Online Appendix for the following article in the European Heart Journal:

Predicted Benefit of the Implantable Cardioverter-Defibrillator: The MADIT-ICD Benefit Score

Arwa Younis[1], MD, Jeffrey J. Goldberger[2], MD, Valentina Kutyifa[1], MD, PhD, Wojciech Zareba[1], MD, PhD, Helmut Klein[1], MD, Mehmet K. Aktas[1], MD, MBA, David Huang[1], MD, James Daubert[3], MD, Mark Estes[4], MD, David Cannom,[5] MD, Scott McNitt[1], Bronislava Polonsky[1], MS, Ilan Goldenberg[1,] MD

1. Clinical Cardiovascular Research Center, University of Rochester, NY, USA
2. Miller School of Medicine, University of Miami, Miami, FL, USA
3. Division of Cardiology, Duke University, Durham, NC, USA
4. University of Pittsburgh Medical Center, Pittsburgh, PA, USA
5. Good Samaritan Hospital, Los Angeles, CA

INDEX

Online Supplementary Table A - List of the Multicenter Automatic Defibrillator Implantation Trials (MADIT)

Trial name	Year	Number of subjects	Study population	Enrollment criteria	Randomization	Mean follow up duration (years)
MADIT II	2002	1232	ICM	Prior MI LVEF ≤30%	ICD versus medical therapy	2
MADIT Risk	2005	765	ICM	Prior MI LVEF ≤30%	ICD arm only	2
MADIT CRT	2009	1820	ICM and non-ICM	NYHA I or II LVEF ≤30% QRS ≥130 ms	CRT-D versus ICD	2.4
MADIT RIT	2012	1500	ICM and non-ICM	Patients who met primary prevention critieria for ICD implantation	Three arms based on programming: i. Conventional ii. High rate cuttoff iii. Delay in therapy	1.4
RAID	2017	1012	ICM and non-ICM	Patients with ICD or CRT-D	Ranolazine vs. Placebo	2.3

Online Supplementary Table B - Arrhythmia definition by the adjudication committee per protocol.

Trial name	Arrhythmia definition according to the study protocol
MADIT II, MADIT RISK and MADIT CRT	Devices were programmed to monitor + therapy, with a protocol recommendation to a setting of the VT zone at 180 bpm and the VF zone at 250 bpm. Sensitivity was programmed according to physician discretion. Detection was 2.5 seconds for the VT zone and 1.0 second for the VF zone. The protocol recommended programming the VT zone first therapy to burst-type antitachycardia pacing with 8 pulses at 88% of the measured cycle length with a 10-ms decrement between bursts, then shock therapy; second therapy should be shock at the defibrillation threshold plus at least 10 J (if possible). The remaining therapies should be maximal energy shocks. The ICDs were interrogated quarterly. All Events were adjudicated blindly by at least 2 committee members.
MADIT RIT	1. VT – based on combined evaluation of frequency, QRS morphology, and regularity of the rhythm. Has to last for more than 30 beats, or if therapy was administered and terminated arrhythmia. (Includes polymorphic VT). Detection zone was 145 bpm in all treatment arms. 2. VF – based on combined evaluation of frequency (>200 BPM), QRS morphology, and regularity of the rhythm.

Online Supplementary Table C - List of Variables that were included in the Fine and Gray models.

Age at enrollment dichotomized at 65 years
Atrial arrhythmia[ǂ]
Female
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker
Beta-blocker
Diuretic
Amiodarone
Aspirin
Body mass index at enrollment dichotomized at 23 kg/m^2 (lowest quartile)
Body mass index at enrollment dichotomized at 30 kg/m^2
Cardiac resynchronization therapy
Left ventricular ejection fraction dichotomized at 25%
Heart rate dichotomized at 75 bpm
Age at enrollment dichotomized at 75 years
Heart rate dichotomized at 70 bpm
Systolic blood pressure dichotomized at 120 mmHg
Diastolic blood pressure dichotomized at 80 mmHg
Hypertension
Prior coronary artery bypass grafting
Prior percutaneous coronary intervention (balloon and/or stent)
Diabetes
New York Heart Association functional class ≥II
Previous smoking
Prior non-sustained ventricular tachycardia[♯]
Prior clinical myocardial infarction*
Hispanic ethnicity
Ischemic cardiomyopathy^

ǂ Any atrial arrhythmia (beside sinus tachycardia) requiring medical treatment (drugs or ablation).

♯ Non-sustained ventricular tachycardia (<30 seconds) requiring medical treatment (drugs or ablation).

* Symptomatic clinical myocardial infarction with enzyme positive or ECG positive presentation, more than 90 days before enrollment.

^ Ischemic cardiomyopathy was defined as; a documented (Q-wave, enzyme-positive, radiological evidence) of prior myocardial infarction more than 90 days before enrollment, and/or one or more prior coronary artery bypass graft surgeries or percutaneous coronary interventions (ballon and/or stent angioplasty) more than 90 days before enrollment.

