Do Beta-Blockers Impact Microvolt T-Wave Alternans Testing in Patients at Risk for Ventricular Arrhythmias? A Meta-Analysis

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Beta-Blockers and Microvolt T-Wave Alternans. ***Introduction:*** **Results of microvolt T-wave alternans (MTWA) studies vary and may be influenced by whether beta-blocker therapy was withheld prior to MTWA assessment. We conducted a meta-analysis of the predictive value of MTWA screening for ventricular arrhythmic events in primary prevention patients with left ventricular dysfunction and examined whether results differed depending upon whether beta-blocker use was withheld prior to MTWA testing.**

Methods and Results: **Prospective studies that evaluated whether MTWA predicted ventricular arrhythmic events published between January 1980 and September 2008 were identified. Summary estimates for the predictive value of MTWA were derived with random-effects models. Nine studies involving 3,939 patients were identified. Overall, an abnormal MTWA (positive and indeterminate) test was associated with an almost 2-fold increased risk for arrhythmic events (pooled RR = 1.95, 95% CI: 1.29–2.96; P = 0.002). However, significant heterogeneity across studies was observed (P = 0.024). In the 4 studies in which beta-blocker therapy was not withheld prior to MTWA assessment, an abnormal MTWA test was associated with a 5-fold increased risk for arrhythmic events (pooled RR = 5.39, 95% CI: 2.68–10.84; P < 0.001) and was robust to sensitivity analyses. In contrast, the association was much weaker in those studies where the use of beta-blocker therapy was withheld prior to MTWA testing (pooled RR = 1.40, 95% CI: 1.06–1.84; P = 0.02).**

Conclusions: **In primary prevention patients with left ventricular dysfunction, the predictive power of MTWA varied widely, based on whether beta-blocker therapy was withheld prior to its assessment. This observation may explain the inconsistent results of MTWA studies in this population.** *(J Cardiovasc Electrophysiol, Vol. 21, pp. 1009-1014, September 2010)*

beta-blocker, microvolt T-wave alternans, cardiomyopathy, prognosis, sudden death

Background

Implantable cardioverter defibrillator (ICD) therapy has been shown to reduce mortality among primary prevention patients with left ventricular dysfunction.[1,2] However, enthusiasm for their use has been tempered by high initial costs, device complication rates,[3,4] and recent manufacturer recalls.[5,6] Given these concerns and because as few as 1 in 5 patients receives a therapeutic defibrillation from their ICD,[2] there is great interest in further risk stratification of patients at risk for sudden cardiac death. Microvolt T-wave alternans (MTWA), which detects abnormalities in ventricular repolarization that are associated with the onset of ventricular arrhythmias,[7,8] has been proposed as a method to improve the efficient use of ICD therapy by identifying patients at highest risk for sudden cardiac death.[9,10]

Although a prior meta-analysis found that MTWA predicts ventricular arrhythmic events among patients with ischemic and nonischemic heart failure,[11] recent studies have reported less consistent results.[12–15] Notably, studies of MTWA varied in their screening protocols as to whether beta-blocker therapy was withheld prior to testing, despite evidence that beta-blockers suppress MTWA amplitude and affect the presence of MTWA during testing.[16] Indeed, 1 in 6 patients who screened MTWA positive when beta-blocker therapy was withheld converted to a negative test result during re-testing on beta-blocker therapy,[16] and the amplitude of MTWA is significantly decreased by acute beta-blockade.[17] Under ideal circumstances, a screening test for prognostication should be performed in a pharmacologic environment consistent with the patient's medical therapy to ensure that test results reflect the potential benefits of chronic drug therapy. Differences in protocols between MTWA studies regarding discontinuation of beta-blocker therapy prior to testing may therefore lead to discordant results.

Accordingly, we performed a meta-analysis to assess for heterogeneity in prognosis among MTWA studies of primary prevention patients with left ventricular dysfunction and, if present, assessed whether the ability of MTWA to predict

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ventricular arrhythmic events varied based on whether beta-blocker therapy was withheld prior to testing.

