Effect of Amiodarone and Sotalol on Ventricular Defibrillation Threshold

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) Trial

Stefan H. Hohnloser, MD; Paul Dorian, MD; Robin Roberts, MTEch; Michael Gent, MSc; Carsten W. Israel, MD; Eric Fain, MD; Jean Champagne, MD; Stuart J. Connolly, MD

Background—Many patients with implanted cardioverter defibrillators (ICDs) receive adjunctive antiarrhythmic drug therapy, most commonly amiodarone or sotalol. The effects of these drugs on defibrillation energy requirements have not been previously assessed in a randomized controlled trial.

Methods and Results—The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial was a randomized clinical trial evaluating the efficacy of amiodarone plus β-blocker and sotalol versus β-blocker alone for reduction of ICD shocks. Within OPTIC, a prospectively designed substudy evaluated the effects of the 3 treatment arms on defibrillation energy requirements. Defibrillation thresholds (DFTs) were measured (binary step-down protocol) at baseline and again after 8 to 12 weeks of therapy in 94 patients, of whom 29 were randomized to receive β-blocker therapy (control group), 35 to amiodarone plus β-blocker, and 30 to sotalol. In the control group, the mean DFT decreased from 8.77 ± 5.15 J at baseline to 7.13 ± 3.43 J (P = 0.027); in the amiodarone group, DFT increased from 8.53 ± 4.29 to 9.82 ± 5.84 J (P = 0.091). In the sotalol group, DFT decreased from 8.09 ± 4.81 to 7.20 ± 5.30 J (P = 0.21). DFT changes in the β-blocker and the amiodarone group were significantly different (P = 0.006). In all patients, adequate safety margins for defibrillation were maintained. No clinical variable predicted baseline DFT or changes in DFT on therapy.

Conclusion—Although amiodarone increased DFT, the effect size with modern ICD systems is very small. Therefore, DFT reassessment after the institution of antiarrhythmic drug therapy with amiodarone or sotalol is not routinely required.

Key Words: defibrillation • antiarrhythmia agents • tachyarrhythmias

Implantable cardioverter defibrillators (ICDs) improve outcome in patients who present with sustained ventricular tachyarrhythmias1 or with cardiomyopathy and signs of congestive heart failure.2–5 Although ICDs reduce mortality compared with antiarrhythmic drug therapy,1 it is estimated that up to 50% of patients with an ICD ultimately need antiarrhythmic drug therapy to suppress frequent episodes of ventricular tachycardia or supraventricular tachyarrhythmias. Sotalol and amiodarone are the most commonly used drugs for this purpose.6,7 The efficacy of the ICD for terminating ventricular tachyarrhythmias is contingent on the presence of an adequate safety margin for defibrillation energy. Experimental data and early clinical studies indicate that antiarrhythmic drugs may significantly alter defibrillation energy requirements, usually measured as the defibrillation threshold (DFT).8–10 Amiodarone in particular was found in nonrandomized clinical studies to significantly increase the DFT.11,12 However, none of these investigations used a prospective, controlled design, all comprised only small patient populations, and the ICDs used were devices without active pectoral pulse generators and biphasic shock waveforms. Despite these shortcomings, these findings led to the recommendation to reassess the DFT after initiation of antiarrhythmic drug therapy.13 The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial was a randomized clinical trial that evaluated the efficacy of...
amiodarone and sotalol compared with β-blockers in reducing all-cause ICD shocks.\textsuperscript{14} At present, there are no data derived from randomized clinical trials available on the effects of amiodarone or sotalol on defibrillation energy requirements in patients with active pectoral leads systems and generators delivering biphasic shock waveforms, and therefore, this issue was addressed in a prospectively designed substudy of OPTIC.

