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AND THE GOVERNMENT OF NEW ZEALAND

# **Horizon Scanning Technology Horizon Scanning Report**

## **Microvolt T-wave Alternans Test**

**March 2009**

**HSAC**



HEALTH SERVICES  
ASSESSMENT COLLABORATION

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## Executive Summary

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Recently there has been a marked increase in the use of implantable cardioverter defibrillators (ICDs) in a variety of patient populations in Australia and New Zealand. At a cost exceeding AUD\$50,000 per defibrillator, the finding that only a minority of defibrillators are ultimately required to discharge, is of interest. At present there is no definitive prognostic tool used to risk stratify patients who are suitable for implantation with an ICD, and in whom the defibrillator will be required to discharge. The microvolt t-wave alternans (MTWA) test has been suggested as one such tool which could assist physicians in the decision of whether or not to implant an ICD. The MTWA test measures small beat-to-beat fluctuations in the t-wave not detectable through routine ECG and therefore requires specialised sensors combined with computer algorithms to evaluate results. A MTWA test result can be positive, negative or indeterminate, with negative test results reported to assist in identifying a low-risk subgroup of patients who actually receive no benefit or net harm from ICD therapy.

There was one systematic review conducted on this topic in 2005 (Gehi *et al.*). This Horizon Scan summarises the results of that review, and subsequently summarises the findings of MTWA studies undertaken since then. The meta-analysis conducted by Gehi included 19 studies of the MTWA test conducted using exercise as the stressor and examining various patient populations. This study found that the presence of significant MTWA predicted nearly a four-fold risk of ventricular tachyarrhythmic events compared to the absence of significant MTWA. It should be noted that the primary analysis excluded indeterminate MTWA test results, only comparing positive and negative patients. This is important because since then it has been shown that positive and indeterminate results can be grouped into an 'abnormal' test category.

In addition to the systematic review, a further 11 prospective cohort studies (Level II prognostic evidence) met the inclusion criteria for this Horizon Scan. The included studies were generally NHMRC level II prognostic studies of good quality providing sufficient detail on recruitment and selection, patient characteristics, methods of conducting and analysing the MTWA test, and relevant outcomes. Overall, the MTWA test was found to have a high negative predictive value (NPV) ranging from 93% to 100%. This high NPV led researchers to conclude that, after adjustment for confounding factors, the MTWA test is useful for the risk stratification of cardiac patients prior to ICD implantation. However, despite the positive overall conclusions, there is still some concern around cardiac events occurring in patients who have an MTWA negative/normal result, given the morbidity and mortality associated with such events.

It is probable that if the MTWA test was to become widely available in Australia and New Zealand, the test results would be considered by clinicians in addition to, rather than as a replacement for, other cardiac clinical investigations such as LVEF. The ultimate value of the MTWA test in clinical, economic and financial terms will be determined by the willingness of the clinician to act upon the MTWA test result, either alone or in combination with other prognostic information.

## HealthPACT Advisory

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There is currently no definitive prognostic tool to risk stratify patients who are suitable for ICDs. The MTWA test has been suggested as one such tool that could assist decision-making on whether to implant an ICD.

A review of the published evidence on the MTWA test suggests that the test is useful for risk stratification of cardiac patients prior to ICD implantation. Further analysis of the technology is required to confirm this and to provide better advice with regard to clinical care pathways, diagnostic categories and the patient context. It is likely that this test would be used in conjunction with other cardiac clinical investigations rather than as a substitute.

Clinical use of the MTWA test in Australia would, however, be predicated on this technology being registered on the Australian Register of Therapeutic Goods (ARTG).

## Introduction

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The Health Services Assessment Collaboration (HSAC), on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of the microvolt t-wave alternans (MTWA) test (ARTG No. 65760 and MedSafe registration No. 080730).

The MTWA test has emerged as a promising risk stratification tool for determining which patients should receive an implantable cardioverter defibrillator (ICD). The diagnostic test is offered through Medtel NZ Ltd and is currently in limited use by cardiologists in Australia and New Zealand.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of the MTWA test, its present use, the potential future application of the technology, and its likely impact on the Australian and New Zealand health care systems.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with the MTWA test.

### *Sudden cardiac death (SCD) and implantable cardioverter defibrillators (ICDs)*

Cardiovascular disease is Australia's second leading cause of disease burden, primarily because of the number of deaths it causes (AIHW 2008). In 2005, there were 46,134 deaths attributable to cardiovascular disease, representing 35% of all deaths in Australia (AIHW 2008). Sudden cardiac death (SCD) is one complication arising from underlying cardiovascular disease. The magnitude of SCD as a public health problem is self-evident, but the precise incidence remains uncertain (Myerburg 2001). Sudden death has been reported to cause 20% to 50% of all deaths (Stevenson and Sweeney 1997). In Australia and New Zealand, up to 80,000 people die suddenly each year from all causes (Tunstall-Pedoe and Kuulasmaa 1994). Although ischaemic heart disease accounts for numerous episodes, many other causes are thought to contribute (Doolan and Langlois 2004).

The presence of asymptomatic ventricular arrhythmias, positive signal-averaged electrocardiogram (ECG), low heart rate variability index, or inducible ventricular tachycardia (VT) or ventricular fibrillation (VF) has been reported to increase the risk of SCD (Hilleman and Bauman 2001). Individuals at the highest risk of ventricular arrhythmias and SCD are those with a history of myocardial infarction (MI), congestive heart failure (CHF), coronary artery disease, left ventricular dysfunction and cardiomyopathies. Individuals with a family history of SCD or genetic defects such as long QT syndrome are also at a high risk of SCD (Lopshire and Zipes 2006).

Implantable cardioverter-defibrillators (ICDs) have had a major impact on the prevention of SCD. An ICD is a device designed to quickly detect a life-threatening, rapid heartbeat coming from the bottom chamber of the heart. It tries to convert an abnormal rhythm back to normal by delivering an electrical shock to the heart (i.e. defibrillation) (US National Library of Medicine and National Institutes of Health 2009). Initially, ICDs were used to treat patients who had survived cardiac arrest or an episode of documented sustained VT; however, the majority of patients who die from SCD have not previously had such an event (Blue Cross and Blue Shield Association 2008). Consequently, recent research has focused on the use of ICDs as a form of primary prevention.

The Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II) and the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT), were the two pivotal primary prevention trials that established the utility of ICD therapy, for the prevention of SCD in patients without a history of prior sustained VT (Moss *et al.* 2002; Bardy *et al.* 2005). MADIT-II investigated ICD use in patients with a prior myocardial infarction and left ventricular ejection fraction (LVEF)  $\leq 0.30$ , whilst SCD-HeFT examined ICD therapy in patients with LVEF  $\leq 0.35$  with New York Heart Association (NYHA) class II or II heart failure on the basis of either ischemic or non-ischemic cardiomyopathy. The results from MADIT-II indicated that compared with conventional medical therapy, use of an ICD was associated with a 31% reduction in the risk of mortality (Moss *et al.* 2002) The SCD-HeFT trial reported a 23% reduction in mortality for those with an ICD.

Although SCD can be prevented through the implantation of an ICD, cardiologists have lacked appropriate diagnostic tools to accurately determine which patients are at high risk of experiencing ventricular arrhythmias. Despite the overall reductions in mortality reported in the MADIT-II and SCD-HeFT, Bardy *et al.* (2005) calculated that in the SCD-HeFT study only 5.1% of implanted ICDs fired appropriately on an annual basis. Therefore, it appears only a small percentage of patients experience any benefit from an ICD. In the MADIT-II trial, only 23 per cent of patients in the treatment arm received appropriate ICD pacing or defibrillation during the follow-up period (mean 17.2 months) (Singh *et al.* 2005). There is concern that the majority of ICD patients, for whom the ICD never discharges, are still subject to the morbidity and mortality associated with ICD therapy without any clinical benefit (Blue Cross and Blue Shield 2008).

Based on current guidelines, most electrophysiologists today are implanting cardioverter-defibrillators using a low left ventricular ejection fraction alone as the sole stratifier for the risk of sudden cardiac death. However, left ventricular ejection fraction is a better marker of total mortality than of SCD *per se*. As a result, it has been suggested that this strategy is flawed because it exposes many patients to the risk and cost of ICD therapy without its benefits. Primary prevention trials based on this strategy show that the rate of appropriate ICD shocks is only 5% to 10% per year (Amit and Costantini 2007).

These concerns aside, the reductions in mortality reported in recent ICD trials such as MADIT-II and SCD-HeFT has led to a marked increase in the use of ICDs in a variety of patient populations in Australia and New Zealand. According to data from an pacemaker and ICD survey conducted every four years, there were 2,864 new ICDs implanted in Australia in 2005 compared with 956 in 2001, and 134 in New Zealand in 2005 compared with 86 in 2001 (Mond and Whitlock 2008).

According to Australian Medicare statistics, in 2005, there were 1,246 automatic defibrillators (Item No. 38390) implanted for patients without previous heart failure and not for primary prevention of tachycardia arrhythmias. In 2007, there were 893 (Item no. 38390) implanted for the same reason. Also in 2007, there were 483 (Item no. 38384) automatic defibrillators implanted for primary prevention of sudden cardiac death. There were no data reported for ICD use for primary prevention under the same item number in 2005 (Medicare Australia 2009). This suggests that ICD use has increased as a form of primary prevention for private patients. However it is important to recognise that these data relate only to private patients, as it excludes patients implanted with ICDs in Australian hospitals. Given the rapid increases in ICD utilisation in Australia and New Zealand, improved risk stratification of ICD candidates could improve resource allocation and therefore reduce unnecessary morbidity and mortality as well as costs.

## Description of the technology

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### *Functional description*

MTWA refers to small beat-to-beat electrocardiographic variability in T-wave amplitude and morphology. The MTWA test is a provocative, non-invasive, diagnostic test requiring gradual elevation of the heart rate to above 110 beats per minute. This is typically achieved through exercise (Bloomfield *et al.* 2002).

Prior to exercise, 14 sensors (7 Micro-V alternans sensors and 7 standard electrodes) are placed in the Frank-lead configuration, with the electrodes connected to the digital ECG amplifier that leads back to the microvolt T-wave enabled system (Cambridge Heart 2008). The MTWA test has the potential to be obscured by artifacts and as such, careful preparation of the patient's skin and vigilant test conduct is required. However, if necessary, the test can be performed in conjunction with an exercise stress test. During exercise, sequential ECG cycles are aligned with the QRS complex along the measurement of T-wave amplitude. Beat-to-beat fluctuations in T-wave amplitude are then analysed using consecutive measurements with a fast Fourier transformation (Klingenheben and Hohnloser 2002; Bloomfield *et al.* 2002). The test can be performed by a technician in approximately 30 minutes.

Importantly, because the MTWA test relies upon a regular atrial rhythm, patients with atrial fibrillation or atrial flutter or requiring ventricular pacing at the time of examination are unable to be tested.

