

## Commentary

# Debate: Do all patients with heart failure require implantable defibrillators to prevent sudden death?

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### Abstract

Sudden death is a major cause of mortality in patients with ventricular dysfunction. The highest risk occurs among patients with less severe functional impairment. Current methods of risk stratification are inadequate, and a rational therapy for prevention of sudden death is not available. The implantable cardioverter-defibrillator (ICD) has proven to be more effective than drugs in reducing sudden-death risk in some subsets of patients. Empiric ICD therapy, targeting the general population with mild to moderate heart failure, will maximize the impact of such a strategy to prevent sudden death and improve long-term survival.

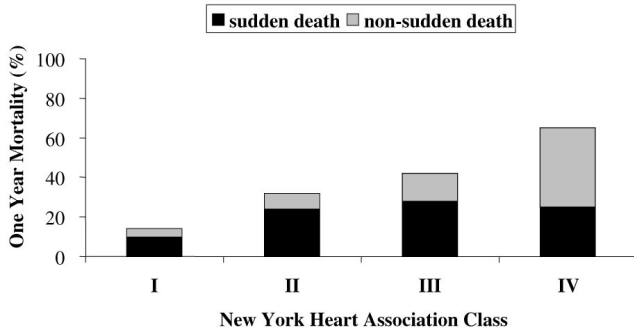
**Keywords:** defibrillator, heart failure, sudden death, therapy, trials

### Introduction

The major causes of death in patients with congestive heart failure are sudden death and death from progressive pump failure [1]. Mortality remains unacceptably high despite recent pharmacological advancements in treatment, with sudden, 'unexpected' death occurring in up to 40–70% of patients [2,3]. Although the total mortality among patients with mild heart failure is low, the relative proportion of patients dying suddenly is significant (50–70%) [2,3]. The relative proportion of sudden death in patients with more advanced heart failure amounts to less than 30% of all causes of death. The risk is still substantial,

however, given the annual mortality of 40–60% in advanced heart failure [2,4] (Figure 1). The major cause of death in patients with severe congestive heart failure (class III and IV) is from progressive myocardial dysfunction and hemodynamic deterioration. The absolute incidence of sudden death, however, remains comparable with that of functional class II patients, at approximately 30%. Sudden death tends to occur early in the course of heart failure, and probably results from ventricular tachycardia or ventricular fibrillation [5]. Although severe bradycardia or electromechanical dissociation may be more prevalent in patients with advanced heart failure [6], high

**Figure 1**



Annual mortality of heart failure.

risk for developing life-threatening sustained ventricular arrhythmias persists. An effective strategy for reducing that risk would prevent sudden death and would save many lives throughout the various stages of heart failure.

The causes of sudden death in heart failure are complex and poorly understood. A rational therapeutic strategy based on physiologic mechanisms is not available at this time. Recommendations for prevention of sudden death in patients with left ventricular dysfunction have evolved largely from the results of clinical trials [4,7]. Patient populations have, however, been highly diverse among these different studies, and formulating a consensus on a management strategy has therefore been difficult. Although several clinical variables have been associated with an increased cardiac mortality in patients with heart failure [8,9], major limitations remain in identifying the individual at highest risk of sudden death.

Risk stratification for sudden death using non-invasive methods or programmed stimulation is inadequate and, at best, limited to patients with coronary artery disease and non-sustained ventricular arrhythmia [10–12]. Importantly, preliminary analysis of outcomes in this subset of patients who participated in the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT) suggests persistent high risk, even in those patients without inducible ventricular tachycardia. Moreover, ventricular programmed stimulation has proven to be of no value in patients with non-ischemic cardiomyopathy [13]. Prevention of sudden death in patients with left ventricular dysfunction should thus be based on a logical strategy that optimizes effective pharmacologic and non-pharmacologic therapies.

**Pharmacologic strategy**

The efficacy of angiotension-converting enzyme (ACE) inhibitors in decreasing overall mortality has been well established in populations with various degrees of myocardial sys-

toxic impairment. However, the impact of ACE inhibitors on sudden death rate is probably minimal [1,14,15].

Most trials using anti-arrhythmic drugs have resulted in worsening outcomes in the drug treatment arms [16], especially in patients with left ventricular dysfunction [17]. The possible exception to this rule is amiodarone, which does not appear to have an adverse effect on either survival or heart failure. In the Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy (CHF-STAT), amiodarone did not reduce the incidence of sudden death or prolong survival [18]. The Argentinean GESICA trial did show a reduction of total mortality with amiodarone compared with placebo. The relative risk reduction of sudden death was, however, insignificant [3]. Other studies such as EMIAT [19] and CAMIAT [20] focused on patients with ischemic heart disease and prior myocardial infarction. These results suggested amiodarone may reduce arrhythmic death, but failed to improve survival. The conflicting outcomes of the studies evaluating amiodarone suggest that the protective beta-blocking effects of the drug may be offset by its pro-arrhythmia properties. The only drug class that convincingly reduces total mortality as well as the risk of sudden death has been beta-blockers. Relative reductions of cardiac death and sudden death in some trials ranged from 30 to 50%, and may involve mechanisms related to anti-ischemic, anti-fibrillatory effects of beta-blockade, neuro-endocrine deactivation or ventricular remodeling [21,22]. Previous studies involving high-risk patients, however, had consistently showed low rates of beta-blocker use (<50%) [11,12,23,24]. The utility of beta-blockers may be limited by bradyarrhythmias or worsening heart failure in patient populations with heart failure.

