MASTER I: Disappointment for T-wave alternans testing

November 6, 2007 | Sue Hughes

Orlando, FL - T-wave alternans (TWA) testing did not predict life-threatening ventricular tachyarrhythmic events in post-MI patients with left ventricular ejection fractions less than 30% in the **MASTER I** trial. The study was presented at the **American Heart Association 2007 Scientific Sessions** today by **Dr Theodore Chow** (Lindner Center at the Christ Hospital, Cincinnati, OH).

Dr Theodore Chow

Chow explained that it was hoped that TWA testing would help stratify which patients who currently fit the **MADIT-2** criteria would gain most from having an ICD implanted. But although patients with an abnormal TWA test were shown to have a higher risk of all-cause death in this study, they did not have a higher rate of life-threatening ventricular tachycardia as judged by ICD shocks or an increased risk of sudden cardiac death. "The TWA test does appear to have predictive value in terms of all-cause mortality, but how best to use this test in clinical practice is still not clear. That is a major disappointment," he said.

The MASTER I trial included 654 patients who met the MADIT-2 indication for ICD implantation and were not in atrial fibrillation. Patients underwent TWA testing with the Cambridge Heart CH2000 or Heartwave devices and then underwent ICD implantation with prespecified programming to minimize the likelihood of shocks for non-life-threatening arrhythmias. Minimum follow-up was two years, and the analysis was conducted in 575 patients.

Results showed that TWA testing was negative in 214 patients (37%), positive in 293 patients (51%), and indeterminate in 68 patients (12%). The primary end point of life-threatening ventricular tachyarrhythmic events (as assessed by ICD shocks) was not significantly different between patients with negative and nonnegative TWA tests.

MASTER I: Primary end point

End point	Negative TWA test (n=214), n (%)	Nonnegative TWA test (n=361), n (%)	HR (95% CI)	p
Life-threatening ventricular tachyarrhythmias	22 (10.3)	48 (13.3)	1.26 (0.76-2.09)	0.37

Mortality results showed that all-cause deaths were increased in the patients with nonnegative tests, but this appeared to be accounted for mainly by an increase in noncardiac deaths.

MASTER I: Mortality results

Outcome	Negative TWA test (n=214), n (%)	Nonnegative TWA test (n=361), n (%)
Total mortality*	13 (6)	46 (13)
Sudden cardiac death	3 (23)	7 (15)
Non-sudden cardiac death	5 (39)	17 (37)
Noncardiac	3 (23)	15 (33)
Unknown	2 (15)	7 (15)

*Hazard ratio for total mortality=2.04; 95% CI=1.10-3.78; p=0.02
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Chow concluded that TWA testing should not be used to withhold ICDs in MADIT-2-indicated patients and that the biological evidence for excess mortality in patients with nonnegative TWA tests requires further study.

ICD shocks not ideal surrogate end point

Discussing the study at the late-breaking clinical-trial session, **Dr Alan Kadish** (Northwestern University Medical School, Chicago, IL) pointed out that ICD shocks were not an ideal surrogate end point, as they tended to overpredict true mortality events, but this trial had tried to overcome this problem by conservatively programming the ICDs.

He noted that in contrast to the MASTER I study, a previous study by Bloomfield showed a "vast difference" in arrhythmic events in patients who were TWA positive and those were TWA negative. "So how can we explain this discrepancy?" he asked. He suggested that the low overall event rate in the MASTER I trial may have limited its power and that the necessity of excluding patients with atrial arrhythmias and those with recent positive EP studies or TWA tests may have removed those patients with the highest event rates.

Kadish said the effect on total mortality but not on arrhythmic mortality was surprising, as was the fact that the total mortality increase in TWA-positive patients was driven by noncardiac deaths. "I don't know why this occurred. Possible reasons could be statistical aberration, wrong classification of deaths, positive TWA tests associated with severity of systemic disease, or simply that the low event rate made a positive finding unlikely. And we don't have enough information to distinguish among these possibilities," he commented.

So where does this leave us?

Kadish reported that there had been five studies of TWA testing reported in the past year, three of which have suggested the test to be predictive of life-threatening arrhythmias and two showing no predictive value. He pointed out that one variable between these studies seems to be whether ICDs were utilized and whether shocks were used as the end points. "In general, it appears that when shocks are used as a surrogate end point for life-threatening arrhythmias, TWA is less predictive of outcome."

He added that the mechanism by which TWA testing is a better predictor of total mortality than it is of ICD shocks remains to be defined. "It may be that this test is a better predictor of ventricular fibrillation than ventricular tachycardia," he speculated.

Kadish concluded: "Despite the large number of clinical studies done, more studies are necessary to better define the predictive ability of TWA testing. There is not enough concordance among the data at the present time to produce clear indications for TWA use, which is frustrating for all of us who were hoping for a consensus of results and for a clear indication of TWA use for predicting outcomes."

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