Role of sotalol in rhythm control of atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is a major cause of morbidity and mortality. It represents an extremely costly public health problem with a negative impact on the quality of life of patients affected. Despite many drugs that are currently available in preventing recurrences of AF after successful cardioversion to normal sinus rhythm, their efficacy remains unsatisfactory, with a great number of recurrences and several short- and long-term adverse effects. Sotalol is an antiarrhythmic drug with a combination of class II (β-adrenoceptor blocking) and class III (cardiac action potential duration prolongation) properties, making it an attractive option for the treatment and prevention of AF.

KEYWORDS: atrial fibrillation ■ class III antiarrhythmic drug ■ rhythm control ■ sotalol

Alessandro Marinelli[1], Alessandro Rosi[2] & Alessandro Capucci[†1]

[1]Università Politecnica delle Marche, Azienda Ospedaliero Universitaria Ospedali Riuniti, Clinica di Cardiologia, Via Conca 71, Località Torrette, 60126 (AN), Italy
[2]Ospedale Privato San Giacomo, Unità Funzionale di Riabilitazione Cardiologica, Via San Bono 3, Pontedellolio, Italy
[†]Author for correspondence
Tel.: +39 071 596 5440
Fax: +39 071 596 5624
a.capucci@univpm.it

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, with an increasing prevalence with age [1]. AF can be associated with other cardiovascular diseases, such as congestive heart failure, hypertension, valve disease and myocardial infarction [2], or it can occur in patients without clinical or instrumental evidence of cardiopulmonary disease (thus called 'lone' AF) [3]. A recent study reported a prevalence of 0.95% in adults older than 20 years, with a prevalence increasing from 0.1% in adults younger than 55 years to 9.0% in persons aged 80 years or older [4]. It has been estimated that 2.2 million people in the USA and 4.5 million in the EU have paroxysmal or persistent AF, with the number of patients affected likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of elderly individuals [4].

Atrial fibrillation is a major cause of morbidity and mortality and is associated with a twofold increased risk of death and a fivefold increased risk of stroke [5–7]. It represents an extremely costly public health problem [8], with hospitalizations as the primary cost driver. Considering the prevalence of AF in the general population it appears clear why the total economical burden is huge: in the USA the annual costs for treatment of AF were estimated at US$6.65 billion [9] and approximately €13.5 billion (approximately $15.7 billion) in the EU [10].

Available data also suggest that quality of life is considerably impaired in patients with AF compared with age-matched healthy controls, due to the frequent discomfort and disabling symptoms associated with AF in a large percentage of patients [11].

The treatment of AF is currently based on two different strategies: conversion to and maintenance of sinus rhythm (SR) (rhythm-control strategy) or lowering the ventricular rate response with rate-controlling drugs (rate-control strategy). Several clinical trials found no difference in survival between these two strategies in patients on anticoagulation treatment [12–17]. Nevertheless, pharmacological therapy to maintain SR after successful cardioversion (CV) could be preferred as the initial strategy, especially in patients who have troublesome symptoms related to paroxysmal AF or recurrent AF, who can tolerate antiarrhythmic drugs (AADs) and have a good chance of remaining in SR over an extended period.

Sotalol is an AAD with class II (β-adrenoceptor blocking) and class III (cardiac action potential duration prolongation) properties. This peculiar feature makes this drug an attractive option for the treatment and prevention of AF. Comparative trials have demonstrated that sotalol has a similar efficacy in preventing recurrences of AF as flecainide and propafenone [18,19], despite a generally high rate (approximately 50%) of recurrences at 12-months follow-up.

The current American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) 2006 practice guidelines for the management of patients with AF [1] do not recommend oral or intravenous administration of sotalol for pharmacological CV of AF, but limits its use to maintenance of SR in patients with paroxysmal or persistent AF and little or no heart disease (lone AF or AF associated with hypertension in absence of left ventricular hypertrophy). In the

rhythm-control algorithm of the guidelines [1], sotalol is also recommended in patients with coronary artery disease, in absence of signs of heart failure.

Overview of the market

A number of different AADs are approved in both the USA and EU for rhythm control in patients with paroxysmal or persistent AF (Table 1).

A recent Cochrane systematic review demonstrated that several class IA, IC and III drugs are more effective than placebo in maintaining SR, such as quinidine, flecainide, propafenone, amiodarone, sotalol, dofetilide and the most recent dronedarone [20].

Comparative trials in AF treatment have demonstrated that flecainide, propafenone, quinidine and sotalol are equally effective in preventing recurrences of AF at 12 months, despite a high rate of recurrences (approximately 50%) for all these drugs [18,19,21].

Amiodarone is the most effective drug for long-term rhythm control in patients with paroxysmal or persistent AF [22–24]. However, its use is associated with a relatively high incidence of potentially severe extra cardiac toxic effects, making it a second-line or last-resort agent in many cases.

Current guidelines recommend the use of propafenone or flecainide as a first-line therapy for maintaining SR in patients with AF without structural heart disease [1]. The use of other AADs, sotalol included, is to be considered as a second-choice therapy in this group of patients.

There is currently an unmet need for more effective and safer drugs in the prevention of recurrences of AF. The limited efficacy and considerable toxicity of all the available agents have started a recent interest in development of innovative drugs, such as selective atrial ion channel blockers and nonselective ion channel blockers (blockers of multiple potassium, sodium and calcium currents), such as azimilide, vernakalant, ranolazine and dronedarone [25]. In the recent Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation (DIONYSOS) trial, dronedarone was shown to be safer but less effective than amiodarone in maintaining SR in 504 patients with persistent AF for a mean follow-up of 7 months [101]. Intravenous use of the atrial-selective vernakalant demonstrated rapid conversion of short-duration AF in a recent randomized, placebo-controlled trial [26] and the oral formulation is being investigated for the maintenance of normal heart rhythm following termination of AF. Ranolazine, another atrial-selective agent initially developed as an antianginal, demonstrated efficacy in AF and this finding is being tested in prospective clinical trials [27]. Azimilide did not come to the market for lack of efficacy.

Another different and attractive approach to the disease is the use of non-AADs, such as inhibitors of the renin–angiotensin system, n-3 polyunsaturated fatty acids and statins, which might modify the underlying atrial remodeling, however prospective positive clinical trials are lacking.

Introduction to the compound

Sotalol is marketed as the racemic mixture of its stereoisomers, D- and L-sotalol, with the D-isomer having less than 1/50 the β-blocking activity of the L-isomer [28,29]. It is an effective antiarrhythmic and antifibrillatory agent, especially in patients with ventricular arrhythmias. Nevertheless, sotalol appeared to be moderately effective in terminating and preventing

Table 1. Drugs of proven efficacy in rhythm control of atrial fibrillation and main adverse effects.		
Drug	**Daily dosage**	**Potential adverse effects**
Quinidine	320–1000 mg	Diarrhea, GI upset, torsade de pointes, nervous system and ocular side effects, hypersensitivity-induced hepatic toxicity, hematologic disorders (leukopenia, thrombocytopenia)
Disopyramide	400–750 mg	Torsades de pointes, HF, glaucoma, urinary retention, dry mouth
Flecainide	200–300 mg	Ventricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV node
Propafenone	450–900 mg	Ventricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV node
Dofetilide[†]	500–1000 µg	Torsades de pointes
Sotalol[†]	160–320 mg	Torsades de pointes (long QT syndromes, renal insufficiency), HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease
Amiodarone[‡]	100–400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications

[†]Dose should be adjusted for renal function and QT interval response during in-hospital initiation phase.
[‡]Loading dose of 600 mg/day for 1 month or 1000 mg/day for 1 week.
AV: Atrioventricular; GI: Gastrointestinal; HF: Heart failure.

recurrence of various supraventricular arrhythmias and it is currently used for the prophylaxis of paroxysmal supraventricular tachycardia and in the maintenance of SR after successful CV of AF and atrial flutter.

Sotalol was first approved by the US FDA on 30 October 1992 for the treatment of ventricular arrhythmias. The indication for its use in maintenance of normal SR in patients with symptomatic AF and atrial flutter was approved on 22 February 2000 (with the brand name Bpace AF).

The available tablets for oral administration contain 80, 120, 160 or 240 mg of sotalol hydrochloride.

Chemistry

Sotalol hydrochloride is a white, crystalline solid with a molecular weight of 308.8. It is hydrophilic, soluble in water, propylene glycol and ethanol, but is only slightly soluble in chloroform. Chemically, sotalol hydrochloride is D,L-N-[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]methane-sulfonamide monohydrochloride and the molecular formula is $C_{12}H_{20}N_2O_3S \bullet HCl$ (FIGURE 1).

Pharmacodynamics

Sotalol hydrochloride is a potent noncardioselective β-adrenoceptor blocking agent devoid of intrinsic sympathomimetic and membrane-stabilizing actions [30]. Unlike other β-adrenoceptor blocking drugs, sotalol prolongs the duration of action potentials recorded in cardiac tissue, increases the refractory period and lengthens the QT interval on the surface electrocardiogram (ECG) [31,32]. Therefore, sotalol is a drug with combined class II (β-adrenoceptor blocking) and class III (cardiac action potential duration prolongation) antiarrhythmic properties. Higher doses of sotalol are necessary to prolong cardiac repolarization than to achieve adrenergic blockade [33,34], and significant class III effects are seen only at daily doses of 160 mg and above.

The effect of sotalol in prolonging the action potential is concentration-dependent and it is most likely caused by a substantial reduction in the delayed rectifier potassium current, together with a small decrease in the inward rectifier potassium current [35]. At the currently used dosage (160–320 mg/day), there are no relevant effects on Phase 0 upstroke velocity of the action potential.

