TO REVASCULARIZE OR NOT TO REVASCULARIZE: IMAGING FOR DECISION-MAKING IN ISCHEMIC CARDIOMYOPATHY

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Disclosures

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- Amgen (consultant fees, research funding)

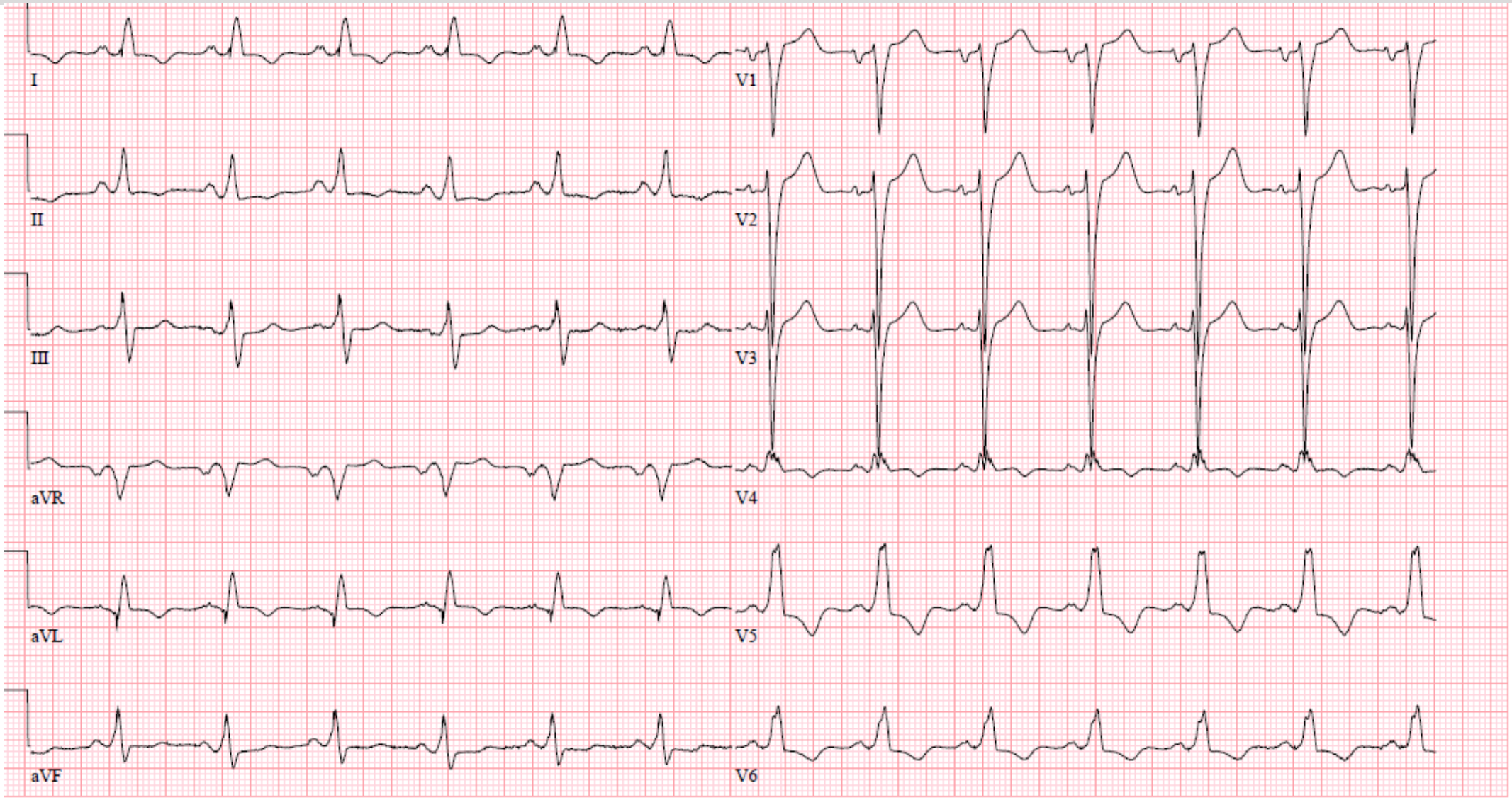
A Clinical Case: Mr. GS

- 56 year old male
- Known CAD
  - Felt inoperable from previous angiogram 5 years previously
- HTN
- Dyslipidemia
- PVD
- Smoker/significant EtOH
- ICD for primary prevention with recent appropriate shock for VT

- Referred for progressive HF symptoms
  - FC III
- No chest pain, no recent ACS
- On Exam:
  - BP 95/60
  - HF 70
  - No evidence of significant volume overload

- Medications
  - Bisoprolol 10 mg daily
  - Ramipril 10 mg daily
  - Sprionolactone 25 mg daily
  - Lasix 40 mg daily
  - ASA
  - Crestor 40 mg daily

ECG



Echocardiogram

Measurement		Normal
LV Diastole:	7.0 cm	< 5.8 cm
LV Systole:	6.2 cm	< 4.8 cm
IV Septum:	0.99 cm	< 1.2 cm
Posterior Wall:	0.97 cm	< 1.2 cm
Fract Short:	11.5 %	> 25%
Left Atrium:	5.4 cm	< 4.1 cm
Aortic Root:	3.0 cm	< 3.8 cm
EF MOD-bp:	15.3 %	> 55%

Additional Measurements (2D,Doppler) & Calculations

LA vol: 85.0 ml

LA vol index: 45.9 ml/m^2

LV mass(C)d: 315.1 grams

LV mass(C)di: 170.1 grams/m^2

MV E max vel: 85.4 cm/sec

MV A max vel: 40.0 cm/sec

MV E/A: 2.1

MV dec time: 0.14 sec

Lat Peak E' Vel: 3.0 cm/sec

RVSP(TR): 39.5 mmHg

asc Aorta Diam: 2.8 cm

Chambers

The left ventricle is moderately dilated. Walls are relatively thin. Left ventricular systolic function is severely reduced. Ejection Fraction by Simpson's is 15.3 %.

There is severe global hypokinesis of the left ventricle. Thin and bright LV wall segment suggests a myocardial infarction.

The right ventricle is normal in size and function. There is a pacemaker lead in the right ventricle.

The left atrium is moderately dilated. Right atrial size is normal. There is a catheter/pacemaker lead seen in the right atrium. The interatrial septum is intact with no evidence for an atrial septal defect.

Valves

The aortic valve is normal in structure and function. No aortic regurgitation is present.

The reduced mitral leaflet separation suggests decreased flow through the mitral valve and poor cardiac output. There is a prominent "B-hump" in the mitral valve, consistent with elevated left ventricular end-diastolic pressure. There is mild (1+) mitral regurgitation. There is functional MR secondary to LV dysfunction.

The tricuspid valve is normal. There is trace tricuspid regurgitation.

The pulmonic valve is normal in structure and function. Trace pulmonic valvular regurgitation.

Coronary Angiogram

- 99% proximal LAD with diffuse disease distally
- RCA 90%
- OM1 (large) occluded
- LCx diffuse moderate-severe disease

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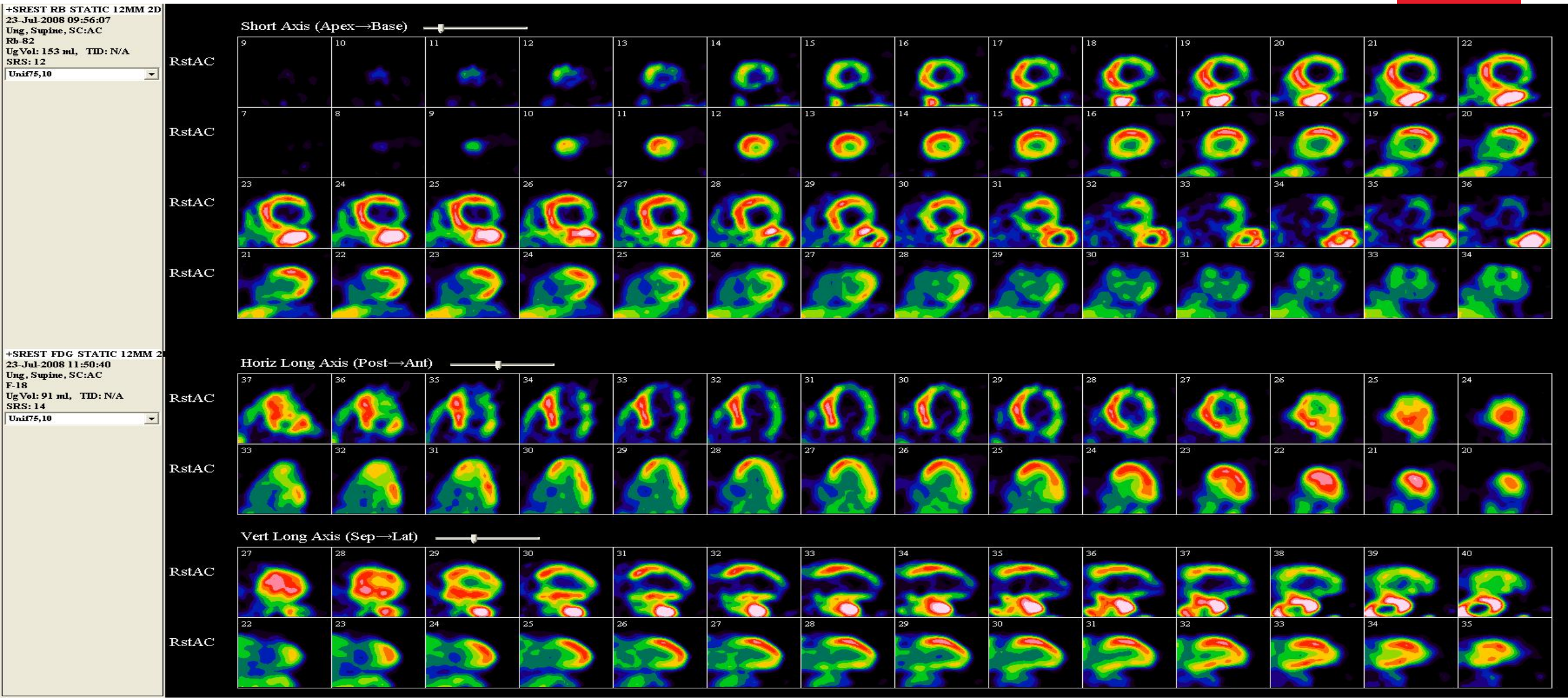
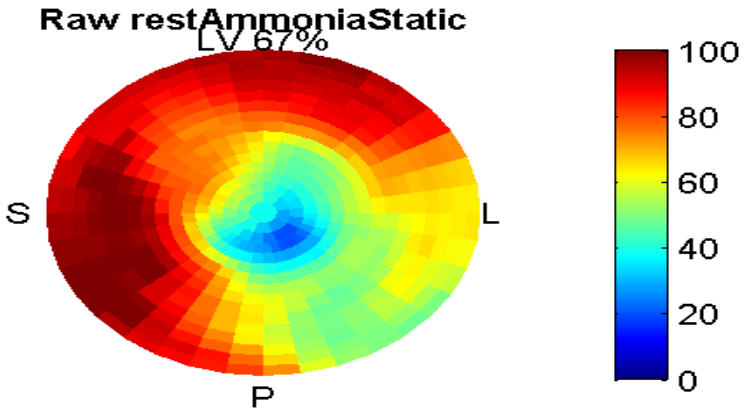
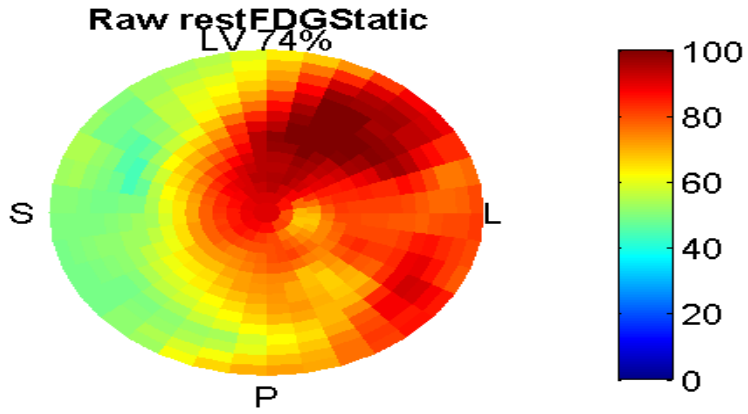
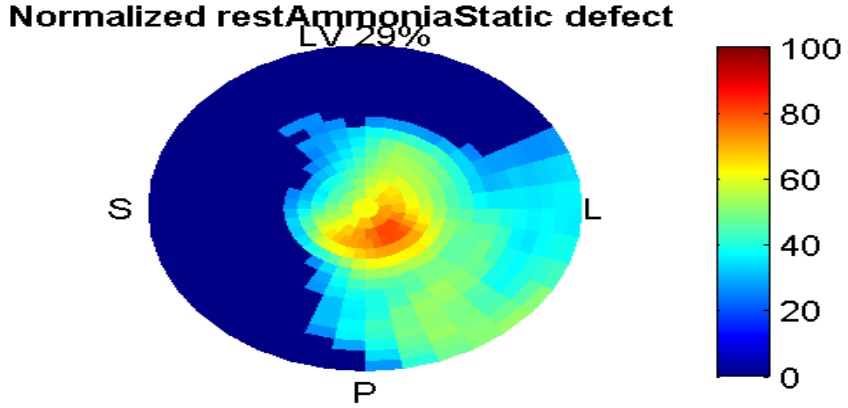
Preview

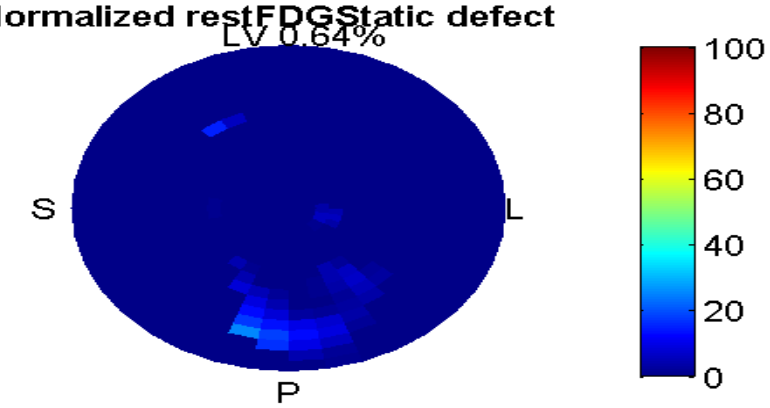
PET Viability Results

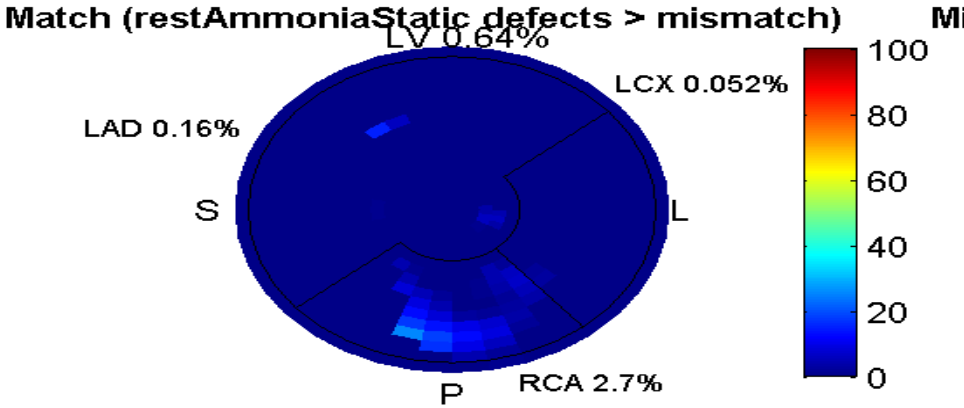


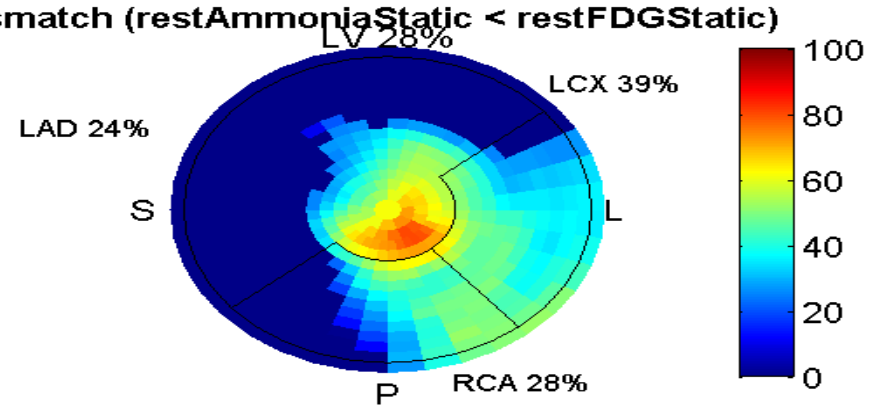

Raw restAmmoniaStatic
LV 67%
S
L
P
100
80
60
40
20
0


Raw restFDGStatic
LV 74%
S
L
P
100
80
60
40
20
0


Normalized restAmmoniaStatic defect
LV 29%
S
L
P
100
80
60
40
20
0


Normalized restFDGStatic defect
LV 0.64%
S
L
P
100
80
60
40
20
0


Match (restAmmoniaStatic defects > mismatch)
LV 0.64%
LCX 0.052%
LAD 0.16%
S
L
P
RCA 2.7%
100
80
60
40
20
0


Mismatch (restAmmoniaStatic < restFDGStatic)
LV 28%
LCX 39%
LAD 24%
S
L
P
RCA 28%
100
80
60
40
20
0

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Preview

One Year Later:

- Returned to work as a part-time machinist
- FC II
- No further HF symptoms

Impression

1. **Respiratory Spirometry**

   FVC: 2.56 L / 64 % predicted VE/VCO_2 Slope 34

   FEV1: 1.74 L / 58 % predicted

   FEV1/FVC: 68 %

   Resting spirometry is moderate obstructive abnormality. Breathing reserve at peak 20 % is reduced. Breathing pattern is Exaggerated beyond AT.

