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## **Prophylactic Defibrillator Implantation—Toward an Evidence- Based Approach**

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## EDITORIALS



## Prophylactic Defibrillator Implantation — Toward an Evidence-Based Approach

Alan Kadish, M.D.

Most patients who have an out-of-hospital cardiac arrest do not survive. Thus, the use of a prophylactic implantable cardioverter–defibrillator (ICD) for the primary prevention of sudden death is a conceptually attractive option for high-risk patients. Several clinical trials have previously shown that ICDs reduced mortality in patients with coronary artery disease who had not yet had a life-threatening arrhythmia and who were selected on the basis of either the results of electrophysiological testing or left ventricular dysfunction.<sup>1–4</sup> In the past year, four multicenter clinical trials have helped refine the selection of appropriate patients for ICD therapy. In addition to confirming and expanding data on patients with chronic coronary artery disease, these studies added new information about the treatment of patients with nonischemic cardiomyopathy,<sup>5</sup> recent myocardial infarction,<sup>6</sup> and wide QRS complexes.<sup>7</sup>

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),<sup>8</sup> reported in this issue of the *Journal*, included patients with left ventricular dysfunction regardless of cause and used the presence of heart failure despite medical therapy and a left ventricular ejection fraction of less than 36 percent as an entry criterion. The trial convincingly showed that amiodarone does not decrease mortality among patients with left ventricular dysfunction and heart failure. The study also showed that patients who received an ICD have a better outcome than those who were treated with medical therapies, including angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers. The study confirmed the effectiveness of ICDs in prolonging survival among patients with heart failure and coronary disease, although the benefit was smaller than that seen in prior studies, perhaps because of better medical therapy in the control group.<sup>2,3</sup>

Only one large study had previously examined

the ability of the ICD to decrease mortality among patients with nonischemic cardiomyopathy. The Defibrillators in NonIschemic Cardiomyopathy Treatment Evaluation (DEFINITE) study showed a relative 35 percent decrease in overall mortality with the use of ICD therapy, a difference that did not quite reach statistical significance.<sup>5</sup> In SCD-HeFT, there was a 27 percent relative decrease in mortality among patients with nonischemic cardiomyopathy. The results of these two studies are broadly consistent and suggest that ICDs can improve survival among patients with nonischemic cardiomyopathy and severe left ventricular dysfunction.

Although the results of SCD-HeFT are generally consistent with previous clinical trials, there are some differences that require further investigation. As noted by the authors, the benefit of the ICD in SCD-HeFT appeared to be more marked in patients with less severe congestive heart failure (New York Heart Association class II) than it did in those with class III heart failure — a finding that differed from those of other trials. Other studies have shown that the benefit of the ICD either did not vary according to heart-failure class or was greater among patients with class III congestive heart failure. The SCD-HeFT investigators believe that this difference may be a statistical aberration. To investigate this hypothesis further, it will be necessary to analyze data on the relative benefits of ICD among patients with ischemic and nonischemic cardiomyopathy who have class II and class III congestive heart failure.

Although the ICD has been shown to be beneficial in patients with chronic left ventricular dysfunction, this is not the case when the ICD is used immediately after myocardial infarction.<sup>7</sup> Thus, ICD therapy for the primary prevention of sudden death in patients with left ventricular dysfunction should be considered a long-term rather than a short-term intervention.

The addition of a left ventricular lead to provide resynchronization therapy has been shown to improve heart failure and decrease mortality among patients with left ventricular dysfunction and wide QRS complexes.<sup>9</sup> Patients with class III congestive heart failure who meet indications for the prophylactic use of an ICD and have wide QRS complexes should receive resynchronization therapy with an ICD. There are not yet sufficient data to recommend such therapy for patients with class II congestive heart failure and wide QRS complexes or for patients with narrow QRS complexes but with evidence of mechanical dyssynchrony. ICD therapy is not specifically recommended for the primary prevention of sudden death for patients with class IV congestive heart failure, since the competing risk of progressive pump failure may outweigh the survival benefit from rapid termination of ventricular tachyarrhythmias. However, since some patients who receive resynchronization therapy will have improvement in their heart failure, the potential benefits of such therapy in this population should be studied further.

Although ICDs have been shown to be lifesaving, they are expensive. The cost (including follow-up) may reach as much as \$40,000, even if single-lead, “low-cost” ICDs are used. The effect of routine prophylactic use of ICDs on health care costs in the United States must be carefully considered.<sup>10</sup> A recent preliminary analysis of data from SCD-HeFT suggests that ICDs are indeed cost-effective on the basis of routinely accepted norms.<sup>11</sup> The Center for Medicare and Medicaid Services has recently suggested in a preliminary coverage decision that patients with left ventricular dysfunction and an ejection fraction of less than 31 percent should be eligible to receive a single-chamber ICD as long as they are enrolled in a prospective registry, as discussed elsewhere in this issue of the *Journal*.<sup>12</sup> This proposed coverage decision is a reasonable compromise between ensuring that patients at highest risk receive ICD therapy and avoiding a large escalation in health care costs. It is based on post hoc analyses of SCD-HeFT and DEFINITE, in both of which the benefit of ICDs appeared to be less in patients with left ventricular ejection fractions of 31 to 35 percent (Al-Khatib S: personal communication).