The class III electrophysiological effects in humans include prolongation of the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrioventricular accessory pathways (if present) in both the anterograde and retrograde directions. These effects are exerted in both Purkinje fibers and ventricular muscle types of tissue, with a somewhat greater effect on Purkinje fibers, and they are not related to its β-blocking action [36]. Sotalol has a modest reverse use dependent effect [37,38], so its action on the action potential is inversely proportional to heart rate.

Pharmacokinetics & metabolism

Orally administered sotalol is virtually completely absorbed and is not metabolized. Its excretion is primarily through the kidneys [33,34]. It does not undergo first-pass metabolism in the liver, resulting in an absolute bioavailability of 90–100% [39]. Consequently, the pharmacokinetics of sotalol in patients with hepatic insufficiency is comparable to those in normal subjects [40]. The median time to peak plasma concentrations generally occur 2.5–4 h after oral administration and the steady state plasma concentrations are attained within 2–3 days (i.e., after 5–6 doses when administered twice daily). There is a linear relation between the administered dose of sotalol and the plasma concentration [41,42], especially over the dosage range of 160–640 mg/day. Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 12 h. Sotalol does not bind to plasma proteins [42] and age and food have slight but insignificant effects on bioavailability.

Sotalol plasma levels and half-life are directly related to creatinine clearance and glomerular filtration rate [41,43,44]; therefore, lower doses are necessary in conditions of renal impairment. In patients with normal renal function, the mean elimination half-life is approximately 8 h, as compared with 24 h in patients with moderate renal failure [43].

The minimally effective antiarrhythmic dose of orally administered sotalol is 80–160 mg/day given in two equal doses [45], but the dose can be increased if necessary every 3–4 days to a maximum of 640 mg/day. Most studies have reported control of arrhythmia within this dose range. With oral doses ranging from 160 to 640 mg/day, the surface ECG shows dose-related
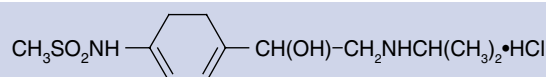

CH_3SO_2NH —⟨ ⟩— $CH(OH)-CH_2NHCH(CH_3)_2 \bullet HCl$

Figure 1. Sotalol.

QT interval prolongation of 40–100 msec [46–48]. Excessive prolongation results in a predisposition to polymorphic ventricular tachycardia (VT) of the torsade de pointes (TdP) type [49]. Sotalol-induced prolongation of the QT interval is more pronounced at a slow heart rate and may not be apparent during exercise-induced tachycardia. For that reason it is preferable to use the corrected QT (QTc) interval in monitoring ECG changes during sotalol therapy, with a maximal recommended QTc of 500 msec.

An initial 48–72-h continuous ECG control monitoring is advised after the initiation of treatment and in hospital settings. Sotalol should be titrated to higher doses only with a careful evaluation of the clinical response, since the risk of a proarrhythmic effect is dose-related [50] and with each dose increase, an increase in the risk of TdP has to be expected.

Appropriate dose adjustment must be made for patients with impaired renal function with a modification in dosing interval (time between divided doses) according to creatinine clearance. In patients with mild renal failure (creatinine clearance >60 ml/min), the initial dose of sotalol should be 80 mg twice daily, and the dose should subsequently be titrated upward with care according to the clinical response. In patients with moderate renal impairment (creatinine clearance 30–59 ml/min) an initial dose of 80 mg with a dosing interval of 24 h is recommended. In end-stage renal insufficiency (creatinine clearance <29 ml/min), the elimination half-life is increased to 41 h [51] and intervals of 36–48 h between doses are recommended. In the case of an overdose, hemodialysis effectively reduces the plasma drug concentration.

Clinical efficacy

Results of clinical studies on electrophysiologic effects of sotalol demonstrated that like other β-adrenoceptor antagonists, sotalol decreases the heart rate and increases the AH interval, thus slowing conduction in the atrioventricular node [52]. In addition, it possesses a class III anti-arrhythmic activity, prolonging the duration of cardiac action potential.

Evidence from both experimental and clinical studies indicates that the antiarrhythmic and antifibrillatory actions of sotalol are superior to those of conventional β-blockers, maybe because of these additional effects on duration of action potentials and refractoriness. However, the class III antiarrhythmic properties of sotalol alone are not optimal without the concomitant β-adrenoceptor blocking action and in experimental studies, the β-blocking action was determined essential for the efficacy in preventing ventricular fibrillation (VF) in patients with acute myocardial ischemia and elevated sympathetic tone [53].

■ Efficacy of sotalol on supraventricular arrhythmias

Owing to its effects in blocking β-adrenergic receptors and prolonging action potential, sotalol can be expected to be effective in the treatment of supraventricular tachyarrhythmias (SVT). Its efficacy on the termination and prevention of different types of SVT and especially of AF has been evaluated in different settings and several studies.

■ Termination of acute AF/atrial flutter

Several studies have evaluated the role of sotalol in the termination of acute AF, flutter or paroxysmal SVT. Both intravenous and oral administrations were tested at different doses.

Teo et al. demonstrated how an intravenous bolus dose of sotalol terminated 33% of episodes of atrial flutter and 20% of episodes of AF evaluated 24 h after infusion, with an increase in efficacy during continuous infusion, especially for atrial flutter (success rate during infusion improved to 86%) in 29 patients with acute or chronic, persistent or intermittent SVT [54]. Jordaens et al. performed a double-blind, placebo-controlled study on the efficacy of a single dose of intravenous sotalol for termination of SVT in 43 patients with paroxysmal SVT lasting more than or equal to 15 min [55]. SR conversion evaluated after 30 min was significantly higher in the sotalol group than in the placebo group, with a success rate of 83% in the patients treated. Another randomized, placebo-controlled study evaluating the safety and efficacy of intravenous sotalol on SVT was performed by Sung et al. [56]. They enrolled 93 patients without underlying heart disease and with SVT (48%) and AF/atrial flutter (52%) lasting more than 5 min and less than 7 days. After 1 h of observation, the conversion rate with 1.5-mg/kg sotalol intravenous infusion was very high in the SVT group (67%) but less effective in the AF/atrial flutter group (24%). The same limited efficacy of sotalol infusion in CV of new-onset AF is confirmed by a recent study performed by Thomas et al. in 140 patients, half of which with no structural heart disease, experiencing their first episode of AF [57]. The study demonstrated that, even with high-dose rapid infusion, the overall rate of

conversion to SR at 12 h was poor and comparable between patients treated with amiodarone (51%), sotalol (50%) or digoxin (50%).

Oral administration of sotalol also showed a poorer rate of conversion to SR in the recent double-blind Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), including patients with AF duration superior to 72 h and also with long-lasting forms [24]. The rate of conversion, evaluated at day 28 after randomization, of 244 patients in the sotalol group was 24.2%, similar to the rate of the amiodarone group (27.1% of conversion), despite significantly higher than spontaneous conversions in the placebo group (0.8%).

Considering this poor rate of conversion, considerably lower than the conversion rate of other available drugs, such as flecainide, propafenone and ibutilide [58], sotalol should not be used for pharmacological CV of acute AF [59]. According to the very good efficacy rate of class IC drugs to convert AF to SR, it is most likely that the drugs that primarily act on impairing conduction velocity are the most useful to convert AF. Sotalol, due to its class III properties, is a drug that prolongs refractoriness more than acting on delaying the conduction velocity and this effect is particularly evident in a reverse use dependent phase. This may be the main reason why its power to convert AF to SR is feeble, and a better efficacy is observed in maintaining SR.

However sotalol, such as other class III antiarrhythmic agents, can be useful to enhance the success of direct-current CV and to prevent immediate recurrences of AF.

In a substudy of the SAFE-T [60], including 504 patients who did not achieve conversion to SR at day 28 and then undergoing direct-current CV, sotalol significantly facilitated successful CV compared with placebo.

Pretreatment with sotalol is one of the options presented in the current AF guidelines for pharmacological enhancement of direct-current CV [1]. However, after effective SR conversion the patient should be continuously monitored for at least 12–24 h owing to possible bradycardia-related ventricular proarrhythmic events, even hours after sinusalization (FIGURE 2).

■ Prevention of AF
Despite its limited efficacy in the conversion of AF to SR, sotalol may be used to prevent AF. The efficacy of oral administration of the drug for prevention of arrhythmia recurrence in patients with paroxysmal AF or relapse of AF after successful CV has been investigated in several studies (TABLE 2).
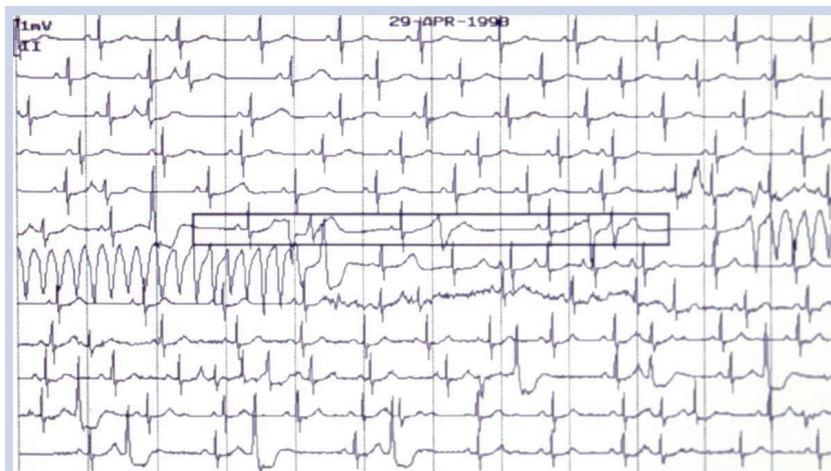
Figure 2. Spontaneous onset of nonsustained ventricular tachycardia during the night in a female patient during sotalol treatment (80 mg three-times daily). The patient was successfully cardioverted from atrial fibrillation to sinus rhythm 12 h before. A compensatory pause related to a premature ventricular contraction causes a QT prolongation with the onset of ventricular tachycardia.

