Can We Personalize Risk Stratification for Sudden Death?

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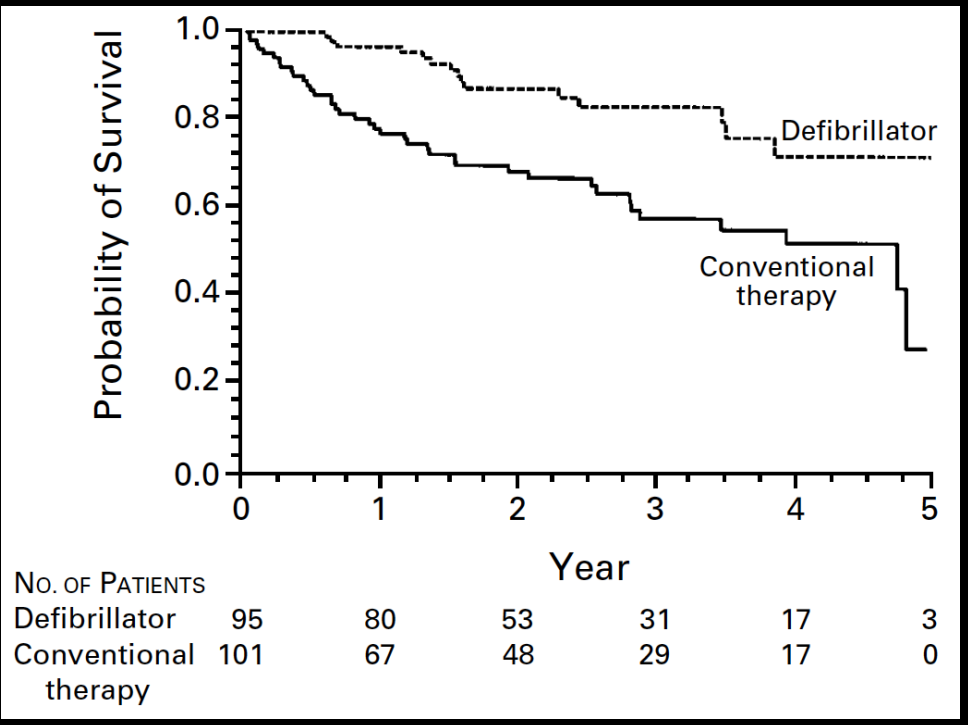
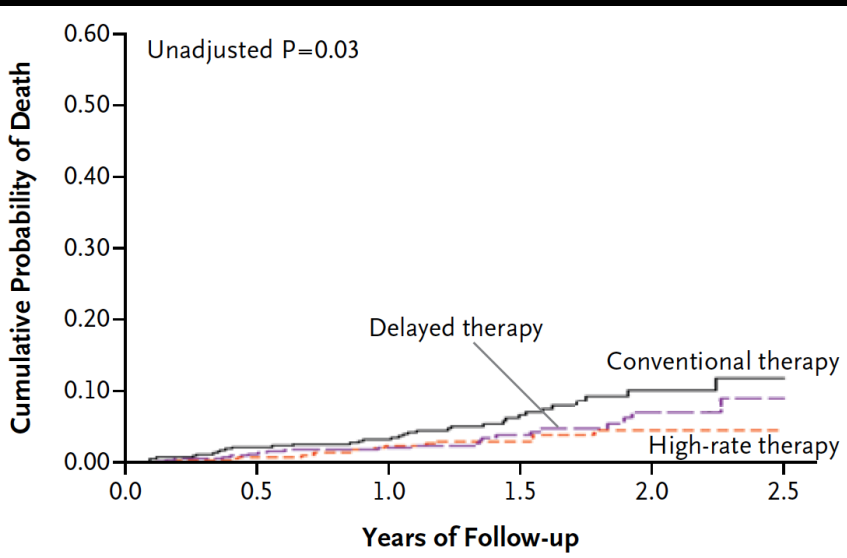
Guideline-based vs Individualized Care

- Individualized therapy
  - Human input – MD, patient preferences
  - Data – genetic, physiologic, other characteristics
- Guidelines
  - RCT to expert opinion – Quality of data
  - Trial design – adequate # of endpoints
    - Enrich population risk - trials on focused population have limited scope of applicability
    - Broad populations - may obscure interindividual differences that are important determinants of treatment outcome
  - RCTs report average effects – responders vs nonresponders
  - Reflect best known science, commonly changes

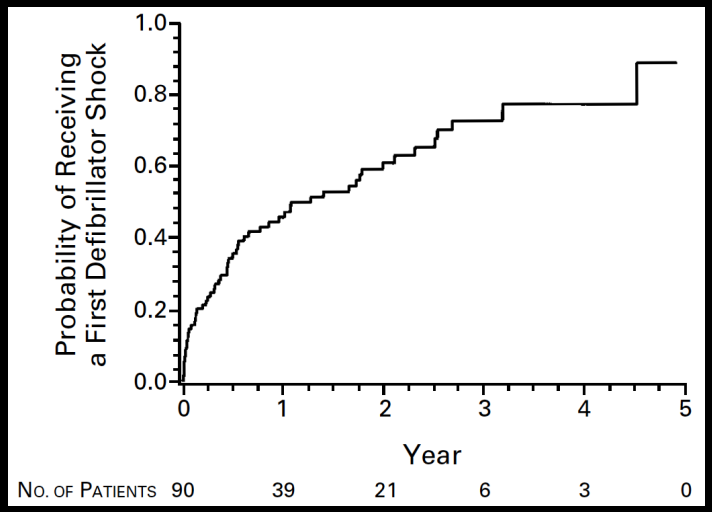
MADIT (1996) vs MADIT-RIT (2012)



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0



No. at Risk						
Conventional therapy	514	490 (0.02)	392 (0.03)	219 (0.07)	89 (0.10)	14 (0.12)
High-rate therapy	500	478 (0.01)	372 (0.02)	221 (0.03)	90 (0.05)	21 (0.05)
Delayed therapy	486	471 (0.01)	375 (0.02)	205 (0.04)	99 (0.07)	14 (0.09)



- **Average f/u 1.4 years**
- **Appropriate therapy – delayed group: 6%**

Changing face of ICD Therapy

- Less patients are getting shocked
- The vast majority of patients derive no benefit from their ICD
- The vast majority of patients who experience SCD still do not qualify for an ICD
- How can we do better?

The Old Paradigm of Risk Stratification

- Sick population – low EF
- Noninvasive risk markers
  - SAECG
  - HRV
  - TWA
  - VEA

Left Ventricular Ejection Fraction

References	Prior Probability (Incidence of MAE) (%)	No. of Patients	A Fo (r	TN	FP	Sensitivity	Specificity	Positive Predictive Accuracy	Relative Risk	Odds Ratio
				IES						
Bigger (40)	14.1	715		446	168	0.584	0.726	0.260	3.0	3.7
De Chillou (20)	7.4	244		188	38	0.556	0.832	0.208	5.1	6.2
Copie (47)	8.1	520		373	105	0.405	0.780	0.139	2.2	2.4
el-Sherif (22)	3.9	1,158		768	345	0.711	0.690	0.085	5.1	5.5
Farrell (23)	5.8	416		294	98	0.458	0.750	0.101	2.4	2.5
Gomes (24)	14.5	110		69	25	0.688	0.734	0.306	4.5	6.1
Hermosillo (25)	11.9	201		142	35	0.708	0.802	0.327	7.0	9.9
Hohnloser (41)	7.7	325		261	39	0.480	0.870	0.235	5.0	6.2
Iesaka (53)	8.3	133		106	16	0.545	0.869	0.273	6.1	8.0
Kuchar (27)	7.1	210		144	51	0.867	0.738	0.203	14.8	18.4
Lander (28)	9.2	173		121	36	0.563	0.771	0.200	3.7	4.3
La Rovere (43)	3.8	1,276		045	182	0.449	0.852	0.108	4.3	4.7
McClements (30)	4.0	300		233	55	0.750	0.809	0.141	11.1	12.7
Pedretti (32)	6.3	303		242	42	0.789	0.852	0.263	16.2	21.6
Richards (33)	4.9	347		243	87	0.706	0.736	0.121	6.0	6.7
Rodriguez (54)	17.4	190		124	33	0.455	0.790	0.313	2.5	3.1
Steinberg (36)	8.8	182		101	65	0.563	0.608	0.122	1.9	2.0
Strasberg (37)	12.0	100		69	19	0.417	0.784	0.208	2.3	2.6
Verzoni (38)	5.4	111		65	40	0.667	0.619	0.091	3.0	3.3
Zabel (55)	6.8	280		185	76	0.579	0.709	0.126	3.1	3.3
LVEF Total		7,294								

