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Role of antiarrhythmic drugs: frequent implantable cardioverter-defibrillator shocks, risk of proarrhythmia, and new drug therapy.

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Abstract

The Implantable Cardioverter Defibrillator (ICD) has become the standard of care in patients with ischemic and non-ischemic cardiomyopathy who are at high risk for arrhythmic events and sudden cardiac death. Recurrent ventricular arrhythmias are common after ICD implantation and the majority of ICD recipients receive one or more shocks within a year of implantation. Although ICDs save lives, the shocks from these devices are associated with profound physical, emotional and psychological trauma, increased morbidity, and poor quality of life. More than half of these patients receive adjuvant antiarrhythmic drug therapy to circumvent episodes of recurrent ventricular and supraventricular arrhythmia. Electrical storm is also common in this high risk population and requires prompt therapeutic intervention with antiarrhythmic drug therapy. Evidence suggests that antiarrhythmic drugs including β-blockers, sotalol, amiodarone and azimilide, are effective at reducing the shock burden in ICD patients. Although, some antiarrhythmic drugs can interfere with proper ICD function, cautious administration and subsequent monitoring with adjustment of device algorithms can help curtail this problem. Data supporting the need for and potential risk-benefits of adjuvant antiarrhythmic drug therapy in ICD patients are described in this paper.

Synopsis

The Implantable Cardioverter Defibrillator (ICD) has become standard of care in patients with ischemic and non-ischemic cardiomyopathy. Although ICD saves life, ICD shocks are emotionally and physically debilitating. Adjuvant antiarrhythmic drug therapy with β-blockers, sotalol, amiodarone and azimilide is effective in preventing ICD shocks. The

article examines benefits, pitfalls of adjuvant antiarrhythmic drug therapy in patients with an ICD.

Introduction

Use of Implantable Cardioverter Defibrillators (ICD) have revolutionized the care of patients with ischemic and non-ischemic cardiomyopathy.[1,2] The primitive ICD introduced in the 1980s by Mirowski and colleagues has become much more sophisticated with programming capabilities, atrial and left ventricular leads, anti-tachycardia pacing (ATP) algorithms, bi-ventricular pacing and cardioverting and defibrillating shocks.[1,3] Similarly, indications for ICD implantation are expanding as well.[4] Assessment for eligibility of an ICD implantation is considered one of the integral parts of management of cardiomyopathy patients due to mortality benefits. [1,2] Consequently, the number of ICD implantations has increased significantly in the last decade with a concurrent decrease in the use of stand-alone antiarrhythmic drugs for ventricular arrhythmia indications.[5-7]

The ICD prevents sudden cardiac death (SCD) by terminating the episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF), delivering ATP therapy or ICD shock. Therefore, patients with ICD typically receive one or more ICD therapies for spontaneous arrhythmias following implantation.[1,8] Despite the technological evolution of ICD systems, more than 20% of shocks that are delivered are due to supraventricular arrhythmia and are categorized as "inappropriate".[9-11] ICD shocks are physically and emotionally painful and most patients dread future shocks. [12] Many patients experience symptoms such as dizziness, palpitations, nervousness, flushing or even syncope before

receiving an ICD shock.[13] A higher incidence of depression and poor quality of life has been reported in patients who have received one of more ICD shocks, and adverse psychological outcomes directly correlate to the number of ICD shocks. [14-16]

Several anti-arrhythmic drugs have been shown to reduce ICD therapies including shocks. Upward of 70% patients end up receive adjuvant antiarrhythmic drug therapy for this indication. [17,18] This was best exemplified in the device arm of the Antiarrythmic versus Implantable Defibrillator (AVID) trial. [19] About 18% patients in the ICD arm of the AVID trial had to be started on adjuvant antiarrhythmic drug therapy (amiodarone 42%, sotalol 21%, and mexiletine 20%) to reduce frequent ICD shocks and to prevent recurrent ventricular arrhythmia. [19] Adjuvant antiarrhythmic drug therapy in these crossover patients reduced the one year arrhythmia event rate from 90% to 64%. Potential benefits, pitfalls, need for caution and the clinical trials of adjuvant antiarrhythmic drugs in ICD implanted patients will be discussed in this review.