Online Supplementary Table D – Baseline Characteristics of RAID Cohort.

Clinical Characteristics	No. (%)/ or Mean ± stdv
Number of Patients, #	669
Ranolazine treatment	337(50)
Age at enrollment	64.0±10.1
Ischemic Cardiomyopathy	340(51)
NYHA Class: I/II	454(70)
NYHA Class: III	189(30)
Hypertension	523(79)
Diabetes	251(38)
Atrial Fibrillation	160(24)
Left ventricular ejection fraction (%)	28.1±9.1
QRS duration (ms)	134.3±31.1
ICD	315(47)
CRT-D	354(53)
Serum creatinine (mg/dl)	1.1±0.3
GFR mL/min/1.73 m2	74.8±23.9
B-type natriuretic peptide (pg/ml)	1417.3±1996.6
Beta Blockers	631(94)
ACE/ARBs	585(88)
Statins	485(73)
Digitalis	130(19)
Diuretics	541(81)
Mineralocorticoid antagonists	269(40)
Amiodarone	55(8)
Metformin	118(18)

Online supplementary Table E – Number of patients, their frequency, and the corresponding VT/VF Risk-Score group.

VT/VF Risk-Score group	Score points	Number of patients	Percent	Cumulative number of Patients	Cumulative Percentage
Low (<7)	**0**	6	0.15	6	0.15
	1	14	0.35	20	0.50
	2	102	2.54	122	3.04
	3	100	2.49	222	5.52
	4	399	9.93	621	15.45
	5	365	9.08	986	24.53
	6	763	18.98	1749	43.52
High (≥7)	**7**	575	14.31	2324	57.83
	8	770	19.16	3094	76.98
	9	548	13.64	3642	90.62
	10	271	6.74	3913	97.36
	11	84	2.09	3997	99.45
	12	21	0.52	4018	99.98
	13	1	0.02	4019	100.00

Online Supplementary Table F – Number of Patients, their Frequency, and the Corresponding Non-arrhythmic Mortality Risk Group

Non-arrhythmic Mortality Risk Group	Points	Number of Patients	Percent	Cumulative Number	Cumulative Percentage
Low (≤2)	**-1**	48	1.18	48	1.18
	0	389	9.60	437	10.78
	1	647	15.96	1084	26.75
	2	782	19.29	1866	46.04
High (≥3)	**3**	781	19.27	2647	65.31
	4	629	15.52	3276	80.83
	5	417	10.29	3693	91.12
	6	360	8.87	4053	100.00

MADIT-ICD Benefit Score Matrix –

VTVF Score	Mortality Score	Benefit Score	ICD Benefit Group	VTVF Score	Mortality Score	Benefit Score	ICD Benefit Group	VTVF Score	Mortality Score	Benefit Score	ICD Benefit Group
0	≥6	0	Lowest	2	1	34	Intermediate	11	4	67	Intermediate
0	5	1	Lowest	2	0	35	Intermediate	11	3	68	Intermediate
0	4	2	Lowest	2	-1	36	Intermediate	12	≥6	69	Intermediate
0	3	3	Lowest	3	2	37	Intermediate	12	5	70	Intermediate
1	≥6	4	Lowest	3	1	38	Intermediate	12	4	71	Intermediate
1	5	5	Lowest	3	0	38	Intermediate	12	3	71	Intermediate
1	4	6	Lowest	3	-1	39	Intermediate	13	≥6	72	Intermediate
1	3	7	Lowest	4	2	40	Intermediate	13	5	73	Intermediate
2	≥6	8	Lowest	4	1	41	Intermediate	13	4	74	Intermediate
2	5	9	Lowest	4	0	42	Intermediate	13	3	75	Intermediate
2	4	10	Lowest	4	-1	43	Intermediate	7	2	76	Highest
2	3	11	Lowest	5	2	44	Intermediate	7	1	77	Highest
3	≥6	12	Lowest	5	1	45	Intermediate	7	0	78	Highest
3	5	13	Lowest	5	0	46	Intermediate	7	-1	79	Highest
3	4	13	Lowest	5	-1	46	Intermediate	8	2	79	Highest
3	3	14	Lowest	6	2	47	Intermediate	8	1	80	Highest
4	≥6	15	Lowest	6	1	48	Intermediate	8	0	81	Highest
4	5	16	Lowest	6	0	49	Intermediate	8	-1	82	Highest
4	4	17	Lowest	6	-1	50	Intermediate	9	2	83	Highest
4	3	18	Lowest	7	≥6	51	Intermediate	9	1	84	Highest
5	≥6	19	Lowest	7	5	52	Intermediate	9	0	85	Highest
5	5	20	Lowest	7	4	53	Intermediate	9	-1	86	Highest
5	4	21	Lowest	7	3	54	Intermediate	10	2	87	Highest
5	3	21	Lowest	8	≥6	54	Intermediate	10	1	88	Highest
6	≥6	22	Lowest	8	5	55	Intermediate	10	0	88	Highest
6	5	23	Lowest	8	4	56	Intermediate	10	-1	89	Highest
6	4	24	Lowest	8	3	57	Intermediate	11	2	90	Highest
6	3	25	Lowest	9	≥6	58	Intermediate	11	1	91	Highest
0	2	26	Intermediate	9	5	59	Intermediate	11	0	92	Highest
0	1	27	Intermediate	9	4	60	Intermediate	11	-1	93	Highest
0	0	28	Intermediate	9	3	61	Intermediate	12	2	94	Highest
0	-1	29	Intermediate	10	≥6	62	Intermediate	12	1	95	Highest
1	2	29	Intermediate	10	5	63	Intermediate	12	≤0	96	Highest
1	1	30	Intermediate	10	4	63	Intermediate	13	2	97	Highest
1	0	31	Intermediate	10	3	64	Intermediate	13	1	98	Highest
1	-1	32	Intermediate	11	≥6	65	Intermediate	13	0	99	Highest
2	2	33	Intermediate	11	5	66	Intermediate	13	-1	100	Highest

