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Reviews

Unexpected Instant Death Following Successful Coronary Artery Bypass Graft Surgery (and Other Clinical Settings): Atrial Fibrillation, Quinidine, Procainamide, et cetera, and Instant Death

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Summary: *Primum non nocere.* Atrial fibrillation (AF) occurs commonly following coronary artery bypass graft surgery, although new onset atrial fibrillation in this setting is usually transient. When AF reverts or is converted to sinus rhythm it is unlikely to recur, whether or not the patient takes preventive medication. As no benefit (and sometimes increased risk) associated with reduced mortality or morbidity in this setting has been reported for antiarrhythmic agents, standard treatment should consist of observation or control of ventricular response with an appropriate agent until AF relapses to sinus rhythm. If an antiarrhythmic agent, especially a class I agent, is used because of persistent or recurrent AF in the early postoperative period, heart rhythm should be monitored as long as the class I agent is administered and treatment initiated if an undersirable rhythm develops. Atrial fibrillation in other clinical settings in patients with structural heart disease presents a more difficult management problem. Class I agents are reported to be associated with an increased risk of death, despite an efficacious effect of maintaining sinus rhythm. Amiodarone is reported to be well tolerated with respect to the cardiovascular system, but unacceptable noncardiac effects are reported. A safe amiodarone-like agent is greatly needed. Atrial fibrillation in patients with no structural heart disease is not discussed in this presentation.

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Coronary Artery Bypass Surgery

The Problem

Have you had a patient who was doing well after coronary artery bypass graft (CABG) surgery and then collapsed and died instantly just before planned hospital discharge or in the days or weeks after discharge? "Damned bad luck!" Or was it, "just bad luck?" Could it have been "bad treatment?" The patient had had a brief episode of atrial fibrillation in the early postoperative period and had responded to medication (quinidine, procainamide, or another class I agent of the Singh, Vaughn Williams classification of antiarrhythmic drugs[1,2]) by returning to sinus rhythm. The patient had been maintained on the same medication; discontinuance was planned in the next several weeks or months.

Atrial fibrillation (AF) commonly develops in the first days (2 to 4 days being the most common) after CABG, occurring in 8 to 40% of patients.[3–8] The managing physician often feels compelled to treat this arrhythmia despite the fact that sinus rhythm spontaneously returns within hours in many patients. In the report by Frost *et al.*[9] to study the efficacy of the new antiarrhythmic agent, dofetilide, in the acute termination of early postoperative AF or flutter, 21% (8/33) of patients receiving placebo reverted to sinus rhythm within 3 h. In the excellent review by Viskin *et al.*[10] it is pointed out that "perioperative AF is frequently brief" and that it is not surprising that many drugs have been found to be effective for terminating perioperative AF.[11] After the antiarrhythmic agent has been started and the rhythm has returned to a sinus mechanism, it is tempting to continue the agent, at least for a short period (weeks or months), in an effort to prevent the recurrence of AF.[11] This reasoning is flawed for several reasons: (1) AF complicating

the postoperative period, once reverted or converted to sinus rhythm, is unlikely to recur (if the patient had not been plagued by this disordered rhythm preoperatively); (2) class I antiarrhythmic drugs have many undesirable effects, the most important of which are the so-called "proarrhythmic" effects, including ventricular tachycardia and ventricular fibrillation; (3) class I drugs can have other serious and sometimes life-threatening adverse effects such as thrombocytopenia, agranulocytosis, allergies, lupus-like syndromes, gastrointestinal disturbances, and others; (4) quinidine, procainamide, and all other class I antiarrhythmic agents depress myocardial function; (5) these agents may confuse the medication program, may interact with other drugs, and are not inexpensive.

There is still another persuasive reason not to put a patient in sinus rhythm (after reversion from AF in the early postoperative period) on any agent with proarrhythmic and life-threatening potential: With extremely rare exception, relapse into AF is not critical in patients recovering from CABG. On the other hand, ventricular fibrillation induced by the antiarrhythmic agent can, indeed, be fatal.

Documentation

Let's review the data that address items 1–5 presented above:

1. Frequency of relapse into atrial fibrillation after reversion/conversion to sinus rhythm postoperatively: Few studies directly attempt to answer the question: Once AF has reverted to or has been converted to sinus rhythm in the early postoperative period, what is the likelihood that it will reappear or continue indefinitely and what methods (drugs or otherwise) should be used to prevent its recurrence or continuation in the next several weeks or months?

Yilmaz *et al.*,[12,13] at the Gulhane Military Medical Academy, Ankara, Turkey, found placebo comparable to any study medication in preventing recurrence of AF. In the study reported in 1996,[12] the relapse rate within 90 days of surgery was 1 of 30 patients taking a placebo, 2 of 30 taking quinidine fumarate, 2 of 30 taking verapamil, and 2 of 30 taking amiodarone. In the study reported in 1997,[13] they found that only 1 patient of 20 receiving no antiarrhythmic medications relapsed to AF within 90 days after discharge from the hospital. Two of 20 patients taking quinidine fumarate and 2 of 20 taking acebutolol relapsed into AF.