### *Outcome measures*

Two measures are obtained from the testing procedure; the magnitude of the T-waves (expressed in microvolts) and the alternans ratio, a quantity defined as the number of standard deviations by which the peak signal of the T-wave exceeds background noise. A positive test result is generally defined as an alternans voltage of  $\geq 1.9 \mu\text{V}$  at 0.5 cycles-per-beat during exercise with an onset heart rate  $\leq 110$  beats per minute, or  $1.0 \mu\text{V}$  at rest for a period of at least one minute, provided that the alternans ratio is  $\geq 3$ . A negative test result is defined as the absence of alternans at 0.5 cycles-per-beat when the heart rate is sustained at  $> 105$  beats per minute for a period of at least one minute. Otherwise, the test is considered to be indeterminate (Klingenheben *et al.* 2005). An indeterminate test may be caused by patient factors or technical factors. Patient factors include the failure to maintain the required heart rate for the given period of time, unsustained MTWA, or excessive ectopy during exercise. Technical factors include high noise levels, a rapid rise in heart rate through the target exercise heart rate range and lead malfunctions (Bloomfield *et al.* 2002 and Kaufman *et al.* 2006).

Furthermore, it should be noted that slight variations in interpretation of MTWA test results have been reported in published studies in terms of the definition of positive, negative and indeterminate tests. As stated in the publication by Bloomfield *et al.* (2002), a number of alternative classification schemes have been developed in an attempt to

minimise indeterminate test results. The criteria for a positive, negative and indeterminate test result are stated for each included study in **Appendix A**.

It is also important that the interpretation of individual MTWA results be integrated with the clinical history of that patient (Gehi *et al.* 2005).

#### *Internal validity of the test*

Short term reproducibility has been reported among patients derived from at least two different clinical populations. In one study, 22 of 35 patients with congestive heart failure had two determinate tests over 15 minutes, (Bloomfield *et al.* 2002) with results concordant in 82% of tests (kappa 0.58, a moderate level of agreement). Turitto and colleagues (2002) examined reproducibility over four hours among 42 patients undergoing electrophysiological testing. Concordant results were obtained in 39 of 42 patients (93%).

#### *Commercially available MTWA equipment*

There are several devices, along with processing software, that have been approved by the FDA for performing MTWA including the HeartWave Alternans Processing System™, the Model APS Alternans Processing System™, and the CH 2000 Cardiac Diagnostic System™. These instruments are all manufactured by Cambridge Heart, Inc., Bedford, MA.

The only approved and commercially available equipment in Australia and New Zealand is the HearTwave® II Cardiac Diagnostic System which consists of an LCD screen display, a computer, digital ECG amplifier, a signal input (multi-lead ECG), and a signal processor and analysis module. Data are obtained from electrodes and sensors attached through a lead wire set to a belt-worn patient module. Following completion of the test, the system generates a printed report which states whether the result was positive or negative. If the test result is indeterminate, it is recommended that the test is repeated immediately and this will usually produce a definitive outcome (personal communication Medtel NZ Ltd December 2008).

It is purported that a routine ECG cannot detect these slight fluctuations and therefore, this test requires specialised sensors to detect fluctuations combined with computer algorithms to evaluate results, although the reader should be aware that at least one research group has used non-proprietary equipment with normal ECG electrodes (Nieminen *et al.* 2007).

#### *Intended purpose*

MTWA testing has emerged as a promising risk stratification tool for determining which patients with low LVEF should receive an ICD. Potentially, MTWA could be used amongst ICD candidates, to identify a low-risk subgroup of these patients who actually receive no benefit or net harm from ICD therapy (i.e. those with a negative test result).

### *Clinical need and burden of disease*

Sudden cardiac death resulting from ventricular arrhythmias is a leading cause of mortality in patients with ischemic heart disease and left ventricular dysfunction (Greenberg *et al.* 2004). A recent Australian study investigated the causes of SCD in people less than 35 years of age (Doolan *et al.* 2004). In the cross-sectional study, 10,199 autopsies performed between January 1994 and December 2002 were reviewed. A total of 193 cases were classified as SCDs. The cause of SCD was not established but presumed to be due to a primary arrhythmia in 31% of cases. Coronary artery disease was reported in 24% of cases, hypertrophic cardiomyopathy or unexplained left ventricular hypertrophy in 15% of cases, and myocarditis in 12% of cases.

The ICD has evolved from a bio-electronic treatment of last resort to the 'gold standard' therapy for people at risk of SCD (Anderson 2005). As a result, there has been an increase in the utilisation of ICDs in Australia and New Zealand over the last 10 years. In 2005, a total of 2,864 ICDs were implanted in Australia and 134 in New Zealand (Mond and Whitlock 2008). The procedure has been reported to be associated with an average length of stay in hospital of 5.5 days (AIHW 2008). In 2006-2007, a total of 5,474 automatic defibrillator patches, electrodes or generators were implanted in patients in Australian public hospitals (AIHW 2008). Although utilisation is increasing, it is likely that a much larger patient group would be eligible for ICD implantation and subsequently MTWA testing if MADIT-II inclusion criteria were adopted. In 2006-2007, 8,842 Australians were diagnosed with left ventricular failure, while a further 51,667 experienced an acute myocardial infarction (AIHW 2009).

One of the main issues with ICD use is the patient selection process (Arya *et al.* 2006). In the MADIT-II trial, the majority of patients were implanted with a device that provided no therapy, creating unnecessary costs and morbidity associated with the implantation procedure (Singh *et al.* 2005). The usefulness of the MTWA test as a risk stratification tool has been examined in a wide variety of patient populations; including patients with a history of MI, cardiomyopathy, or other cardiac conditions such as left ventricular dysfunction. Patients with a positive MTWA test result are hypothesised to show an increased risk for dangerous ventricular tachyarrhythmia events (e.g. SCD, sustained ventricular tachycardia and ventricular fibrillation). A negative MTWA test is proposed as a method to eliminate the risk of inappropriate placement of an ICD in patients at low risk of ventricular arrhythmias and SCD (Blue Cross and Blue Shield Association 2007).

### *Stage of development*

At this stage, the HearTwave® II Cardiac Diagnostic System is in limited use in New Zealand and not in use in Australia. This may be due to the lack of reimbursement for MTWA testing through the MBS. The primary users of the MTWA test will be cardiac technicians and cardiac specialist nurses under the direction of cardiologists.

The MTWA test is currently reimbursed through Medicare in the United States for the purpose of risk stratification of sudden cardiac death.

### *Australian Therapeutic Goods Administration approval*

In Australia, the HearTwave® II Cardiac Diagnostic System is marketed through Medtel NZ Ltd. It is not currently registered on the Australian Register of Therapeutic Goods (ARTG). This diagnostic technology was granted Medsafe approval in New Zealand on the 30<sup>th</sup> of July 2008 (Medsafe No. 080730).

## **Treatment Alternatives**

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### **Existing comparators**

There is no standard non-invasive test currently being used specifically to select patients for ICD placement. However, there are a number of other potential techniques used for risk stratification including the detection of arrhythmias using a Holter monitor or during an electrophysiological study, the measurement of heart rate variability, LVEF, QRS duration, baroreceptor sensitivity and signal averaged electrocardiography. It is probable that the results of the MTWA test would be considered in addition to, rather than as a replacement for, clinical investigations such as LVEF.

Outlined below are the NSW clinical guidelines governing the use of ICDs for prognostic reasons in patients with impaired ventricular function without known ventricular tachyarrhythmias in public hospitals (NSW Health 2008). However it appears that the economic evaluation suggested in these guidelines is not proceeding (personal communication, CHERE).

#### **Figure 1: NSW Health Guidelines governing the use of ICDs**

##### **Safety**

The Medical Services Advisory Committee (MSAC) report on Implantable Cardioverter Defibrillators (ICDs) in March 2006 found that the short-term safety profile for the insertion of an ICD plus optimal pharmacological therapy (OPT) is acceptable.

The success rate for implantation of an ICD is very high (98%) and the rate of complications is low at 0.5 - 3% as reported in clinical trials.

No differences were reported in the mortality rates within 30 days of implantation of an ICD when comparing groups with ICD plus optimal pharmacological therapy (OPT) and those who only received OPT.

##### **Indications**

Prophylactic implantable defibrillators are recommended for patients with:

1. Previous myocardial infarction (MI) with LVEF <36%, or
2. Dilated cardiomyopathy with Class 2 or 3 heart failure who have received optimal pharmacological therapy (ACE inhibitor or angiotensin blocker, beta blocker and aldosterone antagonist in some cases) for 3 months followed by estimation of ejection fraction showing LVEF <36%, or
3. Expected longevity  $\geq$  3 years.

### **Provisos**

1. If the patient has Coronary Artery Disease (CAD), ischaemia should be adequately investigated and treated.

2. The ICD should be implanted more than 1 month after the most recent acute MI.

**Note:** patients within 1 month of an acute MI who have inducible sustained monomorphic Ventricular Tachycardia (VT) at Electrophysiology Study (EPS) should receive an ICD as the capacity to support VT has been demonstrated and there is data to show this group is at high risk.

3. Patients with Class 4 heart failure should not receive an ICD unless cardiac resynchronisation is performed.

It is also recommended that all patients receiving a public hospital funded ICD should be included in a registry with basic information on indications, cardiac data and comorbidity. Outcomes should be analysed using data from death certificates and other information if available and the results studied by the Electrophysiology Subcommittee of the GMCT Cardiac Network.

These indications align with those recommended for funding by the US Centers for Medicare and Medicaid Services published in January, 2005 and the National Institute for Health and Clinical Excellence guidance. The indications are also the same as the recommendations in the MSAC Report on ICDs with one additional indication i.e. insertion of ICDs for patients within 1 month of an acute MI who have inducible sustained monomorphic Ventricular Tachycardia (VT) at Electrophysiology Study (EPS).

### **Cost Effectiveness**

There are a substantial number of patients who are eligible for ICDs and the implantation of these devices will have a significant impact on the budgets of the hospitals where these procedures take place. As more evidence becomes available, it may be appropriate to offer these devices to other groups of patients which will further increase expenditure.

It is possible that high risk groups may be identified on the basis of inducible VT at electrophysiological studies, ambulatory ECG monitoring or other non-invasive parameters that would reduce significantly the number of patients needing ICDs. It is suggested that a study is commenced at the major implanting institutions (Westmead Hospital, Royal Prince Alfred Hospital, The Royal Newcastle Centre and others who wish to participate) in conjunction with the Centre for Health Economics Research and Evaluation (CHERE) using these potential screening tests in all patients receiving a prophylactic ICD. Analysis of the outcomes would assist in determining the value of these filters and the cost-benefit ratios in the various groups.

The decision to implant an implantable cardiac defibrillator must be a clinical judgement based on individual patient assessment and the complexity of each case.

Source: NSW Health 2008

### Safety

The MTWA test is a non-invasive prognostic test that poses little risk to the patient. However, it is not recommended in patients who may not be able to tolerate the exercise test. This includes patients with a serious ongoing cardiac arrhythmia, unstable coronary artery disease, atrial fibrillation, or patients who have experienced a MI in the last six days. All patients should be closely monitored whilst the MTWA test is performed (Haghjoo *et al.* 2006).

### Effectiveness

Full data extraction tables describing trial design and trial results for the 12 included studies (Gehi systematic review and 11 subsequent studies) are provided in **Appendix A** and **Appendix B**.

### Study design

Initially, one systematic review (Level I prognostic evidence) by Gehi and colleagues (2005) was identified through the search of the literature. A summary of the studies included in the systematic review is shown below in **Table 1**. The authors used PubMed and Cochrane databases to articles published between January 1990 and December 2004. Nineteen prospective studies, which included 2,608 subjects, were found which met the study inclusion criteria. Study sample sizes ranged from 16 to 834 participants with the mean age of subjects between 25 and 64 years. Mean ejection fraction (EF) of study participants ranged from 23% to 71%. Patients were followed up for an average of 21 months.