How to calculate the MADIT-ICD Benefit Score -

The score can be calculated in 2 ways:

1. Using the free provided website (https://is.gd/madit)
2. Manually – 4 steps approach:

Step I) Calculate the VTVF Score (by adding the points of the variables found in Table 2):

VTVF Score [variable (given points if positive)]= LVEF≤25% (1) + ATA (1) + HR>75bpm (1) + SBP<140mmHg (2) + MI (2) + Age<75yrs (2) + Male (2) + NSVT (2) = Range 0 to 13 points

Step II) Calculate the Non-arrhythmic Mortality Score (by adding the points of the variables found in table 3):

Non-arrhythmic Mortality Score = ATA (2) + Diabetes (1) + BMI<23kg/m^2 (2) + NYHA≥II (1) + LVEF≤25% (2) + Age≥75yrs (2) – CRTD (1) = Range -1 to 10 points

Step III) The MADIT-ICD Benefit Group:

Find the Benefit Group and the estimated risk by performing cross tabulation using the graphical abstract main figure, or using the following "If statement":

- If VTVF Score ≥ 7 and Non-arrhythmic Mortality Score < 3 then Highest Benefit Group
- If VTVF Score ≥ 7 and Non-arrhythmic Mortality Score ≥ 3 then Intermediate Benefit Group
- If VTVF Score < 7 and Non-arrhythmic Mortality Score < 3 then Intermediate Benefit Group
- If VTVF Score < 7 and Non-arrhythmic Mortality Score ≥ 3 then Lowest Benefit Group

Step IV) The Numerical MADIT-ICD Benefit Score:

Find the corresponding score based on the Matrix found above (page 8).

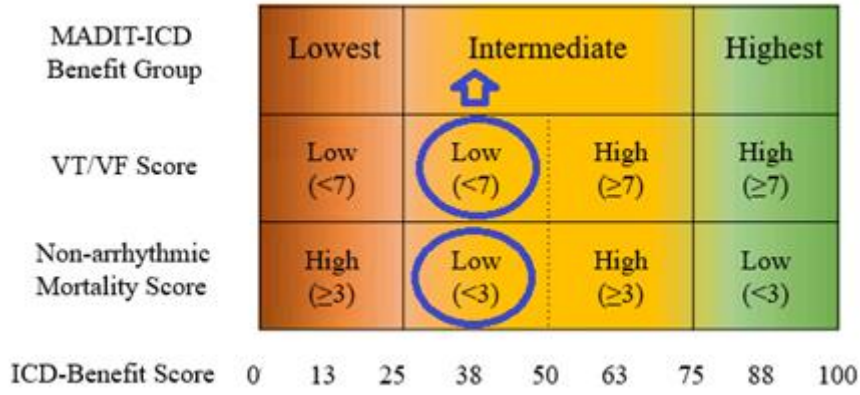
Example = Patient #1: Female, 67yrs, HR 72bpm, SBP 145mmHg, BMI 24kg/m^2, LVEF 28%, NYHA II, diabetes, and is not CRT-D candidate.

Step I) VTVF 2 points

Step II) Mortality 2 points

Step III) <u>The MADIT-ICD Benefit Group</u>

- **Cross tabulation using the graph:**



- **Cross tabulation using the "If statement"**:

In this case we will be using the third "If statement";
If VTVF Score < 7 and Non-arrhythmic Mortality Score < 3 then Intermediate Benefit Group

Step IV) Find the numerical MADIT-ICD Benefit Score and the corresponding predicted benefit using the Matrix.