Methods

Study Inclusion Criteria and Outcome Measures

A systematic review of the literature was conducted to identify prospective studies that: (1) evaluated MTWA in patients with left ventricular systolic dysfunction (ejection fraction $\leq$40%) and no prior sustained ventricular arrhythmia or cardiac arrest; (2) used a standard *noninvasive* MTWA screening protocol (i.e., electrophysiologic assessments of MTWA were excluded); (3) had a minimum of 6 months of follow-up and at least 100 patients in the study; (4) provided clear definitions of normal and abnormal MTWA results; and (5) provided sufficient quantitative data on the study outcome of ventricular arrhythmic events. Ventricular arrhythmic events were defined as any event involving ventricular tachycardia or fibrillation, cardiac arrest, arrhythmic death, and appropriate ICD shocks.

Data Sources and Search Strategy

We searched for published studies in the English language between January 1 1980 through September 30 2008 using PubMed, EMBASE, and all EBM Reviews (which included Cochrane Database of Systematic Reviews, Database of Abstracts and Reviews of Effects, ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, and Health Technology Assessment). The search used both key words and MeSH terms using a Boolean Search Strategy and included the following medical subject headings: prospective studies, follow-up studies, T-wave alternans, prognosis, predictive value of tests, sudden death, ventricular fibrillation, ventricular tachycardia, and ICD shocks. In addition, a hand search of bibliographies of key articles identified through the automated search was performed.

Data Extraction

Data extraction was performed by a study author (PSC) using a pre-piloted, standardized form. From each study, the following variables were abstracted: year of publication; number of study centers; study sample size; withholding of beta-blocker therapy prior to MTWA screening; etiology of left ventricular dysfunction; proportion of study patients treated with beta-blockers; proportion of patients with abnormal and normal MTWA test results; and proportion of study patients with ICDs. Information on whether beta-blocker therapy was withheld prior to MTWA screening was obtained from investigators through electronic mail when not reported in published articles.[12,18,19] When results from more than one follow-up time period were reported (e.g., at 1 year and 2 years),[15] we used estimates from the longer follow-up period.

Statistical Analysis

Consistent with prior work, we compared outcomes between patients with MTWA abnormal (positive and indeterminate) and normal (negative) studies.[20,21] Data for the outcome of ventricular arrhythmic events were summarized using basic descriptive statistics (simple counts and proportions). A meta-analysis was conducted using a random-effects model with the restricted maximum likelihood method developed by DerSimonian and Laird.[22] To evaluate for heterogeneity between studies, we calculated Cochran's Q test and I^2, which represents the degree of inconsistency among studies. We focused on unadjusted results to be consistent, because not all studies performed multivariable analyses. One study reported no events in patients with normal MTWA,[18] and so we assigned a non-zero (0.5) correction factor to calculate its relative risk ratio.[23] Publication bias was evaluated using the Begg's test.

Since we hypothesized *a priori* that withholding beta-blocker therapy prior to MTWA testing would lead to significant heterogeneity across the trials, we report our findings stratified by this category using subgroup analyses. Additional subgroup analyses were conducted to explore the heterogeneity in risk ratios between studies based upon other study criteria, which included: proportion of study patients with ICDs (low [$<$40%] vs high [$\geq$40%]); time period of publication (before vs since 2006); number of study centers ($<$10 vs $\geq$10); and etiology of left ventricular dysfunction (ischemic, nonischemic, or both). Finally, we performed sensitivity analyses to examine the influence of each study on the pooled estimate by omitting each study one at a time. All statistical tests were 2-sided and were evaluated at a significance level of 0.05. STATA version 10.0 (College Station, TX, USA) was used to conduct all analyses.

Results

Nine studies involving 3,939 patients met study inclusion criteria.[10,12-15,18,19,24,25] Of these, 4 conducted MTWA testing on beta-blocker therapy, while 5 withheld beta-blocker therapy for at least 24 hours prior to testing (Table 1). Four of the studies were conducted among patients with left ventricular dysfunction due to an ischemic etiology, 3 were among patients with a nonischemic etiology, and 2 were among patients with either an ischemic or nonischemic etiology. Six of the studies were multicentered trials, while 3 were single institution studies.

