Noninvasive risk stratification after myocardial infarction: Rationale, current evidence and the need for definitive trials

Derek V Exner MD MPH FRCPC FHRS

DV Exner. Noninvasive risk stratification after myocardial infarction: Rationale, current evidence and the need for definitive trials. *Can J Cardiol* 2009;25(Suppl A):21A-27A.

Despite advances in therapies for myocardial infarction (MI), death attributed to a cardiac arrest from ventricular tachycardia (VT) or ventricular fibrillation (VF) remains an important problem. The implantable cardioverter defibrillator (ICD) is effective in preventing death from VT/VF, but reliably identifying which post-MI patients would benefit from an ICD remains a major challenge. Beyond the initial post-MI period, the presence of significant left ventricular (LV) dysfunction, alone or in combination with the induction of sustained VT/VF during invasive testing, is the only proven means of selecting patients for a prophylactic ICD. However, these approaches identify only a fraction of those at risk. Furthermore, most patients with significant LV dysfunction after MI have a low, near-term risk of VT/VF. Noninvasive risk stratification tools have been developed to better identify patients likely to benefit from an ICD. To date, none of these tools has been proven useful in this regard.

The factors leading to a cardiac arrest are complex, and a single test is unlikely to reliably predict risk. Noninvasive assessment of cardiac structure, conduction and repolarization along with autonomic modulation appear to be useful in predicting the risk of a cardiac arrest after MI, particularly when assessed in combination. However, randomized trials assessing the efficacy of ICD therapy in patients identified as being at risk are required. Until such data are available, significant LV dysfunction alone and in combination with the induction of VT/VF during invasive testing in the nonacute post-MI period remain the only proven methods to guide prophylactic ICD therapy.

Key Words: Autonomic tone; Ejection fraction; Myocardial infarction; Repolarization; Risk stratification; Sudden cardiac death

Significant advances in the treatment of patients during the acute and convalescent phases of myocardial infarction (MI) have occurred over the past two decades (1). These advances have resulted in reductions in total mortality and the various modes of death, including death from cardiac arrest (2). Nonetheless, death attributed to ventricular tachycardia (VT) or ventricular fibrillation (VF) after MI remains a significant problem (3). The implantable cardioverter defibrillator (ICD) is an effective treatment for VT/VF (4). Strategies to better identify post-MI patients at risk of VT/VF are required to guide prophylactic ICD therapy. The present review discusses the results of trials of ICD therapy after MI, methods proven useful in targeting prophylactic ICD therapy and the rationale for using noninvasive tools to better identify patients at risk. The need for randomized trials to definitively prove that these noninvasive tests do, in fact, identify post-MI patients likely to derive significant benefit from prophylactic ICD therapy is also reviewed.

La stratification non effractive du risque après un infarctus du myocarde : La raison d'être, les données probantes courantes et la nécessité d'essais décisifs

Malgré les avancées des traitements de l'infarctus du myocarde (IM), les décès attribués à un arrêt cardiaque imputable à une tachycardie ventriculaire (TV) ou à une fibrillation ventriculaire (FV) demeurent un problème important. Le défibrillateur cardiaque implantable (DCI) est efficace pour prévenir les décès causés par une TV ou une FV, mais il demeure très difficile de dépister avec fiabilité les patients ayant subi un IM qui en profiteraient. Après la période initiale suivant l'IM, la présence d'une dysfonction ventriculaire gauche (VG) importante, seule ou associée à l'induction d'une TV ou d'une FV pendant les examens effractifs, représente le seul moyen démontré de sélectionner les patients à qui installer un DCI prophylactique. Cependant, ces approches ne permettent de repérer qu'une fraction des patients vulnérables. De plus, la plupart des patients présentant une dysfonction VG importante après un IM ont un faible risque de TV ou de FV à court terme. Il existe des outils de stratification non effractifs du risque pour mieux dépister les patients susceptibles de profiter d'un DCI, mais jusqu'à présent, on n'a pu démontrer l'utilité d'aucun d'entre eux.

Les facteurs entraînant un arrêt cardiaque sont complexes, et un seul test est peu susceptible de prédire le risque avec fiabilité. L'évaluation non effractive de la structure cardiaque, de la conduction et de la repolarisation, conjointement avec la modulation autonome, semble utile pour prédire le risque d'arrêt cardiaque après un IM, notamment lorsqu'ils sont évalués conjointement. Cependant, des essais aléatoires s'imposent pour évaluer l'efficacité du DCI chez les patients dépistés comme vulnérables. Tant que ces données ne seront pas disponibles, une dysfonction VG importante, seule et en association avec l'induction d'une TV ou d'une FV pendant l'examen effractif au cours de la période non aiguë suivant l'IM, demeure le seul moyen démontré d'orienter l'installation prophylactique d'un DCI.

