Is There an Association Between External Cardioversions and Long-Term Mortality and Morbidity?

Insights From the Atrial Fibrillation Follow-Up Investigation of Rhythm Management Study

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Background—Cardiac electric therapies effectively terminate tachyarrhythmias. Recent data suggest a possible increase in long-term mortality associated with implantable cardioverter-defibrillator shocks. Little is known about the association between external cardioversion episodes (ECVe) and long-term mortality. We sought to assess the safety of repeated ECVe with regard to cardiovascular mortality and morbidity.

Methods and Results—We analyzed the data of the 4060 patients from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial. In particular, associations of ECVe with all-cause mortality, cardiovascular mortality, and hospitalizations after ECVe were studied. Over an average follow-up of 3.5 years, 660 (16.3%) patients died, 331 (8.2%) from cardiovascular causes. A total of 207 (5.1%) and 1697 (41.8%) patients had low ejection fraction and nonparoxysmal atrial fibrillation, respectively; 2460 patients received no ECVe, whereas 1600 experienced ≥1 ECVe. Death occurred in 412 (16.7%), 196 (16.5%), 39 (13.5%), and 13 (10.4%) of patients with 0, 1, 2, and ≥3 ECVe, respectively. There was no significant association between ECVe and mortality within any of the 4 subgroups defined by ejection fraction and atrial fibrillation type, although myocardial infarction, coronary artery bypass graft, and digoxin were significantly associated with death (estimated hazard ratios, 1.65, 1.59, and 1.62, respectively; P<0.0001). ECVe were associated with increased cardiac hospitalization reported at the next follow-up visit (39.3% versus 5.8%; estimated odds ratio, 1.39; P<0.0001).

Conclusions—In the AFFIRM study, there was no significant association between ECVe and long-term mortality, even though ECVe were associated with increased hospitalizations from cardiac causes. Digoxin, myocardial infarction, and coronary artery bypass graft were significantly associated with mortality. (Circ Arrhythm Electrophysiol. 2011;4:465-469.)

Key Words: death □ arrhythmia □ atrial fibrillation □ cardioversion □ heart failure

Implantable cardioverter-defibrillators (ICDs) reduce mortality by terminating ventricular tachyarrhythmias. However, recent data have led to questions regarding the safety of internal shock by demonstrating an association between appropriate ICD shocks and long-term mortality. The risk of death was shown to increase 3- to 6-fold in various studies.1-5 Although an argument can be made regarding worsening heart failure leading to more ventricular arrhythmias and shocks, inappropriate ICD shocks, most commonly caused by atrial fibrillation (AF) and sinus tachycardia, also were associated with a 2-fold increase in mortality.1,6 The nature of this association remains unclear about whether this increased mortality results from the electric shock itself, the shock is a surrogate for a deteriorating myocardial substrate, or both. These new findings also have led to questions about whether repeated external shocks are safe in the long term? Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) was a large, prospective, randomized, multicenter study that assessed the effect of rate control versus rhythm control in management of AF. This study demonstrated that treatment of patients with AF at risk for stroke undergoing a rhythm-control strategy offered no survival advantage over a rate-control strategy. Use of external electric cardioversions to help maintain sinus rhythm was an important component of the treatment strategies. The goals of the present study were to determine whether external cardioversion episodes (ECVe) were associated with increased cardiac hospitalizations, cardiovascular mortality, and overall mortality among patients in the AFFIRM study.
Methods

Database Access

The AFFIRM study design, baseline characteristics, and results have been published previously. In brief, the study enrolled 4060 patients with AF compared to risk for stroke. These patients were randomized to rate control versus rhythm control over a 4-year period with a mean follow-up of 3.5 years. All patients gave informed consent to participate in the AFFIRM study, and all participating institutions received approval from their respective institutional review boards. Patients were seen for follow-up at 2 and 4 months after randomization and then every 4 months to a maximum of 6 years. The number of ECVe before randomization and during follow-up, major cardiac procedures, and primary and secondary end points were recorded. After approval from our institutional review board, a formal request was submitted through the Biological Specimen and Data Repository Information Coordinating Center to obtain archived data on the patients in the AFFIRM study.

