

Trial's mixed message challenges TWA test's image for predicting sudden-death risk

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Orlando, FL - When one of the top experts on a risk-stratification test says the results of a key clinical trial of its effectiveness were "disappointing," people listen. But interpreting such remarks in a

vacuum can lead to the wrong message.

In his presentation of the **MASTER 1** trial at the **American Heart Association (AHA) 2007 Scientific Sessions**, **Dr Theodore Chow** (Lindner Center at the Christ Hospital, Cincinnati, OH) made just such a statement about the performance of the microvolt T-wave alternans (TWA) test as a predictor of "life-threatening ventricular arrhythmias." The trial had enrolled post-MI patients with an LVEF <30% who received an implantable cardioverter-defibrillator (ICD) for primary prevention. Ventricular arrhythmic events in the trial were documented from the shocks delivered by the devices.



Dr Theodore Chow

As covered then by **heartwire**, Chow reported that a "nonnegative" microvolt TWA result, the test's conventional marker of increased risk, showed a 1.26 hazard ratio (HR) for the life-threatening arrhythmias, the primary end point, that wasn't even close to significant. But its HR for total mortality was 2.04 (p=0.02). Some news stories on MASTER 1 in the public media that day, by reporters apparently stymied by the subject's nuances and complexity and unaware of the vast amount of earlier observational data that reflect well on the microvolt TWA test, overlooked the big picture, focused on the negative results, and overstated Chow's downbeat conclusions. On Wall Street, shares of the microvolt TWA test's developer and marketer, Cambridge Heart, fell almost a third, from a previous closing price of \$2.28 to \$1.53 the day of Chow's presentation.

Media culpa

Chow told **heartwire** that he had been misquoted or misinterpreted in some press reports. One quote "went something like, 'T-wave alternans has turned out to be a major disappointment.' . . . I was very careful to say that the results of the trial were disappointing, not that T-wave alternans was disappointing," he said. His job at the dais "was to present the results of

the clinical trial. My job really wasn't to present a broader perspective of T-wave alternans and whether I think it's useful or not useful."

When interviewed by reporters at the meeting, however, "I tried to give a reasoned response that had some element of my understanding of the broader literature but at the same time respected the results of this trial. I think in that context, people were getting confused, because clearly the primary results were negative," Chow said. "Now the simplest, most linear way to interpret that is that T-wave alternans doesn't work. But in fact, the story is more complicated than that."

For example, he said, the media generally didn't pick up on the finding that the test predicted total mortality. "Nobody really focused on that, but I think that's incredibly interesting. And I think people are still stuck on the concept of ICD shocks being equivalent to mortality, and clearly they are not. That 90% of the end points in MASTER 1 were shock-driven makes that point critically important.

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"I think people overreacted to a single trial without looking at the broader landscape of T-wave alternans and recognizing that this is one piece, a very important piece, but one piece in the total story," he said.

"It's interesting that the ALPHA trial came out at almost the same time as the MASTER 1 trial, and yet nobody is talking about that," Chow said, referring to the **T-Wave Alternans in Patients with Heart Failure Trial**, published in the November 6, 2007 *Journal of the American College of Cardiology* [2]. The ALPHA report had been released online a week earlier and the results presented months earlier at the **American College of Cardiology 2007 Scientific Sessions**.

As reported by **heartwire**, in that study a nonnegative test's HR for the primary end point of "cardiac death or life-threatening arrhythmias" among ALPHA's patients with nonischemic systolic heart failure was 3.2 ($p=0.013$). The HR for total mortality was 4.6 ($p=0.002$). The trial was interpreted largely as a success for the microvolt TWA test.

Shocks are not sudden deaths

After meeting his responsibility to be objective when discussing MASTER 1 at the AHA sessions, Chow said he could now give his own interpretations.

That's what he did in a November 15, 2007 press release, issued by Cambridge Heart, that he told **heartwire** was intended to provide "a more thoughtful, broader view of T-wave alternans" than what apparently came across at the meeting [3].

In the release, Chow says "the recent MASTER and ALPHA trials have helped to clarify the role of microvolt TWA testing in current practice" and "are consistent with the notion that microvolt TWA testing identifies patients more or less likely to suffer 'hard end points' (ie, mortality) but is less able to discriminate which ICD-treated patients will receive shocks.



Dr Eric Prystowsky

"I believe that microvolt TWA testing in today's clinical practice can add value to the patient encounter. Microvolt TWA testing provides additional information about a patient's mortality risk profile that could influence the chosen therapy," Chow's statement continues. "In those cases where more data about mortality risk help make one a better doctor, I advocate microvolt TWA testing."