There was a wide range of subject populations including CHF, ischemic CHF, non-ischemic CHF, post MI, athletes, and healthy subjects. Studies that assessed MTWA and outcomes in different patient populations were presented individually for each patient population. With regards to the methodological quality of included studies, none of the studies were considered to be of poor quality, testing revealed appropriate heterogeneity, and no evidence of publication bias was found. However MTWA was absent in 25% to 54% of subjects, which can be considered a significant portion of subjects, and therefore care should be taken in interpreting results. Because there were inconsistencies in the definition of abnormal MTWA (including or excluding indeterminate MTWA), outcomes for each study were stratified by this definition. Summary estimates were calculated defining abnormal MTWA excluding indeterminate MTWA tests, however a sensitivity analysis based on the definition of an abnormal test (including or excluding indeterminate test as abnormal) was performed on the studies that provided these data to see whether this would affect the predictive value of the test (Gehi *et al.* 2005). It is important the reader considers this in their interpretation of these results, as it is now more common to group indeterminate and positive results.

**Table 1: Characteristics of 19 prospective studies of the microvolt T-wave alternans test**

Author (year)	Total (n)	Mean age (yrs)	Men (%)	Population	Mean EF (%)	End point	History of arrhythmic event?	Average follow-up (months)	Quality
Hohnloser <i>et al.</i> (1998)	62	60	81	ICD recipients	36	ICD event	Yes	15	Good
Hennersdorf <i>et al.</i> (2000)	16	44	68	Nonischemic CHF	55.6	VT/VF	Yes	6	Fair
Hennersdorf <i>et al.</i> (2000)	44	49	70	Nonischemic CHF	59.5	VT/VF	No	6	Fair
Klingenheben <i>et al.</i> (2000)	107	56	80	CHF	28	SCD/VT/VF	No	21	Good
Adachi <i>et al.</i> (2001)	64	53	81	Non-ischemic CHF	NA	SCD/VT/VF	No	24	Good
Schwab <i>et al.</i> (2001)	104	60	76	Post-MI	56	SCD/VT/VF	No	15	Fair
Tapaneinen <i>et al.</i> (2001)	246	62	72	Post-MI	45	Cardiac death	No	14	Good
Sakabe <i>et al.</i> (2001)	30	53	91	Non-ischemic CHF	33	VT	No	13	Fair
Sakabe <i>et al.</i> (2001)	41	54	80	Non-ischemic CHF	48	VT/VF	Yes	13	Good
Ikeda <i>et al.</i> (2002)	834	63	84	Post-MI	51	SCD/VF	No	25	Good
Kitamura <i>et al.</i> (2002)	83	52	81	Non-ischemic CHF	NA	SCD/VT/VF	No	21	Good
Grimm <i>et al.</i> (2003)	110	45	69	Healthy	71	SCD/VT/VF	No	32	Good
Grimm <i>et al.</i> (2003)	263	48	73	Non-ischemic CHF	30	SCD/VT/VF	No	52	Good
Hohnloser <i>et al.</i> (2003)	137	55	77	Non-ischemic CHF	29	SCD/VT/VF	Yes <sup>a</sup>	15	Good
Sarzi Braga <i>et al.</i> (2004)	46	59	89	CHF	29	Cardiac death	No	19	Fair
Rashba <i>et al.</i> (2004)	144	64	81	Ischemic CHF	28	SCD/VT/VF/ICD shock	Yes	17	Good
Furlanello <i>et al.</i> (2004)	48	25	100	Healthy	NA	Syncope/VT	No	36	Good
Furlanello <i>et al.</i> (2004)	52	28	90	Athletic heart	NA	Syncope/VT	Yes	25	Good
Bloomfield <i>et al.</i> (2004)	177	61	85	Ischemic CHF	23	Death	No	20	Good

Source: Gehi *et al.* (2005): Table 1, page 77.

Abbreviations: CHF = coronary heart failure; EF = ejection fraction; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; NA = not available; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

<sup>a</sup> A total of 24% of subjects had a history of arrhythmic events in this study

In the updated search for the period following the publication by Gehi *et al.* (2005), a total of 11 prospective cohort studies (Level II prognostic evidence) were identified for inclusion in this Horizon Scan. A summary of the design of the included studies is shown in **Table 2**. The publication by Baravelli *et al.* (2007) refers to a cohort recruited from the same population as the study cohort reported in Baravelli *et al.* (2005), and the publication by Kaufman *et al.* (2006) refers to the same study data as Bloomfield *et al.* (2006), however all used different criteria to classify the results of the MTWA test and Baravelli *et al.* (2007) examined different clinical outcomes to Baravelli *et al.* (2005). In addition, three publications by Chow *et al.* (2007a and 2007b) and Chan *et al.* (2008)

referred to the same study data as reported in Chow *et al.* (2006). There were differences in the type of results reported and the length of follow-up, so all publications have been included.

The inclusion criteria varied slightly between studies depending on the patient population under investigation. Patients of New York Heart Association (NYHA) class II and III formed part of the inclusion criteria of Baravelli *et al.* (2005) and Salerno-Uriarte *et al.* (2007), with Bloomfield *et al.* (2006) excluding patients in class IV. Another inclusion or exclusion criteria common across studies was ejection fraction. It has been previously reported that most electrophysiologists are implanting cardioverter-defibrillators using a low LVEF alone as the main stratifier for the risk of sudden cardiac death (Amit and Costantini 2007). The included studies incorporated patients with a wide range of ejection fractions ranging from 25.0% to 65.0%. The majority of included studies examined patients with a mean EF less than 30.0%. In addition, because MTWA can only be measured during a regular atrial rhythm, patients who had persistent atrial fibrillation or flutter or required ventricular pacing at the time of MTWA testing were excluded from all included studies except for Nieminem *et al.* (2007). This study used the time-domain modified moving average (MMA) analysis method and this condition does not hinder MTWA assessment by this method.

The studies selected for inclusion were generally NHMRC level II prognostic studies of good quality providing sufficient detail on recruitment and selection, patient characteristics, methods of conducting and analysing the MTWA test, and relevant outcomes. The studies generally recruited a large cohort however the number of patients ranged significantly between 70 and 1,041 participants. Although the study by Ikeda *et al.* (2006) recruited 1,041 patients, only 1,003 were considered 'evaluable' because 38 patients died of non-arrhythmic causes. Mean follow-up was greater than 18 months for all but one of the included studies. The demographic characteristics of patients in the included studies were typical of candidates for ICDs with mean age between 56.0 years and 66.7 years and the proportion of males between 65.0% and 84.9%. The use of the MTWA test has been examined in a variety of patient populations. Examples of patient populations examined in the included studies were those with congestive heart failure, ischemic congestive heart failure, cardiomyopathy, previous myocardial infarctions or ICD recipients. Some studies included patients with no history of arrhythmic events (i.e. primary prevention) and some recruited patients with a history of arrhythmic events (i.e. secondary prevention), and it is important that the reader consider this when interpreting the findings. All of the included studies conducted the MTWA test using an exercise stress test, as was specified in the Horizon Scan inclusion criteria. The MTWA test was recorded using the commercially available CH2000 or HearTwave systems (Cambridge Heart, Inc) in all included studies except for the study by Nieminem *et al.* (2007).

A study by Kaufman *et al.* (2006) examined the correlation between MTWA test result and all-cause mortality or documented non-fatal sustained ventricular arrhythmia (SVA) over a mean follow-up period of 20 months. The authors concluded that an indeterminate MTWA test result predicted death or SVA at least as well as a positive MTWA test, and therefore, it would be appropriate to combine patients with an indeterminate or positive

MTWA test into one high-risk group who would benefit from an ICD. As a result, most studies conducted since the publication of the Kaufman finding have grouped these test results (i.e. Baravelli *et al.* 2007 and Salerno-Uriarte *et al.* 2007). Of the other included studies, two did not group the results (Ikeda *et al.* 2006 and Nieminem *et al.* 2007) and one excluded indeterminate results from analyses completely (Baravelli *et al.* 2005). The authors of this Horizon Scan have made no attempt to reclassify indeterminate results in order to recalculate results with indeterminate treated as positive results. The criteria for a positive, negative and indeterminate result are stated for each study in **Appendix A**.

As was specified in the inclusion criteria, studies must have provided data for the MTWA test and subsequent clinical outcomes, including any of the following: SCD, cardiac death, ventricular arrhythmias, and/or ICD shock. The included study endpoints are shown below in **Table 2**.

It is important that study results be interpreted within the context of the included patient population and test characteristics.

**Table 2: Summary of the study design of included trials**

Authors (yr)	Total (n)	Mean Age (yrs)	Male (%)	Population	Mean EF, %	Equipment/analysis used for test	Positive and indeterminate results grouped?	End point(s)	History of arrhythmic events?	Average follow-up (months)
Baravelli <i>et al.</i> (2005)	73	64.0	83.0%	CHF (ischemic or non-ischemic cardiomyopathy) NYHA class: II	35.5%	CH2000 or HeartWave Systems (Cambridge Heart, Inc)/Spectral	Indeterminate excluded	SCD/ VT/VF/ICD shock	Yes	7.0
Baravelli <i>et al.</i> (2007)	70 <sup>a</sup>	64.5	72.0%	Cardiomyopathy NYHA class: NR	29.0%	CH2000 or HeartWave Systems (Cambridge Heart, Inc)/Spectral	Yes	Death/VT/VF/ICD shock	No	19.2
Bloomfield <i>et al.</i> (2006)	549	56.0	71.0%	Ischemic CHF NYHA class: II or III	25.0%	CH2000 or HeartWave Systems (Cambridge Heart, Inc)/Spectral	Yes	All-cause mortality VT/VF/ICD shocks	No	20.0
Kaufman <i>et al.</i> (2006)	As above	As above	As above	As above	As above	As above	No	As above	As above	As above
Chow <i>et al.</i> (2006)	768	66.7 <sup>b</sup>	81.5% <sup>b</sup>	Ischemic CHF NYHA class: NR	27.4% <sup>b</sup>	CH2000 or HeartWave Systems (Cambridge Heart, Inc)/Spectral	Yes	All-cause mortality/ICD shocks	No	18.0
Chan <i>et al.</i> (2008)	As above	As above	As above	As above	As above	As above	As above	As above	As above	18.0
Chow <i>et al.</i> (2007a)	As above	As above	As above	As above	As above	As above	As above	As above	As above	As above
Chow <i>et al.</i> (2007b)	As above	As above	As above	As above	As above	As above	As above	As above	As above	27.0
Ikeda <i>et al.</i> (2006)	1,041 <sup>c</sup>	64.0	79.0%	Infarct survivors NYHA class: NR	55.0%	CH2000 or HeartWave Systems (Cambridge Heart, Inc)/Spectral	No	SCD/Cardiac arrest/VF	Yes	32.0
Nieminen <i>et al.</i> (2007)	1,037	58.0	65.0%	Undergoing stress test NYHA class: NR	65.0%	Digital ECG test/MMA analysis	No	SCD/CV mortality All-cause mortality	Yes and No	44.0
Salerno-Uriarte <i>et al.</i> (2007)	446	59.0	78.2%	Non-ischemic CHF NYHA class: II or III	29.5%	CH2000 or HeartWave Systems (Cambridge Heart, Inc)/Spectral	Yes	Cardiac death/VA/Mortality	Yes	NR