Methods

Patient Population and Randomization

The methods of the OPTIC trial have been reported recently.\textsuperscript{14} In brief, patients were eligible if they had any of the following: (1) sustained ventricular tachycardia; (2) ventricular fibrillation (VF) or cardiac arrest (not within 72 hours of acute myocardial infarction) and left ventricular ejection fraction (LVEF) ≤0.40; (3) inducible ventricular tachycardia or fibrillation by programmed ventricular stimulation with LVEF ≤0.40; or (4) unexplained syncope with ventricular tachycardia or fibrillation, inducible by programmed ventricular stimulation. In addition, patients were required to receive a dual-chamber active-chron St Jude Medical (St Paul, Minn) defibrillator (Photon DR, Photon Micro DR, Atlas+ DR, Epic DR, Epic+ DR; maximum device output 30 to 36 J) within 21 days before randomization. The use of single- or dual-coil defibrillator leads was left to the discretion of the local investigator. Patients were randomized to receive a β-blocker (any 1 of 3 study β-blockers: metoprolol, recommended daily dose of 100 mg; carvedilol, recommended daily dose of 50 mg; or bisoprolol, recommended daily dose of 10 mg), amiodarone plus β-blocker (loading dose of 400 mg twice daily for 2 weeks, followed by 400 mg/d for 4 weeks, followed by 200 mg/d), or sotalol (240 mg/d). Patients treated with β-blockers served as controls against which the results obtained with amiodarone or sotalol were compared. At 4 study sites, all OPTIC patients were approached to participate in the DFT substudy. Patients were excluded from participation in this substudy if they had signs of congestive heart failure class IV, their LVEF was <0.20, or they had received amiodarone or sotalol for >20 consecutive days at any time.

Determination of DFT

DFT testing\textsuperscript{15} was performed at the time of device implantation and repeated 8 to 12 weeks after initiation of drug therapy. VF was induced with DC voltage applied across the defibrillation leads of the ICD. The first defibrillation shock was delivered at 550 V, with decrements of 100 V after each successful shock until defibrillation failure occurred. A rescue shock was applied and not used for DFT calculation. VF was again induced, and the shock voltage was increased by 50 V above the failed shock voltage for the subsequent shock. In case of failed defibrillation at 550 V, shock energy was increased by 100 V until the first success, and then decreased by 50 V. All shocks were biphasic, and shock duration was automatically adjusted to deliver 65% tilt shocks for each phase. Delivered energy and impedance were measured by the device programmer, digitally displayed, and recorded. The DFT was defined as the lowest shock strength that produced successful defibrillation. For better comparison with prior studies, all values are given in joules in the present report. Patients who were unable to remain on allocated therapy (ie, for reasons of adverse effects) were excluded. Patients were also excluded if in the intervening period they developed myocardial infarction or underwent coronary artery revascularization. In addition to DFT testing, the ventricular effective refractory period (VERP) was determined to assess drug-induced prolongation of refractoriness, and the shock electrogram duration (intracardiac electrogram intracardiac QRS duration) was measured as an index of conduction during ventricular pacing at a cycle length of 600 ms. VERP was measured at a drive cycle length of 600 ms, with extrastimuli applied after 12-beat drive trains, starting at a 20-ms coupling interval and incremented by 10 ms until the first ventricular capture, then decremented to 5 ms to measure the VERP within a 5-ms precision.

Statistical Analysis

The representativeness of the DFT subgroup was assessed by comparing the status of important baseline variables between the DFT patients and the remaining OPTIC patients not participating in the substudy. Quantitative variables were compared with t tests and categorical variables with Fisher exact tests. To determine the effect of treatment, the mean changes in DFT (baseline to follow-up measurement) were compared between groups via independent 2-sample t tests. The significance of within-group changes in DFT were assessed via the paired form of the t test. The relationship between baseline variables and baseline DFT, as well as change in DFT, were investigated with multiple linear regression. We calculated 95% CIs for the primary treatment effects on DFT. Statistical significance was assumed at a 2-sided P value of <0.05.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population

Baseline DFT was measured in 126 patients, of whom 94 underwent repeated testing during drug therapy. There were no significant differences in baseline characteristics between the 3 drug groups. Similarly, patients participating in this substudy had similar clinical characteristics as the entire OPTIC patient population (Table 1). Reasons for not repeating the testing included discontinuation of assigned drug therapy in 22 patients and withdrawal of consent in 10 patients. Thus, the present analysis is based on data obtained from 94 patients with complete assessment, of whom 29 were randomized to receive β-blocker therapy, 35 to amiodarone plus β-blocker, and 30 to sotalol (Table 2).