Although the addition of an atrial lead to an ICD could theoretically decrease the incidence of inappropriate ICD shocks, there have been no prospective studies showing convincing clinical benefit through the addition of an atrial lead. Thus, until more data are available, implanting single-chamber ICDs in most patients who receive a pro-

phylactic ICD is appropriate. However, allowing atrial leads to be added for arrhythmia discrimination and therapy in patients with documented supraventricular tachyarrhythmias seems reasonable. Additional data regarding outcome from a registry of patients receiving ICDs will be beneficial. However, whether the data in this registry will be sufficiently comprehensive to permit meaningful outcome analyses will take several years to determine.

How should physicians apply the results of the recent ICD trials in clinical practice? Patients with ejection fractions of less than 31 percent should be considered for a single-chamber ICD to improve their survival. Resynchronization therapy should be used when appropriate. Patients with ejection fractions of 31 to 40 percent pose a more difficult treatment challenge. For patients with coronary disease, data from some trials support the use of electrophysiological testing as an additional risk-stratification tool.<sup>4</sup> For patients with nonischemic cardiomyopathy, reimbursement guidelines and clinical judgment should be used to evaluate the risk–benefit ratio of the use of ICDs for patients with an ejection fraction of 31 to 35 percent, and the use of ICDs is probably not beneficial for patients with an ejection fraction of more than 35 percent.

Although the ICD is effective in reducing mortality among patients with left ventricular dysfunction, it may also result in morbidity, including a high incidence of inappropriate shocks. Not all patients with left ventricular dysfunction should immediately receive an ICD. However, physicians should evaluate and discuss the risk–benefit ratio for each patient regardless of the cause of heart failure, keeping in mind that evidence now supports the concept that ICDs will prolong life and should be used in most patients with severe left ventricular dysfunction.

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## Reducing the Risks of Gastrointestinal Bleeding with Antiplatelet Therapies

Byron Cryer, M.D.

In the treatment of cardiovascular disease, clinicians commonly are caught between the competing considerations of cardiovascular benefit and gastrointestinal risks. Low-dose aspirin (325 mg or less daily) lowers the risk of cardiovascular and cerebrovascular thrombotic events. Aspirin prevents thromboses and blocks platelet aggregation through inhibition of the cyclooxygenase enzyme, thereby reducing thromboxane synthesis. Owing to the inhibition of cyclooxygenase in the gastrointestinal tract, aspirin also causes gastrointestinal ulceration and major bleeding, which limit its usefulness as an antithrombotic agent.

The risk of gastrointestinal bleeding generally increases by a factor of two to three with the use of low-dose aspirin.<sup>1</sup> Although the gastrointestinal risks associated with aspirin can be reduced by lowering the dose to the lowest effective amount,<sup>2</sup> even the lowest doses have considerable risks — 75 mg daily doubles the risk of gastrointestinal bleeding,<sup>1</sup> and the subtherapeutic dose of 10 mg daily substantially inhibits gastric cyclooxygenase and causes gastric ulceration.<sup>3</sup> Thus, it is unlikely that there is a daily dose of aspirin that has antithrombotic efficacy without gastrointestinal risks.

A common clinical dilemma is how to manage patients who need antiplatelet therapy but are also at high risk for gastrointestinal bleeding, an example being patients with a recent history of upper gastrointestinal bleeding induced by aspirin or other nonsteroidal antiinflammatory (NSAID) drugs. Current cardiology guidelines recommend clopidogrel for patients unable to take aspirin because of previous gastrointestinal intolerance.<sup>4</sup> Clopidogrel is an effective antithrombotic agent because it blocks

the platelet activation of adenosine diphosphate (ADP) by irreversibly binding to the ADP receptors of platelets; this, in turn, prevents the ADP-dependent activation of the glycoprotein IIb/IIIa complex, the primary platelet receptor for fibrinogen. In a randomized, prospective study of the efficacy of 75 mg of clopidogrel given daily as compared with 325 mg of aspirin for the secondary prevention of thrombotic vascular events, clopidogrel was marginally more effective than aspirin and resulted in a moderately lower rate of gastrointestinal bleeding (0.5 percent vs. 0.7 percent).<sup>5</sup> In endoscopic evaluations of healthy volunteers at one week, clopidogrel caused less gastroduodenal damage than did 325 mg of aspirin given daily.<sup>6</sup>

Several factors increase the risk of gastrointestinal complications with the use of NSAIDs such as aspirin. These include a history of ulcer or gastrointestinal complications, increased age, congestive heart failure, and concurrent anticoagulant or corticosteroid therapy.<sup>7,8</sup> Among these factors, a history of gastrointestinal bleeding is associated with the highest risk of recurrent gastrointestinal bleeding in patients treated with NSAIDs.<sup>7,9</sup> Conventional wisdom suggests that clopidogrel should be a safer, nonulcerogenic alternative for patients at high risk for aspirin-induced ulcers. For those at highest risk because of a history of gastrointestinal bleeding, however, the risk of subsequent bleeding with the use of clopidogrel had not been evaluated prospectively. Furthermore, a small, retrospective study suggested that a history of gastrointestinal bleeding was an important risk factor for gastrointestinal bleeding during treatment with clopidogrel.<sup>10</sup>