Abbreviations: CHF = congestive heart failure; EF = ejection fraction; ICD = implantable cardioverter defibrillator; MMA = modified moving average; NR = not reported; NYHA = New York Heart Association; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia

<sup>a</sup> Up to 22 may have been included in Baravelli *et al.* (2005)

<sup>b</sup> Calculated *post-hoc* by crude average of reported means for four sub-groups

<sup>c</sup> Although 1,041 were recruited, only 1,003 were considered 'evaluable' due to 38 non-arrhythmic deaths

## Study results

A summary of the positive predictive value (PPV), negative predictive value (NPV), and univariate relative risk for arrhythmic events, excluding indeterminate MTWA, in the 19 studies included in the meta-analysis by Gehi *et al.* (2005) is presented in **Table 3**. Summary estimates in several subgroup populations are also presented. The study reported a summary positive PPV for cardiac arrhythmic events of 19.3% (17.7%–21.0%) and a summary NPV of 97.2% (96.5%–97.9%) at 21 months. Within the 19 individual studies, the relative risk (RR) of having a cardiac event ranged from 0.85 to infinity. Overall, the study found that the presence of significant MTWA predicted nearly a four-fold risk of ventricular tachyarrhythmic events compared to the absence of significant MTWA (RR: 3.77, 2.39 to 5.95). The absence of MTWA carries a 3% risk of arrhythmic events during an average 21 months of follow-up. The study also indicated there was no significant difference in PPV, NPV, or RR of MTWA testing between subjects with ischemic and non-ischemic CHF, as well as no significant difference in the NPV or RR of MTWA testing between CHF and post-MI subjects. A sensitivity analysis of the summary estimates from the eight studies which included outcomes for subjects with indeterminate MTWA, demonstrated no significant difference in whether or not indeterminate MTWA was included in the definition of an abnormal test ( $p>0.05$ ). The reader should consider the heterogeneity of the patient populations when interpreting the findings of the Gehi meta-analyses.

**Table 3: Summary estimates of PPV, NPV and RR in 19 included studies of MTWA for the prediction of cardiac arrhythmic events**

Summary estimates	PPV (%) (95% CI)	NPV (%) (95% CI)	RR (95% CI)	Average follow-up (months)	No. studies
All studies	19.3 (17.7–21.0)	97.2 (96.5–97.9)	3.77 (2.39–5.94)	21	19
Subgroups					
CHF	25.5 (22.7–28.3)	93.8 (92.3–95.4)	2.51 (1.71–3.65)	18	12
Ischemic CHF	29.7 (23.5–35.8)	91.6 (87.8–95.3)	2.42 (1.30–4.50)	19	2
Non-ischemic CHF	21.3 (17.8–24.7)	95.2 (93.5–97.0)	3.67 (1.50–8.96)	20	7
Post-MI	6.0 (4.5–7.4)	99.4 (98.9–99.9)	4.74 (1.11–20.19)	18	3

Source: Gehi *et al.* (2005): Table 3, page 78

A summary of the results from the 11 included prospective cohort studies published after the literature search of Gehi is shown below in **Table 4** and more detail of the results is provided in **Appendix B**.

The study by Baravelli *et al.* (2005) examined how well the MTWA test result predicted the risk of arrhythmic events and SCD. The MTWA test was positive in 30 (41%) of patients, negative in 26 (36%) of patients and indeterminate in 17 (23%) of patients. During an average follow-up of  $17.1 \pm 7.4$  months, seven patients had an arrhythmic event in the MTWA positive group, whereas one and no events occurred in the indeterminate and negative group respectively. There was also one death; however the MTWA result of this participant was not reported. The PPV and NPV for SCD and arrhythmic events were 24% and 100%, respectively. Using a Kaplan-Meier univariate analysis, MTWA was a statistically significant predictor of arrhythmic events, in both the entire population ( $p=0.01$ ), or in the sub-group of patients suffering from ischemic cardiomyopathy ( $p=0.04$ ). Multivariate Cox regression analysis also revealed that MTWA was an independent predictor of events in the population ( $p=0.035$ ). A second study by Baravelli *et al.* (2007) examined the prognostic value of peak oxygen uptake and MTWA in patients with idiopathic dilated cardiomyopathy. The study classified patients as 'normal' or 'abnormal', by grouping those with an MTWA test result of positive or indeterminate as 'abnormal'. During a mean follow-up of  $19.2 \pm 10.7$  months, there were 11 major cardiac events (three deaths and six arrhythmic events in the abnormal group and two deaths and no arrhythmic events in the normal group). This study reported a PPV for major cardiac events of 22.0%, and a NPV of 93.0% for the same event. From multivariate analysis, MTWA was found to be a statistically significant predictor of arrhythmic events ( $p=0.04$ , hazard ratio [HR]=0.32, 0.14–0.93).

Bloomfield and colleagues conducted a study analysing the usefulness of the MTWA test in predicting the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. Of 549 patients, 360 were classified as abnormal (positive or indeterminate) and 189 as normal. There were 40 deaths (38 abnormal MTWA, 2 normal MTWA) and 11 non-fatal ventricular arrhythmias (9 abnormal MTWA, 2 normal MTWA) over a follow up period that averaged  $20 \pm 6$  months. The two-year actuarial event rate was 15.0% in the patients with an abnormal MTWA test and 2.5% in those with a normal test (HR 6.5, 95% CI 2.4 to 18.8,  $p < 0.001$ ). The authors concluded that MTWA was useful in identifying a high risk group, and a low-risk group likely to survive two or more years without experiencing death or sustained ventricular arrhythmia (Bloomfield *et al.* 2006). A further study by Kaufman *et al.* (2006) examined the same patient cohort but examined whether indeterminate MTWA tests predicted high risk of death or sustained ventricular arrhythmias. The two-year event rate was 17.8% for those with an indeterminate MTWA test result. With a Cox model to compare indeterminate MTWA tests with positive tests, the HR was 1.3 (95% CI 0.9 to 1.7). The results indicate that an indeterminate MTWA test predicts the primary end point as well as positive tests.

A study by Chow *et al.* (2006) investigated the prognostic utility of MTWA in risk stratification of patients with ischemic cardiomyopathy. There were 514 (67%) patients with a non-negative (positive or indeterminate) MTWA test result and 254 (33%) with a negative result. Patients were stratified based on whether or not they had an ICD (392 [51%] had an ICD implanted). In the non-ICD group, there were 58 deaths (MTWA negative: 15 [8.4%]; MTWA non-negative: 43 [21.8%]) and in the ICD group there were 41 deaths (MTWA negative: 6 [8.0%]; MTWA non-negative: 35 [11.0%]). There were

also 26 appropriate ICD therapies not associated with death in the ICD group (MTWA negative: 2 [2.7%]; MTWA non-negative: 24 [7.6%]). After multivariate adjustment, a non-negative MTWA test was associated with a significantly higher risk of all-cause (stratified HR=2.24 [95% CI 1.34 to 3.75; p=0.002]) and arrhythmic mortality (stratified HR=2.29 [95% CI 1.00 to 5.24; p=0.049]) but not of non-arrhythmic mortality (stratified HR=1.77 [95% CI 0.84 to 3.74; p=0.13]).

Further studies by Chow *et al.* (2007a), Chow *et al.* (2007b) and Chan *et al.* (2008) investigated the same cohort of patients. The study by Chow *et al.* (2007a) supported the authors previous findings with results showing that a non-negative MTWA test result was associated with a significantly higher risk for all-cause mortality in patients without an ICD (HR=2.27, 1.22 to 4.24; p=0.01) and for all-cause mortality and ICD shocks in patients with an ICD (HR=2.42, 1.07 to 5.41; p=0.04) compared with a negative MTWA result. A further study by Chow *et al.* (2007b) examined whether ICDs have different mortality benefit among patients with ischemic cardiomyopathy who screen negative and non-negative for MTWA. The study found after multivariable adjustment, ICDs were associated with lower all-cause mortality in MTWA non-negative patients (HR=0.45, 0.27 to 0.76; p=0.003) but not in MTWA-negative patients (HR=0.85, 0.33 to 2.20; p=0.73), with the mortality benefit in MTWA non-negative patients largely mediated through arrhythmic mortality reduction (HR=0.30, 0.13 to 0.68; p=0.004). The number needed to treat with an ICD for two years to save one life was nine among MTWA-non-negative patients and 76 among MTWA-negative patients. The study by Chan *et al.* (2008) examined that stratified HR at one, two and three years using the same cohort with results indicating a non-negative MTWA test was associated with a greater than two-fold increased risk for events in each of the three years of follow-up (year 1: HR=2.19, 1.10 to 4.34; p=0.03; year 2: HR=3.36, 1.28 to 8.83; p=0.01; year 3: HR=2.06, 0.81 to 5.22, p=0.13). The authors concluded that MTWA reliably and consistently predicts mortality and arrhythmic risk throughout the first 2 to 3 years of follow-up.

A study by Ikeda *et al.* (2006) analysed the predictive value of the MTWA test for SCD in patients with preserved cardiac function after acute MI. Of the 1,003 evaluable patients (i.e. those who did not die of non-arrhythmic causes), 169 (18%) had a positive, 747 (74%) a negative and 87 (9%) an indeterminate MTWA test result. There were 18 patients who reached an end point during the follow-up period of  $32 \pm 14$  months; 14 died suddenly, two experienced cardiac arrest and two had resuscitated ventricular fibrillation. A positive MTWA test had a HR for predicting arrhythmic events of 19.7 (5.5 to 70.4; p < 0.0001). Patients with a negative MTWA test had few events (data not shown). These authors summarised their findings by stating that although a positive MTWA test could be used for risk stratification in patients with acute MI and LVEF  $\geq 40\%$ , further assessments may be necessary for selection of patients who need an ICD because of the low PPV.

Nieminem *et al.* (2007) conducted a large prospective cohort study on low-risk patients referred for exercise testing for suspected CHD. The authors tested several MTWA cut-off points before assigning  $<65 \mu\text{V}$  as the cut-off for negative patients, and  $\geq 65 \mu\text{V}$  for positive patients. During the follow-up period ( $44 \pm 7$  months) there were 59 deaths, of

which 34 were classified as cardiovascular death, 20 as SCD and four unknown. The number of deaths among patients classified as positive and negative for the MTWA test was not stated however a MTWA  $\geq 65$   $\mu\text{V}$  at baseline was associated with a significant RR of 7.4 for SCD, 6.0 for cardiovascular mortality, and 3.3 for total mortality. The authors concluded that an elevated TWA seems specifically to predict an increased 3-4 year risk of SCD.

Another publication reported on the prognostic value of the MTWA test in patients with heart failure due to nonischemic cardiomyopathy and left ventricular ejection fraction  $\leq 40\%$  (Salerno-Uriarte *et al.* 2007). Among the 446 patients enrolled, 154 (34.6%) had negative, 200 (44.8%) positive, and 92 (20.6%) indeterminate MTWA tests. Patients with positive and indeterminate tests were grouped as abnormal. The primary endpoint (cardiac death and life threatening arrhythmia) was reached in 29 of 292 patients (9.9%) from the abnormal and 4 of 154 patients (2.6%) from the normal TWA test group. The study found a very high NPV for those with a normal (i.e. negative) MTWA test result. It was 98.7% (95.4%–99.8%) at 12 months for the primary endpoint (cardiac death and life threatening arrhythmia's) and 97.3% (93.3%–99.3%) at 18 months. Using multivariate analysis, the adjusted HR for the primary endpoint was 3.21 (1.12-9.22). A significantly increased risk was also found when comparing patients with a positive versus patients with a negative MTWA test, with a HR of 3.16 (1.06-9.45). The present study states that given that patients with a normal MTWA test appear to have a very good prognosis, as shown by the high NPV of the test at 12 months, the test may be effectively used to identify a subgroup of patients who are likely to have little benefit from ICD therapy despite heart failure and left ventricular dysfunction.