Two placebo-controlled trials involving patients in SR and at least one documented prior episode of AF, found sotalol safe and effective at doses ranging from 80 to 160 mg twice daily [61,62].

In the study by Benditt et al., a group of 253 patients with a history of symptomatic documented AF or atrial flutter within the previous 3 months, and in SR at the moment of randomization, were treated with sotalol at different doses or with placebo. The relapse-free survival probability at 12 months for the placebo group, and the 80-, 120- and 160-mg sotalol daily-dose groups were 28, 30, 40 and 45% respectively, with a dose-response relation in reducing the risk of symptomatic recurrences [61]. The same dose dependence in clinical efficacy was shown in the other small study performed by Wanless et al. in patients with paroxysmal AF [62].

The superiority of sotalol in rhythm control over placebo was confirmed by a recent randomized controlled study performed to compare the time to AF recurrence documented by transtelephonic monitoring after successful CV in patients with persistent and long-lasting AF treated with amiodarone, sotalol or placebo [24]. In the group of 261 patients treated with sotalol, the median time to AF recurrence was 209 days, compared with a median time of 13 days in the placebo group [24].

Randomized trials have been conducted to evaluate the efficacy of sotalol in comparison with other active AADs in the maintenance of SR, such as quinidine, amiodarone, flecainide [21] and propafenone (TABLE 3).

Table 2. Summary of randomized comparative trials on the efficacy of oral sotalol in rhythm control compared with placebo

Author	Year published	No. of patients	Type of arrhythmia	Primary end point	Sotalol daily dose (mg)	Efficacy		p-value	Ref.
						Sotalol	Placebo		
Benditt et al.	1999	253	AF or atrial flutter in previous 3 months and in SR at randomization	Time (days) to first symptomatic AF/atrial flutter recurrence	160 / 240 / 420	106 days / 229 days / 175 days	27 days	NS / 0.001 / 0.012	[61]
Bellandi et al.	2001	300	Recurrent symptomatic paroxysmal or persistent AF after successful CV	Patients (%) free from symptomatic AF/atrial flutter recurrence at 12 months	120–240	73%	35%	0.001	[18]
Kochiadakis et al.	2000	186	Symptomatic chronic or paroxysmal AF after successful CV	Patients (%) free from symptomatic AF recurrence or discontinuation due to AEs at 12 months	80–240	36%	22%	0.001	[23]
Kochiadakis et al.	2004	254	Symptomatic paroxysmal or persistent AF after successful CV	Patients (%) free from symptomatic AF recurrence at 12 months	480	50%	30%	0.001	[69]
Patten et al.	2004	1012	Symptomatic paroxysmal AF documented within 1 month prior to randomization	Time (days) to first symptomatic AF recurrence or time to discontinuation during 12 months of follow-up	320	147 days	106 days	0.002	[64]
Fetsch et al.	2004	848	Persistent AF after successful direct-current CV	Patients (%) free from any (symptomatic and asymptomatic) AF recurrence or death during 12 months of follow-up	320	23%	17%	NA	[65]
Singh et al.	2005	665	Persistent or chronic AF after successful CV	Time (days) to first AF recurrence	320	74 days	6 days	0.001	[24]

AE: Adverse event; AF: Atrial fibrillation; CV: Cardioversion; NA: Data not available; NS: Nonsignificant; SR: Sinus rhythm.

Sotalol was shown to be as effective as and better tolerated than quinidine in maintaining SR after direct-current CV of long-lasting AF in a multicenter trial conducted in Sweden [63]. In this study, including patients with AF duration from 2 months to 1 year, 98 patients received sotalol (160–320 mg/day) and 85 received quinidine, within 2 h after successful electrical CV. At 6 months, 52% of the sotalol-treated patients remained in SR, compared with 48% of the quinidine-treated patients [63]. Moreover, after a relapse of AF, the heart rate was significantly higher in the quinidine-treated patients than in the sotalol-treated patients (109 vs 78 beats/min) and side effects led to discontinuation of therapy more often in the quinidine group (26% in the quinidine group vs 11% in the sotalol group). Because of better control of the heart rate, relapses into AF were less symptomatic in the patients receiving sotalol.

However, in two large European multicenter studies the combination of quinidine plus verapamil resulted as being as effective as, or superior to, sotalol in preventing recurrences of symptomatic paroxysmal AF and persistent AF after successful CV [64,65]. In the Suppression Of Paroxysmal Atrial Tachyarrhythmias (SOPAT) trial [64], 1033 patients with frequent episodes of symptomatic paroxysmal AF and with a documented episode within the previous 4 weeks either received high-dose quinidine plus verapamil (480/240 mg/day; 263 patients), low-dose quinidine plus verapamil (320/160 mg/day; 255 patients), sotalol (320 mg/day; 264 patients) or placebo (251 patients). Each of the active treatments was statistically superior to placebo but not that different from one another with respect to the time to occurrence of the composite primary end point, which was time to first recurrence of symptomatic AF or drug discontinuation. The primary end point occurred after 105.7 ± 8.7 days (mean ± standard deviation) in the placebo group, versus 150 ± 10 days in the high-dose quinidine/verapamil group, versus 148.9 ± 10.6 days in the low-dose quinidine/verapamil group, versus 145.6 ± 93 days in the sotalol group.

The Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial [65] compared the efficacy and safety of the combination of quinidine plus verapamil (377 patients), sotalol (383 patients) and placebo (88 patients) in preventing AF recurrence in patients with persistent AF following successful direct-current CV, with daily transtelephonic monitoring.

Table 3. Summary of randomized comparative trials on the efficacy of oral sotalol in rhythm control compared with other antiarrhythmic agents.

Author	Year published	No. of patients	Type of arrhythmia	Primary end point	Sotalol daily dose (mg)	AAD and daily dose (mg)	Efficacy Sotalol	Efficacy AAD	p-value	Ref.
Juul-Moller et al.	1990	174	Chronic AF after successful direct-current CV	Maintenance of SR and AAD treatment at 6 months	160–320	Quinidine 600 mg b.i.d.	52%	48%	NS	[63]
Patten et al.	2004	1012	Symptomatic paroxysmal AF documented within 1 month prior to randomization	Time (days) to first symptomatic AF recurrence or time to discontinuation during 12 months of follow-up	320	Quinidine + verapamil 480/240 mg/day	147 days	150 days	NS	[64]
						Quinidine + verapamil 320/160 mg/day		149 days	NS	
Fetsch et al.	2004	848	Persistent AF after successful direct-current CV	Patients (%) free from any (symptomatic and asymptomatic) AF recurrence or death during 12 months follow-up	320	Quinidine + verapamil 480/240 mg/day	23%	25%	NA	[65]
Reimold et al.	1993	100	Recurrent symptomatic paroxysmal or persistent AF after successful CV	Maintenance of SR at 12 months	80–480	Propafenone 150–300 mg t.i.d.	$37 \pm 8\%$	$30 \pm 8\%$	NS	[68]
Bellandi et al.	2001	300	Recurrent symptomatic paroxysmal or persistent AF after successful CV	Patients (%) free from symptomatic AF/atrial flutter recurrence at 12 months	120–240	Propafenone 150–300 mg t.i.d.	73%	63%	NS	[18]
Kochiadakis et al.	2004	254	Symptomatic paroxysmal or persistent AF after successful CV	Patients (%) free from symptomatic AF recurrence at 12 months	480	Propafenone 150 mg t.i.d.	50%	59%	NS	[69]
Carunchio et al.	1995	66	Recurrent symptomatic paroxysmal AF	Patients (%) free from symptomatic AF recurrence at 12 months		Flecainide	70%	60%	NS	[21]
Kochiadakis et al.	2000	186	Symptomatic chronic or paroxysmal AF after successful CV	Patients (%) free from symptomatic AF recurrence or discontinuation due to AEs at 12 months	80–240	Amiodarone 200 mg/day (after loading phase)	36%	58%	0.008	[23]
AFFIRM substudy	2003	256	Paroxysmal or persistent symptomatic AF in patients older than 65 years	Patients (%) free from symptomatic AF recurrence, discontinuation due to AE or death at 12 months	240	Amiodarone 200 mg/day (after loading phase)	38%	60%	0.002	[66]
Singh et al.	2005	665	Persistent or chronic AF after successful CV	Time (days) to any (symptomatic and asymptomatic) AF recurrence	320	Amiodarone 200 mg/day (after loading phase)	74 days	487 days	0.001	[24]

AAD: Antiarrhythmic drug; AE: Adverse event; AF: Atrial fibrillation; b.i.d.: Twice daily; CV: Cardioversion; NA: Data not available; NS: Nonsignificant; SR: Sinus rhythm; t.i.d.: Three-times daily.

Over 1 year, recurrence rates were 83% with placebo, 67% with sotalol and 65% with the combination of quinidine plus verapamil; the combination of quinidine plus verapamil was statistically superior to placebo but not different from sotalol. Adverse effects (AEs) were comparable on sotalol and quinidine/verapamil (73 vs 75%, respectively), with serious adverse events occurring with equal frequency in all groups (23% in the placebo group, 25% in the sotalol group, 24% in the quinidine/verapamil group), except that TdP was confined to patients on sotalol (nine of 383 patients; 2.3%).