Landymore and Howell,[14] at the Dalhousie University in Halifax, Nova Scotia, Canada, also found that AF "rarely recurred following discharge from the hospital and was never symptomatic." Of the 43 patients who experienced AF in the early postoperative period and underwent 24-h Holter monitoring 3 weeks post discharge, only 1 patient had a long run of AF lasting 518 beats (about 7 min), which was asymptomatic and reverted spontaneously to sinus rhythm. Four other patients had very short runs of AF, all of which lasted for < 22 beats and all of which were asymptomatic. They[14] recommended that patients who had AF following surgery be placed on digoxin (to control the ventricular response) and that it be discontinued at 3 weeks after discharge.

Many studies exist concerning prevention of the development of AF in the early postoperative period; these include studies of the use of class I, II, and III agents.[8,15–20] However, none of these studies addresses prevention of recurrence of AF or the prevention of sudden (instant) death in the late-hospital or early postdischarge periods. The report by Dagud *et al.*[8] comparing amiodarone with placebo for the prevention of postoperative AF, did give some follow-up information. Of 60 patients who received placebo, 7 developed AF at a mean of 12 ± 5 days after discharge. However, in the placebo-treated group, 32 of 60 patients had valvular heart surgery; only 24 of 60 had isolated coronary artery surgery. It is possible that all seven of the patients who developed AF postoperatively had had valvular heart surgery and that none of the patients who had isolated coronary surgery developed postoperative AF. In addition, this report indicates that all patients were in sinus rhythm at the time of the return visit to the cardiac-surgery outpatient clinic at 24 ± 9 days after discharge.

In one study[21] reviewing the causes for readmission to the hospital within 30 days of discharge after CABG, AF was found to be the indication for readmission in 13% of the 110 rehospitalized patients. Hence, AF certainly can be an important undesirable postdischarge event. When comparing the 110 patients who were readmitted with 224 matched patients who were not readmitted, the use of antiarrhythmic agents at the time of discharge from the hospital was associated with an increased risk of being readmitted to the hospital. It was not reported whether the antiarrhythmic agents were being given for AF or other arrhythmias and it was not reported whether AF was the indication for readmission in the patients taking antiarrhythmic agents. Mortality was not presented in this report. It is interesting that the use of beta blockers at the time of discharge was associated with a reduced risk of rehospitalization. Unfortunately, this report does not present the denominator—110 patients were readmitted from *how many* patients who were discharged after CABG during the study period of October 1, 1991, through September 30, 1994?

2. Proarrhythmias: In 1964, Selzer and Wray[22] brought to our attention the possibility that patients who are treated with quinidine, the most commonly used class I antiarrhythmic agent,[23] for the prevention of recurrence of AF might develop serious ventricular arrhythmias, syncope, and sudden death.

Subsequently there have been other reports of serious ventricular arrhythmias developing in patients who are given class I antiarrhythmic agents for purpose of preventing the recurrence of AF. In the nonrandomized study by Radford and Evans,[24] there were two deaths and one new episode of sustained arrhythmia in 34 patients receiving quinidine, whereas there were no deaths in 83 patients who received no antiarrhythmic agents.

A meta-analysis by Coplen *et al.*[25] of studies of patients randomly assigned to quinidine or placebo to prevent recurrence of AF after cardioversion indicated that patients taking quinidine were three times more likely to die in the 12 months after cardioversion than patients taking placebo. The increased risk of death was present despite the finding that quinidine was su-

perior to placebo in preventing the recurrence of AF at 3, 6, and 12 months.

In the Stroke Prevention in Atrial Fibrillation Study (SPAF),[26] the cardiac mortality rate in patients taking class I antiarrhythmic agents (mostly quinidine) was approximately two-and-one-half times higher than the mortality in patients not taking such drugs. The difference in cardiac mortality was limited to patients with a history of heart failure and was not seen in patients without such history. This study had not been designed to evaluate the influence of antiarrhythmic agents on mortality, and patients were not randomized between antiarrhythmic agents and no antiarrhythmic agents.

Stevenson *et al.*[27] reported that patients with heart failure and AF treated primarily with amiodarone and angiotensin-converting enzyme inhibitors had a markedly better 2-year survival and sudden death-free survival than those treated primarily with class I antiarrhythmic agents and hydralazine during a 2-year follow-up period. It is interesting that Stevenson entitled the article "Improving Survival for Patients with Atrial Fibrillation and Advanced Heart Failure" and concluded that the best way to improve survival was to avoid class I antiarrhythmic drugs.

Faber *et al.*[28] report life-threatening arrhythmias in three patients treated with quinidine, quinidine and sotalol, or sotalol and amiodarone for AF. Two of these patients required electrical defibrillation.

There are no reports of large series of patients who are treated with procainamide or disopyramide to prevent recurrence of AF. However, there are many reports of the association of these drugs with ventricular tachyarrhythmias.[29–32]

There are fewer data about flecainide (a class IC agent); The Flecainde Supraventricular Tachycardia Study Group[33] reported that there was one death among the approximately 50 patients treated with flecainide and no deaths in the placebo group. In this study, seven cardiac adverse effects were observed in the flecainide-treated group; three of the patients taking flecainide had to be withdrawn from the study because of adverse cardiac arrhythmias. The Flecainide Multicenter Atrial Fibrillation Study Group[34] reported no deaths within 1 year among the 122 patients treated with flecainide and "no life-threatening proarrhythmic response . . . was observed." Nevertheless, of the 122 patients in the flecainide group, "3 patients had transient wide QRS tachycardia, 2 had sinus pauses, 1 had the development of nonsustained ventricular tachycardia, and 1 had unexplained syncope." The two Flecainide Studies were funded by a pharmaceutical company; Stelfox *et al.*[35] pointed out their concern about a possible conflict of interest in such studies and reports.