**Table 4: Summary of study results of the included trials**

Author (yr)	PPV	NPV	MTWA Result	Primary outcome(s)	HR/RR (95% CI)
Baravelli <i>et al.</i> (2005)	24%	100%	Positive: 30 (41%) Negative: 26 (36%) Indeterminate: 17 (23%)	1 death (MTWA result NR) 8 arrhythmic events (7 positive, 0 negative, 1 indeterminate)	MTWA predictive value for sudden cardiac death and arrhythmic events: RR: $\infty$ ( $\infty$ to $\infty$ )
Baravelli <i>et al.</i> (2007)	22%	93%	Abnormal: 40 (57%) Normal: 30 (43%)	11 major cardiac events (9 abnormal, 2 normal)	Predictive power of MTWA for major cardiac events: HR: 0.24 (0.08-0.94)
Bloomfield <i>et al.</i> (2006)	NR	NR	Abnormal: 360 (66%) Normal: 189 (34%)	40 deaths 11 non-fatal ventricular arrhythmias	Abnormal vs. normal for deaths and non-fatal sustained ventricular arrhythmias: HR: 6.5 (2.4-18.1)
Kaufman <i>et al.</i> (2006)	NR	NR	Positive: 163 (29.7%) Negative: 195 (35.5%) Indeterminate: 191 (34.8%)	As above	Indeterminate vs. positive for all-cause mortality and non-fatal sustained ventricular arrhythmia: HR: 1.3 (0.9-1.7)
Chow <i>et al.</i> (2006)	NR	NR	Non-negative: 514 (67%) Negative: 254 (33%)	Non-ICD group: 58 deaths (15 negative, 43 non-negative). ICD group: 41 deaths (6 negative, 35 non-negative)	Non-negative vs. negative for all cause mortality: HR: 2.24 (1.34-3.75)
Chan <i>et al.</i> (2008)	NR	NR	Non-negative: 514 (67%) Negative: 254 (33%)	99 deaths (21 negative, 78 non-negative)	Non-negative vs. negative for all-cause mortality: HR Yr 1: 2.19 (1.10-4.34) HR Yr 2: 3.36 (1.28-8.83) HR Yr 3: 2.06 (0.81-5.22)
Chow <i>et al.</i> (2007a)	NR	NR	Non-negative: 514 (67%) Negative: 254 (33%)	99 deaths (21 negative, 78 non-negative)	Non-negative vs. negative for all-cause mortality: HR: 2.27 (1.22-4.24)
Chow <i>et al.</i> (2007b)	NR	NR	Non-negative: 514 (67%) Negative: 254 (33%)	129 deaths (30 negative, 99 non-negative)	ICD associated with reduced all-cause mortality in non-negative group: HR: 0.45 (0.27-0.76) Negative group: 0.85 (0.33-2.20)
Ikeda <i>et al.</i> (2006)	8.9%	99.6%	Positive: 169 (18%) Negative: 747 (74%) Indeterminate: 87 (9%)	18 primary events (14 sudden cardiac death, 2 cardiac arrests and 2 resuscitated ventricular fibrillation).	A positive MTWA test predicted serious arrhythmic events with a HR of 23.5 (6.8 to 81.0)
Nieminen <i>et al.</i> (2007)	65 $\mu$ V: 14.9%	65 $\mu$ V: 95.2%	TWA <65 $\mu$ V: 950 (91.6%) TWA $\geq$ 65: 87 (8.4%)	59 deaths (34 cardiovascular and 20 sudden cardiac death)	TWA $\geq$ 65 $\mu$ V vs. TWA <65 $\mu$ V for all-cause mortality: HR: 3.3 (1.8-6.3)
Salerno-Uriarte <i>et al.</i> (2007)	9.0%	97.3%	Normal: 154 (34.5%) Abnormal: 292 (65.5%)	Cardiac death and life threatening arrhythmia: 33 (29 abnormal, 4 normal)	Abnormal vs. normal for cardiac death and life threatening arrhythmia: Adjusted HR: 3.21 (1.12-9.22)

*Abbreviations:* CHF = congestive heart failure; HR = hazard ratio; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; MTWA = microvolt t-wave alternans; NPV=negative predictive value; NR= not reported; PPV=positive predictive value; RR = risk ratio; TWA = t-wave alternans.

Although the majority of MTWA tests are conducted using exercise as the stressor, atrial pacing has also been used. For example, a study by Cantillon *et al.* (2007) examined the ability of the MTWA test using atrial pacing to risk stratify 286 patients with LVEF  $\leq$  35% who underwent electrophysiologic evaluation into high and low risk groups for arrhythmia free survival. There were 90 patients with negative and 196 patients with non-negative (positive or indeterminate) MTWA test results. A total of 174 patients underwent ICD implantation with similar numbers in the MTWA negative patients (n=49, 54%) and the MTWA non-negative patients (125, 64%). After two years, there were nine deaths in the MTWA negative group and 34 deaths in the non-negative group. Although the MTWA test using atrial pacing was found to be a significant predictor of arrhythmia-free survival (HR 2.33 (1.44 to 3.67)), the authors were concerned about the number of events in the MTWA negative group.

## Potential Cost Impact

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### Cost Analysis

Medtel NZ Pty Ltd has indicated that the initial purchase cost of the HearTwave® II Cardiac Diagnostic System in Australia is around AUD\$30,000 for the basic package, or around AUD\$40,000 with treadmill and stress functionality included (personal communication Medtel NZ Pty Ltd, January 2009). In New Zealand, the cost is approximately NZD\$40,000 NZD excluding the treadmill.

The unit cost per MTWA test in Australia and New Zealand is currently unknown, however in the United States the average cost of an MTWA test ranges from US\$400 to US\$650 (Daccarett *et al.* 2006). By way of context, the MBS fee for a standard exercise ECG in Australia is currently AUD\$140.50.

If all 2,864 ICD recipients (2005 data, irrespective of reason for implantation) were to get the MTWA test prior to implantation, at a cost of AUD\$400, the approximate cost per year in Australia would be AUD\$1,145,600. Similarly, if all 134 patients in New Zealand (2005 data) were tested at a cost of NZD\$400, the total cost for New Zealand would be NZD\$53,600. Potential cost savings accrued through the reduced ICD use and associated resource use have not been estimated, but could be substantial.

With regard to cost-effectiveness, a recent study by Chan *et al.* (2006) investigated the cost-effectiveness of MTWA testing in determining which patients satisfying MADIT-II inclusion criteria should receive an ICD. Three therapeutic strategies were compared in the study: ICD placement in all patients; ICD placement in only those patients reporting a non-negative MTWA result; and medical management. The authors reported an incremental cost-effectiveness ratio (ICER) of US\$88,700 per quality adjusted life year (QALY) when comparing a strategy of ICD implantation in all patients compared to medical management. However, when risk stratification with MTWA testing was applied, the cost effectiveness relative to medical management fell to US\$48,700. These results suggest the use of MTWA for pre-implantation decision making improves the cost-

effectiveness of ICD implantation. Further critical appraisal of this economic evaluation is warranted. Applicability of these cost effectiveness results will also be affected by the extent to which clinicians are willing to act upon the results of the MTWA test in practice.

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## Ethical Considerations

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There were no ethical, cultural or religious issues identified in the literature or reported anecdotally that were associated with the use of the MTWA test.

### Access Issues

Although the MTWA test is relatively easy to conduct, a trained cardiac specialist nurse, cardiac technician or cardiologist must undertake the evaluation. The HearTwave® II Cardiac Diagnostic System is estimated to cost \$30,000 and \$40,000 including treadmill in Australia and \$40,000 without the treadmill in New Zealand (personal communication, Medtel NZ Pty Ltd, January 2009). This may limit its introduction into areas other than major metropolitan hospitals and cardiac centres.

MTWA is not suitable for patients with atrial fibrillation, atrial flutter, or who require pacing at the time of investigation.

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## Training and Accreditation

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### Training

The HearTwave® II Cardiac Diagnostic System is relatively simple to operate and only requires brief instruction on use. Appropriately trained individuals to operate the system include cardiac technicians, cardiac specialist nurses and cardiologists.

### Clinical Guidelines

At the time of writing, no Australian clinical practice guidelines exist for the use of ICDs. However, there is 'Clinical Guidelines for the use of Implantable Cardiac Defibrillators for Prognostic Reasons in Patients with Impaired Ventricular Function Without Known Ventricular Tachyarrhythmias in Public Hospitals in NSW' ([http://www.health.nsw.gov.au/resources/gmct/cardiac/pdf/implantable\\_cardiac\\_defibrillators.pdf](http://www.health.nsw.gov.au/resources/gmct/cardiac/pdf/implantable_cardiac_defibrillators.pdf)) and there are NICE guidelines titled 'Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias' (<http://www.nice.org.uk/Guidance/TA95>).

## Limitations of assessment

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Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the MTWA test, its present and potential use, and future implications for the use of this technology in the Australian and New Zealand public health system.

### Research question

The clinical question investigated in this Horizon Scan was defined by staff from the New Zealand of Ministry of Health in conjunction with staff from Health Services Assessment Collaboration. In general, the aim of this Horizon Scan was to evaluate the safety, effectiveness and cost effectiveness of the MTWA test in patients who are candidates for ICDs.

The primary research question to be addressed by this report is:

- Can the MTWA test be used as a risk stratification tool for determining the likely benefit of ICD therapy in the prevention of sudden cardiac death?

The review question was defined according to the PICO criteria:

- Patient population
- Intervention / test
- Comparator
- Outcomes

For inclusion in this Horizon Scan, the evidence had to fulfil the criteria outlined in **Table 5** and **Table 6**. These criteria were developed *a priori* and described in the scoping protocol prepared prior to commencement of the review proper.

**Table 5: PICO criteria for this report**

<b>Patient population</b>	The broad patient population is individuals who are candidates for an ICD. This includes patients with no history of arrhythmic events (primary prevention) and patients who have had an event (secondary prevention). Healthy patient populations were excluded.
<b>Intervention</b>	The MTWA test, recorded using a commercially available diagnostic system, and an equivalent system. Studies must clearly define MTWA test results as positive, negative and/or indeterminate, or normal/abnormal to qualify for inclusion. Only those studies where the stressor for the MTWA test is exercise will be included.
<b>Comparator</b>	Not appropriate for non-comparative prognostic research questions such as that being addressed by the Horizon Scan. The current review includes studies examining the prognostic value of the MTWA test, irrespective of whether this information is sourced from comparative studies or not.
<b>Outcomes</b>	The primary outcome must be the ability of the MTWA test to predict SCD or ventricular arrhythmias. Included studies must provide data for the MTWA test and subsequent clinical outcomes, including SCD, cardiac death, ventricular arrhythmias, and/or ICD shock.

**Table 6: Nature of the evidence**

<b>Publication type</b>	Studies published in the English language, including primary (original) research published as full original reports and secondary research (systematic reviews and meta-analyses) appearing in the published literature.
<b>Study design</b>	All levels of evidence for prognosis research questions according to the National Health and Medical Research Council (NHMRC) interim levels of evidence were included.
<b>Study duration</b>	At least six months of follow-up.
<b>Sample size</b>	At least 40 evaluable patients with an MTWA test result in the total cohort.