Therefore in these two large studies, the combination of quinidine plus verapamil appeared as useful and as safe as sotalol to prevent symptomatic recurrences in patients with paroxysmal AF and to prevent any type of AF after CV in persistent AF.

Sotalol was shown to be less effective than amiodarone in maintaining SR after successful CV of long-lasting AF. In the SAFE-T trial [24] amiodarone and sotalol were demonstrated to be equally efficacious and superior to placebo in converting AF to SR, with a rate of conversion of 27.1 and 24.2% for the amiodarone and sotalol group, respectively. Nevertheless, amiodarone was superior to sotalol in the primary end point of prolonging time to recurrence of AF after successful CV: the median times to a recurrence of AF evaluated with weekly transtelephonic monitoring were 809 days in the amiodarone group and 209 days in sotalol group.

In a substudy of the AFFIRM trial [66], based on patients in the rhythm-control arm of the study, among 256 patients randomized between amiodarone and sotalol, 60 versus 38% were in SR assessed by surface ECG after 1 year.

These data are concordant with two previous smaller studies performed by Kochiadakis *et al.* [23,67]. In the first study, 70 patients with recurrent paroxysmal symptomatic AF (49 patients) or cardioverted persistent AF (21 patients) were randomized to receive sotalol or amiodarone, and during the 12-months observation period ten of the 35 patients taking amiodarone developed AF, compared with 21 of the 35 who were taking sotalol [23]. In the second study, among 186 consecutive patients with recurrent symptomatic paroxysmal or persistent AF, 65 received amiodarone (200 mg/day after a 30-day loading phase), 61 sotalol (160–480 mg daily) and 60 placebo after successful restoration of SR. Amiodarone was superior to sotalol in the long term, with the following percentage of patients in SR and free

of side effects for amiodarone, sotalol and placebo: 58, 36 and 22%, respectively at 1 year, and 26, 13 and 10% at 2 years [67].

Despite its better efficacy in maintaining SR, amiodarone is generally associated with more side effects and organ toxicity than sotalol.

Sotalol demonstrated a comparable efficacy with propafenone in maintaining SR after conversion of recurrent AF at 1 year, but it seems to be less effective during longer follow-up. In an open-label randomized study involving 100 patients with AF (with balanced proportions of paroxysmal and persistent AF), propafenone and sotalol were equally effective in maintaining SR (30 vs 37% of patients in SR at 12 months, respectively) [68].

A similar efficacy was confirmed in a subsequent randomized double-blind, placebo-controlled study performed in a larger group of 300 patients with recurrent AF (defined as ≥4 episodes in the previous year) having AF lasting 48 h or less at enrolment and successfully cardioverted. After 1-year follow-up, the proportion of patients remaining in SR was comparable between the propafenone (63%) and sotalol (73%) groups and superior to the proportion of the placebo group (35%) [18]. A subsequent study with a longer follow-up period (mean follow-up of 25 months) performed by Kochiadakis *et al.* on 254 patients with symptomatic paroxysmal or persistent AF [69], showed a similar efficacy of the two drugs at 1 year, but a greater efficacy of propafenone (almost doubled) at 30 months. After 30 months of treatment, approximately 50% of patients who received propafenone remained in SR, whereas the proportion of patients in SR in the sotalol group approached that in the placebo group [69]. In another randomized study comparing the long-term efficacy and safety of amiodarone, propafenone and sotalol in the prevention of AF in 214 patients with recurrent symptomatic AF after restoration of SR, amiodarone and propafenone were superior to sotalol in maintaining normal SR [70].

In the algorithm for the maintenance of SR present in the current international AF guidelines [1], the use of sotalol is recommended in paroxysmal or persistent AF only in patients with little or no heart disease and in patients with coronary artery disease (in absence of signs of heart failure).

Postoperative AF

A promising indication for sotalol seems to be the prevention and the reversion of postoperative AF after open-heart surgery. The incidence of

atrial arrhythmias including AF in this setting is between 20 and 50% and is increasing, perhaps more because of the age of surgical patients than because of technical factors, and this is associated with increased morbidity and costs [71]. Age has been identified as one of the most powerful contributing risk factors for AF after cardiac surgery [72]. Other risk factors include a previous history of AF, mitral valvular heart disease, atrial enlargement or cardiomegaly, long bypass and aortic cross-clamp times, previous cardiac surgery, chronic obstructive pulmonary disease, obesity and withdrawal of either β-blockers or angiotensin-converting enzyme inhibitors before or after surgery [73,74]. An elevated postoperative adrenergic tone is one of the contributing factors and predictors of development of postoperative AF [74] and it often makes it difficult to control the ventricular rate in patients with postoperative AF. Therefore, due to its combined anti-arrhythmic and β-blocking properties, sotalol seems to be appealing in this situation in slowing the ventricular rate and promoting conversion to normal SR. Several studies have been performed to evaluate the efficacy of sotalol in the prevention of postoperative AF and validate this interesting hypothesis.

In a placebo-controlled trial of 300 patients who had undergone coronary-artery bypass surgery (CABG), low-doses of orally administered sotalol (40 mg every 6 h) significantly reduced the incidence of AF and atrial flutter [75]. Of 150 placebo-treated patients, 42 (28%) had AF, and three (2%) had atrial flutter, whereas only 24 of the 150 patients (16%) in the sotalol group had AF and none had atrial flutter [75]. In another study by the same group, the slightly increased success rate of high-dose (240 mg daily) over low-dose (120 mg daily) sotalol was shadowed by increased numbers of AEs, necessitating discontinuation of the drug (10.5 vs 2.8%) [76]. The most common AEs in the sotalol high-dose group leading to drug discontinuation were bradycardia (4.5%), hypotension (3.8%) and respiratory distress (2.2%).

Gomes *et al.* analyzed 85 patients who underwent CABG surgery randomized to either receive oral sotalol or placebo, started 24–48 h before the surgery and continued for 4 days postoperatively [77]. The incidence of AF was significantly lower in patients on sotalol (12.5%) compared with placebo (38%) [77].

Pfisterer *et al.* in another prospective, double-blinded, randomized, placebo-controlled trial, looked at a total of 255 patients referred for elective CABG (220 patients) or aortic valve replacement (35 patients) [78]. Patients were randomized to receive either 80 mg of sotalol twice daily (126 patients) or placebo for 3 months, with the first dose given 2 h before operation. In the low-dose sotalol group, AF developed in 30 patients compared with 45 patients in the placebo group [78]. Evard *et al.* prospectively enrolled in a randomized trial 206 consecutive eligible patients on the first postoperative day of CABG and compared the incidence of AF in the group receiving sotalol (80 mg twice daily, 103 patients) with the incidence in the control group, treated with neither β-adrenoceptor blockers nor AADs (103 patients) [79]. There was approximately a 16% AF occurrence in the sotalol group compared with 48% in the control group, confirming how oral low-dose sotalol provided considerable and reliable protection in selected nondepressed cardiac function patients, reducing the occurrence of AF after CABG [79].

A difficult issue regarding sotalol efficacy is understanding if the favorable effects in preventing postoperative AF are due to either the β-blocking effect alone, or together with its additional class III antiarrhythmic properties. In fact, β-blocker therapy has a great effect in preventing postoperative arrhythmias [80] and a meta-analysis of 24 trials showed how prophylactic administration of β-adrenoceptor blockers is able to protect against SVT [71].

If these therapies have equal efficacy, class II β-blockers would be preferred owing to the absence of ventricular proarrhythmia that can occur with sotalol therapy.

Parikka *et al.* performed a randomized comparison study to examine whether sotalol was superior to the pure β-blocker metoprolol in the prevention of postoperative AF [81]. A total of 191 consecutive patients undergoing CABG were randomized to receive oral sotalol 120 mg daily (93 patients) or metoprolol 75 mg daily (98 patients), postoperatively. The doses were adjusted if the β-blockade was inadequate or excessive. The ventricular rate of AF did not differ in the two study groups. AF occurred in 16 (16%) of 98 sotalol patients and in 30 (32%) of 93 metoprolol patients [81]. The study demonstrated that in low doses, sotalol significantly reduced the incidence of AF shortly after CABG surgery compared with a standard β-blocker, and demonstrated a class III effect, prolonging ventricular repolarization, together with a more efficient heart rate slowing [81].

Another meta-analysis conducted by Crystal *et al.* [72] analyzed a total of 52 randomized trials (controlled by placebo or routine

treatment) on effectiveness of β-adrenoceptor blockers, sotalol, amiodarone or pacing in prevention of post-CABG AF. The authors concluded that β-adrenoceptor blockers, sotalol and amiodarone all reduce the risk of postoperative AF with no marked difference between them [72]. In this meta-analysis there were eight trials that evaluated the use of sotalol versus placebo for the prevention of postoperative AF (1294 patients) and sotalol was shown to reduce the percentage of patients with AF from 37% in the control group to 17% in the treatment group.

Sotalol and other β-blockers were only directly compared in four trials [76,81–83], involving 900 patients. Sotalol was shown to reduce the percentage of patients with AF from 22% in the other β-adrenoceptor blockers group to 12% in the sotalol group.

The Pilot Study of Prevention of Postoperative Atrial Fibrillation (SPPAF) was a randomized, double-blind, placebo-controlled trial conducted in 253 patients undergoing cardiac surgery including CABG, valve surgery or both [84]. Patients received either metoprolol (62 patients), amiodarone plus metoprolol (63 patients), and sotalol (63 patients) or placebo (65 patients) to assess whether each of the active oral drug regimens was superior to placebo for the prevention of postoperative AF and whether there were differences in favor of one of the preventive strategies. Patients receiving combination therapy (amiodarone plus metoprolol) and those receiving sotalol had a significantly lower frequency of AF (30.2 and 31.7%, respectively) compared with patients receiving placebo (53.8%). Metoprolol alone also reduced rates of AF (40.3%) compared with placebo, but this reduction did not reach statistical significance.