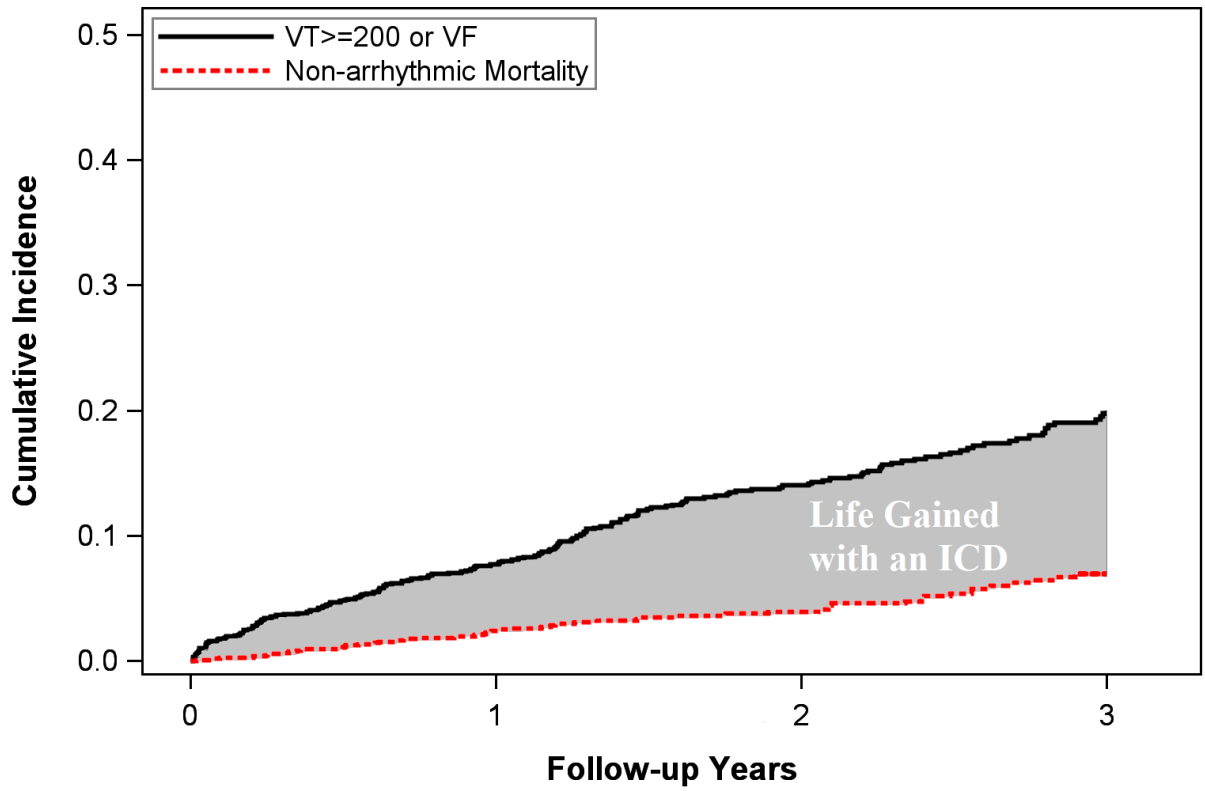
VTVF Score	Mortality Score	Benefit Score	ICD Benefit Group
1	-1	32	Intermediate
2	2	33	Intermediate
2	1	34	Intermediate
2	0	35	Intermediate

Accordingly, for this patient (VTVF score=2 and Non-arrhythmic Mortality Score=2) the predicted score of 33 (100 reflects highest benefit and 0 reflects lowest benefit)

Online Supplementary Table G – Life-gained with the ICD at Three Years' Time Post Implantation stratified by MADIT-ICD Benefit Group.

