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Oral *d,l* Sotalol Reduces the Incidence of Postoperative Atrial Fibrillation in Coronary Artery Bypass Surgery Patients: A Randomized, Double-Blind, Placebo-Controlled Study

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OBJECTIVES The purpose of this prospective, randomized, double-blind, placebo-controlled study was to assess the efficacy of preoperatively and postoperatively administered oral *d,l* sotalol in preventing the occurrence of postoperative atrial fibrillation (AF).

BACKGROUND Atrial fibrillation is the most common arrhythmia following coronary artery bypass surgery (CABG). Its etiology, prevention and treatment remain highly controversial. Furthermore, its associated morbidity results in a prolongation of the length of hospital stay post-CABG.

METHODS A total of 85 patients, of which 73 were to undergo CABG and 12 CABG plus valvular surgery (ejection fraction ≥28% and absence of clinical heart failure), were randomized to receive either sotalol (40 patients; mean dose = 190 ± 43 mg/day) started 24 to 48 h before open heart surgery and continued for four days postoperatively, or placebo (45 patients, mean dose = 176 ± 32 mg/day).

RESULTS Atrial fibrillation occurred in a total of 22/85 (26%) patients. The incidence of postoperative AF was significantly ($p = 0.008$) lower in patients on sotalol (12.5%) as compared with placebo (38%). Significant bradycardia/hypotension, necessitating drug withdrawal, occurred in 2 of 40 (5%) patients on sotalol and none in the placebo group ($p = 0.2$). None of the patients on sotalol developed Torsade de pointes or sustained ventricular arrhythmias. Postoperative mortality was not significantly different in sotalol versus placebo (0% vs. 2%, $p = 1.0$). Patients in the sotalol group had a nonsignificantly shorter length of hospital stay as compared with placebo (7 ± 2 days vs. 8 ± 4 days; $p = 0.24$).

CONCLUSIONS The administration of sotalol, in dosages ranging from 80 to 120 mg, was associated with a significant decrease (67%) in postoperative AF in patients undergoing CABG without appreciable side effects. Sotalol should be considered for the prevention of postoperative AF in patients undergoing CABG in the absence of heart failure and significant left ventricular dysfunction. (J Am Coll Cardiol 1999;34:334–9) © 1999 by the American College of Cardiology

Atrial fibrillation (AF) represents the most common arrhythmic complication of coronary artery bypass surgery (CABG). It occurs in approximately 20% to 40% of patients undergoing cardiac surgery (1–14). Furthermore, it usually tends to occur within four days after the operation in most patients, resulting in inappropriate tachycardia, increased morbidity and significant prolongation of the length of hospital stay. Although the etiology of postoperative AF is incompletely understood, stimuli such as atrial ischemia (13), preexisting structural changes related to age and hypertension or mechanical damage, electrolyte imbalances and pericardial irritation are thought to play a role (14). Studies on signal averaging of the P wave have suggested that patients with prolonged signal averaged P-wave duration may be predisposed for the development of postoperative AF (15). In the absence of a specific pathophysiologic

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Abbreviations and Acronyms

AF = atrial fibrillation
AV = atrioventricular
CABG = coronary artery bypass surgery
LVEF = left ventricular ejection fraction

target, no clear strategies have been proposed to reduce the incidence of post-CABG AF. In this study we sought to determine whether *d,l* sotalol could reduce the incidence of post-CABG AF maintaining an acceptable safety profile.

METHODS

Patients. From February 1997 to August 1997, a total of 130 consecutive patients scheduled to undergo CABG were screened. Of these, 85 patients (55 male, 30 female; mean age 65 ± 11 years) were randomized to receive either oral *d,l* sotalol or placebo. Of these 85 patients, 73 were scheduled to undergo CABG, and 12 patients were to receive CABG with concomitant valvular surgery. The remaining patients either did not satisfy the entry criteria or refused to participate in the study. For all patients, an evaluation of left ventricular myocardial function by echocardiography, left ventricular angiography or radionuclide scan had been obtained in the preceding two months. Exclusion criteria included emergent open heart surgery; a prior history of AF or atrial flutter; a left ventricular ejection fraction (LVEF) < 28% (16) or clinically active congestive heart failure; first-degree or higher degrees of atrioventricular (AV) block; QTc (>450 ms); impaired renal function (serum creatinine >2 mg/dl); chronic obstructive pulmonary disease; and current use of antiarrhythmic drugs. Of the 85 patients enrolled in the study, 20% had an LVEF of 30% to 40%, 42.5% of patients between 40% to 50%, and 37.5% of patients above 50%. Medication was started 24 to 48 h before scheduled surgery.

