A randomized trial of prophylactic antiarrhythmic agents (amiodarone and sotalol) in patients with atrial fibrillation for whom direct current cardioversion is planned

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Background Antiarrhythmic agents enhance maintenance of sinus rhythm (SR) after direct current cardioversion (DCC) for atrial fibrillation but there are few comparative trials. The aims of the study were (1) to establish whether patients successfully cardioverted to SR are more likely to stay in SR over 6 months if taking amiodarone or sotalol, and if so, to establish whether one agent is better than the other; (2) to establish whether taking amiodarone or sotalol is better at achieving chemical cardioversion within the 6 weeks before DCC; and (3) to establish whether DCC is more likely to be successful on a drug.

Methods Randomized, prospective, nonblinded, controlled study of treatment with either amiodarone (n = 27), sotalol (n = 36), or no antiarrhythmic agent (n = 31).

Results Chemical cardioversion occurred in 7 patients in the amiodarone group (A), 7 patients in the sotalol group (S), but none in the no-antiarrhythmic group (N). A total of 33 (92%) patients in the sotalol group, 22 (81%) patients in the amiodarone group, and 23 (74%) patients in the no-antiarrhythmic group were in SR after cardioversion. Of the original cohort of patients, 17 (63%) patients in the amiodarone group remained in SR at 6-month follow-up, compared with 14 (39%) in the sotalol group and 5 (16%) in the no-antiarrhythmic group (A vs N, P < .0002, P < .0006B [after Bonferroni correction]; A vs S, P = .05, P = .15B; and S vs N, P = .03, P = .09B).

Conclusions Amiodarone and sotalol achieved chemical cardioversion before planned electrical cardioversion in 26% and 19% of patients, respectively. After successful cardioversion, amiodarone appears better than sotalol at maintaining SR at 6 months. (Am Heart J 2006;151:863.e1-863.e6.)
with a higher chance of maintenance of SR, which is more likely to result in chemical cardioversion before electrical cardioversion and which drug increases the rate of electrical cardioversion. We therefore undertook a prospective, randomized study designed to establish whether patients successfully cardioverted to SR were more likely to remain in SR over a period of 6 months if taking an antiarrhythmic drug and, if so, to establish whether one agent was better than the other. In addition, we aimed to establish the relative impacts of these drugs in achieving chemical cardioversion within the 6 weeks before planned DCC, as well as on the efficacy of electrical cardioversion itself.

Methods
The study was carried out in a regional cardiothoracic unit. The local research ethics committee of our institution approved the study protocol. After informed consent, a full explanation of the benefits and risks of electrical cardioversion and the drug therapy was provided to the study patients.

Inclusion criteria
Patients for whom DCC of AF was planned were eligible for the study. Only patients with the time of onset of AF within the last 1 year were included.

Exclusion criteria
They were as follows:

- Patients <18 years of age;
- Atrial fibrillation of >1-year duration;
- AF associated with evidence of rheumatic mitral valve disease;
- AF associated with prosthetic mitral valves;
- AF after cardiac surgery within the previous 30 days;
- Patients with a contraindication to β-blockers (heart block, significant chronic obstructive airways disease, and asthma);
- Patients with marked left ventricular dysfunction (New York Heart Association class ≥3 or ejection fraction <30%);
- Patients with Wolff-Parkinson-White syndrome;
- Patients with AF in the context of thyrotoxicosis or pregnancy;
- Prior participation in the trial; and
- Patients who were unable to provide informed consent.

Randomization, investigation, and therapy
After informed consent, suitable patients were randomly assigned using a computer-generated randomization sheet to receive either no additional treatment, amiodarone or sotalol. All study patients were anticoagulated with warfarin 6 weeks before DCC with a target international normalized ratio (INR) of 1.8-2.5. The general practitioners were informed of their patient’s entry into the study. Regular INR monitoring was carried out either by the general practitioners or by the anticoagulation clinic. Complete medical histories were recorded including history of angina, previous coronary revascularization, hypertension, congestive cardiac failure, alcohol ingestion, asthma or chronic obstructive pulmonary disease. Peripheral vascular disease and features suggestive of thyroid disorders. The history was reviewed to establish the probability that the AF had started within the previous year.

At trial entry, patients underwent electrocardiography, echocardiography, a full blood count, chemical evaluation of urea and electrolytes, and thyroid function tests, and the INR was checked.

