

Cardial MRI; Approaching the Level of Gold Standard for Viability Assessment

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Viability

- Hibernating myocardium
 - a state of myocardial **hypocontractility** during chronic **hypoperfusion**, in the presence of completely viable myocardium which **recovers functionally** upon revascularization.
 - ‘Viable’ and ‘hibernating’ myocardium have previously been used interchangeably
- Mechanism
 - Smart heart hypothesis
 - Repetitive stunning hypothesis

Variable methods

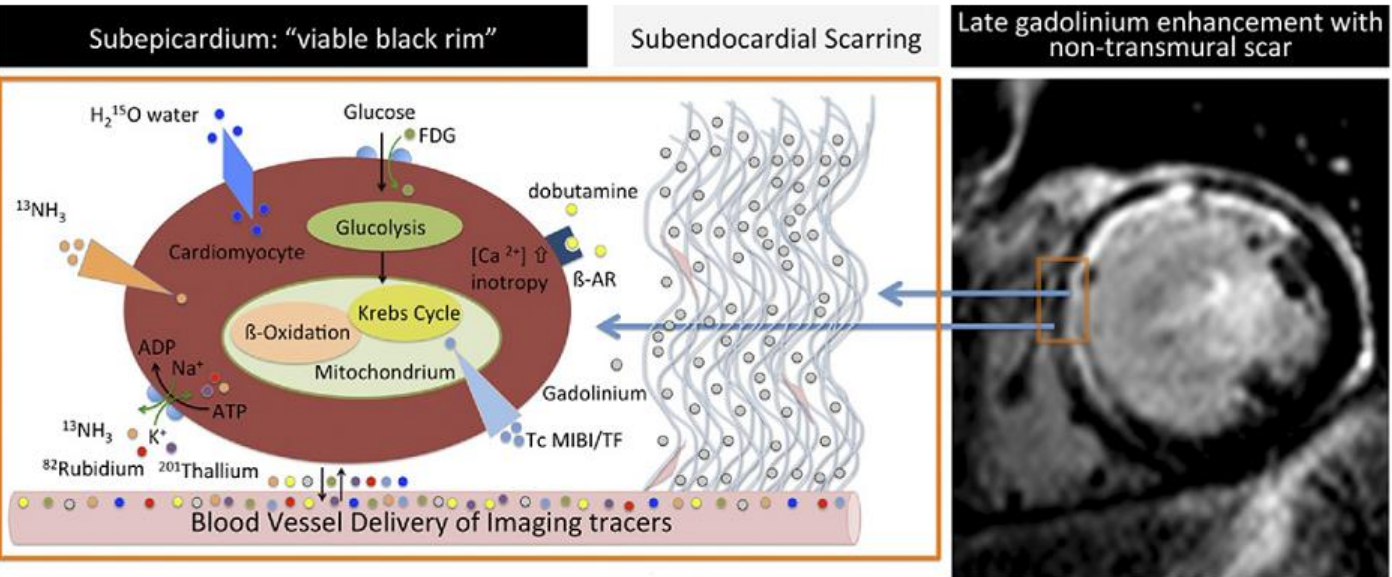


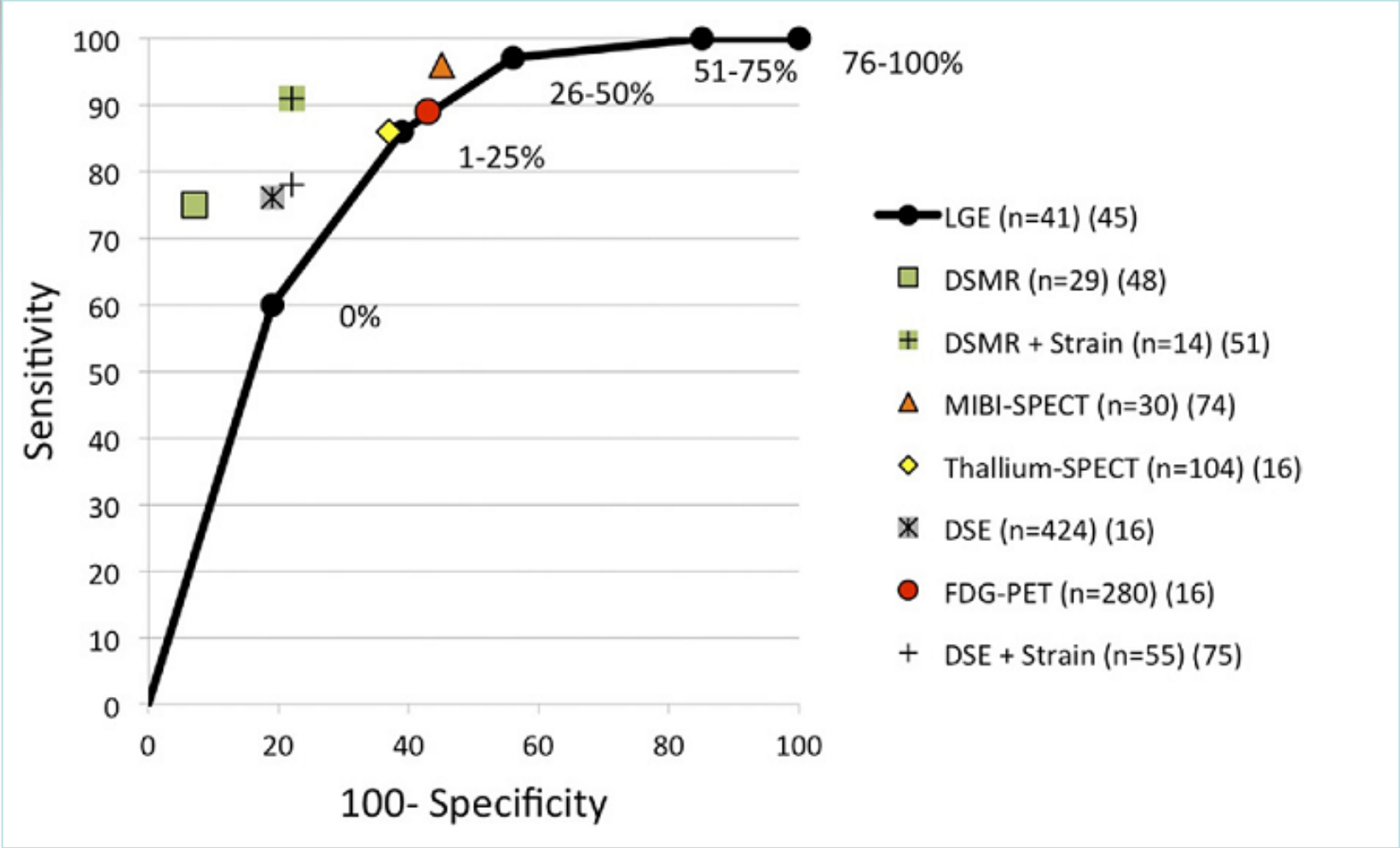
Figure 2 Pathophysiological Targets of Different Imaging Methods

²⁰¹Thallium-single-photon emission computed tomography (SPECT) depends on intact cellular membranes and energy-dependent uptake via the Na⁺K⁺-antiporter. Technetium-labeled tracers tetrofosmin (TF) and methoxyisobutylisonitrile (MIBI) are lipophilic cations that can be imaged with SPECT after passively crossing the mitochondrial membranes (driven by the transmembrane electrochemical gradient), where they are retained. Dobutamine targets β_1 and β_2 adrenoreceptors (β -AR), leading to increased intracellular Ca²⁺ and positive inotropy. Responses to dobutamine stress are mainly imaged with dobutamine stress echocardiography and dobutamine stress magnetic resonance. 18-fluorodeoxyglucose (¹⁸F-FDG) targets glucose metabolism and is mainly imaged with positron emission tomography (PET) after uptake via the glucose transporter uniporter. FDG is intracellularly phosphorylated by hexokinase to FDG-6-phosphate, which is not further used in glycolysis or glycogen synthesis. ⁸²Rubidium (⁸²Rb)-PET depends on intact cellular membranes and energy-dependent uptake via the Na⁺-K⁺-antiporter similarly to ²⁰¹thallium. ¹³NH₃-PET depends on passive diffusion or on the active Na⁺-K⁺-antiporter mechanism. H₂¹⁵O diffuses freely through the membrane and reaches equilibrium between extravascular and intravascular compartments. Gadolinium is an extracellular contrast agent that passively diffuses into the extracellular space. When the extracellular space is significantly increased (e.g., after cell membrane rupture in acute myocardial infarction or in collagenous subendocardial scar as shown in this case), gadolinium accumulates and is retained due to altered wash in/wash out kinetics and can then be imaged with late gadolinium enhancement-cardiac magnetic resonance imaging.

Variable methods

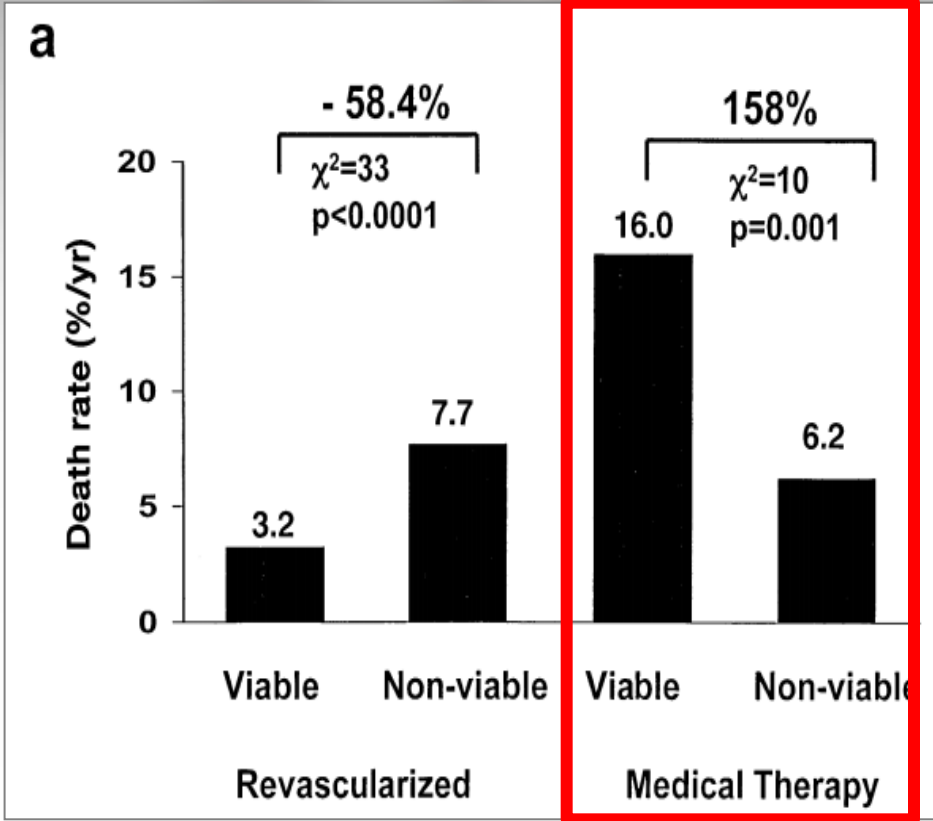
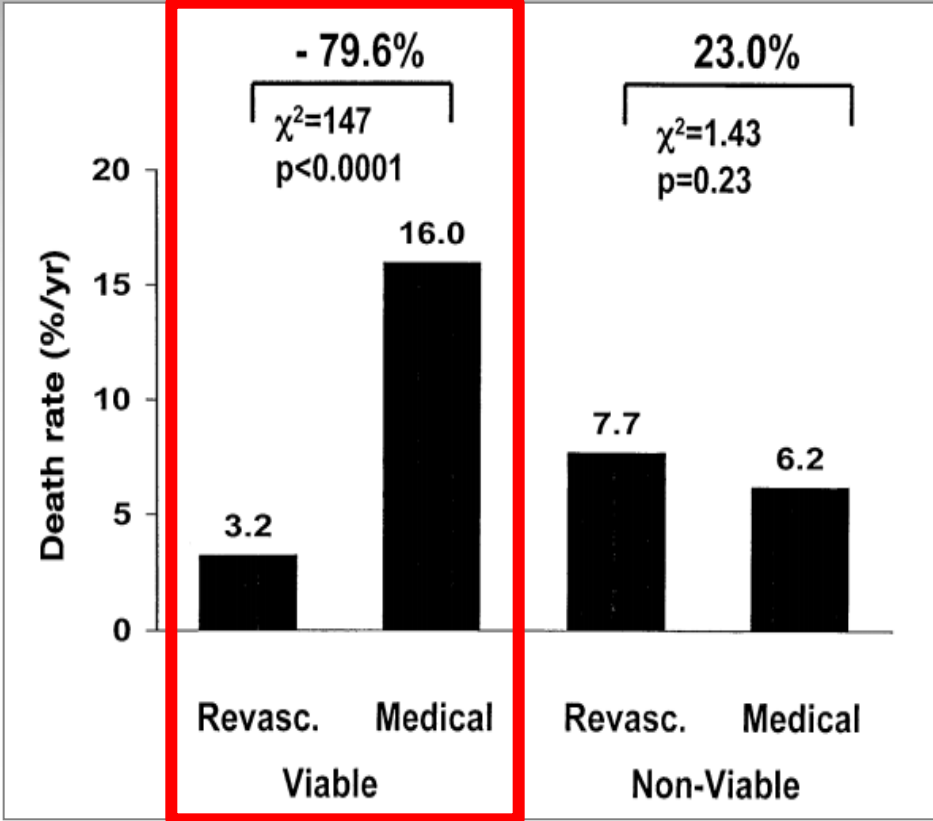
Targets and Modalities	Metabolism	Perfusion	Scar	Contractile Reserve
CMR	X	O	O	O
CT	X	O	O	X
Echo	X	O	Δ	O
PET	O	O	X	X
SPECT	O	O	X	Δ
	Functional integrity of myocardial cells	Blood flow toward the myocardium	Localization and quantification of necrosis/fibrosis	Contractile function

