Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

National Horizon Scanning Unit
Horizon scanning prioritising summary

Volume 15, Number 2

Microvolt T-wave alternans for the determination of patients likely to benefit from ICD therapy

February 2007

AHTA

Adelaide Health Technology Assessment

[add ISSN]
[add Publications Approval Number]

Electronic copies can be obtained from http://www.horizonscanning.gov.au

Enquiries about the content of this summary should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

The production of this *Horizon scanning prioritising summary* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This *Horizon scanning prioritising summary* was prepared by Tom Sullivan and Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, Mail Drop 511, University of Adelaide, South Australia, 5005.

PRIORITISING SUMMARY

REGISTER ID: **000238 REFERRAL FROM HEALTHPACT**

NAME OF TECHNOLOGY: **MICROVOLT T-WAVE ALTERNANS**

PURPOSE AND TARGET GROUP: **DETERMINING THE LIKELY BENEFIT OF ICD THERAPY IN THE PREVENTION OF SUDDEN CARDIAC DEATH**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☐ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☒ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☒ Yes — ARTG number 65760
- ☐ No
- ☐ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States			✓
Europe		✓	
Australia		✓	

IMPACT SUMMARY:

Recent clinical trials have demonstrated that implantable cardioverter defibrillators (ICDs) improve survival in post myocardial infarction patients with low ejection fraction. In this group of patients however, only a small percentage will experience any benefit from an ICD. Given the high costs and procedural morbidity associated with ICD implantation, a strong emphasis has been placed on risk stratification techniques to determine among eligible patients those that are likely to benefit from ICD implantation. Microvolt T-wave alternans (MTWA) testing, a non-invasive measure strongly related to arrhythmic events, has shown promise as a risk stratification technique amongst patients with low ejection fraction. The current prioritising summary outlines the technique of MTWA testing and investigates its effectiveness and cost implications in the risk stratification of ICD eligible patients.

BACKGROUND

Sudden cardiac death (SCD) resulting from ventricular arrhythmias is a leading cause of mortality in patients with ischemic heart disease and left ventricular dysfunction

(Greenberg et al 2004). 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. ICDs were first used as a secondary prevention measure in patients with previously documented ventricular arrhythmias. While these patients are at high risk of SCD, they account for only a small percentage of total SCD cases. Most patients with left ventricular dysfunction who die from ventricular arrhythmias do so during their first cardiac arrest (Huikuri et al 2006). Clinical interest has therefore focused on primary prevention strategies in patients yet to experience life-threatening arrhythmic events.

Several recent clinical trials have demonstrated the benefits of ICD implantation in all patients with ischemic or non-ischemic heart disease and left ventricular dysfunction. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) compared ICD implantation to conventional therapy in post myocardial infarction patients with a left ventricular ejection fraction of 0.30 or less. Over an average follow-up period of 20 months, the trial reported a 28 per cent relative reduction in mortality rates (or 5.6% absolute reduction) in patients implanted with an ICD in comparison to patients that received conventional therapy (Moss et al 2002). Similarly, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) investigated the effectiveness of ICD implantation in patients with a left ventricular ejection fraction of 0.35 or less and previous heart failure of ischemic or non-ischemic nature. During an average follow-up period of 45.5 months, ICD implantation was associated with a 23 per cent relative reduction in overall mortality rates (Bardy et al 2005). Despite the apparent survival benefits in this patient group, only a small percentage of patients experience any benefit from an ICD. In the MADIT-II trial for example, only 23 per cent of patients in the treatment arm received appropriate ICD pacing or defibrillation during the follow-up period (Singh et al 2005). The majority of patients were implanted with a device that provided no therapy, creating unnecessary costs and morbidity associated with the implantation procedure. In addition to ischemic or non-ischemic heart disease and left ventricular dysfunction, further diagnostic tests are required to better discriminate between patients likely to and unlikely to benefit from ICD implantation.