Relative Risk	Odds Ratio
3.0	3.7
5.1	6.2
2.2	2.4
5.1	5.5
2.4	2.5
4.5	6.1
7.0	9.9
5.0	6.2
6.1	8.0
14.8	18.4
3.7	4.3
4.3	4.7
11.1	12.7
16.2	21.6
6.0	6.7
2.5	3.1
1.9	2.0
2.3	2.6
3.0	3.3
3.1	3.3

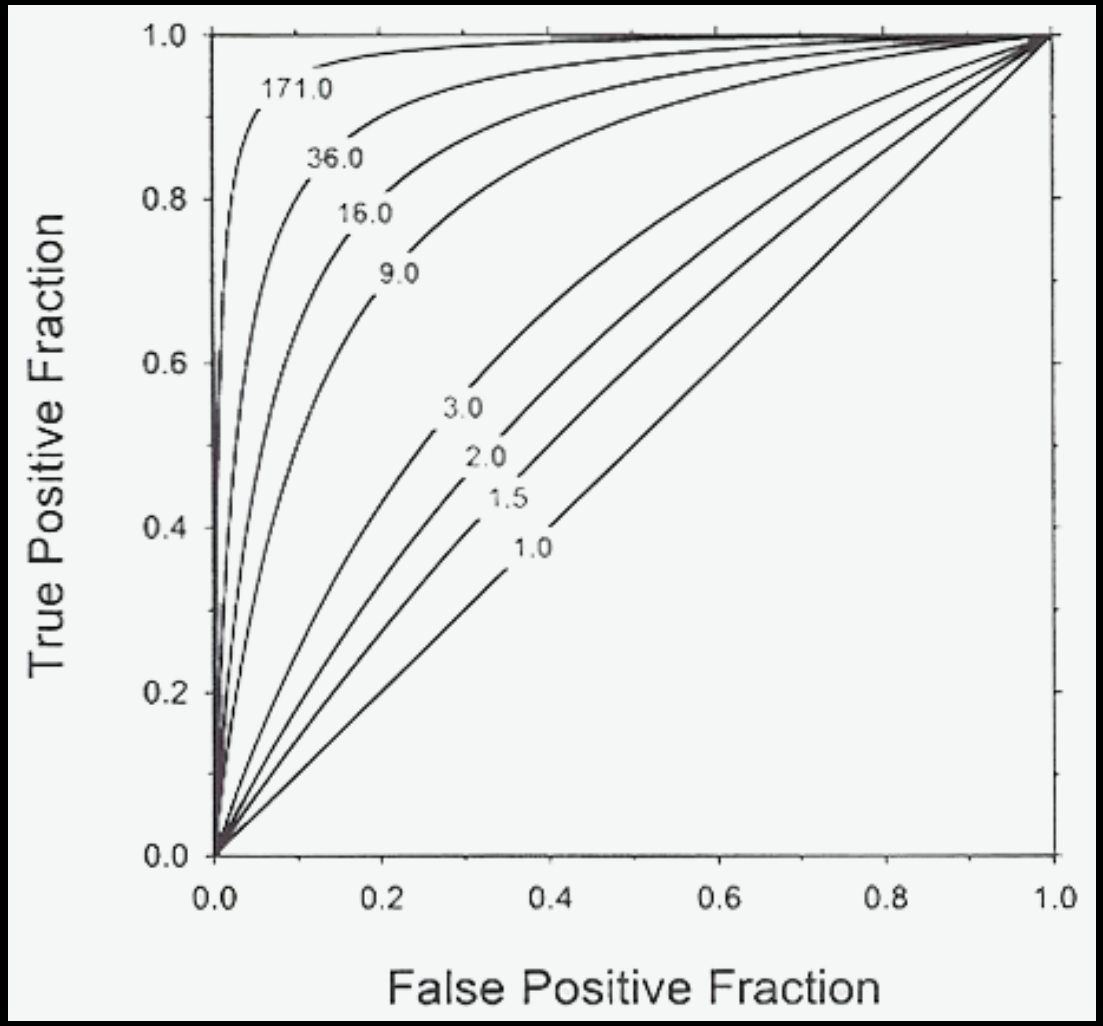
Bailey et al JACC 2001

Association vs Classification

"Traditional statistical methods used by epidemiologists to assess etiologic associations are not adequate to determine the potential performance of a marker for classifying or predicting risk for persons"

Pepe et al Am J Epidemiol 2004

Relation of Sensitivity to 1-Specificity for a Binary Marker for Given Odds Ratios



Pepe et al Am J Epidemiol 2004

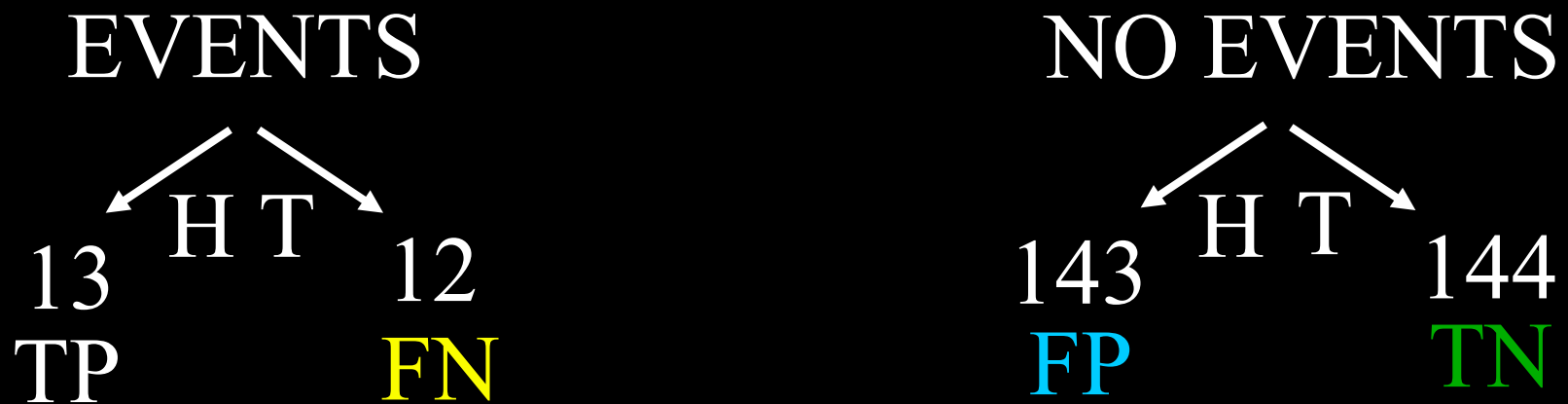
Cardiac Arrhythmias and Risk Stratification after Acute MI

- Screened 5869 patients w/i 2-7 days of MI
- 1393 (23%) had LVEF ≤ 40%
- 312 enrolled
- Age 65 ± 11 years
- LVEF 31 ± 6%
- Battery of risk stratification tests
- All had ILR
- 1° Endpoint - SD 8, resuscitated CA 3, syncope/VF 2, symptomatic sust VT 12

Huikuri et al European Heart Journal 2009

CARISMA - Risk Stratification

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Adjusted hazard ratio
LVEF	**57**	53	9	94	1.3
SDNN	35	90	21	95	4.6
VLF	41	91	26	95	7.0
FSE	65	71	15	96	3.5
HRT slope	53	74	14	95	2.8
SAECG QRSd	44	85	20	95	2.9
PES-MVT	47	90	23	96	4.8
PES-VT/VF	53	78	14	96	3.5



$$\text{Sensitivity} = \frac{TP}{TP+FN} = \frac{13}{13+12} = 50\%$$

$$\text{PPV} = \frac{TP}{TP+FP} = \frac{13}{13+143} = 8.3\%$$

$$\text{Specificity} = \frac{TN}{TN+FP} = \frac{144}{144+143} = 50\%$$

$$\text{NPV} = \frac{TN}{TN+FN} = \frac{144}{144+12} = 92.3\%$$

CARISMA

Variable	PPV (%)	NPV (%)	HR
LVEF<35%	9	94	
SDNN	21	95	4.6
VLF	26	95	7.0
Fractal scaling	15	96	3.5
HRT	14	95	2.8
QRS>120	20	95	1.4
EPS-MVT	23	96	4.8
EPS-VT/VF	14	96	3.5
Coin toss	8	92	1.0