The study was designed as a two-center, double-blind, randomized, placebo-controlled trial and was approved by the human research committees of both institutions. This study was not funded by a pharmaceutical company nor was a pharmaceutical company involved in its formulation or execution. The study was primarily supported by intramural divisional funds.

Randomization and double-blind period. The patients were enrolled in a registry by the hospital central pharmacy of each institution, which randomized the patients in a double-blind fashion and dispensed the medication and placebo pills for all patients starting 24 to 48 h before surgery and continued for up to four days postsurgery. In all patients, the study medication was discontinued after the fourth postoperative day. The placebo (mean dose = 176 ± 32 mg/day) was administered in identical fashion using, respectively, two pills instead of the 80-mg and 120-mg dose of sotalol. The study medication was started in-hospital on the telemetry floor as 80 mg p.o. b.i.d., and advanced up to 120 mg p.o. b.i.d., if there was no bradycardia defined as a rate of ≤40 beats/min, congestive heart failure and QTc prolongation of >500 ms. The study medication was discontinued if the QTc was >500 ms. All other drugs were continued unchanged except beta-adrenergic blocking agents, the dose of which was halved on the day of the start of study medication if the dose of beta-blocker was ≥200 mg/day of metoprolol or its equivalent. Only two patients were on dosages above 200 mg/day, and their dosage of beta-blocker was halved. The dose of beta-blocker (metoprolol or atenolol) ranged from 25 to 100 mg/day in the placebo group and 25 to 50 mg/day in the sotalol group. The postoperative dose of sotalol was not changed. Sixty-five percent of the patients were on a total dose of sotalol of 160 mg/day and the remaining 35% were on 240 mg/day. The mean dose of sotalol was 190 ± 43 mg/day. There was no significant difference ($p = 0.1$) in the total daily placebo and sotalol dose.

This study design was devised to avoid the occurrence of beta-blocker withdrawal and assess the feasibility and effectiveness of a strategy where sotalol is utilized in parallel with prior beta-blocker regimen to minimize untoward effects of this drug combination.

All patients were placed on cardiopulmonary bypass. Seventy-three patients (86%) underwent CABG, and the remaining 12 patients (14%) underwent CABG and concomitant valvular surgery. Myocardial protection was provided in all patients utilizing cold cardioplegia and topical hypothermia. Immediate postoperative administration of study medication was done by nasogastric tube.

All patients were monitored continuously with electrocardiographic (ECG) telemetry equipment, and their 24-h report was reviewed by a study physician or study nurse coordinator every day for any episode of AF. The end point of the study was the occurrence of AF lasting more than or equal to 30 min or for any length of time requiring intervention due to symptoms (chest pain) or hemodynamic compromise (hypotension, heart failure) or the completion of four days of postoperative therapy. The study medication was withheld if bradycardia resulting in hypotension occurred. Both QT and QTc were monitored daily.

Follow-up. All patients were followed for the duration of their hospital stay from the day of surgery. For placebo group, mean = 8 ± 4 days, range = 1 to 29 days; sotalol group, mean = 7 ± 2 days, range = 1 to 15 days.