MTWA testing has emerged as a promising risk stratification tool for determining which patients with low left ventricular ejection fraction should receive an ICD. MTWA refers to beat-to-beat changes in T wave amplitude and morphology, and has been closely linked to susceptibility to ventricular arrhythmias and SCD in a wide variety of patient populations (see for example Hohnloser et al 1998; Ikeda et al 2000; Klingenheben et al 2000). A regular electrocardiogram cannot detect fluctuations in T-waves due to their small size, and thus the test requires specialised recording and signal processing methods. MTWA is typically recorded during a period of controlled exercise (as the test requires elevation of the heart rate to above 110 beats per minute) and later analysed using spectral decomposition methods. Two measures are obtained

from the testing procedure, the magnitude of the T-waves (typically 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 defined as alternans voltage of ≥1.9 μV at 0.5 cycles-per-beat and an alternans ratio of ≥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 & Hohnloser 2002).

MTWA can be measured using the commercially available HearTwave® II Cardiac Diagnostic System (Cambridge Heart, Inc., Bedford, MA). The system 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. The system is typically used to measure and interpret MTWA during bicycle or treadmill stress tests, but can also be used during pharmacological or echocardiographic stress tests. Following completion of the test, the system generates a printed report.

CLINICAL NEED AND BURDEN OF DISEASE

Individuals at the highest risk of ventricular arrhythmias and SCD are those with a history of myocardial infarction, 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 & Zipes 2006). 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 (level IV Aetiology evidence), 10,199 autopsies performed between January 1994 and December 2002 at a major Sydney forensic unit 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 per cent of cases. Coronary artery disease was reported in 24 per cent of cases, hypertrophic cardiomyopathy or unexplained left ventricular hypertrophy in 15 per cent of cases, and myocarditis in 12 per cent of cases.

In 2004-2005, a total of 3,216 ICDs were implanted in patients in Australian public hospitals, the procedure associated with an average length of stay of 5.5 days (AIHW 2006). It is likely however that a much larger patient group would be eligible for ICD implantation and subsequently MTWA testing if MADIT-II inclusion criteria were adopted. In 2004-2005, 10,056 Australians were diagnosed with left ventricular failure, while a further 47,633 experienced an acute myocardial infarction (AIHW 2006).

DIFFUSION

MTWA testing was first available in the United States in 2002 when the FDA provided 510(k) clearance for the HearTwave™ Alternans Processing System or CH2000 (Cambridge Heart, Inc., Bedford, MA). Since that time, Cambridge Heart, Inc. has received 510(k) clearance from the FDA for the HearTwave® II Cardiac Diagnostic System. The system has been commercially available in the United States since April 2005 and is reimbursed through Medicare for the purposes of risk stratification of SCD. In Australia, the HearTwave® II Cardiac Diagnostic System is marketed through Equipmed Pty Ltd after recent approval from the TGA (ARTG Number 65760). At this stage uptake of the system in Australia has been limited however, this may be due to the lack of reimbursement for MTWA testing through the MBS (personal communication Equipmed Pty Ltd, December 2006).

COMPARATORS

There are a number of comparators to MTWA testing in the risk stratification of patients with ischemic heart disease and left ventricular dysfunction. Other potential techniques of risk stratification include the detection of arrhythmias using a Holter monitor or during an electrophysiological study, the measurement of heart rate variability, QRS duration and baroreceptor sensitivity. Signal-averaged electrocardiography is another risk stratification method that measures beat-averaged conduction rather than beat-to-beat fluctuations. It is therefore conceivable that MTWA could be used in conjunction with a variety of other prognostic tests in order to more efficiently stratify patients for ICD implantation. Among patients with ischemic heart disease and left ventricular dysfunction, the measurement of MTWA is an attractive option given the high negative predictive ability and non-invasive nature of the test.

EFFECTIVENESS AND SAFETY ISSUES

Gehi et al (2005) conducted a meta-analysis of the value of MTWA in predicting future arrhythmic events (level I prognostic evidence). In the analysis, a total of 19 studies published between January 1990 and December 2004 were identified. All studies met the following inclusion criteria: prospective cohort study involving more than 10 human subjects who underwent MTWA testing for the prediction of ventricular arrhythmias or SCD; provided data on MTWA test results and clinical outcomes; provided a clear definition of the criteria used to classify MTWA results as normal or abnormal; and had a follow-up time of 6-months or longer. A total of 2,608 patients across a wide range of populations were analysed in the study, including patients with congestive heart failure (CHF), ischemic CHF, non-ischemic CHF, post myocardial infarction, athletes and healthy participants. The mean age of participants in the studies ranged between 25 and 64 years, with a mean length of follow-up of 19-

months. A negative MTWA test result was reported in 25 to 54 per cent of study subjects.