2. **Cardiovascular**

   exercised for 7:28 on the slow ramp protocol, stopping because of dyspnea.

	Rest	*AT*	*Peak*
Blood Pressure	134 / 76 mmHg	130 / 64 mmHg	150 / 66 mmHg
Heart Rate	81 bpm	91 bpm	118 bpm

   Heart rate reserve at peak exercise is 38 %.

3. **Metabolic**

   The test was maximal with an RER of 1.19. The peak VO_2 achieved was 16.1 ml/kg/min or 4.6 METs. This represents 58 % predicted using the Wasserman equation for overweight individuals.
   is at the <5 percentile for normal men age 50-59 according to the Cooper Clinic published normals .
   The anaerobic threshold is 2.4 METs or 30 % predicted maximal VO_2 uptake.
   The O_2 pulse at peak is 11.8 which is reduced. The O_2 saturation 97% at rest and 99% at peak.

Measurement		Normal
LV Diastole:	6.7 cm	< 5.8 cm
LV Systole:	6.2 cm	< 4.8 cm
IV Septum:	0.91 cm	< 1.2 cm
Posterior Wall:	0.88 cm	< 1.2 cm
Fract Short:	8.1 %	> 25%
Aortic Root:	2.7 cm	< 3.8 cm

Additional Measurements (2D,Doppler) & Calculations

LA vol: 68.6 ml
LA vol index: 36.9 ml/m^2
LV mass(C)d: 260.5 grams
LV mass(C)di: 140.1 grams/m^2
MV E max vel: 91.7 cm/sec
MV A max vel: 38.8 cm/sec
MV E/A: 2.4
MV dec time: 0.13 sec
Lat Peak E' Vel: 3.5 cm/sec
Septal Peak E' Vel: 3.3 cm/sec
RVSP(TR): 25.4 mmHg

asc Aorta Diam: 3.0 cm
LVOT diam: 1.8 cm
RAP systole: 8.0 mmHg

Chambers

The left ventricle is moderately dilated. There is eccentric left ventricular hypertrophy. Left ventricular systolic function is severely reduced. Ejection Fraction is 17.5%. The ejection fraction is calculated using Teichholz method. The E/Ea ratio suggests that LA pressure is elevated. There is severe global hypokinesis of the left ventricle.
There is severe (grade 3 or 4- restrictive) diastolic dysfunction.
There is a pacemaker lead in the right ventricle. The right ventricle is normal size. The right ventricular systolic function is mildly reduced.
The left atrium is mildly dilated. Right atrial size is normal. The interatrial septum is intact with no evidence for an atrial septal defect.

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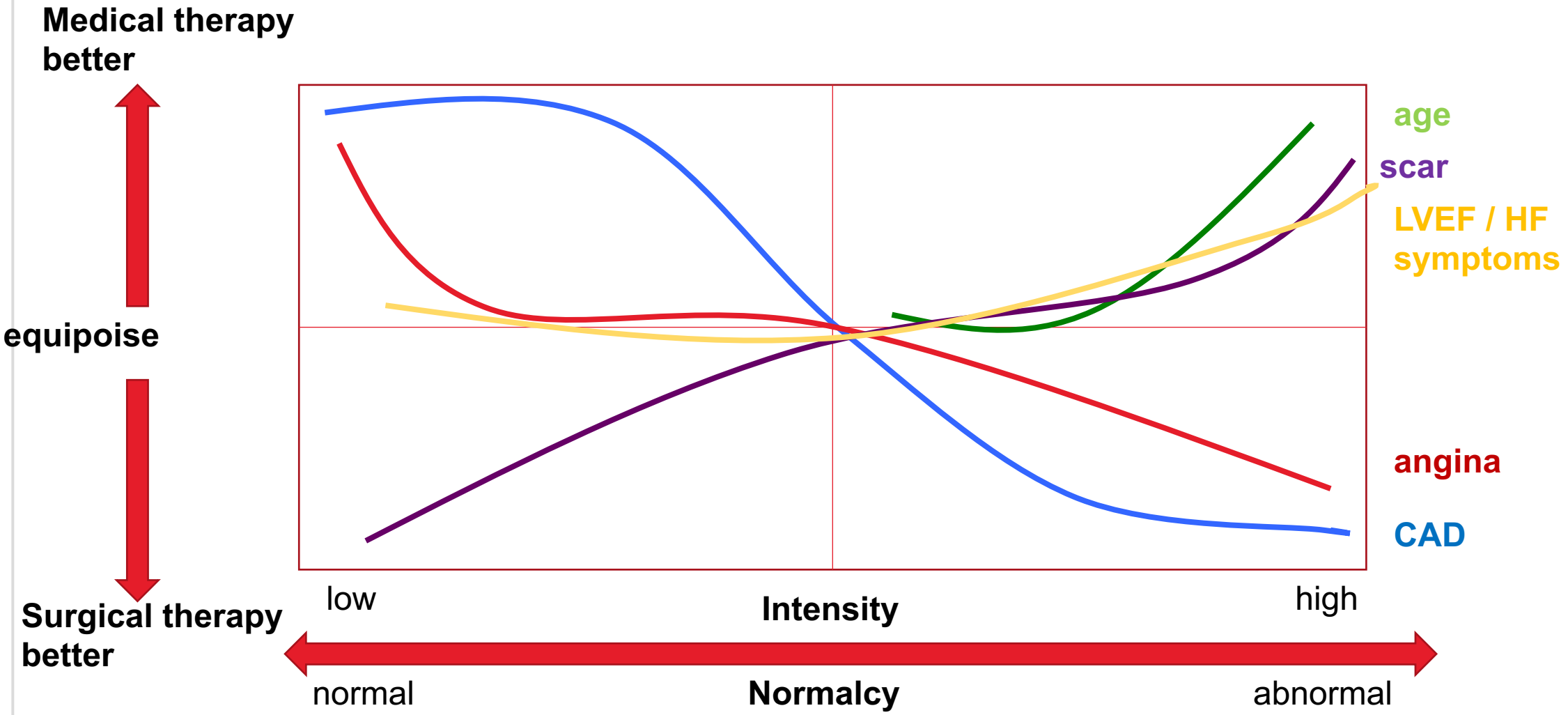
Preview

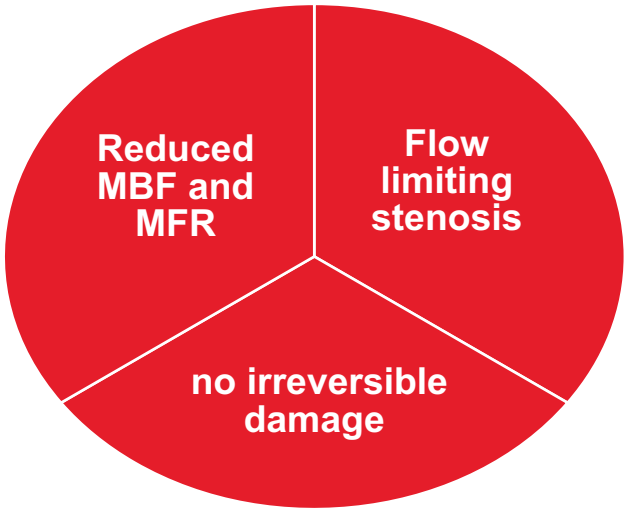
Refining Risk and Maximizing Benefit



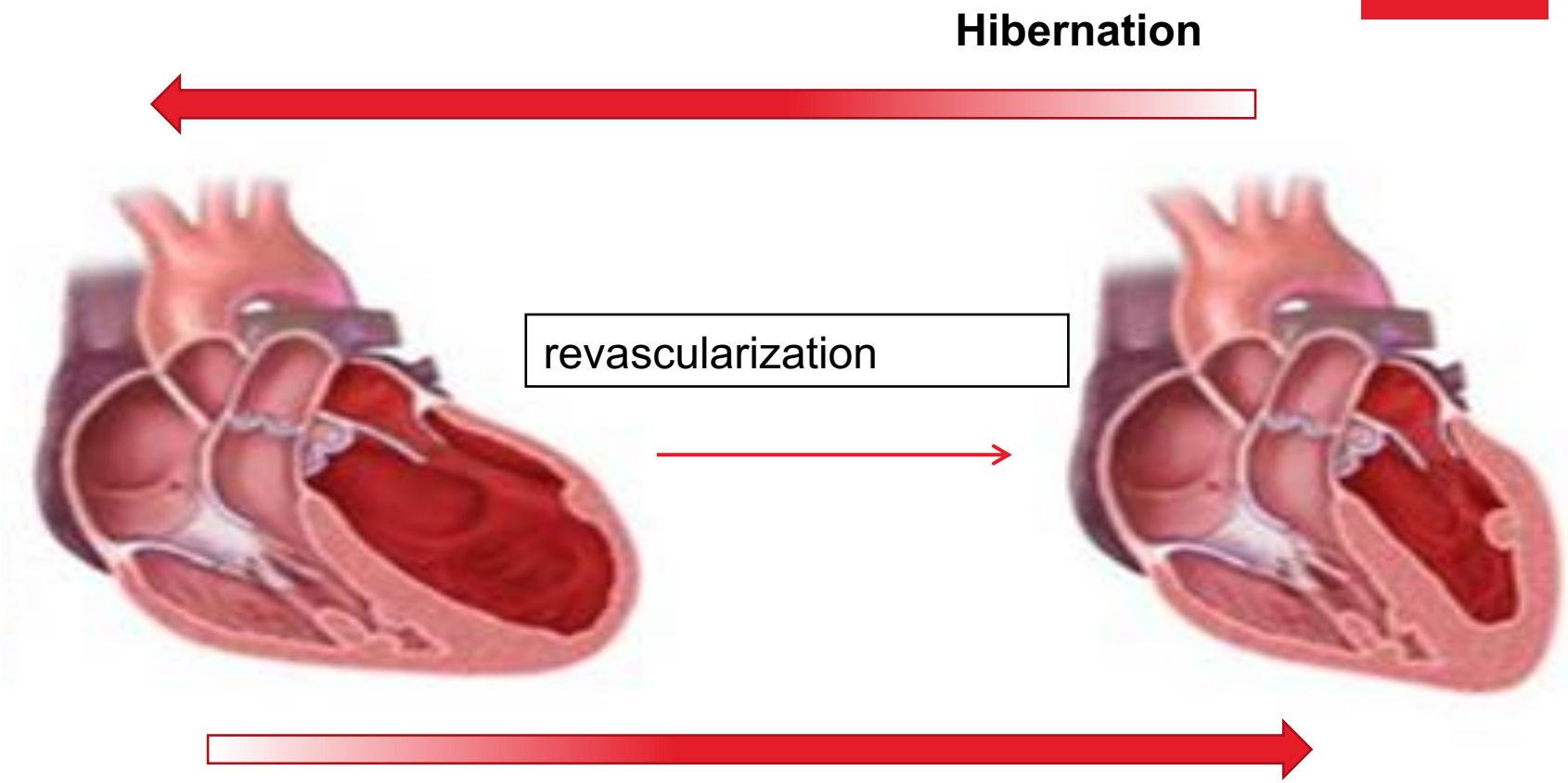
Adapted from Rouleau: Can J Cardiol 2014; 281-287

Where is the Evidence that a Viability Based Strategy Improves Long-Term Outcomes?

Stunning, Hibernation and Viability



Triad of Hibernation



Spectrum of Myocardial Dysfunction in Ischemic Cardiomyopathy

Repetitive ischemia

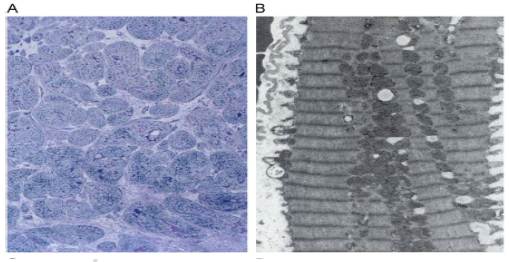
Persistent Repetitive ischemia

Cell death

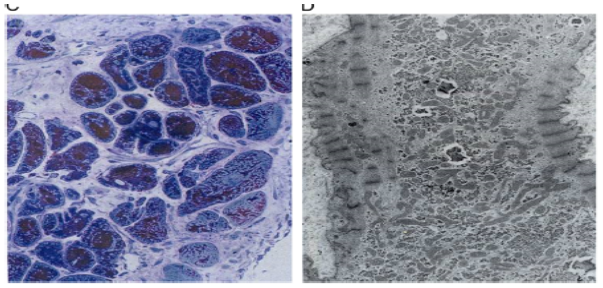
Normal myocardium → Stunned myocardium → Hibernating myocardium → Myocardial Scar