Diagnostic accuracy



Myocardial Viability Testing and Impact of Revascularization on Prognosis in Patients With Coronary Artery Disease and Left Ventricular Dysfunction: A Meta-Analysis

Technique	Author	Year	Imaging Technique	Viability Criterion	Patients Entered	Age (yrs)	Follow-up (months)	LVEF (%)
Thallium	Gioia (14)	1995	rest/redistribution TI SPECT	TI uptake score	85	65	31	30
	Gioia (15)	1996	rest/redistribution TI SPECT	rest redistribution	89	69	31	27
	Pagley (18)	1997	rest/redistribution planar TI	Viability index 0.67	70	66	37	28
	Petretta (19)	1997	rest/reinjection TI SPECT	TI uptake score	104	57	22	40
	Cuocolo (24)	1998	rest/redistribution TI SPECT	rest redistribution	84	55	17	37
	Pasquet (31)	1999	stress/rest/reinjection TI SPECT	TI reversibility	141	62	33	35
FDG	Eitzman (8)	1992	FDG PET	flow/FDG mismatch	110	59	12	34
	Tamaki (9)	1993	stress redistribution TI SPECT/ FDG PET	FDG uptake	158	60	23	46
	Yoshida (10)	1993	rubidium/FDG PET	Rubidium/FDG uptake	35	54	36	44
	Dreyfus (12)	1994	rest redistribution TI SPECT/ FDG PET	rest redistribution/FDG uptake	50	58	18	23
	Di Carli (11)	1994	FDG PET	flow/FDG mismatch	107	65	14	25
	Lee (13)	1994	FDG PET	flow/FDG mismatch	137	62	17	38
	Haas (17)	1997	FDG PET	FDG uptake	34	62	15	28
	Vom Dahl (20)	1997	mibi SPECT/FDG PET	flow/FDG mismatch	161	57	29	45
	Di Carli (25)	1998	FDG PET	flow/FDG mismatch	93	68	46	25
	Beanlands (23)	1998	mibi SPECT/FDG PET	viability score	85	62	18	26
Huitink (26)	1998	rest planar TI and FDG	flow/FDG mismatch	59	61	47	51	
Echocardiography	Williams (16)	1996	DASE	regional wall motion	136	67	16	30
	Afridi (21)	1998	DASE	"	353	64	18	27
	Anselmi (22)	1998	LDDE	"	210	59	16	33
	Meluzin (27)	1998	LDDE	"	274	58	20	35
	Smart (33)	1999	DASE	"	350	61	18	30
	Senior (32)	1999	LDDE	"	87	62	40	25
	Bax (30)	1999	DASE	"	76	61	19	28
					3,088	61	25	33



The hibernating myocardium: current concepts, diagnostic dilemmas, and clinical challenges in the post-STICH era

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Table 2 Summary of the HEART, PARR-2, and STICH trials

Study feature	HEART	PARR-2	STICH
Number of patients	138	430	1212
Countries/sites	1/13	2/9	22/99
Timeline	2002–2004	2000–2004	2002–2007
Clinical question	Is REV superior to OMT in patients with significant HM?	Is imaging-guided care superior to standard care in ICM?	Is REV superior to OMT in patients with ICM?
Baseline LVEF (%)	24	27	28
Imaging techniques	DbE, PET, SPECT	PET	DbE, SPECT
Revascularization	CABG/PCI	CABG/PCI	CABG only
Median follow-up (months)	59	12	56
Result	No significant benefit of REV over OMT	No difference between PET-guided care and standard care	No benefit of REV over OMT
Key caveat	Severely underpowered (only recruited 138 of intended 800 patients)	25% patients did not adhere to recommended management based on PET findings	Numerous potential confounding factors affecting both the main trial and viability sub-study

STICH Viability Sub-study

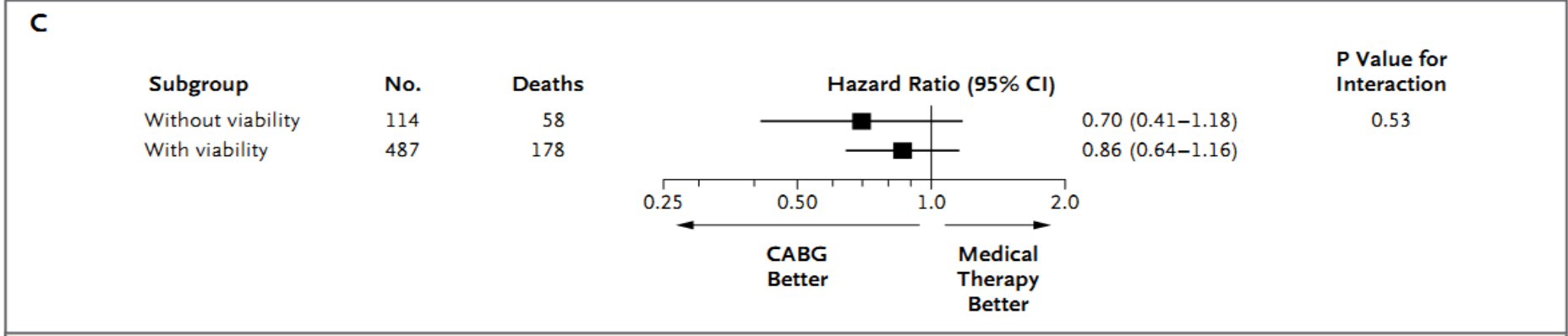
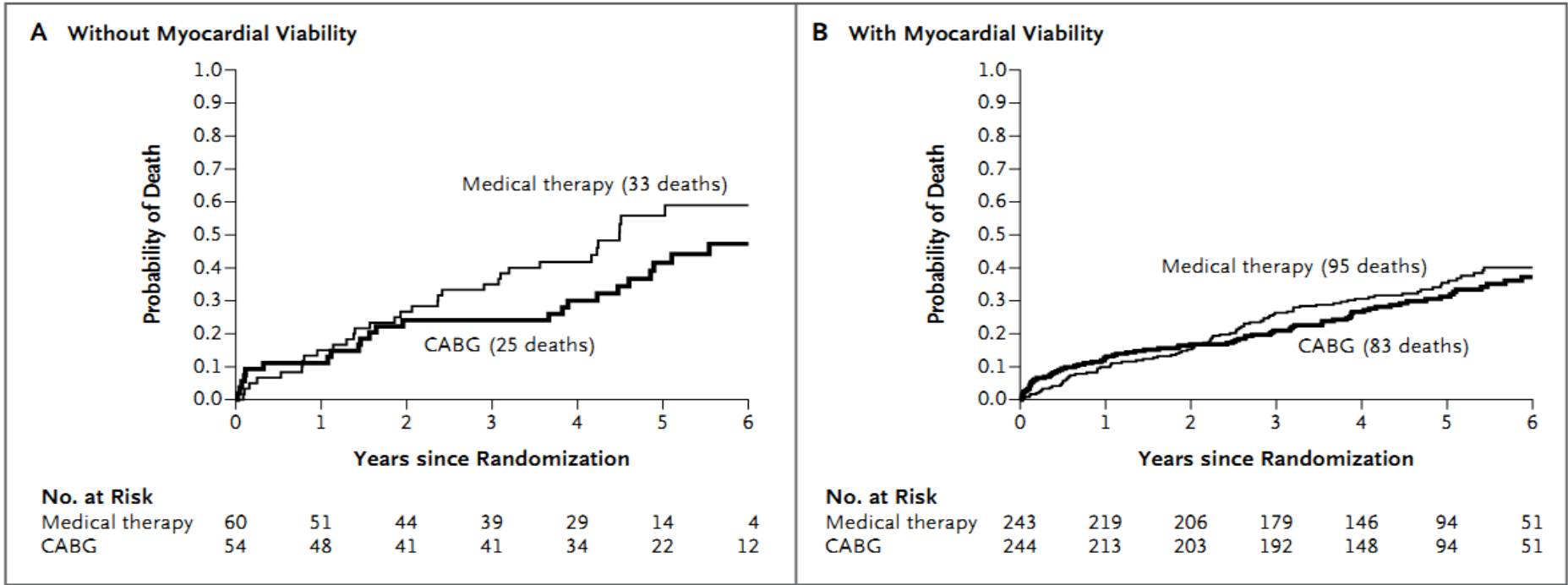


Table 1. Limitations of the STICH Viability Substudy

Limitations of overall trial

Crossover in 17% of patients assigned to medical therapy and 9% of patients assigned to CABG

Randomization of a very small proportion of eligible patients

Average of only 2 patients per site per year at 127 sites in 26 countries over 5 years

Outcome of the large number of patients screened but not randomized not reported

Lack of randomization in viability substudy

Optional viability testing performed at clinician's discretion

Only about one-half of eligible patients from the main trial

Significant differences in baseline characteristics between those with versus those without viability testing

Nonsignificant trend toward higher rates of CABG among patients with viability testing on the day of randomization or on the following day than among those who had testing before randomization

Acceptable **viability tests do not have highest sensitivity or negative predictive value** for identifying viable myocardium

Binary classification of viability with controversial thresholds for extent and uptake

Stress-induced ischemia not consistently addressed by viability testing

Revascularization not guided by the presence of viable myocardium

Small sample size of the group with nonviable myocardium

CABG = coronary artery bypass graft; STICH = Surgical Treatment for Ischemic Heart Failure.

