

Research letters

T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation

S H Hohnloser, T Ikeda, D M Bloomfield, O H Dabbous, R J Cohen

In a trial of prophylactic implantation of a defibrillator, a mortality benefit was seen among patients with previous myocardial infarction and a left-ventricular ejection fraction of 0.30 or less. We identified 129 similar patients from two previously published clinical trials in which microvolt T-wave alternans testing was prospectively assessed. At 24 months of follow-up, no sudden cardiac death or cardiac arrest was seen among patients who tested T-wave alternans negative, compared with an event rate of 15.6% among the remaining patients. Testing of T-wave alternans seems to identify patients who are at low risk of ventricular tachyarrhythmic event and who may not benefit from defibrillator therapy.

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In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)¹ among 1232 patients with previous myocardial infarction (MI) and left-ventricular ejection fraction of 0.30 or less, prophylactic defibrillator therapy reduced mortality from 19.8% to 14.2% (absolute mortality reduced by 5.6%) over an average of 20 months. Therefore, 18 defibrillators would need to be implanted to save 20 months of life. Thus, implantation of defibrillators in all MADIT II-type

patients would subject a large group of patients to costly invasive therapy to extend life in only a small proportion.

Microvolt T-wave alternans testing^{2–4} involves analysis of variation in microvolt level in the morphology of electrocardiographic T wave, on an alternate-beat basis, during exercise stress. T-wave alternans testing is non-invasive and is proven to be a highly specific and sensitive predictor of the occurrence of ventricular tachyarrhythmic events. The test compares favourably with invasive electrophysiology testing and other non-invasive risk-stratification methods. We assessed the role that non-invasive T-wave alternans testing might have in the prediction of tachyarrhythmia in MADIT II-type patients by analysis of data pooled from two previously published studies, in which microvolt T-wave alternans was prospectively assessed as a risk stratifier for ventricular tachyarrhythmias in patients without known previous sustained ventricular tachyarrhythmias. Ikeda and colleagues⁴ studied 850 consecutive MI survivors who underwent T-wave-alternans testing a mean of 2.7 months after MI. Klingenhöfen and colleagues³ studied 107 consecutive patients with New York Heart Association class II and III heart failure and no MI in the previous 6 weeks. We analysed all patients in the two studies who had previous MI and left-ventricular ejection

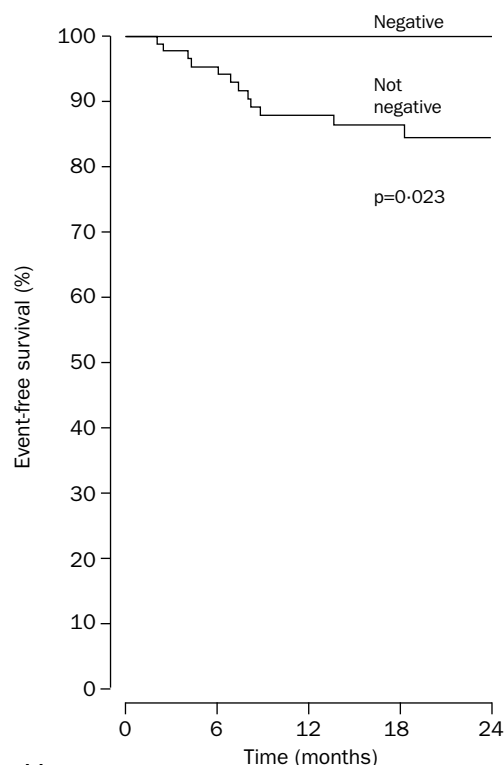


Figure 1: Event-free survival for primary endpoint according to outcome of T-wave alternans test

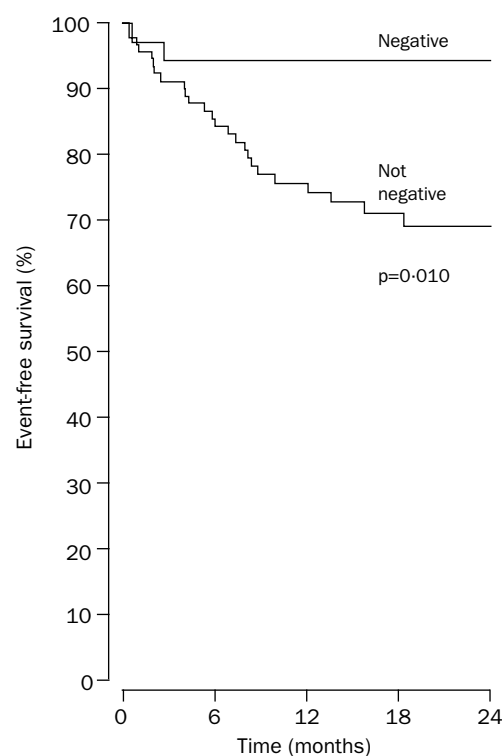


Figure 2: Event-free survival for secondary endpoint according to outcome of T-wave alternans test

fraction of 0.30 or less. Our primary endpoint was sudden cardiac death or cardiac arrest, the same as the primary endpoint of Ikeda and colleagues.⁴ Our secondary endpoint was ventricular tachyarrhythmic events, including sudden cardiac death, cardiac arrest, and sustained ventricular tachycardia, the endpoint of Klingenheden and colleagues.³ We pooled the data from the two studies, including the original T-wave alternans and endpoint-event classifications, follow-up durations, and ejection fraction data, into a central database.