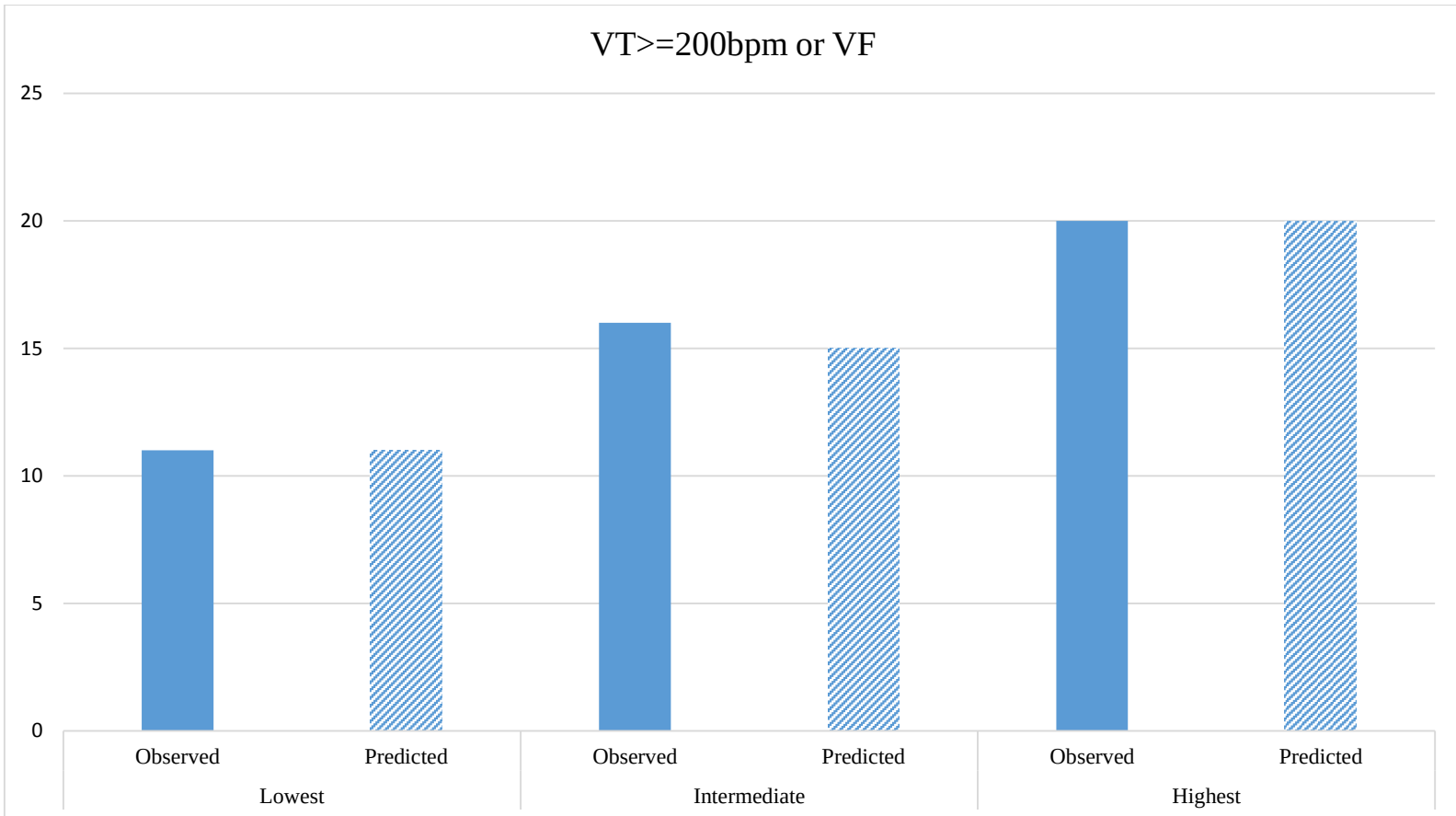
MADIT-ICD Benefit Group	Life Gained in Days		
	At 1 year	At 2 years	At 3 years
Highest	11	41	74
Intermediate	5	18	31
Lowest	3	4	6