KEY INCLUSION / EXCLUSION CRITERIA

INCLUSION

- Severe ICM (EF < 35% & significant CAD)
- Dyspnoea as a dominant symptom

EXCLUSION

- Severely remodelled LV (LV ESV > 140 ml)
- Angina as a dominant symptom
- NYHA Class I
- Previous CABG
- Prohibitive surgical risk (e.g. Euro score >50%)

TRIAL ENDPOINTS

PRIMARY

- All-cause mortality

SECONDARY

- Acute myocardial infarction
- Hospitalisation for worsening heart failure
- Reverse remodelling (e.g. ↓ in LVESV by ≥15%)
- Patient outcomes (e.g. NYHA Class, QoL questionnaire, 6-minute walk distance)

PRE-TREATMENT

ECHOCARDIOGRAPHY - DbE

Visual assessment of contractile reserve (CR). If no CR seen in segment >6 mm thickness, can use MCE to further delineate viability

≥5/17 segments with CR → HM +
<5/17 segments with CR → HM -

Ischaemia: Present if > 3 segments affected

NUCLEAR IMAGING - SPECT

>50% peak tracer uptake → viable
<50% peak tracer uptake → non-viable

≥5 / 17 viable segments → HM +
<5 / 17 viable segments → HM -

Ischaemia: Present if >10% myocardium affected

MAGNETIC RESONANCE - CMR

>75% TEI → Non-viable
50-75% TEI → Dobutamine
<50% TEI → Viable

≥5 / 17 viable segments → HM +
<5 / 17 viable segments → HM -

Ischaemia: Present if >10% myocardium affected

Patients with significant HM randomised to OMT alone or OMT + revascularisation

Patients without significant HM are not randomised and receive OMT alone

TREATMENT

Revascularisation: CABG only. LIMA graft & complete revascularisation in all cases where feasible.

OMT: Maximally tolerated doses of ACEi, beta-blocker, statin, spironolactone (NYHA III/IV), aspirin +/- diuretic

POST TREATMENT

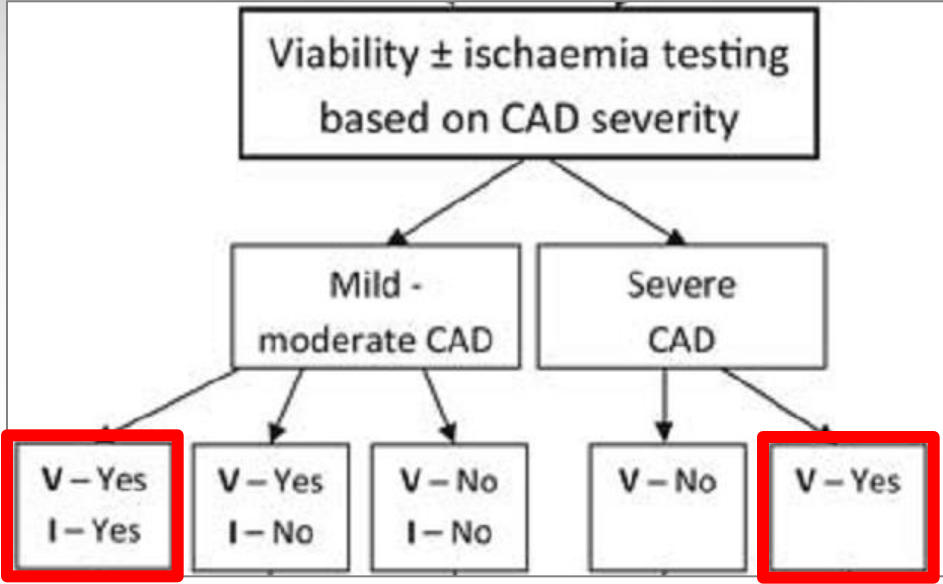
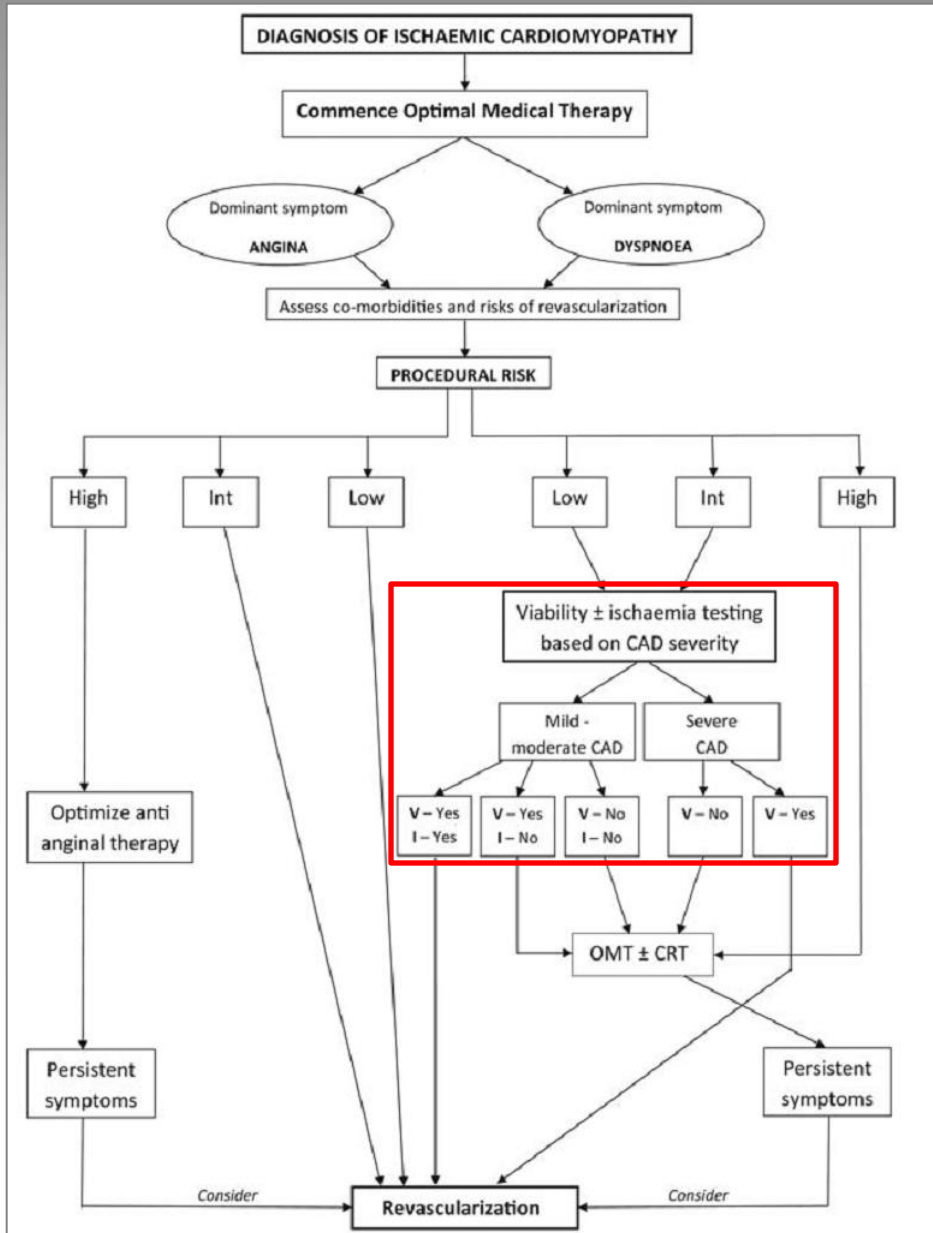
Regular follow-up for symptom status, functional class and mortality outcome

MAGNETIC RESONANCE - CMR

>75% TEI → Non-viable
50-75% TEI → Dobutamine
<50% TEI → Viable

≥5 / 17 viable segments → HM +
<5 / 17 viable segments → HM -

Ischaemia: Present if >10% myocardium affected



		EF	Scar	Hibernation	Ischemia					
Protocol	Protocol 1: Function and Scar									
Basic										
	SSFP cines Rest: 3 SAX and 3LAX	SAX SSFP cine stack volumetry	Scar	++	++	-	-			
+ LD-DSMR	Protocol 2: Hibernating Myocardium with DSMR and Scar									
	SSFP cines Rest: 3 SAX and 3LAX	DSMR 5-10 mcg/kg/min 3SAX/ 3 LAX	SAX SSFP cine stack volumetry	Scar	++	++	+	-		
+ LD-DSMR & + HD-DSMR	Protocol 3: Hibernating Myocardium and Ischemia with DSMR and Scar									
	SSFP cines Rest: 3 SAX and 3LAX	SAX SSFP cine stack volumetry	DSMR 5-10 mcg/kg/min 3SAX/ 3 LAX	DSMR 20-40 mcg/kg/min + atropine 3SAX/ 3 LAX	Scar	++	++	++	?	
+ LD-DSMR & Adenosine Perfusion	Protocol 4: Hibernating Myocardium and Ischemia with DSMR, Adenosine and Scar									
	SSFP cines Rest: 3 SAX and 3LAX	DSMR 5-10 mcg/kg/min 3SAX/ 3 LAX	SAX SSFP cine stack volumetry	Adenosine Stress Perfusion	Rest Perfusion	Scar	++	++	++	?
Time course of the cardiac magnetic resonance examination (min)										
	Survey	10	20	30	40	50	60			

CMR: various variables

- DE-CMR
 - **transmural extent of infarction**
 - Kim RJ et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000; 343:1445-1453.
 - unenhanced residual rim thickness
 - Ichikawa Y et al. Late gadolinium-enhanced magnetic resonance imaging in acute and chronic myocardial infarction. Improved prediction of regional myocardial contraction in the chronic state by measuring thickness of nonenhanced myocardium. *J Am Coll Cardiol* 2005; 45:901-909.
- LDD-CMR
 - **contractile reserve during dobutamine stress**
 - Wellnhofer E et al. Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. *Circulation* 2004; 109:2172-2174.
- Cine CMR
 - end-diastolic wall thickness
 - Kuhl HP et al. Relation of end-diastolic wall thickness and the residual rim of viable myocardium by magnetic resonance imaging to myocardial viability assessed by fluorine-18 deoxyglucose positron emission tomography. *Am J Cardiol* 2006; 97:452-457.
 - segmental wall thickening of the unenhanced rim
 - Kirschbaum SW et al. Combining magnetic resonance viability variables better predicts improvement of myocardial function prior to percutaneous coronary intervention. *Int J Cardiol*; 159:192-197.