Patients were randomized to receive amiodarone, sotalol or, no additional antiarrhythmic agent. Amiodarone was given at a dose of 200 mg/d after a loading dose of 200 mg 3 times daily for a week and twice daily for the following week. The loading dose was that recommended by the British National Formulary. Sotalol was given at a dose of 160 milligrams twice a day. The dose was decreased to 80 mg twice daily if the patient was intolerant of the higher dose. If the patient was on digoxin, this was withdrawn if patients developed bradycardia. If the patient was unable to tolerate the medication, it was withdrawn. All patients were asked to report any adverse symptoms associated with these medications. The usual clinical advice was given to all patients concerning the potential adverse effects of antiarrhythmic agents, and histories were reviewed and electrocardiograms checked at the preadmission visit before cardioversion as well as on the morning of cardioversion. For those patients being started on anticoagulant therapy, the study medications were commenced before complete anticoagulation was obtained.

To achieve satisfactory rate control for patients treated with amiodarone, half dose digoxin and/or low dose of a standard β-blocker (usually atenolol) were added. For patients randomized to sotalol, half-dose digoxin was added if necessary. If randomized to the no-antiarrhythmic arm, digoxin and/or a standard β1 selective β-blocker were added to obtain rate control.

Direct current cardioversion
Six weeks after randomization, patients attended the cardiology day unit for monophasic DCC carried out using handheld defibrillators. Patients in SR were discharged to be followed up in clinic. For those remaining in AF, the cardioversion protocol started with paddles in the apico-ternal position with the first shock being delivered at 100 joules, followed by 200 joules. If unsuccessful, then a further 1 to 2 shocks at 360 joules were delivered. If still unsuccessful, a further shock at 360 joules using paddles in the anteroposterior position was delivered. If unsuccessful at this stage, a further shock at 360 joules using new pads was delivered after the administration of 600 μg of intravenous atropine. The procedure was abandoned if unsuccessful at this stage. A patient was deemed to have undergone a successful cardioversion if the patient continued to remain in SR before discharge form the hospital.

Follow-up
All patients were followed up at 6 weeks and 6 months post DCC. If at 6 weeks a patient had reverted back to AF, the patient involvement in the study ended. Further treatment was at the discretion of the attending clinician. A patient could not be included as “another case” in the trial. If the patient was in SR at 6 weeks, warfarin and digoxin were discontinued (aspirin was considered) and patients were seen 6 months after DCC. If the patient was in SR at 6 months, continuing care of the patient was at the discretion of the attending physician.
A total of 94 patients were enrolled: 31 patients in the no-antiarrhythmic group (N), 27 patients in the amiodarone group (A), and 36 patients in the sotalol group (S). The patient, clinical, and echocardiographic characteristics at the time of enrolment into the study are shown in Tables I and II. There was a significant difference in the number of male patients between the no-antiarrhythmic group and the sotalol group (A vs N, \( \chi^2 = 2.3 \ [1 \ df], \ P = .1 \); A vs S, \( \chi^2 = 0.8 \ [1 \ df], \ P = .4 \); and S vs N, \( \chi^2 = 6.5 \ [1 \ df], \ P = .01, 0.03 \)). There was no difference in the duration of AF between the 3 groups (\( P = .1 \)). None of the patients in the current study had significant renal impairment.

### Therapy
All patients in the amiodarone arm received a loading dose and were taking 200 mg of amiodarone at 6-month follow-up, except for 1 patient who was non-compliant with the protocol and stopped taking his medications before DCC. In the sotalol group, 23 patients continued taking 160 mg twice a day but in 7 patients the dose was reduced to 80 mg twice a day. Two patients in this group stopped treatment before DCC and in another 4 patients’ medication were withdrawn because of adverse effects.

### Outcome treatment strategies
In the no-antiarrhythmic arm, 1 patient died after enrolment in the study before DCC, owing to a previously undiagnosed lung cancer, and another died of fibrosing alveolitis before 6-week follow-up. Electrical cardioversion was cancelled by an anesthetist in 1 patient in the sotalol arm because of obesity and another patient in the no-antiarrhythmic arm subsequently declined cardioversion.