Results from the individual studies are summarized in Table 2. Overall, 5 studies found an association between an abnormal MTWA test and increased risk for ventricular arrhythmic events.[10,14,18,19,25] Individual study hazard ratios (HRs) for the 9 studies ranged from 1.11 (95% confidence interval [CI]: 0.63–1.95) to 6.53 (95% CI: 2.35–18.11). When the results from all 9 studies were pooled, an abnormal MTWA result was associated with a 2-fold increased risk for ventricular arrhythmic events (pooled risk ratio [RR] of 1.95, 95% CI: 1.29–2.96; $P = 0.002$). However, significant heterogeneity was present in the overall pooled estimate ($P = 0.024$).

Because of the heterogeneity across studies, we stratified our analyses based on our *a priori* criteria of whether beta-blocker therapy was withheld prior to MTWA assessment. Among studies where the use of beta-blockers was continued during MTWA testing,[14,18,19,25] an abnormal MTWA test was associated with a greater than 5-fold increased risk for ventricular arrhythmic events (pooled RR of 5.39, 95% CI: 2.68–10.84; $P < 0.001$) (Fig. 1). This result was robust to sensitivity analyses when each study was systematically eliminated one at a time. In contrast, the association was much weaker in those studies where the use of beta-blocker therapy

TABLE 1

Characteristics of Prospective Studies of Microvolt T-Wave Alternans in Primary Prevention Patients with Left Ventricular Dysfunction

Study	Year of Publication	Number of Centers	Population Type	Number of Patients	Mean Follow-Up (months)	Beta-Blocker Withheld Prior to Testing?	Proportion on on Beta-Blockers, %	Proportion with ICDs, %
Klingenheben[18]	2000	1	Ischemic	107	15	No	Not reported	0
Hohnloser[19]	2003	1	Nonischemic	137	14	No	Not reported	27
Grimm[24]	2003	1	Nonischemic	263	52	Yes	73	0
Bloomfield[25]	2006	11	Both	587	24	No	81	12
Chow[10]	2006	7	Ischemic	768	18	Yes	82	51
ALPHA[14]	2007	9	Nonischemic	446	19	No	80	8
SCD-HeFT[13]	2008	37	Both	490	35	Yes	74	34
MASTER[12]	2008	50	Ischemic	575	26	Yes	87	100
ABCD[15]	2009	42	Ischemic	566	24	Yes	86	87

ICD = implantable cardioverter defibrillator.

was withheld prior to MTWA testing[10,12,13,15,24] (pooled RR of 1.40, 95% CI: 1.06–1.84; P = 0.02; Fig. 1) and was not robust to sensitivity analysis when a key study[10] was eliminated (pooled RR = 1.27, 95% CI: 0.96–1.68; P = 0.10). In both subgroups, stratifying results by whether beta-blocker therapy was withheld prior to MTWA assessment eliminated the presence of statistical heterogeneity in the pooled analyses (P for heterogeneity = 0.84 for studies not withholding beta-blockers and P for heterogeneity = 0.38 for studies withholding beta-blockers). Notably, all 4 studies that did not find an increased risk of ventricular arrhythmic events with an abnormal MTWA result had withheld use of beta-blocker therapy prior to MTWA testing.[12,13,15,24]

The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of MTWA testing for each individual study and stratified by whether beta-blocker use was withheld prior to MTWA testing are depicted in Table 3. In the 5 studies where beta-blocker therapy was withheld prior to testing, MTWA screening yielded an overall sensitivity of 77% and an NPV of 91% for predicting ventricular arrhythmic events during follow-up. In contrast, in the 4 studies where beta-blocker therapy was continued during testing, MTWA screening yielded an overall sensitivity of 92% and an NPV of 98%.

Finally, subgroup analyses found that use of beta-blocker therapy during MTWA assessment was the variable that best explained the statistical heterogeneity in prognosis among the MTWA studies (Table 4). Most notably, the pooled RR among studies with a low (<40%) proportion of patients with ICDs was not substantially different among studies with a high (≥40%) proportion of patients with ICDs.