Online Supplementary Figure A – Example for Life-Gain Estimation at Three Years

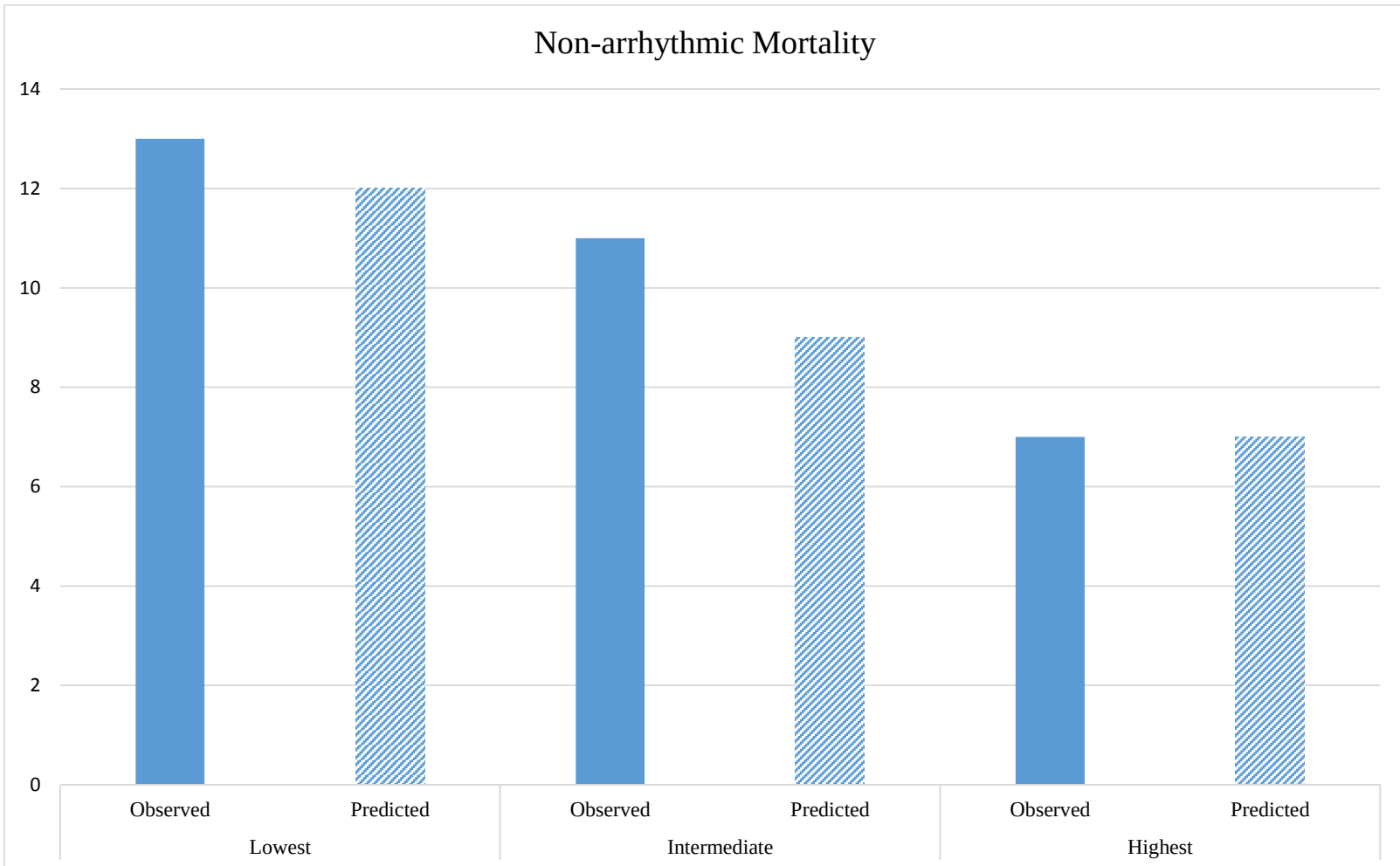


Online Supplementary Figure B – Comparison between the predicted and the observed rates for fast ventricular tachycardia (≥200 bpm or ventricular fibrillation) and non-arrhythmic mortality.