Severe CAD

CFR	CR	PERF	MET	SCAR
✓	✓	✓	✓	X



CFR	CR	PERF	MET	SCAR
↓	✓	✓	✓	X

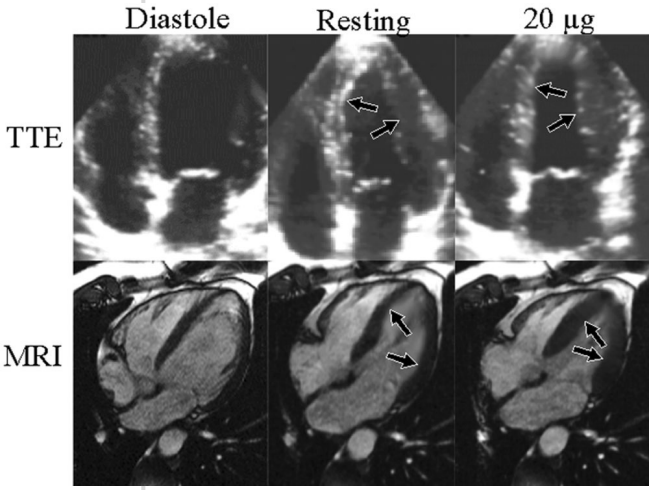


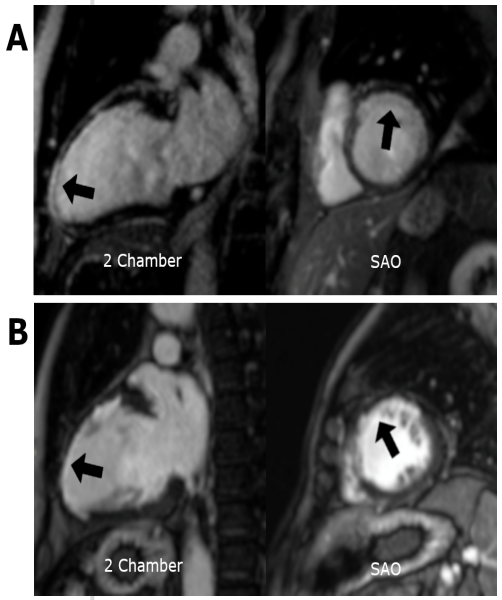
CFR	CR	PERF	MET	SCAR
↓↓	↔	↔	✓	X

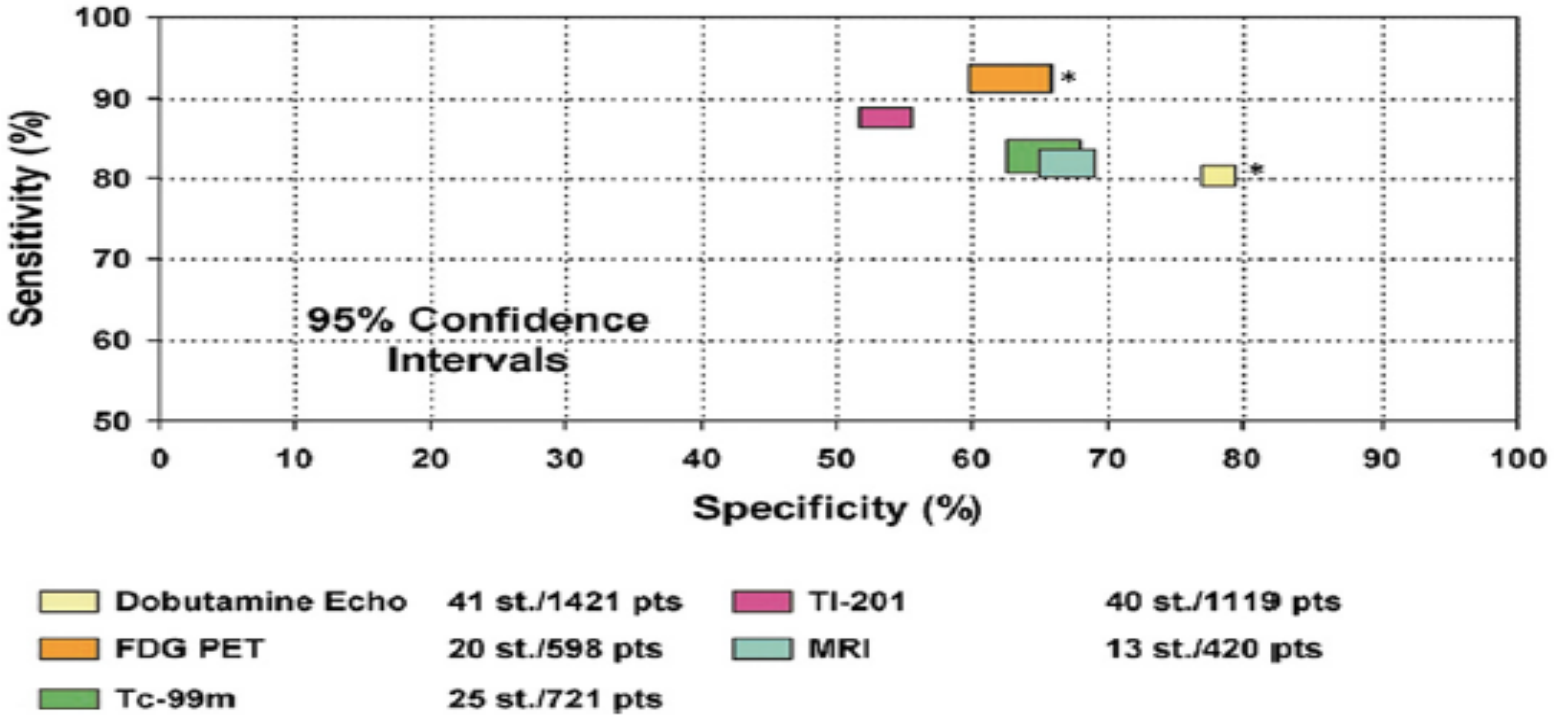
CFR	CR	PERF	MET	SCAR
↓↓↓	X	X	X	✓

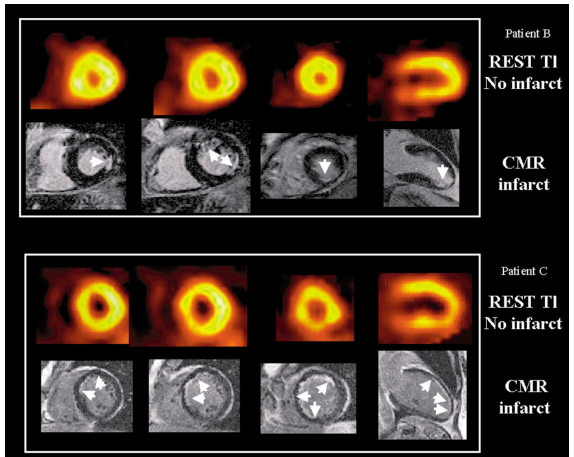
Adapted from:Shah Eur Heart J; 2013:34:1323

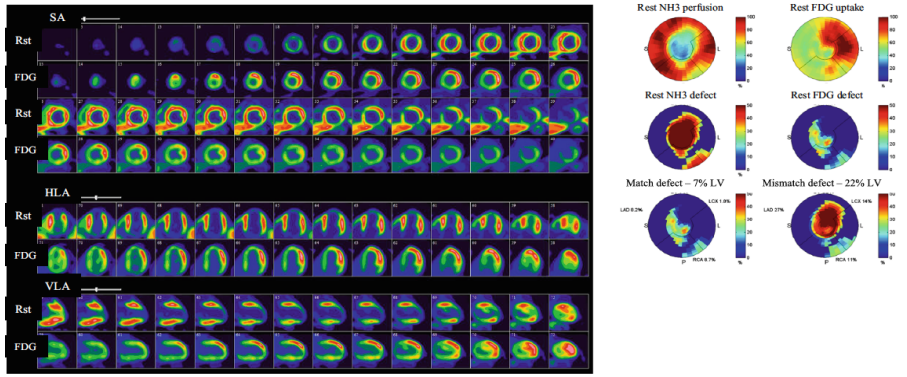
Multiple Modalities Available to Assess for “Viability”











Schinkel; Curr Prob Cardiol 2007;32:375

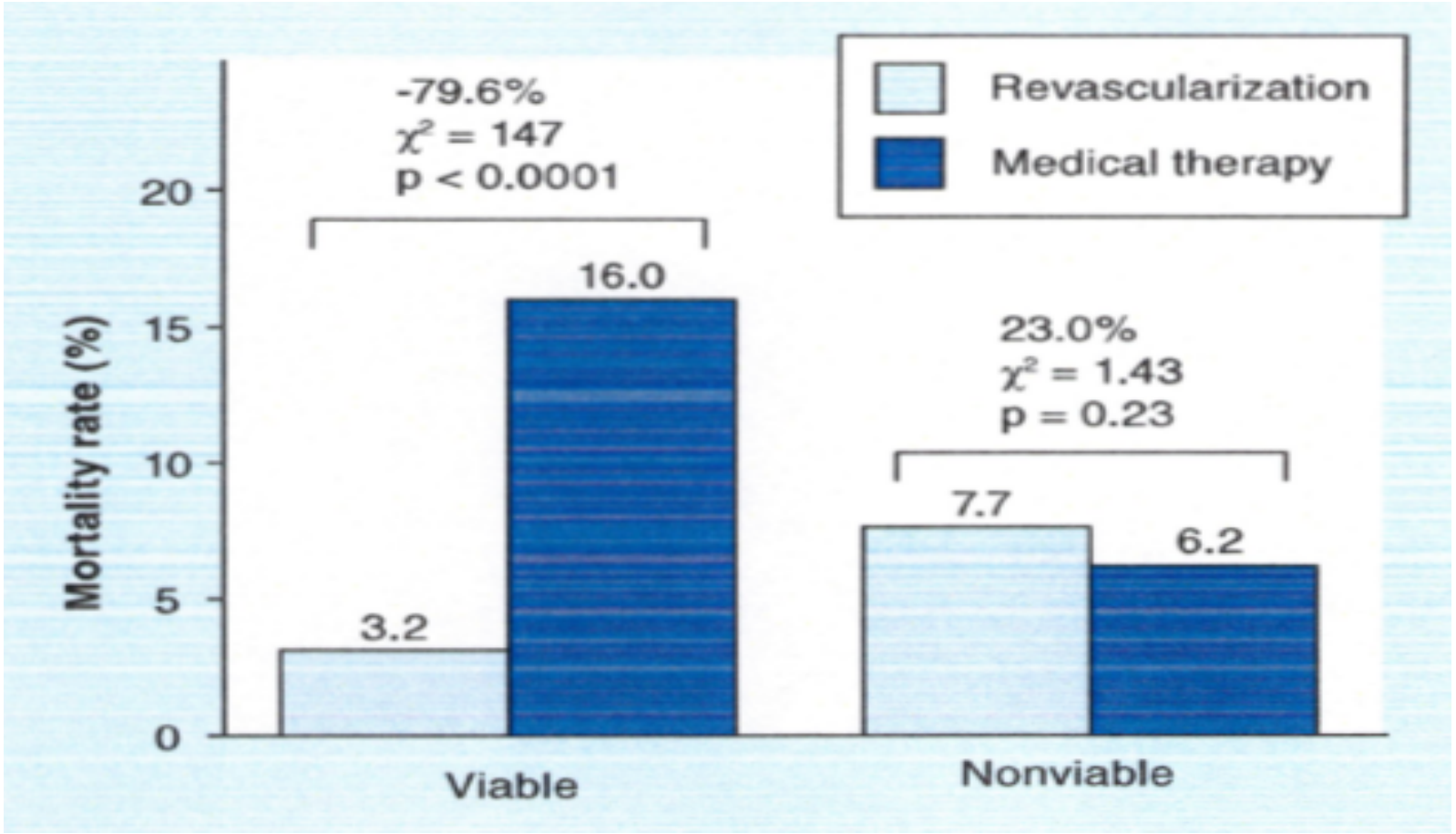
Imaging Modalities to Assess Myocardial Viability

Modality	Mechanism	Findings to Suggest Viability	Advantages/Disadvantages
CMR	LGE Wall thickness	LGE<50% wall thickness Systolic thickening of a dyskinetic segment	A: highly sensitive, no radiation, assess valves D: limited availability, cost, devices, renal failure
Dobutamine echo (CMR)	Contractile reserve	Improvement by visual or strain rate imaging	A: highly specific, widely available, no radiation, assess ischemia D: interobserver variability, dobuatmine risks
SPECT Thallium-201	Perfusion: sarcolemma membrane integrity (K analogue)	Tracer uptake:>50% of max	A: available, moderate cost D: radiation dose, moderate sensitivity with low specificity
Technietium-99m labeled tracers	Mitochondrial membrane integrity	>50-65% maximum	A: available, cost D: moderate accuracy
PET	Perfusion: 13NH3, 82Rb, 150-water Glucose utilization: FDG	Flow-metabolism mismatch = hibernation Match =nonviable	A: highly sensitive D: limited availability, high cost, complex in diabetics

How Do I Pick a Test?

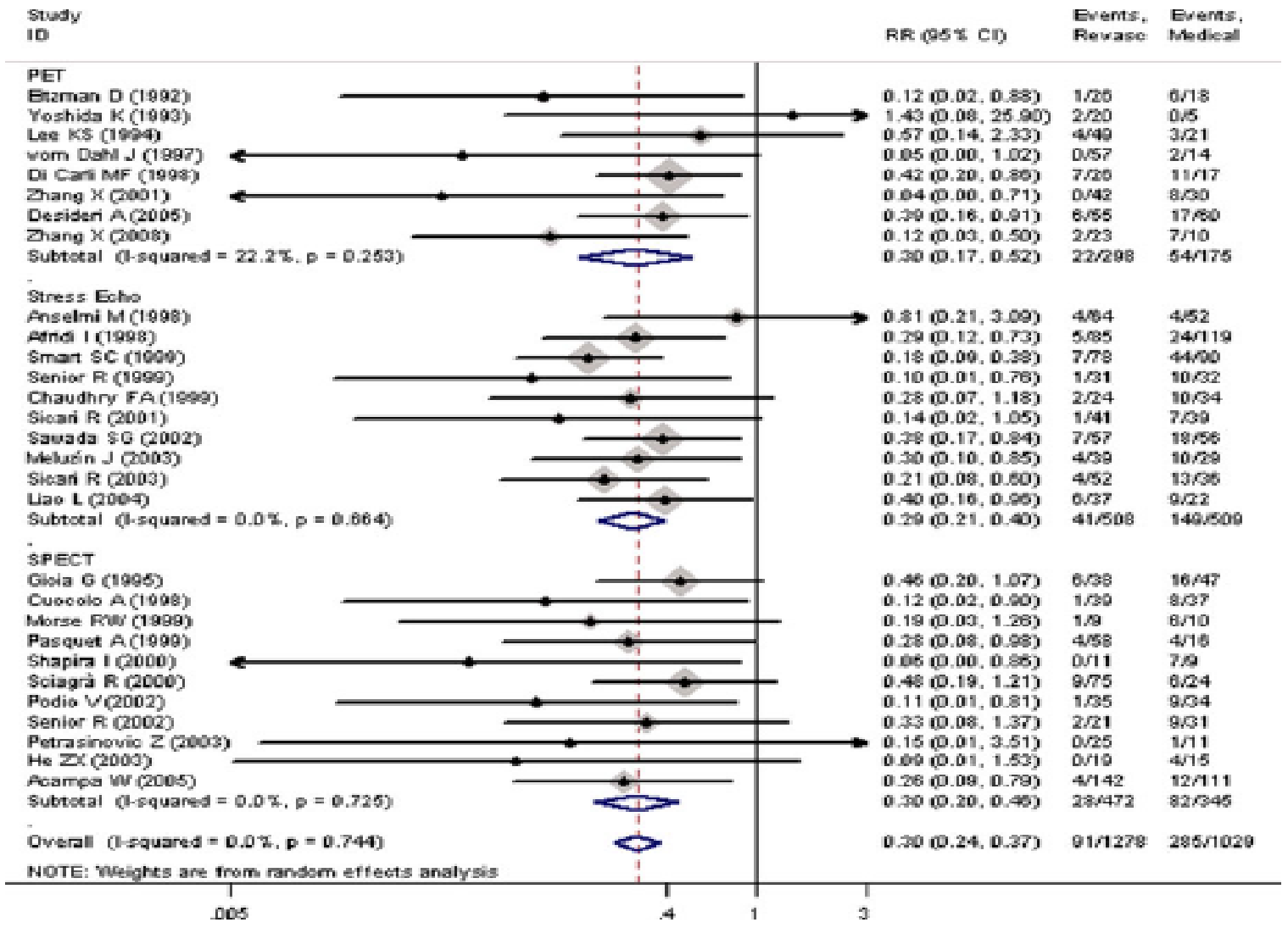
- Moderate LV dysfunction – any modality with local expertise
- Severe LV dysfunction – nuclear methods (SPECT, PET) or CMR LGE – more sensitive than contractile reserve
- Renal failure (GFR<30) or CMR incompatible devices – avoid CMR
- Critical left main or proximal 3VD – avoid dobutamine
- Equivocal or negative results on another viability test – consider PET or CMR as highly sensitive methods

Effect of Revascularization on Mortality



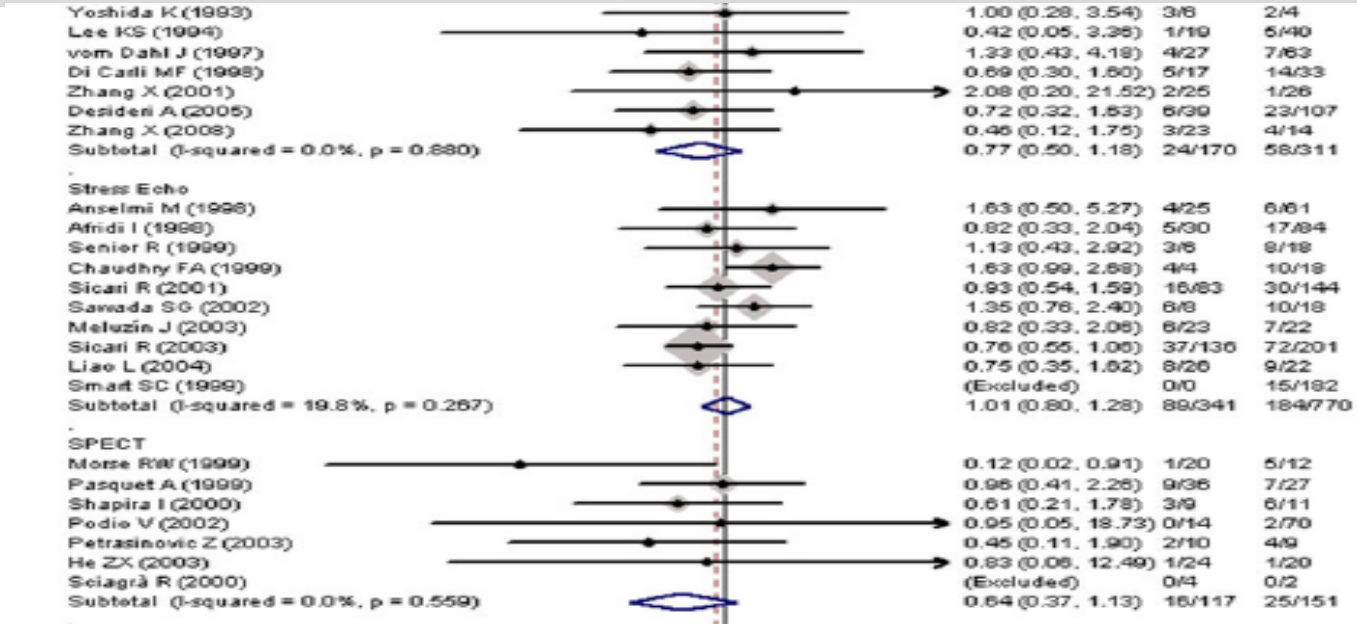
Allman, JACC 2002

Effect of Revascularization on Mortality in Patients with Viability



Inaba, et al. J Nuc Cardol 2010;17(4) 646

Effect of Revascularization on Mortality in Patients with NO Viability



Group	Weighted Average Annual Mortality (95%CI)
Medical therapy – viability present	10.64 (8.17 -13.12)
Medical therapy – viability absent	11.69 (8.87 – 14.51)
Revascularization – viability present	3.71 (2.31, 5.12)
Revascularization – viability absent	8.45 (5.80, 11.10)