Huikuri et al European Heart Journal 2009

Association vs Classification

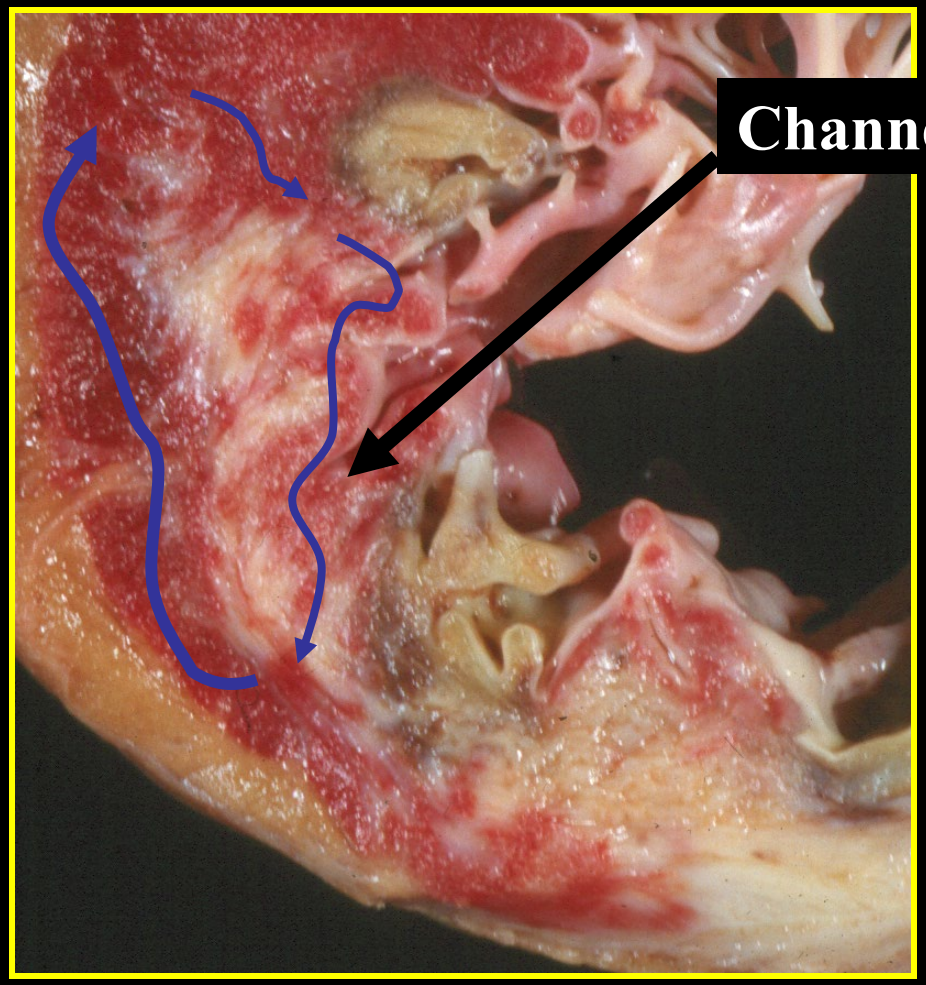
"Traditional statistical methods used by epidemiologists to assess etiologic associations are not adequate to determine the potential performance of a marker for classifying or predicting risk for persons"

Pepe et al Am J Epidemiol 2004

Test Combinations	Results of Tests	Proportion of Population (%)	Probability (Predictive Accuracy) of a MAE over 2 Years
Stage 1 = SAECG and LVEF	Both -	56.6	2.2
	Only 1 +	35.8	10.6
	Both +	7.6	38.7
Stage 2 = AECG (SVA, HRV)	Both -	23.3	4.7
performed on "only 1 +"	Only 1 +	10.8	17.5
patient of stage 1	Both +	1.7	48.2
Stage 3 = EPS performed on	-	8.2	8.9
"only 1 +" patient in stage 2	+	2.6	45.1
Aggregate results	Low-risk group	80.0	2.9
	High-risk group	11.8	41.4
	Unstratified group	8.2	8.9
Low LVEF, SVA and + EPS (MADIT criteria)		1.9	66.5

Bailey et al J Am Coll Cardiol 2001

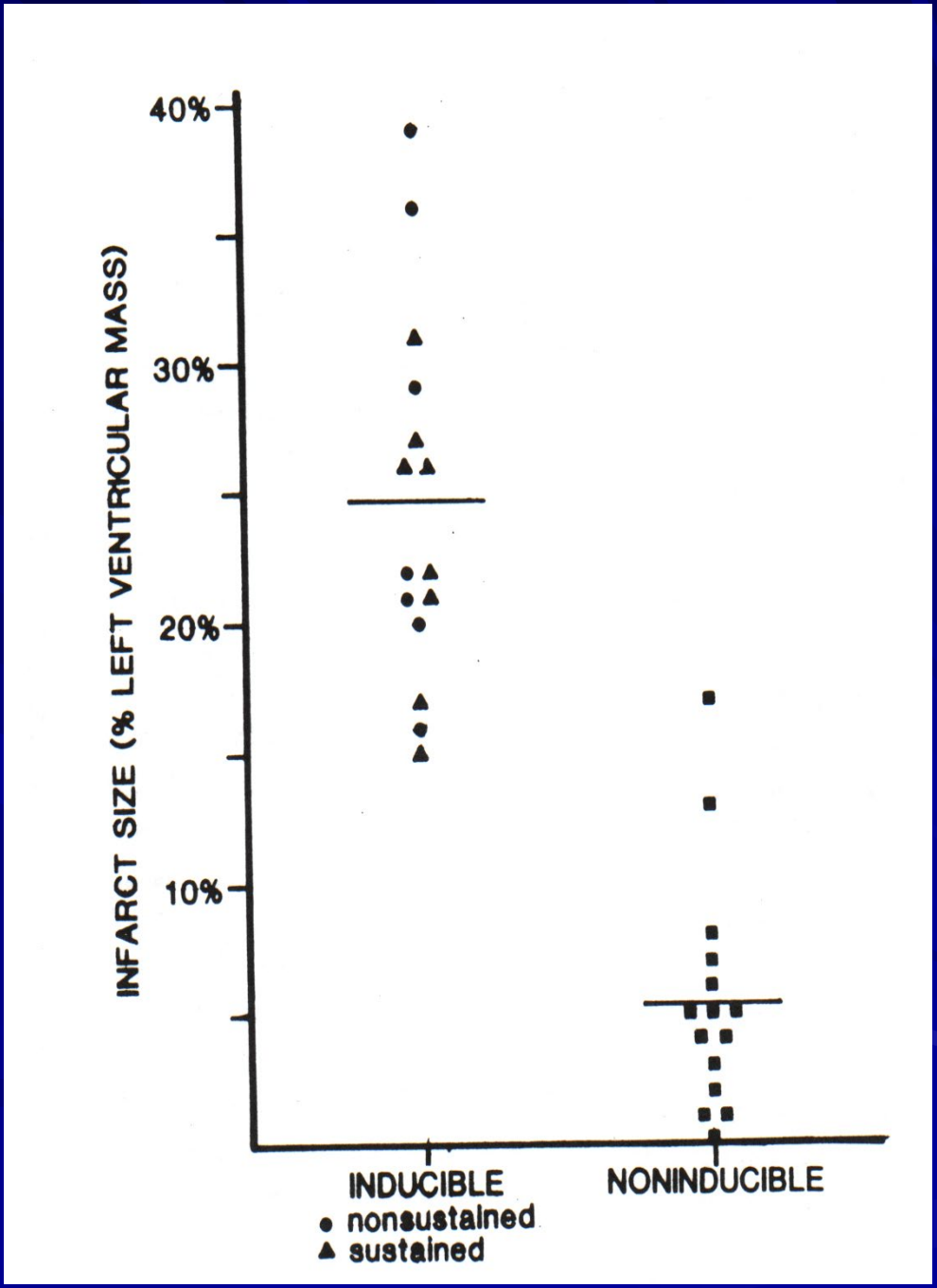
Sustained Monomorphic VT: Reentry in an infarct scar