## Search strategy used for the Horizon Scan

The sources searched in this assessment are listed in **Table 7**. A systematic review on this topic by Gehi *et al.* (2005) has been published and it was decided that only this report and studies published since the Gehi *et al.* (2005) literature search date would be discussed in this Horizon Scan. Therefore, this Horizon Scan forms an update summarising the literature published on this topic after December 2004. To find additional literature, the medical literature was searched with the search terms outlined in **Table 8**. The aim of the search was to identify relevant studies that had been conducted between December 2004 and December 2008, in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched. Given the volume of published evidence in this case, the grey literature and unpublished material such as conference abstracts were not searched.

**Table 7: Literature sources utilised in assessment**

Source	Location
<b>Electronic databases</b>	
Cochrane library- including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trilas , the Health Technology Assessment Database, the NHS Economic Evaluation Database	<a href="http://www.cochrane.org/">www.cochrane.org/</a>
Embase	<a href="http://www.embase.com/">http://www.embase.com/</a>
Medline	<a href="http://www.embase.com/">http://www.embase.com/</a>
<b>Internet</b>	
Blue Cross and Blue Shield Association’s Technology Evaluation Centre	<a href="http://www.bcbs.com/tec/">http://www.bcbs.com/tec/</a>
Canadian Agency for Drugs and Technologies in Health	<a href="http://www.cadth.ca">http://www.cadth.ca</a>
Clinical Trials Registry	<a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a>
International Network for agencies for Health Technology Assessment	<a href="http://www.inahta.org">http://www.inahta.org</a>
Medicines and Healthcare products Regulatory Agency (UK)	<a href="http://www.mhra.gov.uk/">http://www.mhra.gov.uk/</a>

**Table 8: Search terms utilised**

<b>Search terms</b>
<b>MeSH</b>
‘Microvolt t-wave alternans test’, ‘MTWA’, ‘TWA and microvolt’, ‘TWA and sudden cardiac death’, ‘t-wave alternans and sudden cardiac death’.
<b>Limits</b>
English, human, December 2004-December 2008

## Availability and Level of Evidence

Studies were selected for appraisal using a two-stage process. First, titles and abstracts (where available) identified from the search strategy were scanned and excluded as appropriate. Second, the full text articles were retrieved for the remaining studies and selected for inclusion and appraisal in the Horizon Scan if they met the pre-defined study selection criteria outlined below. Double-checking of the eligibility of studies by a second reviewer was not undertaken.

As mentioned earlier, non-human and non-English publications were excluded at the database searching stage. Identified citations were excluded for the following reasons:

1. Not a clinical study: including non-systematic reviews, case reports, short notes, letters, editorials and conference abstracts.

2. Wrong intervention: did not examine the MTWA test, including those that did not provide a clear definition of a positive, negative or indeterminate test or normal/abnormal test.
3. Wrong outcomes: the primary outcome must be the ability of the MTWA test to predict SCD or ventricular arrhythmias. Included studies must provide data for the MTWA test and subsequent clinical outcomes, including any of the following: SCD, cardiac death, ventricular arrhythmias, and/or ICD shock.
4. Wrong patient group: participants were not deemed candidates for ICD therapy.
5. Inappropriate study design: less than six months follow-up or fewer than 40 patients.

There were 480 citations reviewed from Embase and Medline, nine from the clinical trials registry and two from the Cochrane databases. No additional studies were found from the search of the major HTA databases online.

A total of 12 studies met the inclusion criteria for this Horizon Scan and were retrieved from the search of the medical literature described above. One of these was a systematic review by Gehi *et al.* (2005). A list of the included studies, including the level of prognostic evidence, study design, definition of MTWA test and study outcomes is summarised in **Table 2** and presented in more detail in **Appendix A**.

The Horizon Scan commenced with the highest available level of evidence, proceeding to lower levels of comparative evidence where necessary. Each study was assigned a level of evidence in accordance with the NHMRC (2005) interim levels of evidence for prognostic research questions (**Table 9**).

**Table 9: Prognostic levels of evidence (NHMRC, 2005)**

Level	Prognosis
I <sup>a</sup>	A systematic review of level II studies
II	A prospective cohort study <sup>b</sup>
III-1	All or none <sup>c</sup>
III-2	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
III-3	A retrospective cohort study
IV	Case series, or cohort study of persons at different stages of disease

<sup>a</sup> A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

<sup>b</sup> At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

<sup>c</sup> All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect.

In accordance with Horizon Scan methodology, no formal quality assessment was performed.

## Data synthesis

Data was extracted from the included studies into two specifically designed data extraction forms. The first included information regarding study design, patient characteristics, details of the intervention and relevant study outcomes. The second included a summary of the relevant results. Completed data extraction tables can be found in **Appendix A** and **Appendix B**.

## Sources of Further Information

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Searches on [www.clinicaltrial.gov](http://www.clinicaltrial.gov) and current controlled trials ([www.controlled-trials.com](http://www.controlled-trials.com)) did not reveal any ongoing studies on MTWA testing for the risk stratification of ICD candidates.

## Impact Summary

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Given the evidence presented in this Horizon Scan, it appears that the MTWA test could be used as an additional risk stratification tool for patients who are candidates for an ICD.

Excluding purchase costs, the crude estimated annual cost to the Australian and New Zealand health systems would be ~AUD\$1.1 million and NZD\$54,000 if all patients currently receiving an ICD were tested prior to implantation at hypothetical test cost of \$400. Potential cost savings accrued through the reduced ICD use and associated resource use has not been estimated, but could be substantial.

On the basis of the currently available evidence, introduction is likely to improve the cost-effectiveness of ICD implantation through identification of those patients most likely to benefit. The extent to which clinicians will act upon the results of the MTWA test in the context of other prognostic information may affect the impact of the test.

## Conclusions

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A meta-analysis and a number of large prospective studies have demonstrated the effectiveness of MTWA testing in predicting future arrhythmic events across a variety of patient populations. The test appears to be a useful method for identifying which patients with heart disease and left ventricular dysfunction are unlikely to receive benefit from ICD therapy. However, although the NPV of the test is high, there is still some concern surrounding the number of events occurring in patients who test MTWA negative, particularly given the nature of such events. Furthermore, the potential value of the MTWA test in clinical, economic and financial terms will be determined by the willingness of the clinician to act upon the MTWA test result, either alone or in combination with other prognostic information.

## Appendix A: Profiles of studies

Author (yr)	Country	Study design	Patient characteristics	Test characteristics		Study endpoints		History of arrhythmic events	Mean follow-up (months)
				Features of test	Classification	Prognostic endpoint(s)	Other endpoints		
<b>LEVEL I EVIDENCE</b>									
Gehi <i>et al.</i> (2005) <sup>a</sup>	NR	Meta-analysis of 19 studies conducted between January 1990 and December 2004	N = 2,608 Age range: 25 to 64 years 68% to 100% Males Mean EF range: 23 to 71 CHF, ischemic CHF, non-ischemic CHF, post-MI, athletes, and healthy subjects.	Studies were included if they examined the MTWA test after 1994. Only those who underwent exercise induced MTWA testing were included.	Only those studies that provided a clear definition of normal and abnormal MTWA were included. All results presented exclude subjects with indeterminate MTWA tests.	Clinical outcomes including SCD, cardiac death, ventricular arrhythmias and/or implantable cardioverter-defibrillator shock	-	Of the 19 included studies: 6 Yes; 13 No.	Studies must have followed patients for at least six months  Mean: 21 months
<b>LEVEL II EVIDENCE</b>									
Baravelli <i>et al.</i> (2005)	Italy	Prospective cohort study	N = 73 Mean age: 64 ± 9.3 years 83% Males Mean LVEF: 35.5% ± 7.3% CHF patients NYHA class II Inclusion criteria: NYHA II class, LVEF ≤45%. Exclusion criteria: Very low LVEF ≤20%, atrial fibrillation or flutter, MI or unstable angina in the last 2 months.	MTWA: exercise test (bicycle) TWA recorded using CH2000 or Heartwave systems (Cambridge Heart, Inc.) Spectral analysis	Positive: sustained alternans were present at the resting HR or had onset of heart rate ≤ 110 beats/min Negative: at least 1 min of artefact-free data without sustained alternans at a HR ≥ 105 beats/min Indeterminate: all others Were positive and indeterminate grouped: NO, indeterminate excluded.	Sudden cardiac death Sustained VT/VF Appropriate ICD shock	-	Yes	7 ± 7.4 months
Baravelli <i>et</i>	Italy	Prospective	N = 70	MTWA: exercise	Positive: alternans	Total major cardiac	Arrhythmic events:	No	19.2 ±

Author (yr)	Country	Study design	Patient characteristics	Test characteristics		Study endpoints		History of arrhythmic events	Mean follow-up (months)
				Features of test	Classification	Prognostic endpoint(s)	Other endpoints		
<i>al.</i> (2007)		cohort study	<p>Mean age: 64.5 ± 11.0 years</p> <p>72% Males</p> <p>Mean LVEF: 29.0% ± 6.4%</p> <p>Dilated cardiomyopathy patients<sup>b</sup></p> <p>Inclusion criteria: if diagnostic criteria for DCM were met according to WHO.</p> <p>Exclusion criteria: prior VT/VF, permanent atrial flutter/fibrillation, pace-maker dependency.</p>	<p>test (bicycle)</p> <p>TWA recorded using CH2000 or Heartwave systems (Cambridge Heart, Inc.)</p> <p>Spectral analysis</p>	<p>longer than 1 min at onset HR &lt;110 beats/min with the Valt &gt;1.8 microV and a Ralt &lt;3.</p> <p>Negative: 1 min of artefact-free ECG without sustained alternans with a HR &gt; 105 beats/min.</p> <p>Indeterminate: all others</p> <p>Were positive and indeterminate grouped: YES</p>	<p>events [including deaths due to worsening HF, SCD and documented sustained VT/VF (including appropriate ICD shock)]</p>	<p>SCD or sustained VT/VF</p>		10.7
Bloomfield <i>et al.</i> (2006)	US	Prospective cohort study	<p>N = 549</p> <p>Mean age: 56 ± 10 years</p> <p>71% Males</p> <p>Mean LVEF: 25.0% ± 6.0%</p> <p>Outpatients</p> <p>Half of patients had ischemic heart disease</p> <p>Two thirds had NYHA class II or III heart failure</p> <p>Inclusion criteria: ≥18 years, LVEF ≤40.0%, no history of sustained ventricular arrhythmia.</p> <p>Exclusion criteria: unstable CAD, atrial fibrillation or flutter, NYHA class IV, unable to exercise.</p>	<p>MTWA: exercise test (bicycle or treadmill)</p> <p>TWA recorded using CH2000 or Heartwave systems (Cambridge Heart, Inc.)</p> <p>Spectral analysis</p>	<p>Positive: onset HR ≤ 110 beats/min</p> <p>Negative: maximum negative HR ≥105 beats/min</p> <p>Indeterminate: all others</p> <p>Were positive and indeterminate grouped: YES</p>	<p>All cause mortality</p>	<p>Non-fatal sustained ventricular arrhythmias (including ICD shocks with intracardiac electrocardiograms documented rapid VT or VF)</p>	No	20 ± 6 months
Kaufman <i>et</i>	As	As above	As above	As above	Positive: ≥1 min of	As above	As above	As above	As above