Clinical trials supporting the efficacy of adjuvant antiarrhythmic drug therapy

Major clinical trials establishing the role of adjuvant antiarrhythmic drugs and their principle outcomes are listed in table 1. The majority of patients enrolled in these trials received an ICD for secondary prevention of SCD or a documented episode of VT/VF.

Sotalol was one of the first antiarrhythmic drugs tested for such an indication by Pacifico et al.[20] In this double-blind prospective multicenter trial, 302 patients with ICDs were randomized to receive either 160-320 mg of d,l-sotalol (n=151) or matching

placebo (n=151) and were followed for 12 months. In this study, compared to placebo, treatment with sotalol led to a 48% risk reduction of all-cause mortality and delivery of first shock for any reason (Figure 1). When ICD shock was categorized as appropriate vs. inappropriate, there was a 64% risk reduction for all-cause death or first inappropriate shock and a 44% risk reduction for all-cause death or first appropriate shock. The results remained unchanged when stratified by left ventricular ejection fraction or concomitant use of β-blockers. The mean frequency of all-cause shock was 1.43 ± 3.53 in the sotalol group compared to 3.89 ± 10.65 in control group. Rate of discontinuation of the drug was about 33% at one year in the sotalol and placebo groups. Patients receiving sotalol were more likely to have bradycardia and QT prolongation, but only one episode of torsades de pointes (TdP) was reported. Similar efficacy of sotalol was reported in another small scale study of 46 patients.[21] Similar to sotalol, dofetilide, a pure class I_{Kr} blocker, was shown to be effective in increasing the median time to first all-cause ICD shocks in a study by O'Toole et al.[27] However, dofetilide administration was associated with a high incidence of TdP in this study.

Although most of the patients with ICDs receive β-blockers as part of a comprehensive medical regimen, it is worth underscoring the importance of β-adrenergic blockade in prevention of ICD shocks. Simple β-blockers have been shown to be at least equally or more effective than sotalol in the prevention of ICD shocks. In a small prospective trial of 100 patients with an existing ICD, Kettering et al showed that metoprolol was as effective as sotalol in preventing VT/VF and resultant ICD interventions. [23] Similarly, in a post hoc analysis of 691 patients with ischemic cardiomyopathy in the Multicenter Automatic Defibrillator Implantation Trial II

(MADIT-II), patients receiving higher doses of metoprolol, atenolol and carvedilol had a 52% relative risk reduction for recurrent VT/VF requiring ICD therapy as compared to patients not on β-blockers. Superior efficacy of metoprolol to sotalol was demonstrated in a small prospective study of 70 patients with an ICD.[22] The probability of reaching a combined end point of symptomatic recurrence of fast VT or VF, or death was significantly lower at 1 and 2 years in the metoprolol group (83% and 74% respectively) as compared to the sotalol group (47% and 38% respectively, $p = 0.004$). ICD interventions in the form of ATP and shocks were significantly lower in the metoprolol compared to the sotalol arm.

Azimilide is a novel class III drug that blocks both the rapid and slow component of the delayed rectifier cardiac potassium current, and is effective in a variety of supraventricular arrhythmias.[28] Recent clinical trials have demonstrated its role in the prevention of ICD shocks. In a dose-range, pilot study of 172 ICD patients, Singer at el demonstrated that azimilide reduced the relative risk of appropriate ICD therapy (Shocks and ATP) by 69% at all administered doses (35 mg, 75 mg or 125 mg) as compared to placebo at one year follow-up. Azimilide did not have adverse effects on left ventricular function, resting heart rate, defibrillation or pacing thresholds. [24]

The efficacy of azimilide was further investigated by Dorian et al in the large prospective double-blind trial, SHock Inhibition Evaluation with azimiLiDe[25] (SHIELD) in 633 ICD recipients. The 2 primary end points of this trial were (1) all-cause shocks plus symptomatic tachyarrhythmias terminated by ATP and (2) all-cause shocks. A single secondary end point was all appropriate ICD therapies. Azimilide was tested in 75 mg

and 125 mg doses. At a median follow-up of 1 year, azimilide significantly reduced the first primary end point of all-cause shocks plus symptomatic arrhythmia terminated by ATP in both doses as compared to placebo (HR: 0.43 for 75 mg dose and HR: 0.53 for 125 mg dose) (Figure 2). There was no statistically significant difference in efficacy between the two doses, and there was a trend toward a reduction in the primary end point of all-cause shock alone with both doses of azimilide.