Discussion

We found a significant association between an abnormal MTWA test and increased risk for ventricular arrhythmic events among primary prevention patients with left ventricular dysfunction in the current literature, but also noted significant heterogeneity across these trials. Notably, studies continuing use of beta-blocker therapy during MTWA testing showed a stronger and more consistent 5-fold increased risk for ventricular arrhythmic events, whereas a much weaker relationship was observed among studies withholding beta-blocker therapy prior to MTWA testing.

In prior work, administration of beta-blocker therapy at the time of MTWA testing was found to significantly reduce the amplitude of MTWA.[16,17] One in 6 patients with a positive MTWA test off beta-blockers converted to a normal test result upon rescreening on beta-blocker therapy, as their maximal T-wave amplitude had decreased below the threshold of 1.9 mV for a positive test.[16] Another study found that 1 in 2 patients with a positive MTWA result converted to a normal

TABLE 2

Results of Prospective Studies of Microvolt T-Wave Alternans in Primary Prevention Patients with Left Ventricular Dysfunction

	MTWA Abnormal			MTWA Normal			Hazard Ratio
Study	N	Event	No Event	N	Event	No Event	(95% CI)
Klingenheben[18]	74	13	61	33	0	33	Undefined†
Hohnloser[19]	103	16	87	34	2	32	3.44 (0.03–459.0)
Grimm[24]	191	31	160	72	7	65	1.30 (0.59–2.90)
Bloomfield[25]	360	51	309	189	4	185	6.53 (2.35–18.11)
Chow[10]	514	57	457	254	11	243	2.93 (1.33–6.46)
ALPHA[14]	292	29	263	154	4	150	4.01 (1.41–11.41)
SCD-HeFT[13]	355	59	296	135	16	119	1.11 (0.63–1.95)
MASTER[12]	361	48	313	214	22	192	1.26 (0.76–2.09)
ABCD[15]	401	49	352	165	16	149	1.4 (0.8–2.2)‡

MTWA = microvolt T-wave altnernans.

†Hazard ratio undefined as there were no events in the MTWA normal group.

‡Two-year outcomes obtained from study authors.