NEED FOR RISK STRATIFICATION

Sudden cardiac death – death due to a cardiac or unexplained cause that occurs within 1 h of symptom onset – is a huge public health problem. It results in the premature deaths of more than 300,000 persons annually in North America alone (5). A cardiac arrest secondary to VT/VF is responsible for most of these deaths in stable ambulatory populations (6). In contrast, bradyarrhythmias and electromechanical dissociation are common mechanisms of sudden death among hospitalized patients with end-stage heart failure (7).

Most sudden deaths occur in patients with known heart disease (8) – frequently in patients with known coronary artery disease or a prior MI (5). Thus, this population accounts for a significant proportion of all sudden deaths. However, most sudden deaths occur in patients who are not recommended to receive a prophylactic ICD based on current guidelines (9,10). Establishing a risk stratification approach that incorporates sufficient positive accuracy, ie, patients identified are at sufficient risk to justify long-term ICD therapy, plus has reasonable

Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta

Correspondence and reprints: Dr Derek V Exner, 3330 Hospital Drive Northwest, Room G208, Calgary, Alberta T2N 4N1. Telephone 403-220-3219, fax 403-210-8140, e-mail exner@ucalgary.ca

Received for publication April 6, 2009. Accepted April 7, 2009

Figure 1 Efficacy of implantable cardioverter defibrillator (ICD) therapy after myocardial infarction (MI): risk assessment and timing. Relative risk estimates (boxes) and CIs surrounding those estimates (lines) for the efficacy of ICD therapy for mortality. The use of invasive testing (MADIT I) and the presence of a low ejection fraction (EF) alone (MADIT II, SCD-HeFT) remote after a MI predicted a significant reduction in mortality with ICD therapy. In contrast, ICD therapy was not found to be efficacious with invasive testing early after MI (BEST-ICD), noninvasive testing late after MI (CABG Patch), or noninvasive testing early after MI (DINAMIT, IRIS). See text and Tables 1 and 2 for details and study references

sensitivity so that most of those at risk will be identified, has been a major barrier. This dilemma is related, in part, to the extremely large number of patients at risk of sudden death and the sub-optimal diagnostic accuracy of many risk stratification approaches. There are more than 50 million North American adults with coronary artery disease and more than seven million have had an MI (11). However, only a fraction of these patients will suffer a cardiac arrest. Developing reliable methods to identify post-MI patients at risk and evaluating whether these methods do, in fact, select patients who would significantly benefit from prophylactic ICD therapy are critical areas of ongoing research (12).

METHODS THAT PREDICT BENEFIT FROM PROPHYLACTIC ICD THERAPY AFTER MI

To date, only two approaches have been proven useful in guiding prophylactic ICD therapy after MI (Figure 1): the presence of significant left ventricular (LV) dysfunction alone or LV dysfunction in combination with the induction of sustained VT/VF using programmed electrical stimulation during an invasive electrophysiology study (inducible VT/VF) beyond the initial post-MI period (9,13-17). However, these methods have important limitations (Table 1).

LV dysfunction

Significant LV dysfunction has been shown to identify post-MI patients who benefit from a prophylactic ICD (15,16). The Second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) (15) and the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) (16) clearly demonstrated a mortality benefit from prophylactic ICD therapy in patients with a history of MI and LV ejection fraction (LVEF) values of 0.30 or lower and 0.35 or lower, respectively (Figure 1). However, the absolute mortality reduction in these trials was modest: 5.6% over 27 months in MADIT II and 7.3% over 60 months in SCD-HeFT. Furthermore, most patients who suffer a cardiac arrest after MI have better-preserved LV systolic function (18,19). In fact, less than one-third of contemporary managed post-MI patients who suffer sudden cardiac death have an LVEF of 0.35 or less (18-20). In addition to poor sensitivity, a significantly depressed LVEF also lacks specificity. Fewer than one in five ICD recipients in MADIT II and SCD-HeFT received appropriate ICD therapies over average follow-up periods of 20 and 60 months, respectively (15,16). Moreover, because appropriate ICD therapies overestimate the mortality benefit of ICD therapy by at least twofold (21), fewer than one in 10 patients who receive a

prophylactic ICD for an LVEF of 0.35 or less post-MI are likely to receive a survival benefit in the near term. Finally, significant variations in LVEF values are obtained when different techniques are used, and there is evidence that prognosis, and hence risk, depends on the method by which the LVEF is measured (22).

Invasive electrophysiological assessment

Inducible VT/VF is thought to be a more reliable marker for the subsequent development of a cardiac arrest than LVEF (23). The First Multicenter Automatic Defibrillator Implantation Trial (MADIT I) study (13) clearly demonstrated that those patients with inducible VT/VF and LVEF values of 0.35 or less late after MI are likely to benefit from an ICD (Figure 1). Moreover, the absolute mortality reduction in MADIT I (26.2% over 27 months) was substantially greater than what was found in either MADIT II or SCD-HeFT (see 'LV dysfunction'). Similar results were found in the Multicenter UnSustained Tachycardia Trial (MUSTT) (24); however, ICD use was nonrandomized in that study.