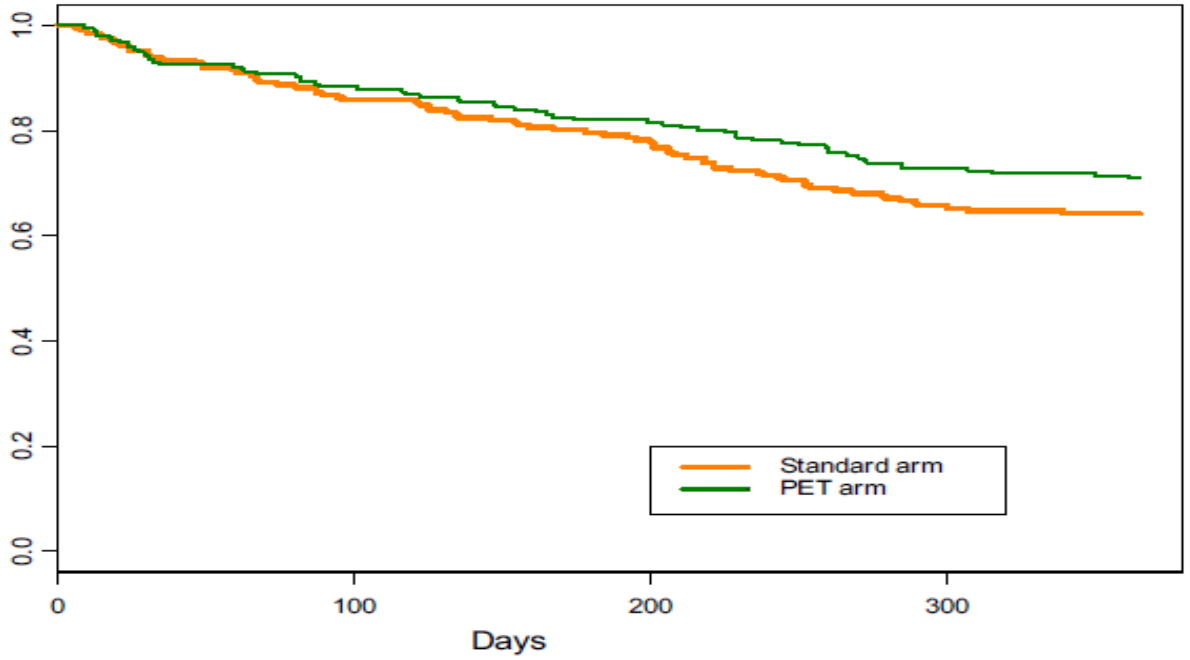
Inaba, et al. J Nuc Cardol 2010;17(4) 646

Limitations of the literature on viability testing

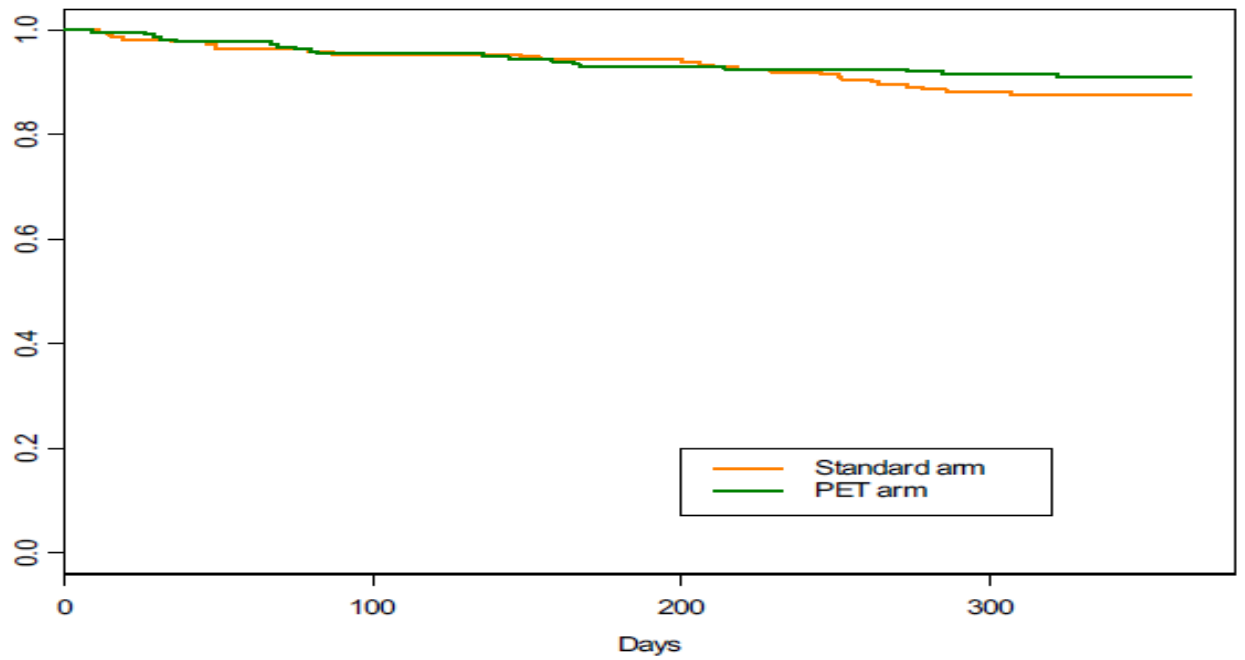
- Nonrandomized studies with small sample sizes
- Referral and selection bias
- Lack of uniformity of medical therapy
- Lack of head-to-head comparisons between techniques
- No evaluation of graft/vessel patency at time of post revascularization functional assessment
- Unknown duration and severity of LV dysfunction prior to revascularization
- Frequent exclusion of patients who did not get revascularized or died during revascularization

Viability Testing and Prognosis: The PARR 2 Trial

Time to Composite Endpoint (CV death, MI, cardiac admission)