**Non-pharmacologic strategy**

Non-pharmacological therapy has proven more effective in improving survival and reducing sudden death risk. The utility of the implantable defibrillators in ‘secondary prevention’ has been well established in patients resuscitated from cardiac arrest or syncopal ventricular tachycardia [23,24]. Those patients with highest risk appear to benefit most from ICD therapy [25]. Importantly, the effectiveness of ICDs in primary prevention has also been established in the subgroup of patients with coronary artery disease and non-sustained ventricular tachycardia. MADIT was the first study to evaluate the prophylactic use of ICDs in patients with prior myocardial infarction, low ejection fraction, and inducible but non-suppressible ventricular arrhythmias. The use of ICDs is associated with a significant survival benefit compared with ‘conventional’ anti-arrhythmic drug therapy (mostly amiodarone) [11]. MADIT has been criticized for its small sample size and the low rate of beta-blocker use in patients on ‘conventional’ therapy (5%) compared with the ICD arm (27%). However, this difference alone cannot mitigate the magnitude of mortality reduction (54%) observed in the defibrillator group.

The randomized, controlled MUSTT evaluated the utility of electrophysiologically guided therapy to reduce the risk of sudden death [12]. The study included a larger patient population, but similar to that of the MADIT, and had a higher rate of beta-blockers and ACE inhibitor use among patients. MUSTT demonstrated that, in this relatively asymptomatic population, inducible sustained arrhythmia is associated with a substantial risk of dying suddenly, and therapy guided by electrophysiologic testing resulted in a significant reduction of sudden death. This survival benefit was, however, solely due to the use of defibrillators. Among patients who received defibrillators, there was no difference in sudden death rate based on beta-blocker use. It is also noteworthy that the 2-year mortality rate in patients who received defibrillators was similar in both MADIT and MUSTT, even though the rate of beta-blocker use in MUSTT was twice that in MADIT. These data confirm that the benefit of ICD therapy is independent of the beneficial effects of beta-blockers.

Other ongoing trials, such as the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE), will address the utility of prophylactic ICD therapy in the subset of patients with dilated cardiomyopathy and non-ischemic heart failure. The counterpart of DEFINITE for patients with coronary artery disease is the MADIT II trial, in which patients are randomized to either ICD or no anti-arrhythmic drug therapy. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is the first heart failure trial focusing on prophylactic intervention for sudden death. It is unique because its entry criteria are based only on the presence of heart failure and low ejection fraction. Arrhythmia markers are not considered. Patients with either ischemic or non-ischemic cardiomyopathy are included in this study. Although we have been concerned that this study may not be powered sufficiently to identify a small, but nevertheless, important improvement in survival, we are optimistic, given the effectiveness of the ICD, that a positive outcome favoring ICD therapy will be forthcoming. Most of these ongoing trials included an empiric ICD arm and incorporated maximal heart failure therapy with ACE inhibitors and beta-blockers. At the conclusion of these trials, we should have a better understanding of which group of the high-risk patients will benefit most from ICD therapy.

With the current transvenous lead systems, defibrillator implantation can be now achieved with a brief (<24 h) hospital stay, and is associated with less than 1% mortality and minimal morbidity risk. Defibrillators can additionally provide sophisticated monitoring and diagnostic functions that allow one to more accurately assess arrhythmia recurrence and determine the mode of death. Furthermore, current generation devices are capable of providing a full range of physiologic pacing, which can facilitate the optimum utilization of beta-blocker therapy, potentially

Figure 2

	Total Mortality	Sudden Death
ACE Inhibitors	++	+/-
β-Blockers	+++	++
Amiodarone	+/-	+/-
ICDs	++	+++
Antiarrhythmic Drugs	-	-

Impacts of interventions on mortality.

resulting in even greater synergistic benefits on improving survival. ICD therapy has also been shown to be cost-effective in long-term management of patients with life-threatening ventricular arrhythmias [26].

**Conclusion**

To summarize, patients with heart failure will undoubtedly benefit from implantable defibrillators for prevention of sudden death (Figure 2). Since the highest risk of arrhythmia death occurs among patients with less severe functional impairment (New York Heart Association class II–III), defibrillator implantation should be considered early in the course of illness. Empiric ICD therapy, targeting the population with mild to moderate heart failure, will maximize the impact of such therapy on improving long-term survival. Our efforts should no longer be directed at trying to determine whether ICDs are effective in preventing sudden death and improving survival in patients with heart failure. We are confident that ICDs are effective, and believe the outcomes of DEFINITE, MADIT II, and SCD-HeFT trials will support this hypothesis. Our efforts should be re-directed. First, we should be working with device manufacturers to reduce ICD costs and improve device longevity to maximize cost-effectiveness of ICD therapy. We should also optimize and standardize practice guidelines and troubleshooting strategies to guarantee safety and effectiveness of ICD therapy. Finally, with the advent of bi-ventricular and other newer modalities of pacing for hemodynamic support, survival benefits may even be extended to those with end-stage heart failure. We can then focus on identifying the appropriate patient who will experience the greatest improvement in heart failure symptoms and hemodynamic survival, because sudden death will have been eradicated in this protected population.

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