### On the day of cardioversion
The results are shown in Table III. There was a significant difference in the number of patients who were already in SR in the amiodarone and sotalol groups compared with the no-antiarrhythmic group on the day of cardioversion.
A total of 29 patients (1 died, 1 declined) in the no-antiarrhythmic arm, 20 patients in the amiodarone arm, and 28 patients (1 cancelled because of obesity) in the sotalol arm underwent electrical cardioversion. Of the patients who underwent cardioversion, this was successful in restoring SR in 79% (23/29) patients in the no-antiarrhythmic group, 75% (15/20) patients in the amiodarone group, and 26/28 (93%) patients in the sotalol group. There was no significant difference in cardioversion success between the 3 groups (A vs N, P = .7, A vs S, P = .1 and S vs N, P = .1), respectively. All patients who were in SR immediately after DCC remained in SR at discharge.

Recurrence of AF

**Six-week follow-up.** At 6-week follow-up, 67% of patients in the amiodarone group, 53% of patients in the sotalol group and 42% of patients in the no-antiarrhythmic group remained in SR.

**Six-month follow-up.** Of the original cohort of patients, the number of patients remaining in SR at 6 months in the amiodarone group (63%) was greater than the no-antiarrhythmic group (16%) and the sotalol group (39%) (A vs N, \( \chi^2 = 12.3 \) [1 df], \( P = .0002 \), \( \chi^2 = .006^b \), where \(^b\) represents value after Bonferroni correction; A vs S, \( \chi^2 = 3.6 \) [1 df], \( P = .05 \), \( \chi^2 = .15^b \); and S vs N, \( \chi^2 = 3.6 \) [1 df], \( P = .03 \), \( \chi^2 = .09^b \). All 7 patients chemically cardioverted in the amiodarone group remained in SR at 6 months compared with 5 of 7 patients in the sotalol group.

**Major clinical events and discontinuation of study drug.** During the course of the study, 2 patients died. Both were in the no-antiarrhythmic group. Death was due to noncardiac causes as previously discussed. One patient in the amiodarone group developed sunburn after 2 weeks of treatment, and amiodarone was changed to propafenone 150 mg twice a day. No clinical thyroid abnormalities were detected in this group, and there were no other adverse events. In the sotalol group, medication was discontinued in 4 patients during the first 6 weeks after randomization: 1 patient developed ankle swelling, 1 patient developed wheeze, 1 patient developed severe nausea and vomiting, and in the other patient, sotalol was discontinued because of extreme fatigue. There was no significant difference in the intolerance between the sotalol group (n = 4 [12%]) and the amiodarone group (n = 1 [4%]) (\( P = .28 \)).

**Discussion**

Our results show that treatment with either sotalol or amiodarone significantly increased the chance of reversion to SR before planned DCC. For those going on to electrical cardioversion, 75% of the amiodarone group and 93% of the sotalol group were successfully converted to SR. This is comparable with a previous study by Roy et al.\(^9\)

In the previous study by Roy et al.,\(^9\) 35% of patients assigned to amiodarone and 63% of patients assigned to sotalol or propafenone had recurrence of AF over the course of a mean follow-up period of 468 (150) days. The inclusion criteria for patients in the Canadian Trial of Atrial Fibrillation were different to ours in that their patients did not have to have persistent AF, they excluded patients with a history of AF extending for >6 months before inclusion, and they included those in whom long-term therapy was planned. We included only those for whom electrical cardioversion was planned.\(^9\)

Our findings extend the results of the recently reported SAFE-T.\(^1^7\) These investigators concluded amiodarone and sotalol are equally efficacious in converting AF to SR. Amiodarone is superior for maintaining SR. There are, however, some differences between their study and ours. Their study population was different, consisting of more men who were slightly older with a greater proportion of patients who had diabetes, hypertension, and congestive cardiac failure. Our study
excluded those with AF for more than a year, whereas in their study, over a fifth of their population had AF for longer than this. In SAFE-T, patients underwent cardioversion using both monophasic and biphasic defibrillators, whereas we used only monophasic devices. Biphasic devices have subsequently been obtained by our center but were not used in this study. Given the results of SAFE-T, it is likely that these results stand up whichever device is used to achieve electrical cardioversion. If patients had a recurrence of AF in SAFE-T, they underwent repeat cardioversion. However, overall, fewer shocks were delivered, compared with our study. Despite a slight difference in loading doses of the drugs, the chemical cardioversion rate in our study was not significantly different to theirs. At 1-year follow-up, in their study, 87% versus 48% versus 68% (placebo vs amiodarone vs sotalol) of patients had recurrence of AF. In our study at 6-month follow-up, 84% versus 37% versus 61% (no-antiarrhythmic group vs amiodarone vs sotalol) of patients had recurrence of AF. Despite the differences in populations and protocols, the results are remarkably similar.