Antiarrhythmic Drug-Induced Changes in DFT

Repeated DFT testing was performed a median of 66 days (interquartile range [IQR] 57 to 89 days) after baseline

TABLE 1. Baseline Patient Characteristics: DFT Versus Non-DFT Patients in OPTIC

<table>
<thead>
<tr>
<th>Demographic/ Clinical Feature</th>
<th>DFT Substudy Group</th>
<th>Non-DFT Substudy Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>79 (84)</td>
<td>257 (80)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>65±10</td>
<td>64±10</td>
<td>0.56</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>74 (79)</td>
<td>254 (80)</td>
<td>0.66</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>23 (24)</td>
<td>46 (14)</td>
<td>0.028</td>
</tr>
<tr>
<td>History of nonischemic CMP</td>
<td>7 (8)</td>
<td>33 (10)</td>
<td>0.55</td>
</tr>
<tr>
<td>CHF symptoms of NYHA class II</td>
<td>54 (57)</td>
<td>142 (45)</td>
<td>0.034</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>0.35±11</td>
<td>0.34±11</td>
<td>0.24</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>23 (24)</td>
<td>68 (21)</td>
<td>0.57</td>
</tr>
<tr>
<td>History of pulmonary disease</td>
<td>5 (5)</td>
<td>15 (5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Unmonitored syncope</td>
<td>35 (37)</td>
<td>86 (27)</td>
<td>0.071</td>
</tr>
<tr>
<td>Spontaneously occurring VT or VF</td>
<td>72 (77)</td>
<td>223 (70)</td>
<td>0.15</td>
</tr>
<tr>
<td>Only inducible VT or VF</td>
<td>21 (22)</td>
<td>95 (30)</td>
<td>0.12</td>
</tr>
<tr>
<td>β-Blocker use at baseline</td>
<td>76 (81)</td>
<td>247 (78)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

β-blocker, and 30 to sotalol (Table 2).
assessment in patients taking β-blockers, 60 days (IQR 56 to 78 days) for patients treated with amiodarone and β-blockers, and 57 days (IQR 56 to 63 days) in patients given sotalol (P=0.053 for between-group comparison). There were no significant differences in baseline DFT between the 3 groups (Table 3; Figure 1). In patients assigned to receive β-blockers only, the mean DFT decreased by 1.64 J (95% CI −3.08 to −0.20), which was significantly different (P=0.006) from the mean increase of 1.29 J (95% CI −0.22 to 2.80) observed in the amiodarone group. After sotalol treatment, the mean DFT decreased by 0.89 J (95% CI −2.30 to 0.52; P=0.45 compared with β-blocker group and P=0.038 compared with the amiodarone group). The corresponding mean changes in DFT in terms of volts were −36 (β-blocker), +27 (amiodarone plus β-blocker), and −34 (sotalol). VERP increased by 14.6 ms (SD 32.6 ms) in the β-blocker group, by 35.7 ms (SD 26.7 ms) in the amiodarone group, and by 25.8 ms (SD 31.9 ms) in the sotalol group; only the difference between the β-blocker and amiodarone groups was statistically significant (P=0.012).

Of all patients who had a baseline DFT ≥10 J, none had an increase of >10 J on repeat testing (Figure 2). Only 1 patient, who had a baseline DFT of 2.5 J, had an increase of >10 J, to 19.5 J; this patient had been assigned to receive amiodarone. Thus, in all patients, an adequate safety margin of at least 10 J was maintained during drug treatment.