CMR Imaging Assessing Viability in Patients With Chronic Ventricular Dysfunction Due to Coronary Artery Disease

A Meta-Analysis of Prospective Trials

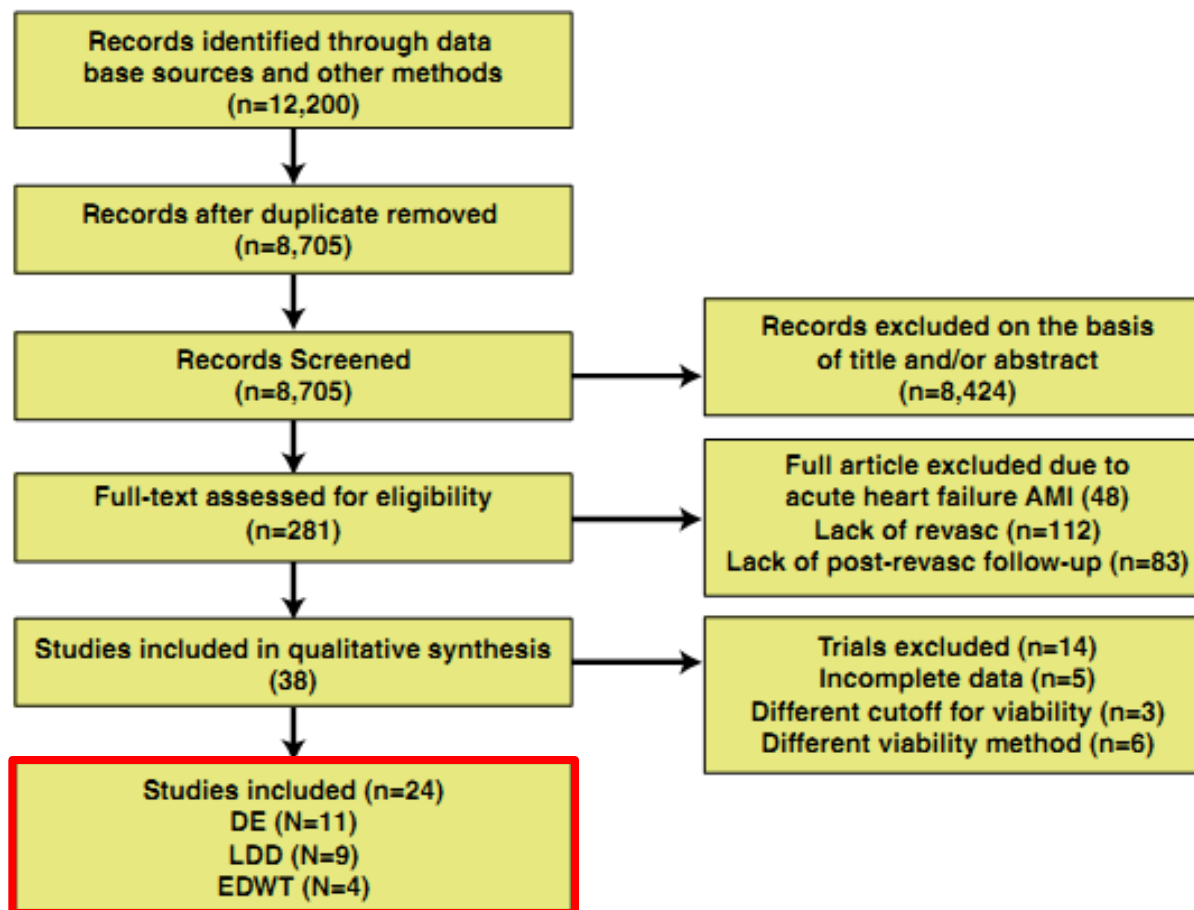


Table 7. Summary Estimates for Sensitivity, Specificity, and DOR From the Bivariate Model

CMR	Mean Sensitivity (95% CI)	Mean Specificity (95% CI)	Mean DOR (95% CI)	PPV (95% CI)	NPV (95% CI)
DE CMR	0.95 (0.93–0.97)	0.51 (0.40–0.62)	21.12 (10.98–40.55)	0.69 (0.56–0.80)	0.90 (0.85–0.93)
LDD CMR	0.81 (0.73–0.86)	0.91 (0.84–0.95)	41.57 (18.25–94.68)	0.93 (0.87–0.97)	0.75 (0.65–0.83)
EDWT CMR	0.96 (0.91–0.98)	0.38 (0.23–0.57)	13.33 (4.16–42.74)	0.71 (0.49–0.86)	0.85 (0.70–0.93)
p Value DE vs. LDD	<0.001	<0.001	0.21	<0.001	0.001
p Value DE vs. EDWT	0.89	0.25	0.34	0.87	0.37
p Value LDD vs. EDWT	<0.001	<0.001	0.08	0.01	0.21

DE CMR	Sensitivity	Specificity	PPV	NPV
<0%	53	87	77	68
<25%	78	71	70	79
<50%	95	51	69	90
<75%	99	21	52	97

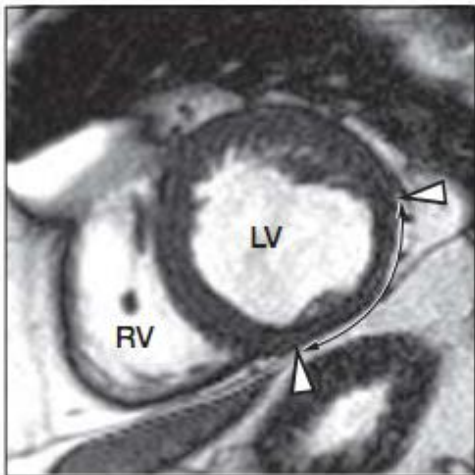
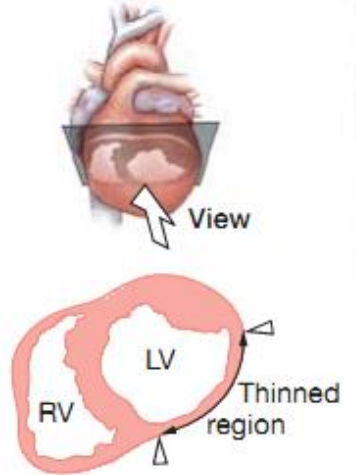
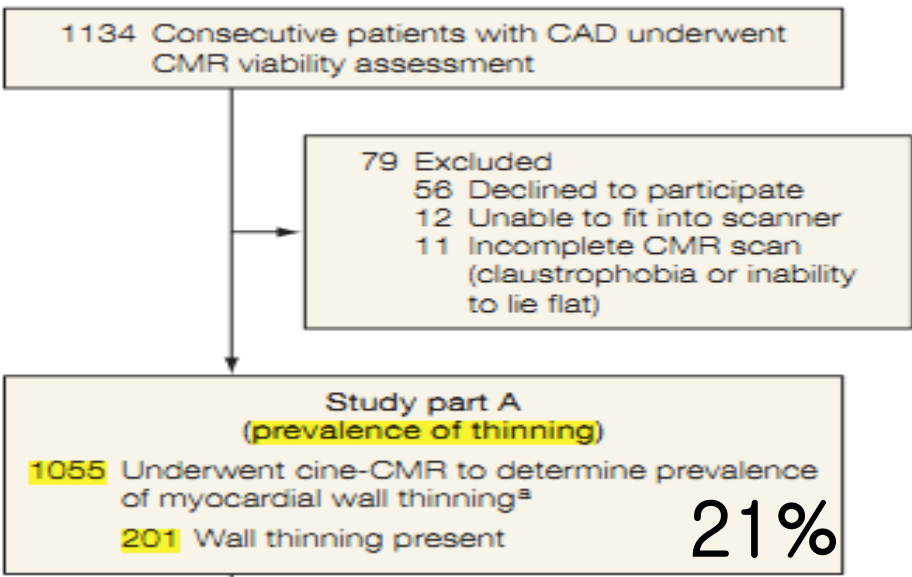
Combining viability variables

- 72 pts with CTO
- Successful (43/72) or unsuccessful (29/72) PCI
- Cardiac MRI before and 6 months after PCI
 - ① **Transmural extent of infarction (TEI)**
 - ② **Contractile reserve during dobutamine stress**
 - ③ **End diastolic wall thickness**
 - ④ **Unenhanced rim thickness**
 - ⑤ **Segmental wall thickening of the unenhanced rim(SWTur)**

	Sensitivity (%)		Specificity (%)	
	Mean	SD	Mean	SD
LDD (>7%)	90.0	3.6	81	11.4
TEI (<50%)	92.3	3.6	45.0	13.8
EDWT (>6 mm)	92.6	3.6	27.7	11.3
Unenhanced rim thickness (>3 mm)	96.3	2.9	43.2	13.8
SWTUR (<45%)	87.2	4.1	40.2	11.9

	OR	95% confidence interval for OR
Univariate		
LDD	1.82	(1.49-2.22)
TEI	0.68	(0.58-0.79)
EDWT	1.3	(1.1-1.7)
Unenhanced rim thickness	1.4	(1.2-1.5)
SWTur	0.85	(0.76-0.95)
Multivariate		
LDD	1.06	(1.02-1.09)
TEI	0.96	(0.94-0.97)
SWTur	0.98	(0.97-0.99)

Myocardial Thinning and Scarring



$$\text{Mean EDWT of thinned region, mm} = \frac{\text{Area}}{\text{Arc length}}$$



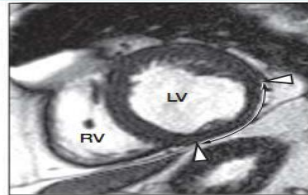
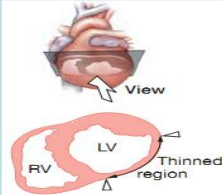
Myocardial Thinning and Scarring

Study part A
(prevalence of thinning)

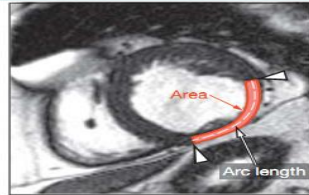
1055 Underwent cine-CMR to determine prevalence of myocardial wall thinning^a

201 Wall thinning present

854 Wall thinning absent



$$\text{Mean EDWT of thinned region, mm} = \frac{\text{Area}}{\text{Arc length}}$$

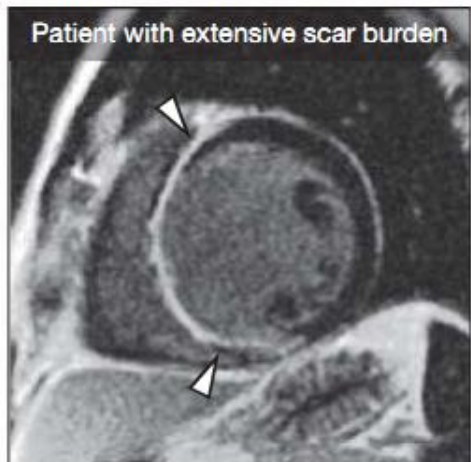
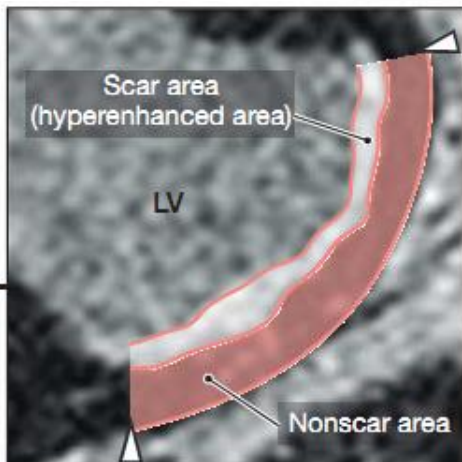
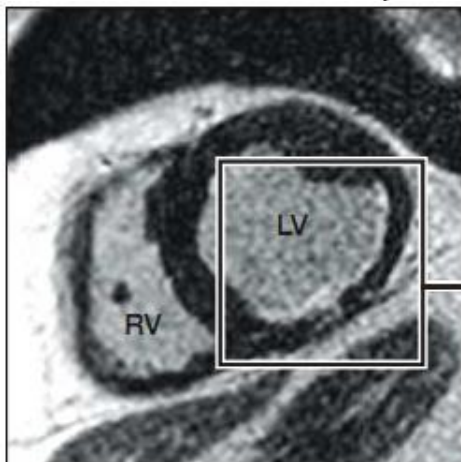


Study part B
(prevalence of limited scarring in thinned regions)

201 Underwent delayed-enhancement CMR to determine prevalence of limited scar burden in thinned regions^b

37 Limited scar burden (≤50% scarring) 18%

164 Extensive scar burden (>50% scarring)

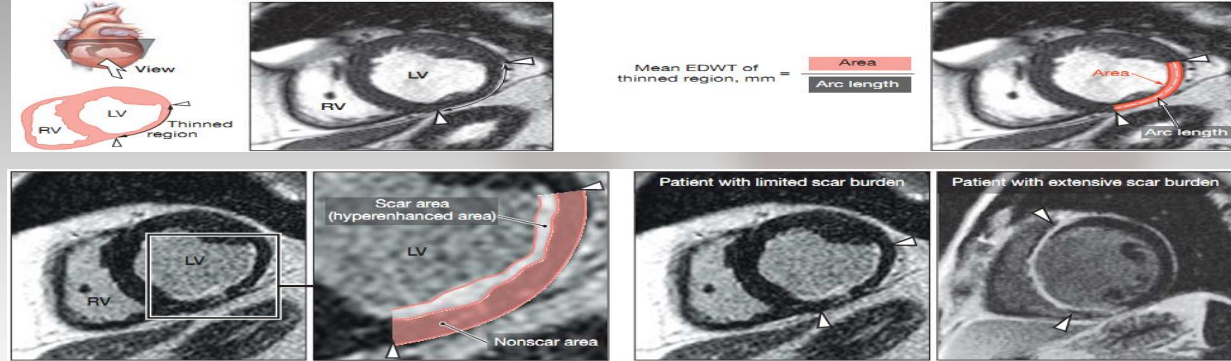


Myocardial Thinning and Scarring

Study part A (prevalence of thinning)
 1055 Underwent cine-CMR to determine prevalence of myocardial wall thinning^a
 201 Wall thinning present