In the recent Reduction in Postoperative Cardiovascular Arrhythmic Events (REDUCE) trial, sotalol shared a similar efficacy and safety with amiodarone in reducing postoperative AF [85]. In this study, 160 patients that underwent open-heart surgery were randomized to receive either sotalol 80 mg twice daily (76 patients) or intravenous amiodarone 15 mg/kg over 24 h followed by oral amiodarone 200 mg three-times per day (83 patients). The study drug was started at the time of surgery and continued for 7 days or until discharge, whichever came first. AF occurred in 17% of patients randomized to amiodarone and in 25% of the patients randomized to sotalol, with no statistical significance. However, patients receiving sotalol required more inotropic and vasopressor support and were more likely to need pacing than patients given amiodarone.

The most recently available meta-analysis [86] identified and analyzed 94 trials of prevention of postoperative AF. All five commonly tested interventions, β-adrenoceptor blockers, sotalol, amiodarone, magnesium and atrial pacing, and were effective in preventing AF. Sotalol reduced AF compared with placebo and conventional β-blockers [86].

A total of 14 trials evaluated sotalol for preventing postoperative AF, comprising 2583 patients with 2622 patient comparisons. Five trials used β-adrenoceptor blockers in the control arm, seven used placebo control and two trials had both placebo and β-blocker control arms [86]. Overall, AF was reduced from 33.7 to 16.9%. In the trials that compared sotalol directly with β-blockers, sotalol reduced AF from 25.7 to 13.7%, showing a significant additional protection over standard β-blockers. Significantly more patients were withdrawn from treatment in the groups receiving sotalol than those receiving placebo because of AEs (6.0 vs 1.9%), predominantly due to hypotension and bradycardia [86].

In conclusion, although there is some evidence that sotalol is slightly more effective than conventional β-blockers in preventing postoperative AF, results are not consistent.

However, this possible benefit is probably related to the β-blocking effect of the drug. In addition, its potential to create proarrhythmic side effects could counterbalance its possible superior efficacy.

Different recommendations come from the currently available guidelines. The ACC/AHA /ESC guidelines [1] limit the use of sotalol to prevent AF in patients at high risk of developing AF following cardiac surgery, while the prophylactic treatment with an oral β-blocker is recommended in all patients. Current guidelines of the American College of Chest Physicians [87] indicate that sotalol therapy may be considered for this purpose, despite being associated with increased toxicity and an intermediate net benefit; current Guidelines of the European Association for Cardio-thoracic Surgery state that sotalol may be more effective than standard β-blockers for the prevention of AF without causing an excess of side effects [88].

The efficacy of sotalol regarding the acute treatment of postoperative AF has been evaluated in two old studies [83,89] with limited results. Further studies are needed and at the moment the administration of intravenous or oral sotalol is not recommended in the termination of acute postoperative AF.

Adverse effects & safety

The side effects of sotalol are related to either its β-adrenergic antagonism or its propensity to prolong the QT interval. Overall, discontinuation because of unacceptable side effects was necessary in approximately 17% of all patients in clinical trials, and in 13% of patients treated for at least 2 weeks. The most common adverse reactions leading to discontinuation of sotalol were fatigue (4%), bradycardia (<50 bpm) (3%), dyspnea (3%), proarrhythmia (3%), asthenia (2%) and dizziness (2%).

Adverse reactions due to β-adrenoceptor blockade, such as fatigue, dizziness, dyspnea, headache or worsening of bronchospasm, are similar to those associated with conventional β-adrenoceptor antagonists. The more serious effects related to β-blocking activity are sinus bradycardia, hypotension [90] and exacerbation or *de novo* induction of congestive heart failure. Aggravation of congestive heart failure seems to be less frequent than might be expected with a β-adrenoceptor antagonist [46,47,91] and its occurrence is approximately 1.5%. Nevertheless, this AE may occur at relatively low doses (160–320 mg) and sotalol use is thus contraindicated in patients with decompensated heart failure.

The dextrorotatory optical isomer of sotalol (D-sotalol) was expected to be better tolerated than racemate D,L-sotalol by patients with severe left ventricular dysfunction. It is a pure potassium-channel blocker without clinically significant β-blocking activity. A beneficial effect on mortality of patients with left ventricular dysfunction after myocardial infarction was expected, due to its antifibrillatory activity, and was tested in a controlled trial. Nevertheless, the results of the Survival With Oral D-Sotalol (SWORD) trial, showed that administration of D-sotalol was associated with increased mortality, which was presumed primarily to be due to arrhythmias [92].

Like other AADs with class III antiarrhythmic properties, sotalol can provoke new or worsened ventricular arrhythmias in some patients, including sustained VT or VF, with potentially fatal consequences. The most dangerous AE is the risk of TdP, a polymorphic VT associated with prolongation of the QT interval [49], occurring in approximately 4% of high-risk (history of sustained VT/VF) patients. A study performed by Kühlkamp *et al.* in 81 patients with inducible sustained VT or VF receiving oral D,L-sotalol to prevent induction of the ventricular tachyarrhythmias reported a 5% rate of TdP during the initiation of oral treatment [93].

The risk of TdP progressively increases with increasing dose, prolongation of the QT interval, or predisposing factors, such as hypokalemia, bradycardia or concomitant use of other drugs that prolong repolarization [94]. Proarrhythmic events most often occur within 7 days of initiating therapy or of an increase in dose.

A review of data from controlled trials of sotalol conducted by Soyka *et al.* in a total of 1288 patients reported proarrhythmic events in 56 patients (4.3%) [90]. Oral sotalol doses ranged from 40 to 960 mg/day, with the majority of patients receiving doses of 160–640 mg/day. In 27 patients, the events were characterized as severe: TdP with hemodynamic compromise in 12 patients, sustained VT in nine, and VF in six. A total of 24 patients had TdP, resulting in an overall incidence of 2% [90]. The baseline QTc interval was significantly longer in patients experiencing severe proarrhythmia than that in patients free of proarrhytmia (455 vs 428 msec).

A prospective analysis of 3257 patients receiving sotalol for treatment of supraventricular and ventricular arrhythmias identified 78 cases of drug-induced TdP, with an overall incidence of 2.4% [59]. Sotalol-induced TdP was clearly dose-related, occurring predominantly with sotalol doses in excess of 320 mg/day [59], was more frequent among patients with a history of sustained VT/VF, and generally occurred during the first week of sotalol treatment. In patients with a history of nonsustained ventricular arrhythmias and supraventricular arrhythmias, the incidence of TdP was 1 and 1.4%, respectively.

It is thus reasonable to suppose that the incidence of serious AEs and proarrhythmic effects may be reduced with the lower doses usually used in the prevention of AF.

In a recent systematic review on antiarrhythmics used in maintaining SR in AF [20], sotalol was associated with an increased withdrawal from treatment and increased proarrhythmic effects (counting both bradyarrhythmias and tachyarrhythmias attributable to treatment) in all the studies with the exception of the PAFAC and SOPAT trials [64,65]. Discontinuation due to AEs appears to be related to daily dosage and occurred in approximately 10% of patients, with a variable rate (from 6 to 29%) in the different studies.

In the PAFAC and SOPAT trials [64,65], two recent and large trials that compared efficacy of treatment with sotalol, quinidine or placebo in paroxysmal and persistent AF, no significant differences were shown in withdrawals or AEs between the active treatment group and placebo group, with usual doses of sotalol used

(320 mg/day). This may probably be explained by the lower proportion of patients with structural heart disease included in these two trials, compared with earlier studies. In the SAFE-T trial only one of 261 patients randomized to receive sotalol 160 mg twice daily had an episode of nonfatal TdP [24].

A retrospective analysis conducted by Chung *et al.* analyzed the complications of in-hospital initiation of oral sotalol for treatment of AF [95]. Of the 120 patients included, seven (6%) developed ventricular arrhythmias, two of whom (2%) had TdP.

Considering a total of 384 patients included in eight studies treated with sotalol for AF and a daily dose of 160–320 mg, only one had TdP during the first days of treatment and during reduced serum potassium level (3.7 mmol/l) [96].

From these data, it is evident that the incidence of TdP at the dose commonly used to prevent recurrence of AF seems to be a very rare complication. In addition, a number of risk factors and clinical settings predisposing to TdP have been identified and could be useful in helping the clinician to identify patients at low risk of arrhythmic events.

Conditions predisposing to TdP include hypokalemia, hypomagnesemia, history of sustained ventricular arrhythmias, congestive heart failure, baseline QTc over 500 ms, excessive prolongation of the QTc interval during treatment with sotalol, female gender, advanced age, concurrent use of more than one QT-prolonging drug and sotalol doses over 320 mg/day [94].

Sotalol should not be used in the setting of acute myocardial infarction, severe congestive heart failure (NYHA IV), cardiogenic shock, congenital or acquired long QT syndromes, bronchial asthma, severe hepatic and renal impairment, hypotension and in all conditions in which the use of a β-blocker is contraindicated (sinus bradycardia with a heart rate <50 bpm and bradyarrhythmias, second- and third-degree atrioventricular block, sick sinus syndrome and sino-atrial block).

Sotalol is primarily eliminated by renal excretion; therefore, drugs that are metabolized by CYP450 are not expected to alter the pharmacokinetics of sotalol and it is not expected to inhibit or induce any CYP450 enzymes. No pharmacokinetic interactions were observed with hydrochlorothiazide and warfarin and no significant interactions with other commonly used cardiovascular drugs are reported.