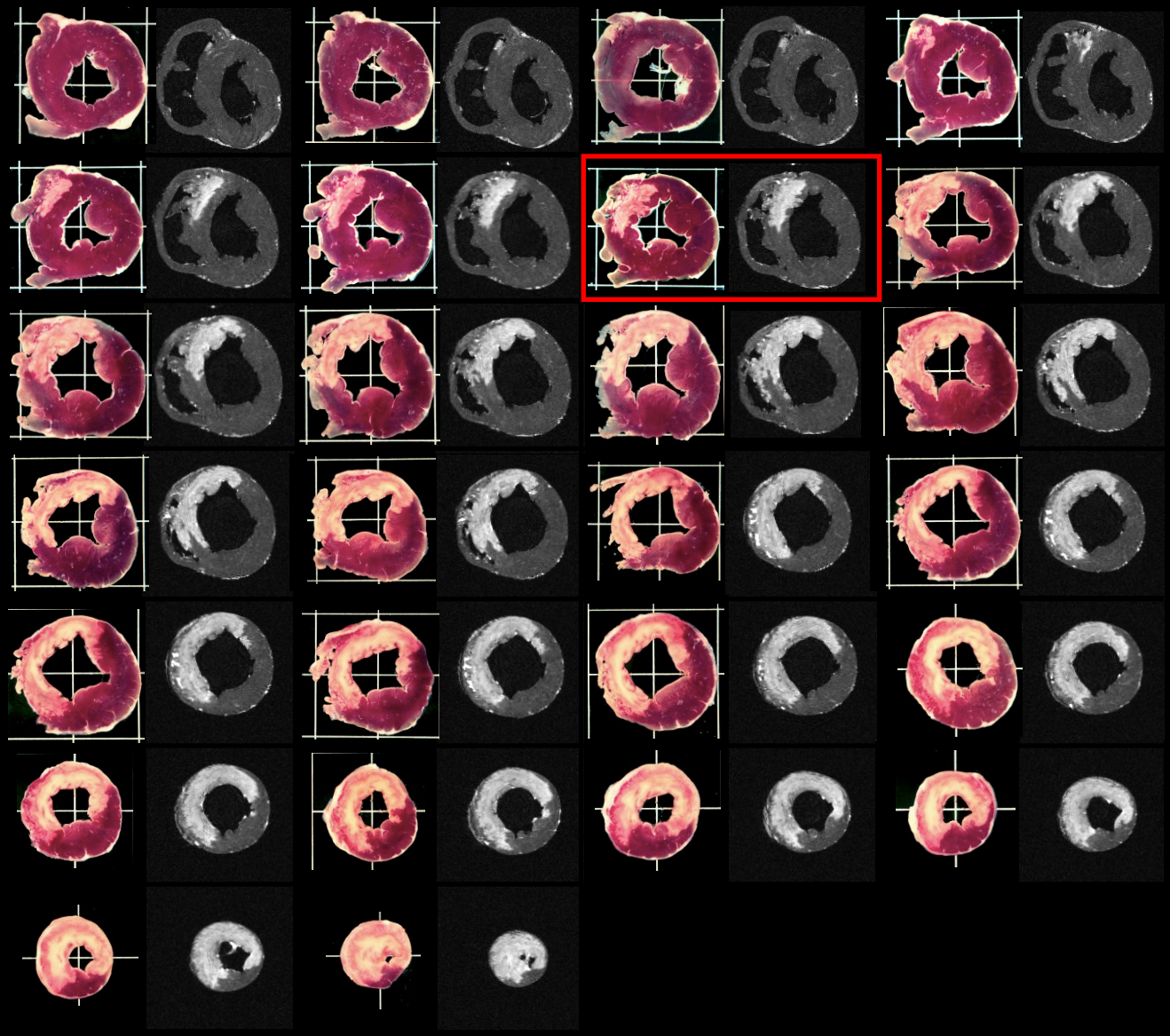
Courtesy of Bill Stevenson

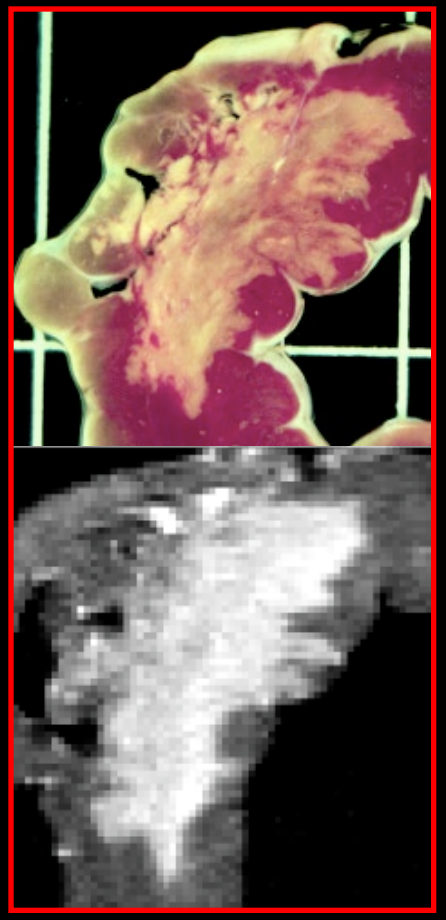
Canine Model

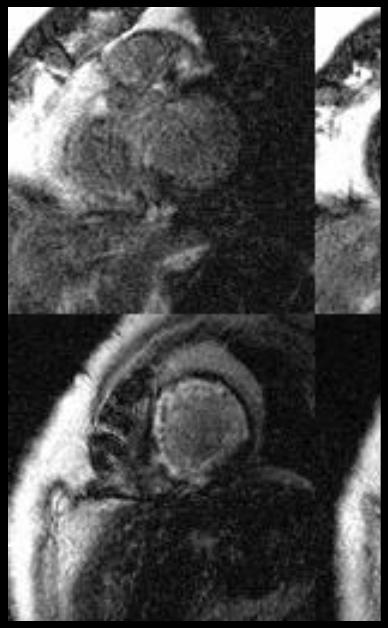
Extent of myocardial scar is related to inducibility of VT