Falk[36] has reported three patients who developed ventricular tachycardia and fibrillation while taking flecainide for AF; one of these died.

In Denmark, Sihm *et al.*[37] report that severe arrhythmogenic events occurred within 5 days in 7 of 100 patients treated with flecainide, and in 2 patients after 60 and 240 days of flecainide treatment, respectively. All of these patients were without severe heart failure. One patient died at home 5 days after the initiation of flecainide and five patients were resuscitated successfully—ventricular fibrillation in two, ventricular tachycardia in two, and asystole in one.

There are no reports in the literature that indicate that patients taking class I antiarrhythmic agents for the purpose of preventing the recurrence of AF have a lower mortality than similar patients taking no antiarrhythmic agents or taking a placebo.

3. Other undesirable effects of class I antiarrhythmic agents: Serious allergic-immune reactions can occur with any of the class I antiarrhythmic agents. The most common reaction is the lupus-like syndrome that develops in a significant number of patients who take procainamide for any period of time.[38,39] This sometimes can cause serious renal, pulmonary, and cardiac disorders. Thrombocytopenia,[40] agranulocytosis, aplastic anemia, and other blood element disorders have all been reported with the class I antiarrhythmic agents. Intolerance, including gastrointestinal disturbance (especially with quinidine), blurred vision, dry mouth, and others is also seen with most of the agents.

4. Myocardial depression by antiarrhythmic agents: All class I antiarrhythmic agents depress myocardial function. While not all patients undergoing CABG have impaired left ventricular function, many, if not most, do. Acute myocardial infarction is an uncommon but not rare complication of CABG. The use of class I antiarrhythmic agents has been shown to increase the risk of death in patients who have had a recent myocardial infarction.[41]

5. Unnecessary drugs: It is self-evident that the medication program of any patient should be kept as simple as possible. Why give a drug that has not been shown to be necessary, that is potentially dangerous, that is poorly tolerated by many, that further complicates a confusing medication program, and that is expensive? *Primum non nocere.* These patients may be taking aspirin, a beta blocker, a lipid-lowering agent, and possibly a peripheral arterial dilator.

Possible Solutions

The standard of care for the patient who develops transient AF in the first several days following CABG should consist of regular observation and screening for the return of AF. No antiarrhythmic agent need be given.

Atrial fibrillation that develops in the early postoperative period and does not revert spontaneously in a short period of time usually needs to be managed. Management options include the following:

1. Control of the ventricular response with digoxin, beta blockers, and/or calcium-channel blocking agents. The positive inotropic effect of digoxin makes this an attractive option. The Canadian Cardiovascular Society Consensus Conference on Atrial Fibrillation[11] recommended that digoxin be given. Essentially all patients returned to sinus rhythm without the use of other antiarrhythmic agents. Others[7] find that digoxin is not very effective in slowing the ventricular response in the early postoperative period and suggest the use of a beta

blocker or a calcium-channel blocking agent. Davison *et al.*[42] warn that verapamil, while effectively slowing ventricular response, was associated in this setting with a high incidence of unacceptable hemodynamic side effects. In their study, 13 of 100 patients assigned to the verapamil arm of the study developed hypotension, pulmonary edema, or both, while only 1 patient in the placebo arm experienced these hemodynamic complications. Diltiazem may be better tolerated, but neither verapamil nor diltiazem are efficacious for long-term use to control the ventricular response to AF.[43] Olshansky[44] has reported that beta blockers are especially effective in this setting. These patients will often convert to sinus rhythm a day or so later, probably spontaneously, but possibly in part due to the digoxin, beta blocker, or calcium-channel blocker.

2. A class I agent could be administered in an attempt to convert AF to sinus rhythm, usually after one of the drugs that slow atrioventricular conduction has been established. However, the patient should be in a monitored unit while these agents are being given so that any serious arrhythmias that develop can be detected and treated immediately.

3. Amiodarone could be given in an attempt to convert the patient to sinus rhythm.[45–47] Following conversion to sinus rhythm, amiodarone can be continued in an effort to prevent recurrence of AF.[48,49] Sotalol has been proven to be of little value as an agent to convert AF to sinus rhythm[50] despite its effectiveness at preventing recurrence of AF once sinus rhythm has been restored.

