RISK STRATIFICATION TESTS FOR DETERMINING ARRHYTHMIAS (Signal-Averaged Electrocardiography [SAECG] and T-Wave Alternans)

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COVERAGE:

Signal-Averaged Electrocardiography (SAECG), as a technique of risk stratification for arrhythmias after prior myocardial infarction, IS considered NOT medically necessary. There is no evidence that SAECG should be used in lieu of other risk stratification tests, such as Holter monitoring or electrophysiologic studies.

Other applications of SAECG are considered experimental or investigational. They include, but are not limited to the following:

- Its use in patients with cardiomyopathy
- Assessment of success after surgery for arrhythmia
- Detection of acute rejection of heart transplants
- Assessment of efficacy of antiarrhythmic drug therapy, or
- Assessment of success of pharmacological, mechanical, or surgical interventions to restore coronary artery blood flow

T-Wave Alternans is considered experimental or investigational as a technique of risk stratification for arrhythmias after prior myocardial infarction.

DESCRIPTION:

Risk Stratification Tests, for predicting major arrhythmic events (MAE) in post myocardial infarction patients, are used to identify patients at high risk of developing an arrhythmic event and possibly reduce these events with an intervention.

This policy will specifically address the following two risk stratification tests.
- Signal Averaged Electrocardiography (SAECG), and
- T-Wave Alternans

SAECG

SAECG is a technique involving computerized analysis of small segments of a standard EKG in order to detect abnormalities, termed ventricular late potentials (VLP), that would be otherwise obscured by “background” skeletal muscle activity. VLP’s reflect aberrant, asynchronous electrical impulses arising from viable isolated cardiac muscle bordering an infarcted area and are thought to be responsible for ventricular tachyarrhythmias. Therefore, VLPs, as measured by signal averaged SAECG, have been investigated as a risk factor for arrhythmic events in patients with a variety of cardiac conditions, including cardiomyopathy and prior history of myocardial infarction. Patients considered being at high risk of ventricular arrhythmias and thus sudden death may be treated with drugs to suppress the emergence of arrhythmias or automatic implantable cardiac defibrillators to
promptly terminate a tachyarrhythmias when they occur. Since sudden cardiac death, whether from arrhythmias or pump failure, is one of the most common causes of death after a myocardial infarction (MI), there is intense interest in risk stratification in order to target therapy.

**T-Wave Alternans**

T-Wave alternans refers to a beat-to-beat variability in the amplitude of the T wave. A routine EKG cannot detect these small fluctuations, and thus this test requires specialized sensors to detect the fluctuations and computer algorithms to evaluate the results. T-wave alternans is a provocative test that necessitates gradual elevation of the heart rate to above 110 beats per minute. The test can be performed in conjunction with an exercise tolerance stress test.

The presence of T-wave alternans has been investigated as a risk factor for fatal arrhythmias and sudden cardiac death in patients with a history of MI or cardiomyopathy. High-risk patients may be treated with drugs to suppress the emergence of arrhythmias or undergo implantation of an automatic implantable cardioverter defibrillator (AICD) to promptly terminate tachyarrhythmias when they occur. Since sudden cardiac death is one of the most common causes of death after a MI or in patients with dilated cardiomyopathy, there is intense interest in risk stratification to target therapy. Patient groups are divided into those who have not experienced a life-threatening arrhythmia (primary prevention) and those who have (secondary prevention). T-wave alternans is just one of many risk factors that have been investigated. Others include left ventricular ejection fraction, arrhythmias detected on Holter monitor or electrophysiologic studies, heart rate variability, and baroreceptor sensitivity. SAECG measures beat-averaged conduction, while T-wave alternans measures beat-to-beat variability.

T-wave alternans has also been investigated as a diagnostic test for patients with syncope of unknown origin and as a noninvasive test to identify candidates for further invasive electrophysiologic testing of the heart.