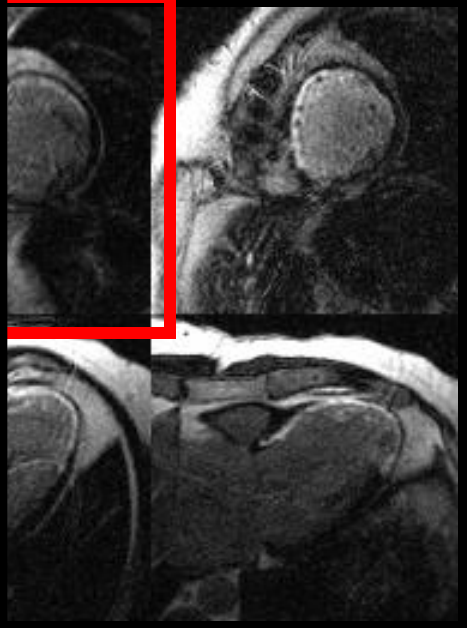


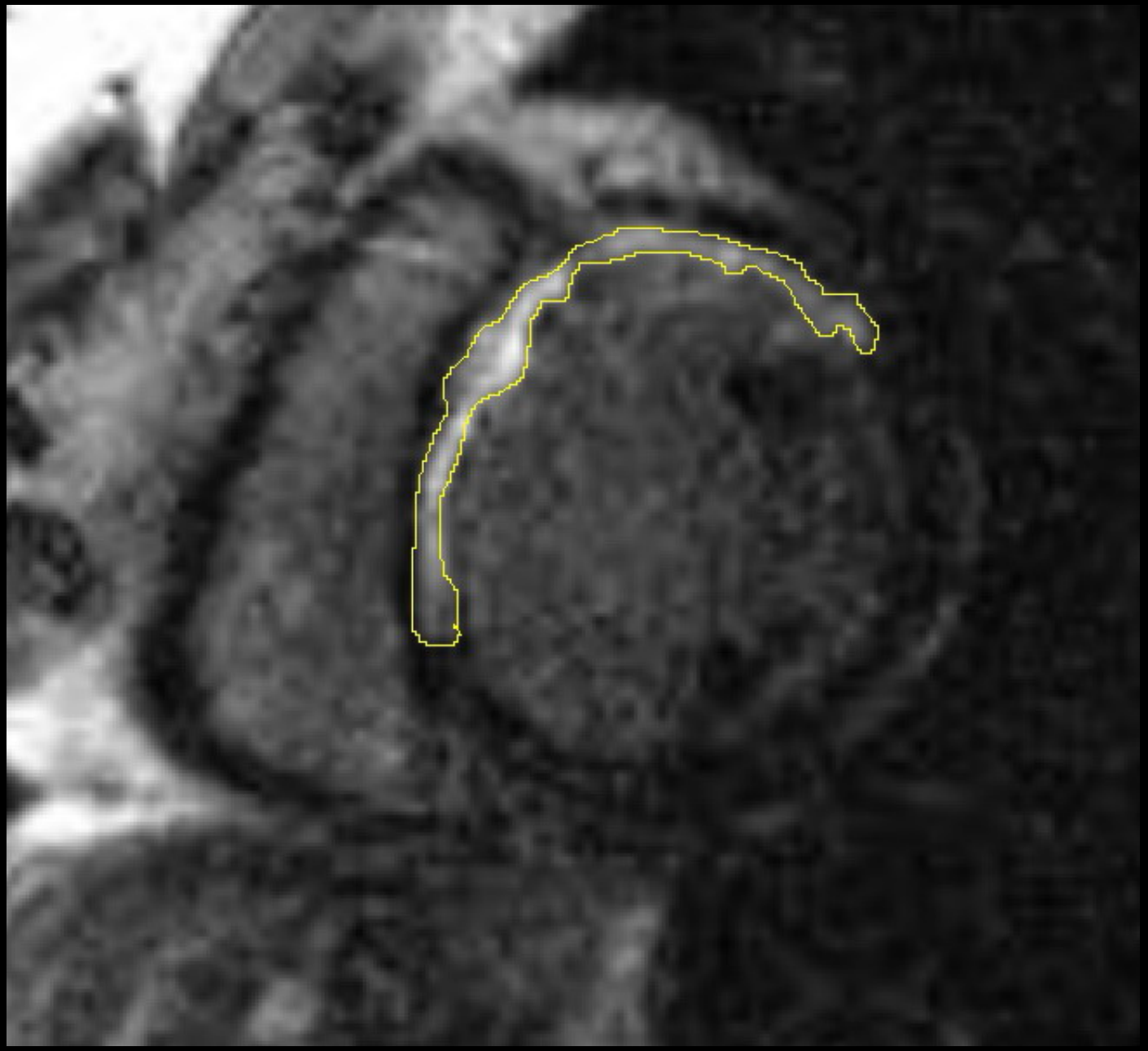
Wilber et al *Am Heart J* 1985

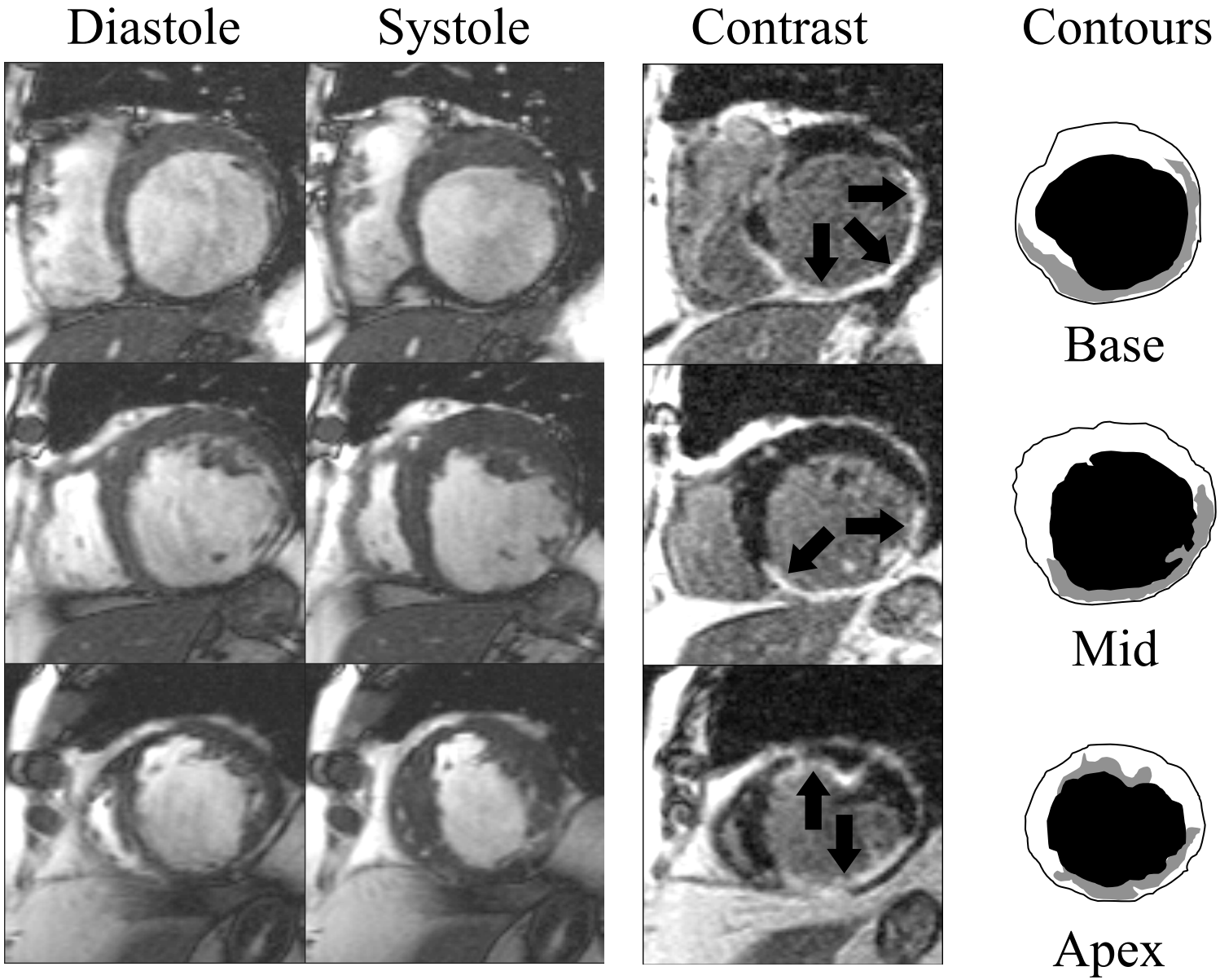











Diastole
Systole
Contrast
Contours
Base
Mid
Apex

Infarct Morphology Identifies Patients With Substrate for Sustained VT

- **48 pts with CAD undergoing EPS**
  - 21 not inducible — EF 35 ± 3 %
  - 18 MVT — EF 28 ± 2 %
  - 9 PVT/VF — EF 34 ± 6 %
- **MRI results**
  - 21 NI: Inf mass 14 ± 3% — SA 93 ± 14 cm^2
  - 18 MVT: Inf mass 26 ± 3% — SA 172 ± 15 cm^2