4. Electrical reversion to sinus rhythm may be necessary. A class I agent could be given following conversion, but the patient should remain in the monitored unit for as long as these agents are given. Again, amiodarone is a possible alternative after electrical cardioversion, especially if it is anticipated that the drug must be continued for several weeks.[48,49]

5. Anticoagulation therapy should be added if AF persists for more that 24–72 h.[7,51–54]

Conclusions

Patients who develop AF in the early postoperative period after CABG and who revert spontaneously, who convert after the introduction of an antiarrhythmic agent, or who are converted with electrical cardioversion, will remain in sinus rhythm indefinitely on no antiarrhythmic treatment in most instances. This should be considered the standard of care. The rare patient who does not follow this pattern should be managed as any patient with recurrent or chronic AF complicating any structural heart disease, as discussed immediately below.

Atrial Fibrillation in Patients with Structural or Organic Heart Disease

The patient with structural heart disease who has a single, transient episode of AF (or extremely rare recurrence) and who reverts spontaneously or converts easily with an antiarrhythmic agent or electrical cardioversion should be managed in the same way as one who has a transient episode of AF following CABG. Many such patients, without medication, will experience no further episodes within a year or more. The general health program should be checked to ensure that the patient is not hyperthyroid, taking an excessive dose of thyroid replacement drug, using gross amounts of caffeine, or taking excessive amounts of drugs which contain sympathomimetic agents, and so forth.

However, for those patients who relapse into AF and require a second, third, or more conversions, or for those patients who have had AF for a long time and who are being converted to sinus rhythm with drugs or electrically, the problem is entirely different. These patients are likely to redevelop AF following conversion if methods cannot be applied to prevent the recurrences.

Persistent AF is not a desirable rhythm for a host of reasons:[55,56] the patient does not feel as well in AF due to palpitations, fatigue, a sense of ill feeling, shortness of breath at rest or on exercise, symptoms of inadequate cerebral perfusion, and other symptomatic problems. In addition, the patient in AF is at increased risk of systemic emboli, the most devastating of which are those to the brain. Patients with AF, especially those with a rapid ventricular response at rest and/or on mild exercise, are liable to develop a cardiomyopathy due to arrhythmia.[56–58] The overall risk of death for patients in AF is twice that of a group of matched patients in sinus rhythm.[59,60] Hence, AF is an undesirable rhythm and there are many reasons for converting to and maintaining sinus rhythm in most patients.

Unfortunately, all the treatments that are effective in preventing the recurrence of AF have undesirable side effects. One must ask which is worse—the treatment or the disease?

An excellent discussion of the possible answers to this question is presented by Grace and Camm[61] in the Drug Therapy section of the January 1, 1998, issue of the *New England Journal of Medicine*. They review the problems of patient selection and study design, and thus the inconclusiveness, of the reports by Coplen *et al.*[25] and Flaker *et al.*[26] mentioned above. These two studies indicate that patients treated with class I agents to prevent recurrence of AF actually had a higher overall mortality than patients not taking such drugs. Grace and Camm[61] concluded that "quinidine may still have a role in the prophylactic treatment of AF, although we anticipate that it will increasingly be used as a second-line drug." Whenever quinidine is given, the possibility of proarrhythmia and interactions with other drugs should be carefully considered, and most patients should be directly observed at the start of the treatment." They, and others,[62] note that undesirable events are likely to occur sooner rather than later after the introduction of a class I antiarrhythmic agent. However, the Cardiac Arrhythmia Suppression Trial (CAST)[41] presented data indi-

cating that proarrhythmic complications of class I agents persisted long after the initial introduction of the drugs. In a review of the literature, Prystowsky[63] found that proarrhythmic events that occurred in patients being treated for supraventricular tachyarrhythmias (AF being the most common) developed the complication in the first 3 days in 53% of events, but that another 40% developed between Days 4 and 17 after the introduction of the antiarrhythmic agent. He noted that one patient who had been taking quinidine for 17 years developed torsade de pointes 1 day after an increase in dose.

Many reports indicate that the administration of class I antiarrhythmic agents is associated with the maintenance of sinus rhythm in about 50% of patients at 1 year following conversion of AF.[25,64] In these reports, approximately 25% of patients who received placebo remained in sinus rhythm at 1 year. Thus, 75% of patients received the class I agent unnecessarily! Fifty percent relapsed into AF despite taking the class I agent and 25% would have remained in sinus rhythm even had they not taken the drug. One must question whether the value to 25% of these patients is worth the risk and expense of the drugs and the inconvenience of taking a medicine several times a day, or whether it is preferable to administer the class I agents for only several days following conversion to monitored patients, in the hope that these will be among the 25% who will maintain sinus rhythm on no antiarrhythmic agent.

For those patients who relapse into AF and cannot be returned to sinus rhythm for any reasonable period of time, it is important to maintain ventricular response to the AF in the physiological range, preferably between 60 and 90 beats/min. This can usually be accomplished with the use of digoxin alone, but in some patients a beta blocker or calcium-channel blocker may also be needed. Many older patients have a slow ventricular response on no medication at all due to intrinsic slow atrioventricular conduction. In a rare patient, control of the ventricular response requires a more aggressive approach with radiofrequency atrioventricular node modification[65–67] or radiofrequency elimination of atrioventricular node conduction and the use of an artificial pacemaker.[68–70] Implantable atrial defibrillators are also being evaluated.[71]