**Predictors of DFT at Baseline and of DFT Changes During Therapy**

Eight clinical variables (age, left ventricular function, gender, type of heart disease, spontaneous versus induced ventricular tachycardia or VF, unmonitored syncope, VERP, and intracardiac QRS duration) were tested by univariate and multivariate analysis as to their role as predictors of baseline DFT. Changes in DFT during repeat on-drug testing were correlated with the same variables plus treatment assignment. None of these variables served as an independent predictor of either baseline DFT or changes in DFT during repeat on-drug testing.

**Discussion**

This is the first randomized controlled study to assess the effects of amiodarone and sotalol on defibrillation energy requirements in patients implanted with contemporary dual-chamber ICDs. In the amiodarone group, DFT increased by 1.29 J (SD 4.39 J), which was significantly different from the small decline in DFT observed in the β-blocker group. However, this increase is extremely unlikely to affect patient outcome. Adequate safety margins for defibrillation were maintained in all patients. Accordingly, routine DFT reassessment after initiation of antiarrhythmic drug therapy does not appear to be required.

**Defibrillation Energy Requirements**

The baseline DFT was very low in patients in the present study (mean 8.6 J). This is in agreement with previous studies that reported similarly low average DFTs in patients receiving active pectoral pulse generators capable of delivering biphasic shocks.16–18 This implies that a safety margin of at least 10 J between the maximum output of the

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**TABLE 2. Dose of Study Drug (Milligrams per Day)**

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>β-Blocker Group (n=29)</th>
<th>Amiodarone and β-Blocker Group (n=35)</th>
<th>Sotalol Group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>101 ± 21 (n=19)</td>
<td>88 ± 35 (n=20)</td>
<td>100 ± 2 (n=3)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>15.7 ± 13.2 (n=2)</td>
<td>21.9 ± 21.9 (n=6)</td>
<td>...</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5.9 ± 2.7 (n=8)</td>
<td>3.4 ± 2.1 (n=7)</td>
<td>...</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>...</td>
<td>314 ± 243</td>
<td>...</td>
</tr>
<tr>
<td>Sotalol</td>
<td>...</td>
<td>167 ± 65</td>
<td>...</td>
</tr>
</tbody>
</table>

**TABLE 3. Results of DFT Testing**

<table>
<thead>
<tr>
<th>Visit</th>
<th>β-Blocker</th>
<th>Amiodarone and β-Blocker</th>
<th>Sotalol</th>
<th>P (Group Comparisons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, J</td>
<td>8.77 ± 5.15</td>
<td>8.53 ± 4.29</td>
<td>8.09 ± 4.81</td>
<td>...</td>
</tr>
<tr>
<td>Follow-up, J</td>
<td>7.13 ± 5.43</td>
<td>9.82 ± 5.84</td>
<td>7.20 ± 5.30</td>
<td>...</td>
</tr>
<tr>
<td>ΔDFT, J</td>
<td>−1.64 ± 3.53</td>
<td>1.29 ± 4.39</td>
<td>−0.89 ± 3.78</td>
<td>BB/A&amp;BB: 0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB/S: 0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A&amp;BB/S: 0.038</td>
</tr>
</tbody>
</table>

P (baseline; with therapy) | P=0.027 | P=0.091 | P=0.21 | ... |

BB/A&BB indicates comparison between β-blocker and amiodarone plus β-blocker groups; BB/S, comparison between β-blocker and sotalol groups; and A&BB/S, comparison between amiodarone plus β-blocker and sotalol groups.
device and the energy needed for defibrillation can be maintained in almost every patient. Whereas DFTs tended to increase over time with older transvenous lead systems,\textsuperscript{19,20} it has been shown that biphasic shock waveforms prevent the chronic rise of DFTs, and a small decrease in DFT is usually seen.\textsuperscript{21,22} This observation was confirmed in the present study, in which control (β-blocker group) and sotalol patients showed a small decrease in their average DFT at repeat testing.