The secondary end point of all appropriate ICD therapies (shocks or ATPs) was reduced by both 75 and 125 mg/day azimilide (HR = 0.52 and 0.38 with p = 0.017 and 0.0004 respectively, Figure 2) with a trend toward a more significant effect at the 125 mg dose. Additional analysis revealed that treatment with azimilide led to significant decrease in the incidence of all ICD interventions and all-cause shocks with an increased inter-event interval suggesting a possible benefit in the treatment of electrical storm. This was confirmed by subsequent analysis of SHEILD data by Hohnloser et al who showed that treatment with 75 mg and 125 mg/day azimilide reduced the risk of electrical storm by 37% and 55% respectively as compared to placebo. These beneficial effects of azimilide translated into reduced emergency department visits and hospitalizations.[29]

Azimilide was well tolerated as an addition to conventional therapy. About 86% patient were on concomitant β-blocker therapy suggesting that benefits of azimilide were over and above traditional therapy. The overall incidence of adverse events and rates of early discontinuation (35-36%) were similar to placebo.[24-26] Azimilide therapy led to a dose dependent prolongation of the QT interval, however, TdP was reported in 5 patients without any consequences [25] One patient had severe but reversible neutropenia with 75

mg of azimilide.[25] In the context of the above data, azimilide is the first drug submitted to the Food and Drug Administration for use with an ICD and is currently under review to be used for this indication.

Amiodarone remains one of the most commonly used antiarrhythmic drugs, especially in patients with advanced cardiomyopathy due to its established efficacy and cardiac safety profile compared to other antiarrhythmic drugs. The OPTIC (Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients) study investigated the efficacy of β-blocker, sotalol and β-blocker plus amiodarone in the prevention of ICD shocks.[26] The OPTIC investigators randomized 412 patients with an ICD to receive β-blocker alone, sotalol alone, and amiodarone in addition to β-blocker and followed them for one year. The results showed that the patients treated with sotalol or amiodarone had reduced risk of shock of 56% compared to β-blocker alone. In addition, amiodarone plus β-blocker was more effective than β-blocker alone (HR = 0.27, $p < 0.001$) or sotalol (HR: 0.43, $p = 0.02$) in preventing both appropriate and inappropriate ICD shocks (Figure 3). Mortality was not significantly different among the three groups and no cases of TdP were reported. Rates of study drug discontinuation at 1 year were 18.2% for amiodarone, 23.5% for sotalol and 5.3% for β-blocker alone group. Adverse pulmonary, thyroid, and bradycardic events were more common with amiodarone treatment.

Similar to its congener amiodarone, dronedarone was effective in reducing the rate of appropriate ICD intervention during a 30 day follow-up in a small study.[30]

Benefits of Adjuvant antiarrhythmic drug therapy

Clearly, antiarrhythmic drugs reduce the incidence of both appropriate as well as inappropriate ICD therapies (both ATP and Shock) by more than half. [20,25,26] Such a reduction in ICD shocks would be expected to decrease emergency department visits as well as the rate of hospitalization.[25,29] A decrease in the number of ICD discharges also prolongs the battery life of the device.[31] As such, antiarrhythmic drug therapy result in overall improvement in quality of life of ICD implanted patients. Additionally, most antiarrhythmic drugs tend to prolong the tachycardia cycle length and may render the tachycardia more hemodynamically stable and thus amenable to termination with ATP.[32] Some antiarrhythmic drugs may reduce the defibrillation threshold (DFT) and facilitate defibrillation of VT/VF as discussed below.