Another alternative to a class I drug to prevent recurrence of AF would be a class III antiarrhythmic agent (amiodarone, sotalol, ibutelide, or dofetilide). Many studies report amiodarone to be efficacious in preventing the recurrence of AF.[48, 49, 72–74] Compared with quinidine or any other antiarrhythmic agent, amiodarone is associated with a higher percentage of maintenance of sinus rhythm in follow-up at all time periods. Amiodarone has a relatively low, but certainly not negligible, proarrhythmic risk.[75–79] Hohnloser *et al.*[79] reviewed the literature and concluded that in patients with structural heart disease and rhythm disturbances requiring antiarrhythmic therapy, the use of amiodarone was associated with a proarrhythmic event rate of 1–2% compared with 3–5% with sotalol and 5–8% with quinidine. The use of sotalol[75, 80–84] and ibutelide[85, 86] is reported to be associated with significant risks of serious ventricular arrhythmias at about the same rate as quinidine. Also, in patients with impaired left ventricular function, oral amiodarone is reported to be well tolerated.[87–90] Chun *et al.*[72] report that amiodarone not only is a reasonable alternative, but that it is effective when class I agents have failed and that it is more efficacious in maintaining sinus rhythm than any other agent. Actuarial rates for maintenance of sinus rhythm were 0.87, 0.70, and 0.55 at 1, 3, and 5 years, respectively. Twenty-one patients (19%) with arrhythmia recurrence had an increase in amiodarone dose, and after a mean additional follow-up of 2.5 years, 86% remained in normal sinus rhythm. They did report actuarial rates for withdrawal because of adverse effects of 0.08, 0.22, and 0.30 at 1, 3, and 5 years, respectively. The most frequent adverse effects necessitating withdrawal were skin discoloration (4.5%), pulmonary fibrosis (3.6%; none fatal), and thyroid toxicity (2.7%).

The long-term use of amiodarone is fraught with the hazards of many unacceptable, noncardiac adverse effects, especially amiodarone pulmonary toxicity, which occurs in 5 to 10% of patients on long-term therapy. It is estimated that 5 to 10% of these patients will die from the pulmonary complications of the drug.[88] Hepatic toxicity is also a potential life-threatening complication of long-term amiodarone use.[91, 92] A nontoxic amiodarone-like agent is desperately needed for the management of this type of patient.

We await with hope the results of the National Heart, Lung, and Blood Institute's multicenter study to evaluate various approaches to the management of AF (Atrial Fibrillation Follow-Up Investigation of Rhythm Management—AFFIRM).[93, 94]

Atrial Fibrillation in Patients with Normal Hearts–Lone Atrial Fibrillation

It is said that the class I antiarrhythmic agents can be safely used in the absence of organic or structural heart disease to prevent recurrences or to markedly reduce the frequency of attacks in patients experiencing disabling symptoms during episodes of paroxysmal atrial fibrillation.[62, 95] This story must be the subject of discussion at another time.

References

1. Vaughn Williams EM: Classification of antiarrhythmic drugs. In *Symposium on Cardiac Arrhythmias* (Eds. Sandoe E, Flensted-Jensen E, Olesen KH), p. 449–472. Sodertalje, Sweden: AB Astra, 1970
2. Vaughn Williams EM: Classification of anti-arrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* 1984;82: 1932–1939
3. Frost L, Mortensen PE, Tingleff J, Platou ES, Christiansen EH, Christiansen N: Efficacy and safety of dofetilide, a new class III antiarrhythmic agent, in acute termination of atrial fibrillation or flutter after coronary artery bypass surgery. *Int J Cardiol* 1997;58: 135–140
4. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL: Hazards of postoperative atrial arrhythmias. *Ann Thorac Surg* 1993;56: 539–549
5. Gaylard E: Changing incidence of atrial fibrillation following coronary artery bypass grafting: A retrospective analysis. *Br J Clin Pract* 1996;50:164–165
6. Matthew JP, Parks R, Savino JS, Friedman AS, Koch C, Manago DT, Browner WS: Atrial fibrillation following coronary artery by-