Sotalol should be administered with caution in conjunction with other drugs known to prolong the QT interval, such as other class III antiarrhythmic agents, phenothiazines, tricyclic antidepressants, astemizole, bepridil, certain oral macrolides and certain quinolone antibiotics. Thus, concomitant therapy with class III AADs are not recommended, because of their potential in prolonging refractoriness, and no experience is available on combination therapy with class I antiarrhythmics.

An additive class II effect is expected with concomitant use of other β-blocking agents and in conjunction with calcium channel blocking drugs. Possible additive effects on atrioventricular conduction, ventricular function and blood pressure with increased risk of bradyarrhythmias and hypotension is to be expected.

In conclusion, it seems reasonable to state that oral sotalol, used to current dosage and adjusted to renal function and QT interval, with accurate monitoring and prevention of the proarrhythmic conditions, is safe for maintenance of SR in patients with AF. Therapy should be initiated at 80 mg twice daily with a gradual upward dose titration and appropriate evaluations for efficacy and safety prior to dose escalation. The manufacturer's recommendations in the USA include initiating therapy in a setting where the patient can be monitored.

Regulatory affairs

Sotalol hydrochloride is currently approved in the USA and EU for the treatment of life-threatening ventricular arrhythmias. In these countries, sotalol is also indicated for rhythm control in patients with symptomatic AF or atrial flutter who are in SR. For this specific indication the only formulation available that has been approved in the USA is Bpace AF, distributed with a patient package insert appropriate for patients with these supraventricular arrhythmias.

Conclusion

In conclusion, D,L-sotalol is a useful AAD in AF therapy in patients without heart disease. Its main effect is in favor of rhythm control and its efficacy is not superior to class IC drugs in long-term follow-up.

Sotalol efficacy is limited in converting AF to SR, whereas drugs such as class IC drugs are more powerful in delaying conduction and are preferable.

The strong β-blocking effect of sotalol is probably the main mechanism in preventing postoperative AF; however, its efficacy is slightly superior to the conventional β-adrenoceptor blockers.

In controlled conditions, sotalol is a safe drug, although it has to be initiated in a hospital setting and under continuous monitoring, during at least 48–72 h. Patients consuming sotalol that are successfully cardioverted to SR have to be continuously monitored for at least 12–24 h.

Its employment in coronary heart disease patients has not been sufficiently proven and therefore current guidelines promoting use of the drug in that subset of patients should be revised.

Future perspective

Despite the fact that many drugs are currently available in AF rhythm control, their efficacy remains unsatisfactory, with a great number of arrhythmia recurrences and several short- and long-term AEs.

Recent studies are testing the hypothesis of a better efficacy and tolerability with the combination of different AADs. Theoretically, the combined use of two or more agents with different pharmacological profiles would improve

Executive summary

Atrial fibrillation
- Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and can occur in association with other cardiovascular diseases or in the absence of cardiopulmonary disease.
- AF is a major cause of morbidity and mortality, has a negative impact on patient quality of life and represents an extremely costly public health problem.
- Treatment of AF is currently based on two different strategies, rhythm control or rate control, with no difference on survival between these two approaches in patients on anticoagulation therapy. Nevertheless, rhythm control could be preferred as an initial strategy, especially in symptomatic patients and those with a good chance of remaining in sinus rhythm (SR).
- First-line therapy in rhythm control is represented by class IC drugs depending on an underlying disease. Nevertheless, sotalol showed a good efficacy in maintaining SR after successful cardioversion (CV) and the current guidelines also recommend its use in patients with no heart disease or coronary heart disease.

Sotalol
- Sotalol hydrochloride is an effective antiarrhythmic and antifibrillatory agent approved for the treatment of life-threatening ventricular arrhythmias and for maintenance of SR in symptomatic AF and atrial flutter.
- Sotalol has combined class II (β-blocking) and class III (cardiac action potential prolonging) properties.

Pharmacokinetic properties
- Orally administered sotalol is completely absorbed, is not metabolized and its bioavailability is absolute (90–100%). Plasma concentrations are dose-related.
- Time to peak plasma concentration is 2.5–4 h after oral administration and a steady state is attained within 2–3 days.
- Sotalol excretion is primarily through the kidneys, with plasma levels and half-life directly related to renal function. Mean half-life elimination time is 8 h in healthy subjects.

Clinical evidence
- Sotalol is not recommended for pharmacological CV of AF.
- Sotalol is superior to placebo in maintaining normal SR after successful CV and its efficacy is comparable to other available antiarrhythmic drugs, except for amiodarone, which is superior to sotalol but associated with more side effects.
- Its use is recommended in the rhythm control of AF in patients with little or no heart disease and in patients with coronary artery disease in the absence of heart failure.
- Sotalol is superior to conventional β-blockers in the prevention of postoperative AF and its use is a valid alternative to β-blockers in this setting.

Safety & tolerability
- Adverse reactions due to β-adrenergic receptor blockade, such as fatigue, dizziness, dyspnea, headache or worsening of bronchospasm, are similar to those associated with conventional β-blockers.
- The most dangerous adverse effect linked to its class III properties is the risk of torsade de pointes. This risk progressively increases with increasing dose, prolongation of QT interval or predisposing factors, such as renal function impairment, hypokalemia, bradycardia or concomitant use of other drugs that prolong repolarization.

Drug interactions
- Sotalol should be administered with caution in conjunction with other drugs known to prolong the QT interval because of their potential in prolonging refractoriness and proarrhythmic effects.
- Additive class II effects are expected with concomitant use of other β-blocking agents and in conjunction with calcium channel-blocking drugs.

Dosage & administration
- In patients with normal renal function, the initial dose of orally administered sotalol is 80 mg twice daily. An initial 48–72 h electrocardiogram control monitoring is advised.
- The minimally antiarrhythmic dose is 80–160 mg twice daily, but doses can be increased every 3–4 days to a maximum of 640 mg/day.

the efficacy in preventing recurrences and allow the assumption of lower dosages of single drugs, thus reducing the potential AEs.

Sotalol, due to its β-blocking properties and its ability to obtain rate control during recurrences, could be a possible candidate for combination therapy with class IC drugs. However, controlled studies are lacking.

Another possibility that has to be further validated is the efficacy of sotalol in the rhythm control of patients with coronary artery disease. In fact, it seems that the drug may have a better efficacy in this subgroup of AF patients, with an efficacy comparable to amiodarone. Nevertheless, this finding comes from a subgroup analysis of one study only and needs stronger evidence.

To evaluate the efficacy of sotalol in these settings, there is a need for randomized, controlled studies in the next few years and it is likely that its use could assume relevance in clinical practice only if no other competitive drugs enter the AADs market.

Among the competitors dronedarone, benzofuran derivative, has recently been shown to reduce AF recurrences compared with control [97], although to a lesser extent compared with amiodarone [101]. In addition, it seems to be the only AAD that was shown to reduce mortality in the ATHENA trial [98]. These favorable results are the basis for the worldwide market launch of the drug, which is already marketed in Germany, the UK and Canada.

Financial & competing interests disclosure

Bibliography

Papers of special note have been highlighted as:
▪ of interest
▪▪ of considerable interest

1   Fuster V, Rydèn LE, Cannom DS *et al.*: ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation. *J. Am. Coll. Cardiol.* 48(4), 149–246 (2006).
▪▪   **Clinical practice guidelines currently followed for the treatment of atrial fibrillation (AF) and prevention of its thromboembolic events.**

2   Benjamin EJ, Levy D, Vaziri SM *et al.*: Independent risk factor for atrial fibrillation in a population-based cohort: the Framingham heart study. *JAMA* 271, 840–844 (1994).

3   Kopecky SL, Gersh BJ, McGoon MD *et al.*: The natural history of lone atrial fibrillation. A population-based study over three decades. *N. Engl. J. Med.* 317, 669–674 (1987).

4   Go AS, Hylek EM, Phillips KA *et al.*: Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 285, 2370–2375 (2001).

5   Benjamin EJ, Wolf PA, D'Agostino RB *et al.*: Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 98, 946–952 (1998).

6   Stewart S, Hart CL, Hole DJ *et al.*: A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am. J. Med.* 113, 359–364 (2002).

7   Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 22, 983–988 (1991).

8   Stewart S, Murphy N, Walker A *et al.*: Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 90, 286–292 (2004).

9   Coyne KS, Paramore C, Grandy S *et al.*: Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 9(5), 348–356 (2006).

10   Le Heuzey JY, Paziaud O, Piot O *et al.*: Cost of care distribution in atrial fibrillation patients: the COCAF study. *Am. Heart J.* 147, 121–126 (2004).

11   Thrall G, Lane D, Carroll D, Lip GY: Quality of life in patients with atrial fibrillation: a systematic review. *Am. J. Med.* 119(5), 448, e1–e19 (2006).

12   Wyse DG, Waldo AL, DiMarco JP *et al.*: A comparison of rate control and rhythm control in patients with atrial fibrillation. *N. Engl. J. Med.* 347, 1825–1833 (2002).
▪   **A key study evaluating the prognostic impact of different strategies in AF treatment.**

13   Van Gelder IC, Hagens VE, Bosker HA *et al.*: A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N. Engl. J. Med.* 347, 1834–1840 (2002).

14   Hohnloser SH, Kuck KH, Lilienthal J: Rhythm or rate control in atrial fibrillation. Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 356, 1789–1794 (2000).

15   Carlsson J, Miketic S, Windeler J *et al.*: Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J. Am. Coll. Cardiol.* 41, 1690–1696 (2003).

16   Opolski G, Torbicki A, Kosior DA *et al.*: Rate control vs. rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest* 126, 476–486 (2004).