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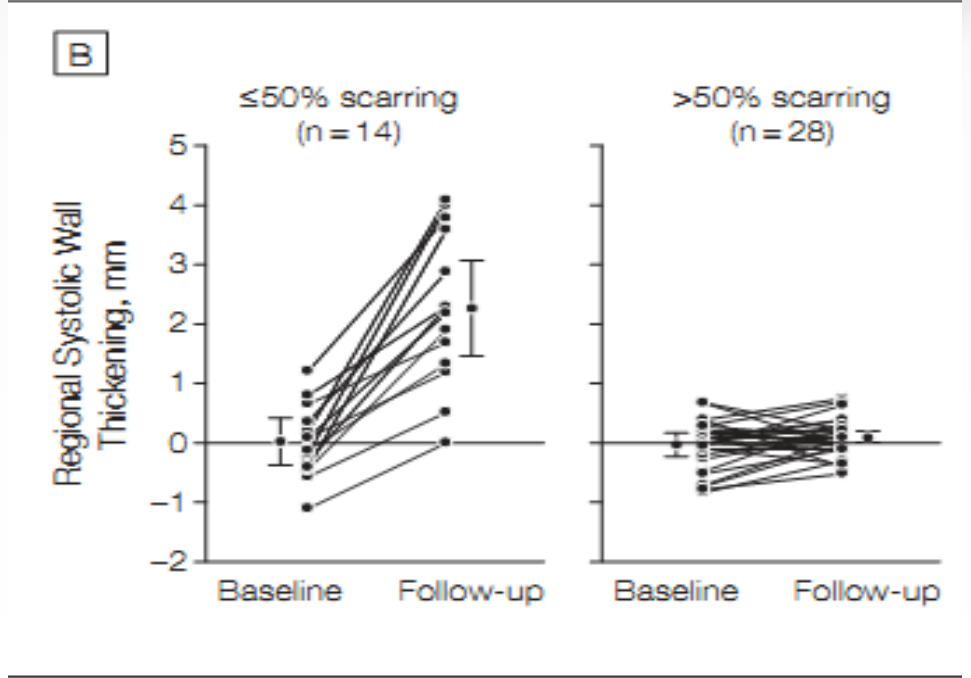
Study part B (prevalence of limited scarring in thinned regions)
 201 Underwent delayed-enhancement CMR to determine prevalence of limited scar burden in thinned regions^b
 97 Limited scar burden (≤50% scarring)
 164 Extensive scar burden (>50% scarring)



Study part C (relationship of limited scarring to functional improvement and myocardial remodeling)
 72 Underwent revascularization of thinned region

129 Did not undergo coronary revascularization

42 Underwent follow-up cine-CMR to assess relationship of scar burden to functional improvement and tissue remodeling
 30 Underwent revascularization but excluded for other reason
 22 Declined follow-up visit
 5 Pacemaker or ICD in place
 3 Died

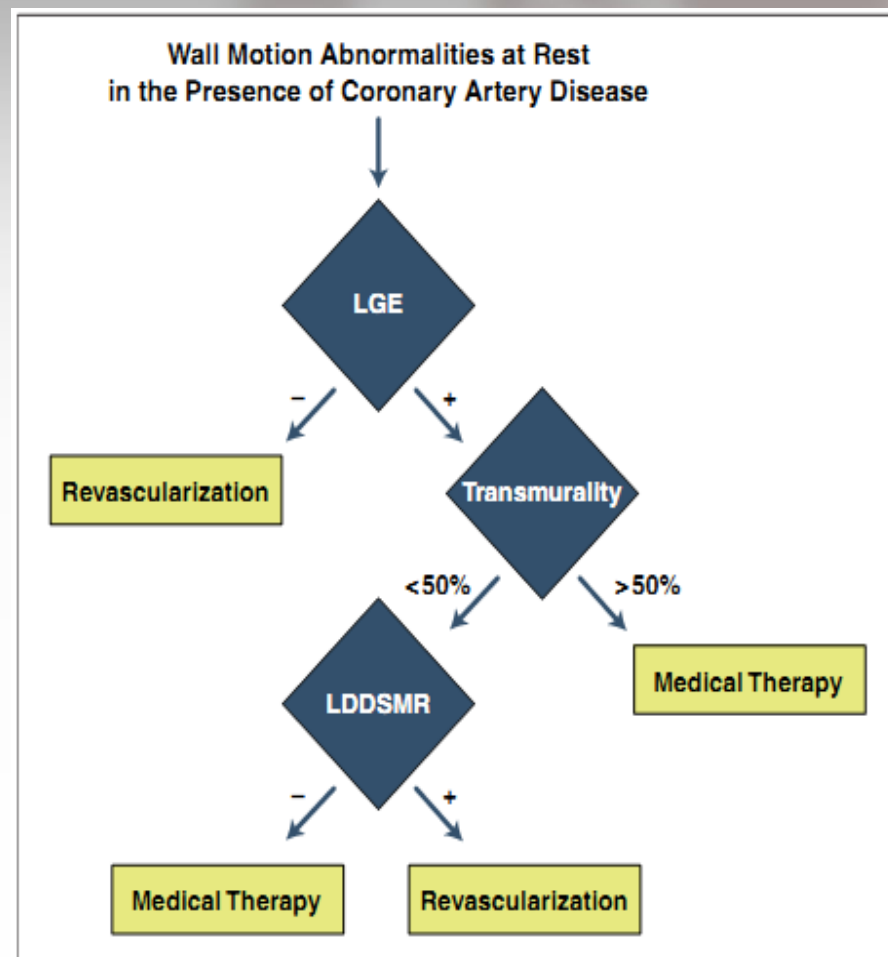


Approaching the Level of Gold Standard

- Accuracy
 - Basis of segments rather than patients
 - Functional improvement rather than outcome.
- Clinical availability
- Cost
 - 국민건강보험공단 급여보장부
 - "4대 중증질환 등 보장성 확대계획 수립을 위한 의견을 요청"

Accuracy

- Look at **dead tissue** with scar imaging
→ excellent sensitivity (95%) and NPV (90%)
- Look at **living tissue** with dobutamine test
→ excellent specificity (91%) and PPV (93%)



DE-CMR

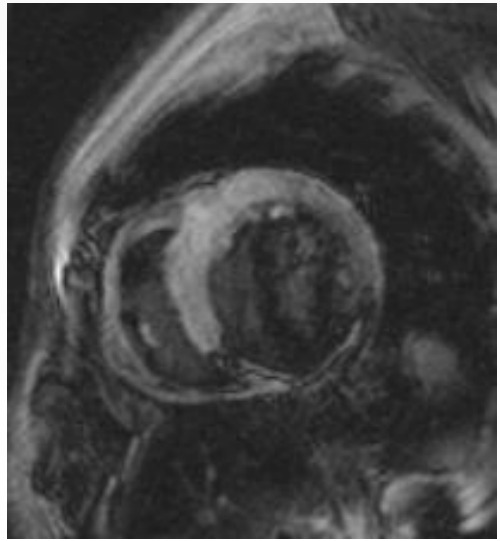
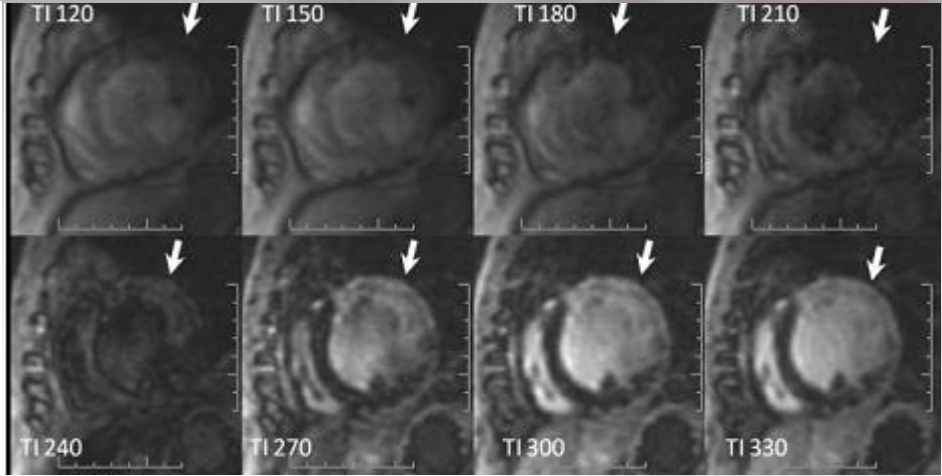
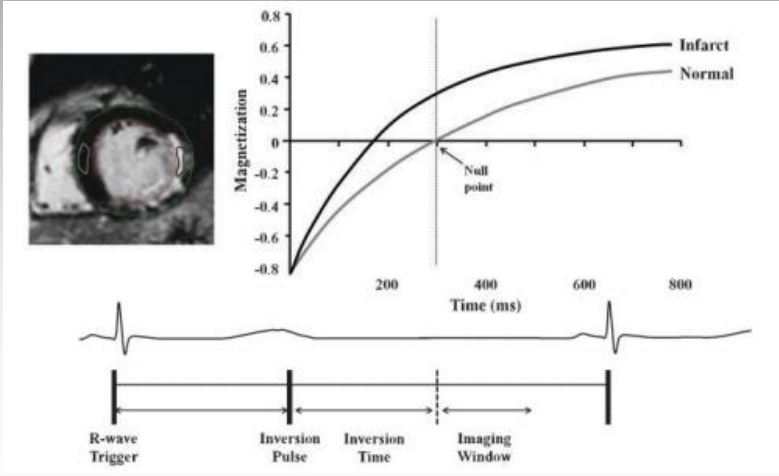
Table 1. Baseline Characteristics of Studies Included in the Meta-Analysis Using CMR With DE

First Author (Ref #), Year	Study Design	n	Male (%)	Age (yrs)	LVEF (%)	Revascularization	Follow-Up MRI (Weeks)	Technique to Assess LVEF	Time After Gadolinium Administration (min)	Hyperenhancement (SD Above Normal Intensity)	Cutoff for Viability (%)
Becker et al. (44), 2008	Prospective	21	62	59	41	CABG/PCI	36	CMR	15	>3	<50
Bondarenko et al. (53), 2007	Prospective	36	84	62	39	CABG	12	CMR	13	>5	<50
Gutberlet et al. (45), 2005	Prospective	20	95	64	29	CABG	24	CMR	15	>2	<50
Kim et al. (10), 2000	Prospective	43	88	63	43	CABG/PCI	11	CMR	NR	>6	<50
Kuhl et al. (46), 2006	Prospective	29	72	66	32	CABG/PCI	24	CMR	15	>3	<50
Pegg et al. (47), 2010	Prospective	33	94	66	38	CABG	24	CMR	6	>2	<50
Sandstede et al. (48), 2000	Prospective	12	83	61	NR	CABG/PCI	12	CMR	15	NR	<50
Schvartzman et al. (49), 2003	Prospective	29	79	62	28	CABG	6	ECHO	25	NR	<50
Selvanayagam et al. (50), 2004	Prospective	52	NR	NR	62	CABG	24	CMR	10	>2	<50
Wellnhofer et al. (51), 2004	Prospective	29	93	68	NR	CABG/PCI	12	CMR	13	NR	<50
Wu et al. (52), 2007	Prospective	27	78	66	38	CABG	24	CMR	15	NR	<50