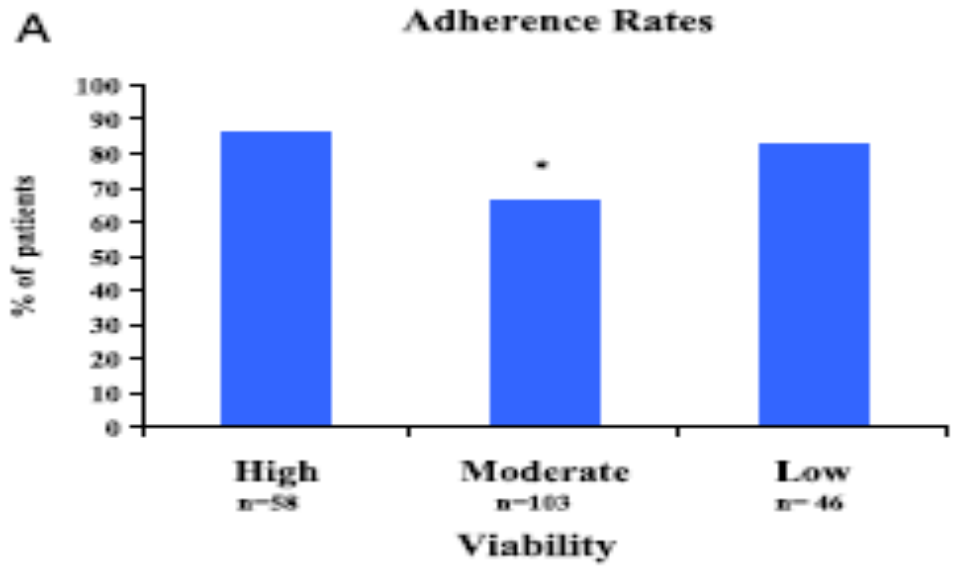


Time to Cardiac Death

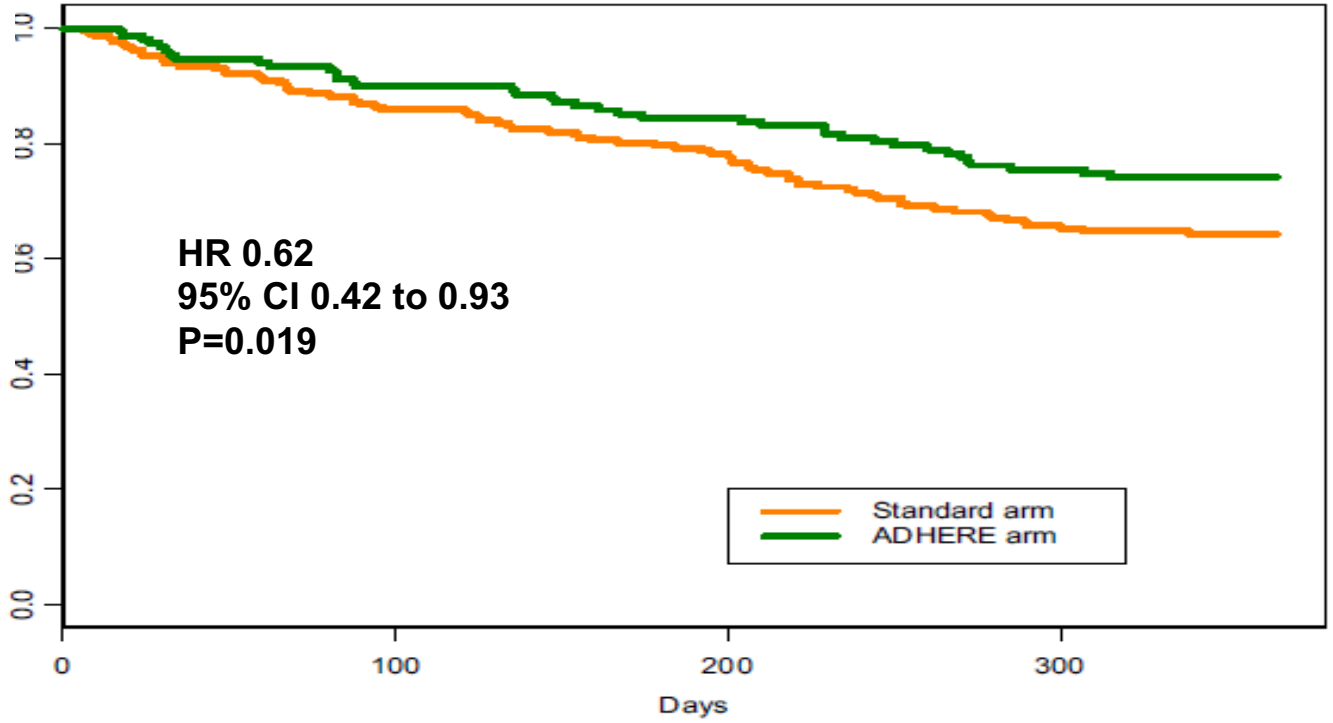


Beanlands; JACC 2007;50:2002

Adherence to Recommendations

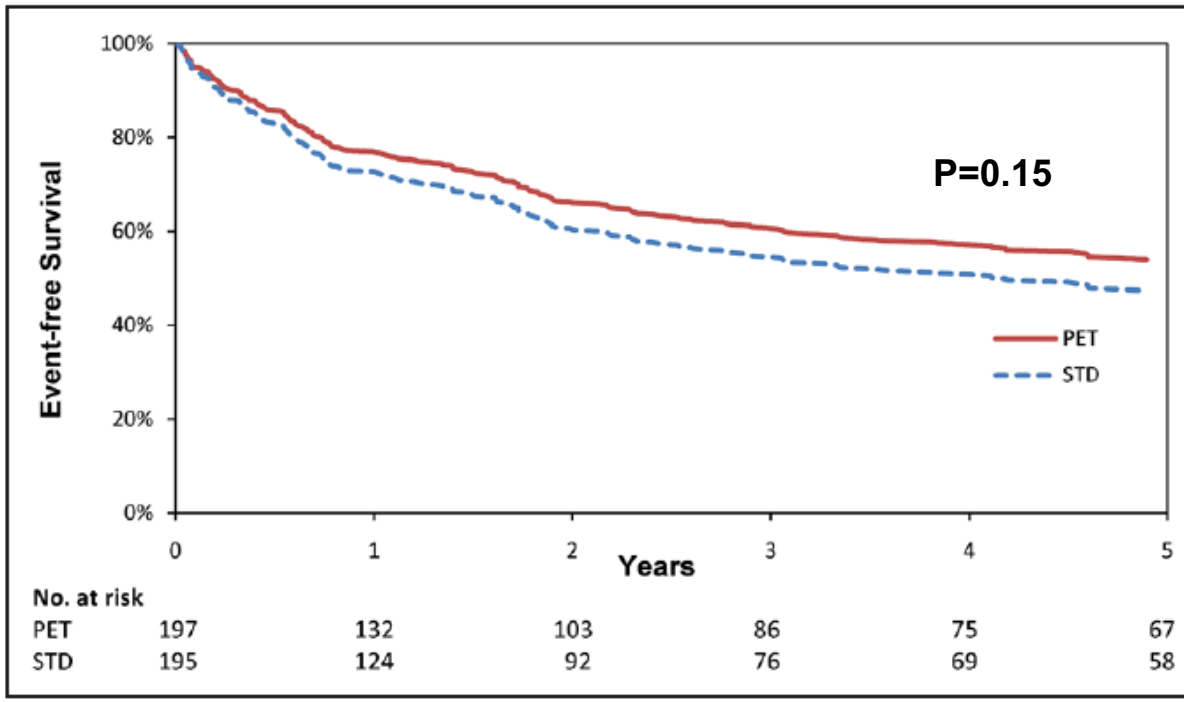


Time to Composite Endpoint

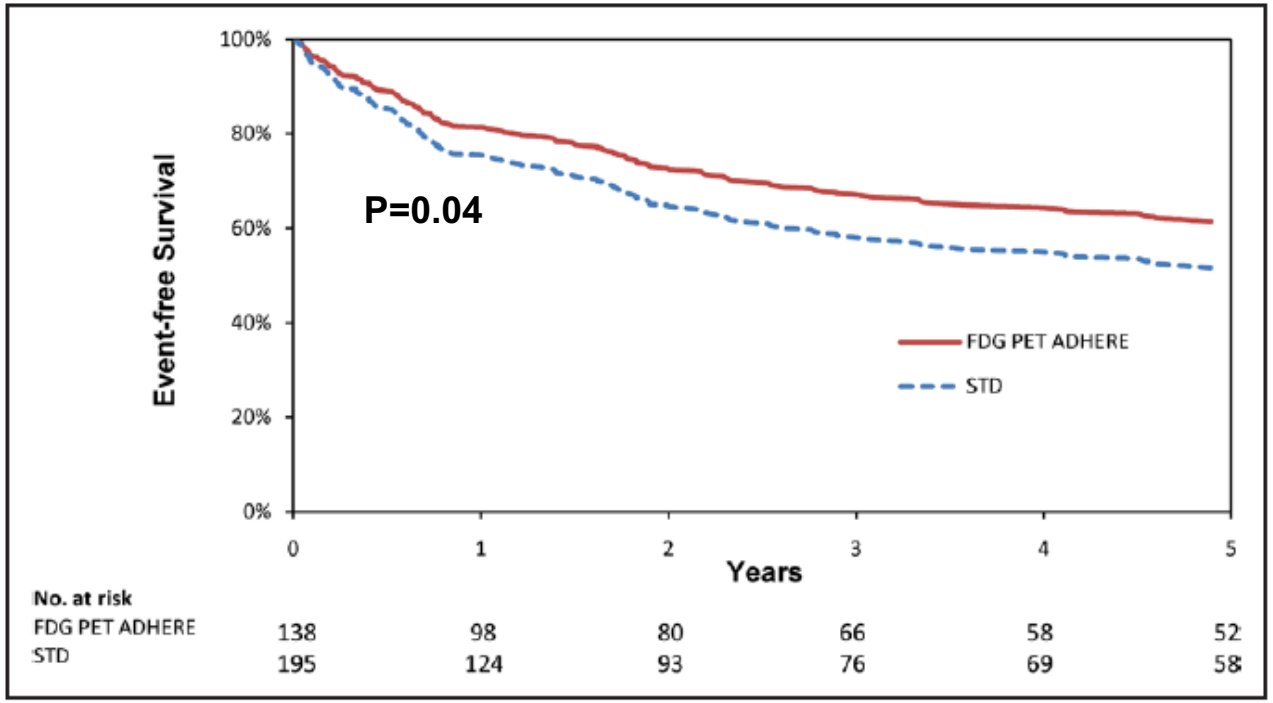


Beanlands; JACC 2007;50:2002

Long Term Follow-Up of PARR-2



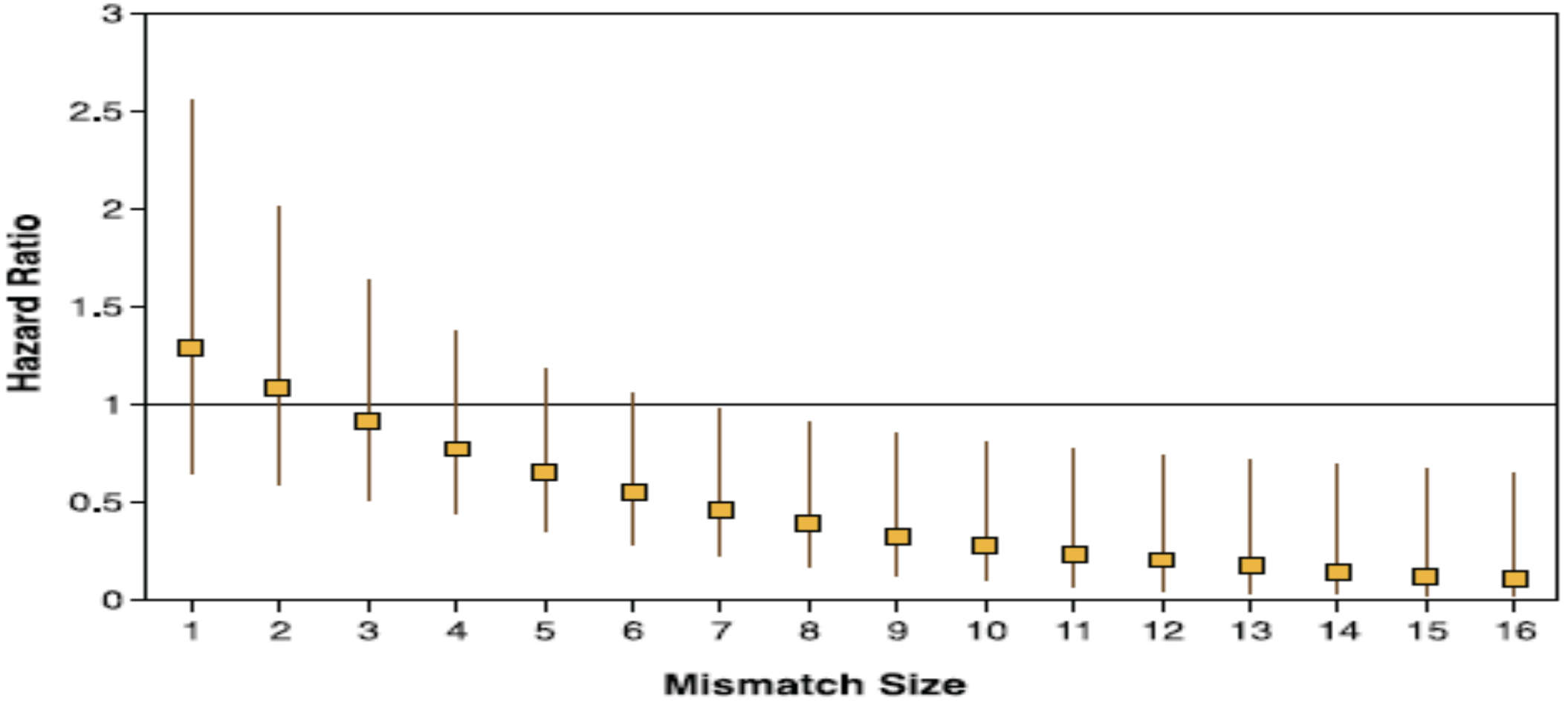
Whole Cohort



Patients who Adhered to Imaging Recommendations

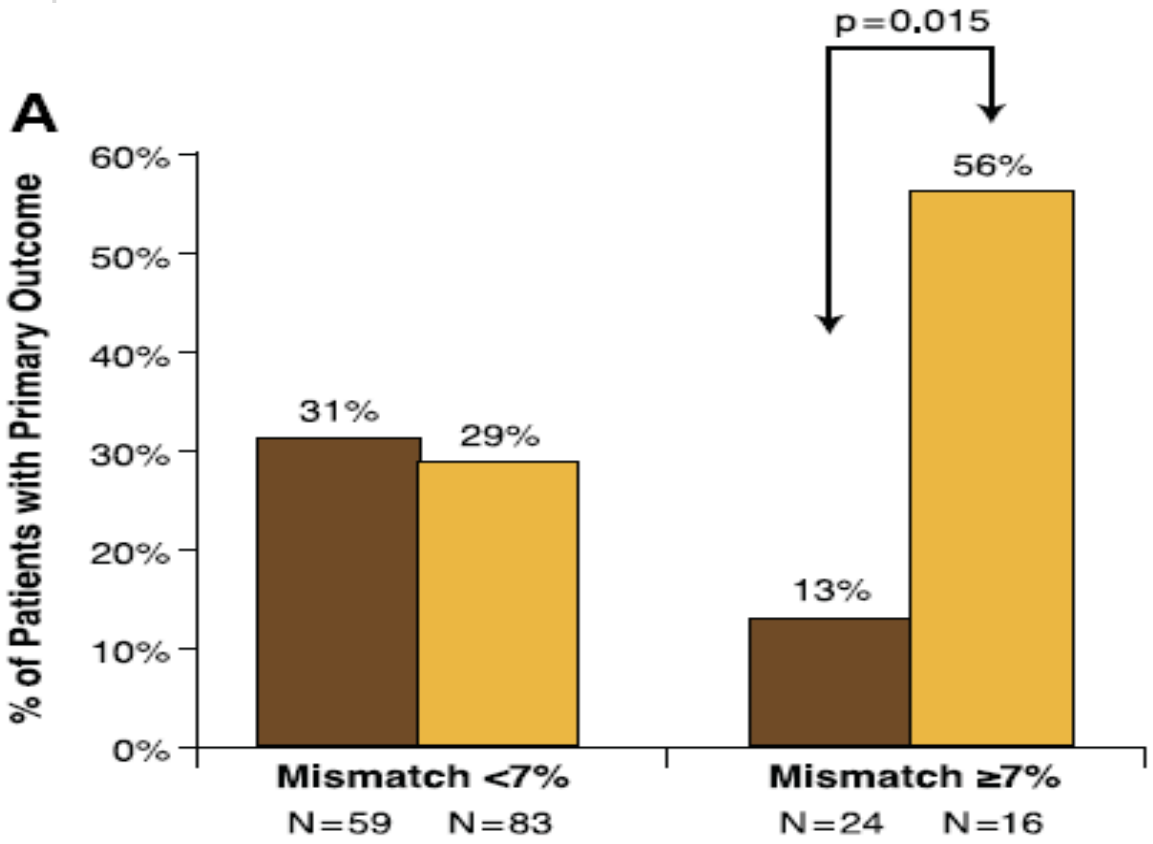
McCardle at al. Circ CV Imag 2016

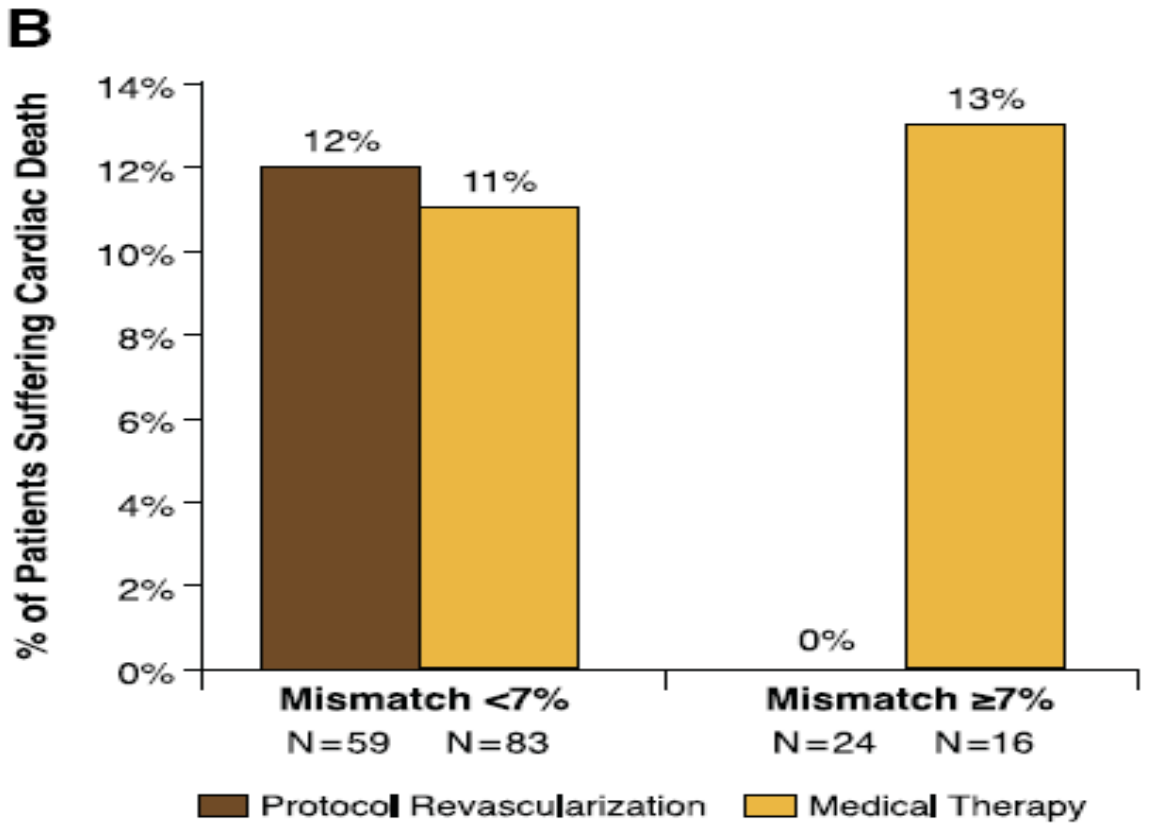
Increasing Benefit with Increasing Hibernation



D'Egidio JACC 2009;2:1060

Increasing Benefit with Increasing Hibernation





D'Egidio JACC 2009;2:1060

STICH Results

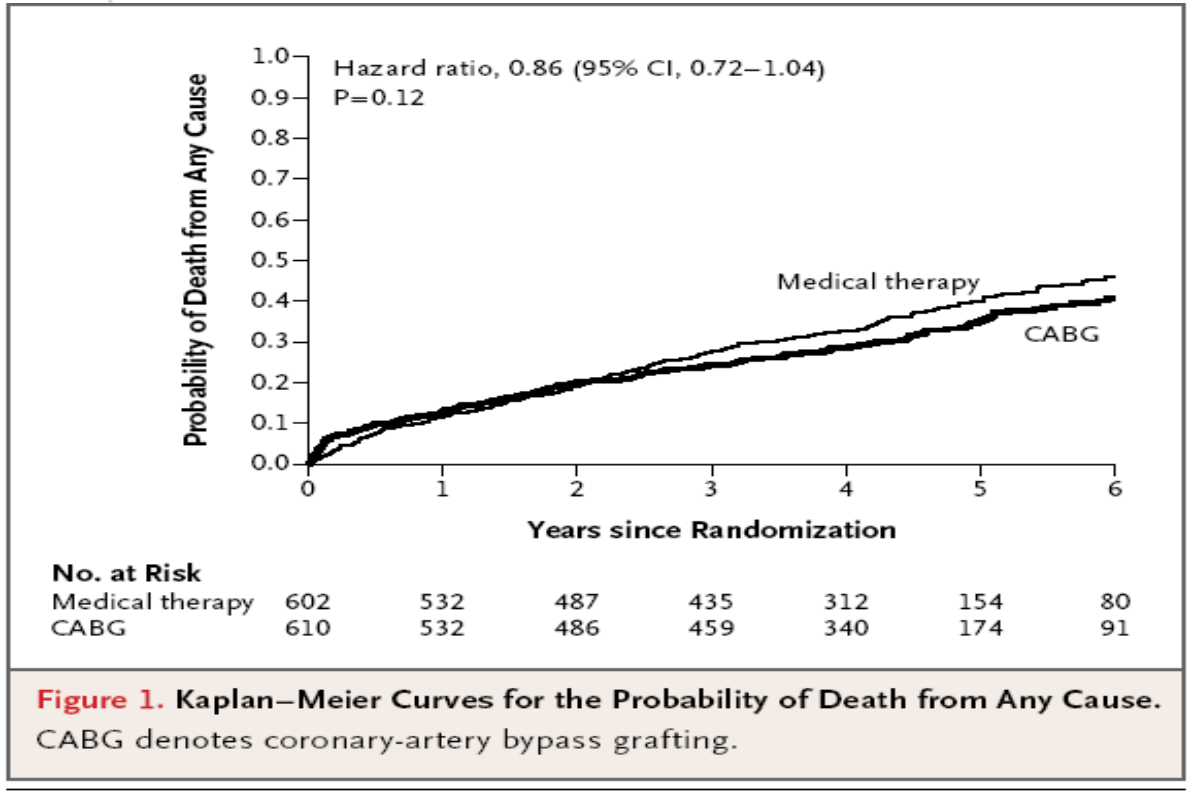
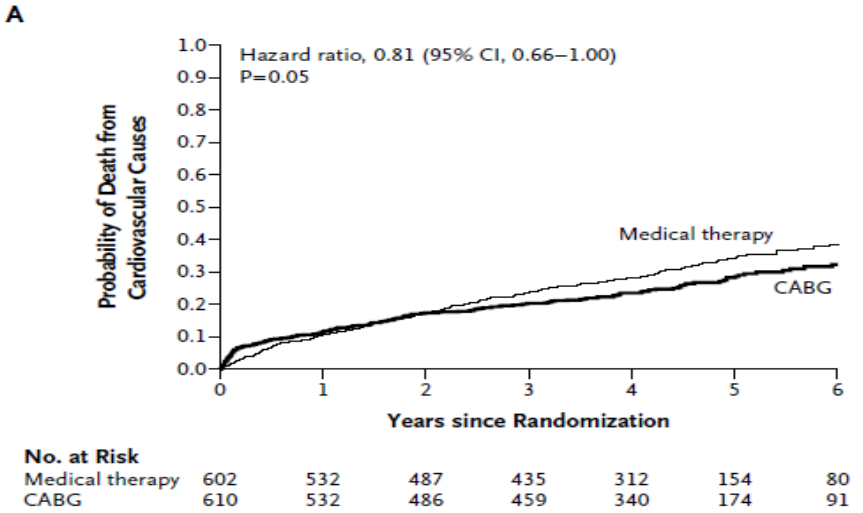
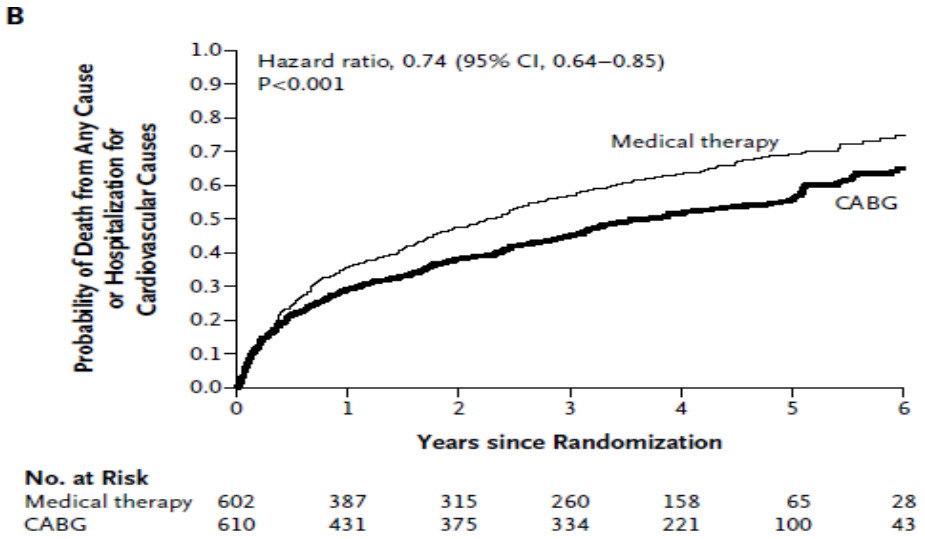


Figure 1. Kaplan–Meier Curves for the Probability of Death from Any Cause. CABG denotes coronary-artery bypass grafting.



