockers may also be indicated alone or in combination with amiodarone or non- pharmacological therapy in the management of sustained or non-sustained ventricular tachyarrhythmias (Class of recommendation IIa, Level of evidence C) (Steinbeck et al., 1992). <p>Class III Anti-arrhythmics</p> <ul style="list-style-type: none"> Amiodarone is effective against most supraventricular and ventricular arrhythmias (Class of recommendation I, Level of evidence A). It may restore and maintain sinus rhythm in patients with heart failure and atrial fibrillation even in the presence of enlarged left atria, or improve the success of electrical cardioversion, and amiodarone is the preferred treatment in this condition ("Effect of prophylactic amiodarone," 1997; Levy et al., 1998). Amiodarone is the only anti-arrhythmic drug without clinically relevant negative inotropic effects. <p>Routine administration of amiodarone in patients with heart failure is not justified (Class of recommendation III, level of evidence A) (Singh et al., 1995; Bardy et al., 2005).</p> <p><u>Ventricular Arrhythmias</u></p> <ul style="list-style-type: none"> In patients with ventricular arrhythmias, the use of anti-arrhythmic agents is only justified in patients with severe, symptomatic, sustained ventricular tachycardias and where amiodarone should be the preferred agent (Class of recommendation IIa, level of evidence B) ("Effect of prophylactic amiodarone," 1997; Singh et al., 1995). ICD implantation is indicated in patients with heart failure and with life threatening ventricular arrhythmias (i.e., ventricular fibrillation or sustained ventricular tachycardia) and in selected patients at high risk of sudden death (Class of recommendation I, level of evidence A) (Moss et al., 1996, 2002; "A comparison of antiarrhythmic-drug therapy," 1997; Buxton et al., 1999, Priori et al., 2001). <p><u>Atrial Fibrillation</u></p> <ul style="list-style-type: none"> For persistent (non-self-terminating) atrial fibrillation, electrical cardioversion could be considered, although its success rate may depend on the duration of atrial fibrillation and left atrial size (Class of recommendation IIa, level of evidence B). In patients with atrial fibrillation and heart failure and/or depressed left ventricular function, the use of anti-arrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone (Class of recommendation I, level of evidence C) and, if available, to dofetilide (Class of recommendation IIa, level of evidence B) (Torp-Pederson et al., 1999). In asymptomatic patients, beta-blockade, digitalis glycosides, or the combination may be considered for control of ventricular rate (Class of recommendation I, level of evidence B). In symptomatic patients with systolic dysfunction digitalis glycosides are the first choice (Class of recommendation IIa, level of evidence C). In PLVEF, verapamil can be considered (Class of recommendation IIa, level of evidence C). Anti-coagulation in persistent atrial fibrillation with warfarin should always be considered unless contraindicated (Class of recommendation I, level of evidence C). Management of acute atrial fibrillation is not depending on previous heart failure or not. Treatment strategy is depending on symptoms and haemodynamic stability. For options see Fuster et al., 2001. <p><u>ATRIAL FIBRILLATION Recommendations</u></p> <ul style="list-style-type: none"> In patients with persistent (nonself-terminating) atrial fibrillation, electrical cardioversion may be considered, although its success rate may depend on the duration of atrial fibrillation and the left atrial size (class IIa, level B).

