

T-Wave Alternans: Not Ready for Prime Time

BY BRUCE JANCIN
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SNOWMASS, COLO. — The value of T-wave alternans testing as a risk stratification tool for selecting implantable cardioverter defibrillator candidates has been cast into serious doubt by the disappointing results of two recent large clinical trials.

This test is clearly not ready for prime-time application in clinical practice. Further well-designed studies are needed to resolve the existing confusion surrounding its role. And yet the Centers for Medicare and Medicaid Services has reimbursed for T-wave alternans (TWA) testing for risk stratification in ICD candidates since 2006, in a noteworthy instance of the “federal follies,” Dr. William H. Spencer III observed at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

“Talk about paradoxical reactions by our government,” commented Dr. Spencer, professor of medicine at the Medical University of South Carolina, Charleston.

The hypothesis underlying TWA testing is that it non-invasively identifies patients having an electrophysiologic substrate for reentrant ventricular tachyarrhythmias. If true, that would allow more selective placement of costly ICDs than is currently possible. Many patients who receive an ICD for primary prevention solely on the basis of the current criterion of a left ventricular ejection fraction below 35% will never use the device during their lifetime.

However, the results of the recent Microvolt T-Wave Alternans Testing for Risk Stratification of Post-MI Patients (MASTER 1) and Alternans Before Cardioverter Defibrillator (ABCD) trials raise a question as to whether the test merely identifies a population that’s relatively sick and therefore at increased risk for all-cause mortality rather than specifically for the arrhythmic sudden cardiac deaths (SCDs) that ICDs are designed to prevent.

In other words, TWA testing might not provide incremental value over clinical markers of increased mortality risk, such as comorbid conditions, advanced age, and low-

er left ventricular ejection fraction (EF), the cardiologist said.

MASTER 1, a Medtronic Inc.–sponsored trial presented at the 2007 American Heart Association meeting, involved 575 patients who received an ICD because they had a prior MI and an EF below 30%. At 3 years’ follow-up, the primary end point—the rate of life-threatening ventricular tachyarrhythmias—was not significantly different between patients with a positive or indeterminate TWA and those who were TWA-negative.

“Very disappointing. TWA did not point out the kind of patient we would put an ICD in,” Dr. Spencer said at the meeting, which was cosponsored by the American College of Cardiology.

A positive or indeterminate TWA result did predict, however, significantly increased risk of all-cause mortality. “There are two alternative explanations for this. Maybe the people with indeterminate or positive tests drove their cars faster. But it’s more likely that they had more markers for mortality. It tells you that there are clinical variables we’re not measuring with TWA,” Dr. Spencer said.

The St. Jude Medical Inc.–sponsored ABCD study was presented at the March 2006 meeting of the ACC yet remains unpublished to date. It involved 566 patients with ischemic heart disease and a low EF who met current criteria for an ICD. All underwent both TWA and invasive electrophysiologic testing. The results showed that the two tests were equivalent at predicting SCD or appropriate ICD shocks at 12 and 24 months. Dr. Spencer’s reaction: So what? Saying TWA is equivalent to electrophysiologic testing is faint praise, because most electrophysiologists no longer routinely do invasive testing in an effort to identify ICD candidates because of its lack of incremental value.

The TWA test reimbursed by CMS is conducted on a treadmill using a modified Bruce protocol at a heart rate of 110-120 beats per minute. The test relies on proprietary equipment marketed by Cambridge Heart Inc. The results can be interpreted with minimal training.

Earlier observational studies of TWA yielded conflict-

ing results. MASTER 1 and ABCD were supposed to clear matters up but have had the opposite effect, in Dr. Spencer’s view.

Dr. Michael R. Gold predicted that in the long run, genetic testing for predisposition to SCD will be far more useful than TWA or any of the other risk-stratification methods for ICD candidates now being investigated. He pointed to several intriguing studies that suggest family history might be an important risk factor for cardiac arrest.

That’s a provocative finding because physicians haven’t traditionally been trained to ask about family history of SCD in patients with coronary disease, noted Dr. Gold, professor of medicine and director of adult cardiology at the Medical University of South Carolina.

In a retrospective case-control study, Dr. Kari S. Kaikkonen and colleagues at the University of Oulu (Finland) scrutinized 138 consecutive individuals who experienced SCD, 254 consecutive patients who survived an acute MI, and 470 healthy controls. Individuals with a history of SCD in a first-degree relative were 2.2 times more likely to experience SCD than were controls. A family history in two or more first-degree relatives was associated with an 11.3-fold increased risk (Circulation 2006;114:1462-7).

In a population-based study conducted by Yechiel Friedlander, Ph.D., of Hebrew University, Jerusalem, and colleagues at several American universities, a history of MI or primary cardiac arrest in a first-degree relative was associated with a 57% increased risk of primary cardiac arrest after adjustment for other common risk factors (Circulation 1998;97:155-60).