About 10 to 30% patients with ICD develop electrical storm, defined as three or more episodes of hemodynamically destabilizing VT/VF occurring in a 24-hour period. Development of electrical storm is associated with increased morbidity, and a 40% 3-month mortality.[33-35] Although, recent clinical trials have suggested role of catheter ablation techniques as a first line treatment for electrical storm, antiarrhythmic drugs still remain the cornerstone for the therapy for electrical storm. Reversal of precipitating factors, optimization of β-blocker therapy and addition of intravenous amiodarone followed by oral maintenance dosing is required in most cases to abort and prevent recurrent ventricular arrhythmia.[33,36] As outlined above, the investigational agent azimilide has been shown to reduce risk of electrical storm by 37-55%.[37] The principle advantages of adjuvant antiarrhythmic drug therapy can be summarized as in Table 1.

Drug-device Interaction

A great deal of caution needs to be exercised when a new antiarrhythmic drug is started in a patient with an implanted device. Potential adverse drug-device interactions are listed in Table 2.

One of the most important drug-device interactions is a drug-induced increase in defibrillation and pacing thresholds leading to failure of treatment of life threatening arrhythmia. Although most antiarrhythmic drugs increase the defibrillation threshold (DFT), some may lower it. In a sub-study of 94 patients from OPTIC, amiodarone plus β-blocker therapy led to a small but statistically significant increase (1.29 J) in DFT after 8-13 weeks of therapy.[38] In contrast, treatment with sotalol and β-blocker was associated with decrease in DFT by 0.89 J and 1.67 J respectively. Careful testing of DFTs should be performed in all the patients, with special attention to those who have monophasic waveform ICDs, those with an epicardial lead system[39], patients with a high DFT at baseline, and patients treated with high dose,[40] chronic amiodarone. [41-44]

Azimilide has been shown to have minimal effects on the DFT or pacing thresholds in ICD patients.[24,45] Similarly, dronedarone has been shown to have no effect on defibrillation safety margin or pacing thresholds at its therapeutic dose or higher.[30,46]

Antiarrhythmic drugs are usually increase the cycle length of VT, which improve hemodynamic tolerability and effectiveness of ATP in most situations. The downside is that the drugs like amiodarone and sotalol may slow the tachycardia rate to such a degree that it becomes lower that the programmed tachycardia detection rate of the ICD leading to failure to sense VT.[47] Appropriate adjustments in the detection algorithm are necessary when adjuvant antiarrhythmic drugs are instituted. Antiarrhythmic drugs, especially Class

IC agents, may also affect the morphology of the QRS complex and thus impact morphology sensing and rhythm stability criterion leading to incorrect rhythm interpretation by the ICD and resultant inappropriate treatment.[48]

Drug induced proarrhythmia, especially TdP, is rare but serious problem when drugs with Class III effects like azimilide, sotalol, dofetilide and amiodarone are used, especially in patients with compromised repolarization reserve.[49] Extra-cardiac side effects of antiarrhythmic drugs like amiodarone are a limitation to its long term use. This may be less of an issue with new drugs like dronedarone or azimilide.[46]

Expert Opinion

In conclusion, adjuvant antiarrhythmic drug therapy should be considered an integral part of the management of patients with an ICD. Unanswered questions are: 1) Which patients should receive adjuvant antiarrhytmic drug therapy? 2) When to start the therapy? 3) What drugs to start? 4) When to consider catheter based ablation techniques?

The majority of clinical trials outlined above enrolled patients for whom the ICD was implanted for secondary prevention of SCD. Similar evidence in patients who have received the ICD for primary prevention is lacking. Such patients appear to have fewer device activations.[50,51] In the context of a lower risk population, adjuvant antiarrhythmic drug therapy should be started only if one or more ICD shocks have been delivered, with the expectation that well designed therapy can reduce ICD shocks and improve quality of life. The timing of antiarrhythmic drug therapy in patients should always be based on best physician judgment and patient preference.

It should be emphasized here that no drug has achieved approval for the prevention of ICD shocks, and we have no data to support early, prophylactic use. Although starting antiarrhythmic drug therapy before an ICD shock is delivered might be valuable, it should be kept in mind that antiarrhythmic drug therapy itself carries substantial risk.

When patients need drugs because of frequent shocks, the weight of evidence supports optimizing β-blocker therapy. If they are ineffective or poorly tolerated, amiodarone, azimilide, or sotalol may provide benefit. Any antiarrhythmic drug prescribed to treat serious ventricular arrhythmias, including those that have triggered an ICD shock, should be started under observation not only to observe for toxicity, but also to gauge efficacy. If proarrhythmia occurs, it tends to become manifest during the early stages of therapy, as drug concentrations approach steady state.