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
	and management		<ul style="list-style-type: none"> • In patients with atrial fibrillation and clinical heart failure or a reduced LVEF, the use of antiarrhythmic therapy to achieve and maintain sinus rhythm should be restricted to amiodarone (class I, level C). • In patients who are asymptomatic with an LVEF less than 40%, beta-blocker, digoxin or a combination may be considered for control of the ventricular rate (class I, level B). • In patients who are symptomatic with systolic dysfunction, digoxin is the first choice, and beta-blocker may be added when the patient has stabilized (class IIa, level C). • In heart failure patients with PSF, rate-limiting calcium channel blockers may be considered (class IIa, level C). • In patients with chronic atrial fibrillation, anticoagulation should always be considered and used unless contraindicated (class I, level C). <p><u>IMPLANTABLE CARDIOVERTER DEFIBRILLATOR AND CARDIAC RESYNCHRONIZATION THERAPY</u></p> <p><u>Recommendations</u></p> <ul style="list-style-type: none"> • The decision to implant a device in a heart failure patient should be made with assessment and discussion between the heart failure and arrhythmia specialists (class I, level C). • An implantable cardioverter defibrillator (ICD) should be considered in patients with ischemic heart disease with or without mild to moderate heart failure symptoms and an LVEF less than or equal to 30%, measured at least one month postmyocardial infarction and at least three months postcoronary revascularization procedure (class I, level A). • An ICD may be considered in patients with nonischemic cardiomyopathy present for at least nine months, NYHA functional class II to III heart failure, and an LVEF less than or equal to 30% (class IIa, level B) or an LVEF of 31% to 35% (class IIb, level C). • An ICD may be considered in patients with ischemic heart disease, prior myocardial infarction, three months postcoronary revascularization, left ventricular dysfunction (LVEF 31% to 35%), and with inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study (class IIa, level B), or with either no inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study or without an electrophysiology study (class IIb, level C). • An ICD should not be implanted in patients with NYHA class IV heart failure who are not expected to improve with any further therapy and who are not candidates for cardiac transplantation (class III, level C). • Antiarrhythmic drug therapy is discouraged in heart failure patients unless symptomatic arrhythmias persist despite optimal medical therapy with ACE inhibitor plus betablocker and correction of any ischemia or electrolyte and metabolic abnormalities (class I, level B).
21	Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006	National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand - 2006	<p><u>Executive summary - Key therapeutic approaches or considerations include:</u> [...]drugs to avoid include anti-arrhythmic agents (apart from beta-blockers and amiodarone), non-dihydropyridine calcium-channel antagonists (in systolic CHF), tricyclic antidepressants, non-steroidal anti-inflammatory drugs and COX-2 inhibitors, thiazolidinediones and tumour necrosis factor antagonists</p> <p><u>Recommendations for device-based treatment of symptomatic CHF</u></p> <p>Biventricular pacing (cardiac resynchronisation therapy, with or without ICD) should be considered in patients with CHF who fulfil each of the following criteria: A</p> <ul style="list-style-type: none"> • NYHA symptoms Class III–IV on treatment • dilated heart failure with LVEF $\leq 35\%$ • QRS duration ≥ 120 ms • sinus rhythm. <p>ICD implantation should be considered in patients with CHF who fulfil any of the following criteria: A</p>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
22	Comprehensive Heart Failure Practice Guideline	HFSA - 2006	<ul style="list-style-type: none"> • survived cardiac arrest resulting from ventricular fi brillation or ventricular tachycardia not due to a transient or reversible cause • • spontaneous sustained ventricular tachycardia in association with structural CHD • LVEF $\leq 30\%$ measured at least 1 month after acute MI, or 3 months after coronary artery revascularisation surgery • symptomatic CHF (i.e. NYHA functional class II–III) and LVEF $\leq 35\%$. <p><u>Atrial fibrillation and atrial flutter</u></p> <p>If it is apparent that sinus rhythm cannot be maintained for prolonged periods, therapy should be directed at controlling ventricular response rate (with digoxin, beta-blockers or amiodarone) and reducing thromboembolic risk with warfarin. For patients in whom adequate rate control cannot be achieved pharmacologically, tachycardia-mediated cardiomyopathy may lead to deterioration of CHF symptoms. For these patients, AV node ablation and permanent pacing is an important option. In this group, biventricular pacing may be better than pacing the right ventricular apex. However, this has not been tested in a randomised controlled trial (see Section 8.2 for more information).</p> <p>Prophylactic anti-arrhythmic therapy for patients with atrial fibrillation and CHF usually requires amiodarone, the most effective agent available. However, long-term effi cacy will be limited by patient intolerance and side effects. Sotalol is an alternative, particularly when LV function is only mildly impaired. However, it is associated with a 1–3% incidence of ventricular proarrhythmia, and effi cacy at one year is only 40–50%.</p> <p><u>Ventricular tachycardia and ventricular fi brillation</u></p> <p>Large randomised studies of amiodarone therapy versus placebo have not shown any survival benefit with the drug for primary prevention in high-risk patients.</p> <p>Treatment with sotalol or amiodarone may be required in 20–70% of ICD recipients to reduce frequency of ventricular tachycardia and shocks. Radiofrequency ablation is suitable for some patients with recurrent ventricular tachycardia to reduce ICD shock frequency.</p> <p>Therapy with class I anti-arrhythmic agents (e.g. flecainide) is generally contraindicated in the presence of systolic heart failure.</p> <p><u>Antiarrhythmic Agents</u></p> <p>Ventricular arrhythmias are common in HF patients, and sudden cardiac death continues to account for a significant proportion of the mortality in this syndrome. Despite the obvious clinical need, antiarrhythmic drug therapy remains ineffective at reducing mortality in patients with HF. Furthermore, virtually all antiarrhythmic agents have been shown to have adverse hemodynamic effects sufficient to have negative consequences in patients with HF.</p> <p>7.39 Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with HF. (Strength of Evidence = A)</p> <p>7.40 In patients with HF and an implantable cardioverter defibrillator (ICD), amiodarone may be considered to reduce the frequency of repetitive discharges. (Strength of Evidence = C)</p> <p>7.41 It is recommended that patients taking amiodarone therapy and digoxin or warfarin generally have their maintenance doses of many commonly used agents, such as digoxin, warfarin, and statins, reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)</p>
23	Heart Failure in Adults	ICSI - 2006	<p><u>Antiarrhythmics</u></p> <p>Only amiodarone and dofetilide have been shown to be mortality neutral when treating arrhythmias in patients with heart failure</p>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
27	Management of Chronic Heart Failure	SIGN - 2007	<u>Implantable cardioverter defibrillator (ICD)</u> improves mortality in patients with ischemic and nonischemic heart disease with LV ejection fraction of less than 30%, regardless of symptoms or arrhythmias. ICD without CRT does not improve symptoms or reduce hospitalization from heart failure. Not specific recommendations concerning amiodarone