**Antiarrhythmic Drug–Associated Changes in DFT**

The use of antiarrhythmic drugs as adjunctive therapy for suppression of supraventricular and ventricular arrhythmias is an important part of management of ICD patients,\textsuperscript{6,7} with amiodarone and sotalol being the most widely used drugs. Experimental studies have indicated that amiodarone increases defibrillation energy requirements.\textsuperscript{10,23,24} Early uncontrolled clinical studies using thoracotomy and nonthoracotomy ICDs found that the use of amiodarone was associated with higher DFTs.\textsuperscript{9,11,12,25–27} For instance, Khalighi et al.\textsuperscript{27} using nonthoracotomy monophasic defibrillators, found in a series of 119 ICD recipients that LV dilatation and amiodarone use were predictors of high DFTs. Shukla et al.\textsuperscript{28} retrospectively analyzed data from 968 patients who were enrolled in 2 separate clinical studies evaluating biphasic shock generators. In these uncontrolled studies, 11% of patients had high (defined as ≥18 J) DFTs. Several indices of advanced structural heart disease, such as New York Heart Association functional class III/IV or low LVEF and the preoperative use of amiodarone, were predictive of higher DFTs. Although no randomized trial has evaluated the effects of amiodarone on defibrillation energy requirements, observations from uncontrolled studies have been incorporated in current practice guidelines.\textsuperscript{13}

The OPTIC trial provided the opportunity to perform a properly controlled evaluation of the effects of amiodarone and sotalol in a randomized trial of patients with contemporary defibrillators that would be less affected by the potential biases of nonrandomized evaluations. Furthermore, it updates the evaluation of amiodarone to current ICD technology. In patients exposed to 6 to 8 weeks of amiodarone therapy, a very small increase in defibrillation energy requirement of 1.29 J was observed, which was statistically significant when compared with a small decrease in energy in the control group. However, a 1-J mean increase in required defibrillation energy is unlikely to have any effect on outcomes, particularly in light of the very low thresholds routinely observed with modern ICD systems. Large increases in DFT with amiodarone were rare. In the 1 case with a >10-J increase in DFT, an adequate safety margin of 10 J was maintained because of very low DFT at baseline (2.5 J). This increase may be due in part to regression to the mean rather than only an effect of amiodarone. In the present study, no significant delay in detection of VF on repeat DFT assessment was reported.

The present results are supported by recent nonrandomized studies that have reported little or no effect of amiodarone on DFTs with modern ICD systems.\textsuperscript{29,30} Hodgson et al.\textsuperscript{30} studied 102 patients receiving active-can biphasic ICDs, 11 of whom also received amiodarone. They reported a mean DFT of 9.3±4.8 J in patients without compared with 9.3±3.6 J in those with amiodarone therapy.\textsuperscript{30}

In animal experiments, sotalol has been shown to decrease defibrillation energy requirements.\textsuperscript{31} There have been no

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**Figure 2.** A, Individual changes in DFT for patients with a baseline DFT ≥10 J assigned to β-blocker therapy (mean change not significant). B, Individual changes in DFT for patients with a baseline DFT ≥10 J assigned to amiodarone plus β-blocker therapy (mean change not significant). C, Individual changes in DFT for patients with a baseline DFT ≥10 J assigned to sotalol therapy (mean change not significant).
systematic studies in humans of the effects of oral sotalol on DFT. In an uncontrolled study in patients with epicardial patch electrodes, Dorian and Newman reported a lowering in defibrillation energy requirements in patients treated with sotalol. In a retrospective analysis of patients with biphasic transvenous defibrillators, the average DFT of patients taking sotalol was 17 ± 6.1 J compared with 14.4 ± 7.2 J in patients not receiving antiarrhythmic drug therapy. The present study is thus the first randomized evaluation and demonstrates that in patients with modern ICDs, the effects of sotalol on DFT are similar to those of conventional β-blockers without class III antiarrhythmic properties.

