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A new indication for implantable defibrillators?
A discussion of the MADIT trial

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The implantable cardioverter-defibrillator (ICD) is increasingly perceived by many as the preferred treatment for patients with life-threatening ventricular arrhythmias. This growing enthusiasm is likely to grow further still as a result of the recent presentation of the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT)[1] at the recent meeting of the North American Society for Pacing and Electrophysiology (NASPE) in Seattle, Washington.

Survivors of sudden death are at markedly increased risk for future ventricular tachycardia and ventricular fibrillation with a combined incidence in untreated patients of up to 40% over 2 years. Implantable defibrillators have repeatedly been shown to reliably detect VT and VF and successfully cardiovert or defibrillate in approximately 98% of cases. Recent advances in design now allow these devices to be inserted in the pectoral region and deliver therapy through a single or two transvenously inserted electrodes. Procedure-related complications are rare, with mortality of less than 1%. Battery life is now typically 5-7 years. As the effectiveness of these devices continues to improve and the related morbidity declines, it is expected that the perceived benefit/risk will further favor their use.

Currently approved indications for ICD use include sustained VT or VF due to non-reversible causes when antiarrhythmic drug therapy is ineffective, has adverse effects, or is contraindicated. The effectiveness of ICDs as prophylactic treatment in patients without a history of sustained VT or VF has not previously been addressed. The recently announced MADIT trial is the first published randomized study of the use of ICDs in patients with non-sustained ventricular tachycardia (NSVT).

The population studied consisted of 196 patients who had documented NSVT post MI in the setting of significant left ventricular dysfunction (ejection fraction less than 35%;

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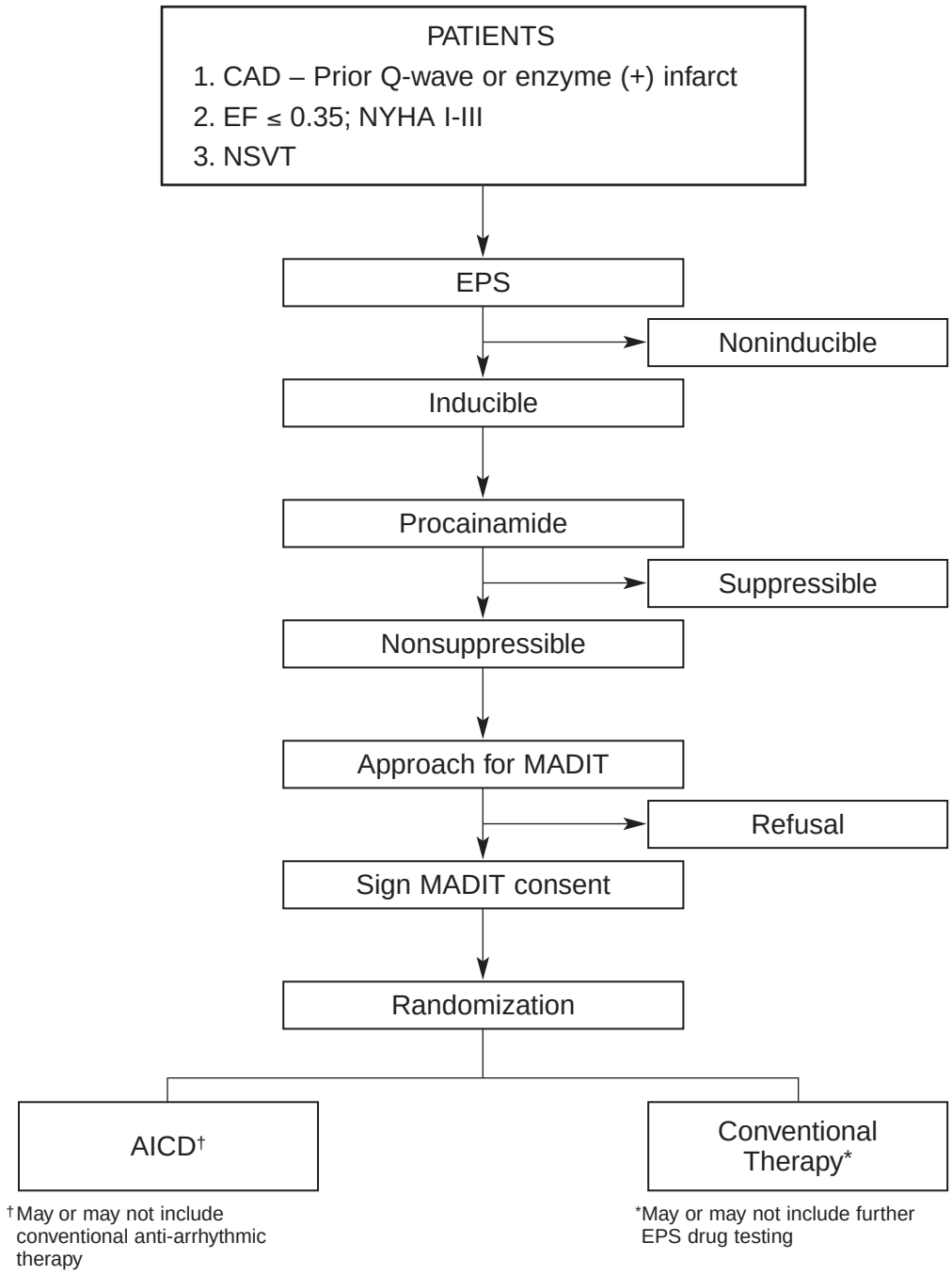
Multicenter Automatic Defibrillator Implantation Trial

