APPENDIX A

Evidence Table

Author/Year	Study Design	Demographics	Interventions Outcome Measures Instrument	Results	Methodologic Comments
Gehi, Stein, Metz, Gomes 2005	Meta-analysis of prospective studies of the predictive value of exercise-induced MTWA published from Jan 1990 to December 2004.	2608 total subjects 19 studies met inclusion/exclusion criteria. Wide range of populations included in analysis: CHF, ischemic CHF, non-ischemic CHF, post MI, athletes and healthy subjects.	MTWA used as diagnostic test Endpoints included SCD, T, VF, ICD placement, cardiac death PPV, NPV and RR computed	Presence of MTWA predicted a 4-fold higher risk of VAE. For all studies, PPV=19.3 (CI 18-21) NPV=97.2 (CI 97-98) RR=3.77 (CI 2.4-6) For CHF, PPV=25.5 (CI 23-28) NPV=93.8 (CI 92-95) RR=2.51 (CI 1.7-3.6) For post MI, PPV=6 (CI 4.5-7.4) NPV=99 (CI 99-100) RR=4.74 (CI 1.1-20.1)	Meta – analysis, no evid of publication bias or lack of heterogeneity Unable to determine the incremental prognostic value of MTWA independent of other predictors of arrhythmic events End pts of the individual studies used in summary calculations were variable Subjects primarily male Inconsistency in the exclusion of subjects using beta blockers or anti-arrhythmic meds
Gold, Bloomfield, Anderson, El-Sherif, Wilber, Groh, Estes, Greenberg, Rosenbaum 2000	Prospective, multi-center	313 participants, had to have NSR and capable of bicycle exercise Mean age 56+/-16, mean EF 44% +/- 18% 34% had history of	MTWA, SAE, and ventricular stimulator (EPS) were diagnostic tools VTE and death as endpoints Sn, Sp, PPV,	For MTWA, Sn=77.8% Sp=72.5% PPV=42.9% NPV=92.5% RR=5.7 For SAE, Sn=55.6% Sp=83.3%	Heterogeneous pt population Majority of VTE were nonfatal No powered to assess the predictors of mortality only

		CHF, including 22% with NYHA Class II symptoms, and 12% with Class III symptoms No structural heart dis in 30% of this cohort	NPV and RR	PPV=46.9% NPV=87.65% RR=3.8 For MTWA, w/VTE as endpoint, RR=6.1, and w/VTE or death as endpoint RR=8 For SAE, w/VTE as endpoint, RR=4.6, and w/VTE or death as endpoint RR=2.9	
Hohnloser, Klingenheben, Bloomfield, Dabbous, Cohen 2003	Prospective observational study; 87 participants taken from Ikeda and colleague study, and 42 subjects taken from Klingenheben study.	129 participants Eligibility criteria included: confirmed dx of dilated cardiomyopathy, no intercurrent illnesses limiting life expectancy, sinus rhythm at initial presentation Mean age 55, 77% male 18 month follow up	Endpoints included: sudden death, cardiac arrest due to VF, or hemodynamically unstable VT or VF Diagnostic tools included: MTWA, LVEF, BRS, SAE, SDNN, IVCD, NSVT Sn, Sp, PPV, NPV, RR computed	MTWA pos in 48%, neg in 25%, indeterminate in 27% of participants Multivariate analysis revealed that MTWA was the only statistically signif predictor of arrhythmic events (Chi-square 3.67) For MTWA, Sn-87% Sp=38% PPV=22% NPV=94% RR=3.4 For SAE, Sn=47% Sp=63% PPV=17% NPV=88% RR=1.4 For LVEF, Sn=80% Sp=21% PPV=15% NPV=8.6% RR=1.0	

