Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med 2007;357:2657-65.

ELECTRONIC SUPPLEMENTARY APPENDIX

***Author Contributions*:** The contributions to this manuscript by the various authors included those who designed the study (M.E.J.), gathered the data (All Authors), analyzed the data (M.R.R., K.J.), vouch for the data and analysis (V.Y.R., M.E.J., P.N., M.R.R.), wrote the paper (V.Y.R., M.E.J.), and decided to publish the paper (All Authors).

***Catheter Ablation Procedure*:** Conscious sedation anesthesia was administered according to standard lab protocol. After femoral vascular access had been achieved, the procedure was divided into 3 steps: 1) induction of VT, 2) localization of the myocardial infarct, and 3) targeting the "arrhythmogenic portions" of the infarct for catheter ablation. Programmed stimulation was performed using up to triple extrastimuli and rapid pacing from the right ventricular apex, right ventricular outflow tract or left ventricle. If only VF or polymorphic VT was inducible, stimulation was repeated after first infusing a Class I antiarrhythmic drug intravenously (Procainamide or Ajmaline). VT was repeatedly induced until either the same VT morphology was induced, or the patient required multiple shocks to terminate induced rhythms during the procedure. Electrocardiograms were obtained for all inducible arrhythmias.

Electroanatomical substrate mapping using the CARTO system (Biosense-Webster, Inc., Diamond Bar, CA) was performed using the retrograde aortic and/or transseptal approaches during sinus rhythm or, if AV conduction was not present, ventricular pacing. This mapping system uses a low intensity magnetic field to localize and guide the intracardiac mapping/ablation catheter.[1] During catheter manipulation,

bipolar contact electrograms were recorded and used to create a 3-dimensional map of the chamber based on the voltage amplitude.

Once the substrate map was constructed, a number of strategies were employed to identify those regions of the infarct that represented the arrhythmogenic tissue to target for catheter ablation (see **Figure A1**).[2-4] One was pace-mapping during sinus rhythm/ventricular pacing along the infarct border – as defined by the 1.0 – 1.5 mV voltage zone. The site with a paced 12-lead QRS morphology similar to an inducible monomorphic VT was assumed to be the exit site of that particular VT. At each such exit site, linear bisecting ablation lesions were made: one from the exit site toward the center of the substrate, and the second along the scar border zone perpendicular to the first line. Each line was composed of multiple sequential lesions placed ~5 mm apart. Particular care was taken to minimize any potential adverse effect on ventricular function and as such, all lesions were made at the ≤ 1.0 mV border. In patients with severe ventricular dysfunction, a second strategy including targeting late / fractionated potentials deeper within the scar was used. Entrainment was attempted if monomorphic VT was at least transiently hemodynamically stable. In the setting of a smaller identifiable infarct with poor pacemap sites and no late potentials, catheter-based ablation lesions were placed completely around the scar.

Of note, pace mapping is limited by the fact that it is performed during sinus rhythm and only gives a general idea of where the VT is exiting from the scar. Unlike entrainment mapping, which is performed during VT, one does not gain definitive information about whether a particular site is within a critical portion of a VT circuit. Instead, the “good” pacemap site gives a general idea of where the VT exits, and based

upon this information, the operator makes targeted lesions to transect a critical portion of the circuit. This is a probabilistic approach to VT ablation with limitations, but it has the advantage of being performed in sinus rhythm – thereby allowing the operator to target even hemodynamically unstable VTs.

Catheter mapping and radiofrequency ablation was performed using either the Navistar 4mm-tip standard or the Thermocool 3.5mm-tip saline-irrigated catheter (Biosense-Webster, Inc., Diamond Bar, CA). When using the latter, saline was infused at 2 ml/min during mapping and 30 ml/min during ablation. In the U.S., the irrigated catheter was not used because it had not been approved for clinical use until after the end of enrollment. Intravenous heparin was administered to achieve an activated clotting time > 220 seconds. Programmed stimulation was repeated at the end of the procedure.

APPENDIX – RESULTS

Given the imbalance in some baseline characteristics (as shown in Table 1 of the manuscript), a multivariate analysis was performed to correct for all of the baseline features of the patients in the trial. The result is shown in the attached **Table A**. This model, which included all baseline characteristics and therapies, yielded an adjusted hazard ratio for catheter ablation versus no ablation of 0.31 (95% CI 0.13-0.76), and a multivariate p-value of 0.01. Alternative models with fewer covariates were also explored; in no case did the hazard ratio for catheter ablation exceed 0.36 or the p-value exceed 0.02 (data not shown). This confirmatory analysis further strengthens the evidence for a significant effect of catheter ablation.