DE-CMR: Potential pitfalls and artefacts

- Inversion time adjustment (Optimal Myocardial Nulling)
- Differentiation of subendocardial infarct from blood pool
- Ghosting artefacts
- Partial volume effects
- Quantification of myocardial scar size

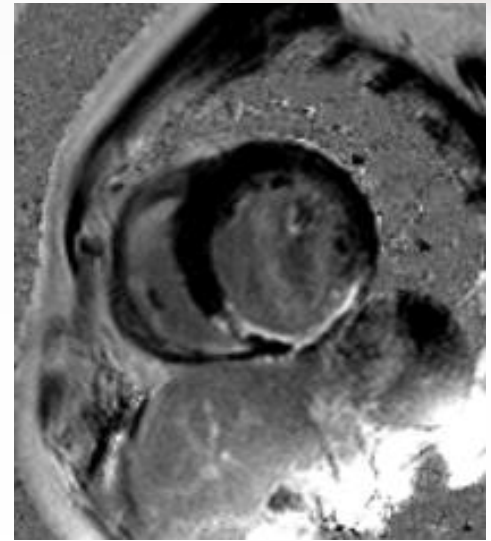
Optimal Myocardial Nulling



Wrong nulling

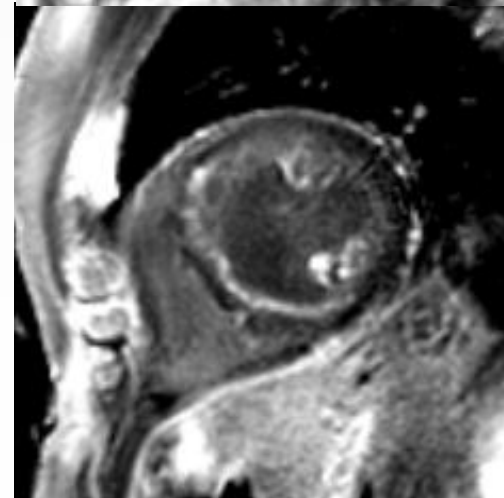
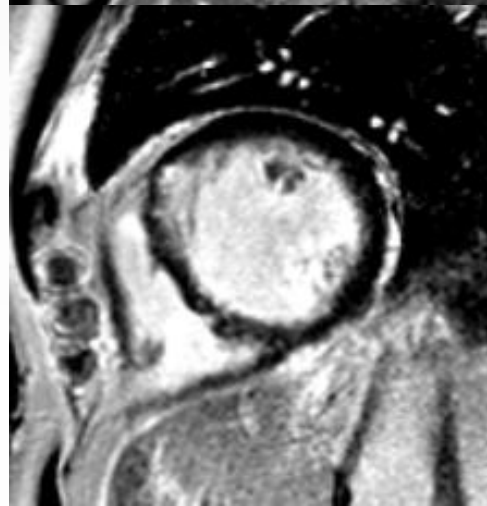
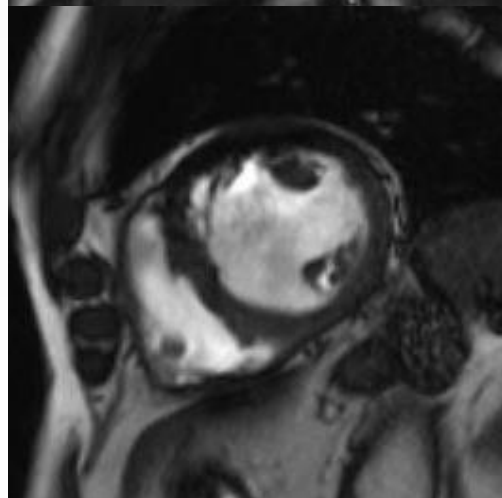
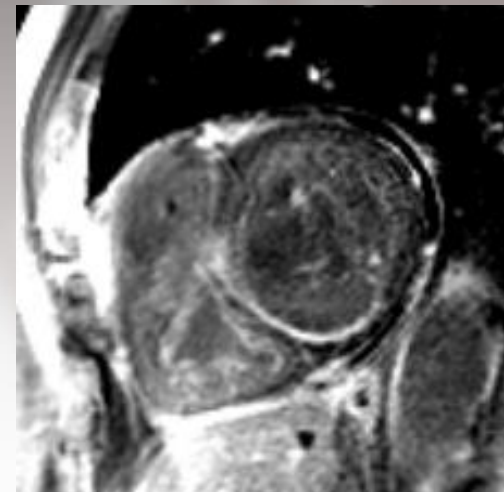
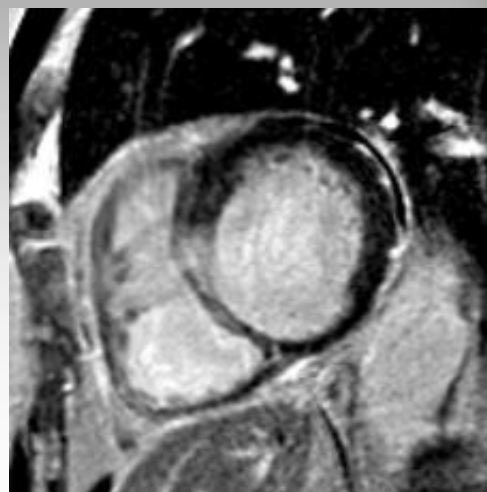
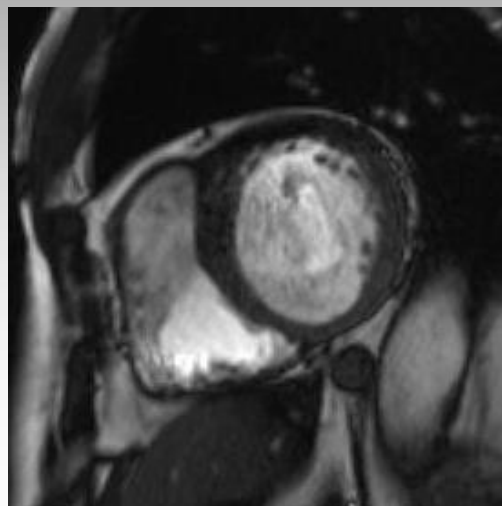