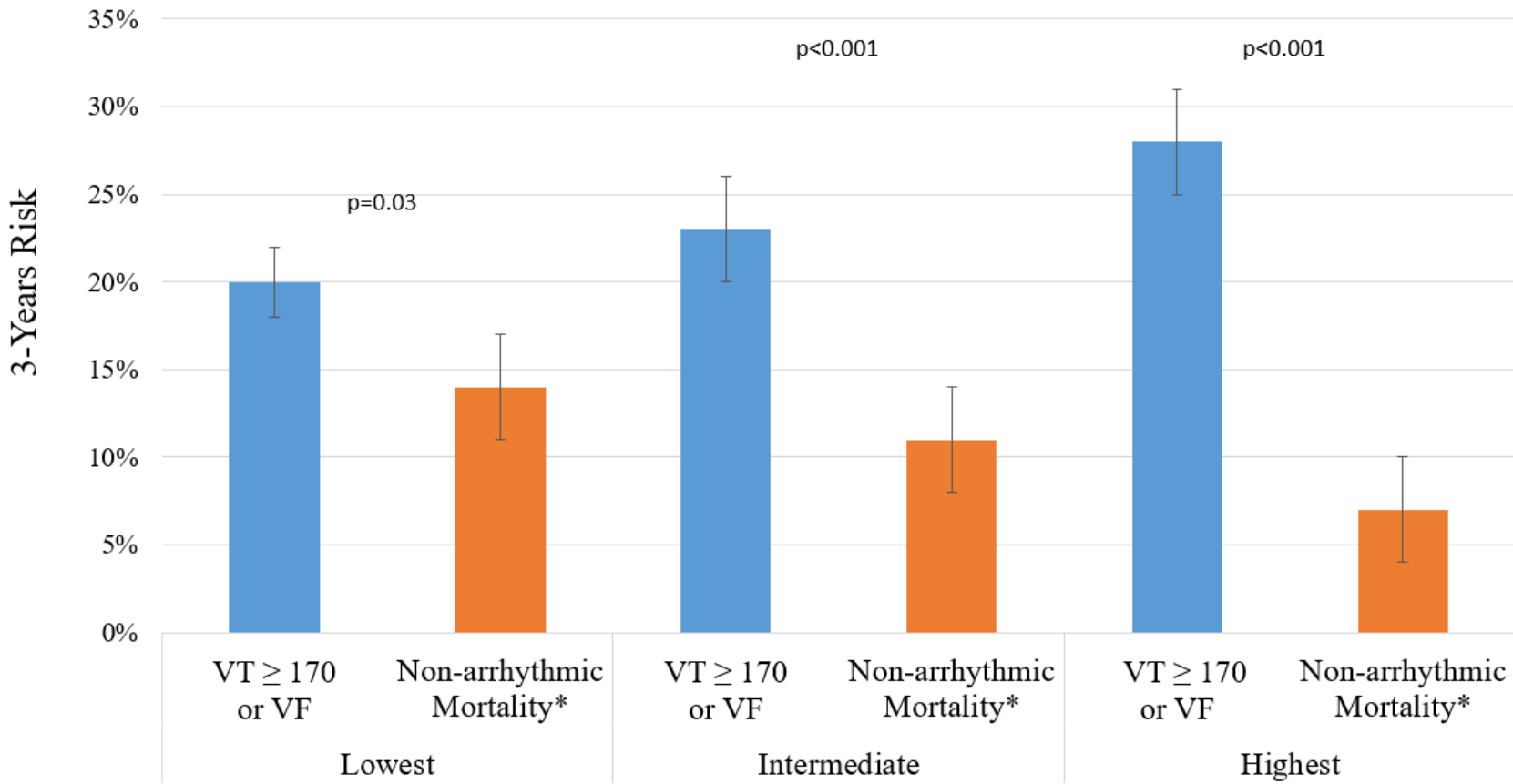
B1) VT≥200 or VF



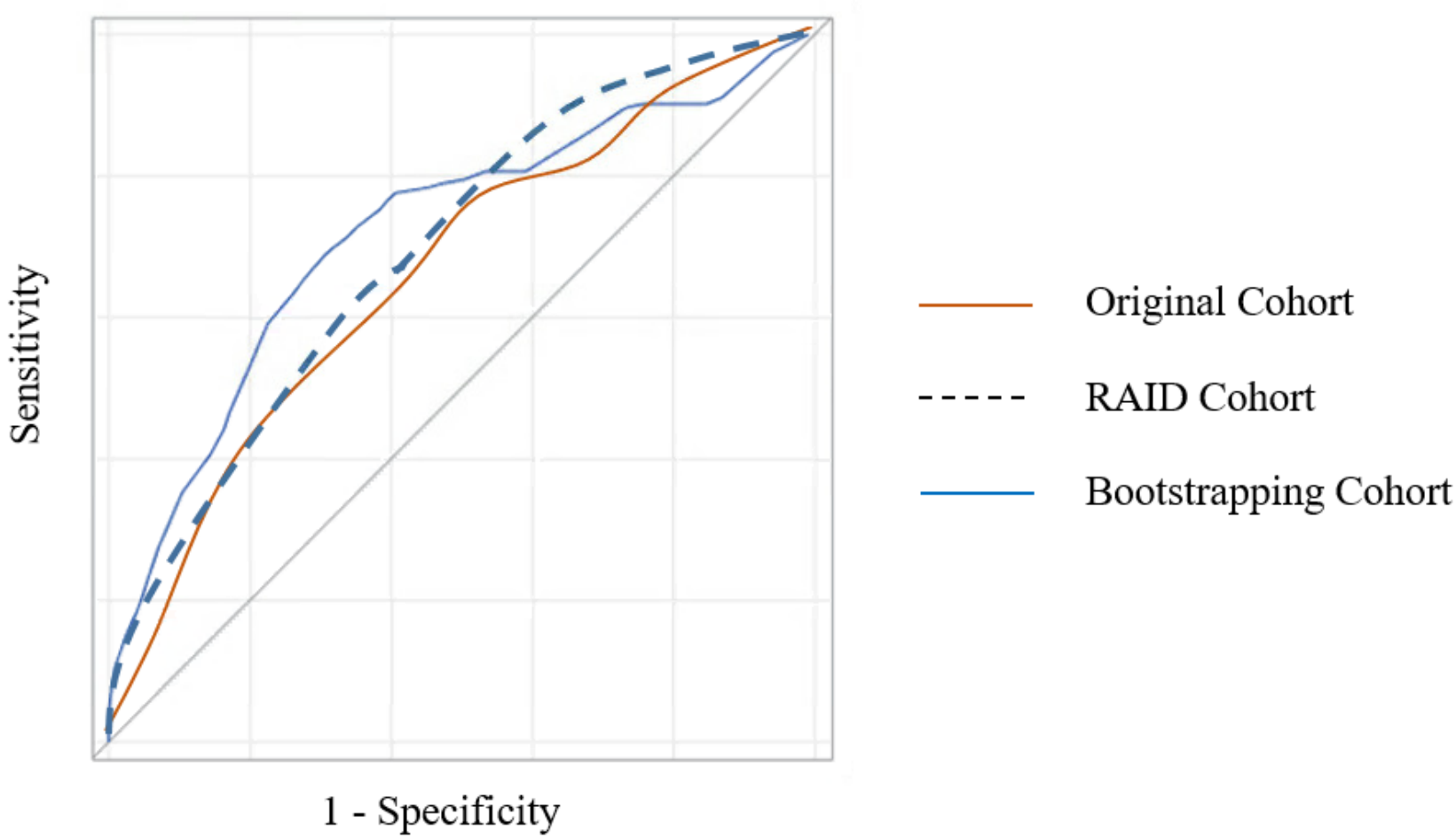
B2) Non-arrhythmic mortality



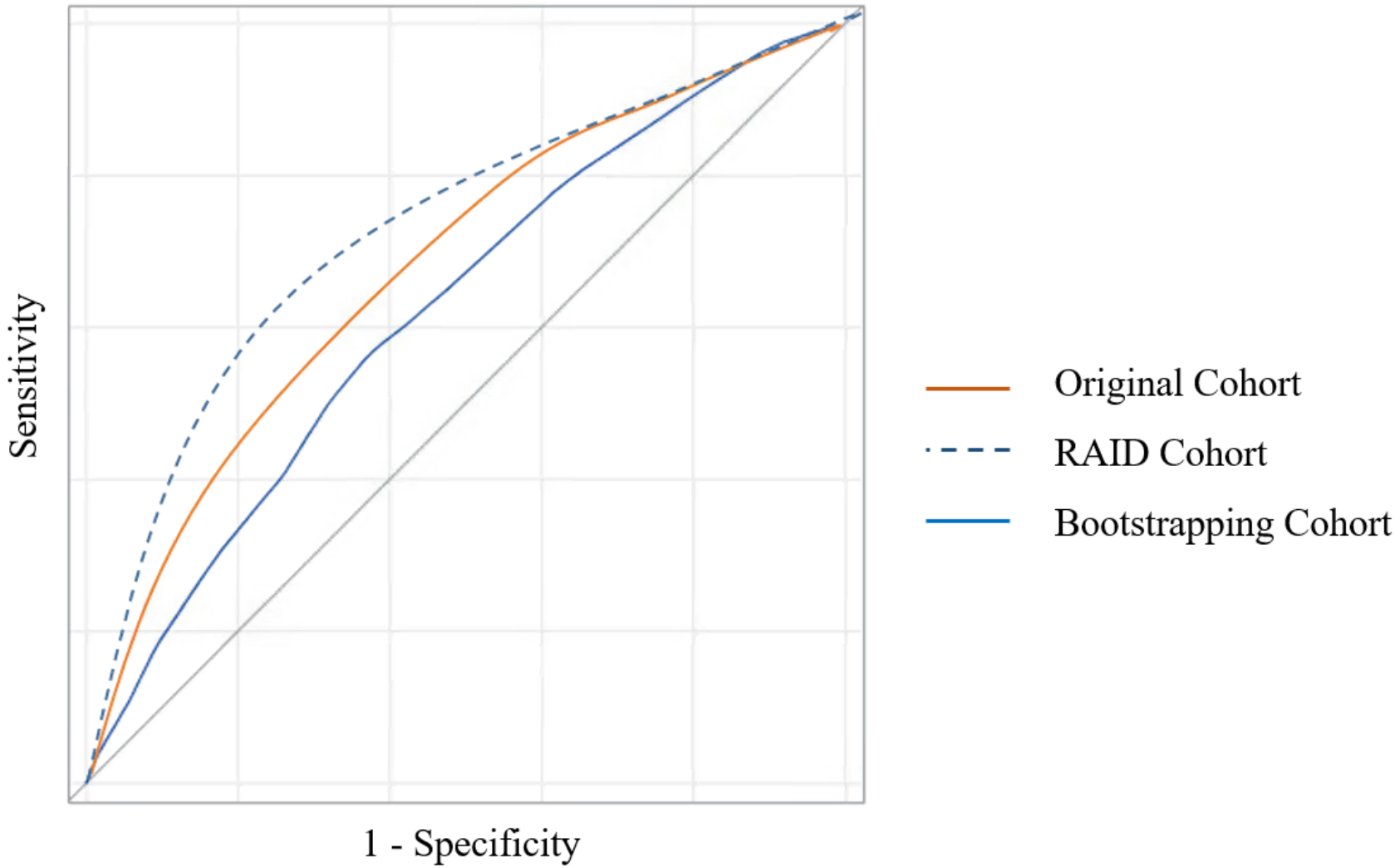
Online Supplementary Figure C – The Cumulative 3-Year Rates of Any Monitored/Treated Ventricular Tachycardia/Fibrillation (VT/VF) faster or equal to 170 bpm Compared with the Rates of Non-arrhythmic Mortality (Death without Prior VT/VF at a rate of ≥170 bpm) stratified by the MADIT-ICD Benefit Group.



Online Supplementary Figure D1 – Receiver Operating Characteristic Curve for the Non-arrhythmic Mortality Score (Death without prior Ventricular Tachy-Arrhythmia (VT/VF)) Risk-Score.



Online eFigure D2 – Receiver Operating Characteristic Curve for the Ventricular Tachy-Arrhythmia (VT≥200 bpm or VF) Risk-Score.



Word count

Abstract = 246

Text + references + figure legends + tables = 5380

Permissions information

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Ilan Goldenberg, MD

DISCLOSURE

Arwa Younis, Jeffrey J. Goldberger, Helmut Klein, Mehmet K. Aktas, David Huang, Scott McNitt, and Bronislava Polonsky – none

Valentina Kutyifa – has received research grants from Boston Scientific, Biotronik, and ZOLL Inc., Spire Inc., and has consultant agreements with ZOLL Inc., and Biotronik

Wojciech Zareba – research grants from Boston Scientific

James Daubert - research grants from Boston Scientific

Mark Estes - research grants from Boston Scientific, consulting Fees, Boston Scientific, Abbott, and Medtronic.

David Cannom - research grants from Boston Scientific

Kenneth Stein – Chief Medical Officer for Rhythm Management at *Boston Scientific*.

Ilan Goldenberg - research grants from Boston Scientific, Medtronic, Zoll