pass graft surgery: Predictors, outcomes, and resource utilization. *J Am Med Assoc* 1996;276:300–306
7. Ommen SR, Odell JA, Stanton MS: Atrial arrhythmias after cardiothoracic surgery. *N Engl J Med* 1997;336:1429–1434
8. Dagud EG, Strickberger SA, Man KG, Goyal R, Deeb GM, Bolling SF, Pagani FD, Bitar C, Meissner MD, Morady F: Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med* 1997;337:1785–1791
9. Frost L, Molgaard H, Christiansen EH, Hjortholm K, Paulsen PK, Thomsen PEB: Atrial fibrillation and flutter after coronary artery bypass surgery: Epidemiology, risk factors and prevention trials. *Int J Cardiol* 1992;36:253–261
10. Viskin S, Barron HV, Olgin JE, Hellet K, Scheinman MM: The treatment of atrial fibrillation: Pharmacologic and nonpharmacologic strategies. *Curr Probl Cardiol* 1997;22:44–108
11. Page PL, Pym J: Atrial fibrillation following cardiac surgery: Canadian Cardiovascular Society Consensus Conference on Atrial Fibrillation. *Can J Cardiol* 1996;12A:40A–44A
12. Yilmaz AT, Demirkilic U, Arslan M, Kurulay E, Ozal E,Tatar H, Ozturk O: Long-term prevention of atrial fibrillation after coronary artery bypass surgery: Comparison of quinidine, verapamil, and amiodarone in maintaining sinus rhythm. *J Cardiac Surg* 1996;11: 61–64
13. Yilmaz AT, Demirkilic U, Kuralay E, Arslan M, Cicek S, Ozal E, Bingol H, Tatar H, Ozturk OY: Long-term prevention of atrial fibrillation after coronary artery surgery. *Panminerva Med* 1997;39: 103–105
14. Landymore RW, Howell F: Recurrent arrhythmias following treatment for postoperative atrial fibrillation after coronary bypass operations. *Eur J Cardiothor Surg* 1991;5:436–439
15. Hammon JW, Wood A, Prager R, Wood M, Muirhead J, Bender H: Perioperative beta blockade with propranolol: Reduction in myocardial oxygen demands and incidence of atrial and ventricular arrhythmias. *Ann Thorac Surg* 1984;38:363–367
16. Janssen J, Loomans L, Harink J, Taams M, Brunninkhuis L, van der Starre P, Kootstra G: Prevention and treatment of supraventricular tachycardia shortly after coronary artery bypass grafting: A randomized open trial. *Angiology* 1986;37:601–609
17. Andrews TC, Reimold SC, Berlin JA, Antman EM: Prevention of supraventricular arrhythmias after coronary artery bypass surgery. A meta-analysis of randomized control trials. *Circulation* 1991; 84(suppl III):III236–III244
18. Laub GW, Janeira L, Muralidharan S, Riebman JB, Chen C, Neary M, Fenandez J, Adkins MS, McGrath LB: Prophylactic procainamide for prevention of atrial fibrillation after coronary artery bypass grafting: A placebo-crontolled pilot study. *Crit Care Med* 1993;21:1474–1478
19. Gold MR, O'Gara PT, Buckley MJ, DeSanctis RW: Efficacy and safety of procainamide in preventing arrhythmias after coronary artery bypass surgery. *Am J Cardiol* 1998;78:975–979
20. Nurozler F, Tokgozoglu L, Pasaoglu I, Boke E, Ersoy U, Bozer AY: Atrial fibrillation after coronary artery bypass surgery: Predictors and the role of MgSO4 replacement. *J Cardiol Surg* 1996;11: 421–427
21. Beggs VL, Birkemeyer NJ, Nugent WC, Dacey LJ, O'Connor GT: Factors related to rehospitalization within thirty days of discharge after coronary artery pass grafting. *Best Practices and Benchmarking I Healthcare* 1996;1:180–186
22. Selzer A, Wray HW: Quinidine syncope: Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation* 1964;30:17–26
23. Brodsky MA, Chun JG, Podrid PJ, Douban S, Allen BJ, Cygan R: Regional attitudes of generalists, specialists, and subspecialists about management of atrial fibrillation. *Arch Intern Med* 1996; 156:2553–2562
24. Radford MD, Evans DW: Long-term results of DC reversion of atrial fibrillation. *Br Heart J* 1968;30:91–96
25. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC: Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. *Circulation* 1990;82:1106–1116
26. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG: Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 1992;20:527–532
27. Stevenson WG, Stevenson LW, Middlekauff HR, Fonarow GC, Hamilton MA, Woo MA, Saxon LA, Natterson PD, Steimle A, Walden JA, Tillisch JH: Improving survival for patients with atrial fibrillation and advance heart failure. *J Am Coll Cardiol* 1996;28: 1458–1463
28. Faber TS, Zehender M, Van de Loo A, Hohnloser S, Just H: Torsade de pointes complicating drug treatment of low-malignancy forms of arrhythmia: Four case reports. *Clin Cardiol* 1994;17: 197–202
29. Strasberg B, Sclarovsky S, Erdberg A, Duffy CE, Lam W, Swiryn S, Agmom J, Rosen KM: Procainamide-induced polymorphic ventricular tachycardia. *Am J Cardiol* 1981;47:1309–1314
30. Riccioni N, Castiglioni M, Bartolomei C: Disopyramide-induced QT prolongation and ventricular tachyarrhythmia. *Am Heart J* 1983;105:870–871
31. Stratmann HG, Walter KE, Kennedy HL: Torsade de pointes associated with elevated N-acetylprocainamide levels. *Am Heart J* 1985;109:375–376
32. Herre JM, Thompson JA: Polymorphic ventricular tachycardia and ventricular fibrillation due to N-acetyl procainamide. *Am J Cardiol* 1985;55:227–228
33. Anderson JL, Gilbert EM, Alpert BL, Henthorn RW, Waldo AL, Bhandari AK, Hawkinson RW, Pritchett ELC: Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy. *Circulation* 1989;80: 1557–1570
34. Naccarelli GV, Dorian P, Hohnloser SH, Coumel P: Prospective comparison of flecainide versus quinidine for the treatment of paroxysmal atrial fibrillation/flutter. *Am J Cardiol* 1996;77: 53A–59A
35. Stelfox HT, Chua A, O'Rourke K, Detsky AS: Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med* 1998;338:101–106
36. Falk RH: Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med* 1989;111:107–111
37. Sihm I, Hansen FA, Rasmussen J, Pedersen AK, Thygesen K: Flecainide acetate in atrial flutter and fibrillation. *Eur Heart J* 1990;11:145–148
38. Woosley RL, Drayer DE, Reidenberg MM, Nies AS, Carr K, Oates JA: Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N Engl J Med* 1978;298:1157–1159
39. Ellenbogen KA, Wood MA, Stambler BS: Procainamide: A perspective on its value and danger. *Heart Dis & Stroke* 1993;2: 473–476
40. Landrum EM, Siegert EA, Hanlon JT, Currie MS: Prolonged thrombocytopenia associated with procainamide in an elderly patient. *Ann Pharmacol* 1994;28:1172–1176
41. Cardiac Arrhythmia Suppression Trial: Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–412
42. Davison R, Hartz R, Kaplan K, Parker M, Feiereisel P, Michaelis L: Prophylaxis of supraventricular tachyarrhythmia after coronary bypass surgery with oral verapamil: A randomized, double-blind trial. *Ann Thor Surg* 1985;39:336–339
43. Heywood JT: Calcium channel blockers for heart rate control in atrial fibrillation complicated by congestive heart failure. *Can J Cardiol* 1995;11:823–826