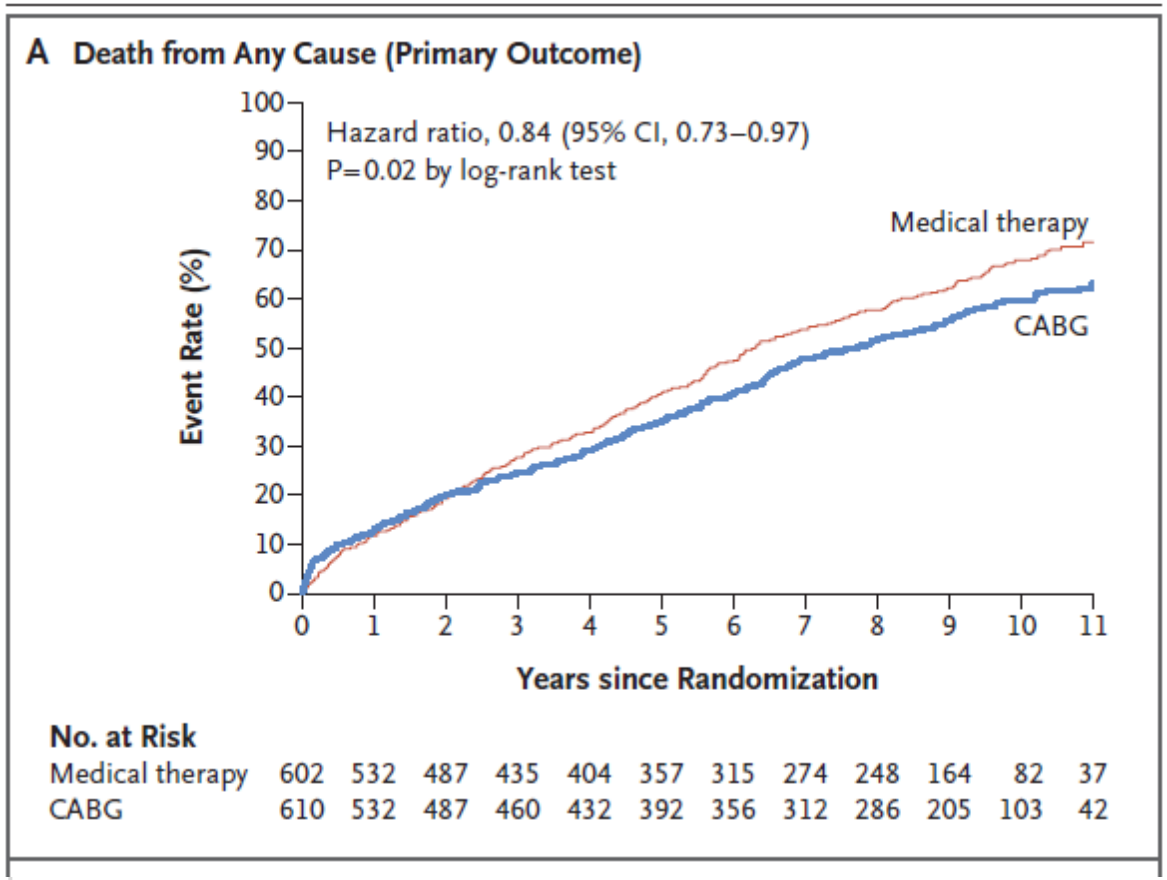
CV Death: 28% CABG vs. 33% medical

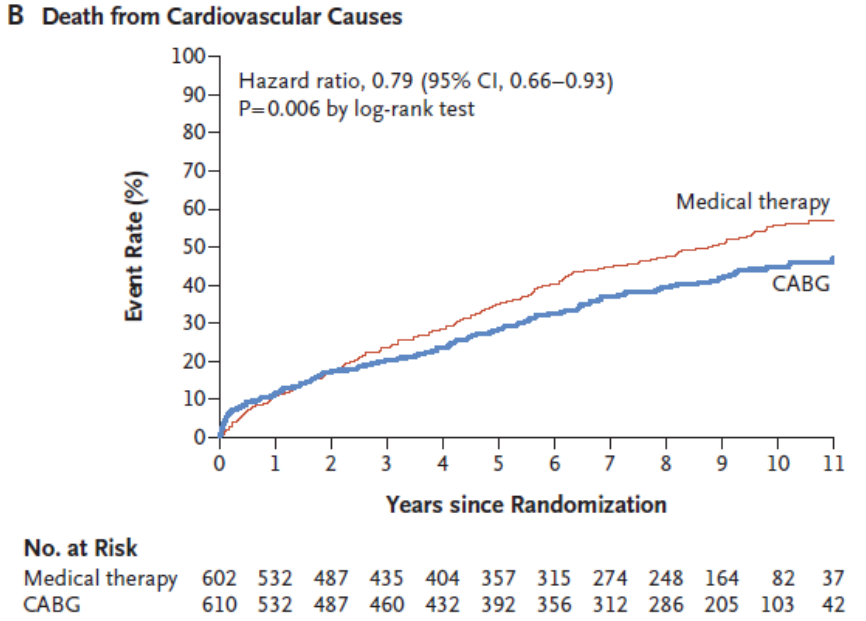


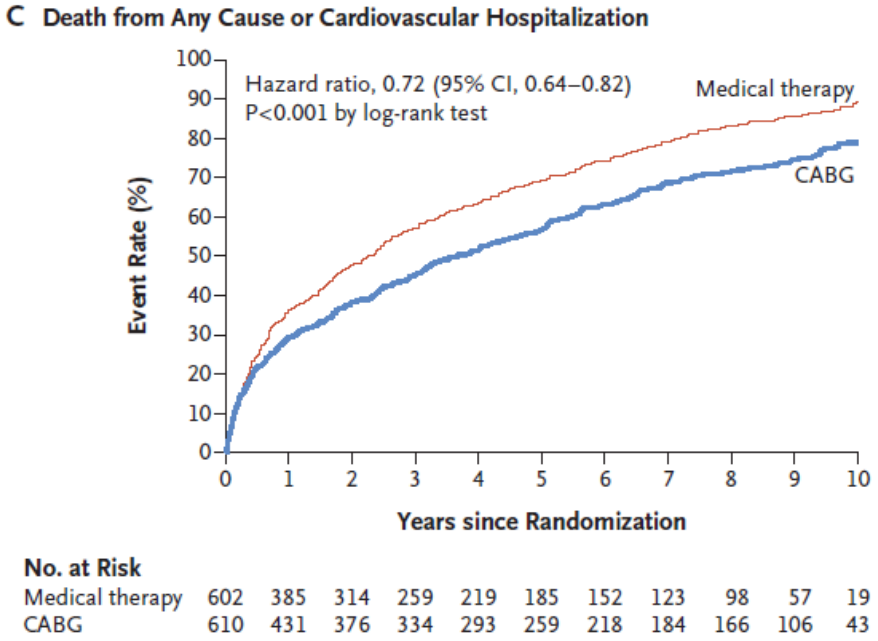
CV Death/admission: 58% CABG vs. 68% medical

Velazquez, et al N Engl J Med 2011, April

STICHES Long Term Extension Study

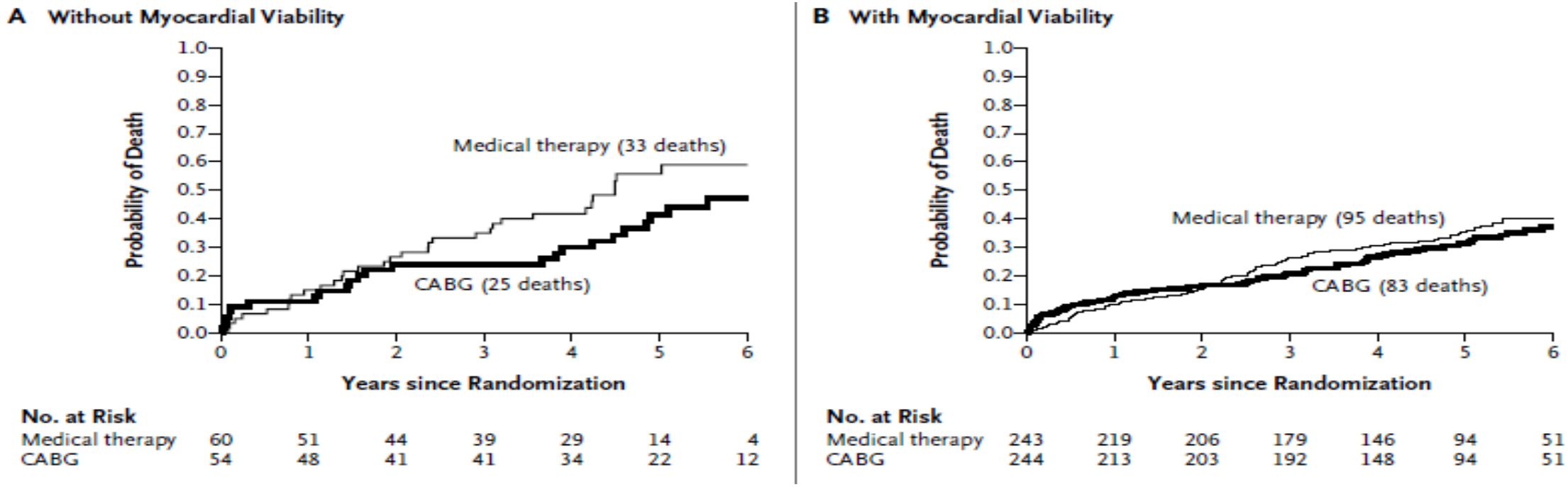






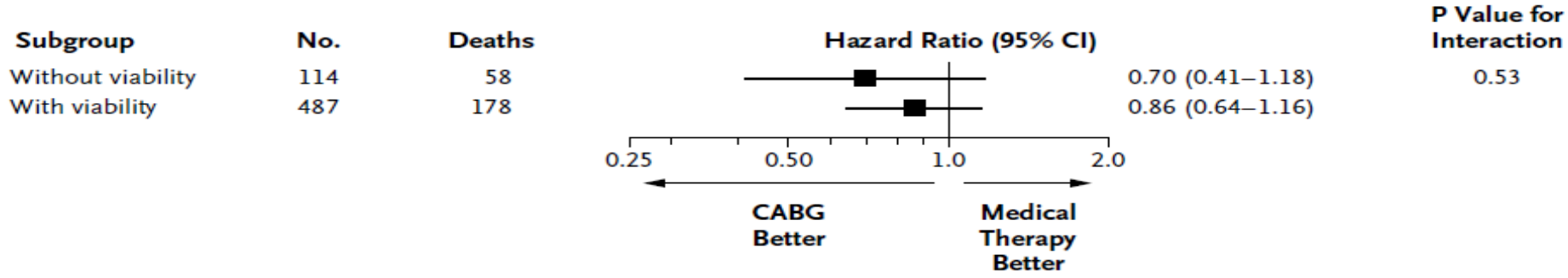
Velazquez, et al N Engl J Med 2016; 374:1511-20

STICH Viability



Mortality 56% medical vs. 41% CABG

Mortality 35% medical vs. 31% CABG



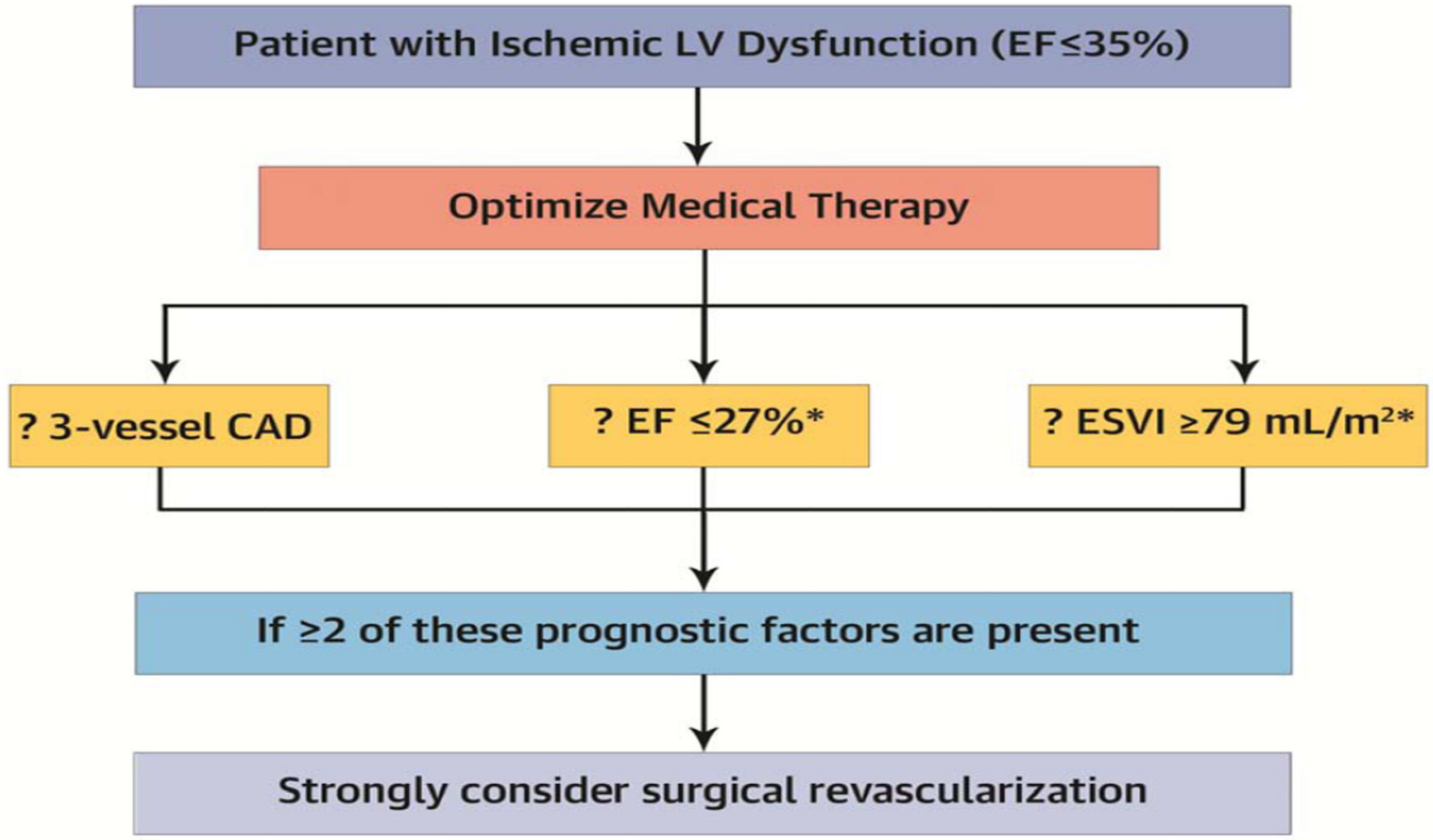
Bonow et al. N Engl J Med 2011; April

Comparing STICH to PARR2

	Variable	STICH Sub-study	PARR2
Patient population	Randomized?	No	Yes
	Mean age (years)	60.7	63
	Male Sex (%)	85	84
	Previous CABG (%)	3	19
	Multi-vessel disease (%)	75	90
	DM (%)	39	39
	GFR<60 (%)	7.5	34
	Mean serum creatinine		108
	Mean LVEF	27	26
Viability testing		SPECT or dobutamine echo 81% viable	PET 22% viable
Report		No report of ischemia or hibernation	Ischemia/hibernation reported

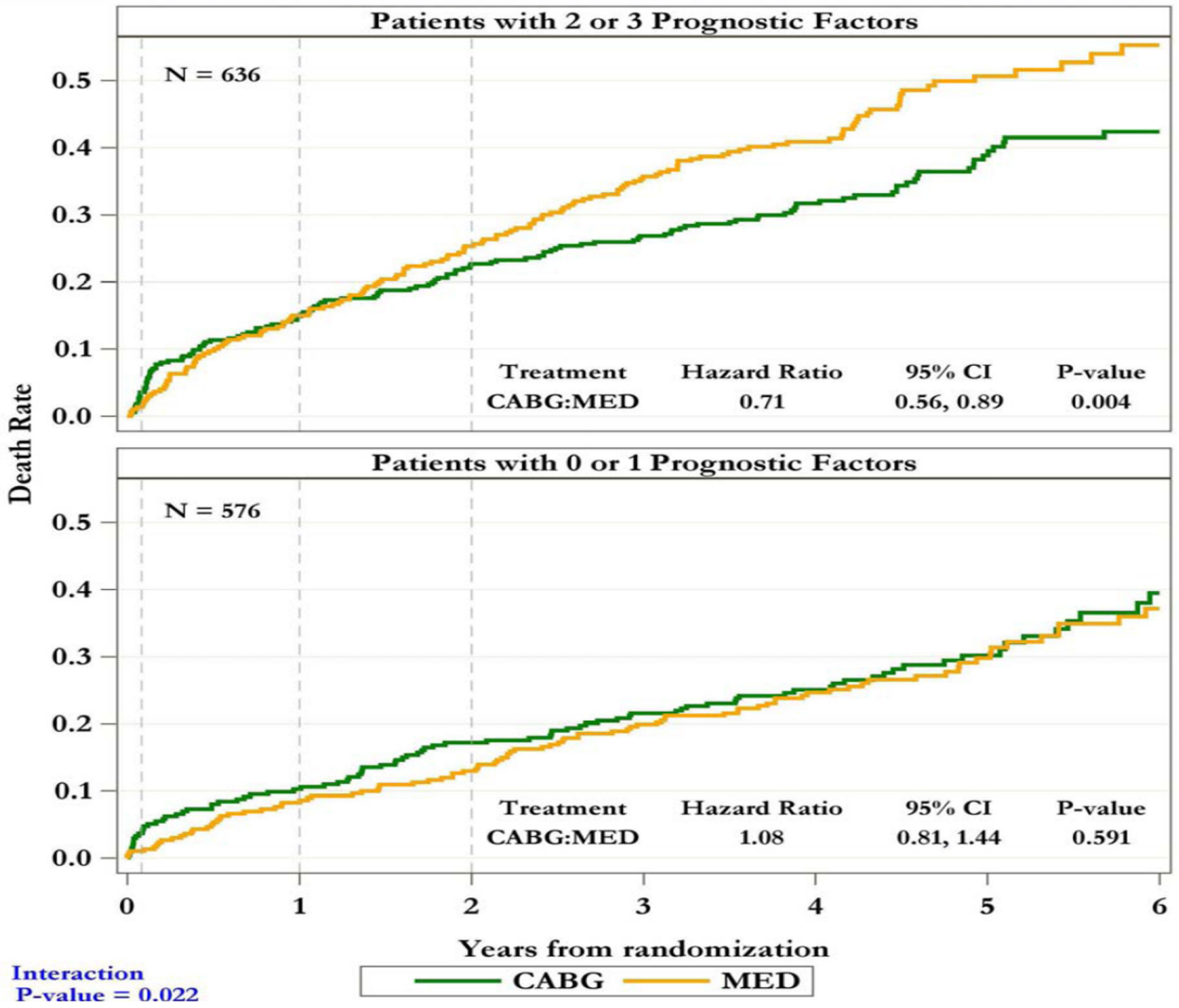
What Other Clinical Factors Can Help Guide Us in Decision Making?