We used Kaplan-Meier analysis to assess event-free survival, with a two-sided log-rank test of significance. Relative risk at 24 months was calculated from the event-free survival at that time point. Follow-up data were capped at 24 months for each patient. Because our objective was to find out which patients do not require defibrillator therapy, we classified the T-wave alternans outcomes as negative or not-negative (positive and indeterminate).

129 patients (87 from Ikeda and colleagues, 42 from Klingenheden and colleagues; 112 male, 17 female) had previous MI and left-ventricular ejection fraction of 0.30 or less. The mean age was 63 years (SD 11) and mean left-ventricular ejection fraction was 0.255 (0.045). Patients were followed up for a mean of 16.6 months (8.0). 35 (27%) patients tested T-wave alternans negative, 77 (60%) positive, and 17 (13%) indeterminate. The primary endpoint was experienced by no negative patient, ten positive patients (six sudden cardiac death, four cardiac arrests), and two indeterminate patients (both sudden cardiac death). For the secondary endpoint, the respective numbers were two, 21, and four.

For the primary endpoint, the event rate was 15.6% at 24 months of follow-up among patients who tested T-wave alternans positive or indeterminate, compared with an event rate of zero among patients who had negative results ($p=0.02$, figure 1). The overall event rate at 24 months for all 120 patients was 11.1%, and for patients with positive tests was 15.5%. For the secondary endpoint, the event rate was 31.1% at 24 months of follow-up among patients with positive or indeterminate results, compared with 5.7% among negative patients ($p=0.01$, figure 2). Relative risk at 24 months was 5.5. Event rate at 24 months for the population of all 120 patients was 24.0% and for positive T-wave alternans results was 31.4%.

In the negative, positive, and indeterminate groups, four, seven, and one patients, respectively, died from non-arrhythmic causes. The reasonably constant proportions of these deaths to the numbers of patients in each of these groups shows that T-wave alternans does not identify patients at risk of non-arrhythmic death. The all-cause mortality was 18.7% in the entire population at 24 months, and mortality was 12.5%, 21.4%, and 21.3% in the T-wave alternans negative, not-negative, and positive groups, respectively. The mortality rate in the entire population is consistent with the MADIT II results. The mortality rate among the patients with negative T-wave alternans tests was 42% lower than among the not-negative patients; this difference is larger than the 31% relative reduction in all-cause mortality in the defibrillator group compared with the control group in MADIT II. The difference in mortality between the negative and not-negative patients was not significant. A study population similar in size to the MADIT II trial would be required to show that a difference in mortality of the magnitude achieved in MADIT II was significant.

Our data suggest that MADIT II-type patients who test negative for microvolt T-wave alternans may not benefit from defibrillator therapy. Conversely, prophylactic defibrillator therapy might be more beneficial in such patients who have positive or indeterminate T-wave alternans results than in

similar patients who have not undergone risk stratification.

Contributors

All researchers participated in designing the study, assembling and analysing the data, and drafting and reviewing the report.

Conflict of interest statement

R J Cohen has an association with Cambridge Heart Inc, who manufacture equipment for the measurement of microvolt T-wave alternans. None declared for the other investigators.

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Human monoclonal thyroid stimulating autoantibody

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A monoclonal autoantibody (MAb) with powerful thyroid stimulating activity has been produced from lymphocytes from a patient with Graves' disease. The autoantibody and its Fab fragment bind to the thyroid stimulating hormone (TSH) receptor (TSHR) with high affinity, inhibit labelled TSH binding to the receptor and stimulate cyclic AMP production in Chinese hamster ovary cells transfected with TSHR. TSHR autoantibodies with TSH agonist or antagonist activities from patients' serum samples are effective inhibitors of labelled monoclonal autoantibody binding to TSHR. Thus, the human monoclonal autoantibody has all the characteristics of serum TSHR autoantibodies. Its availability has important implications for new studies on the pathogenesis of Graves' disease.

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Since the discovery over 40 years ago of the thyroid stimulating autoantibodies that cause hyperthyroidism in Graves' disease many (but unsuccessful) efforts have been made to isolate and characterise the autoantibodies at the molecular level.^{1,2} The autoantibodies exert their stimulating effect by binding to the thyroid stimulating hormone receptor (TSHR) and we³ and others⁴ have produced animal monoclonal antibodies with similar characteristics to patient TSHR autoantibodies. We have now isolated and characterised a human monoclonal TSHR autoantibody that acts as a powerful thyroid stimulator.