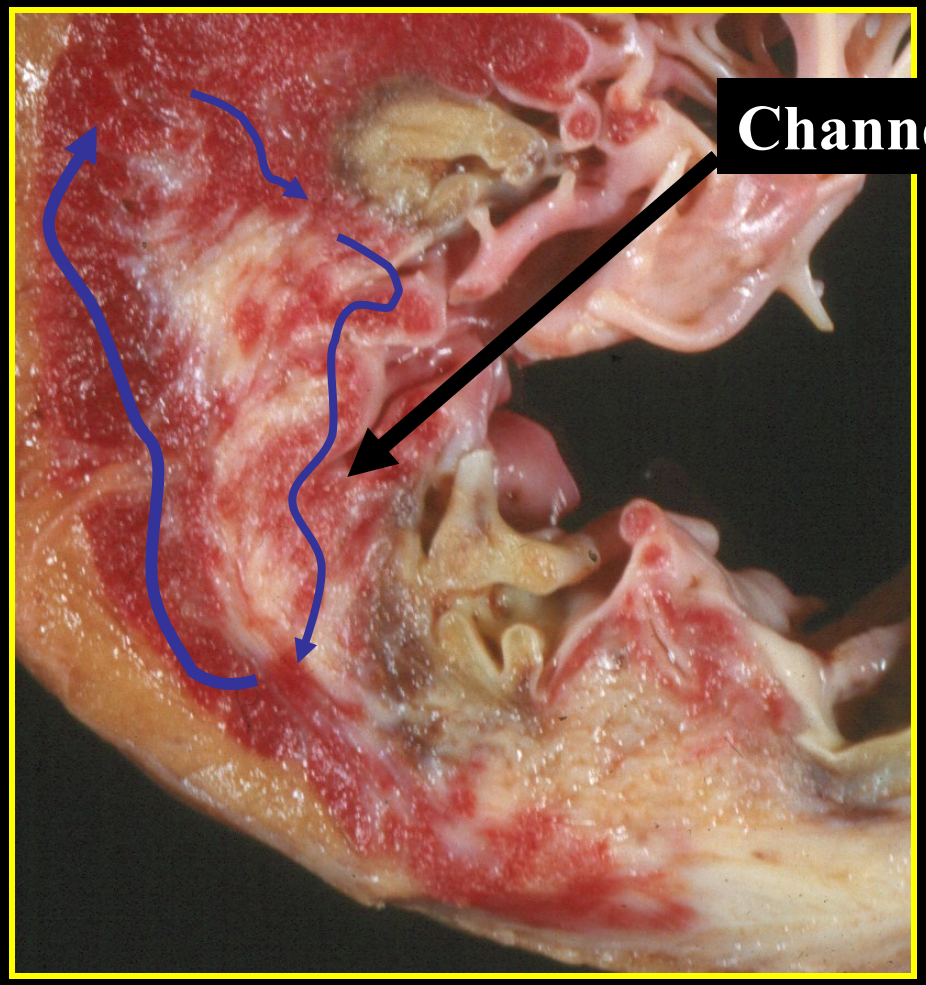
<0.009 <0.002

Bello, Goldberger JACC 2005

STUDY	Population	N	LVEF	Outcome	Finding
Bello 2005(13)	CAD referred for EPS	48	32%	Inducible VT	Infarct size better predictor than LVEF
Kwong 2006(4)	No known prior MI	195	54%	Death, MI, CV hosp, ICD rx	LGE strongest predictor of CV events
Yan 2006(9)	CAD with +LGE on CMR	144	44%	Mortality	Border zone independent predictor of mortality
Assomull 2006(14)	DCM	101	31%	Mortality + CV hosp	LGE only independent predictor
Schmidt 2007(7)	CAD, LVEF ≤ 35%, referred for ICD	47	27%	Inducible VT	Gray zone only predictive variable
Wu 2008(15)	CAD s/p STEMI	128	41%	Death, MI, CV hosp	Acute infarct size better predictor than LVEF
Yokata 2008(16)	CAD, EF≤50%, revasc ± ICD	86	26%	Death, CV hosp, revasc, VA	Infarct size was a predictor, not LVEF
Wu 2008(17)	DCM, LVEF≤ 35%	65	22%	Death, ICD rx, CV hosp	LGE only independent predictor
Cheong 2009(18)	Any pt w/ CMR, no infiltrative dz	857	39%	Transplant-free survival	Scar index and LVEF are independent predictors
Kelle 2009(19)	CAD	177	45%	Mortality + nonfatal MI	Spatial scar extent better predictor than LVEF
Roes 2009(8)	ICM, getting ICD	91	28%	Appropriate ICD rx	Gray zone only predictive variable
Kwon 2009(20)	CAD, LVEF < 45%	349	24%	Transplant-free survival	Infarct size was a predictor, not LVEF
Heidary 2010(21)	CAD, EF≤50%, revasc ± ICD	70	25%	Death, CV hosp, revasc, VA	Border zone and total scar are predictive, not LVEF
Bello 2011(22)	CAD	100	34%	Mortality	Infarct size and LVEF are independent predictors
Perez-David 2011(10)	CAD, ablation of monomorphic VT	36	32%	VT	More heterogeneous tissue channels in VT
Scott 2011(23)	CAD, getting ICD	64	30%	Appropriate ICD rx	Number of transmural segments most predictive
Iles 2011(24)	ICM and DCM getting ICD	103	26%	ICD rx	LGE predictive of ICD rx
Catalano 2012(25)	CAD	376	51%	Mortality+new onset HF	Infarct size and LVEF are independent predictors
Klem 2012(3)	ICM and DCM getting EPS±ICD	73	30%	SCD or ICD discharge	Infarct size is an independent predictor
Gao 2012(26)	ICM and DCM getting ICD	59	26%	SCD or ICD discharge	Infarct size is an independent predictor
Wu 2012(27)	+CAD(53%) and -CAD, for EPS±ICD	137	26%	ICD rx/cardiac death	Gray zone predictive
Dawson(2)	Sustained or Nonsustained VT	373	60%	SCD, VT/VF, ICD rx	LGE only independent predictor

Goldberger JJ and Lee DC. JACC Cardiovascular Imaging 2013

Sustained Monomorphic VT: Reentry in an infarct scar



Courtesy of Bill Stevenson

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Virtual Electrophysiological Study in a 3-Dimensional Cardiac Magnetic Resonance Imaging Model of Porcine Myocardial Infarction

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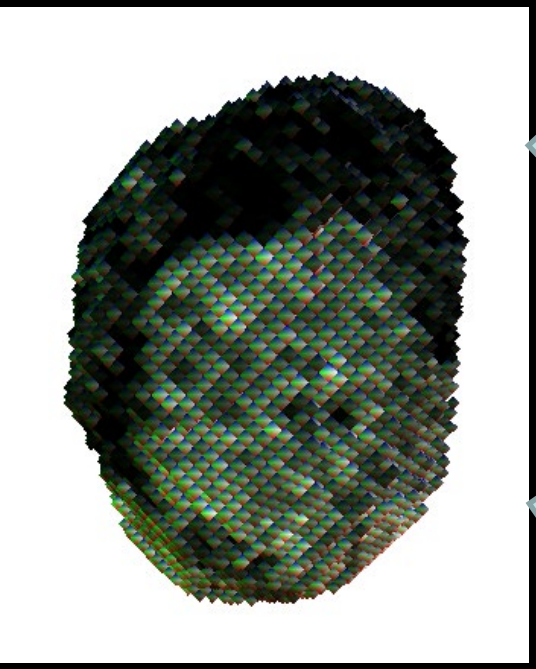
Chicago, Illinois

Building the 3D Computer Model



Normal → **Normal APD**
Normal conduction

Gray-zone → **Prolonged APD**
Slowed conduction

Hyper-enhanced → **No activation**
No conduction

Propagation equation

$$\frac{\partial V}{\partial t} = \frac{-(I_{ion} + I_{stim})}{C_m} + D\left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2} + \frac{\partial^2 V}{\partial z^2}\right)$$

V = transmembrane potential
I_{ion} = Net ion current
I_{stim} = Stimulus current

C_m = Membrane capacitance
D = diffusion constant

Fenton-Karma 3-variable action potential model

$I_{ion} = J_{fi} + J_{so} + J_{si}$

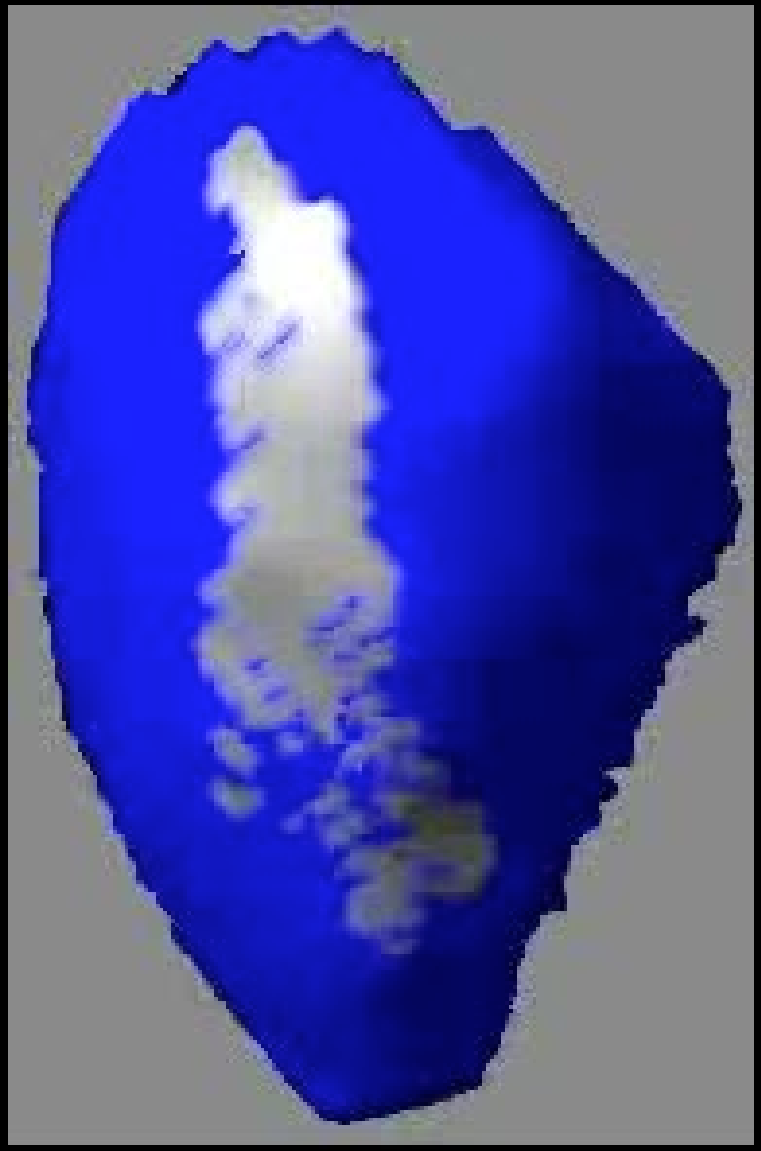
$$J_{fi}(u;v) = -\frac{v}{\tau_d}\Theta(u-u_c)(1-u)(u-u_c),$$ (Fast inward current)