Using inducible VT/VF to guide prophylactic ICD therapy is limited by low sensitivity (25). Furthermore, patients with LVEF values of 0.35 or less after MI and no inducible VT/VF still appear to have a substantial (greater than 25%) risk of serious events over the near term (26). Thus, relying on the combination of a low LVEF and an inducible VT/VF late after MI to identify patients at risk of a cardiac arrest is problematic. There are also no data to support the use of inducible VT/VF in post-MI patients with LVEF values greater than 0.40 (13,14) and no evidence to support the use of an invasive electrophysiology study in the early post-MI period (27). In fact, the Beta-blocker Strategy plus Implantable Cardioverter Defibrillator (BEST-ICD) trial (28) found that inducible VT/VF early after MI does not predict benefit from ICD therapy (Figure 1). In contrast, the Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study (29) found that inducible VT identified at six weeks following an acute MI was a strong predictor of future life-threatening arrhythmias. Thus, while there is some evidence for the use of inducible VT/VF to identify select patients for ICD therapy after MI, it is an imperfect approach and other methods are required.

NONINVASIVE ASSESSMENT OF SUDDEN DEATH RISK

Identifying those at risk

The development of a cardiac arrest after MI is undoubtedly multifactorial. It is probable that multiple events need to coincide for a cardiac arrest to ensue. This likely includes an underlying susceptibility to VT/VF because of myocardial scar, the presence of triggers such as abnormalities in cardiac conduction and cardiac repolarization, along with impaired autonomic modulation. Thus, assessing a single parameter is unlikely to provide sufficient information to reliably categorize a given patient as being at risk or not at risk. Predicting ICD efficacy is even more complex, because not all sudden deaths, and in fact, not all cardiac arrests, can be treated by an ICD (30,31). Thus, prospective randomized trials are required to prove that the use of these noninvasive tests predicts a survival benefit from prophylactic ICD therapy. Noninvasive tests have been developed to assess the extent of myocardial damage and scarring, ventricular conduction, cardiac repolarization and autonomic tone. These data are summarized in Table 2. Genetic assessment may play a role in the future (32-34). However, there is presently no evidence for using genetic testing to identify post-MI patients at risk.

MYOCARDIAL SCAR

Extensive myocardial scar is associated with adverse outcomes in patients with significant LV dysfunction and in patients with better-preserved LV function after MI (35,36). Scarring can be readily obtained from a cardiac magnetic resonance (CMR) imaging through delayed enhancement and other techniques (35-37). CMR imaging also provides the opportunity to further characterize the peri-infarct zone and tissue heterogeneity within infarcts. Increased tissue

TABLE 1
Summary of proven risk assessment strategies in patients after myocardial infarction (MI)

Test	Type of data	Risk prediction	Pros	Cons
Invasive study				
Inducible VT/VF	Randomized	Mortality ICD efficacy predicted in MADIT I (remote MI) No ICD efficacy in BEST-ICD (early after MI)	Proven	Impractical in some areas Poor sensitivity
Left ventricular dysfunctional alone				
Ejection fraction	Randomized	Mortality ICD efficacy predicted in MADIT II and SCD-HeFT (late after MI)	Proven Readily available	Technique dependent Low sensitivity Suboptimal specificity

BEST-ICD Beta-blocker Strategy Plus ICD [implantable cardioverter defibrillator] (28); MADIT Multicenter Automatic Defibrillator Implantation Trial (13,15); SCD-HeFT Sudden Cardiac Death Heart Failure Trial (16); VT/VF Ventricular tachycardia/ventricular fibrillation

TABLE 2
Summary of noninvasive risk assessment parameters used to assess risk in patients after myocardial infarction

Test	Data	Risk prediction	Pros	Cons	ICD efficacy predicted
Cardiac MRI	Observational	Mortality, cardiac death, VT	Detailed anatomy	Limited data	Unknown
QRS width	Observational	Mortality	Standardized	Inconsistent data	Unknown
Signal-averaged ECG	Observational Randomized	Mortality, VT	Standardized	Unclear utility	No (CABG Patch)
Wedensky modulation	Observational	Cardiac death, VT	Standardized	Limited data	Unknown
QT dispersion	Observational	Mortality, cardiac death	Readily available	Poor reproducibility Inconsistent data	Unknown
Dynamic QT measures	Observational	Death, arrhythmic death	May predict arrhythmic death	Limited data	Unknown
T wave alternans	Observational	Mortality, cardiac death, VT	Standardized High negative accuracy	Modest positive accuracy	MMA: Unknown Spectral: No (MASTER I)
Heart rate variability	Observational Randomized	Mortality, cardiac death	Standardized	Predicts nonsudden death	No (DINAMIT and IRIS)
Baroreflex sensitivity	Observational	Mortality, cardiac death	Standardized	Cumbersome	Unknown
Heart rate turbulence	Observational	Mortality, cardiac death, sudden death	Standardized Consistent data	Less reliable in older populations	Unknown
Deceleration capacity	Observational	Mortality	Standardized	Limited data to date	Unknown