REFERENCES

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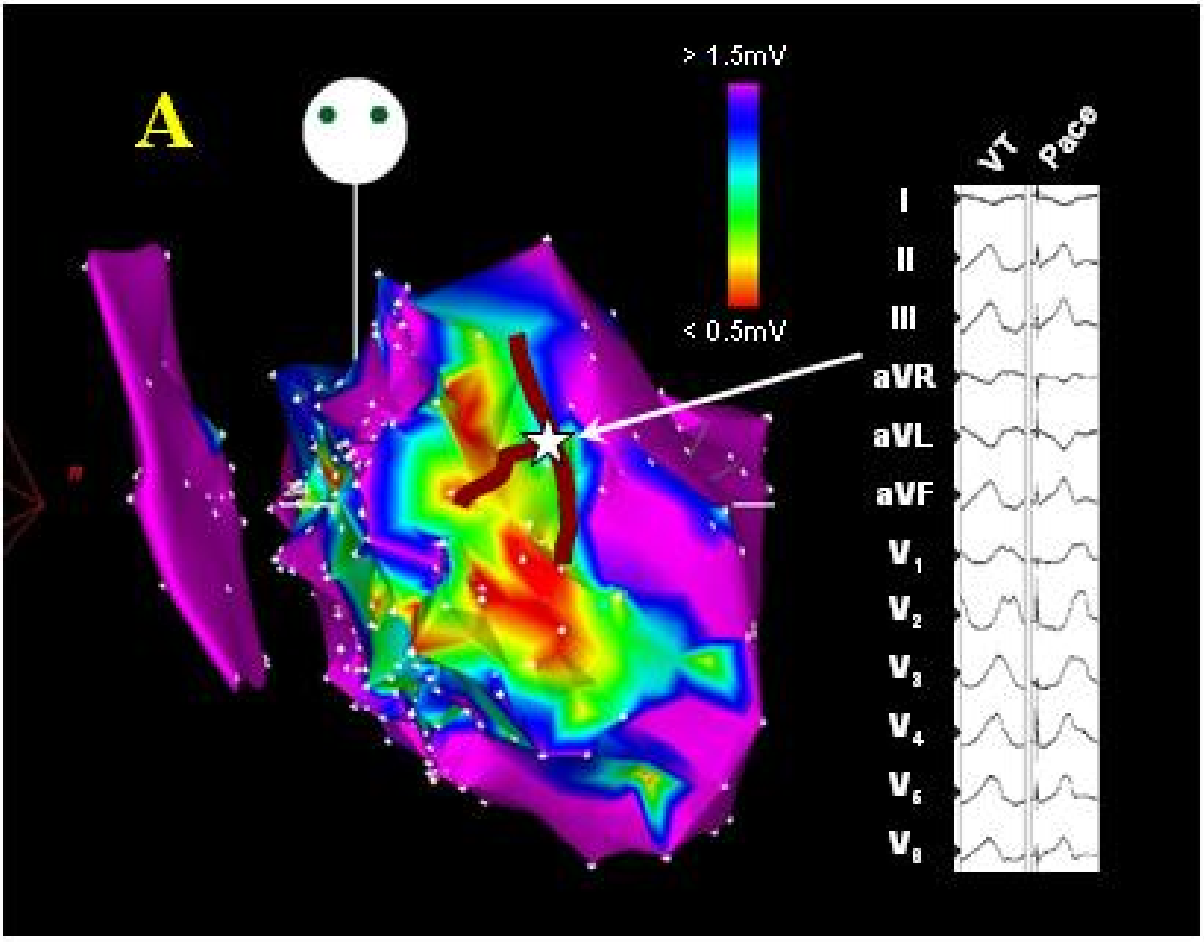
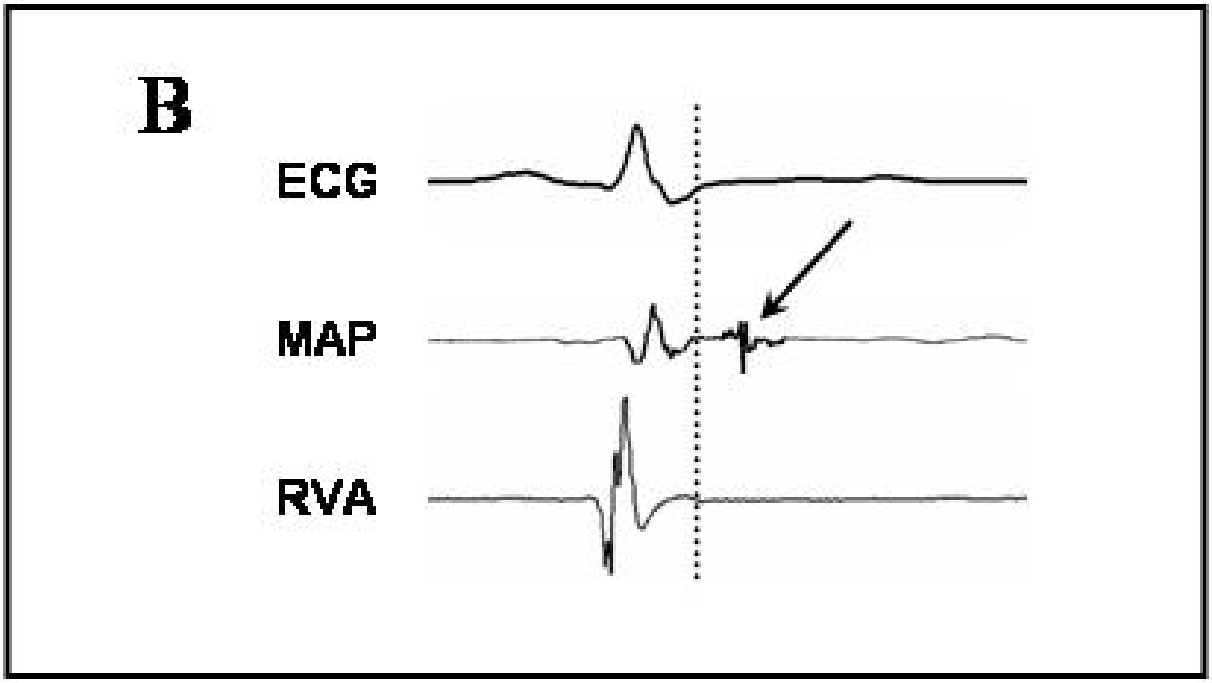
FIGURE LEGEND