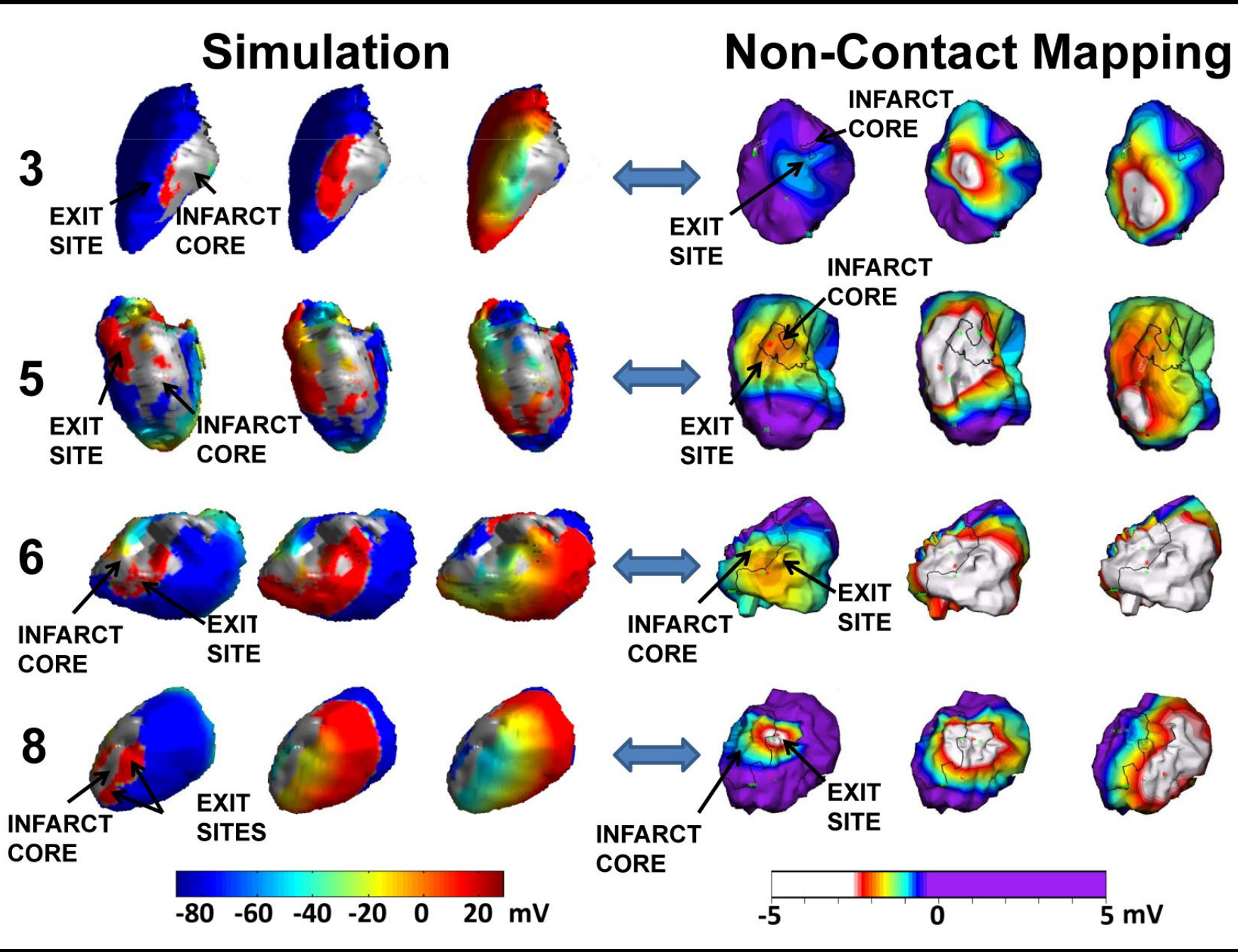
$$J_{so}(u) = \frac{u}{\tau_o}\Theta(u_c-u) + \frac{1}{\tau_r}\Theta(u-u_c),$$ (Slow outward current)

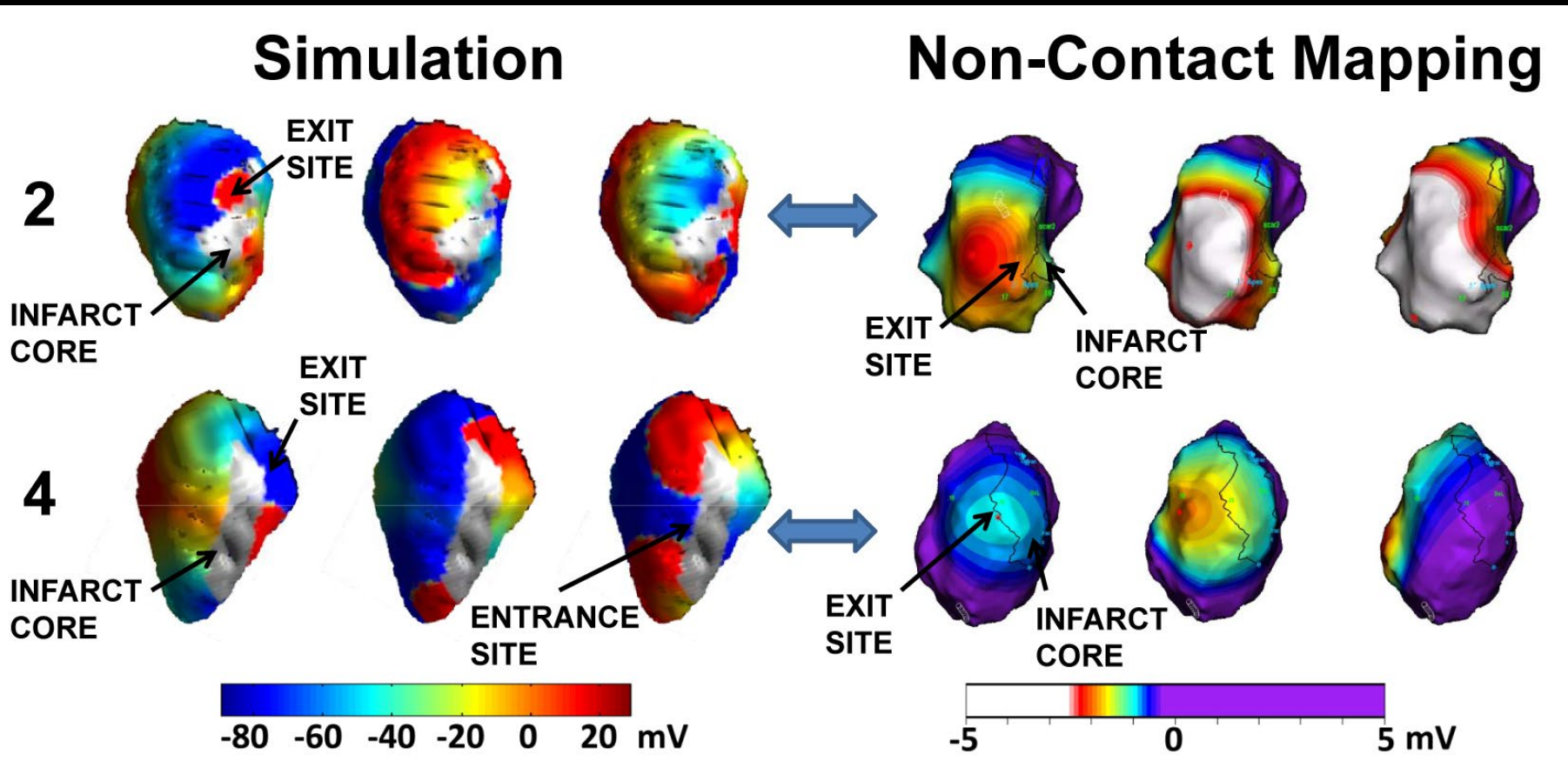
$$J_{si}(u;w) = -\frac{w}{2\tau_{si}}(1+\tanh[k(u-u_c^{si})]).$$ (Slow inward current)

Partial differential equations solved by Euler forward method

VT Induction Example

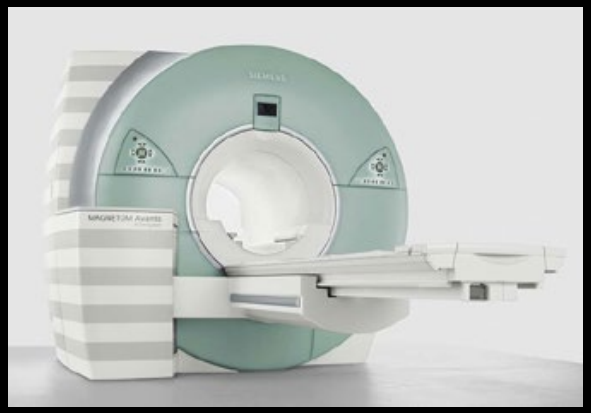



Simulation
Non-Contact Mapping
3
EXIT SITE
INFARCT CORE
INFARCT CORE
EXIT SITE
5
EXIT SITE
INFARCT CORE
INFARCT CORE
EXIT SITE
6
INFARCT CORE
EXIT SITE
INFARCT CORE
EXIT SITE
8
INFARCT CORE
EXIT SITES
INFARCT CORE
EXIT SITE
-80 -60 -40 -20 0 20 mV
-5 0 5 mV

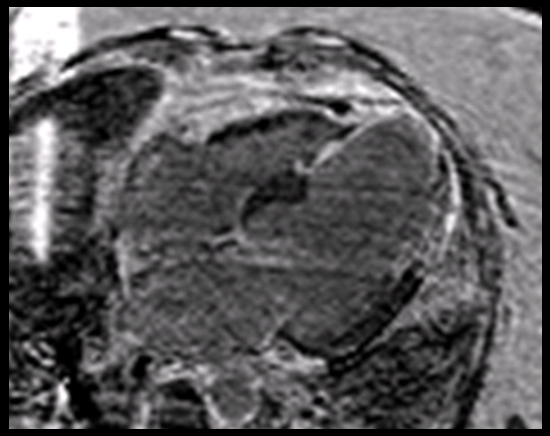

Simulation
Non-Contact Mapping
2
EXIT SITE
INFARCT CORE
EXIT SITE
INFARCT CORE
4
EXIT SITE
INFARCT CORE
ENTRANCE SITE
EXIT SITE
INFARCT CORE
-80 -60 -40 -20 0 20 mV
-5 0 5 mV