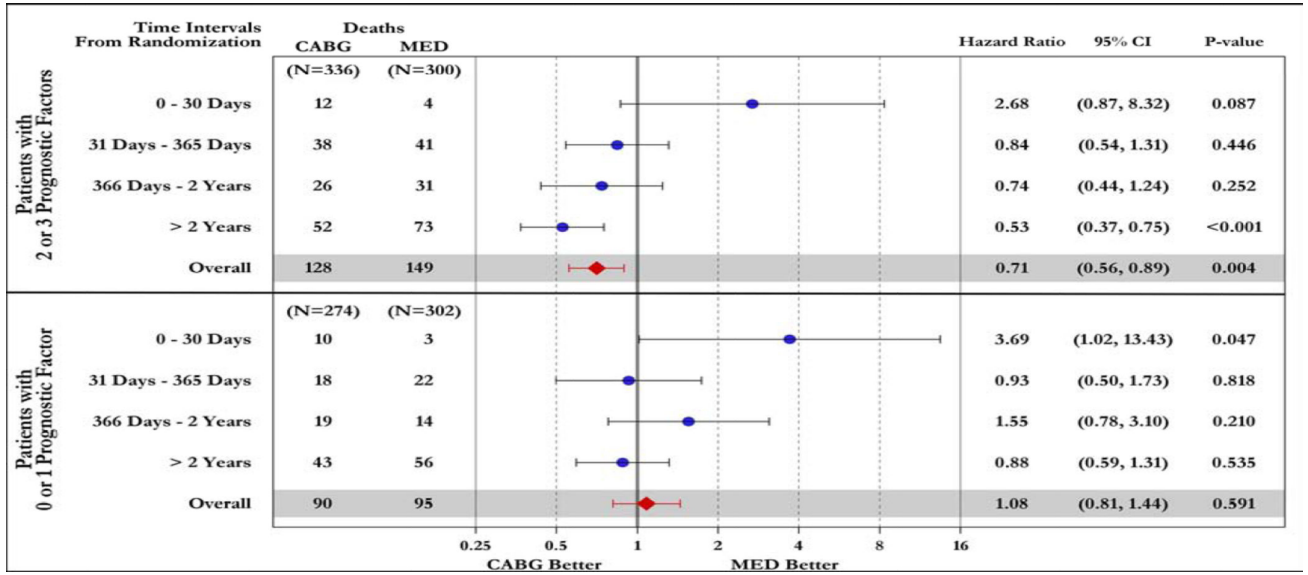
Extent of Disease May Predict Benefit



Panza; J Am Coll Cardiol 2014; 64:553

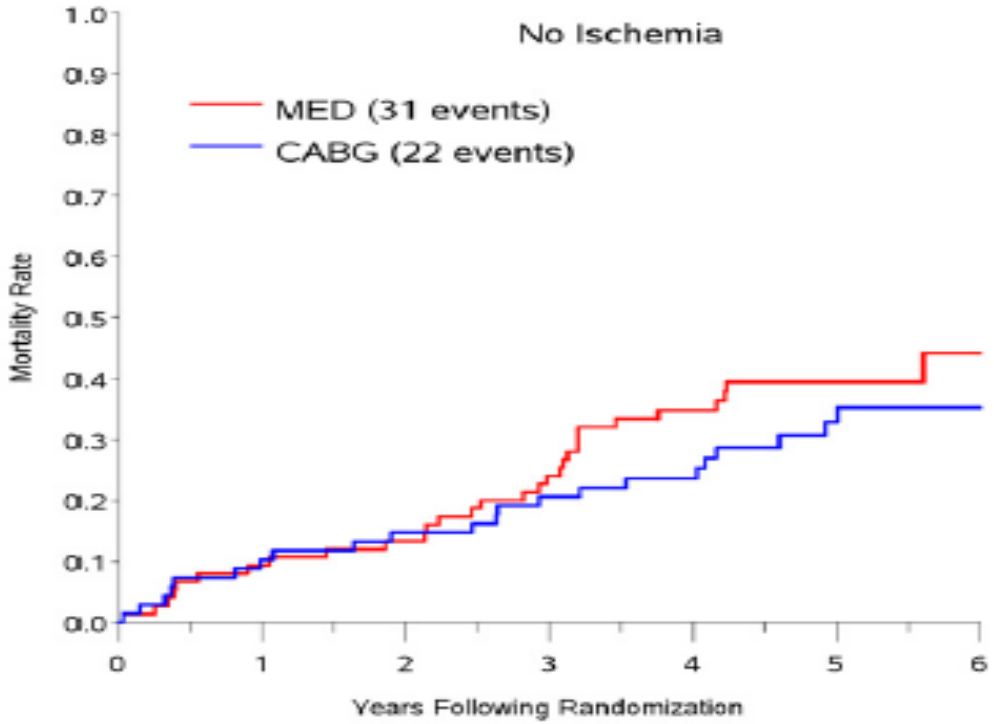
Extent of Disease May Predict Benefit

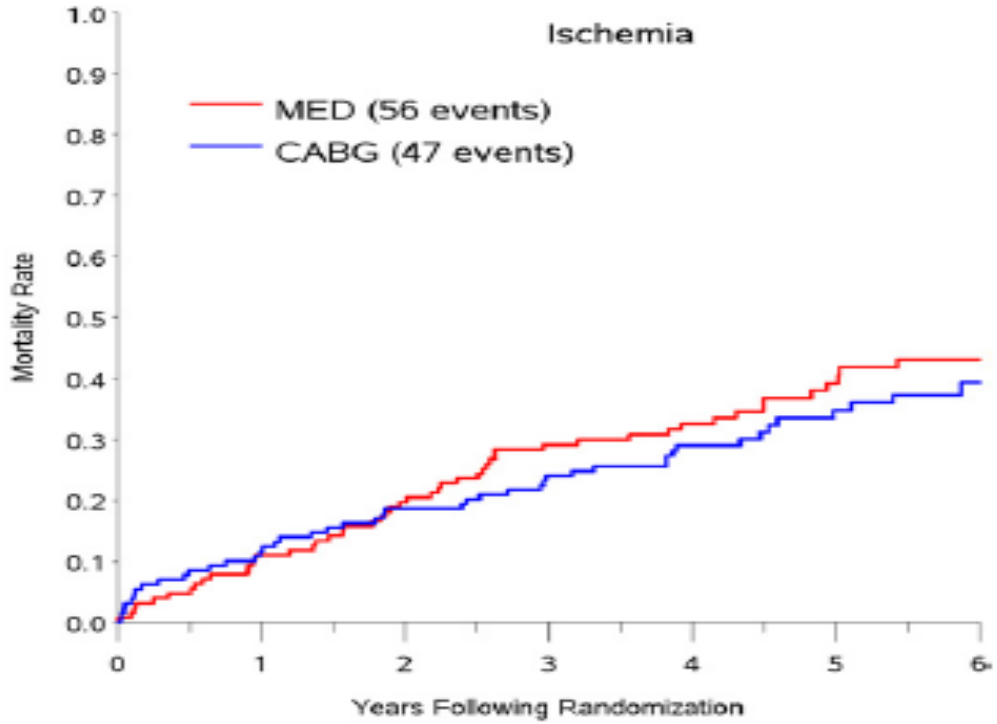




Panza; J Am Coll Cardiol 2014; 64:553

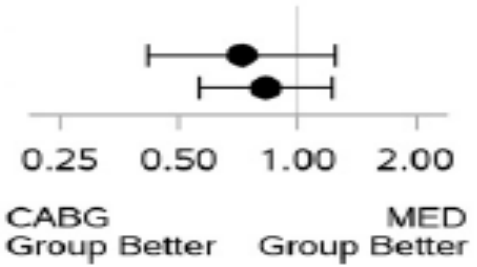
Is Ischemia Testing Relevant?





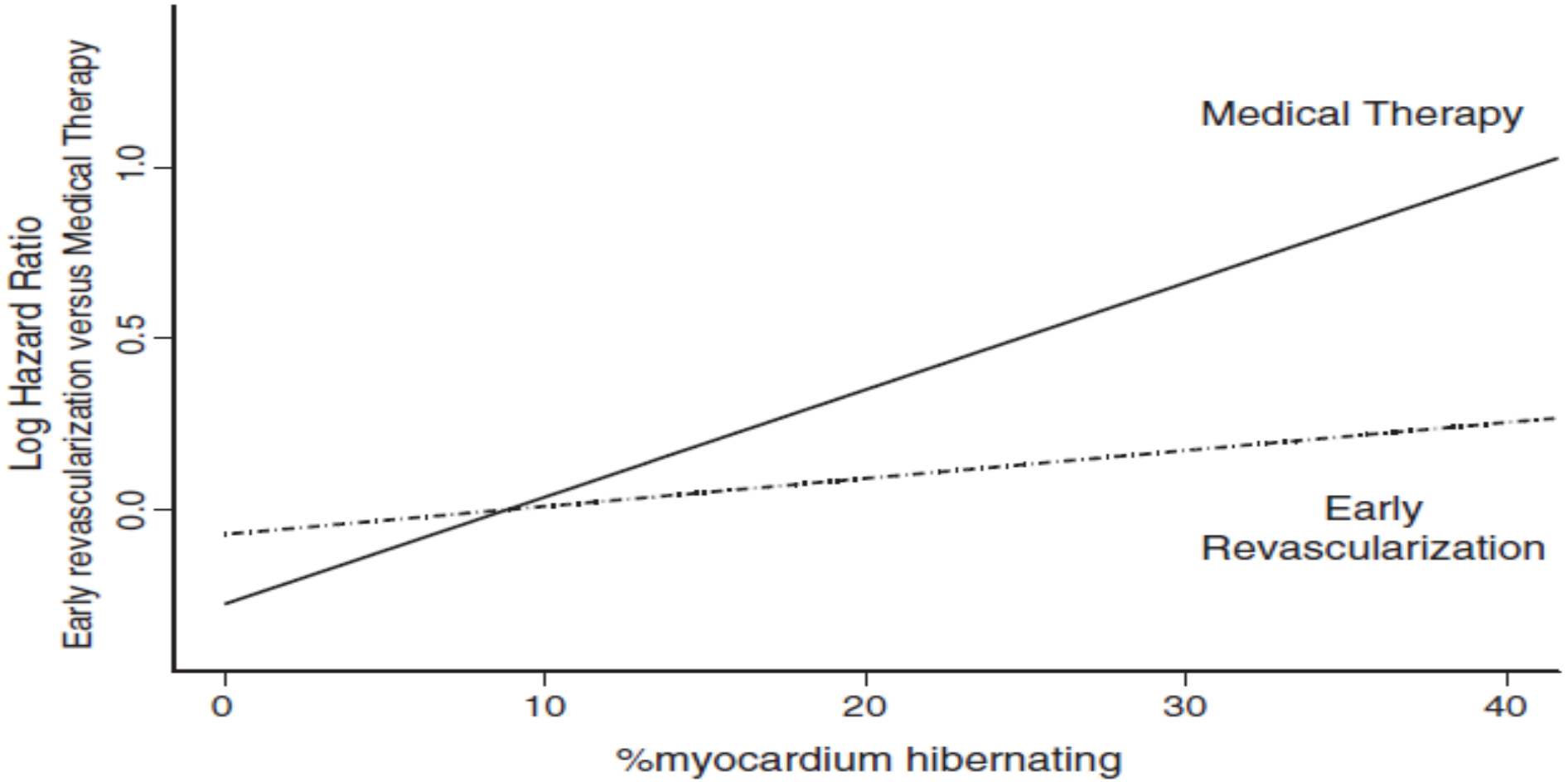
Sub-group	N	Events	Hazard Ratio	95% CI	5 Year Rates MED Group	5 Year Rates CABG Group
No Ischemia	143	53	0.72	0.42, 1.25	39.4 %	32.9 %
Ischemia	256	103	0.83	0.56, 1.23	39.2 %	34.8 %

Interaction with Treatment
P-value = 0.643



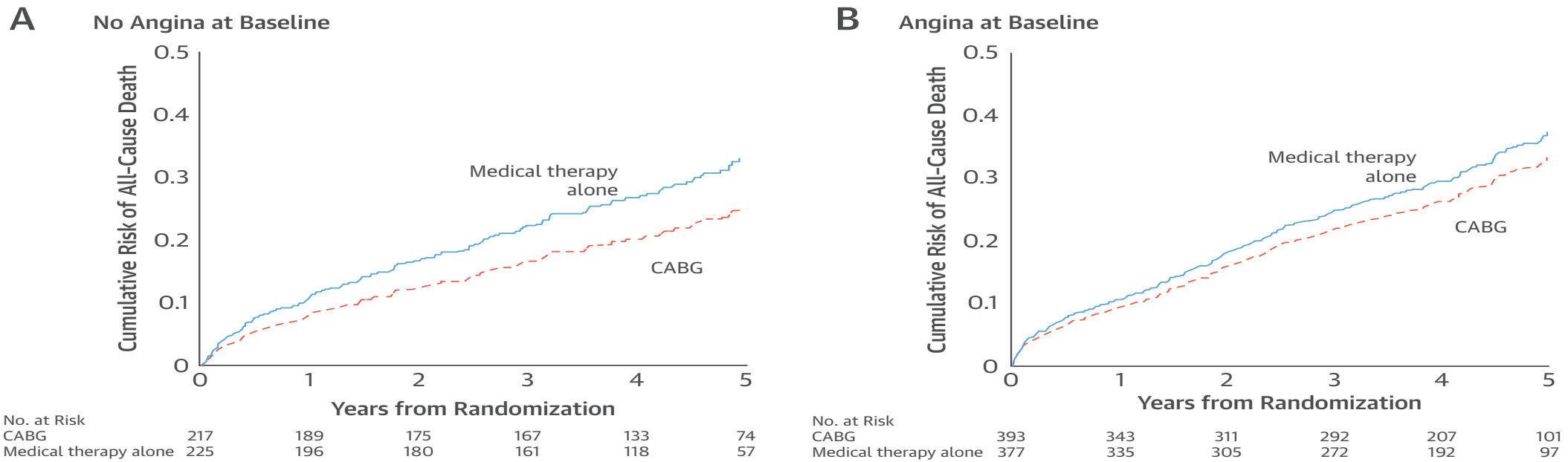
Panza; J Am Col Cardiol 2013; 61: 1860

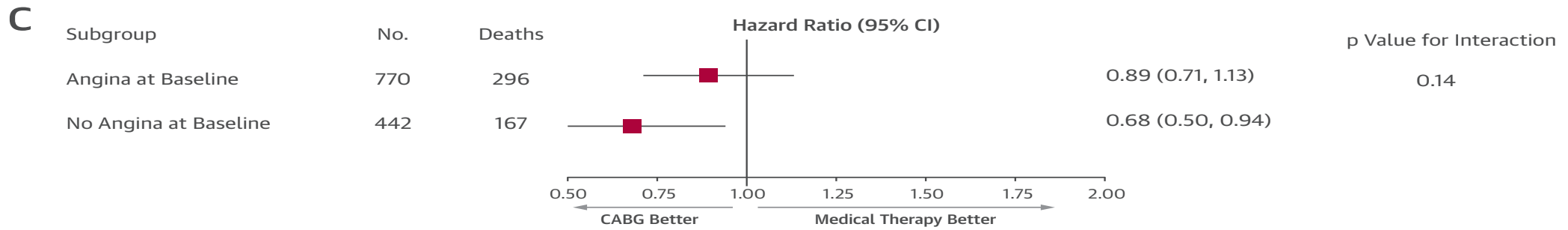
Inducible Ischemia vs. Hibernating Myocardium



Ling; Circ CV Imaging 2013; 6:363

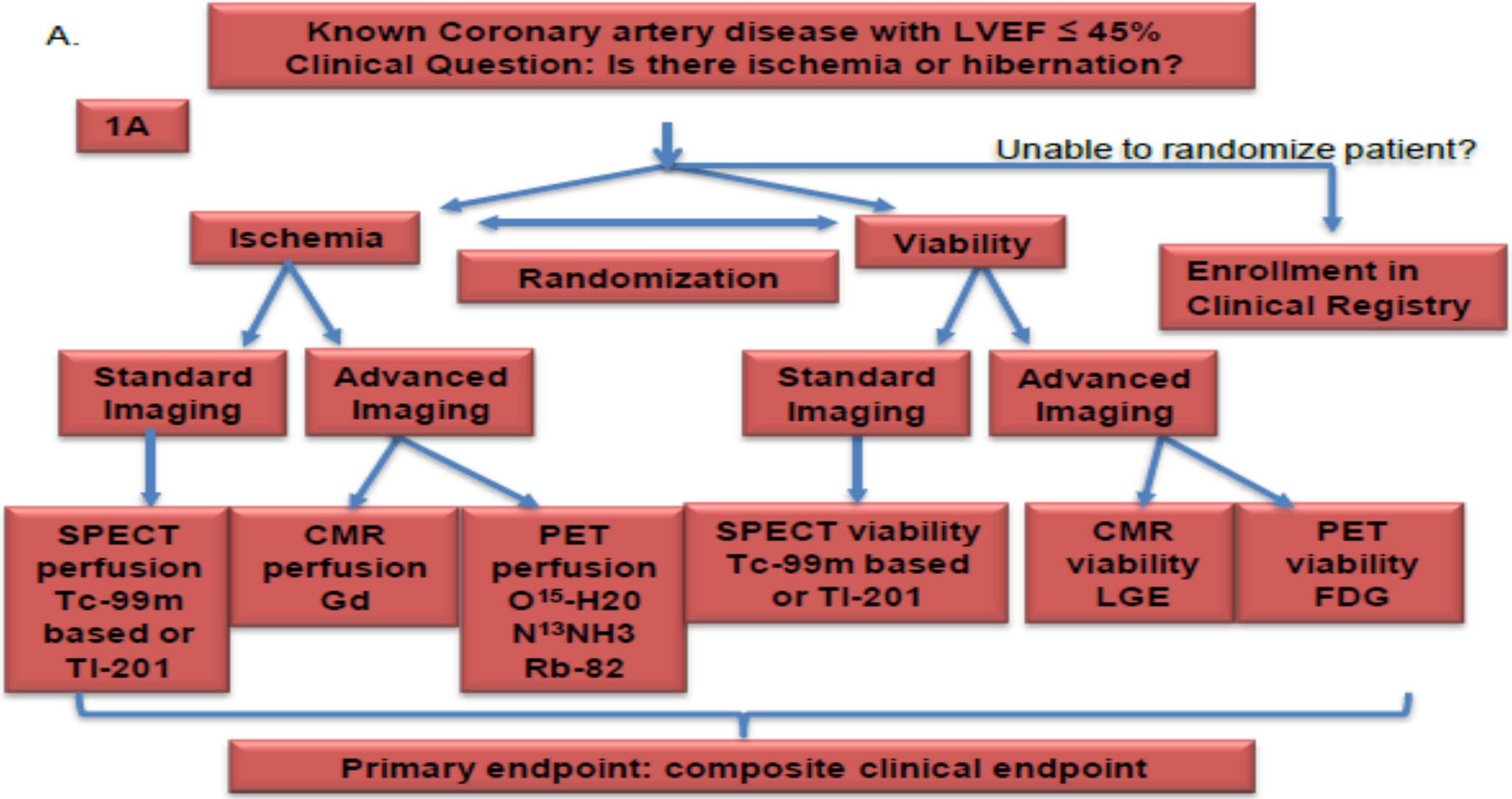
Does The Presence of Angina Matter?