Optimal nulling



PSIR

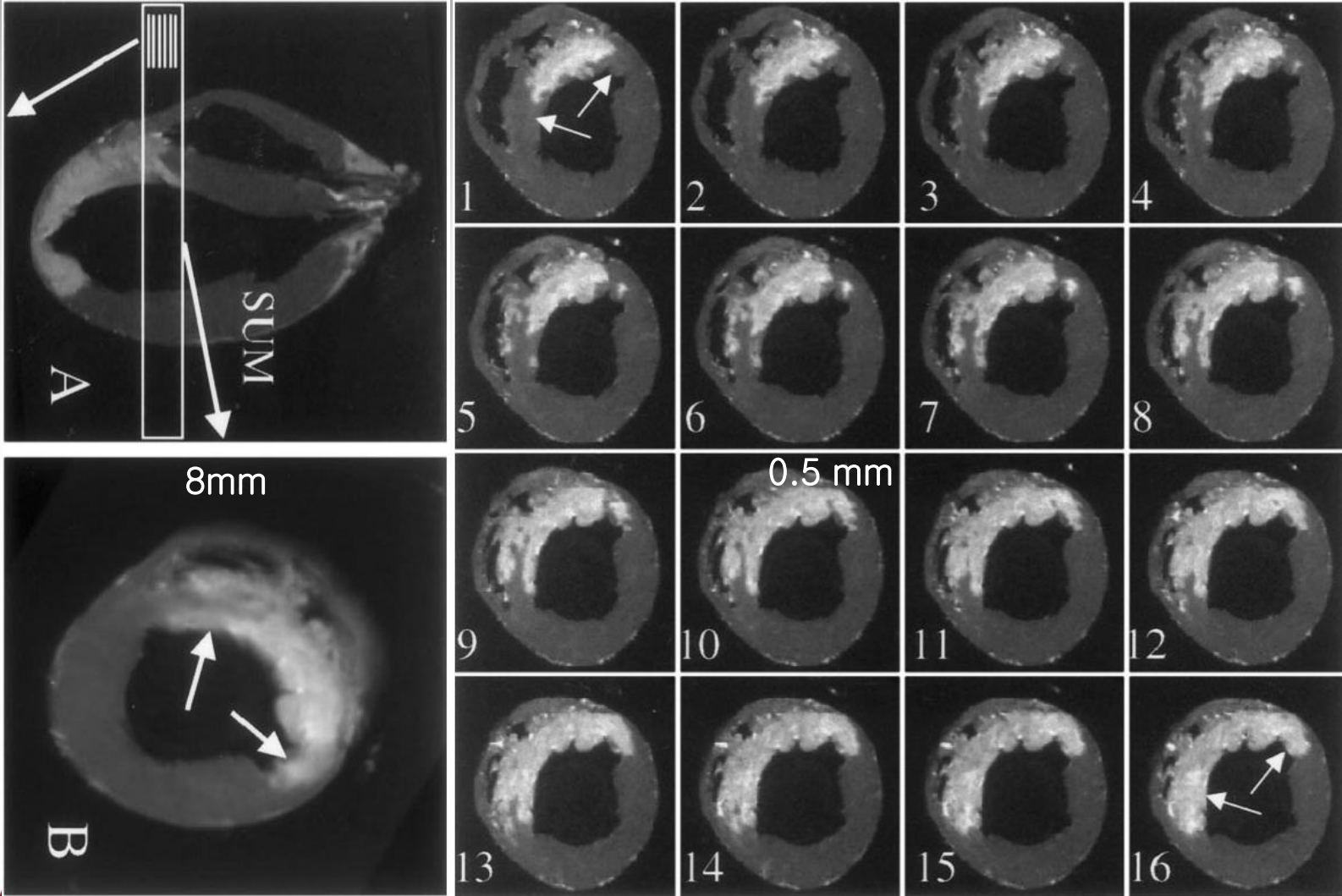
Bright Blood Cavity



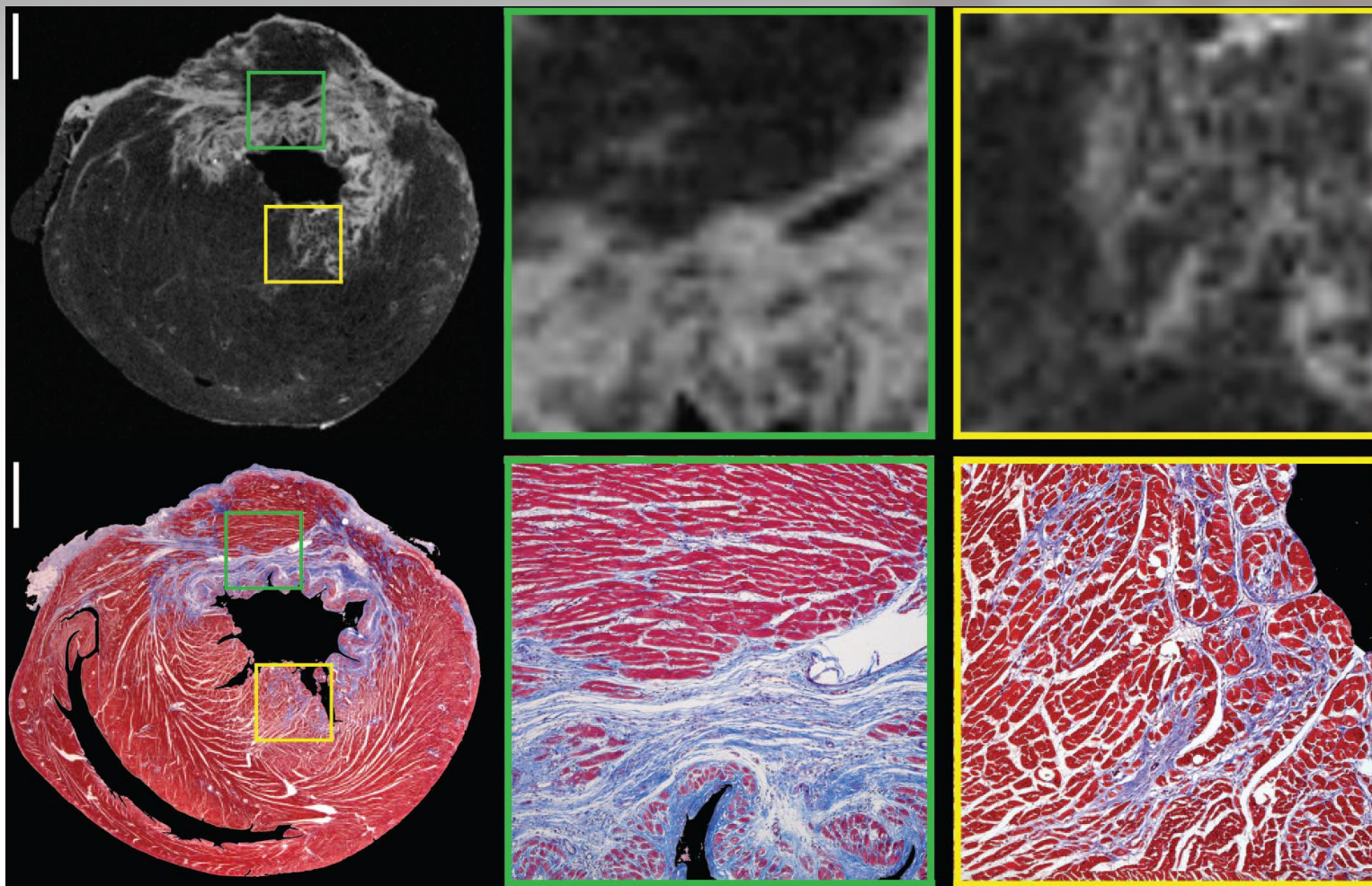
Ghost Artifact



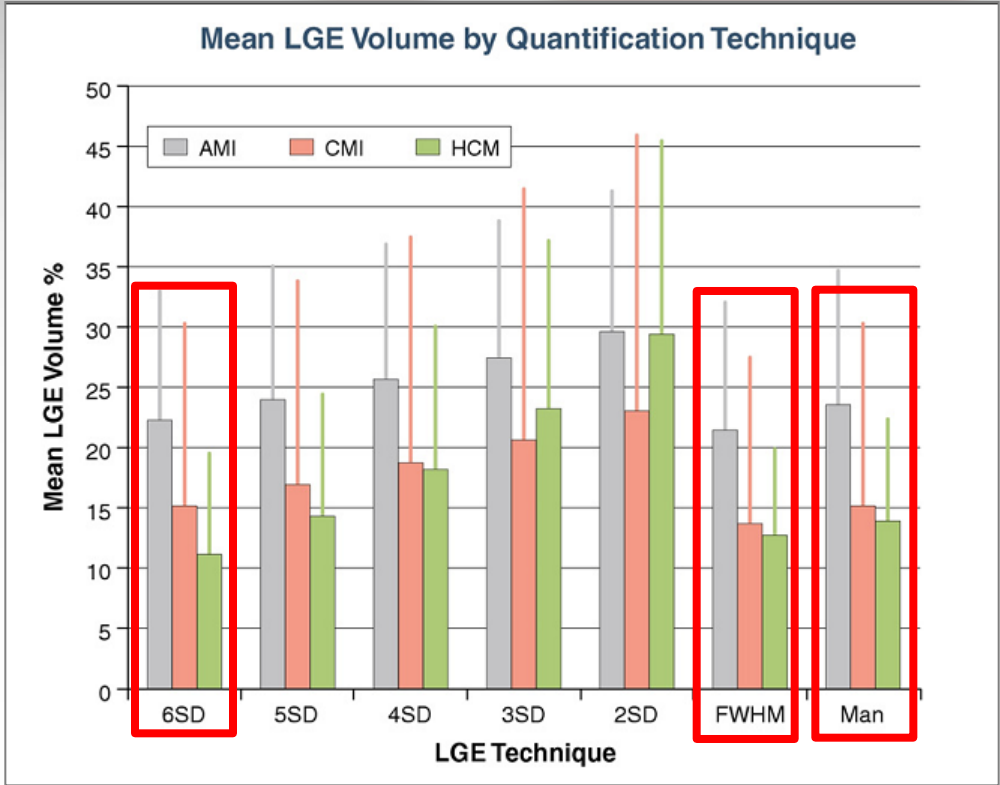
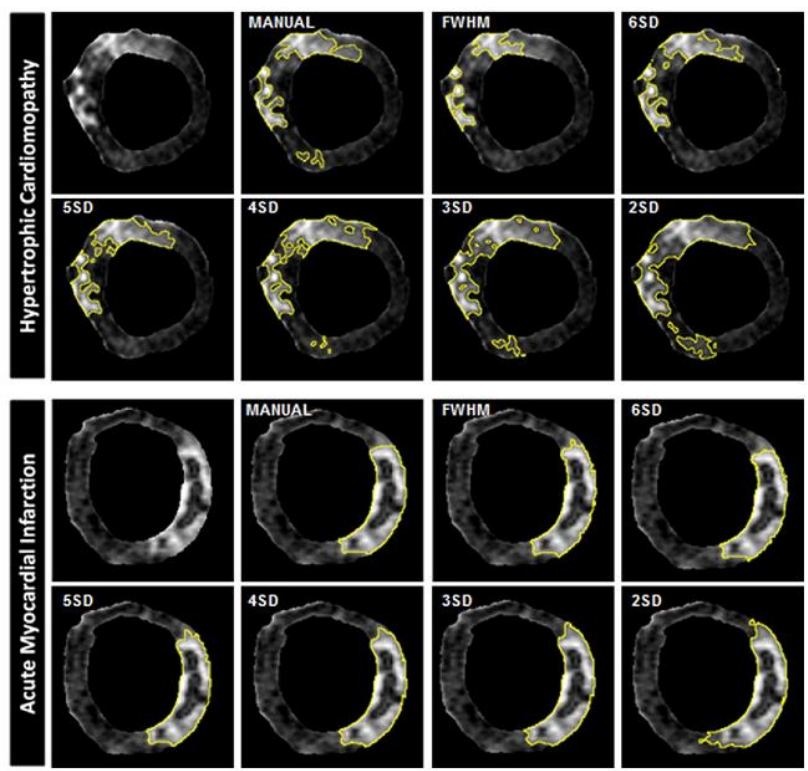
Partial Volume Effect



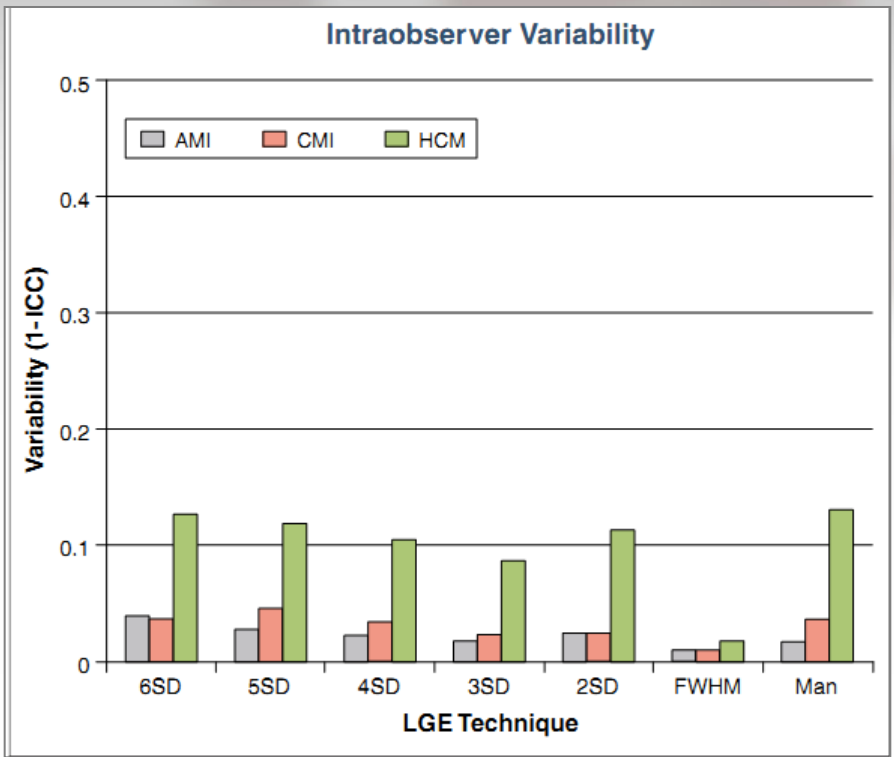
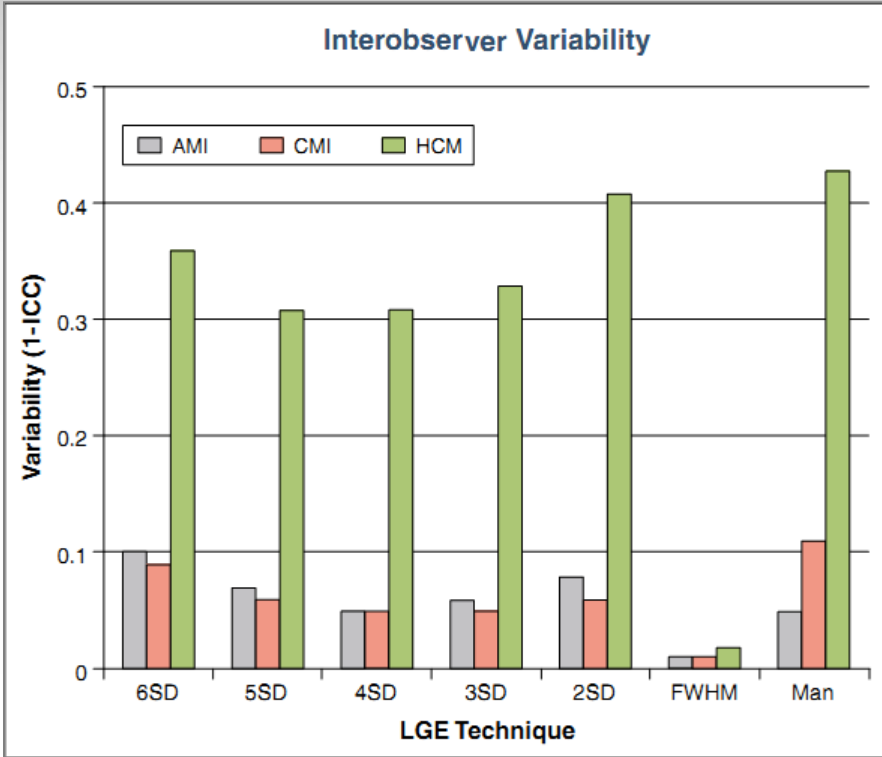
Border Zone