Variable Definitions

The first outcome variable for the present study was death from any cause. The second outcome variable was death from a cardiovascular cause. Both outcome variables are time to event, thereby giving an understanding of how ECVe were related to whether and when the end points occurred. Corresponding to these 2 outcome variables were the following covariates: number of shock episodes (time-dependent covariate), defined as the number of instances in which ≥1 shocks were received based on archived data; normal versus low ejection fraction (EF), with low EF defined as ≤45% (patients with unspecified EF were treated as normal); paroxysmal versus permanent AF (time-dependent covariate), with transition to permanent AF defined by 3 follow-up visits with continuous AF, crossover to rate control, or both; history of myocardial infarction; prior coronary artery bypass graft; prior cardiac intervention procedure; and taking digoxin (time-dependent covariate).

The third outcome variable for our study was whether hospitalization for cardiac causes occurred, measured at each follow-up visit. We excluded trips to the emergency department and stays <24 hours. The corresponding covariates were whether a shock was received since the most recent follow-up visit and whether the patient had congestive heart failure (CHF), low EF, or both.

Statistical Analyses

For the first 2 outcome variables (all-cause and cardiovascular death), we tabulated how often these events occurred according to the number of shock episodes received, both overall and within 2 subgroups: patients with low EF and patients with permanent AF. Because shock episodes could occur weeks to months after randomization, groups of patients compared in these tabulations were not determined prospectively. Moreover, the classification of AF status in these tabulations was based on whether the patients developed permanent AF at any time during follow-up, which in some cases represented a change from baseline. As such, calculation of \( P \) values using methods assuming prospectively determined groups would be inappropriate, and for this reason, we have not reported \( P \) values. However, these tabulations are still useful for descriptive purposes.

Further statistical analysis with Cox proportional hazards models to derive \( P \) values was performed for all-cause mortality and cardiovascular mortality using EF and permanent AF as predictors along with the other covariates identified previously. The number of shock episodes was allowed to interact with both EF and AF status so that separate hazard ratios quantifying the effects of shock episodes could be estimated within each of 4 subgroups defined by EF and AF status: subgroup 1, low EF, permanent AF; subgroup 2, low EF, paroxysmal AF; subgroup 3, normal EF, permanent AF; and subgroup 4, normal EF, paroxysmal AF. The number of shock episodes, AF status, and digoxin were treated as time-dependent covariates in the Cox models. All other covariates, including EF, were measured at baseline. Subgroup membership thus was treated as time dependent in the Cox models, with some patients moving from subgroup 2 to 1 and others from subgroup 4 to 3 during follow-up. The number of shock episodes was defined as 0 at baseline and then increased by 1 at each occasion on which a patient received ≥1 shock. Because the exact number of shocks at each occasion was undocumented, we refer to this covariate as “number of shock episodes” rather than “number of shocks.”

For the third outcome variable (hospitalization for cardiac causes), we recorded the relative frequencies of cardiac hospitalization documented at follow-up visits with and without reported shocks, both overall and within 2 strata: patients with either CHF or low EF at baseline and patients with neither CHF nor low EF. Because hospitalization was a binary variable measured repeatedly, with time intervals between follow-up visits as the units of analysis, calculation of \( P \) values using methods assuming independent observations would be inappropriate. Therefore, further analysis fitting a generalized linear mixed model with subject-specific random effects to derive \( P \) values was performed. We assessed whether a shock was received as a predictor for cardiac hospitalization both overall and in patients who had CHF, low EF, or both. SAS version 9.2 (SAS Institute; Cary, NC) statistical software was used for all data analyses.

Results

Over an average follow-up of 3.5 years (maximum, 6 years), 660 of 4060 subjects died of which 331 deaths were of a cardiovascular etiology. There appeared to be little difference in the number of shock episodes received by patients who did not die versus those who did over the follow-up. As depicted in Table 1, survival was similar among patients with ≥3 shock episodes (89.6%) compared to patients with 2 (86.5%), 1 (83.5%), or 0 (83.3%) shock episodes. In particular, cardiovascular death was similar among patients with ≥3 shock episodes (5.6%) compared to patients with ≤2 shock episodes (6.9% to 8.4%). In subgroup analysis, survival of patients with low EF was somewhat higher among patients with ≥1 shock episode (81.1%) compared to patients with 0 (70.9%) (Table 2). For patients with permanent AF, survival was similar among patients with ≥1 shock episodes (89.0%) compared to patients with 0 (86.5%) (Table 2).