Statistical analysis. All statistical analyses were completed utilizing the SAS software package (Cary, North Carolina). Clinical and hemodynamic variables including age, gender, ejection fraction, presence of bundle branch block, time of cardiopulmonary bypass (pump time), number of coronary grafts, valvular surgery, the use of beta-blockers and the use of sotalol versus placebo for the occurrence of postoperative AF were tested using chi-square analysis, Fisher exact test

Table 1. Characteristics of Patients on Placebo vs. Sotalol

Characteristics	Placebo	Sotalol	p Value
No.	45	40	—
Age (yrs)	69 + 10	61 + 10	0.001
M/F	28/17	27/13	0.61
EF	48 ± 9	50 ± 9	0.40
Pump time	136 ± 52	142 ± 68	0.68
Valvular surgery	8	4	0.39
No. of coronary grafts	3 ± 1	3 ± 1	0.94
Beta-blockers	21 (47%)	8 (20%)	0.01
No. of hospital days	8 ± 4	7 ± 2	0.24

M = male; F = female; EF = ejection fraction; AF = atrial fibrillation; No. = number.

where appropriate, and *t*-testing. Subsequently, a Categorical Data Analysis was performed using the incidence of postoperative AF as the dependent variable, with age, beta-blockers and sotalol as dependent variables. The specific SAS procedure used was PROC CATMOD. All values are expressed as the mean ± SD.

RESULTS

Effect of sotalol on postoperative AF. Of the 85 patients enrolled in the study, 45 were randomized to receive placebo and 40 to receive sotalol. Table 1 summarizes the characteristics of the patients on sotalol and on placebo. There was no significant difference in the male/female ratio, LVEF, pump time, the number of coronary artery grafts or valvular surgery.

A significant difference existed in the occurrence of AF in patients in the placebo group as compared to those receiving sotalol (Table 2), but the day of occurrence of AF between the sotalol and placebo groups was not significantly different. A total of 17 of 45 (38%) patients receiving placebo had postoperative AF onset on days 3 ± 2, whereas only 5 of 40 (12.5%) patients on sotalol (mean dose = 190 ± 43 mg/day) had postoperative AF on days 2 ± 1 (Table 2). This difference was highly significant (p = 0.008). The AF lasted from 0.5 h to 72 h in the placebo group and was paroxysmal in 9 of 17 (56%) patients, whereas AF lasted for 0.5 h to 75 h in the sotalol group and was paroxysmal in 3 of 5 (75%) patients. The difference in the incidence of paroxysmal AF was not statistically significant in the two groups (p = 0.78). The patients on placebo were older (69 ± 10 vs. 61 ± 10 years; p = 0.001) and a higher proportion were on beta-blockers (47% vs. 20%; p = 0.01).

Figure 1 shows the Kaplan-Meier analysis of the percentage of patients free from AF on sotalol as compared with placebo. The estimated percentage of patients free of AF was 87.5% in the sotalol group and 49% in the placebo group for up to 10 days post-CABG. On days 4 to 6, there was also a significant difference in the arrhythmia-free incidence in the sotalol versus the placebo group (88% vs. 68%; p = 0.03). The initial ventricular response during AF

Table 2. Incidence of Postoperative Atrial Fibrillation

Event	Sotalol	Placebo	p Value
AF (no. of patients)	5 (12.5%)	17 (38%)	0.008
AF (postoperative days)	2 ± 1	3 ± 2	0.22

was not significantly different in patients on sotalol as compared with placebo (146 ± 21 vs. 143 ± 39 beats/min).

Because age, beta-blockers and the use of sotalol were highly significant in the chi-square analysis, we assessed the influence of these variables on the occurrence of AF using Categorical Data Analysis. In this analysis, the use of sotalol was still significant (p = 0.03) in decreasing the incidence of AF over all ages (p = 0.68) and regardless of the use of beta-blockers (p = 0.60).

Influence of beta-blocker therapy. Of 45 patients on placebo, 21 (47%) were on beta-blockers (Table 3). Of these, 8 (38%) developed AF, whereas 9 (37.5%) of the patients not taking beta-blockers developed AF. Of the patients on sotalol, 8 were on beta-blockers. Of these, 2 (25%) developed AF, whereas AF occurred in 3 of 32 patients (9%) not on beta-blockers. This difference was not statistically significant (p = 0.24). The dose of sotalol in patients on beta-blockers versus those not on beta-blockers was not significantly different (186 ± 48 mg/day vs. 188 ± 44 mg/day).