Methods (Fig. 1)



†May or may not include conventional anti-arrhythmic therapy

*May or may not include further EPS drug testing

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NYHA class I-III). All patients had inducible VT on electrophysiolgic testing which was not suppressible with procainamide (Fig 1). Patients were then randomized to either ICD or best medical therapy. The cumulative mortality after a mean follow up of 32 weeks is summarized in Table 1. The data safety monitoring committee terminated MADIT prematurely after noting a significant mortality benefit in the defibrillator group: 39 deaths with conventional therapy vs 15 deaths with ICD (hazard ratio 0.46; 95% CI = 0.26 to 0.82; p=0.009). Patients in the two treatment arms were well matched for all clinical variables, including ejection fraction, previous bypass surgery, heart failure history, and other drug use. In the drug arm of the study, 80% of the patients were on amiodarone; amiodarone use had no significant effect on the hazard ratio for death. Based on these data, the American Food and Drug Administration approved the prophylactic use of ICDs in patients such as those in the study group within hours of the release of the study's results.

MADIT has only been presented in abstract form and clinicians should be cautioned that the detailed description of the results has yet to appear in print. However, these new data and the speed with which the FDA acted upon them suggest that ICDs may be the therapy of choice for patients with NSVT, perceived to be at high risk for sudden death, and by extension for the treatment of patients with sustained VT and survivors of sudden death. Several questions regarding the MADIT trial and the use of ICDs remain to be answered before such a conclusion can be reached. The trial appears to be methodologically sound. However, both sudden and non-sudden death were decreased in the ICD treatment group and the mechanism by which ICDs could be expected to lead to

Survival in MADIT		
	ICD	Conventional
1 yr	97%	75
2 yr	90	70
3 yr	85	60
4 yr	80	50
Adverse Effects of Therapy		
	ICD	Conventional
Hypotension	0	1%
Syncope	0	5%
Bradycardia	0	6%
Pulmonary Fibrosis	0	3%
Infection	2%	0
Lead Problems	8%	0
ICD Malfunction	5%	0

Table 1

decreased mortality due to non-arrhythmic causes is unclear. Since the number of patients was relatively small and the patients highly selected, the degree to which they are representative of a broad population of patients with NSVT and poor LV function is unknown. The prognosis and arrhythmia risk of patients with NSVT but no previous symptomatic arrhythmia is not necessarily the same as in patients with previous cardiac arrest. The results of MADIT can not be simply extrapolated to patients with a history of sustained VT or VF.

The impact of ICDs on all cause mortality in patients with a history of sustained VT or VF is currently being addressed in 3 ongoing trials: AVID[2], CASH[3], and CIDS[4]. The Canadian Implantable Defibrillator Study (CIDS) expects to have enrolled its target of 650 patients with sustained VT/VF by December 1996. This study is comparing medical therapy with amiodarone to defibrillators; the primary end point is all-cause mortality and secondary end points include quality of life, cost and compliance. The Antiarrhythmics Versus Implantable Defibrillators

(AVID) study, sponsored by the NHLBI and begun in 1995, seeks to randomize 1200 patients with a history of VF or sustained VT to either a defibrillator or to medical therapy with sotalol or amiodarone. The primary end point is all-cause mortality and secondary endpoints include quality of life, cost and compliance. The CASH study (Cardiac Arrest Study Hamburg) has randomized survivors of sudden death to ICD, metoprolol, or amiodarone. A fourth arm in the original design, propafenone, was stopped prematurely by the monitoring committee due to increased mortality in the propafenone group. No significant difference was seen between the other three treatment groups in a preliminary analysis and the study is ongoing. These three randomized trials, with a total of approximately 2000 patients, are expected to finally define the role of ICDs in survivors of sudden death. Just as importantly, they will hopefully identify those subgroups of patients who are most likely to benefit from this form of therapy and will also help clarify the impact of defibrillators on all-cause mortality, sudden death as well as a number of secondary end points. Although defibrillators are presumably superior to drug therapy in preventing arrhythmic deaths, it is conceivable that those patients at highest risk for sudden cardiac death, who would derive the greatest benefit from an ICD, are also at increased risk for death due to other causes. The overall survival advantage may, therefore, ultimately be smaller than expected or partially offset by the (now small) up-front mortality associated with ICD insertion. In addition, the impact of defibrillators on quality of life remains unclear. This is particularly true in those patients who have received multiple shocks and is the subject of ongoing studies. Finally, the costs associated with defibrillator implantation remain considerable. These issues will have to be resolved before the results of MADIT can be expected to lead to a widespread increase in the use of implantable defibrillators in patients with NSVT or sudden death.

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