Kitamira, Ohnishi, Okajima, Ishida, Galeano, Adachi, Yokoyama 2002	Prospective observational	104 patients with dilated cardiomyopathy (84 males) with mean age 52 24 pts Group A 22 pts Group B	Endpoints include SCD, SVT, VF Diagnostic tools included: MTWA, LVEF, SAE, LVDd	Of the 104 patients, 46 were pos for MTWA, 37 were neg, 21 were indeterminate 83 of 104 were reported at follow up For Group A MTWA pos, there were 9 cardiac events; for Group B MTWA pos, there were 2 cardiac events; for indeterminate there was 1 cardiac event Determination of OHR in combination w/MTWA can identify the high risk subgroup among the 83 pts with dilated cardiomyopathy. Cox hazard analysis revealed that MTWA with an OHR ≤ 100 bpm, and LVEF were independent predictors of arrhythmic events.	Results are based on 83 pts (20% of pts lost to follow up) Low number of arrhythmic events could skew data Cut-off for OHR ≤ 100 bpm needs to be validated Sn, Sp, PPV, NPV not used.
Adachi, Ohnishi, Yokoyama 2001	Prospective observational	82 consecutive pts, mean age 53, 81% male 10 participants in Group A (high risk) 54 participants in Group B (low risk)	Endpts include SCD, SVT, VF Diagnostic tools included MTWA, LVEF, SAE, LVDd, NSVT, QTd	Participants in Group A had more arrhythmic events that those in Group B (90% v 39%) Combination of LVEF ≤ 35% and MTWA	

				were the only statistically signif independent predictors of arrhythmic risk For MTWA, Sn=90% Sp=61% PPV=30% NPV=97% RR=10.2 For SAE, Sn=40% Sp=80% PPV=27% NPV=88% RR=2.2 For LVEF, Sn=70% Sp=80% PPV=39% NPV=93% RR=6	
Momiyama, Hartikainen, Nagayoshi, Albrecht, Kautzner, Saumarez, McKenna, Camm 1997	14 pts with HCM were compared to 9 controls Risk stratification for VTEs made before the study, based on adverse fam hx, detection of VT on ambulatory EKG, and the findings of paced ventriculograms	7 high risk (mean age 32), 7 low risk (mean age 31) and 9 control (mean age 34) Approx equal males:females	MTWA used as diagnostic tool Endpoints included VTEs	Alternans voltage higher in the high risk compared to low risk and control groups (2.8 v 0.6 v 0.3 respectively) In the high risk group the median alternans ratio was also higher that the low risk and controls (3.9 v 0.6 v 0.3 respectively) Of the 7 high risk pts, 5 (71%) had signof alternans	Small sample size Sn, Sp, PPV, NPV not used
Ikeda, Sakata, Takami, Kondo, Tezuka, Nakae, Noro,	Prospective with consecutive pts	102 pts adm to CCU between Feb 1997 and Nov 1998 with MI dx	Late potentials analyzed using SAE, MTWA, and LVEF were used as	MTWA present in 49% of pts, while LP and reduced EF were present in	Small sample size

Enjoji, Abe, Sugi 2000		Mean age 61.6	measures Arrhythmic events (spont vent arrhythmias, sustained ventricular arrhythmias, non-sustained ventricular arrhythmias, and ventricular fibrillation Diag measures inclue Sn, Sp, PPV, NPV, hazard ratio (RH)	21% and 27% of pts respectively. During the followup period, VTE occurred in 15% of pts. Event rates were signif higher in pts w/MTWA, LP, or decreased EF. For MTWA, Sn=93% Sp=59% PPV=28% NPV=98% RH=16.8 For LP, Sn=53% Sp=85% PPV=38% NPV=91% RH=5.7 For EF, Sn=60% Sp=78% PPV=32% NPV = 92% RH=4.7	
Ikeda, Saito, Tanno, Shiizu, Watanabe, Ohnishi, Kasamaki, Ozawa 2002	Prospective with consecutive enrollment	850 initially enrolled, but only 834 included in study Mean age 70	Endpoints include SCD, resuscitated VF, sustained VF Outcome measures include MTWA, EF, LP Diag measures include Sn, Sp, PPV, NPV, RH	MTWA positive in 36%, neg in 52%, indeterminate in 12%. EF abnl in 18%, and LP was pos in 18%. For MTWA, Sn=92% Sp=61% PPV=7% NPV=99% RH=11.4 For EF, Sn=56% Sp=83% PPV=9% NPV=98% RH=6.6	Heart rate variability was not included