CABG Patch Coronary artery bypass graft Patch trial (44); DINAMIT Defibrillator in Acute Myocardial Infarction Trial (61); ECG Electrocardiogram; ICD Implantable cardioverter defibrillator; IRIS Immediate Risk Stratification Improves Survival (62,63); MASTER I Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients (58); MMA Modified moving average; MRI Magnetic resonance imaging; VT Ventricular tachycardia

heterogeneity has been associated with an increased susceptibility toward VT/VF (36). A more extensive peri-infarct zone may also be a predictor of mortality (35). Information on scarring can be acquired through nuclear and positron imaging methods, but these techniques lack the spatial resolution of CMR imaging. Whether assessment of scar can assist with more reliable identification of post-MI patients at risk for arrhythmic death is uncertain. There are presently no data to support the use of CMR imaging to guide prophylactic ICD therapy beyond LVEF assessment.

VENTRICULAR CONDUCTION

Abnormal cardiac substrate is likely another key factor in the development of a cardiac arrest. A variety of noninvasive tools have been developed, including QRS duration, signal-averaged electrocardiogram (SA-ECG) and Wedensky modulation.

QRS duration

Increased QRS duration on a surface ECG has been associated with a higher risk of death after MI and appears to reflect greater LV dysfunction (12). However, a QRS duration of 120 ms or longer, the most commonly applied cutpoint, has no to only modest independent predictive value in identifying patients at risk of a cardiac arrest (38,39). Moreover, a longer QRS duration was not found to be a reliable predictor of benefit from prophylactic ICD therapy in post hoc analyses in the MADIT II or SCD-HeFT studies (40,41).

SA-ECG

This technique identifies fragmented cardiac depolarizations that are not reliably detected on a surface ECG. Multiple complexes are averaged to create a composite recording (42). While an abnormal SA-ECG was found to predict a higher risk of serious outcomes in many older studies (42), its utility appears limited in patients receiving contemporary care (19,43). Moreover, abnormal SA-ECGs failed to identify patients likely to benefit from ICD therapy in the Coronary artery bypass graft Patch trial (CABG Patch) (Figure 1) (44).

Wedensky modulation

This test attempts to identify regions of slow ventricular conduction by assessing for localized perturbations within the QRS following the delivery of a subthreshold impulse when the ventricular tissue is refractory (45). It is based on observations by Wedensky in the early 1800s that an impulse arriving in a blocked region can increase excitability, and that a subthreshold stimulus following a suprathreshold stimulus can produce tetanus that does not result in contraction. To date, there are only limited data on the utility of this test to identify patients at risk for VT/VF and no data to support its use in guiding ICD therapy.

VENTRICULAR REPOLARIZATION

Cardiac repolarization is likely to also be very important in the pathogenesis of a cardiac arrest. A number of measures have been developed to identify patients at risk. Given the unpredictable nature of most

cardiac arrests, it is probable that dynamic measures provide more information on risk than static measures. A number of techniques have been developed in this regard, with T wave alternans (TWA) being the most extensively studied to date.

Static measures of cardiac repolarization

QT dispersion, the difference between the maximum and minimum measured QT interval on a standard 12-lead ECG, has been advocated as a simple approach to predict risk. Furthermore, an association between increased QT dispersion and mortality has been demonstrated in several large studies (46). However, poor inter- and intra-rater variability limit its utility (47). Other measures such as T loop morphology variations hold promise, but have limited data to support their use. The utility of these methods to predict arrhythmic death is unclear, and none has been shown to be useful in guiding ICD therapy.

Dynamic repolarization measures

Multiple methods have been developed to assess dynamic changes in the QT interval. These include measures of QT variability (48), T wave variance (49), QT dynamics (50) and QT/RR slope (51). Increased daytime QT/RR slope has been associated with an increased risk of sudden death and mortality in post-MI patients with relatively preserved LV function (51). For the most part, these techniques have not been validated in independent populations, and their ability to predict arrhythmic death is uncertain. Thus, they cannot be advocated to aid in clinical decision-making based on present evidence.

TWA

TWA is a beat-to-beat alteration in cardiac repolarization. TWA can be assessed using the spectral or the modified moving average (MMA) method. The spectral method typically involves graded heart rate elevation through exercise and the use of specialized electrodes (52). The magnitude of spectral TWA is assessed after mathematical transformation. This allows both the TWA signal and noise to be readily identified and quantified. The MMA method uses standard electrodes and an exercise or Holter platform. MMA TWA is identified by comparing the average T wave amplitude in a series of odd versus even beats (53). Multiple studies have shown that the presence of TWA is associated with an increased risk of serious outcomes (19,54-56). The criteria for defining an abnormal spectral TWA result are well accepted (52). In contrast, differing cutpoints have been used to define the presence of significant TWA using the MMA method, reflecting the setting in which the assessment was performed and the number of beats averaged (updating factor) (57). Both TWA methods are of limited clinical utility as single assessment method, due to low positive accuracy after MI (54,57). Furthermore, the Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients (MASTER I) study (58) demonstrated that spectral TWA does not predict the risk of arrhythmic death or appropriate ICD therapies. While both TWA methods identify a higher risk of death, neither can be advocated to guide provision of ICD therapy based on current data.