The findings of both studies support the view that amiodarone is preferable to sotalol for patients in whom maintenance of SR is desired after successful cardioversion. Although amiodarone appears to be the better agent for maintenance of SR over 6 months, its medium term efficacy has to be balanced against the potential for long-term toxicity. In our study with 6-month follow-up, there was no statistically significant difference in the intolerance between the sotalol group and the amiodarone group. In our study, with a less challenging loading dose and 200 mg daily for 6 months, the side effect profile was acceptably low (4%), consistent with other studies of similar doses in the medium term.18–21 Serious adverse events such as pulmonary or thyroid abnormalities were not observed in this group of patients. The frequency of adverse effects depends largely on the dose, duration of therapy, and severity of the underlying cardiac disease.22 Further study is required to establish the relative risks and benefits of long-term low-dose therapy in the setting of maintenance of SR after cardioversion from AF.

In our study, 11% of patients in the sotalol group experienced adverse effects. Potential life-threatening cardiovascular adverse effects did not occur in any of the patients. In SAFE-T,17 1 of the 261 patients who received sotalol developed non fatal torsades de pointes. The rare occurrence of torsades de pointes permits outpatient initiation of sotalol therapy, as is customary for amiodarone. No patient in our study had impaired renal function, but the dose of sotalol should be modified in patients with impaired creatinine clearance.

We used atropine to facilitate cardioversion. High vagal tone is dominant in patients with structurally normal hearts. This may prevent the termination of AF by standard techniques of DCC. A study performed in our department using the same protocol of cardioversion as in the current study suggested that the abolition of high vagal tone in patients with AF by atropine facilitates the restoration of SR.

**Limitations**

Although this was a randomized study, it was not blinded. However, both amiodarone and sotalol are frequently used in the context of AF and an open-labeled randomized study of the strategy of using these agents was deemed appropriate. This study was not designed to determine the long-term benefit of the trial medications in maintaining SR, compared with their adverse effects. Patients with >1 year of onset of AF, those with poor left ventricular function and postoperative AF, were not included in the study. Hence, the effect of these medications and the potential advantage of one over the other in such group of patients remain unclear.

We used the amiodarone loading dose recommended by the British National Formulary. It is possible that the chemical cardioversion results would have been better with a higher loading dose. In the amiodarone group, 4 patients were also taking other β-blockers for rate control (2 patients 50 mg Atenolol, 1 patient 100 mg of Atenolol, and the other 10 mg of bisoprolol). The patient taking bisoprolol had recurrence of AF at 6 weeks, and the others remained in SR. Studies comparing amiodarone alone and amiodarone in combination with a β-blocker are required to determine the additive effect, if any, in producing and maintaining SR.

The study was discontinued after conventional statistical analysis for the primary end point (maintenance of SR at 6 months) of 90 patients. The subsequent use of the Bonferroni correction reduces the confidence of our main result, that is, amiodarone is better than sotalol at maintaining SR at 6 months. Given that this was the main purpose of the study, one could argue about the need for the Bonferroni correction for this specific result, but given the multiple analyses performed, we accept that it is appropriate. Although this reminds the reader to be cautious of the results and introduces the possibility of a type 1 error, nevertheless, our results are entirely consistent with those of SAFE-T.

Our results only apply to patients undergoing electrical cardioversion with a monophasic defibrillator. However, our results are similar to those in the SAFE-T trial where investigators were allowed to change from monophasic to biphasic devices during the running of the study.

If patients in our study remained in SR at 6-week follow-up, warfarin therapy was discontinued. In retrospect, maintaining patients on warfarin for a longer duration might have been appropriate, given the significant proportion of patients who reverted to AF at
6 months follow-up. In this setting, warfarin was recommenced by the attending physician.

Conclusions
Treatment with either sotalol or amiodarone significantly increased the chance of chemical cardioversion to SR before planned electrical DCC. After successful cardioversion, maintenance of SR at 6 months appeared better if the patient was taking either amiodarone or sotalol, compared with taking no-antiarrhythmic agent. Maintenance of SR appeared better with amiodarone compared with sotalol. These results are entirely consistent with those of SAFE-T, albeit in a different population of patients.

Patients should be on an antiarrhythmic before DCC. Our findings indicate that low-dose amiodarone warrants consideration as a first line therapy for maintenance of SR after DCC, compared with sotalol. Anticoagulation should probably be maintained for at least 6 months after DCC. Further studies are needed to compare the efficacy of amiodarone in maintaining SR with the potential for long-term toxicity.

References