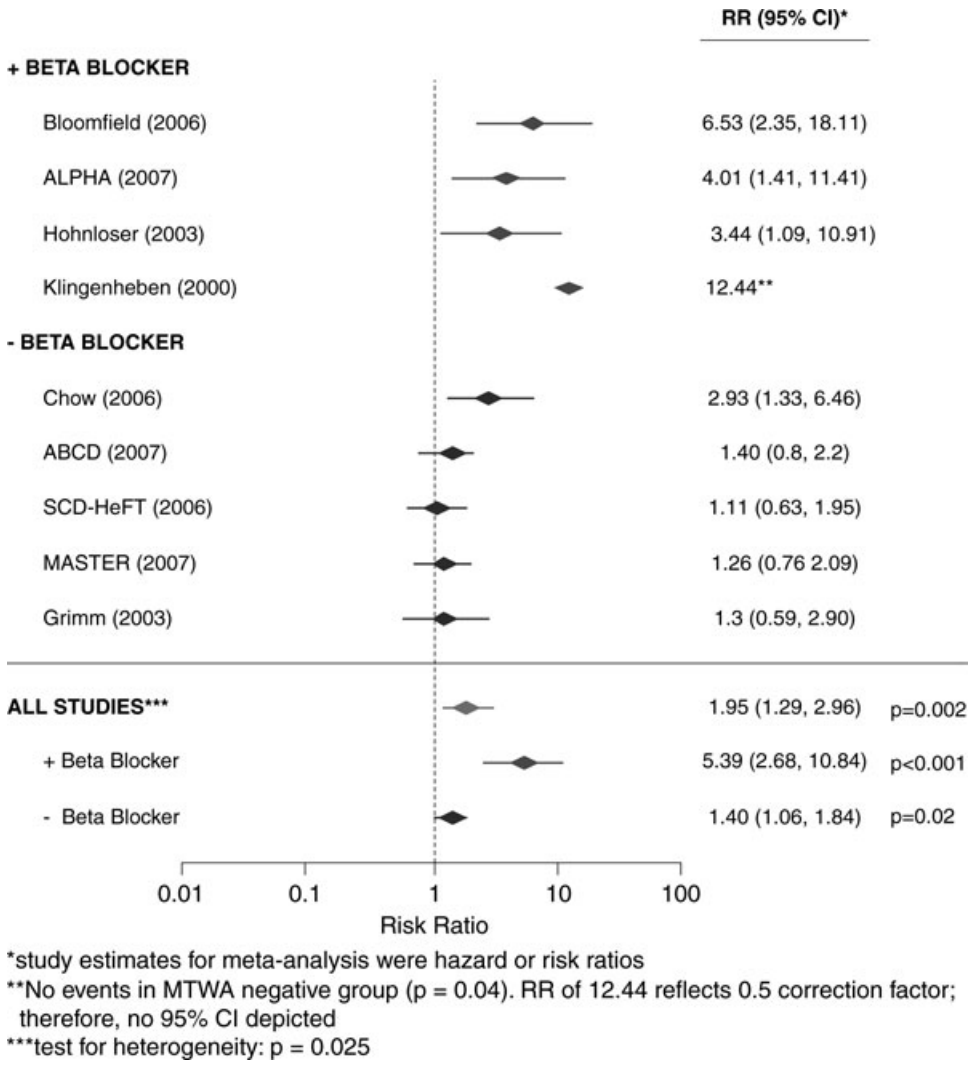

Figure 1. *Association between MTWA and ventricular arrhythmic events, stratified by screening protocol discontinuation of beta-blocker therapy. Significant heterogeneity was observed among studies (P = 0.025). Subgroup analyses found a strong, consistent, 5-fold increased for ventricular arrhythmic events in studies where beta-blocker therapy was not discontinued prior to MTWA assessment. In contrast, a weak association between an abnormal MTWA test and risk for arrhythmic events was observed in studies that withheld beta-blocker therapy prior to MTWA assessment.*

test result upon administration of beta-blocker therapy.[17] A third study found that beta-blocker administration resulted in a negative MTWA test result in 8 of 26 (30.8%) patients who initially screened positive.[26] Because beta-blockers may alter the development of MTWA results, they may also modulate susceptibility to ventricular arrhythmias. Indeed, it has been argued that MTWA testing should be performed on beta-blocker therapy to provide a risk stratification that more reliably reflects the 'pharmacologic milieu' of the patient.[16] By performing MTWA screening off beta-blockers, prior studies may have measured higher MTWA amplitudes than when on beta-blockers and may have classified a certain proportion of otherwise MTWA negative patients as positive (i.e., false-positives). As a result, the predictive power of MTWA for ventricular arrhythmic events in studies where beta-blocker therapy was withheld prior to testing may have been substantially diluted and could account for the wide variation in MTWA study results. This issue deserves further investigation and suggests that future trials should consider assessing MTWA both on and off beta-blockers to confirm the findings of this study.

The rationale for withholding beta-blocker therapy prior to MTWA screening has been to decrease the proportion of indeterminate results, as a negative result requires achieving heart rates of 110–120 beats per minute and documentation of no sustained MTWA.[27] However, recent studies found that indeterminate MTWA tests have similar prognostic utility as positive tests,[20,21] even among patients unable to achieve this heart rate level. This suggests that the protocol requirement of withholding beta-blocker therapy prior to screening may be unnecessary, especially if doing so affects the predictive power of MTWA.

In a recent meta-analysis, Hohnloser *et al*.[28] called into question the validity of including ICD shocks as a clinical endpoint in MTWA studies. The authors found that the predictive power of an abnormal MTWA test result was excellent among studies with low ICD use and mediocre among studies with high ICD use. However, in this meta-analysis, we did not find that the predictive power of an abnormal MTWA test result differed substantially by ICD use. Our results likely differed from the Hohnloser meta-analysis because our study: (1) included only patients with left ventricular systolic

TABLE 3

Summary of Study Accuracy, Stratified by Whether Beta-Blocker Therapy Was Withheld Prior to Microvolt T-Wave Alternans Screening