AUTONOMIC TONE

Impaired autonomic modulation appears to be a key factor in the development of a cardiac arrest. Multiple tools have been developed to evaluate the integrity of the autonomic nervous system, including heart rate variability (HRV), baroreflex sensitivity (BRS), heart rate turbulence (HRT) and deceleration capacity (DC).

Linear HRV

HRV assesses the relative balance of the sympathetic and parasympathetic nervous systems. The most commonly used method of quantifying HRV is the standard deviation of normal beats (SDNN). Impaired SDNN was demonstrated to predict a higher risk of serious outcomes in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study (59). However, impaired SDNN values are not specific for sudden death and predict a higher risk of progressive heart failure (60). It has also been found that SDNN is not a reliable marker

of long-term risk when assessed very early after MI (19). Moreover, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) (61) demonstrated that ICD therapy does not alter mortality in patients with LVEF values of 0.35 or less and severely impairs HRV early after MI. The recently reported Immediate Risk Stratification Improves Survival (IRIS) trial (62,63), which included mostly patients with elevated resting heart rates and LVEF values of 0.40 or less early after MI, also found no benefit from ICD therapy early after MI (Figure 1). Thus, standard measures of HRV do not appear to provide a reliable measure of sudden death risk and there is no evidence to support its use in guiding prophylactic ICD therapy.

Nonlinear HRV

These measures are based on nonlinear system theory: chaos theory and fractals (64). They appear to better predict arrhythmic death versus linear measures (18) but have not been as extensively studied. The CARISMA study found that a reduced, very low-frequency component of HRV predicted a sevenfold higher risk of serious arrhythmia, with reasonable sensitivity (41%) and positive accuracy (26%) (29). While promising, there is no evidence to support the use of nonlinear measures in guiding ICD therapy.

BRS

BRS measures the increase in vagal activity and decrease in sympathetic activity in response to a surge in blood pressure (59). BRS is typically assessed as the change in heart rate for a given change in blood pressure following the administration of phenylephrine. Patients in the ATRAMI study with impaired BRS were at higher risk of cardiac death or cardiac arrest than those with normal BRS values (59). Specifically, patients with severe impairment in BRS had a greater than four-fold risk of death compared with patients with normal BRS, but only 35% of those at risk were identified using this approach. A more recent small study of post-MI patients with preserved LV function found that severe BRS impairment identified patients at risk for cardiovascular mortality with good sensitivity (60%) and positive accuracy (26%) (65). However, these data have not been replicated. While BRS assessment provides information on the risk of cardiovascular death, it is cumbersome to perform, and there are no data to support its use in guiding ICD therapy.

HRT

HRT assesses short-term fluctuations in the baroreflex-mediated sinus node response in response to a premature ventricular complex (PVC) (66). The normal response to a PVC is a brief acceleration in heart rate, followed by a more gradual deceleration. HRT onset describes the change in the RR interval immediately after versus immediately before the PVC. HRT slope measures the change in RR interval after the initial acceleration. Averaging five or more PVCs provides more reliable information than using fewer PVCs (67). HRT assessment has been consistently shown to be a reliable and powerful method to identify patients at risk of arrhythmic death after MI. However, it also appears to predict an increased risk of nonarrhythmic death in patients with heart failure (18,19,43,66,68,69). HRT is thought to be less reliable in elderly patients (67), and similar to other noninvasive measures, there is presently no evidence to support its use in guiding prophylactic ICD therapy.

DC

Phase rectified signal averaging, an advanced signal processing method, is used to separate out deceleration-related modulations in heart rate (20). These are thought to reflect vagal components of HRV. In contrast to HRT, which measures the response of the autonomic nervous system to transient perturbations, DC is thought to measure steady state vagal tone. Severely impaired DC predicts a six-fold higher risk of death (20). Moreover, DC provides more information on the risk of death than do SDNN or LVEF. Like severe BRS, severely impaired DC is limited by low sensitivity (30%) (20). There is currently no evidence to support its use to guide prophylactic ICD therapy.

TABLE 3
Recent studies that have combined noninvasive tests to enhance risk assessment after myocardial infarction

Study (reference)	Test combination	Outcome	Risk predicted	Positive accuracy	Negative accuracy
Munich Cohort (43)	Heart rate turbulence plus signal-averaged ECG	Cardiac death or cardiac arrest	No enhanced risk prediction	–	–
REFINE (19)	Heart rate turbulence or baroreflex sensitivity plus T wave alternans (spectral or MMA)	Cardiac death or cardiac arrest	3- to 4-fold (independent of LVEF)	18% to 23%	94% to 95%
ISAR-Risk (72)	Heart rate turbulence plus deceleration capacity	Mortality and sudden death	4- to 5-fold (independent of LVEF)	39% (mortality) 12% (sudden)	94% (mortality) 95% (sudden)
MUSIC (73)	Heart rate turbulence plus QT/RR slope plus heart rate variability (score)	Mortality and sudden death	3- to 4-fold (independent of LVEF)	–	–