Other heart disorders			
Ref	Argument	Agency - Year	Recommendations
07	Hypertrophic Cardiomyopathy	ACC/ESC 2003	... Combined therapy with disopyramide and amiodarone (or disopyramide and sotalol), or quinidine and verapamil (or quinidine and procainamide), should also be avoided due to concern over proarrhythmia <u>Sudden Risk Death Prevention</u> ... low-dose (less than 300 mg) amiodarone has been associated with improved survival in HCM, but this agent requires careful monitoring and may not be tolerated due to its potential toxicity over the long risk periods incurred by young patients ... There is, at present, an understandable reluctance on the part of pediatric cardiologists to implant such devices chronically in children (particularly for primary prevention) considering the necessary, ongoing commitment required for maintenance and the likelihood that lead or other (ICD-related) complications will occur over very long time periods. However, while adolescence may represent a psychologically difficult age to be encumbered by an ICD, it should also be emphasized that this is coincidentally the period of life consistently showing the greatest predilection for SCD in HCM. One alternative but empiric strategy proposed for some very young high-risk children is the administration of amiodarone as a bridge to later ICD placement after sufficient growth and maturation has occurred. Some investigators also regard the end-stage phase of HCM as a risk factor for SCD, justifying implantation of a cardioverter defibrillator during the waiting period prior to the availability of a heart for transplant. <u>Atrial fibrillation</u> ... Although comparative data regarding the efficacy of antiarrhythmic drugs are not available for HCM patients, amiodarone is generally regarded as the most effective antiarrhythmic agent for preventing recurrences of AF, based largely on extrapolation from its use in other heart diseases.
28	Management of valvular heart disease	ESC 2007	<u>Perioperative monitoring</u> Valvular patients submitted to moderate or high-risk nonsurgical procedures need particular perioperative care, especially ensuring that systemic hypotension or volume depletion or overload is avoided. Particular attention should be paid to avoid hypotension in patients with AS. In patients with moderate-to-severe AS or MS, betablockers or amiodarone can be used prophylactically in order to maintain sinus rhythm in the postoperative period. Whether the beneficial role of beta-blockers on cardiovascular mortality before major vascular surgery applies to valvular patients is not known. It is prudent to electively admit such patients to intensive care postoperatively even if they appear to be doing well.
29	Risk estimation and the prevention of cardiovascular disease	SIGN 2007	Not specific recommendations concerning amiodarone