The Cox proportional hazards models did not reveal any significant effect of shock episodes on either all-cause or cardiovascular mortality, regardless of EF or AF status (all \( P \) values between 0.28 and 0.83), and there were no significant interactions of shock episodes with EF or AF status (all \( P \) values between 0.35 and 0.72). However, myocardial infarction, coronary artery bypass graft, and digoxin were positively associated with both all-cause and cardiovascular mortality (Table 3). In particular, digoxin...
elates the hazard of all-cause mortality by an estimated 62% ($P<0.0001$) and the hazard of cardiovascular mortality by an estimated 71% ($P<0.0001$), controlling for the other covariates in the models (Table 3).

On the other hand, the relative frequency of cardiac hospitalization documented at follow-up visits with reported shocks (39.3%) was much higher than that documented at follow-up visits without reported shocks (5.8%). Similar patterns applied within the stratum of patients with neither CHF nor low EF, with either CHF or low EF, and within the stratum of patients with either CHF or low EF (45.7% versus 8.1%).

The generalized linear mixed model confirmed that for the entire AFFIRM cohort, external shocks were significantly associated with cardiac hospitalization (estimated odds ratio, 1.39 [for any shock versus no shock in the time interval between follow-up visits]; 95% CI, 1.37 to 1.42; $P<0.0001$). This association was consistent among the subgroup of patients with neither CHF nor low EF (36.9% versus 5.1%) and within the stratum of patients with either CHF or low EF (45.7% versus 8.1%).

Discussion

The most important finding in this study is that there was no significant association between ECVe and long-term total or cardiovascular mortality in patients with AF, even in patients with low EF, permanent AF, or both. External cardioversion carried no increase in long-term mortality regardless of the number of attempts or energy level used.

Internal electric therapies are known to increase survival, but recently, concerns have been raised regarding a potential long-term deleterious effect. It was postulated that external cardioversion also may carry an increased risk of mortality based on the theory that ventricular myocytes seem similarly affected by the electric current regardless of the source. It is indeed well established that any type of electric cardiac therapy above a certain magnitude will create temporary or permanent damage to the myocardium. Several pathophysiological mechanisms have been postulated to explain the damage at the cellular or organ level, including the following: increased cellular membrane permeability (electroporation); cellular calcium-generated currents and load abnormalities causing abnormal conduction; myocardial injury with troponin elevation possibly related to heat elevation and free radical generation; alteration in myocardial function with stunning and electromechanical dissociation; and neurohormonal changes with hypothalamic-pituitary-adrenal activation (immediate secretion of cortisol, adrenaline, and noradrenaline). However, these acute effects may not be sufficient to account for the reduced survival observed months after appropriate or inappropriate ICD shocks. It is possible that a delayed mechanism owing to the modification of signaling pathways at a molecular level may cause further neurohormonal and structural changes that accentuate heart failure, ultimately leading to decompensation and death.

Several observations can be made regarding the possible harmful effects of cardiac electric therapies. First, it cannot be completely excluded that ECVe may still be harmful in patients with severe irreversible cardiomyopathy and that a sizable proportion of our patient population may have had a less severe reversible tachycardia-induced cardiomyopathy. Second, the electric fields produced during external and internal electric shocks are very different. The electric field produced by a shock creates a heterogeneous voltage gradient across the myocardium. The highest voltage gradient is present closest to the shocking

Table 2. Death and Cardiovascular Death in Relationship to Shock Episodes in Patients With Low EF or Nonparoxysmal AF

<table>
<thead>
<tr>
<th>No. Cardioversion Episodes</th>
<th>No. Patients</th>
<th>No. Deaths (%)</th>
<th>No. Cardiovascular Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with low EF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>117</td>
<td>34 (29.1)</td>
<td>24 (20.5)</td>
</tr>
<tr>
<td>≥1</td>
<td>90</td>
<td>17 (18.9)</td>
<td>10 (11.1)</td>
</tr>
<tr>
<td>Patients with nonparoxysmal AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>935</td>
<td>126 (13.5)</td>
<td>63 (6.7)</td>
</tr>
<tr>
<td>≥1</td>
<td>762</td>
<td>84 (11.0)</td>
<td>41 (5.4)</td>
</tr>
</tbody>
</table>

Because some episodes occurred weeks to months after randomization and because some patients transitioned to nonparoxysmal AF after randomization, the percentages are best viewed as descriptive. AF indicates atrial fibrillation; EF, ejection fraction.