**RATIONALE:**

**Signal Averaged Electrocardiography**

SAECG has been most thoroughly studied as a risk stratification tool for potentially fatal arrhythmias in patients with a previous MI. As reviewed by the Agency for Health Care Policy and Research (AHCPR), SAECG is associated with a poor positive predictive value ranging from 8% to 44%, depending on the population studied. In contrast, the negative predictive value (i.e., the ability to identify those...
patients who will not experience ventricular arrhythmias) ranges from 88%–97%, suggesting that the negative predictive value may be used to identify patients who would not benefit from antiarrhythmic therapy. The key statistic underlying the negative predictive value is the false negative rate that is directly related to the underlying prevalence of the outcome. Although sudden cardiac death is the most common cause of death in the one-year post infarction period; it is also relatively uncommon (2.5%–11.3%) and declining, due to increasing use of thrombolysis, aspirin, and beta-blockers. Thus, given the relative low prevalence of arrhythmias, the high negative predictive value is not surprising. In 1996, the American College of Cardiology published an expert consensus document that concluded that SAECG had an established or valuable role in clinical care in the following situations:

- Stratification of risk of developing sustained ventricular arrhythmias in patients recovering from MI who are in sinus rhythm without electrocardiographic evidence of bundle branch block or intraventricular conduction delay
- Identification of patients with ischemic heart disease and unexplained syncope who are likely to have inducible sustained ventricular tachycardia.
- Stratification of risk of developing sustained ventricular arrhythmia in patient with nonischemic cardiomyopathy
- Assessment of success of operation for sustained ventricular tachycardia.

However, the ultimate validation of any diagnostic test is to determine how it is used in the management of patients, and whether the management decisions result in improved health outcomes. The following discussion focuses on the clinical use of SAECG as reported in clinical trials of antiarrhythmic therapies.

Over the past two decades there have been a large number of randomized clinical trials evaluating the effectiveness of either antiarrhythmic drugs or AICD implantation in post MI patients. These trials have generally used a variety of risk stratification techniques to positively select patients for intervention. In this setting the positive predictive value (i.e., the number of patients identified at risk who will experience an arrhythmia) is the critical statistical measure, as opposed to the negative predictive value proposed by the AHCPR assessment. For the purpose of this discussion, the most relevant studies are those that look at patients who have not experienced a prior episode of near fatal ventricular arrhythmia or aborted sudden death. Patients with a prior history of a potentially fatal arrhythmia need no further risk stratification. By virtue of this history alone, these patients are considered candidates for both antiarrhythmic therapy and AICD.
Initially, it was thought that pharmacological suppression of premature ventricular contractions (PVCs), identified on post MI monitoring, would reduce the incidence of subsequent sustained symptomatic arrhythmias. The Cardiac Arrhythmia Suppression Trial (CAST) was a placebo controlled, randomized trial that tested the efficacy of either encainide, flecainide, and moricizine in reducing arrhythmic death in patients with a lowered ejection fraction and 6 or more PVCs per hour. CAST was terminated prematurely when an interim analysis suggested that the drug therapy was associated with an increase in the incidence of arrhythmic death. This trial raised concerns about proarrhythmic effects of antiarrhythmic drugs and has lead to caution in the use of any antiarrhythmic drug therapy.

The drugs in the CAST trial are known as class I antiarrhythmics, defined as those, which slow conduction. After the failure of the CAST trial, research was focused on class III agents, which prolong repolarization. The most commonly researched member of this class of drugs is amiodarone. There have been a number of small randomized studies of amiodarone, but the largest are the EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial), both of which assessed the effect of amiodarone on mortality in patients with high-risk markers after MI. In the EMIAT trial, patients with a history of MI were stratified according to their ejection fraction. In the CAMIAT trial, patients were recruited based on results of Holter monitoring. Therefore, neither of these key trials used SAECG as a patient selection criterion.

The results of both of these trials suggested that while amiodarone was associated with a decreased risk of arrhythmias, there was no overall reduction in all-case mortality. Therefore, the major finding of these trials focused on the safety of amiodarone, in contrast to the class I agents studied in the CAST trial. The clinical effectiveness of amiodarone is less certain and may be associated with a reduction of morbidity and quality of life associated with symptomatic arrhythmias, although this outcome has not been specifically studied. It is possible that a normal SAECG could be considered to deselect patients who would be unlikely to benefit from amiodarone therapy. However, this outcome has not been specifically studied, particularly since the overall benefit of amiodarone therapy is still controversial.