17   Roy D, Talajic M, Nattel S *et al.*: Rhythm control versus rate control for atrial fibrillation and heart failure. *N. Engl. J. Med.* 358(25), 2667–2677 (2008).

18   Bellandi F, Simonetti I, Leoncini M *et al.*: Long-term efficacy and safety of propafenone and sotalol for the mainteinance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *Am. J. Cardiol.* 88, 640–645 (2001).

19   Naccarelli GV, Deborah LW, Mazhar K *et al.*: Old and new antiarrhythmic drugs for converting and maintaining sinus rhythm in

atrial fibrillation: comparative efficacy and results of trials *Am. J. Cardiol.* 91(Suppl.), 15D–26D (2003).

■ **A review of available antiarrhythymic drugs (AAD) for rhythm control of AF and their efficacy.**

20 Lafuente-Lafuente C, Mouly S, Angel M *et al.*: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst. Rev.* (4), CD005049 (2007).

■ **Cochrane systematic review examining the evidence on AAD used for the treatment of AF and their efficacy, effects on all-cause mortality and adverse effects (AEs).**

21 Carunchio A, Fera MS, Mazza A *et al.*: A comparison between flecainide and sotalol in the prevention of recurrences of paroxysmal atrial fibrillation. *G. Ital. Cardiol.* 25(1), 51–68 (1995).

22 Roy D, Talajic M, Dorian P *et al.*: Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N. Engl. J. Med.* 342, 913–920 (2000).

23 Kochiadakis GE, Igoumenidis NE, Marketou ME *et al.*: Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo controlled study. *Heart* 84, 251–257 (2000).

24 Singh BN, Singh SN, Reda DJ *et al.*: Amiodarone versus sotalol for atrial fibrillation. *N. Engl. J. Med.* 352, 1861–1872 (2005).

25 Varro A, Biliczki P, Iost N *et al.*: Theoretical possibilities for the development of novel antiarrhythmic drugs. *Curr. Med. Chem.* 11, 1–11 (2004).

26 Roy D, Pratt CM, Torp-Pedersen D *et al.*: Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a Phase 3, randomized, placebo-controlled trial. *Circulation* 117, 1518–1525 (2008).

27 Dobrev D, Nattel S: New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet* 375, 1212–1223 (2010).

28 Lish PM, Weikel JH, Dungan KW: Pharmacological and toxicological properties of two new adrenergic receptor antagonists. *J. Pharmacol. Exp. Ther.* 149, 161–173 (1965).

29 Somani P, Watson DL: Antiarrhythmic activity of the dextro- and levorotatory isomers of 4-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide (MJ 1999). *J. Pharmacol. Exp. Ther.* 164, 317–325 (1968).

30 Hohnloser SH, Woosley RL: Sotalol. *N. Engl. J. Med.* 331(1), 31–38 (1994).

■ **A complete review of sotalol use in supraventricular and ventricular arrhythmias.**

31 Singh BN, Vaughan Williams EM: A third class of anti-arrhythmic action: effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br. J. Pharmacol.* 39, 675–677 (1970).

32 Strauss HC, Bigger JT Jr, Hoffman BF: Electrophysiological and β-receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ. Res.* 26, 661–670 (1970).

33 Nattel S, Feder-Elituv R, Matthews C *et al.*: Concentration dependence of class III and β-adrenergic blocking effects of sotalol in anesthetized dogs. *J. Am. Coll. Cardiol.* 13, 1190–1194 (1989).

34 Wang T, Bergstrand RH, Thompson KA *et al.*: Concentration-dependent pharmacologic properties of sotalol. *Am. J. Cardiol.* 57, 1160–1165 (1968).

35 Carmeliet E: Electrophysiologic and voltage clamp analysis of the effects of sotalol on isolated cardiac muscle and Purkinje fibers. *J. Pharmacol. Exp. Ther.* 232, 817–825 (1985).

36 Kato R, Ikeda N, Yabek SM *et al.*: Electrophysiologic effects of the levo- and dextrorotatory isomers of sotalol in isolated cardiac muscle and their *in vivo* pharmacokinetics. *J. Am. Coll. Cardiol.* 7, 116–125 (1986).

37 Hondeghem LM, Snyders DJ: Class III antiarrhythmic agents have a lot of potential but a long way to go: reduced effectiveness and dangers of reverse use dependence. *Circulation* 81, 686–690 (1990).

38 Schmitt C, Brachmann J, Karch M *et al.*: Reverse use-dependent effects of sotalol demonstrated by recording monophasic action potentials of the right ventricle. *Am. J. Cardiol.* 68, 1183–1187 (1991).

39 Anttila M, Arstila M, Pfeffer M, Tikkanen R, Vallinkoski V, Sundquist H: Human pharmacokinetics of sotalol. *Acta Pharmacol. Toxicol. (Copenh.)* 39, 118–128 (1967).

40 Sotaniemi EA, Anttila M, Pelkonen RO, Jarvensivu P, Sundquist H: Plasma clearance of propranolol and sotalol and hepatic drug-metabolizing enzyme activity. *Clin. Pharmacol. Ther.* 26, 153–161 (1979).

41 Sundquist H: Basic review and comparison of β-blocker pharmacokinetics. *Curr. Ther. Res.* 28, 38S–44S (1980).

42 Schnelle K, Garrett ER: Pharmacokinetics of the adrenergic blocker sotalol in dogs. *J. Pharm. Sci.* 62, 362–375 (1973).

43 Berglund G, Descamps R, Thomis JA: Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. *Eur. J. Clin. Pharmacol.* 18, 321–326 (1980).

44 Sundquist HK, Anttila M, Forsstrom J, Kasanen A: Serum levels and half-life of sotalol in chronic renal failure. *Ann. Clin. Res.* 7, 442–446 (1975).

45 Antonaccio MJ, Gomoll A: Pharmacology, pharmacodynamics and pharmacokinetics of sotalol. *Am. J. Cardiol.* 65(Suppl.), 12A–21A (1990).

46 Anderson JL, Askins JC, Gilbert EM *et al.*: Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized, placebo-controlled evaluation of two doses. *J. Am. Coll. Cardiol.* 8, 752–762 (1986).

47 Hohnloser SH, Zabel M, Krause T, Just H: Short- and long-term antiarrhythmic and hemodynamic effects of D,L-sotalol in patients with symptomatic ventricular arrhythmias. *Am. Heart J.* 123, 1220–1224 (1992).

48 Nademanee K, Feld G, Hendrickson J, Singh PN, Singh BN: Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation* 72, 555–564 (1985).

49 Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R: The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog. Cardiovasc. Dis.* 31, 115–172 (1988).

50 Hohnloser SH, Arendts W, Quart B: Incidence, type, and dose-dependence of proarrhythmic events during sotalol therapy in patients treated for sustained VT/VF. *Pacing Clin. Electrophysiol.* 15, 551–551 (1992).

51 Tjandramaga TB, Thomas J, Verbeeck R, Verbesselt R, Verberckmoes R, De Schepper PJ: The effect of end-stage renal failure and haemodialysis on the elimination kinetics of sotalol. *Br. J. Clin. Pharmacol.* 3, 259–265 (1976).

52 Nademanee K, Feld G, Noll E, Hendrickson JA, Singh BN: Effect of sotalol, class III antiarrhythmic agent, on conduction and refractoriness of the His-Purkinje system in man. *J. Am. Coll. Cardiol.* 5, 438–438 (1985).

53 Vanoli E, Hull SS Jr, Adamson PB, Foreman RD, Schwartz PJ: Effect of D-sotalol on ventricular fibrillation in conscious dogs with a healed myocardial infarction. *Eur. Heart J.* 14(Suppl.), 88–88 (1993).

54 Teo KK, Harte M, Horgan JH: Sotalol infusion in the treatment of supraventricular tachyarrhythmias. *Chest* 87, 113–118 (1985).

55 Jordaens L, Gorgels A, Stroobandt R *et al.*: Efficacy and safety of intravenous sotalol for termination of paroxysmal supraventricular tachycardia. The Sotalol Versus Placebo Multicenter Study Group. *Am. J. Cardiol.* 68(1), 35–40 (1991).

56   Sung RJ, Tan HL, Karagounis L *et al.*:
Intravenous sotalol for the termination of
supraventricular tachycardia and atrial
fibrillation and flutter: a multicenter,
randomized, double-blind, placebo-
controlled study. *Am. Heart J.* 129(4),
739–748 (1995).

57   Thomas SP, Guy D, Wallace E *et al.*: Rapid
loading of sotalol or amiodarone for
management of recent onset symptomatic
atrial fibrillation: a randomized, digoxin-
controlled trial. *Am. Heart J.* 147(1), 1–7
(2004).

58   Vos MA, Golitsyn SR, Stangl K *et al.*:
Superiority of ibutilide (a new class III agent)
over DL-sotalol in converting atrial flutter and
atrial fibrillation. The Ibutilide/Sotalol
Comparator Study Group. *Heart* 79, 568–575
(1998).

59   Hohnloser SH, van de Loo A, Baedeker F:
Efficacy and proarrhythmic hazards of
pharmacologic cardioversion of atrial
fibrillation: prospective comparison of sotalol
versus quinidine. *J. Am. Coll. Cardiol.* 26,
852–858 (1995).

60   Singh SN, Tang XC, Reda D, Singh BN:
Systematic electrocardioversion for atrial
fibrillation and role of antiarrhythmic drugs:
a substudy of the SAFE-T trial. *Heart Rhythm*
6, 152–155 (2009).

      Benditt DG, Williams JH, Jin J *et al.*:
Maintenance of sinus rhythm with oral
D,L-sotalol therapy in patients with
symptomatic atrial fibrillation and/or atrial
flutter. D,L-Sotalol Atrial Fibrillation/Flutter
Study Group. *Am. J. Cardiol.* 84, 270–277
(1999).