Author (yr)	Country	Study design	Patient characteristics	Test characteristics		Study endpoints		History of arrhythmic events	Mean follow-up (months)	
				Features of test	Classification	Prognostic endpoint(s)	Other endpoints			
<i>al.</i> (2006)	above				<p>MTWA with an onset HR <math>\leq</math>110 beats/min that sustained as long as HR remained above the patients specific onset HR</p> <p>Negative: sustained MTWA not present at onset HR <math>\leq</math>110 beats/min and if there was <math>\geq</math>1 min at HR <math>\geq</math>105 beats/min in sinus rhythm with noise level <math>&lt;</math>2 <math>\mu</math>V and ectopy <math>&lt;</math>10%.</p> <p>Indeterminate: all others.</p> <p>Were positive and indeterminate grouped: NO</p>					
Chow <i>et al.</i> (2006)	US	Prospective cohort study	<p>N = 768</p> <p>Mean age: 66.7 years <sup>c</sup></p> <p>81.5% males <sup>c</sup></p> <p>Mean LVEF: 27.4% <sup>c</sup></p> <p>Patients with ischemic cardiomyopathy</p> <p>Inclusion/exclusion criteria: <math>\geq</math>21 years, LVEF <math>\leq</math>35%, no history of ventricular arrhythmic event, in sinus rhythm.</p>	<p>MTWA: Exercise test (treadmill)</p> <p>TWA recorded using CH2000 or Heartwave systems (Cambridge Heart, Inc.)</p> <p>Spectral analysis.</p>	<p>Positive: NR</p> <p>Negative: NR</p> <p>Indeterminate: NR</p> <p>Were positive and indeterminate grouped: YES</p>	All-cause mortality	-	Appropriate ICD shocks (in patients with ICDs)	No	18 $\pm$ 10 months
Chan <i>et al.</i> (2008)	As above	As above	As above	As above	As above	As above	As above	As above	As above	18 $\pm$ 11 months
Chow <i>et al.</i> (2007a)	As above	As above	As above	As above	As above	As above	As above	As above	As above	18 $\pm$ 10 months

Author (yr)	Country	Study design	Patient characteristics	Test characteristics		Study endpoints		History of arrhythmic events	Mean follow-up (months)
				Features of test	Classification	Prognostic endpoint(s)	Other endpoints		
Chow <i>et al.</i> (2007b)	As above	As above	As above	As above	As above	As above	As above	As above	27 ± 12 months
Ikeda <i>et al.</i> (2006)	Japan	Prospective cohort	N = 1,041 Mean age: 64 ± 11 years 79% Males Mean LVEF: 55 ± 10 Consecutive infarct survivors Inclusion criteria: LVEF ≥40% Exclusion criteria: atrial fibrillation/flutter, ventricular pacemaker	MTWA: Bicycle or treadmill test. CH2000 System (Cambridge Heart, Inc.) or HeartWave System (Cambridge Heart, Inc) Spectral analysis.	Positive: Sustained alternans voltage was >1.9 μV with alternans ratio >3.0 in any orthogonal lead or 2 consecutive precordial leads with an onset HR <110 beats/min for ≥1 minute. Negative: Positive criteria were not met and artifact free data were showing a HR maintained at a level >105 beats/min for ≥1 minute. Indeterminate: all others. Were positive and indeterminate grouped: NO	Sudden cardiac death	Cardiac arrest Resuscitated ventricular fibrillation	Yes	32 ± 14 months
Nieminen <i>et al.</i> (2007)	Finland	Retrospective cohort study	N = 1037 Mean age: 58 ± 13 years 65% Males Mean EF for 529 patients: 65 ± 15% Patients undergoing an exercise stress test (indications for testing: CHD, vulnerability to arrhythmia during exercise, work capacity, adequacy of CHD	MTWA: Exercise test. Using domain MMA analysis method and standard electrodes. The maximum MTWA value at a HR <125 beats per minute was used to stratify patients at risk of all-cause	TWA <65 μV = negative TWA ≥65 μV = positive Were positive and indeterminate grouped: NO	Sudden cardiac death Cardiovascular mortality All cause mortality	-	Yes and No	44 ± 7 months

Author (yr)	Country	Study design	Patient characteristics	Test characteristics		Study endpoints		History of arrhythmic events	Mean follow-up (months)
				Features of test	Classification	Prognostic endpoint(s)	Other endpoints		
			treatment, post-MI). Inclusion criteria: technically successful exercise test. Exclusion criteria: NR	death, cardiovascular death and sudden cardiac death.					
Salerno-Uriarte <i>et al.</i> (2007)	Italy	Prospective cohort study	N = 446 Mean age: 59.0 ± 12.5 78.2% Males LVEF %: 29.5 ± 7.1% NYHA functional class II or III Non-ischemic cardiomyopathy Inclusion criteria: NR Exclusion criteria: other etiology, mainly ischemic, of the cardiomyopathy, atrial fibrillation/flutter, LVEF >40%, NYHA class I or IV, age <18 or >80 years, presence of an ICD, history of cardiac arrest, sustained VT or syncope.	MTWA Exercise test: Bicycle or treadmill. CH2000 or Heart Wave Diagnostic System Spectral analysis	Positive: onset HR ≤ 110 beats/min or sustained alternans at resting HR, even if >110 beats/min Negative: if (1) it does not meet the criteria for being positive and (2) maximum negative HR ≥ 105 beats/min Indeterminate: All others Were positive and indeterminate grouped: YES	Cardiac death and life threatening ventricular arrhythmias (ventricular fibrillation, resuscitated cardiac arrest, and sustained ventricular tachycardia)	Total mortality Arrhythmic death and life-threatening arrhythmias Hospitalisation rate	Yes	18-24 months Median follow-up: 19 months

*Abbreviations:* CAD = coronary artery disease; CHD = coronary heart disease; CHF = congestive heart failure; DCM = dilated cardiomyopathy; EF = ejection fraction; HR = heart rate; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MTWA = microvolt t-wave alternans; TWA = t-wave alternans; MI = myocardial infarction; MMA = modified moving average; NYHA = New York Heart Association; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia; WHO = world health organisation.

<sup>a</sup> The meta-analysis by Gehi *et al.* (2005) included studies with healthy patient populations and studies with fewer than 40 patients

<sup>b</sup> It is possible that 22 patients from this cohort were also included in the Baravelli *et al.* (2005) study however insufficient information existed to determine if this was the case.

<sup>c</sup> Calculated *post-hoc* by crude average of reported means for four sub-groups

## Appendix B: Study results

Author (yr)	Positive predictive value (%)	Negative predictive value (%)	MTWA results	Prognostic and other outcomes	HR/RR	P-value
<b>LEVEL I EVIDENCE</b>						
Gehi <i>et al.</i> (2005)	Arrhythmic events (21 months): 19.3% (17.7%-21.0%)	Arrhythmic events (21 months): 97.2% (96.5%-97.9%)	NR	<p><b>Prognostic outcomes</b></p> <p>The presence of significant MTWA predicted almost a four-fold increased risk of a ventricular arrhythmic event compared with the absence of significant MTWA.</p> <p>The absence of MTWA carries a 3% risk of arrhythmic events during an average of 21 months follow-up.</p> <p><b>Other outcomes</b></p> <p>No difference in the predictive value of MTWA test between patients with ischemic and non-ischemic CHF.</p>	<p>RR for cardiac arrhythmic events in all patients: 3.77 (2.39 - 5.94).</p> <p>RR for cardiac arrhythmic events in CHF patients: 2.51 (1.71-3.65)</p> <p>RR for cardiac arrhythmic events in ischemic CHF: 2.42 (1.30-4.50)</p> <p>RR for cardiac arrhythmic events in non-ischemic CHF: 3.67 (1.50-8.96)</p> <p>RR for cardiac arrhythmic events in post-MI: 4.74 (1.11-20.19)</p>	NR
<b>LEVEL II EVIDENCE</b>						
Baravelli <i>et al.</i> (2005)	SCD and arrhythmic events: 24%	SCD and arrhythmic events: 100%	<p>Positive: 30 (41%)</p> <p>Negative: 26 (36%)</p> <p>Indeterminate: 17 (23%)</p>	<p><b>Prognostic outcomes</b></p> <p>1 (1.5%) death (MTWA result not reported) [pump failure]</p> <p>8 (11%) arrhythmic events (7 positive, 0 negative and 1 indeterminate).</p> <p><b>Other outcomes</b></p> <p>9% of patients fitted with an ICD post-MTWA test.</p>	<p>MTWA predictive values for SCD and arrhythmic events, RR: <math>\infty</math> (<math>\infty - \infty</math>).</p>	<p>Kaplan-Meier univariate analysis and multivariate * Cox analysis, MTWA was a significant predictor of arrhythmic events: P=0.01, P=0.04, respectively.</p> <p>* Adjusted for LVEF, age, gender, hypertension, diabetes</p> <p>With ICD recipients removed from analysis: P=0.05.</p>
Bravelli <i>et al.</i> (2007)	<p>Major cardiac events: 22%</p> <p>Arrhythmic events: 15%</p>	<p>Major cardiac events: 93%</p> <p>Arrhythmic events : 100%</p>	<p>Abnormal: 40 (57%)</p> <p>Normal: 30 (43%)</p>	<p><b>Prognostic outcomes</b></p> <p>11 major cardiac events</p> <p>Abnormal: 3 deaths, 6 arrhythmic events</p>	<p>Univariate analysis: MTWA predicted major cardiac event: 0.24 (0.08-0.94)</p> <p>Univariate analysis: MTWA predicted arrhythmic events: HR: 0.00 (0.00-0.74).</p>	<p>Major cardiac event: P=0.07</p> <p>Arrhythmic events: P=0.02</p>

Author (yr)	Positive predictive value (%)	Negative predictive value (%)	MTWA results	Prognostic and other outcomes	HR/RR	P-value
				Normal: 2 deaths, 0 arrhythmic events	Multivariate* analysis: MTWA predicted arrhythmic events: HR:0.32 (0.14-0.93) * Adjusted for peak VO <sub>2</sub> <10 ml/kg/min, abnormal MTWA, LVEF < 30%, presence of non-sustained VT, QRS duration > 120 ms, relevant mitral regurgitation, NYHA class, age, gender, presence of biventricular pacing.	Arrhythmic events: P=0.04
				<b>Other outcomes</b> -	-	-
Bloomfield <i>et al.</i> (2006)	NR	NR	Abnormal: 360 (66%) Normal: 189 (34%)	<b>Prognostic outcomes</b> 40 deaths 11 non-fatal VA Abnormal: 2-year event rate for the primary endpoint: 15% Normal: 2-year event rate for the primary endpoint: 2.5%	HR for primary endpoint (deaths and non-fatal sustained VA) = 6.5 (2.4-18.1) HR adjusted* for other risk predictors for primary endpoint = 5.5 (2.0-15.3) * Adjusted for age, gender, etiology of heart disease, diabetes, NYHA class, LVEF, previous hospital admission.	P < 0.001 P=0.001
				<b>Other outcomes</b> ICD implants: 69 (8 before and 61 after enrolment) Actuarial 2-year implant rate: 14% in normal, 13.6% in abnormal MTWA 2 patients with a normal test had a shock during follow-up, abnormal not reported.	-	-
Kaufman <i>et al.</i> (2006) <sup>a</sup>	NR	NR	Positive: 163 (29.7%) Negative: 195 (35.5%) Indeterminate: 191 (34.8%)	<b>Prognostic outcomes</b> 40 deaths, 11 non-fatal VA Positive: 2-year product-limit event rate for all-cause mortality or non-fatal SVA: 12.3% Negative: 2-year product-limit event rate for all-cause mortality or non-fatal SVA: 2.4% Indeterminate: 2-year product-	HR comparing indeterminate MTWA tests with positive tests: 1.3 (0.9-1.7) Comparing MTWA tests classified as indeterminate owing to patient factors with positive tests: HR ranged from 1.1 to 1.6.	NR