Table 3. Results From Cox Proportional Hazards Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death Estimated HR (95% CI)</th>
<th>P</th>
<th>Cardiovascular Death Estimated HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative no. shock episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal EF, paroxysmal AF</td>
<td>1.05 (0.92–1.21)</td>
<td>0.44</td>
<td>1.08 (0.89–1.31)</td>
<td>0.43</td>
</tr>
<tr>
<td>Low EF, paroxysmal AF</td>
<td>0.86 (0.55–1.35)</td>
<td>0.52</td>
<td>0.84 (0.47–1.51)</td>
<td>0.55</td>
</tr>
<tr>
<td>Normal EF, permanent AF</td>
<td>0.95 (0.80–1.13)</td>
<td>0.58</td>
<td>1.03 (0.81–1.29)</td>
<td>0.83</td>
</tr>
<tr>
<td>Low EF, permanent AF</td>
<td>0.78 (0.50–1.22)</td>
<td>0.28</td>
<td>0.79 (0.44–1.43)</td>
<td>0.44</td>
</tr>
<tr>
<td>History of MI</td>
<td>1.65 (1.35–2.01)</td>
<td>&lt;0.0001</td>
<td>2.35 (1.80–3.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1.59 (1.29–1.97)</td>
<td>&lt;0.0001</td>
<td>1.43 (1.06–1.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior cardiac interventional procedure</td>
<td>0.91 (0.70–1.19)</td>
<td>0.50</td>
<td>0.94 (0.66–1.33)</td>
<td>0.71</td>
</tr>
<tr>
<td>Digoxin use</td>
<td>1.62 (1.38–1.90)</td>
<td>&lt;0.0001</td>
<td>1.71 (1.37–2.15)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Deaths not explicitly classified (47 in total) were treated as noncardiovascular. Patients with unknown EF (3166 in total) were treated as having normal EF. Cumulative number of shock episodes, AF status, and digoxin use are time-dependent covariates. CABG indicates coronary artery bypass graft; HR, hazard ratio; MI, myocardial infarction. Other abbreviations as in Table 2.
electrodes (external pads or internal coils) and fall off quickly with distance.\textsuperscript{13} The difference between the maximum and minimum voltage gradient created for an external shock is much lower than that of an internal shock. The ratio of the maximum to the minimum electric voltage gradient created by an internal defibrillation in the heart can be as high as 30:1 versus 5:1 for external therapy.\textsuperscript{23,24} Therefore, the voltage gradient surrounding the internal defibrillation electrode is much higher compared to the remote external defibrillation pads, potentially damaging the adjacent myocardium.\textsuperscript{13} In particular, the membrane of the myocytes surrounding the internal defibrillation electrode becomes highly permeable after defibrillation, allowing unregulated entry of molecules, such as free radicals (a phenomenon known as electroporation).\textsuperscript{13} This mechanism may account for the discrepancy between the effects of internal shock found in the literature and those of external cardioversion in the present study. Although the amount of energy delivered externally is much higher than internally (typically 100 to 360 J with monophasic shocks versus 5 to 35 J), the amount of current transmitted to the myocardium is <5\% with external shocks.\textsuperscript{25} Third, the effect on the myocytes of a synchronized external shock in patients with predominantly atrial arrhythmias may be different compared with a desynchronized internal shock in patients with predominant ventricular arrhythmias.