ECG Electrocardiogram; ISAR-Risk Improved Stratification of Autonomic Regulation for risk prediction; LVEF Left ventricular ejection fraction; MMA Modified moving average; MUSIC Muerte Subita en Insuficiencia Cardiaca; REFINE Risk Estimation Following Infarction, Non-invasive Evaluation

TABLE 4
Randomized trials of implantable cardioverter defibrillator (ICD) therapy testing risk assessment approaches

Trial	Population	Comparison	Patients, n	Outcome	Status	Registration
DETERMINE	Prior MI LVEF >0.35 Extensive myocardial scar	ICD versus usual care (1:1)	1550	Mortality	Ongoing	NCT00487279
REFINE ICD	Recent MI LVEF 0.36 to 0.49 Abnormal T wave alternans and heart rate turbulence (Holter)	ICD versus usual care (1:1)	1400	Mortality	Planned	NCT00673842

DETERMINE Defibrillators To REduce Risk by Magnetic Resonance Imaging Evaluation; LVEF Left ventricular ejection fraction; REFINE ICD Risk Estimation Following Infarction Non-invasive Evaluation – ICD efficacy

COMBINING NONINVASIVE PARAMETERS TO ENHANCE RISK ASSESSMENT

Given that a cardiac arrest likely requires a confluence of abnormalities, combining noninvasive test results to enhance risk prediction has intuitive appeal (70,71). Table 3 summarizes several recent studies that have combined noninvasive tests to enhance risk prediction. Bauer et al (43) found that combining SA-ECG results with HRT results did not enhance risk prediction. However, HRT alone was a significant independent predictor of outcome. The Risk Estimation Following Infarction, Non-invasive Evaluation (REFINE) study (19) evaluated a battery of tests assessing autonomic modulation (BRS, HRV and HRT) and electrical substrates (SA-ECG, exercise spectral TWA and post-exercise MMA TWA) in the initial two to four weeks after MI, and again 10 to 14 weeks after MI. On average, LVEF improved by 20% over the initial eight weeks post-MI in the REFINE study cohort. Not surprisingly, this altered the utility of the noninvasive test results. Assessments early after MI were less predictive of outcome versus those performed 10 to 14 weeks after MI. Of the combinations assessed, abnormal TWA combined with impaired BRS or HRT best predicted outcome. The Improved Stratification of Autonomic Regulation for risk prediction (ISAR-Risk) study (72) assessed the utility of adding DC to HRT for risk prediction. They found that this combination identified a subgroup of patients with an LVEF greater than 0.30 at high risk of death, cardiac death and sudden death. However, the positive accuracy for sudden death (12%) was less than one-third what was observed for all-cause mortality (38%), indicating that this combination also predicts death from nonarrhythmic causes. Nonetheless, the combination of HRT plus DC clearly identifies patients at a high risk of death after MI. Moreover, patients without abnormal HRT and DC are at very low risk (negative accuracy greater than 95%). Most recently, the Muerte Subita en Insuficiencia Cardiaca (MUSIC) investigators (73) identified that abnormal HRV (SDNN), HRT and QT/RR slope in combination identified patients

at high risk of death and sudden death. Taken together, the results of these studies strongly suggest that combining noninvasive tests results in enhanced identification of patients at risk for a cardiac arrest. However, it is not known whether these combinations of tests can be used to identify patients likely to benefit from a prophylactic ICD after MI.

FUTURE DIRECTIONS: NEED FOR DEFINITIVE TRIALS

Regardless of the technique used, it is essential that these risk stratification methods be subjected to randomized trials to prove that patients identified as being at risk in fact derive benefit from a prophylactic ICD. Despite the promise of several risk stratification methods, the CABG Patch, BEST-ICD, DINAMIT and IRIS trials (Figure 1) provide clear examples of past failures. These studies, as well as MASTER I, highlight the need for risk stratification tools to be tested in a prospective, randomized manner. Two large randomized trials assessing the utility of noninvasive risk assessment after MI are summarized in Table 4. The DEfibrillators To REduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial is assessing the efficacy of prophylactic ICD therapy in post-MI patients with an LVEF greater than 0.35 and extensive myocardial scarring, as assessed using CMR. The Risk Estimation Following Infarction Non-invasive Evaluation – ICD efficacy (REFINE ICD) trial is assessing the efficacy of ICD therapy in post-MI patients with LVEF values of 0.36 to 0.49 plus abnormal Holter TWA and HRT values. These trials and others will help to define the optimal methods of assessing the risk of sudden death after MI and the utility of prophylactic ICD therapy in patients identified to be at risk.