44. Olshansky B: Management of atrial fibrillation after coronary artery bypass graft. *Am J Cardiol* 1996;78(8A):27–34
45. McAlister HF, Luke RA, Whitlock RM, Smith WM: Intravenous amiodarone bolus versus oral quinidine for atrial flutter and fibrillation after cardiac operations. *J Thorac Cardiovasc Surg* 1990;99: 911–918
46. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, Woosley RL: Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized digoxin-controlled study. *Eur Heart J* 1995;16:521–528
47. Galve E, Rius, T, Ballester R, Artaza MA, Arnau JM, Garcia-Corado D, Soler-Soler J: Intravenous amiodarone in treatment of recent-onset atrial fibrillation: Results of a randomized, controlled study. *J Am Coll Cardiol* 1996;27:1079–1082
48. Gosselink ATM, Crijns HJGM, Van Gelder IC, Hillige H, Wiesfeld ACP, Lie KI: Low-dose amiodarone for maintenance of sinus rhythm after cardioversion for atrial fibrillation. *J Am Med Assoc* 1992;267:3289–3293
49. Zdrenghea D, Banu E, Bogdan E, Beudean M: The effect of low-dose amiodarone in prevention of paroxysmal atrial fibrillation. *Rom J Intern Med* 1996;34:199–204
50. Singh S, Saini RK, DiMarco J, Kluger J, Gold R, Chen YW: Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation. The Sotalol Study Group. *Am J Cardiol* 1991;68: 1227–1230
51. Anderson JL: Acute treatment of atrial fibrillation and flutter. *Am J Cardiol* 1996;78:17–21
52. Atrial Fibrillation Investigators: Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med* 1994;154:1449–1457
53. Laupacis A, Albers G, Dalen J, Dunn M, Feinberg W, Jacobson A: Antithrombotic therapy in atrial fibrillation. *Chest* 1995;108: 352S–359S
54. Stroke Prevention in Atrial Fibrillation II Study: Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. *Lancet* 1994;343:687–691
55. Golzari H, Cebui RD, Bahler RC: Atrial fibrillation: Restoration and maintenance of sinus rhythm and indications for anticoagulation therapy. *Ann Intern Med* 1996;125:311–323
56. Waktare JEP, Camm AJ: Atrial fibrillation begets trouble. *Heart* 1997;77:393–394
57. Peters KG, Kienzie MG: Severe cardiomyopathy due to chronic rapidly conducted atrial fibrillation: Complete recovery after restoration of sinus rhythm. *Am J Med* 1988;85:242–244
58. Grogan M, Smith HC, Gersh BJ, Wood DL: Left ventricular dysfunction due to atrial fibrillation in patients originally believed to have idiopathic cardiomyopathy. *Am J Cardiol* 1992;69: 1570–1573
59. Kannel WB, Abbott RD, Savage DD, McNamara PM: Epidemiologic features of chronic atrial fibrillation: The Framingham Study. *N Engl J Med* 1990;323:1509–1511
60. Stroke Prevention in Atrial Fibrillation Study: Final results. *Circulation* 1991;84:527–539
61. Grace AA, Camm AJ: Quinidine. *N Engl J Med* 1998;338:35–45
62. Prystowsky EN, Benson DW, Fuster V, Hart RG, Kay GN, Myerberg RJ, Naccerelli GV, Wyse DG: Management of patients with atrial fibrillation. A statement for healthcare professionals from the subcommittee on electrocardiography and electrophysiology, American Heart Association. *Circulation* 1996;93:1262–1277
63. Prystowsky EN: Proarrhythmia during drug treatment of supraventricular tachycardia: Paradoxical risk of sinus rhythm for sudden death. *Am J Cardiol* 1996;78(suppl 8A):35–41
64. Sopher SM, Camm AJ: Atrial fibrillation: Maintenance of sinus rhythm versus rate control. *Am J Cardiol* 1996;77:24A–37A
65. Feld GK, Fleck P, Fujimura O, Prothro DL, Bahnson TD, Ibarra M: Control of rapid ventricular response by radiofrequency catheter modification of the atrioventricular node in patients with medically refractory atrial fibrillation. *Circulation* 1994;90:2299–2307
66. Williamson BD, Man KC, Daoud E, Niebauer M, Strickberger SA, Marady F: Radiofrequency catheter modification of atrioventricular conduction to control the ventricular response during atrial fibrillation. *N Engl J Med* 1994;331:910–917
67. Morady F, Hasse C, Strickberger SA, Man KC, Daoud E, Bogun F, Goyal R, Harvey M, Knight BP, Weiss R, Bahu M: Long-term follow-up after radiofrequency modification of the atrioventricular node in patients with atrial fibrillation. *J Am Coll Cardiol* 1997;29: 113–121