Catheter based mapping and ablation techniques have been considered a last resort treatment for patients with recurrent VT refractory to adjuvant drug therapy.[52] Although recent clinical trials support the role of catheter ablation techniques as a prime line treatment for prevention of recurrent ICD therapies including electrical storm, these techniques are invasive and results are operator dependent.[53-55] Data supporting the use of catheter ablation therapy are limited and do not address issues such as quality of life and cost. We believe that antiarrhythmic drugs remain first line therapy for prevention of ICD shocks for most patients.[56]

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Tables:

Table 1: Clinical trials summarizing benefits of adjuvant antiarrhythmic drug therapy.

Study	Drug/Dose	N per group	Follow-up	Primary Endpoint	Secondary Endpoint
Pacifico et al.[20]	Sotalol (207±55 mg) Vs. Placebo	151	12 months	All-cause death or all-cause ICD shock: Sotalol: 44%*(HR: 0.52) Placebo: 56%	Mean frequency of shocks due to any cause: Sotalol: 1.43 ± 3.53* Placebo: 3.89 ± 10.65
Kuhlkamp et al[21]	Sotalol (80 to 400 mg) Vs. placebo	≈ 46	12 months	Recurrence of VT/VF: Sotalol: 32.6%* Placebo: 53.2%	Total mortality: Same across the groups
Seidl et al[22]	Metoprolol (104±37 mg) Vs. Sotalol (242±109 mg)	35	26 ± 16 months	Appropriate ICD therapy: VT treated by ATPs: Metoprolol: 20%* Sotalol: 49% Fast VT/VF treated by ICD shocks: Metoprolol: 20%* Sotalol: 54%	Total mortality: Metoprolol: 3 deaths Sotalol: 6 deaths Actuarial survival rate: Not different between the two groups
Kettering et al[23]	Metoprolol (108±44 mg) Vs. Sotalol (319±91 mg)	50	727 days	Recurrent VT/VF requiring ICD Therapy: Metoprolol: 66% Sotalol: 60% Event free survival not different between groups	Total mortality: Metoprolol: 8 deaths Sotalol: 6 deaths Not different between the two groups
Singer et al[24]	Azimilide 35, 75 or 125 mg Vs. placebo	≈ 35-46	374 days	Frequency of appropriate ICD shocks and ATPs: Placebo: 36 35 mg AZ: 10* 75 mg AZ: 12* 125 mg AZ: 9* per patient-year. (HR: 0.31)	

Dorian et al[25] SHIELD	Azimilide 75, 125 mg Vs. placebo	≈199-214	1 year	<u>All-cause shock and ATP:</u> 75 mg AZ: HR=0.43* 125 mg AZ: HR=0.53* as compared to placebo <u>All-cause shock:</u> Tread towards reduction in treatment group	<u>Appropriate ICD therapy:</u> 75 mg AZ: HR=0.52* 125mg AZ: HR=0.38* as compared to placebo
Connolly et al[26] OPTIC	B-blocker vs. Sotalol vs. Amiodarone plus β-blocker	≈134-138	1 year	<u>All-cause ICD shock:</u> β-blocker: 38.5% Sotalol: 24.3% Amiodarone plus β-blocker: 10.3%* (HR: 0.27 Vs. β-blocker, HR: 0.43 Vs. sotalol)	

*, significant p value; AZ, azimilide; ATPs, antitachycardia pacing; HR, hazard ratio; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; SHIELD, Shock Inhibition Evaluation with azimiLiDe; OPTIC, Optimal Pharmacologic Therapy in Cardioverter Defibrillator Patients. Reproduced with permission from reference 8.

Table 2: Benefits and Pitfalls of adjuvant antiarrhythmic drug therapy in ICD patients.