CONCLUSIONS

Noninvasive risk assessment after MI is required to identify patients at risk of a cardiac arrest. While many noninvasive risk assessment methods have been proposed, none have been proven to identify patients

likely to benefit from prophylactic ICD therapy after MI. Ongoing and planned randomized trials will clarify whether newer approaches to noninvasive risk stratification can be used to guide prophylactic ICD therapy in patients identified as being at risk of sudden death.

ACKNOWLEDGEMENT: Dr Exner is a Scholar of the Alberta Heritage Foundation for Medical Research.

CONFLICTS OF INTEREST: None to declare.

REFERENCES

- Canadian Cardiovascular Society; American Academy of Family Physicians; American College of Cardiology; American Heart Association, Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008;51:210-47.
- Zipes DP. Epidemiology and mechanisms of sudden cardiac death. *Can J Cardiol* 2005;21(Suppl A):37A-40A.
- Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352:2581-8.
- Exner DV, Klein GJ, Prystowsky EN. Primary prevention of sudden death with implantable defibrillator therapy in patients with cardiac disease: Can we afford to do it? (Can we afford not to?). *Circulation* 2001;104:1564-70.
- Myerburg RJ. Sudden cardiac death: Exploring the limits of our knowledge. *J Cardiovasc Electrophysiol* 2001;12:369-81.
- Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;117:151-9.
- Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;80:1675-80.
- Rea TD, Pearce RM, Raghunathan TE, et al. Incidence of out-of-hospital cardiac arrest. *Am J Cardiol* 2004;93:1455-60.
- Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1-62.
- Howlett JG, McKelvie RS, Arnold JM, et al. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: Diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials. *Can J Cardiol* 2009;25:85-105.
- National Heart, Lung, and Blood Institute. Morbidity and mortality: 2000 Chartbook on cardiovascular, lung and blood diseases. 2000.
- Goldberger JJ, Cain ME, Hohnloser SH, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *J Am Coll Cardiol* 2008;52:1179-99.
- Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933-40.
- Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 2000;342:1937-45.
- Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.
- Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.
- Ezekowitz JA, Rowe BH, Dryden DM, et al. Systematic review: Implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Ann Intern Med* 2007;147:251-62.
- Makikallio TH, Barthel P, Schneider R, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J* 2005;26:762-9.
- Exner DV, Kavanagh KM, Slawnych MP, et al. Noninvasive risk assessment early after a myocardial infarction: The REFINe study. *J Am Coll Cardiol* 2007;50:2275-84.
- Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: Cohort study. *Lancet* 2006;367:1674-81.
- Ellenbogen KA, Levine JH, Berger RD, et al. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;113:776-82.
- Rashid H, Exner DV, Mirsky I, Cooper HA, Wacławski MA, Domanski MJ. Comparison of echocardiography and radionuclide angiography as predictors of mortality in patients with left ventricular dysfunction (studies of left ventricular dysfunction). *Am J Cardiol* 1999;84:299-303.
- Buxton AE, Lee KL, Hafley GE, et al. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: An analysis of patients enrolled in the multicenter unsustained tachycardia trial. *Circulation* 2002;106:2466-72.
- Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;341:1882-90.
- Andresen D, Steinbeck G, Bruggemann T, Ehlers C, Hoffmann E, Haberl R. Can the MADIT results be applied to myocardial infarction patients at hospital discharge? *J Am Coll Card* 1998;31:308A.
- Daubert JP, Zareba W, Hall WJ, et al. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2006;47:98-107.
- Roy D, Marchand E, Theroux P, Waters DD, Pelletier GB, Bourassa MG. Programmed ventricular stimulation in survivors of an acute myocardial infarction. *Circulation* 1985;72:487-94.
- Raviele A, Bongiorni MG, Brignole M, et al. Early EPS/ICD strategy in survivors of acute myocardial infarction with severe left ventricular dysfunction on optimal beta-blocker treatment. The BEta-blocker STRategy plus ICD trial. *Europace* 2005;7:327-37.
- Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. *Eur Heart J* 2009;30:689-98.
- Pires LA, Lehmann MH, Steinman RT, Baga JJ, Schuger CD. Sudden death in implantable cardioverter-defibrillator recipients: Clinical context, arrhythmic events and device responses. *J Am Coll Cardiol* 1999;33:24-32.
- Mitchell LB, Pineda EA, Titus JL, Bartosch PM, Benditt DG. Sudden death in patients with implantable cardioverter defibrillators: The importance of post-shock electromechanical dissociation. *J Am Coll Cardiol* 2002;39:1323-8.
- Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: The Paris Prospective Study I. *Circulation* 1999;99:1978-83.
- Dekker LR, Bezzina CR, Henriques JP, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: A case-control study in acute myocardial infarction patients. *Circulation* 2006;114:1140-5.
- Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation* 2006;114:1462-7.
- Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation* 2006;114:32-9.