Figure A1. ***Strategies Employed during the Ablation Procedure.*** (**A**) An electroanatomical map of the left ventricular endocardium and a portion of the right ventricular surface of the septum is created by catheter mapping during sinus rhythm. The amplitude of the bipolar electrogram serves as a surrogate for the health of the tissue. The spectrum ranges from purple, representing normal tissue (electrogram amplitude > 1.5 mV) through blue, green and yellow to red, representing the most severely diseased tissue (electrogram amplitude < 0.5 mV). By pacing along the borders of this antero-apical infarct during sinus rhythm, the exit site of the target VT morphology (white star) can be identified. A pair of linear lesions is then placed to empirically transect the putative tachycardia circuit (red lines). (**B**) Other targets within the myocardial infarct include late potentials, which represent channels of activity within the scar. As shown on the electrogram recorded by the mapping catheter (MAP), a late potential (arrow) is characterized by discrete electrical activity after the surface QRS complex. For comparison, a normal electrogram is seen from a catheter placed at the apex of the right ventricle (RVA). Particularly in patients with severe ventricular dysfunction, regions in which such late potentials were identified were targeted for ablation.

Table A. ***Multivariable Cox Proportional Hazards Model***. After adjustment for baseline patient characteristics and medication use, Ablation Group remained the only factor significantly associated with the outcome of Any ICD Rx with a p-value of 0.01. No other variable had a statistically significant relationship with this outcome.

Variable	p-value	Hazard Ratio	HR 95% CI	
Group	0.0107	0.308	0.125	0.760
Age	0.4842	0.984	0.939	1.030
Baseline ASA	0.9762	0.987	0.414	2.350
Baseline statin	0.5247	1.379	0.512	3.716
Gender (women vs. men)	0.7148	0.803	0.248	2.602
NYHA Class (III/IV vs I/II)	0.3836	1.521	0.592	3.907
Hypertension	0.8758	0.932	0.386	2.250
Prior revascularization	0.7694	1.141	0.471	2.764
History of CVA	0.5491	0.625	0.134	2.908
ICD (dual vs. single chamber)	0.3666	0.662	0.271	1.620
Ejection fraction (each 1%)	0.4124	0.980	0.934	1.029
Baseline beta-blocker	0.9729	0.961	0.094	9.771
Baseline ACE/ARB	0.2558	3.446	0.408	29.105
Diabetes Mellitus	0.8753	1.068	0.471	2.423
VF event (vs. VT)	0.2736	0.418	0.088	1.992
Syncope (vs. VT)	0.3479	0.568	0.174	1.851
Old ICD (vs. VT)	0.6966	0.829	0.322	2.130


A
> 1.5mV
< 0.5mV
VT
Pace
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6


B
ECG
MAP
RVA