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# T-wave-alternans-negative MADIT II patients may not need ICDs

Cambridge, MA - Patients who fulfill **MADIT II** criteria but have a negative T-wave alternans (TWA) test are at low risk of sudden cardiac death or ventricular tachyarrhythmic events and so may not need ICDs implanted, according to a research letter appearing in the July 12, 2003 issue of the *Lancet*.[1] But an accompanying commentary questions whether the data are enough to justify withholding ICD therapy from TWA-negative patients.[2]

In the ongoing quest to risk-stratify the MADIT II population, researchers led by **Dr Richard J Cohen** (Massachusetts Institute of Technology, Cambridge, MA) identified 129 patients who satisfied MADIT II criteria from two previously published clinical trials in which there had been prospective microvolt TWA testing.

TWA testing is based on observing subtle fluctuations in the morphology of the T-wave of an ECG on alternate beats during exercise testing. This allows a noninvasive approach to detecting patients at risk for ventricular arrhythmias that has been compared favorably to more invasive EP testing.

Cohen and colleagues took as a primary end point sudden cardiac death or cardiac arrest and as a secondary end point sudden cardiac death, cardiac arrest, and sustained ventricular tachycardia. Because the intent was to find out which patients did not require ICD therapy, patients were classified as TWA negative or nonnegative (positive and indeterminate combined).

Patients were followed for a mean 16.6 months, with follow-up capped at 24 months for each patient. Of the 129 patients, 35 tested TWA negative, 77 positive, and 17 indeterminate. No patients with a negative TWA test experienced the primary end point of sudden cardiac death or cardiac arrest over the course of follow-up, as opposed to an event rate of 15.6% for the other patients.

**Event rates over 24-month follow-up**

| End point | TWA negative (n=35) (%) | TWA nonnegative (n=94) (%) | p |
|---|---|---|---|
| **Primary: sudden cardiac death or cardiac arrest** | 0 | 15.6 | 0.02 |
| **Secondary: ventricular tachyarrhythmic events** | 5.7 | 31.1 | 0.01 |

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## Two facts to consider

In an accompanying commentary, **Dr Darrel Francis** and **Dr Tushar Salukhe** (National Heart & Lung Institute, London, UK) put up two facts to consider before

doctors should decide to withhold defibrillators from MADIT II patients with negative TWA.

First, they argue, the mortality effect in MADIT II was larger than is appreciated. The positive effects of ICD therapy were so clear in MADIT II that the trial was stopped less than two years in, before even 20% of the patients receiving ICDs died. Thus, the absolute reduction in mortality was a relatively small 5.6%, a number that could be significantly higher over time. Therefore, when arguing about the costs of ICD therapy, people are unjustly including the full effort and cost of implantation but only the first 20 months of a typical ICD's 120-month lifespan.

"A toll bridge would never be expected to recoup its costs within a couple of years;" they write, "Why should a defibrillator be expected to do so?"

***"A toll bridge would never be expected to recoup its costs within a couple of years; why should a defibrillator be expected to do so?"***

Their second argument concerns the zero-event rate Cohen and company present in the TWA-negative patients. It is possible that the actual event rate is higher than that, and the zero result a product of chance. Francis and Salukhe argue that a trial involving patients with MADIT-II criteria and negative TWA randomized to ICD or no ICD therapy is needed.

"Until then," they write, "defibrillators could be considered a standard of care for patients with myocardial infarction and poor ventricular function."

## Advantage of noninvasive testing

Cohen told **heart*wire*** that Francis and Salukhe's first point was just speculation. "My own personal view is you don't know whether the mortality curves would separate further or come together later," he said, noting that there were observed increases in heart failure in MADIT II, which over time may counteract the observed ICD benefit.

In addition, the noninvasiveness of TWA testing makes Francis and Salukhe's argument moot, according to Cohen.

"For a noninvasive test, you only need to predict one or two years out and then you can retest the patient because the substrate changes," Cohen said.

Unlike an invasive EP study, a TWA test with a strong negative predictive value over two years becomes an easy way to make sure a patient is doing well and doesn't need ICD therapy right away.

Cohen conceded the zero-event-rate point but doesn't think a trial such as Francis and Salukhe describe is necessary, even if additional information is always useful. He notes that other studies of TWA testing in patients meeting MADIT II criteria, such as that of **Dr Daniel Bloomfield** (Columbia University, New York, NY) at the recent **ACC** meeting (previously reported by **heart*wire*** ) have also shown extremely low mortality rates for TWA-negative patients.

There are now roughly 500 patients with MADIT II criteria who received TWA testing who have been studied, and those with negative TWA have had a very low risk.

"You don't need a treatment trial to prove a negative predictive test," Cohen said.

## Related links

1. Positive T-wave alternans an effective predictor of outcomes in patients with congestive heart failure [*HeartWire> News*; Mar 31, 2003]
2. ICD meta-analysis: Risk stratification remains the challenge [*HeartWire> News*; Mar 17, 2003]
3. MADIT II: Mortality reduction with ICD implantation for patients with prior MI, LV dysfunction [*HeartWire> News*; Mar 19, 2002]

## Sources

**1.** Hohnloser SH, Ikeda T, Bloomfield DM, Dabbou OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *Lancet* 2003; 362:125-126.

**2.** Francis DP, Salukhe TV. Who needs a defibrillator after myocardial infarction? *Lancet* 2003; 362:125-126.

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