61   Wanless RS, Anderson K, Joy M *et al.*:
Multicenter comparative study of the efficacy
and safety of sotalol in the prophylactic
treatment of patients with paroxysmal
supraventricular tachyarrhythmias. *Am. Heart
J.* 133, 441–446 (1997).

62   Juul-Moller S, Edvardsson N,
Rehnqvist-Ahlberg N: Sotalol versus
quinidine for the maintenance of sinus
rhythm after direct current conversion of
atrial fibrillation. *Circulation* 82, 1932–1939
(1990).

63   Patten M, Maas R, Bauer P *et al.*:
Suppression of paroxysmal atrial
tachyarrhythmia – results of the SOPAT
trial. *Eur. Heart J.* 25, 1395–1404
(2004).

64   Fetsch T, Bauer P, Engberding R *et al.*:
Prevention of atrial fibrillation after
cardioversion: results of the PAFAC trial.
Eur. Heart J. 25, 1385–1394 (2004).

65   AFFIRM First Antiarrhythmic Drug
Substudy Investigators: Maintenance of
sinus rhythm in patients with atrial

fibrillation: an AFFIRM substudy of the first
antiarrhythmic drug. *J. Am. Coll. Cardiol.*
42(1), 20–29 (2003).

66   Kochiadakis GE, Igoumenidis NE,
Marketou ME *et al.*: Low-dose amiodarone
versus sotalol for suppression of recurrent
symptomatic atrial fibrillation.
Am. J. Cardiol. 81(8), 995–998 (1998).

67   Reimold SC, Cantillon CO, Friedman PL
et al.: Propafenone versus sotalol for
suppression of recurrent symptomatic atrial
fibrillation. *Am. J. Cardiol.* 71, 558–563
(1993).

68   Kochiadakis GE, Igoumenidis NE,
Hamilos ME *et al.*: Sotalol versus
propafenone for long-term maintenance of
normal sinus rhythm in patients with
recurrent symptomatic atrial fibrillation.
Am. J. Cardiol. 94, 1563–1566 (2004).

69   Kochiadakis GE, Marketou ME,
Igoumenidis NE *et al.*: Amiodarone, sotalol,
or propafenone in atrial fibrillation: which is
preferred to maintain normal sinus rhythm?
Pacing Clin. Electrophysiol. 23(11 Pt 2),
1883–1887 (2000).

70   Andrews TC, Reimold SC, Berlin JA *et al.*:
Prevention of supraventricular arrhythmias
after coronary artery bypass surgery.
A meta-analysis of randomized control trials.
Circulation 84, 236–244 (1991).

71   Crystal E, Connolly SJ, Sleik K, Ginger TJ,
Yusuf S: Interventions on prevention of
postoperative atrial fibrillation in patients
undergoing heart surgery: a meta-analysis.
Circulation 106, 75–80 (2002).

72   Mathew JP, Fontes ML, Tudor IC *et al.*:
A multicenter risk index for atrial fibrillation
after cardiac surgery. *JAMA* 291, 1720–1729
(2004).

73   Creswell LL, Schuessler RB,
Rosenbloom M, Cox JL: Hazards of
postoperative atrial arrhythmias. *Ann.
Thorac. Surg.* 56, 539–549 (1993).

74   Suttorp MJ, Kingma JH, Peels HOJ *et al.*:
Effectiveness of sotalol in preventing
supraventricular tachyarrhythmias shortly
after coronary artery bypass grafting.
Am. J. Cardiol. 68, 1163–1169 (1991).

75   Suttorp MJ, Kingma JH, Tjon Joe Gin RM
et al.: Low and high dose sotalol versus
propranolol in prevention of supraventricular
tachyarrhythmias early after coronary artery
bypass surgery. *J. Thorac. Cardiovasc. Surg.*
100, 921–926 (1990).

76   Gomes JA, Ip J, Santoni-Rugiu F *et al.*:
Oral D,L sotalol reduces the incidence of
postoperative atrial fibrillation in coronary
artery bypass surgery patients:
a randomized, double-blind, placebo-
controlled study. *J. Am. Coll. Cardiol.* 34,
334–339 (1999).

77   Pfisterer ME, Klöter-Weber UC, Huber M
et al.: Prevention of supraventricular
tachyarrhythmias after open heart operation
by low-dose sotalol: a prospective, double-
blind, randomized, placebo-controlled study.
Ann. Thorac. Surg. 64(4), 1113–1119 (1997).

78   Evrard P, Gonzalez M, Jamart J *et al.*:
Prophylaxis of supraventricular and
ventricular arrhythmias after coronary
artery bypass grafting with low-dose sotalol.
Ann. Thorac. Surg. 70, 151–156 (2000).

79   Connolly SJ, Cybulski I, Lamy A *et al.*:
Double-blind, placebo-controlled,
randomized trial of prophylactic metoprolol
for reduction of hospital stay after heart
surgery: the β-blocker length of stay (BLOS)
trial. *Am. Heart J.* 145, 226–232 (2003).

80   Parikka H, Toivonen L, Heikkilä L *et al.*:
Comparison of sotalol and metoprolol in the
prevention of atrial fibrillation after coronary
artery bypass surgery. *J. Cardiovasc.
Pharmacol.* 31(1), 67–73 (1998).

81   Abdulrahman O, Dale HT, Levin V *et al.*:
The comparative value of low-dose sotalol
vs. metoprolol in the prevention of
postoperative supraventricular arrhythmias.
Eur. Heart J. 20, Abstract 372 (1999).

82   Janssen J, Loomans L, Harink J *et al.*:
Prevention and treatment of supraventricular
tachycardia shortly after coronary artery
bypass grafting: a randomized open trial.
Angiology 37, 601–609 (1986).

83   Auer J, Weber T, Berent R *et al.*:
A comparison between oral antiarrhythmic
drugs in the prevention of atrial fibrillation
after cardiac surgery: the pilot study of
prevention of postoperative atrial fibrillation
(SPPAF), a randomized, placebo-controlled
trial. *Am. Heart J.* 147, 636–643 (2004).

84   Mooss A, Wurdeman R, Sugimoto JT *et al.*:
Amiodarone versus sotalol for the treatment
of atrial fibrillation after open heart surgery:
the Reduction in Postoperative
Cardiovascular Arrhythmic Events
(REDUCE) trial. *Am. Heart J.* 148(4),
641–648 (2004).

85   Burgess DC, Kilborn MJ, Keech AC:
Interventions for prevention of post-operative
atrial fibrillation and its complications after
cardiac surgery: a meta-analysis. *Eur. Heart J.*
27, 2846–2857 (2006).
▪   **The most recent and wide meta-analysis on
postoperative AF.**

86   Bradley D, Creswell LL, Hogue CW Jr *et al.*:
Pharmacologic prophylaxis: American
College of Chest Physicians guidelines for the
prevention and management of postoperative
atrial fibrillation after cardiac surgery. *Chest*
128, 39S–47S (2005).
▪▪   **Practice guidelines on prevention and
management of postoperative AF.**

87   Dunning J, Treasure T, Versteegh M *et al.*: Guidelines on the prevention and management of *de novo* atrial fibrillation after cardiac and thoracic surgery. *Eur. J. Cardiothorac. Surg.* 30, 852–872 (2006).

▪▪   **Practice guidelines on the prevention and management of postoperative AF.**

88   Campbell TJ, Gavaghan TP, Morgan JJ: Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass. Comparison with disopyramide and digoxin in a randomised trial. *Br. Heart J.* 54, 86–90 (1985).

89   Soyka LF, Wirtz C, Spangenberg RB: Clinical safety profile of sotalol in patients with arrhythmias. *Am. J. Cardiol.* 65 (Suppl.), 74A–81A (1990).

90   Singh SN, Chen YW, Cohen A *et al.*: Relation between ventricular function and antiarrhythmic responses to sotalol. *Am. J. Cardiol.* 64, 943–945 (1989).

91   Waldo AL, Camm AJ, deRuyter H *et al.*: Effect of D-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 348, 7–12 (1996).

92   Kühlkamp V, Mermi J, Mewis C, Seipel L: Efficacy and proarrhythmia with the use of D,L-sotalol for sustained ventricular tachyarrhythmias. *J. Cardiovasc. Pharmacol.* 29(3), 373–381 (1997).

93   Drew BJ, Ackerman MJ, Funk M *et al.*: Prevention of torsade de pointes in hospital settings. A scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* 121, 1047–1060 (2010).

▪   **Recent guidelines useful in preventing arrhythmic complications in AAD use.**

94   Chung MK, Schweikert RA, Wilkoff BL *et al.*: Is hospital admission for initiation of anthyarrhythmic therapy with sotalol for atrial arrhythmias required? Yield of in-hospital monitoring and prediction of risk for significant arrhythmia complications. *J. Am. Coll. Cardiol.* 32, 169–176 (1998).

95   Marcus FI: Risks of initiating therapy with sotalol for treatment of atrial fibrillation. *J. Am. Coll. Cardiol.* 32, 177–180 (1998).

96   Singh BN, Connolly SJ, Crijns HJ *et al.*: For the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N. Engl. J. Med.* 357, 987–999 (2007).

97   Hohnloser SH, Crijns HJ, van Eickels M *et al.*: for the ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N. Engl. J. Med.* 360, 668–678 (2009).

■ Website

101   Barquet P: DIONYSOS study results showed the respective profiles of dronedarone and amiodarone
http://en.sanofi-aventis.com/press/press_releases/2008/ppc_23625.asp
(Accessed April 2010)