Effects on the QTc interval. The QT interval was measured before the administration of sotalol and 3.4 ± 1 days after sotalol administration to determine any type III effects of sotalol. The QTc interval was significantly prolonged on sotalol as compared to before sotalol administration (458 ± 38 ms vs. 419 ± 29 ms; p = 0.0001). There was no significant difference in the QTc in the placebo group, pre- and postsurgery (418 ± 33 ms vs. 437 ± 30 ms; p = 0.1).

Side effects of therapy. None of the patients on sotalol or on placebo required mechanical cardiac assist for weaning from extracorporeal bypass. Two patients (5%) developed significant side effects necessitating discontinuation of sotalol; there were none in the placebo group. One of these patients developed bradycardia and junctional rhythm postoperatively. Dual-chamber pacing was readily instituted via epicardial temporary wires left in at the time of surgery. In one other patient the medication was discontinued in the surgical ICU because of postoperative hypotension. No patient on sotalol had torsade de pointes or ventricular tachycardia.

Mortality. There was one death in the placebo group (2%), 29 days postoperative, following a cerebrovascular accident. No deaths occurred in the sotalol group.

Length of hospital stay. Patients who were on the sotalol arm of the study had a shorter length of hospital stay as compared with those on placebo (7 ± 2 days vs. 8 ± 4 days).

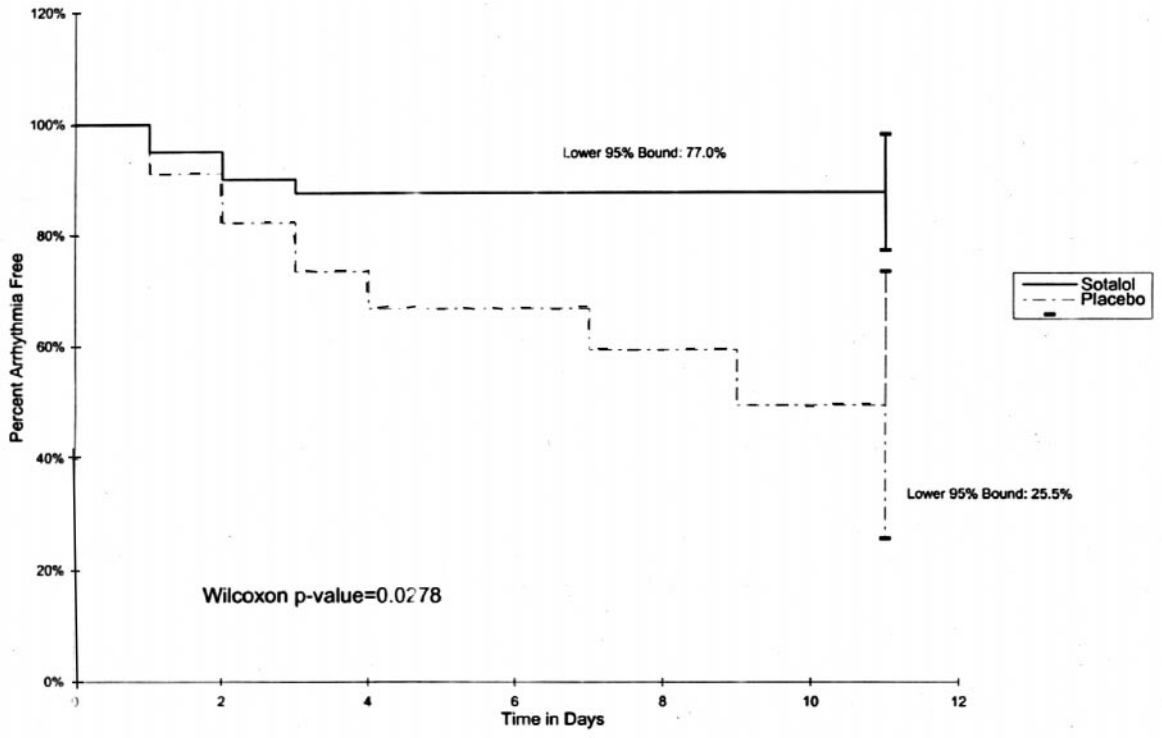

Figure 1. Kaplan-Meier analysis of the percentage of patients free of atrial fibrillation on sotalol as compared to placebo. The abscissa plots the time in days, and the ordinate plots the percentage of patients free of AF.