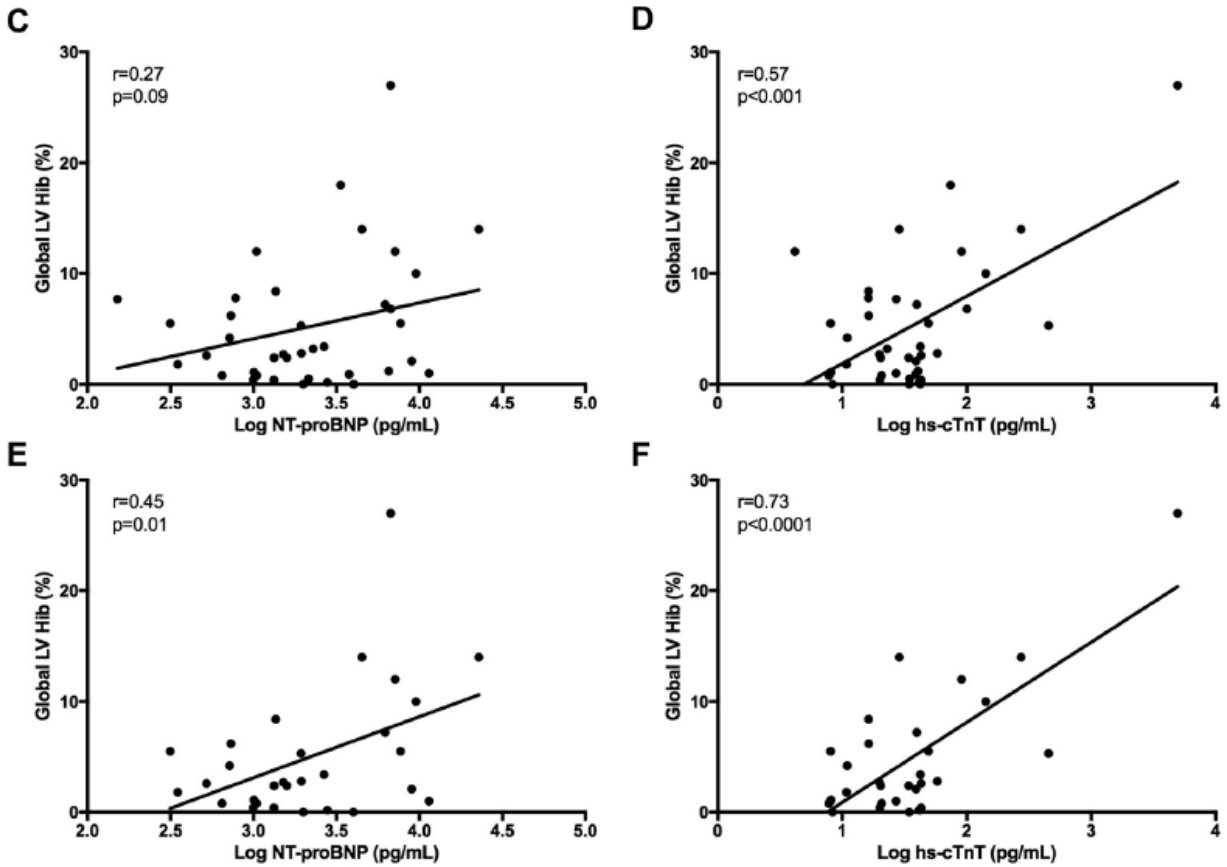
Jolcoeur et al. J Am Coll Cardiol 2015; e pub

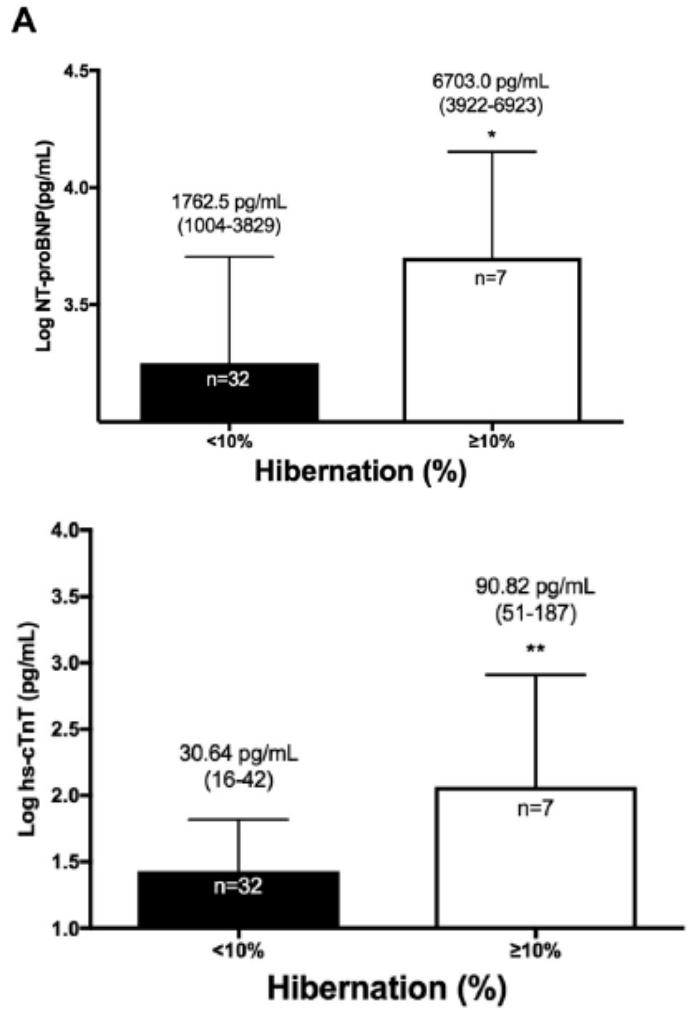
IMAGE 1A Study: AIMI-HF Study: RCT Evaluating Standard vs. Advanced Imaging in Patients with Ischemic CM



O'Meara E, Mielniczuk LM et al. Trials 2013; 14:332

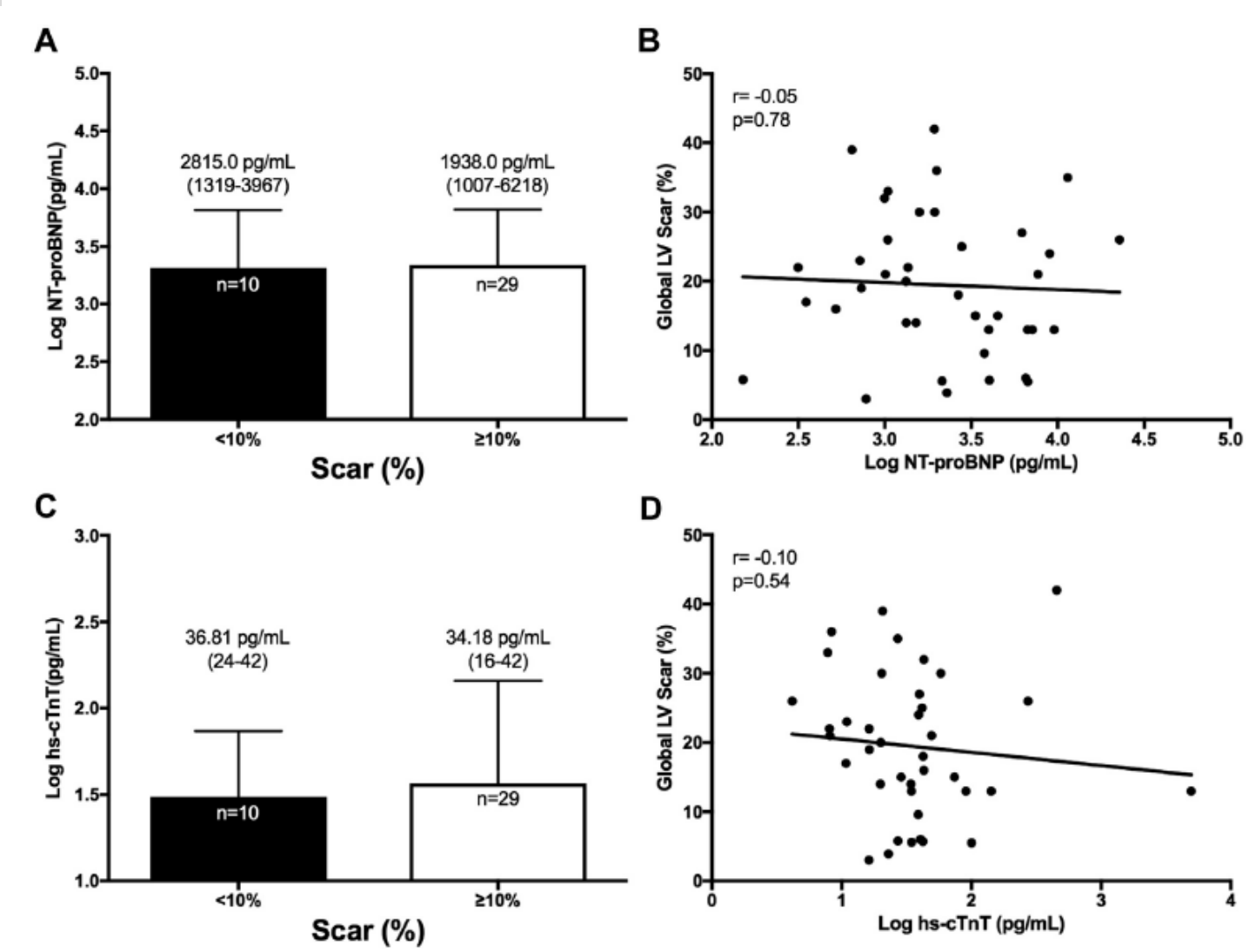
Can Biomarkers Aid in Decision Making?





Zelt JE, Mielniczuk LM, Can J Cardiol 2017; 1478-88

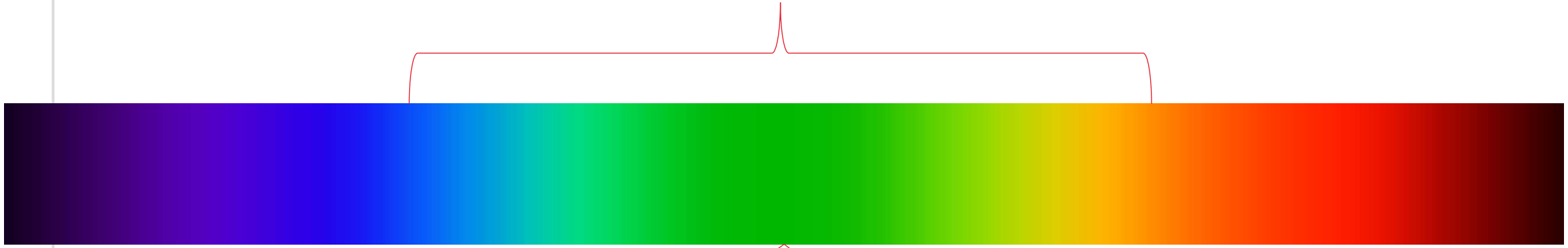
Can Biomarkers Aid in Decision Making?



Zelt JE, Mielniczuk LM, Can J Cardiol 2017; 1478-88

Coronary Disease Spectrum

•Some degree of LV dysfunction
•Mixture of hibernating myocardium
•Evidence of ischemia or symptoms of angina



Severe LV dysfunction
•Significant scar
•Predominant HF symptoms

Normal LV function
•Significant CAD
•Presence of angina

Patients with severe CAD:
•Only demonstration of viability may be necessary

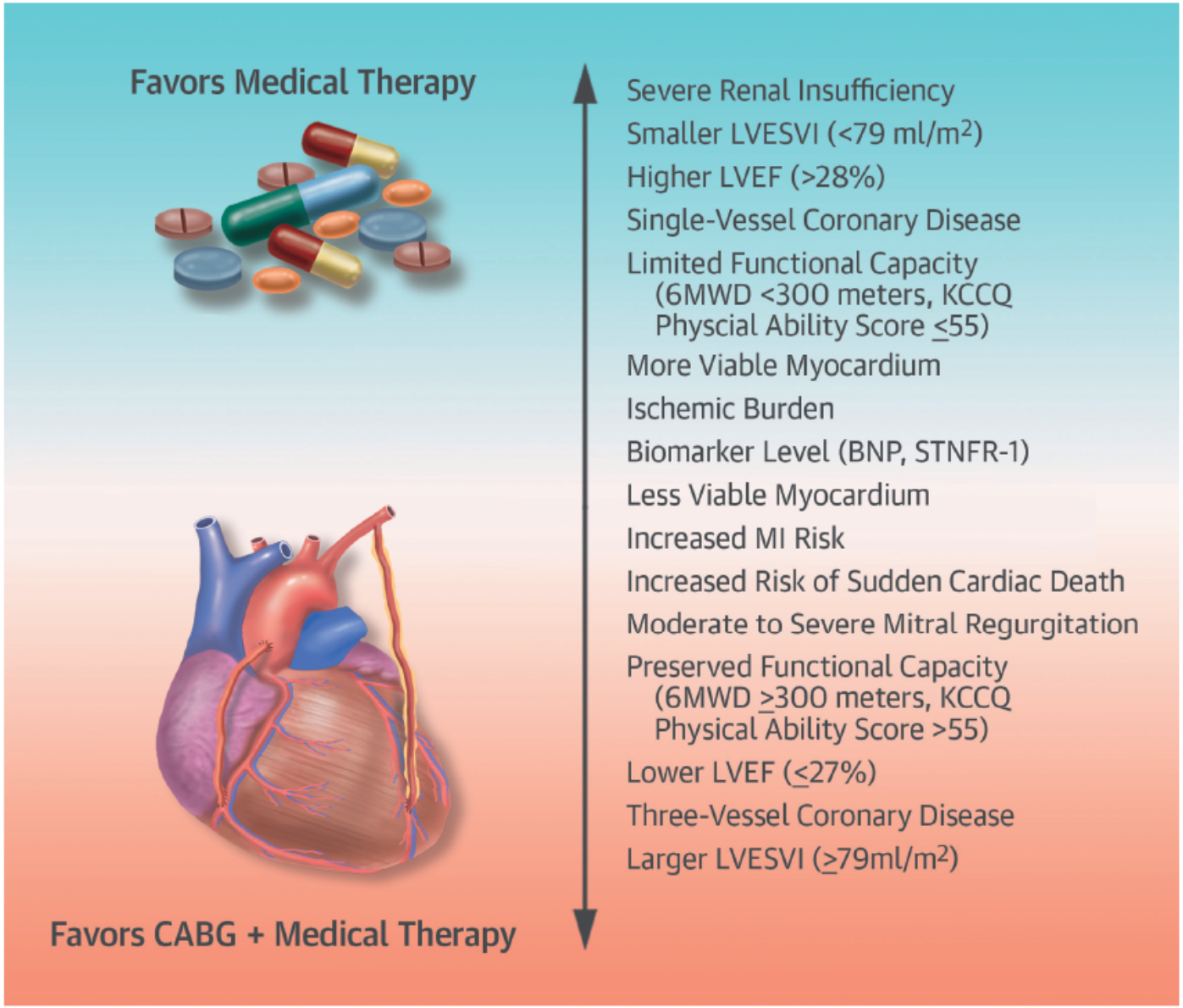
Mild-moderate CAD
•Ischemia testing may be of benefit

Decision Making for Viability Assessments

Viability Testing Unlikely to Add Useful Information	Viability Testing May Be Helpful
Younger patients	Older patients
HFrEF with >class II angina	HFrEF with no angina
Moderate-severe ischemia on provocative testing	No evidence of ischemia
EF>40%	EF<40%
Left main coronary disease	Chronic total occlusions
No or limited co-morbidities	Severe/multiple co-morbid disease

Kandolin, Mielniczuk Can J Cardiol: in press

Decision Making for Revascularization in Heart Failure



Velazquez JACC 2015;65: 615-24

Concluding Remarks

- Viability testing is not for everyone
  - To be considered when it may impact management decisions
- The field has evolved significantly over 20 years
  - Over-reliance on viability info not needed to guide decisions
  - Personalized approaches to revascularization are needed
- Future Directions
  - Role of biomarkers
  - Method of revascularization
  - Novel imaging techniques
  - Heart team and artificial intelligence approaches for complex decisions