With the somewhat disappointing results of these drug trials, attention turned toward the use of AICDs, particularly as these devices became more sophisticated. Early generations of AICDs required thoracotomy for insertion but miniaturization has permitted outpatient insertion under local anesthesia. With this reduction in the risk associated with AICDs, there was an interest in exploring their use in patients without a prior history of sustained, symptomatic ventricular
arrhythmias. Two randomized studies have been completed, the MADIT (Multicenter Automatic Defibrillator Implantation Trial) and the CABG-Patch trial. The MADIT trial recruited post MI patients with left ventricular ejection fraction of less than 35%, non-sustained ventricular tachycardia identified on Holter monitoring or stress test, and inducible, procainide resistant, sustained ventricular arrhythmia on electrophysiologic study (EPS). These characteristics were thought to identify a very high-risk group for ventricular arrhythmias, in part due to the desire to have very high event rates to increase the power of the trial. The MADIT trial reported a marked reduction in mortality in those receiving a defibrillator compared to patients treated conventionally, mostly with amiodarone. Following the publication of the results, the FDA approved expanded labeling for defibrillators in patients who met the MADIT criteria, Medicare announced coverage for AICD in this patient population, and the American College of Cardiology has published guidelines endorsing the study results. As noted above, SAECG was not used as a patient selection criterion, and thus is not included as a recommended test as part of the ACC guidelines.

In contrast to the other trials reviewed above, the CABG-Patch trial used SAECG as a positive patient selection criterion. The CABG-Patch trial recruited patients scheduled for a CABG who had an ejection fraction of less than 36% and abnormalities on the SAECG. The use of an SAECG was based on a pilot study that showed an abnormal SAECG was associated with a mortality rate that was double that seen in those with a normal SAECG in the two years after CABG. Patients were randomized to a defibrillator group or a control group. After an average follow up of 32 months, there was no evidence of improved in the defibrillator group. These results suggest that while patients with a manifest ventricular arrhythmia (i.e., the MADIT criteria) may benefit from an AICD, the presence of a marker of arrhythmia (i.e., an abnormal SAECG) is insufficient to identify a group of patients who will benefit. In addition, the possibility exists that the revascularization procedure itself may have reduced the risk of arrhythmia, which eliminated any demonstrable benefit of an AICD.

Therefore, based on the above review, it can be seen that the SAECG has not been successfully used as a patient selection criterion in the critical randomized trials investigating both drug and device antiarrhythmic therapy in the post MI patient. In the majority of trials, it has not been included as a patient selection criterion, and the one trial in which it was used reported negative results. There are several ongoing studies further investigating the use of AICD in post MI patients. However, these studies, i.e., the MADIT-II and the Sudden Cardiac Death in Heart Failure (SCD-HFT) trials have not included SAECG as a patient selection criterion. (10) The AHCPR assessment suggested that it might be used to deselect patients from further evaluation. However, the focus of research has been on the identification of positive patient selection criteria. Also there is...
no evidence that the SAECG can be used in lieu of other risk stratification tests, such as Holter monitoring or electrophysiologic studies.

There are inadequate data to evaluate the impact of other applications of SAECG, including but not limited to its use in patients with cardiomyopathy, assessment of success after surgery for arrhythmia, detection of acute rejection of heart transplants, assessment of efficacy of antiarrhythmic drug therapy, or assessment of success of pharmacological, mechanical, or surgical interventions to restore coronary artery blood flow.

**T-Wave Alternans**

Studies suggest that in patients with a history of MI, T wave alternans is associated with a negative predictive value of 98% and a positive predictive value of 50%. However, there are no clinical studies that focused on how the results of this test would be used in the management of the patient, either in terms of initiating or altering a drug regimen, used as a patient selection criteria for further electrophysiologic studies, or implantation of an AICD. The same applies to the data in patients with cardiomyopathy.

In addition, over the past two decades clinical trials have been evaluating the effectiveness of antiarrhythmic drugs or AICD implantation in post MI patients. Of these studies there have been no randomized trials of either AICD's or antiarrhythmic therapy that have relied on the results of T-wave alternans as patient selection criteria. Randomized studies of AICD therapy have focused on the presence of arrhythmias as identified on Holter monitoring, electrophysiologic testing, or on the ejection fraction.

**PRICING:**

None

**REFERENCES:**

**Signal Averaged Electrocardiography (SAECG)**


**T-Wave Alternans**


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