However, this difference was not statistically significant ($p = 0.24$).

DISCUSSION

The incidence of AF remains high in post-CABG (1–14) patients and represents a significant clinical burden in terms of associated morbidity and length of hospital stay. Risk factors for post-CABG AF include advancing age, male gender, hypertension, need for an intraoperative balloon pump, postoperative pneumonia, ventilation for more than 24 h and return to the intensive care unit (14). Signal averaging studies of the P wave (15) have suggested that patients who develop postoperative AF may have a substrate for AF. Currently, no strategy is universally accepted and implemented either for its prevention or for its treatment. Because of a continuous rise in the mean age of patients with CABG, more patients are at risk for this complication than in past years. Consequently, a growing need has arisen for optimizing a preventive approach. In light of its clinical consequences, any reduction in its incidence will likely translate into reduced morbidity and length of stay. For these reasons, a search for the optimal prophylaxis is of utmost necessity.

Table 3. Impact of Beta-blocker Therapy in Placebo and Sotalol Groups

	Bb + Placebo	Placebo	Bb + Sotalol	Sotalol
No.	21	24	8	32
AF	8 (38%)	9 (37.5%)	2 (25%)	3 (9%)

Bb = beta-blockers; AF = atrial fibrillation.

Current study. We chose sotalol as a prophylactic agent for the prevention of postoperative AF for the following reasons: 1) it has a type III membrane effect in addition to its beta-blocker function; and 2) in patients already on beta-blockers preoperatively, it would be easy to switch to sotalol and to discontinue the beta-blocker or continue the beta-blocker at a reduced dosage without beta-blocker withdrawal effects. In addition, this approach could prevent inadvertent bradycardia and hypotension.

To our knowledge, this is the first study where patients without a prior history of AF were randomized in a double-blind, placebo-controlled fashion where the study drug was administered orally 24 to 48 h before surgery. In addition, we tested whether moderate dosages would be effective in preventing postoperative AF without significant side effects. Our findings suggest that the use of sotalol in moderate dosages is associated with a significantly lower incidence of postoperative AF without appreciable side effects. Only 5% of our patients developed bradycardia, which required discontinuation of the drug, and none of the patients developed ventricular arrhythmias including Torsade de pointes. Furthermore, the findings in this study

suggest that sotalol need not be continued beyond postoperative day 4 because most AF occurs within four days of surgery.

This study also confirms the previous observations that age is a potent predictor of postoperative AF. Our analysis, however, showed that the benefit of sotalol was independent of age; the mean age of the patients in the placebo group was <70 years.

It remains unclear whether the beneficial effect of sotalol is related to its beta-blocking effect or the class III membrane activity. Although this study was not designed to address that question, our observations of a significant increase in the QTc interval suggest that the beneficial effects of sotalol noted in this report were partly related to its type III effects. It is of interest that in this study, a larger number of patients in the placebo group, despite being on beta-blockers, had a higher incidence of AF as compared to the sotalol group. Furthermore, there was no difference in the incidence of AF in patients in the placebo group who were on beta-blockers when compared with those who were not on beta-blockers (38% vs. 37.5%). It is noteworthy that beta-blockers were not withdrawn in the placebo or the sotalol group; rather, the dose was halved in only two patients who were on a high dose of beta-blockers. Similar observations have been recently reported by Parikka et al. (17), who found a 32% incidence of postoperative AF in patients randomized to metoprolol. In addition, there seems not to have been an additive beneficial effect to the use of beta-blocker therapy in patients on sotalol because the incidence of AF was not significantly different in the patients on beta-blocker plus sotalol in contrast with patients on only sotalol. Thus, these observations lend further support that the benefit noted in the sotalol group was at least partly if not fully related to its type III membrane activity.