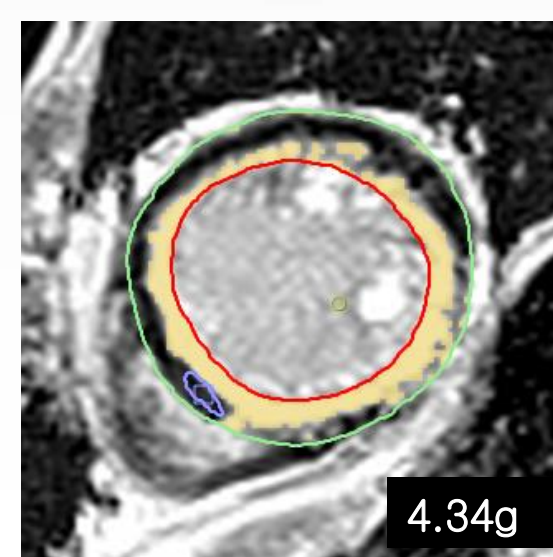
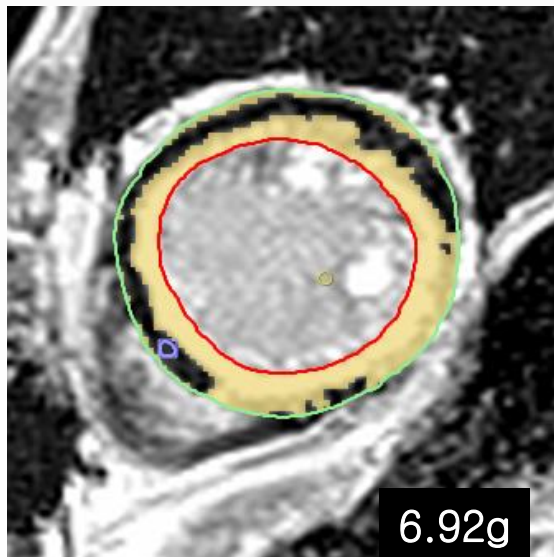
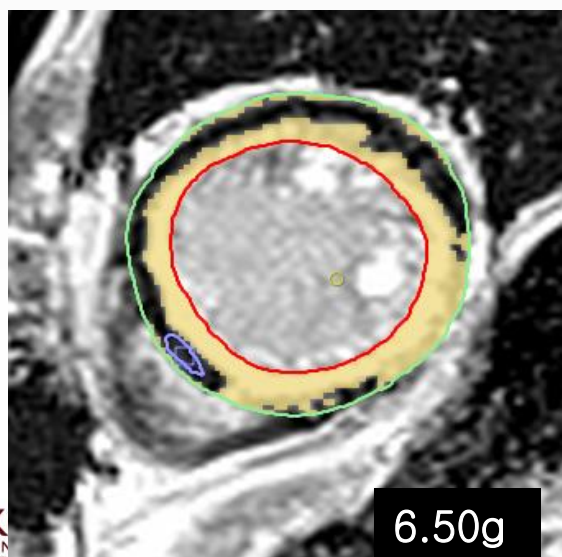
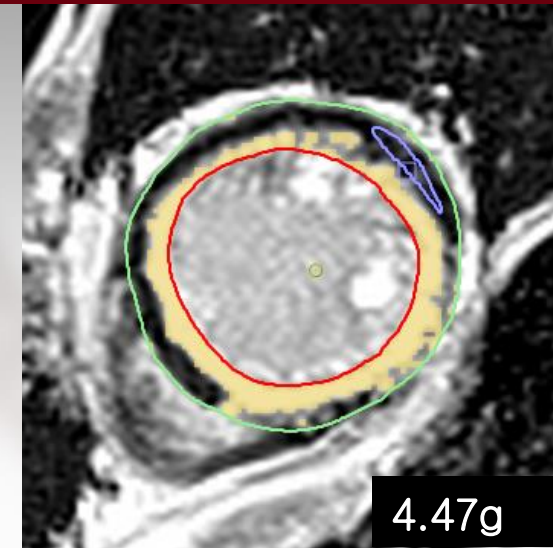
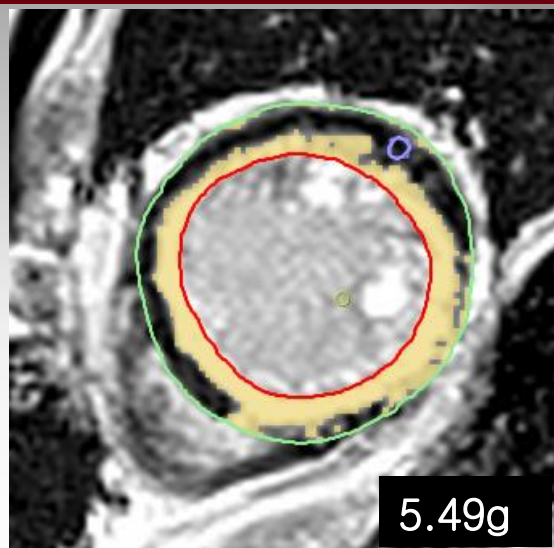
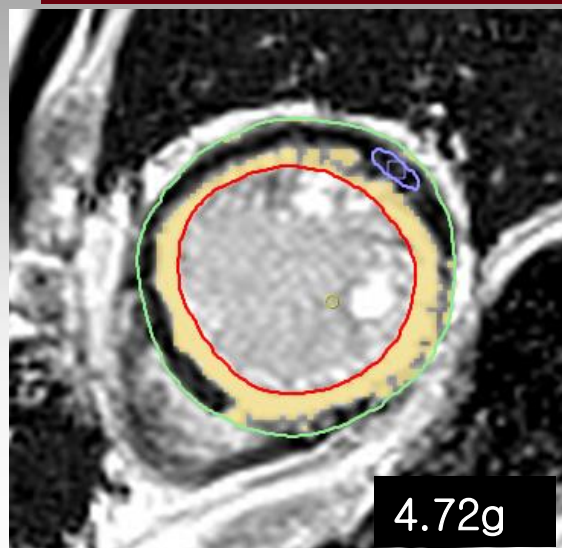
DE MR: Quantification



DE MR: Quantification



Reference Myocardium



Cine-CMR

Table 2. Baseline Characteristics of Studies Included in the Meta-Analysis Using CMR With LDD

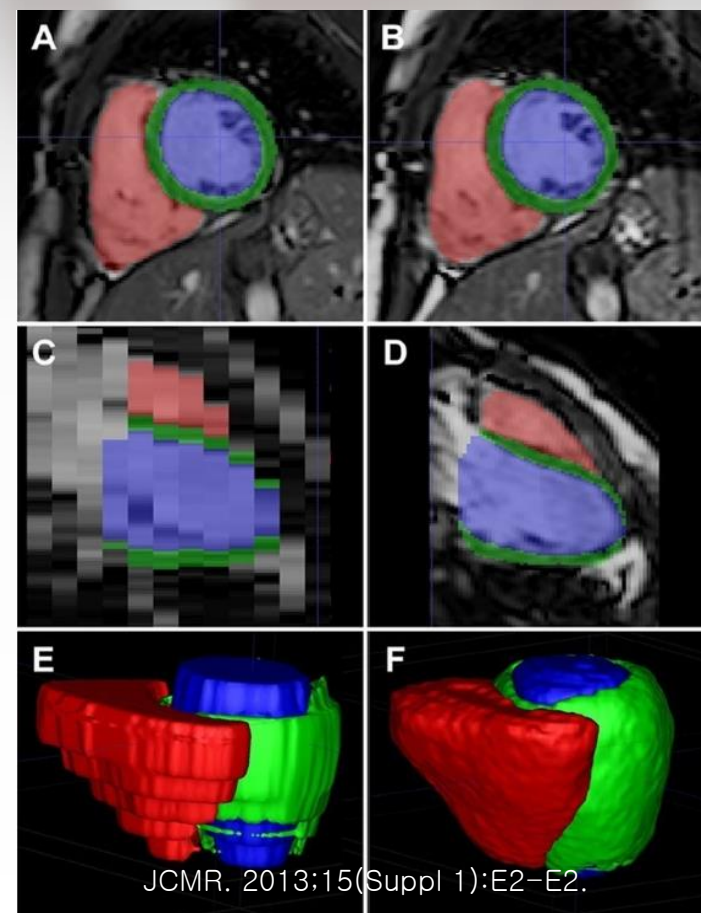
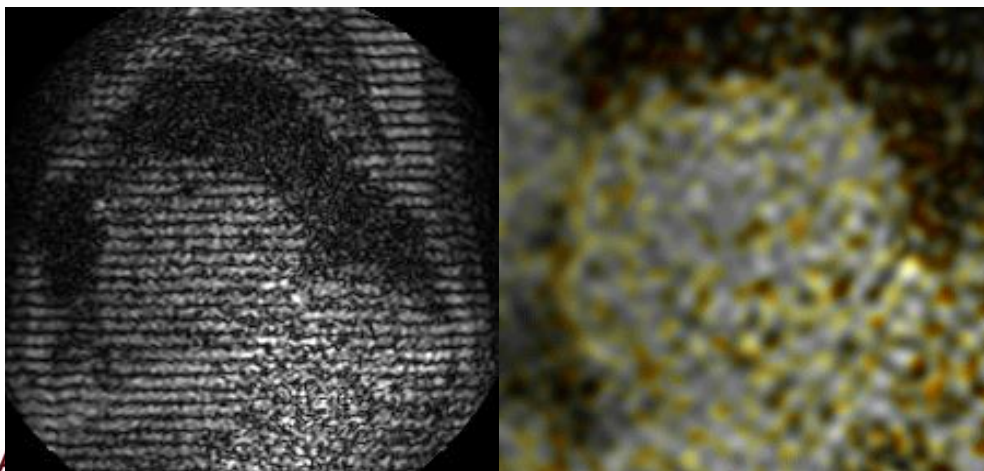
First Author (Ref #), Year	Study Design	n	Male (%)	Age (yrs)	LVEF (%)	Revascularization	Follow-Up CMR (Weeks)	Technique to Assess LVEF	Dobutamine Dose ($\mu\text{g}/\text{kg}/\text{min}$)	Cutoff for Viability (mm)
Baer et al. (55), 1998	Prospective	43	93	58	42	CABG/PCI	20	CMR	10	>2
Baer et al. (54), 2000	Prospective	52	48	58	41	CABG/PCI	NR	CMR	5-10	>2
Gutberlet et al. (45), 2005	Prospective	20	95	64	29	CABG	24	CMR	5-10	>2
Lauerma et al. (56), 2000	Prospective	10	80	69	44	PCI	24	CMR	5	>2
Sandestede et al. (57), 1999	Prospective	25	88	58	NR	CABG/PCI	12	CMR	10	>2
Sayad et al. (58), 1998	Prospective	10	70	NR	NR	CABG/PCI	6	CMR	5-10	>2
Schmidt et al. (59), 2004	Prospective	40	92	57	42	CABG/PCI	20	CMR	10	>2
Van Hoe et al. (36), 2004	Prospective	18	56	62	52	CABG/PCI	36	CMR	10	>2
Wellnhofer et al. (51), 2004	Prospective	29	93	68	NR	CABG/PCI	12	CMR	5-10	>2

Table 3. Baseline Characteristics of Studies Included in the Meta-Analysis Using CMR With EDWT

First Author (Ref #), Year	Study Design	n	Male (%)	Age (yrs)	LVEF (%)	Revascularization	Follow-Up CMR (Weeks)	Technique to Assess LVEF	Cutoff for Viability (mm)
Baer et al. (55), 1998	Prospective	43	93	58	42	CABG/PCI	20	CMR	>5.5
Gutberlet et al. (45), 2005	Prospective	20	95	64	29	CABG	24	CMR	>6
Klow et al. (60), 1997	Prospective	17	88	63	40	CABG	88	CMR	>6
Schmidt et al. (59), 2004	Prospective	40	92	57	42	CABG/PCI	20	CMR	>5.5

Cine-CMR

- Accuracy
 - Temporal & Spatial resolution
 - Scan time
- Quantification
 - Tagging
 - Strain encoded (SENC)



Summary

- CMR is very accurate modality for assessing myocardial viability.
 - DE-CMR: high sensitivity and NPV
 - LDD-CMR: high specificity and PPV
 - Other methods
 - unenhanced residual rim thickness
 - end-diastolic wall thickness
- Need quality control and standardization.
 - Image acquisition
 - Measuring, quantification and reporting

감사합니다.