Annex B4**Evidence Tables – Toxicity and Amiodarone – September, 6th 2007**

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Toxicity			
Ref	Argument	Agency - Year	Recommendations
03	Evaluation and treatment of hyperthyroidism and hypothyroidism	American Association of Clinical Endocrinologists - 2002	<p><u>Patients Taking Amiodarone</u></p> <p>Amiodarone therapy causes thyroid dysfunction in 14 to 18% of the involved patients. Therefore, before initiation of such therapy, patients should have a baseline TSH measurement, and then they should be monitored at 6-month intervals during treatment. In patients receiving amiodarone, either hypothyroidism, which is treated with levothyroxine replacement, or hyperthyroidism may develop. Amiodarone-induced hyperthyroidism is of two types. Type 1 is similar to iodine-induced hyperthyroidism (jodbasedow phenomenon) and manifests with a low TSH level, a high free T4 or T3 estimate, and a low radioiodine uptake. Doppler ultrasonography shows increased vascularity of thyroid tissue, similar to that in Graves' disease. Because of low radioiodine uptake, 131I treatment cannot be used, and use of antithyroid drugs has yielded only varied success. Although mild cases have resolved even when amiodarone therapy has been continued, consideration of ceasing this drug treatment is recommended. Restoration of euthyroidism may take months after cessation of amiodarone therapy. Type 2 amiodarone-induced hyperthyroidism resembles a destructive thyroiditis. Laboratory values and radioiodine uptake are similar to the findings in type 1; however, Doppler ultrasonography shows decreased vascularity of the thyroid tissue. Corticosteroid treatment is recommended, and patients sometimes require surgical removal of the thyroid.</p>
04	Laboratory support for the diagnosis and monitoring of thyroid disease.	National Academy of Clinical Biochemistry - 2002	<p><u>Guideline 5. Patients taking Amiodarone Medication</u></p> <p>Amiodarone therapy can induce the development of hypo- or hyperthyroidism in 14-18% of patients with apparently normal thyroid glands or with preexisting abnormalities.</p> <ul style="list-style-type: none"> • Pretreatment. Thorough physical thyroid examination together with baseline TSH and TPOAb. FT4 and free triiodothyronine (FT3) tests are only necessary if TSH is abnormal. Positive TPOAb is a risk factor for the development of thyroid dysfunction during treatment. • First 6 months. Abnormal tests may occur in the first six months after initiating therapy. TSH may be discordant with thyroid hormone levels (high TSH/highT4/low T3). TSH usually normalizes with long-term therapy if patients remain euthyroid. • Long-term follow-up. Monitor thyroid status every 6 months with TSH. Serum TSH is the most reliable indicator of thyroid status during therapy. • Hypothyroidism. Preexisting Hashimoto's thyroiditis and/or TPOAb-positivity is a risk factor for developing hypothyroidism at any time during therapy.

