Microvolt T-wave alternans as a predictor of mortality and severe arrhythmias in patients with left-ventricular dysfunction: a systematic review and meta-analysis
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CRD summary
The authors concluded that a positive or indeterminate microvolt T-wave alternans test appeared to predict mortality or severe arrhythmias occurring within one to two years in individuals with left ventricular dysfunction and no history of ventricular arrhythmias. The review was in most respects well conducted, the evidence was consistent and these conclusions appear reliable.

Authors' objectives
To evaluate the use of microvolt T-wave alternans in a primary prevention setting to stratify risk among patients with severe left ventricular dysfunction.

Searching
MEDLINE, EMBASE, Current Contents and Web of Science were searched. Search terms were reported. The Cochrane Library, the International Network of Agencies for Health Technology Assessment, the references of articles retrieved and previous meta-analyses were handsearched. The search was limited to full-length studies published in English between January 1990 and May 2007.

Study selection
Randomised controlled trials (RCTs) and cohort studies of exercise-induced application of microvolt T-wave alternans were eligible for inclusion. Eligible studies had to be conducted among patients with left ventricular dysfunction and no history of a previous arrhythmic event. Studies were required to report all-cause mortality, sudden cardiac death, severe arrhythmia, ventricular tachycardia, ventricular fibrillation or implantable cardioverter defibrillator shock. Studies had to have at least 12 months’ follow-up. Studies of patients without severe left ventricular dysfunction (i.e. ejection fraction 35% or less) were excluded.

The primary review outcome was a composite of mortality and severe arrhythmic events. The secondary outcome was mortality only.

Participants in the included studies were predominantly men (71 to 91%); their mean age was 48 to 67 years. Cardiac pathology varied, and included ischaemic cardiomyopathy, dilated cardiomyopathy, previous myocardial infarction and congestive heart failure. Mean left ventricular ejection fractions ranged from 25 to 33 (where reported). Studies measured a variety of single and/or composite outcomes. Mean duration of follow-up ranged from 13 to 52 months.

The authors did not state how many reviewers performed the selection

Assessment of study quality
The following components of study validity were scored, based on a modified version of the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool including: sample size, follow-up rate, reasons for withdrawals, inclusion of indeterminate results, interpretation of results, and clinical relevance. A maximum of 7 points was allocated. Study quality was classified as good (over 6 points), moderate (4 to 6 points) or poor (fewer than 4 points).

Data extraction
For each study, data were extracted on clinical outcomes and microvolt T-wave alternans test results (positive, negative or indeterminate). Positive and negative predictive values (PPV and NPV) were calculated from the clinical event rates associated with positive and negative microvolt T-wave alternans tests; the relative risk (RR) of a positive test was calculated from the ratio of these two values. This analysis was repeated, grouping tests as non-negative (positive and indeterminate) versus negative. Sensitivities and specificities were also calculated from the event rates associated with non-negative (positive and indeterminate) and negative tests, where data were available. Study authors were contacted
for further information if necessary.

Data were extracted independently by two reviewers, with discrepancies resolved by consensus.

**Methods of synthesis**
Study data were combined to calculate the posterior median relative risk for each review outcome, with a 95% credible interval (CrI), using a Bayesian hierarchical model with non-informative prior distributions. Separate meta-analyses were conducted to reflect the variability in the handling of indeterminate tests in the primary studies. Sensitivity analyses were conducted to examine the effect of including only studies with one to two years' follow-up, and excluding those with implantable cardioverter defibrillator shocks as an endpoint.

**Results of the review**
Eight cohort studies were included in the review (n=1,946 participants, range 30 to 768). Four studies were scored as good quality (6 or 7 points) and four studies as moderate quality (4 or 5 points). Three studies excluded from analysis patients with indeterminate test results.

A positive microvolt T-wave alternans test was associated with a significantly higher risk of mortality or severe arrhythmia (combined) than a negative test (RR 2.7, 95% CrI 1.4 to 6.1; seven RCTs). Results were similar when non-negative versus negative tests were compared (RR 2.6, 95% CrI 1.4 to 5.8; five RCTs). There were insufficient data to determine the predictive value of the indeterminate group. Pooling of three RCTs reporting the value of microvolt T-wave alternans for predicting mortality produced inconclusive results (positive versus negative RR 1.94, 95% CrI 0.6 to 10.3; non-negative versus negative RR 1.94, 95% CrI 0.4 to 11.8).

Results of sensitivity analyses were similar to the main findings.

**Authors’ conclusions**
A positive or indeterminate microvolt T-wave alternans test appeared to predict mortality or severe arrhythmia occurring within one to two years in individuals with left ventricular dysfunction and no history of ventricular arrhythmia.

**CRD commentary**
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies. The restriction to published studies in English meant that the review was prone to publication and language biases. The authors acknowledged this possibility, but noted that the findings of three studies, recently published as abstracts, were unlikely to alter the findings of the review. Steps were taken to minimise the risk of reviewer bias and error in the process of data extraction by having more than one reviewer independently make decisions, but it was unclear whether this also applied to the processes of study selection and validity assessment.

Appropriate criteria were used to assess study validity. Suitable statistical techniques appear to have been used to combine the study data; problems related to reporting of indeterminate results in the primary studies were addressed in data analysis. The authors acknowledged possible sources of bias in the review, such as the lack of randomised or long-term evidence, potential selection bias, and heterogeneity between the studies. However, it did not appear that statistical heterogeneity was formally tested.

Although the reporting of study processes was suboptimal, the review was in most respects well conducted, the evidence was consistent and the authors’ conclusions appear reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians could consider microvolt T-wave alternans testing to help identify patients in most need of aggressive primary prevention and prophylactic implantable cardioverter defibrillator implantation.

**Research:** The authors stated that microvolt T-wave alternans testing should be examined in RCTs, in order to clarify its role in decision-making about implantable cardioverter defibrillator implantation and to determine its utility in
predicting long-term outcomes.

**Funding**
Faculty of Medicine of the Radboud University; Foundation of the University of Nijmegen; le Fonds de la Recherche en Sante du Quebec; Nijmegen Medical Center.

**Bibliographic details**
van der Avoort CJ, Filion KB, Dendukuri N, Brophy JM. Microvolt T-wave alternans as a predictor of mortality and severe arrhythmias in patients with left-ventricular dysfunction: a systematic review and meta-analysis. BMC Cardiovascular Disorders 2009; 9:5

**PubMedID**
19175926

**DOI**

**Original Paper URL**
http://www.biomedcentral.com/1471-2261/9/5/abstract/

**Other URL**
http://ukpmc.ac.uk/articlerender.cgi?artid=1725325&rendertype=abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Arrhythmias, Cardiac /prevention & control; Controlled Clinical Trials as Topic; Cost-Benefit Analysis; Defibrillators, Implantable /economics; Exercise Test /mortality; Humans; MEDLINE; Predictive Value of Tests; Quality Assurance, Health Care; Sensitivity and Specificity; Ventricular Dysfunction, Left /diagnosis /mortality /physiopathology

**AccessionNumber**
12009104309

**Date bibliographic record published**
05/08/2009

**Date abstract record published**
17/02/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.