Using random effects models, Gehi et al (2005) calculated a pooled positive predictive value (PPV) for future arrhythmic events (classified as SCD, cardiac death, ventricular fibrillation, ventricular tachycardia or ICD event) of 19.3 per cent (95% CI, 17.7%-21.0%), a pooled negative predictive value (NPV) of 97.2 per cent (95% CI, 96.5%-97.9%) and a pooled relative risk of 3.77 (95% CI, 2.39-5.95). Sub-group analyses revealed no statistically significant differences in the predictive ability of MTWA testing between ischemic and non-ischemic patients. A significant difference in the PPV of MTWA testing between post myocardial infarction patients and CHF patients was reported however (6.0% vs. 25.5%, $p < 0.0001$). No evidence of publication bias was found ($p = 0.15$).

In a recent multicenter prospective cohort study, Chow et al (2006) investigated whether MTWA testing was an independent predictor of mortality in 768 patients with ischemic cardiomyopathy and left ventricular ejection fraction ≤35 per cent (level II prognostic evidence). The mean length of follow-up in the study was 18 ± 10 months. A total of 514 patients (67% of sample) reported a non-negative MTWA test (positive or indeterminate). After adjusting for a variety of prognostic factors (including ICD status), patients with a non-negative MTWA result were found to be at a significantly higher risk of all-cause mortality than those with a negative result (HR = 2.24, 95% CI, 1.34-3.75, $p = 0.002$). The risk of mortality due to arrhythmic events was also found to be significantly higher in patients with a non-negative MTWA result after adjusting for prognostic factors (HR = 2.29, 95% CI, 1.00-5.24, $p = 0.049$).

Bloomfield et al (2006) recently published results of a multicenter prospective cohort study (level II prognostic evidence) involving 587 patients with ischemic heart disease or non-ischemic cardiomyopathy and left ventricular ejection ≤ 40 per cent. The mean length of follow-up in the study was 20 ± 6 months. Of the 549 patients that could be evaluated, 360 (66%) reported a non-negative MTWA test result (positive or indeterminate). A total of 40 deaths and 11 non-fatal sustained ventricular arrhythmias, all of which were appropriate for ICD shocks, were observed during follow-up. The risk for all-cause mortality or ventricular arrhythmias was reported to be significantly higher amongst patients who reported a non-negative MTWA test result in comparison to patients who reported a negative result (HR = 6.5, 95% CI, 2.4-18.1, $p < 0.0001$). Only two deaths and two non-fatal sustained

ventricular arrhythmias occurred in patients with a negative MTWA result, giving the test a PPV and NPV of 13.5 and 97.9 per cent respectively.

COST IMPACT

Equipmed has indicated that the cost of the HearTwave® II Cardiac Diagnostic System in Australia is around $30,000 for the basic package, or around $40,000 with treadmill and stress functionality included (personal communication Equipmed Pty Ltd, December 2006). Although the Australian costs of MTWA testing are unknown, in the United States the average cost of an MTWA test ranges from $400 to $650 US dollars (Daccarett et al 2006).

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 patients reporting a non-negative MTWA result; and medical management. The authors reported an incremental cost-effectiveness ratio (ICER) of $48,700 per quality adjusted life year (QALY) when comparing a strategy of MTWA risk stratification to standard medical management, suggesting that MTWA testing is costly but potentially cost effective. An ICER of $88,700 per QALY was calculated when comparing a strategy of ICD placement in all patients to ICD placement following MTWA risk stratification, suggesting that a strategy of ICD placement in all patients offers little additional benefits at a high cost.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

MTWA should not be measured in patients who may not be able to tolerate the exercise test, which includes patients with a serious ongoing cardiac dysrhythmia, unstable coronary artery disease, atrial fibrillation, or patients who have experienced a myocardial infarction in the last six days. MTWA testing may also be inaccurate in patients with frequent atrial or ventricular ectopy and patients who cannot attain a heart rate between 90 and 110 beats per minute (Haghjoo et al 2006).