Study	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Screening on beta-blockers				
Bloomfield[25]	93	37	14	98
ALPHA[14]	88	36	10	97
Hohnloser[19]	89	27	16	94
Klingenheben[18]	100	35	18	100
SUMMARY	92	36	13	98
Screening off beta-blockers				
Chow[10]	84	35	11	96
ABCD[15]	75	30	12	90
SCD-HeFT[13]	79	29	17	88
MASTER[12]	69	38	13	90
Grimm[24]	82	29	16	90
SUMMARY	77	33	13	91

Studies continuing beta-blocker therapy during microvolt T-wave alternans testing were associated with higher sensitivity and NPV for ventricular arrhythmic events. NPV = negative predictive value; PPV = positive predictive value.

dysfunction; (2) excluded patients with invasive assessments of MTWA; and (3) categorized the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) as a low ICD use study, as only 34% of patients in the MTWA substudy of SCD-HeFT received an ICD.

While an abnormal MTWA was associated with a greater than 5-fold increased risk for ventricular arrhythmic events in studies where beta-blocker therapy was continued during screening, simultaneously demonstrating that patients with normal test results have a low event rate is critical in order for MTWA to be considered for optimal risk stratification of primary prevention patients for ICD therapy. Indeed, we found that the NPV was 98% for an abnormal MTWA test result in studies where beta-blocker therapy was continued during screening. Based on our prior economic model of MTWA screening,[29] a strategy of implanting ICDs in all eligible patients, as compared with a strategy of implanting ICDs only in patients identified as high-risk when the RR is 5 with an abnormal MTWA test, would yield an incremental cost-effectiveness ratio of ~US$150,000 per quality-adjusted life-year and would not be considered cost-effective. However, future studies are needed to confirm the accuracy of MTWA test results when beta-blocker therapy is not withheld prior to screening before endorsement of their routine use in risk stratification.

TABLE 4

Results of All Subgroup Analyses

Stratified By	Studies (Number)	Pooled Risk Ratio (95% CI)
Beta-blocker use		
Continued during MTWA screening	4	5.39 (2.68–10.84)
Withheld prior to MTWA screening	5	1.40 (1.06–1.84)
Proportion of study patients with ICDs		
<40%	6	2.55 (1.18–5.52)
≥40%	3	1.58 (1.03–2.43)
Number of study sites		
<10	5	2.51 (1.42–4.43)
≥10	4	1.64 (0.95–2.81)
Publication year		
Before 2006	3	2.02 (0.59–6.95)
Since 2006	6	2.01 (1.24–3.26)
Etiology of cardiomyopathy		
Ischemic	4	1.71 (1.05–2.79)
Nonischemic	3	2.14 (0.90–5.07)
Ischemic and nonischemic	2	2.55 (0.45–14.45)

The heterogeneity in MTWA studies was best explained by whether beta-blocker therapy was withheld prior to MTWA screening. The pooled risk ratios were not as different from one another when studies were stratified by the proportion of study patients with implantable cardioverter defibrillators (ICD), number of enrolled sites, publication year, or the etiology of left ventricular dysfunction. CI = confidence interval.

Our study should be interpreted in the context of several limitations. We did not have patient-level data to conduct an on-treatment analysis or a multivariable analysis. Additionally, definitions for the study endpoint of ventricular arrhythmic events varied across studies. We were unable to examine the association between MTWA and either mortality or appropriate ICD shocks, as these were not routinely reported in many studies. Moreover, because we did not have patient-level data, we were unable to determine whether some of the heterogeneity across MTWA studies was due to inclusion of appropriate ICD shocks as part of a combined arrhythmic endpoint in more recent studies. We were unable to assess the impact of withholding other medications with antiadrenergic and antiarrhythmic effects (e.g., Vaughan Williams Class III agents) prior to MTWA screening. However, the majority of patients with left ventricular dysfunction are not treated with conventional antiarrhythmic therapy. Finally, while prior studies only examined the acute effect of intravenous beta-blockers on MTWA amplitude, it is unclear whether oral beta-blockers would have similar effects.

In conclusion, an abnormal MTWA test was associated with a 5-fold increased risk for ventricular arrhythmic events among primary prevention patients with left ventricular dysfunction in studies where beta-blocker therapy was continued during MTWA screening, while a weak association was seen in studies where beta-blocker therapy was withheld prior to screening. This observation may help explain the inconsistent results of MTWA studies in this population.

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