Author (yr)	Positive predictive value (%)	Negative predictive value (%)	MTWA results	Prognostic and other outcomes	HR/RR	P-value
				limit event rate for all-cause mortality or non-fatal SVA: 17.8%		
				<b>Other outcomes</b> 69 ICD implants during 2 years follow-up: 13% in patients with a negative test, 13% in those with positive and 12% in those with indeterminate. 11 patients had SVA as endpoint, all patients had ICDs: 2 had negative MTWA, 5 positive, 4 indeterminate		-
Chow <i>et al.</i> (2006)	NR	NR	Non-negative: 514 (67%) Negative: 254 (33%)	<b>Prognostic outcomes</b> <i>Non-ICD group</i> : 58 deaths (MTWA negative: 15 (8.4%); MTWA non-negative: 43 (21.8%). 28 of which were arrhythmic deaths (MTWA negative: 6(3.4%); MTWA non-negative: 22 (11.2%). <i>ICD group</i> : 41 deaths (MTWA negative: 6 (8.0%); MTWA non-negative: 35 (11.0%). 14 of which were arrhythmic deaths(MTWA negative: 3(4.0%); MTWA non-negative: 11 (3.5%).	Adjusted* HR for all-cause mortality comparing those who tested MTWA negative and non-negative: 2.24 (1.34-3.75) Adjusted* HR for arrhythmic mortality comparing those who tested MTWA negative and non-negative: 2.29 (1.00-5.24) Adjusted* HR for non-arrhythmic mortality comparing those who tested MTWA negative and non-negative: 1.77 (0.84-3.74) * Adjusted for age, gender, LVEF, QRS duration >120 ms, clinical comorbid conditions, medication.	P=0.002 P=0.049 P=0.13
				<b>Other outcomes</b> 26 appropriate ICD therapies not associated with death in the ICD group (MTWA negative: 2 (2.7%); MTWA non-negative: 24 (7.6%)	Adjusted HR associated with a non-negative MTWA test did not significantly differ by ICD status: 1.79 (0.66-4.86) Adjusted HR for patients with ICDs: non-negative MTWA showed trend toward higher risk for appropriate ICD shock not associated with death: 3.74 (0.88-15.91).	P=0.25 P=0.07

Author (yr)	Positive predictive value (%)	Negative predictive value (%)	MTWA results	Prognostic and other outcomes	HR/RR	P-value
Chan <i>et al.</i> (2008)	NR	NR	As above	<b>Prognostic outcomes</b> 99 deaths (all-cause) Non-negative: 78 (15.2%) Negative: 21 (8.3%) 42 Arrhythmic deaths Non-negative: 33 (6.4%) Negative: 9 (3.5%)	A non-negative MTWA test result compared to negative test result for all-cause mortality and appropriate ICD shocks: HR: Year 1: 2.19 (1.10-4.34) HR: Year 2: 3.36 (1.28-8.83) HR: Year 3: 2.06 (0.81-5.22) A non-negative MTWA test result compared to negative test result for arrhythmic mortality and appropriate ICD shocks: HR: Year 1: 2.84 (1.07-7.58) HR: Year 2: 3.26 (0.73-14.51) HR: Year 3: 2.40 (0.66-8.79)	P =0.03 P= 0.01 P= 0.13 P=0.04 P=0.12 P=0.18
				<b>Other outcomes</b> 33 appropriate ICD shocks Non-negative: 30 (9.5%) Negative: 3 (4.0%)	-	-
Chow <i>et al.</i> (2007a)	NR	NR	As above	<b>Prognostic outcomes</b> 99 deaths Non-ICD: 58 deaths ICD: 41deaths	Patients with a non-negative MTWA result had a more than twofold increased risk of all cause mortality HR=2.27 (1.22-4.24) than those with an MTWA neg result. Patients with a non-negative MTWA result had a more than threefold increased risk of an arrhythmic death HR=3.32 (1.31-8.41) than those with an MTWA neg result.	P=0.01 P=0.01
				<b>Other outcomes</b> As in Chow <i>et al.</i> 2006	In patients with ICDs, a non-negative MTWA result, predicted the combined end point of all-cause mortality and appropriate ICD shock HR= 2.42 (1.07-5.41). In patients with ICDs, MTWA result did not predict arrhythmic or nonarrhythmic events. Although a non-negative MTWA result showed a strong trend for	P=0.04 P=0.08

Author (yr)	Positive predictive value (%)	Negative predictive value (%)	MTWA results	Prognostic and other outcomes	HR/RR	P-value
					arrhythmic events HR=2.05 (0.93-4.55)	
Chow <i>et al.</i> (2007b)	NR	NR	As above	<p><b>Prognostic outcomes</b> 129 deaths: 99 in the MTWA non-negative group; 30 in the MTWA negative group</p> <p>56 arrhythmic deaths: 44 in the MTWA-non negative; 12 in the MTWA negative group</p> <p><b>Other outcomes</b> In the MTWA negative group, there were 9 (12.0%) deaths in those with ICDs and 21 (11.7%) in those without an ICD</p> <p>In the MTWA non-negative group, there were 46 (14.5%) deaths in the ICD group and 53 (26.9%) deaths in those without an ICD</p> <p>35 appropriate ICD shocks in patients who did not die in the ICD group</p>	<p>Adjusted proportional hazards analyses showed ICDs were associated with significantly reduced all-cause mortality in MTWA non-negative patients HR= 0.45 (0.27-0.76) but <b>not</b> in MTWA negative patients HR=0.85 (0.33-2.20).</p> <p>ICD's associated with reduced arrhythmic mortality in the MTWA non-negative group: 0.30 (0.13-0.68).</p> <p>No significant difference in non-arrhythmic mortality found between ICD groups in either MTWA non-negative or negative cohorts.</p>	P=0.004
Ikeda <i>et al.</i> (2006)	Serious arrhythmic events: 8.9%	Serious arrhythmic events: 99.6%	Positive: 169 (18%) Negative: 747 (74%) Indeterminate: 87 (9%)	<p><b>Prognostic outcomes</b> 18 primary events (14 SCD, 2 cardiac arrests and 2 resuscitated ventricular fibrillation)</p> <p><b>Other outcomes</b> 38 deaths due to non-arrhythmic causes</p>	<p>Univariate analysis: a positive MTWA test predicted serious arrhythmic events with a HR of 23.5 (6.8 - 81.0)</p> <p>Multivariate analysis: a positive MTWA test predicted serious arrhythmic events with a HR of 19.7 (5.5-70.4)</p> <p>Hazard ratio for NSVT and ventricular late potentials were 6.2 and 5.8, respectively.</p>	P < 0.0001  NSVT: P=0.0001 V-LP: P=0.0006
Niemenen <i>et al.</i> (2007)	<i>TWA cut point 65µV</i> SCD: 8.0% Cardiovascular	<i>TWA cut point 65µV</i> SCD: 98.6% Cardiovascular	TWA < 65µV = 950 (91.6%) TWA ≥ 65 µV = 87 (8.4%)	<p><b>Prognostic outcomes</b> 59 patients died: 34 due to cardiovascular causes and 20 due to SCD</p>	<p><i>Adjusted RR of TWA ≥ 65µV:</i>            SCD = 7.4 (2.8-19.4)            Cardiovascular mortality: 6.0 (2.8-12.8)</p>	P<0.001 P<0.001

Author (yr)	Positive predictive value (%)	Negative predictive value (%)	MTWA results	Prognostic and other outcomes	HR/RR	P-value
	mortality: 12.6% All-cause mortality: 14.9% <i>TWA cut point 46µV</i> SCD: 3.7% Cardiovascular mortality: 6.0% All-cause mortality: 7.4%	mortality: 97.6% All-cause mortality: 95.2% <i>TWA cut point 46µV</i> SCD: 98.7% Cardiovascular mortality: 97.6% All-cause mortality: 94.9%	TWA < 46 µV = NR TWA ≥ 46 µV = NR	MTWA positive: NR MTWA negative: NR	<i>Unadjusted RR of TWA ≥ 65µV:</i> SCD = 6.3 (2.5-15.9) Cardiovascular mortality: 5.6 (2.7-11.4) All-cause mortality: 3.3 (1.8-6.3) <i>RR of TWA ≥ 46 µV:</i> SCD = 2.9 (1.2-7.1) Cardiovascular mortality: 2.6 (1.3-5.1) <i>Unadjusted RR of TWA ≥ 46µV:</i> All-cause mortality: NR	P<0.001 P<0.001 P<0.001 P=0.02 P=0.01
				<b>Other outcomes</b> -	-	-
Salerno-Uriarte <i>et al.</i> (2005)	Cardiac death + life threatening arrhythmia (18 months): 9.0% (5.9%-13.0%) Total mortality (18 months): 7.7% (4.1%-11.5%) Arrhythmic death + life-threatening arrhythmia (18 months): 7.0% (4.3%-10.7%)	Cardiac death + life threatening arrhythmia (18 months): 97.3% (93.3%-99.3%) Total mortality (18 months): 98.0% (94.2%-99.6%) Arrhythmic death + life-threatening arrhythmia (18 months): 98.6% (95.2%-99.8%)	Normal: 154 (34.5%) Abnormal: 292 (65.5%)	<b>Prognostic outcomes</b> Cardiac death + life threatening arrhythmia: 33 (29 abnormal MTWA, 4 normal MTWA)	Unadjusted HR for primary endpoint (cardiac death and life threatening arrhythmias) = 4.01 (1.41-11.41) Adjusted* HR for primary endpoint (cardiac death and life threatening arrhythmias) = 3.21 (1.12-9.22) * Adjusted for age, gender, NYHA and LVEF.	P=0.002 P=0.013
				<b>Other outcomes</b> Total mortality: 28 (25 abnormal MTWA, 3 normal MTWA) Arrhythmic death + life-threatening arrhythmia: 22 (20 abnormal MTWA, 2 normal MTWA) Hospitalisation: 85 (61 abnormal MTWA, 24 normal MTWA)	Unadjusted HR for total mortality =4.60 (1.39-15.25) Unadjusted HR for arrhythmic death and life threatening arrhythmia =5.53 (1.29-23.65) Unadjusted IRR for hospitalisation= 1.39 (0.86-2.32)	P=0.002 P=0.004 P=0.165

*Abbreviations:* CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; ICD = implantable cardioverter defibrillator; MTWA = microvolt t-wave alternans; NR = not reported; NSVT = non-sustained ventricular tachycardia; RR = risk ratio; SCD = sudden cardiac death; SVA = sustained ventricular arrhythmia; TWA = t-wave alternans; VA = ventricular arrhythmia; V-LP = ventricular late potentials

<sup>a</sup> The number of patients in the positive plus indeterminate group does not equal the 'abnormal' number in the Bloomfield *et al.* (2006) publication which may be due to slight differences in classification of the MTWA test

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