CONCLUSION:

A large number of studies have demonstrated the diagnostic effectiveness of MTWA testing in predicting future arrhythmic events across a variety of patient populations. Due to its high negative predictive ability, MTWA testing appears to be a useful method for identifying which patients with ischemic or non-ischemic heart disease and left ventricular dysfunction are unlikely to receive benefit from ICD therapy. The

technique is reported to be safe and convenient, and is currently reimbursed through Medicare in the United States for the purposes of risk stratification of SCD.

HEALTHPACT ACTION:

Given the high rates of mortality associated with SCD and the availability of numerous high quality studies on MTWA testing, HealthPACT recommended that a full health technology assessment be conducted on this technology.

October 2007: MSAC have since determined that there is insufficient evidence to warrant a full health technology assessment at this time. Therefore this technology will be monitored for more information in 12-months time.

SOURCES OF FURTHER INFORMATION:

AIHW (2006). *National Hospital Morbidity Database* [Internet]. Australian Institue of Health and Welfare. Available from: http://www.aihw.gov.au/hospitals/datacubes/index.cfm [Accessed 12th December 2006].

Bardy, G. H., Lee, K. L. et al (2005). 'Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure', *N Engl J Med,* 352 (3), 225-237.

Bloomfield, D. M., Bigger, J. T. et al (2006). 'Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction', *J Am Coll Cardiol,* 47 (2), 456-463.

Chan, P. S., Stein, K. et al (2006). 'Cost-effectiveness of a microvolt T-wave alternans screening strategy for implantable cardioverter-defibrillator placement in the MADIT-II-eligible population', *J Am Coll Cardiol,* 48 (1), 112-121.

Chow, T., Kereiakes, D. J. et al (2006). 'Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy', *J Am Coll Cardiol,* 47 (9), 1820-1827.

Daccarett, M., Serafimovski, N. & Machado, C. (2006). 'Epidemiological impact of microvolt T-wave alternans in sudden cardiac death primary prevention', *Int J Cardiol*.

Doolan, A., Langlois, N. & Semsarian, C. (2004). 'Causes of sudden cardiac death in young Australians', *Med J Aust,* 180 (3), 110-112.

Gehi, A. K., Stein, R. H. et al (2005). 'Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events: a meta-analysis', *J Am Coll Cardiol,* 46 (1), 75-82.

Greenberg, H., Case, R. B. et al (2004). 'Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II)', *J Am Coll Cardiol,* 43 (8), 1459-1465.

Haghjoo, M., Arya, A. & Sadr-Ameli, M. A. (2006). 'Microvolt T-wave alternans: a review of techniques, interpretation, utility, clinical studies, and future perspectives', *Int J Cardiol,* 109 (3), 293-306.

Hohnloser, S. H., Klingenheben, T. et al (1998). 'T wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers', *J Cardiovasc Electrophysiol,* 9 (12), 1258-1268.

Huikuri, H. V., Castellanos, A. & Myerburg, R. J. (2001). 'Sudden death due to cardiac arrhythmias', *N Engl J Med,* 345 (20), 1473-1482.

Ikeda, T., Sakata, T. et al (2000). 'Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study', *J Am Coll Cardiol,* 35 (3), 722-730.

Klingenheben, T. & Hohnloser, S. H. (2002). 'Clinical value of T-wave alternans assessment', *Card Electrophysiol Rev,* 6 (3), 323-328.

Klingenheben, T., Zabel, M. et al (2000). 'Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure', *Lancet,* 356 (9230), 651-652.

Lopshire, J. C. & Zipes, D. P. (2006). 'Sudden cardiac death: better understanding of risks, mechanisms, and treatment', *Circulation,* 114 (11), 1134-1136.

Moss, A. J., Zareba, W. et al (2002). 'Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction', *N Engl J Med,* 346 (12), 877-883.

Singh, J. P., Hall, W. J. et al (2005). 'Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)', *J Am Coll Cardiol,* 46 (9), 1712-1720.

LIST OF STUDIES INCLUDED

Total number of studies	
Level I evidence	1
Level II evidence	2

SEARCH CRITERIA TO BE USED:

Ventricular Dysfunction, Left/*complications/*mortality
Myocardial Infarction/*physiopathology/*therapy
Electrophysiology
Defibrillators, Implantable
Death, Sudden, Cardiac/*etiology