New Paradigm - Virtual Electrophysiologic Study (VEPS)

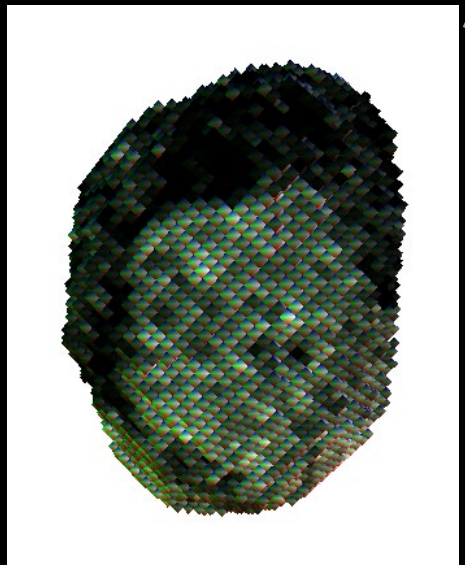
SCAN



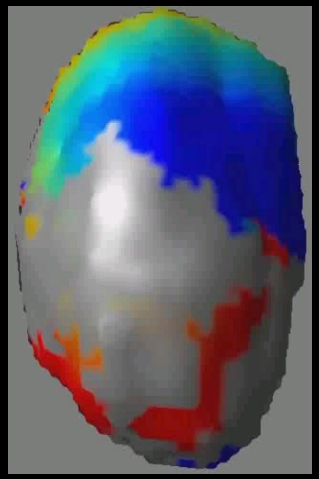
DE-MRI IMAGES



3D LV MODEL



VT INDUCTION SIMULATION



CLINICAL DECISION MAKING?

A Simple Community-Based Risk-Prediction Score for Sudden Cardiac Death

ARIC

Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

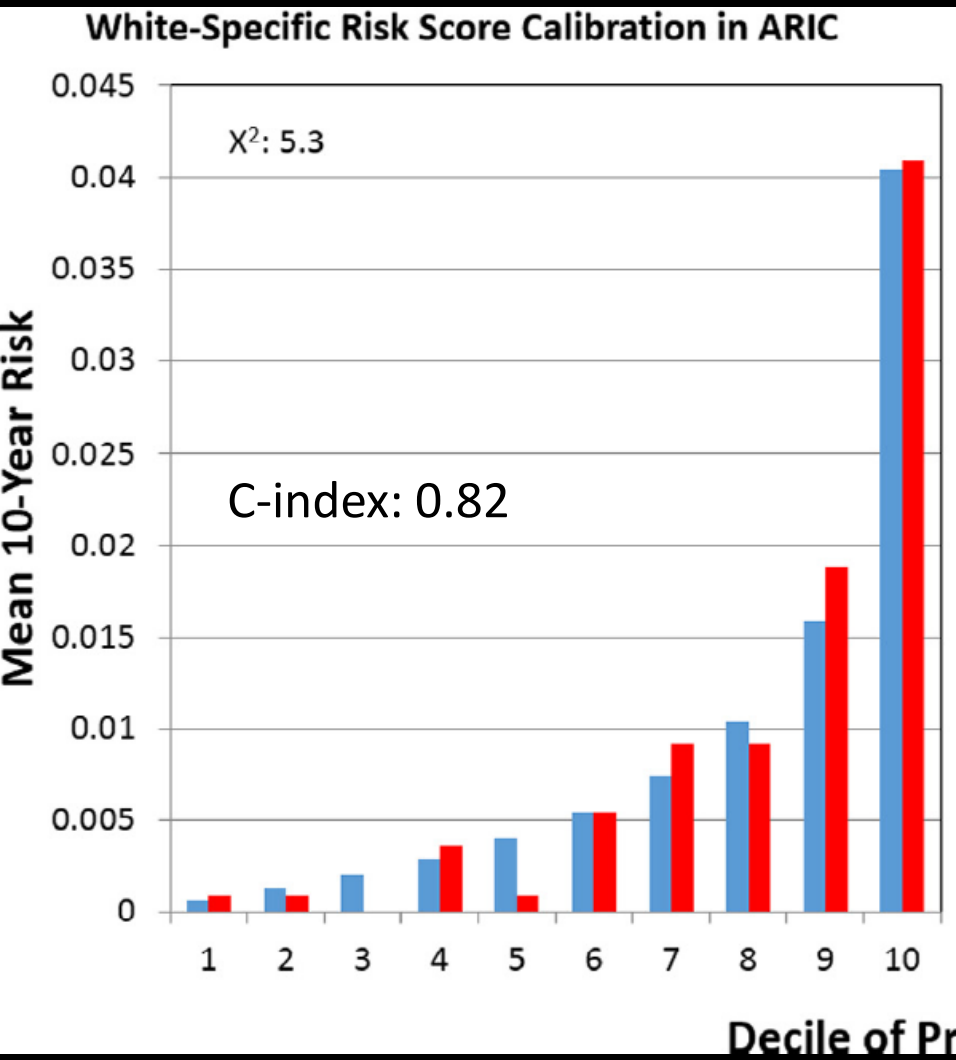
A Simple Community-Based Risk-Prediction Score for Sudden Cardiac Death

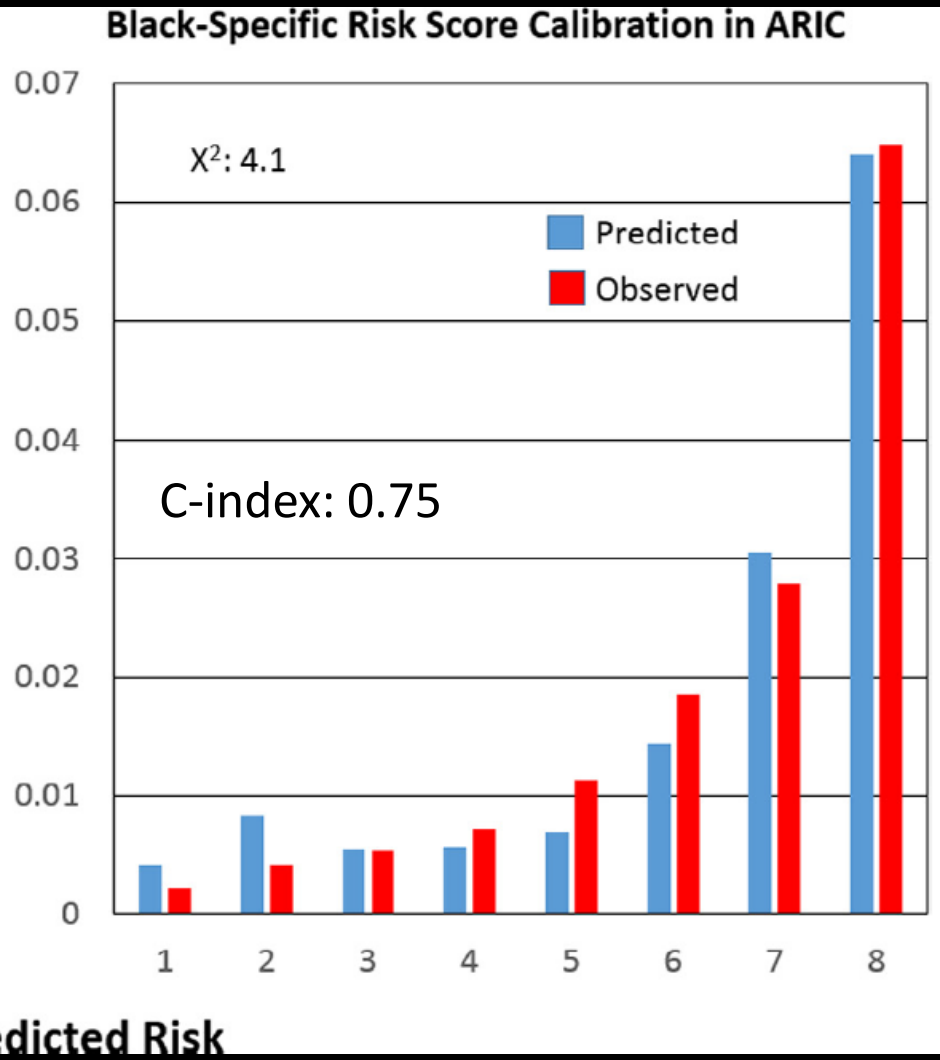
Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

- ARIC Study
  - Aged 45-64 years at baseline
  - 11,335 white and 3,780 black
- Participants were followed over 10 years
- Validated in Framingham Heart Study participants (n=5,626)
- Outcome: Physician Adjudicated SCD

Bogle et al., *Am J Med*. 2018;131:532-539

Calibration





CONCLUSIONS

- New approaches needed to personalize risk stratification
  - New goals
  - New diagnostics – imaging, genetics
- Risk stratification is also feasible in the general population
  - Need new approaches
  - EHR based