Toxicity			
Ref	Argument	Agency - Year	Recommendations
05	Refractive Errors	American Academy of Ophthalmology - 2002	<ul style="list-style-type: none"> Hyperthyroidism. Low serum TSH suggests hyperthyroidism. T3 (total and free) usually remains low during therapy but may be normal. A high T3 is suspicious for hyperthyroidism. <p>Two types of amiodarone-induced hyperthyroidism may develop during therapy, although mixed forms are frequently seen (20%). Distinction between two types is often difficult. Decreased flow on color flow doppler and elevated interleukin-6 suggests Type II. Direct therapy at both Type I and II if etiology is uncertain.</p> <p>Type I = Iodine-induced. Recommended treatment = simultaneous administration of thionamides and potassium perchlorate (if available). Some recommend iopanoic acid before thyroidectomy. Most groups recommend that amiodarone be stopped. Seen more often in areas of low iodine intake. However, in iodine-sufficient areas, radioiodine uptakes may be low precluding radioiodine as a therapeutic option. In iodide-deficient regions, uptakes may be normal or elevated. Type a: Nodular goiter. More common in iodine-deficient areas, i.e. Europe. Type Ib: Graves' disease. More common in iodine-sufficient areas, i.e. United States.</p> <p>Type II = amiodarone-induced destructive thyroiditis--a self-limiting condition. Recommended treatment = glucocorticoids and/or beta-blockers if cardiac status allows. When hyperthyroidism is severe, surgery with pre-treatment with iopanoic may be considered. Radioiodine uptake is typically low or suppressed. Type II is more commonly seen in iodine-sufficient areas.</p> <p><u>Photorefractive Keratectomy</u> <u>Relative Contraindications</u> Certain systemic medications (e.g., isotretinoin, amiodarone, sumatriptan, levonorgestrel implants, colchicine)</p> <p><u>Laser In Situ Keratomileusis</u> <u>Relative Contraindications</u> Certain systemic medications (e.g., isotretinoin, amiodarone, sumatriptan, levonorgestrel implants, colchicine)</p>
30	Investigation and Management of Primary Thyroid Dysfunction	Clinical Practice Guideline Working Group – Canada - 2007	<p><u>RECOMMENDATIONS</u></p> <p>TSH is the single best initial test for the diagnosis of primary hyperthyroidism and hypothyroidism</p> <ul style="list-style-type: none"> When patients are asymptomatic, seemingly healthy, having a periodic examination, NO testing is required When patients have suspected primary thyroid disease follow Category 1 When patients are taking thyroid hormone replacement and dosage needs monitoring follow Category 2 When patients are receiving thyroxine therapy for thyroid cancer follow Category 3 When patients are pregnant and receiving thyroid hormone replacement follow Category 4 When patients are receiving lithium or amiodarone follow Category 5a or 5b

Toxicity			
Ref	Argument	Agency - Year	Recommendations
			<p>CATEGORY 5B: PATIENTS RECEIVING AMIODARONE</p> <ul style="list-style-type: none"> Amiodarone may cause elevated FT4 in the presence of normal TSH (drug effect) Therefore, pretreatment TSH and 3 month post treatment TSH, FT4, and FT3/FT3I are recommended <pre> graph TD A(TSH at baseline) --> B(Normal) A --> C(Abnormal) C --> D(Follow Category 1 Algorithm) B --> E(Commence Therapy) E --> F(3 month TSH, FT4, FT3/FT3I) F --> G(FT4, FT3/FT3I abnormal - see note above TSH abnormal) F --> H(Normal) H --> I(Repeat TSH every 6-12 months) G --> J(CONSULTATION RECOMMENDED DO NOT FOLLOW CATEGORY 1 ALGORITHM) </pre>

Appendix C

PUBMED (21/08/2007): 32 records

("Amiodarone"[Mesh]) AND ("Heart Failure, Congestive"[Mesh]) Limits: Randomized Controlled Trial

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