And in a Dutch case-control study involving 702 patients with a first ST-elevation MI, 330 of whom developed primary ventricular fibrillation, a history of sudden death in a first-degree relative was associated with a 2.7-fold increased risk of primary ventricular fibrillation during the acute phase of the MI (Circulation 2006;114:1140-5).

Dr. Gold is on the speakers bureaus of Medtronic Inc., St. Jude Medical, and Boston Scientific Corp. Dr. Spencer reported no significant commercial relationships. ■

ICDs Have ‘Disappointing’ Impact on Sudden Cardiac Death

BY BRUCE JANCIN
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SNOWMASS, COLO. — Implantable cardioverter defibrillator therapy has failed to make an appreciable dent in the enormous public health problem of sudden cardiac death, the leading cause of mortality in the United States.

“The data are actually somewhat disappointing,” Dr. Michael R. Gold said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

Preliminary 2007 national data indicate that while the total number of cardiovascular deaths continues to decline, the proportion of cardiovascular mortality due to sudden death has climbed to 70%.

Sudden deaths “appear to be, if anything, increasing, despite all the things that we’re doing. ICDs were supposed to be the cure for this problem,” noted Dr. Gold, professor of medicine and director of adult cardiology at the Medical University of South Carolina, Charleston.

The problem with using ICDs for primary prevention of sudden cardiac death (SCD) is that these expensive devices are being placed in the wrong people.

“Right now we’re stuck: 70%-80% of SCDs occur in people who do not meet standard indications for an ICD, and of those who do get ICDs, about 70% aren’t

going to use them in the first 4 or 5 years,” the cardiologist said at the conference, cosponsored by the American College of Cardiology.

Even in those who do get an appropriate ICD shock, it doesn’t mean what it used to. “It used to be we’d pat the patient on the back and say, ‘Congratulations, you just had your life saved.

Go on about your business.’ In fact, that’s not true anymore. If you have a shock, particularly for ventricular fibrillation, it’s almost a death sentence. You’re being told that you’ve had an appropriate shock, it successfully got you out of that rhythm, but now you have roughly a 10-fold increased mortality risk over the next couple of years. They’re not dying of sudden death, they’re dying of nonsudden cardiac death: ischemic events and heart failure events,” he said.

As for the use of ICDs for secondary prevention of cardiac arrest, that’s unlikely to have a major public health impact.

“If we gave an ICD to every person in the U.S. who’s had a cardiac arrest, we would save about 500 lives per year. That’s about 0.1% of the SCDs,” Dr. Gold said.



The difficulty in using ICDs for secondary prevention, he noted, is that so few individuals survive a first out-of-hospital cardiac arrest. In Chicago, New York, and Boston, the rate hovers around 1%.

The basis of the strategy of ICDs for primary prevention is what Dr. Gold calls the rule of 80s: the concept that 80% of SCDs are brought on by ventricular tachycardia degenerating into ventricular fibrillation, 80% occur in men, 80% have coronary artery disease with prior MI, and 80% are associated with heart failure with left ventricular systolic dysfunction. That was true 20 years ago, but it’s no longer the case today because of the remarkable advances in the treatment of acute MI.

For example, a recent analysis of 714 consecutive SCDs in the population-based Oregon Sudden Unexplained Death Study showed only one in six subjects had undergone assessment of left ventricular ejection fraction (EF). In other words, there was no prior suspicion of cardiac disease in 83% of patients with SCD. Moreover, 70% of those with an EF measurement had a value greater than 35%, so

they didn’t meet current criteria for prophylactic ICD placement (J. Am. Coll. Cardiol. 2006;47:1161-6).

Roughly half of Oregon SCDs with a known EF had a normal value. Only 53% in that subgroup were men, and only 50% with a normal EF had known coronary artery disease. So much for the rule of 80s.

Similarly, a history of heart failure was present in only 12% of 492 consecutive patients with out-of-hospital SCD in the Maastricht, Netherlands, area (Eur. Heart J. 2003;24:1204-9). Fifty-four percent of the Dutch patients had SCD as their first manifestation of any cardiac disease. Of those with a prior MI, the average time from MI to cardiac arrest was 9.7 years, in contrast to the standard teaching that the highest-risk period is the first year post MI.

“The paradox is that the patients who are dying suddenly largely have preserved EF. The bottom line is there aren’t a lot of patients with very low EFs anymore because we treat MIs so well. ... It’s that huge pool of patients with only mild reductions in EF that are dying suddenly,” he said.

Dr. Gold stressed that the key to making a bigger impact on SCD is improved non-invasive risk stratification for ICD placement. However, that goal is proving elusive, with the once-promising ECG microvolt-age T-wave alternans measurement the latest disappointment. (See story above.) ■