Also, we found no significant difference in the mean ventricular response during AF in patients on sotalol versus placebo. This observation may be related to the high adrenergic state postoperatively and the small number of patients on sotalol having AF. However, it is possible that increasing the dose of sotalol after developing AF may provide beneficial effects in controlling the ventricular response.

Previous studies. The use of beta-blockers to prevent postoperative AF has been controversial. Whereas some studies have shown a beneficial effect, other studies have shown differing effects (17–22). Two meta-analyses (18,19) have shown a preventive effect of beta-blockers for post-CABG supraventricular tachycardia inclusive of AF. In contrast, no beneficial effect was detected for verapamil and digoxin.

There are few studies investigating the use of antiarrhythmic drugs in the prevention of postoperative atrial arrhythmias. In a small pilot trial, intravenous procainamide followed by oral procainamide, administered postoperatively, was shown to reduce the incidence of postoperative AF (23), whereas the prophylactic uses of quinidine (24) and propafenone (25) have not shown significant beneficial effects. Conversely, intravenous amiodarone given in a loading bolus (26) followed by an infusion for four days was associated with a significant reduction in postoperative AF as compared to placebo (5% vs. 21%; $p < 0.05$). A recent study by Daoud et al. (27) examined the efficacy of oral amiodarone given seven days before surgery and discontinued on the day of hospital discharge. These investigators found that amiodarone significantly reduced the incidence of postoperative AF relative to placebo (23% vs. 42%; $p = 0.03$). However, the major drawback of amiodarone is that it has to be given several days before surgery, at least seven, as was done in their study. Furthermore, amiodarone is known to result in postoperative pulmonary complications in patients undergoing open heart surgery (28).

The effects of sotalol in preventing postoperative AF have been controversial (29–31). Sotalol has been evaluated in two previous European studies, where its use resulted in a reduced incidence of postoperative AF (29,30). However, both of these studies were open-labelled, not placebo-controlled, and the medications were started following open heart surgery. In contrast, Suttrop et al. (31) showed no beneficial effects when comparing the efficacy and safety of low- and high-dose sotalol versus propranolol started after surgery. The lack of benefit noted in their study may be related to the use of sotalol after CABG and the inclusion of supraventricular tachycardia. Furthermore, in the studies discussed, it is not clear whether patients with a past history of recurrent AF were included as well.

Sotalol-related side effects. There was a very low incidence of sotalol-related side effects in this study including significant bradycardia and ventricular tachycardia. The reason for this is unclear although the following explanations can be offered: 1) the high adrenergic state, and the use of inotropes in the postoperative state, may have accounted for an absence of significant bradycardia and bradycardia-related torsade de pointes type of ventricular tachycardia; 2) the dosages of sotalol utilized in this study were low. Sixty-five percent of patients were on a total daily dose of 160 mg and the remaining were on a total daily dose of 240 mg. Side effects from sotalol, particularly the occurrence of Torsade-type ventricular tachycardia, have been reported at dosages above 360 mg/day (32); 3) most patients (80%) had a well-preserved LVEF of ≥40%; 4) patients with renal dysfunction were excluded from the study.

Also, in a recent study comparing low-dose sotalol (160 to 240 mg) to metoprolol, started postoperatively, Parikka et al. (17) did not observe any significant bradycardia, torsade de pointes or ventricular fibrillation in their patients on sotalol. They also reported a significantly higher heart rate postoperatively as compared with preoperatively in both the sotalol and metoprolol groups.

Study implications. Our study suggests that low-dose sotalol is a highly effective drug in preventing post-CABG AF. The use of sotalol was associated with a 67% reduction in AF without significant side effects. Thus, the results of the present study suggest that the prophylactic use of sotalol should be considered in patients undergoing CABG who have relatively well-preserved ventricular function, absence of heart failure and absence of renal dysfunction. However, a larger multicenter study may be needed to determine the ideal patient selection, its influence on hospital length of stay and cumulative side effects of the drug before its general use. It may be possible in the future to stratify patients at risk for AF. Prospective studies in high-risk patients will be necessary to assess the optimal prophylaxis.

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