36. Schmidt A, Azevedo CF, Cheng A, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation* 2007;115:2006-14.
37. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced mapping. *J Am Coll Cardiol* 2008;52:1574-80.
38. Freedman RA, Alderman EL, Sheffield LT, Saporito M, Fisher LD. Bundle branch block in patients with chronic coronary artery disease: Angiographic correlates and prognostic significance. *J Am Coll Cardiol* 1987;10:73-80.
39. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: A report from the Italian network on congestive heart failure. *Am Heart J* 2002;143:398-405.
40. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). *J Am Coll Cardiol* 2004;43:1459-65.
41. Poole JE. Baseline ECG data and outcome in the Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT ECG). Presented at Heart Rhythm 2004 – 25th Annual Scientific Sessions, 2004; San Francisco, California.
42. Steinberg JS, Regan A, Sciacca RR, Bigger JT Jr, Fleiss JL. Predicting arrhythmic events after acute myocardial infarction using the signal-averaged electrocardiogram. *Am J Cardiol* 1992;69:13-21.
43. Bauer A, Guzik P, Barthel P, et al. Reduced prognostic power of ventricular late potentials in post-infarction patients of the reperfusion era. *Eur Heart J* 2005;26:755-61.
44. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med* 1997;337:1569-75.
45. Hnatkova K, Ryan SJ, Bathen J, Hoium HH, Malik M. Non-invasive Wedensky modulation within the QRS complex. *Med Biol Eng Comput* 2002;40:234-40.
46. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000;36:1749-66.
47. Surawicz B. Will QT dispersion play a role in clinical decision-making? *J Cardiovasc Electrophysiol* 1996;7:777-84.
48. Atiga WL, Calkins H, Lawrence JH, Tomaselli GF, Smith JM, Berger RD. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. *J Cardiovasc Electrophysiol* 1998;9:899-908.
49. Couderc JP, Zareba W, McNitt S, Maison-Blanche P, Moss AJ. Repolarization variability in the risk stratification of MADIT II patients. *Europace* 2007;9:717-23.
50. Jensen BT, Abildstrom SZ, Larroude CE, et al. QT dynamics in risk stratification after myocardial infarction. *Heart Rhythm* 2005;2:357-64.
51. Chevalier P, Burri H, Adeleine P, et al. QT dynamicity and sudden death after myocardial infarction: Results of a long-term follow-up study. *J Cardiovasc Electrophysiol* 2003;14:227-33.
52. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:456-63.
53. Nearing BD, Verrier RL. Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. *J Appl Physiol* 2002;92:541-9.
54. Ikeda T, Yoshino H, Sugi K, et al. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: Results of a collaborative cohort study. *J Am Coll Cardiol* 2006;48:2268-74.
55. Nieminen T, Lehtimäki T, Viik J, et al. T-wave alternans predicts mortality in a population undergoing a clinically indicated exercise test. *Eur Heart J* 2007;28:2332-7.
56. Myles RC, Jackson CE, Tsoralis I, Petrie MC, McMurray JJ, Cobbe SM. Is microvolt T-wave alternans the answer to risk stratification in heart failure? *Circulation* 2007;116:2984-91.
57. Slawnych MP, Nieminen T, Kahonen M, et al. Post-exercise assessment of cardiac repolarization alternans in patients with coronary artery disease using the modified moving average method. *J Am Coll Cardiol* 2009;53:1130-7.
58. Chow T, Kereiakes DJ, Onufer J, et al. Stratification of Post MI Patients (MASTER I) Trial. *Circulation* 2007;116:2631.
59. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;351:478-84.
60. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998;98:1510-6.
61. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-8.
62. Steinbeck G, Andresen D, Senges J, Hoffmann E, Seidl K, Brachmann J. Immediate Risk-Stratification Improves Survival (IRIS): Study protocol. *Europace* 2004;6:392-9.
63. Steinbeck G, Andresen D, Senges J, Hoffmann E, Seidl K, Brachmann J. Immediate Risk-Stratification Improves Survival (IRIS): Results. American College of Cardiology (Late Breaking Trials) 2009.
64. Huikuri HV, Makikallio TH, Peng CK, Goldberger AL, Hintze U, Moller M. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000;101:47-53.
65. De Ferrari GM, Sanzo A, Bertoletti A, Specchia G, Vanoli E, Schwartz PJ. Baroreflex sensitivity predicts long-term cardiovascular mortality after myocardial infarction even in patients with preserved left ventricular function. *J Am Coll Cardiol* 2007;50:2285-90.
66. Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;353:1390-6.
67. Bauer A, Malik M, Schmidt G, et al. Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. *J Am Coll Cardiol* 2008;52:1353-65.
68. Cygankiewicz I, Zareba W, Vazquez R, et al. Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients. *Heart Rhythm* 2008;5:1095-102.
69. Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. *Circulation* 2003;108:1221-6.
70. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;18:687-97.
71. Reinhardt L, Makijarvi M, Fetsch T, et al. Noninvasive risk modeling after myocardial infarction. *Am J Cardiol* 1996;78:627-32.
72. Bauer A, Barthel P, Schneider R, et al. Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk). *Eur Heart J* 2009;30:576-83.
73. Cygankiewicz I, Zareba W, Vazquez R, et al. Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction >35%. *Am J Cardiol* 2009;103:1003-10.