Advantages and pitfalls of adjuvant antiarrhythmic drug therapy in patients with ICD
Pros: - Decrease in appropriate ICD shocks due to suppression of recurrent VT/VF -Decrease in inappropriate ICD shocks due to reduced frequency and better rate control of supraventricular rhythm -Slowing of tachycardia leading to improved hemodynamic tolerance -Slowing of rate of tachycardia facilitating successful termination by ATP -Prolongation of ICD battery life -Decrease in frequency of symptomatic non-sustained ventricular arrhythmias -Prevention and better treatment of electrical storm -Improved quality of life and sense of well-being -Reduced defibrillation threshold facilitating easier defibrillation -Improved control of maximal sinus rate -Reduced rate of recurrent ICD related hospitalizations **Cons:** -Interference in ICD function due to -Increase in defibrillation threshold -Increase in pacing threshold -Interference in accurate arrhythmia detection due to

-Slowing of rate of Ventricular tachycardia

-Decrease in amplitude of electrocardiogram interfering with sensing

-Limited effectiveness of rate stability criterion

-Adverse effects

-Cardiac:

-bradyarrhythmia

-Torsades de pointes

-Impairment of myocardial function

-Extra-cardiac toxicity

Reproduced with permission from reference 8.

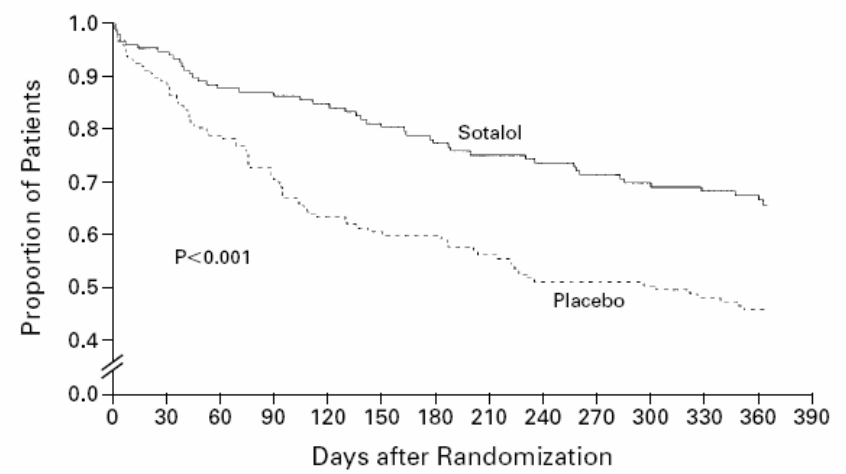
Figure Legends:

Figure 1: The Kaplan-Meier time-to-event curves for combined end point of all-cause death or all-cause shock in control and sotalol group. Treatment with sotalol reduced the relative risk of combined end point by 48%. Reproduced with permission from reference [20].

Figure 2: A: Effect of azimilide (AZ) on all-cause shocks plus symptomatic tachyarrhythmias terminated by antitachycardia pacing. Treatment with 75 mg/day and 125 mg/day azimilide significantly reduced risk of all-cause shocks and symptomatic tachyarrhythmia by 57% and 47% respectively. B: Effect of azimilide on all appropriate ICD therapies. Treatment with 75mg/day and 125 mg/day of azimilide significantly reduced the risk of all appropriate ICD therapies by 48% and 62% respectively. Reproduced with permission from reference [25].

Figure 3: Cumulative risk of shock in all three treatment groups. Amiodarone plus β-blocker significantly reduced the risk of shock compared with β-blocker alone (HR: 0.27, $p < 0.001$) and sotalol (HR: 0.43, $p = 0.02$). Reproduced with permission from reference [26].

Figure 1.



NO. AT RISK

Placebo	151	129	114	101	90	84	84	77	70	70	69	65	49
Sotalol	151	136	123	119	115	109	104	101	99	95	91	90	70

Figure 2.