Finally, it is possible that none of the current clinical electric cardiac therapies are harmful. The association between internal shocks and mortality may not necessarily mean causation (ie, that shocks directly cause mortality). The increased total mortality observed with internal defibrillation\textsuperscript{1–4} may simply be a marker of heart failure progression and cardiac deterioration. In particular, there was a 2-fold increase in mortality with inappropriate shocks in the Multicenter Automatic Defibrillator Implantation Trial II and Sudden Cardiac Death in Heart Failure trial\textsuperscript{1,6} that were predominantly due to AF and supraventricular tachycardias. The presence and consequences of supraventricular arrhythmias in patients with heart failure and low EF may determine the outcome rather than the shock itself. Similarly, the increased nonarhythmic cardiac deaths observed early after a myocardial infarction with ICDS\textsuperscript{26,27} may be related to an irreversible process not associated with or treated effectively by ICD therapy.

Among patients in the AFFIRM study, hospitalizations for cardiac causes were more likely to occur at follow-up visits after an ECVe, regardless of whether patients had CHF, low EF, or both. Several factors may account for those increased hospitalizations after cardioversions, such as a relapse of symptomatic AF or acute CHF (typically seen within 96 hours in up to 3\% of patients).\textsuperscript{28,29} Mechanisms for acute heart failure after ECVes include systolic and diastolic transient dysfunction of the atria and ventricles potentially worsened by antiarrhythmic drugs or anesthetic agents.

Although there was no significant association between ECVes and mortality, the presence of myocardial infarction or coronary artery bypass graft at baseline significantly elevated the risk of mortality among patients in the AFFIRM study, which is consistent with previous data suggesting that the occurrence of AF with ischemic heart disease is associated with a worse prognosis.\textsuperscript{30} The presence of digoxin also was clearly an important predictor of both all-cause and cardiovascular death. A previously proposed explanation for this increased mortality was that patients receiving digoxin in the AFFIRM study had medical conditions with a known increased risk of death, such as CHF.\textsuperscript{31} However, we found that digoxin use remained a significant predictor of cardiovascular and total death even after controlling for EF. Therefore, an alternative explanation to account for this increased mortality relates to elevated serum digoxin concentrations, similar to several recent studies that demonstrated a relationship between digoxin toxicity and mortality.\textsuperscript{32–34}

**Study Limitations**

The archived data limited our ability to ascertain the actual number of shocks received during each ECVe. In addition, the energy delivered during each ECVe could not be verified. However, because the number of ECVes was contained in the archived data, we were still able to investigate whether shocks might be associated with mortality and cardiac hospitalization. The majority of the cardioversions were monophasic because this was the only option available at the time of the AFFIRM study. Biphasic waveforms are now a standard for both external and internal cardioversions. For the same amount of delivered energy, biphasic waveforms are more effective than monophasic waveforms to restore normal rhythm and reduce myocardial damage through a lower peak current.\textsuperscript{35,36} Therefore, our results likely would have been similar with biphasic shocks. Although ECVes were highly significantly associated with hospitalizations for cardiac causes, no detailed analysis of cardiac causes of hospitalizations was possible because the specific cause of cardiac hospitalizations was not supplied in the archived data. Finally, the common limitations inherent to any post hoc analysis apply to this study.

**Conclusions**

In the AFFIRM study cohort, there were no significant associations between ECVes and either cardiovascular or all-cause death. In particular, ECVes were not significantly associated with increased mortality within any of the 4 specific subgroups of patients defined by EF and AF status. On the other hand, ECVes were highly significantly associated with hospitalizations for cardiac causes. Digoxin, coronary artery bypass graft, and myocardial infarction were significantly associated with cardiovascular and all-cause death.

**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

At a time when the safety of internal cardiac electrical therapy delivered by implantable cardioverter-defibrillators is being questioned, we analyzed the Atrial Fibrillation Follow-up Investigation of Rhythm Management study to assess whether repeated external cardioversions are associated with long-term mortality and morbidity. The post hoc analysis of this large, prospective, multicenter randomized controlled trial revealed no significant association between the number of external cardioversion episodes and long-term mortality. Repeated cardioversions also were safe in specific subgroups of patients considered sicker (patients with low ejection fraction, persistent or permanent atrial fibrillation, or both). However cardioversions were associated with increased hospitalizations for cardiac causes. These findings are reassuring in our daily practice when repeated cardioversions at high energy levels are needed.
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