Dr Eric Prystowsky (St Vincent Hospital, Indianapolis, IN) sees the MASTER 1 outcomes in a different light. He observed for **heartwire** that, for the trial's fairly homogeneous MADIT-2-like population with coronary heart disease and LVEFs <30%, "it appears that the T-wave alternans test has lost its discriminatory ability, or at least it has in this trial. And until we have another prospective trial showing the opposite, I think we in the EP community have to stand back and say, we can't use the T-wave alternans test at this point to tell us who can avoid getting an ICD."

Whence the outcomes discrepancy in MASTER-1?

The apparent disconnect between MASTER 1's mortality and ICD-shock data, Chow said in the Cambridge Heart release, "may relate to the fact that many (possibly the majority) of ICD shocks are for ventricular arrhythmias that would not have proven lethal. It is important to view these trials through the lens of the substantial body of existing microvolt-TWA literature."

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Interviewed, Chow described another possible but more theoretical explanation for the disconnect: microvolt TWA might be highly predictive of ventricular arrhythmias, but ICDs may be proarrhythmic, "so you would actually be getting shocks in T-wave alternans-negative people." The potential for ICD-induced shocks is seldom discussed, he said, "but that's an additional layer of uncertainty that surrounds the trial and why we need more studies, basically."

Alternatively, Prystowsky speculated, it may be that the T-wave alternans test simply indicates who has a sick heart, which would be consistent

with the finding that the test was predictive for total mortality but not necessarily life-threatening arrhythmias. So when everyone in a trial has an LVEF <30%, the test "just doesn't have the power to pick up a true negative. That doesn't mean it can't be a valuable tool in the [LVEF] >30%-to-40% group. In those patients—they're the ones we all scratch our heads about—it might still prove to be a very potent discriminator of true risk vs minimal risk."

The ongoing MASTER 2 trial, in fact, is exploring that very idea in post-MI patients [4].

As for seeing MASTER 1 in context with other data, **Dr David S Rosenbaum** (Case Western Reserve University, Cleveland, OH) said what struck him after hearing Chow's presentation of MASTER 1 was that the trial "conflicts with about six other trials that show the opposite result." He observed for *heartwire* that the **Alternans Before Cardioverter Defibrillator** (ABCD) trial, for which he was co-principal investigator, was "similar in many ways" to MASTER 1 yet showed the microvolt TWA test to be significantly predictive of ventricular arrhythmic events. End points in ABCD were defined by ICD responses, either shocks or antitachycardia pacing, to sensed ventricular arrhythmias. The trial was presented at the **AHA 2006 Scientific Sessions** and reported by *heartwire* at the time.



Dr David S Rosenbaum

Rosenbaum agreed that MASTER 1's outcomes were possibly influenced by the ICD's capacity for shocking arrhythmias that wouldn't ultimately prove fatal, not only ventricular arrhythmias but atrial tachycardias as well. He also speculated that the MASTER 1 trial's low overall event rate and its dampening effect on statistical strength might have played a role in the test's failure to predict ventricular arrhythmias. The low event rate could

potentially have been caused by any number of things, he said, such as exceptionally good medical therapy in the trial or selection bias toward lower-risk patients.

"Not as simple as we had hoped"

"I think MASTER was an interesting and carefully executed trial, but I don't think it tells us anything new about [T-wave] alternans," Rosenbaum said. "We have this one negative trial, we have a number of positive trials, [and] you have to put the balance of evidence together before you make any major judgments. I think what MASTER and ABCD showed us is that when you try to correlate [T-wave] alternans with ICD end points, you don't get a terribly strong prediction."

But according to Prystowsky, expecting T-wave alternans to identify patients at truly low risk is "asking a lot of the test. You do a test once and then expect it to be [prognostic] for two years? These aren't patients with a small infarct, these are the ones who get progressively worse over time." Perhaps if the test were repeated at, say, six-month intervals, "maybe somewhere along the way you could pinpoint the major risk group."

Otherwise, he said, it can't identify MADIT-2-like patients who are at low enough risk and going to stay that way to confidently say they won't benefit from an ICD. "To me that's the message here—it won't work in a very-low-LVEF group, and until you can show me a prospective study that counters that, we should just forget about it."

For Chow, on the other hand, the bottom line, according to the collective data, is that in eligible patients who don't have a device, the test "does appear to identify patients at higher and lower risk." But in patients with ICDs, he said, "it does not appear to identify people more or less likely to have ICD shocks."

For now, clinicians must weigh the potential risks and benefits of device therapy in individual patients, "and when more information allows you to arrive at a better judgment for a patient, to the extent that the individual physician thinks that T-wave alternans provides that information, it's a useful test," Chow said. "The main message I got from MASTER 1 is that the [T-wave-alternans] story isn't going to be as simple as we had hoped it would be."