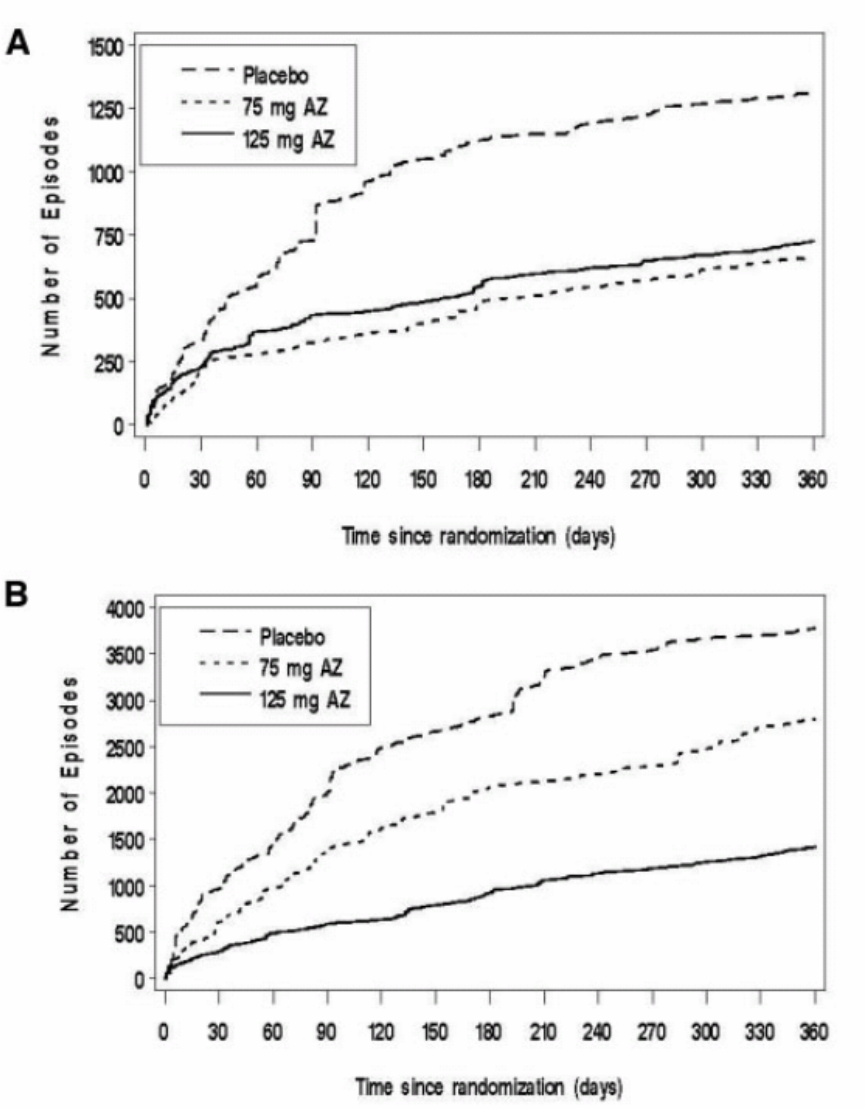
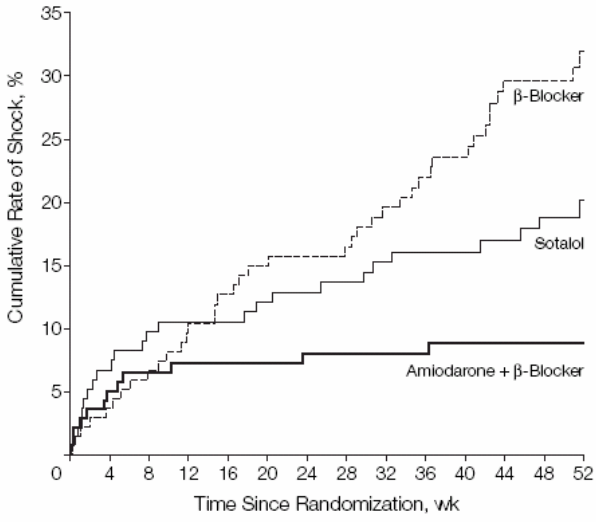

A
Placebo
75 mg AZ
125 mg AZ
Number of Episodes
1500
1250
1000
750
500
250
0
0 30 60 90 120 150 180 210 240 270 300 330 360
Time since randomization (days)
B
Placebo
75 mg AZ
125 mg AZ
Number of Episodes
4000
3500
3000
2500
2000
1500
1000
500
0
0 30 60 90 120 150 180 210 240 270 300 330 360
Time since randomization (days)

Figure 3.



No. at Risk					
β-Blocker	138	119	109	91	42
Sotalol	134	118	108	94	35
Amiodarone + β-Blocker	140	124	115	106	56