				For MTWA/EF, Sn=52% Sp=92% PPV=8% NPV=98% RH=11.9 For LP, Sn=50% Sp=84% PPV=10% NPV=98% RH=5.2	
Bloomfield, Steinman, Namerow, Parides, Dividenko, Russo, Tang, Bigger 2004	Epidemiological study with samples from 11 clinical centers in the US	549 subjects, had to be 18 or older with LVEF ≤ 40% and no prior hx of arrhythmic event 177 had MADIT-II-like characteristics Patients with atrial fib or flutter were excluded	All-cause mortality endpoint MTWA and QRS duration were measures	For all MADIT II-like pts, actuarial 2-year mortality was 13.2%. Based on 2-yr actuarial mortality data, pts w/abnl MTWA (17.8%) had a higher mortality rate than pts w/nl MTWA. For MTWA, actuarial mortality was 17.8% for abnl test, 3.8% for nl test, hazard ratio 4.8; 32.2% were classified as low risk. False neg rate 3.5% For QRS duration, actuarial mortality was 15.9% for abnl test, 12% for nl test. , hazard ratio 1.5; 68.2% of pts were classified as low risk. False neg rate 10.2%	Accuracy measures such as Sn, SP, PPV, NPV not used
Cohen 2003	Review	9 studies included Study size ranged	VTE endpoints MTWA was the	RR ranged btwn 1.4 and 16.8	No inclusion criteria included in

		from 82-834. Follow up period ranfged from 13-72 mos. Population suffered from variety of conditions: MI, CHF, dilated cardiomyopathy, referred for electrophysiologic studies.	only outcome measure mentioned RR was the measure of association measured	According to the aauthor MTWA was shown to be effective across a number of pt populations	selecting the articles to review. Sn, SP, PPV, NPV not reported
Hohnloser, Ikeda, Bloomfield, Dabbous, Cohen 2003	Subgroup analysis of 2 prior studies (Ikeda et al 2002 and Klingenheben et al 2000) which evaluated the used of MTWA in MADIT II type pts	129 pts, all w/prior MI and EF ≤ 30%; 112 males, mean age 63, mean duration of follow up 16 mos	SCD was endpt MTWA was the only outcome measure	Mortality rate among pts w/neg MTWA was 42% lower than among the non-neg pts. No SCD in pts w/neg MTWA test, but 10 pts pos for MTWA and 2 pts indeterminate for MTWA had cardiac events	Sn, SP, PPV, NPV not included
Grimm, Christ, Bach, Muller, Maisch 2003	Prospective observational, with enrollment between March 1996 and June 2001 (MACAS study)	343 participants, including 263 w/sinus rhythm and 80 with a-fib at study entry. Follow up for 52 mos Men and women between 16 and 70 w/ICDs and LV end-diast diam 56 mm by echo. Exclusions include hx of NYHA Class IV, hx of sustained VT or VF, CAD (50% stenosis by angiogram), hx of MI, HBP	VTEs and SCDs were the endpoints Diag tests include: LVEF and size, QTc dispersion, SAE, arrhythmias on Holter, heart rate variability, baroflex sensitivity, MTWA	46 pts (13%) experienced sustained VT, VF, or SCD. On multivariate analysis, LVEF was the only signif arrhythmia risk predictor in pts w/sinus rhythm (RR of 2.3 per 10% decrease in EF) On multivariate analysis, LVEF was also the only signif predictor in pts with heart transplant (RR of 2.51 per 10% decrease in EF) MTWA did not	Pts w/ NYHA Class IV were excluded (other studies included Class III and Class IV pts) Pts w/CAD were excluded (most other studies included pts w/MI) Sn. Sp, PPV, NPV not done

				seem to be helpful for arrhythmia risk stratification	