68. Kay GN, Bubien RS, Epstein AE, Plumb PJ: Effect of catheter ablation of the atrioventricular junction on quality of life and exercise tolerance in paroxysmal atrial fibrillation. *Am J Cardiol* 1988;62: 741–744
69. Twidale N, Sutton K, Bartlett L, Dooley A, Winstanley S, Heddle W, Hassam H, Koutsounis H: Effects on cardiac performance of atrioventricular node catheter ablation using radiofrequency current for drug-refractory atrial fibrillation. *PACE* 1993;16: 1275–1284
70. Brignole M, Gianfranchi L, Menozzi C, Alboni P, Musso G, Bongiorni MG, Gasparini M, Raviele A, Lolli G, Paparella N, Acquarone S: Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: A randomized controlled study. *Circulation* 1997;96: 2617–2624
71. Carlson MD, Biblo LA: Atrial defibrillation. New frontiers. *Cardiol Clin* 1996;14:607–622
72. Chun SH, Sager PT, Stevenson WG, Nademanee K, Middlekauff HR, Singh BN: Long-term efficacy of amiodarone for the maintenance of normal sinus rhythm in patients with refractory atrial fibrillation or flutter. *Am J Cardiol* 1995;76:47–50
73. Mackstaller LL, Alpert JS: Atrial fibrillation: A review of mechanisms, etiology, and therapy. *Clin Cardiol* 1997;20:640–650
74. Podrid PJ: Amiodarone: Reevaluation of an old drug. *Ann Intern Med* 1995;122:689–700
75. Nademanee K, Singh BN, Hendrickson JA, Intarachot V, Lopez B, Feld G, Cannom DS, Weiss JL: Amiodarone in refractory life-threatening ventricular arrhythmias. *Ann Intern Med* 1983;98: 577–584
76. Mason JW: Amiodarone. *N Engl J Med* 1987;16:455–466
77. Nademanee K: The amiodarone odyssey. *J Am Coll Cardiol* 1992; 20:1063–1065
78. Middlekauff HR, Wiener I, Stevenson WG: Low-dose amiodarone for atrial fibrillation. *Am J Cardiol* 1993;72:75F–81F
79. Hohnloser SH, Klingenheben T, Singh BN: Amiodarone-associated proarrhythmic effects. A review with specific references to torsade de pointes tachycardia. *Ann Intern Med* 1994;121:529–535
80. Hohnloser SH, Woosley RL: Sotalol. *N Engl J Med* 1994;331: 31–38
81. Halinen MO, Huttunen M, Paakkinen S, Tarssanen L: Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the sotalol-digoxin-quinidine trial). *Am J Cardiol* 1995;76:495–498
82. Lehman MH, Hardy S, Archibald D, Quart B, MacNeil DJ: Sex difference in risk of torsade de pointes with d,l-sotalol. *Circulation* 1996;94:2534–2541
83. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R: The long QY syndromes: A critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;31:115–177
84. Julian DG, Prescott RJ, Jackson FS, Szekely P: Controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1982;1: 1142–1147
85. Kowey PR, VanderLugt JT, Luderer JR: Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation. *Am J Cardiol* 1996;78(suppl8A):46–52
86. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, VanderLugt JT, and the Ibutelide Repeat Dose Study Investi-

gators: Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;94:1613–1621

87. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D: Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995;333:77–82
88. Wilson JS, Podrid PJ: Side effects from amiodarone. *Am Heart J* 1991;121:158–171
89. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R: Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;344:493–498
90. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ: Randomized trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997;349:667–674
91. Richer M, Robert S: Fatal hepatotoxicity following oral administration of amiodarone. *Ann Pharmacother* 1995;29:582–586
92. Tosetti C, Ongari M, Evangelisti A, Lolli R, Napoli A: Acute hepatotoxicity from amiodarone. *Minerva Med* 1995;86:387–390
93. AFFIRM: Atrial fibrillation follow-up investigation of rhythm management. *Am J Cardiol* 1997;79:1198–1202
94. Brodsky MA, Podrid PJ, Chun JG: Should physicians participate in affirming the best approach to atrial fibrillation management? *Am J Cardiol* 1996;78:1152–1153
95. Blackshear JL, Kopecky SL, Litin SC, Safford RE, Hammill SC: Management of atrial fibrillatin in adults: Prevention of thromboembolism and symptomatic treatment. *Mayo Clin Proc* 1996;71:150–160