Clinical Predictors of Defibrillation Energy Requirements

In contrast to older studies that used monophasic shocks with a variety of lead systems, we did not find any clinical variable to be an independent predictor of DFT. This notion is supported by other studies that similarly failed to prospectively identify those patients who would have high defibrillation energy requirements.

Study Limitations

Some patients at participating DFT centers did not participate in the DFT substudy, and others who initially participated did not complete the substudy. DFT patients differed somewhat from the whole OPTIC population, although there is no reason to suspect a systematic bias that would increase or decrease the effect of amiodarone on DFT. Nonetheless, we acknowledge that the present study does not have the same validity as if patients had been randomly selected for the DFT study from the main study population.

Previous reports have found that severely depressed left ventricular function may be a predictor of high DFTs. Consequently, patients with very low ejection fractions are often excluded from DFT determination in clinical practice. Because we excluded patients with an LVEF <20% and patients undergoing cardiac resynchronization therapy from the present study, we cannot exclude the possibility that amiodarone or sotalol may increase defibrillation energy requirements in this patient subset. Similarly, patients given significantly higher doses of amiodarone than used in the present study may show increased defibrillation energy requirements.

Clinical Implications

The present results do not support the practice of DFT reassessment after the institution of antiarrhythmic drug therapy with amiodarone or sotalol.

Acknowledgments

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Disclosures

Dr. Hohnloser has served on the speakers’ bureaus of Sanofi Synthelabo and St Jude Medical; has received honoraria from Sanofi Synthelabo, St Jude Medical, Medtronic, Solvay Pharmaceuticals, Boehringer Ingelheim, and GlaxoSmithKline; and has served as a consultant to and/or on the advisory boards of Sanofi Synthelabo, St Jude Medical, and Solvay Pharmaceuticals. Dr. Dorian has served on the speakers’ bureaus of and as a consultant to St Jude Medical and Sanofi Synthelabo. Dr. Israel has received honoraria from Medtronic and St Jude Medical. Dr. Fain is employed by St Jude Medical. Dr. Connolly has served on the speakers’ bureaus of, received honoraria from, and served as a consultant to St Jude Medical and Sanofi Synthelabo. The remaining authors report no conflicts.

References

Shocks from implanted defibrillators (ICDs) are unpleasant and affect quality of life. Therefore, many patients with ICDs require adjunctive antiarrhythmic drug therapy, most commonly amiodarone or sotalol, to avoid unnecessary ICD shocks. These drugs, however, may increase defibrillation energy requirements and may cause failure of the ICD to terminate sustained ventricular arrhythmias. The effects of amiodarone or sotalol on defibrillation energy requirements were systematically evaluated in a prospectively designed substudy of the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial, which was a randomized trial evaluating the efficacy of amiodarone plus β-blocker and sotalol versus β-blocker alone for reduction of ICD shocks. Defibrillation thresholds (DFTs) were measured at baseline and again after therapy in 94 patients, of whom 29 were randomized to receive β-blockers (control group), 35 to amiodarone plus β-blocker, and 30 to sotalol. In the control group, the mean DFT decreased from 8.77 ± 5.15 J at baseline to 7.13 ± 3.43 J (P = 0.027), in the amiodarone group, DFT increased from 8.53 ± 4.29 to 9.82 ± 5.84 J (P = 0.091). In the sotalol group, DFT decreased from 8.09 ± 4.81 to 7.20 ± 5.30 J (P = 0.21). In all patients, adequate safety margins for defibrillation were maintained. In summary, although amiodarone increased DFT, the size of the effect with modern ICD systems is very small. Accordingly, DFT reassessment after the institution of antiarrhythmic drug therapy with amiodarone or sotalol is not routinely required when a good DFT safety margin is present before drug therapy.

**CLINICAL PERSPECTIVE**

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