Influence of Mitral Regurgitation Repair on Survival In the Surgical Treatment for Ischemic Heart Failure Trial – SUPPLEMENTAL MATERIAL

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Supplemental Methods

This supplement contains the per-protocol mortality analyses.

Also, baseline treatment of patients with moderate-severe MR is presented.

Supplemental Results

Study population

Of 1212 patients enrolled in the STICH Hypothesis 1 Trial, 435 (36%) were reported to have none or trace MR, 554 (46%) to have mild MR, 181 (15%) to have moderate MR, 39 (3%) to have severe MR at baseline. In 3 patients MR was not assessed.

Among patients with none or trace MR 34 (8%) did not receive their assigned treatment within 12 months of randomization. The number was 61 (11%) in patients with mild MR, 19 (10%) in moderate MR and 6 (15%) in those with severe MR.

Thus 401 patients with none or trace MR, 493 with mild MR, and 195 with moderate-severe MR were available for per-protocol analysis. Supplemental tables 1 and 2 summarize baseline characteristics of patients grouped by MR grade and treatment assignment. As in the intention to treat cohort increasing MR grade was associated with larger LV end-systolic volume index (ESVI), lower LVEF, higher heart failure class and shorter six-minute walk distances.

The therapies at baseline in patients with moderate to severe MR are presented in supplemental table 3 (an intention-to-treat analysis) and supplemental table 4 (per-protocol analysis).

Outcome

Mortality in the patients assigned to MED and treated medically was strongly related to MR severity at baseline (Figure 1). There were 67 deaths (33%) in 203 patients with none or trace MR, 107 (47%) in 227 with mild MR (HR vs. no MR 1.60, 95% CI 1.18–2.18) and 53 (51%) in 104 patients with moderate-severe MR (HR vs. no MR 1.97, 95% CI 1.37–2.83).

Although mortality tended to be lower with surgical treatment at every level of MR, this was only statistically significant in patients with mild MR (Figure 2). Of 266 surgically-treated patients with mild MR, 86 died (32%) (HR vs. MED 0.64, 95%CI 0.48–0.85; P=0.0023).

Supplemantal table 1. Baseline Characteristics of 1089 patients who received their assignment treatment by Mitral Regurgitation Severity

Characteristic	None or Trace MR (n=401)	Mild MR (n=493)	Moderate-Severe MR (n=195)	P Value
Age, median (25th, 75th), yrs	59 (54, 66)	60 (54, 68)	60 (54, 69)	0·207
Male, no. (%)	364 (91)	426 (86)	168 (86)	0·095
Previous MI, no. (%)	306 (76)	384 (78)	149 (76)	0·833
Hyperlipidaemia, no. (%)	261 (65)	289 (59)	111 (57)	0·077
Hypertension, no. (%)	255 (64)	298 (60)	111 (57)	0·279
Diabetes, no. (%)	170 (42)	187 (38)	78 (40)	0·399
Chronic renal disease, no. (%)	32 (8)	33 (7)	18 (9)	0·503
Previous stroke, no. (%)	32 (8)	36 (7)	16 (8)	0·894
Previous PCI, no. (%)	42 (11)	58 (12)	36 (19)	0·018
Previous CABG, no. (%)	10 (3)	11 (2)	8 (4)	0·376
Current CCS angina class, no. (%)				0·241
0	162 (40)	171 (35)	77 (40)	
1	64 (16)	77 (16)	29 (15)	
2	156 (39)	227 (46)	77 (40)	
3	16 (4)	15 (3)	10 (5)	
4	3 (1)	3 (1)	2 (1)	
Highest NYHA class in last 3 months, no. (%)				<0·001
I	28 (7)	27 (6)	10 (5)	
II	170 (42)	175 (36)	57 (29)	
III	158 (39)	227 (46)	90 (46)	
IV	45 (11)	64 (13)	38 (20)	
Region, no. (%)				<0·001
Europe	191 (48)	298 (60)	103 (53)	
US and Canada	88 (22)	103 (21)	33 (17)	

Other	122 (30)	92 (19)	59 (30)	
Risk at randomization	8 (3, 16)	11 (5, 19)	17 (10, 24)	<0·001
CAD distribution, no. of vessel stenosed (75% criterion), no. (%)				0·588
1	102 (25)	125 (25)	46 (24)	
2	163 (41)	179 (36)	76 (39)	
3	136 (34)	189 (38)	73 (37)	
Left main (≥ 50% stenosis), no. (%)	7 (2)	15 (3)	6 (3)	0·422
Proximal LAD (≥75% stenosis), no. (%)	294 (73)	332 (67)	118 (61)	0·006
Duke CAD index, median (25th, 75th), 0–100	65 (39, 77)	65 (39, 77)	52 (39, 77)	0·502
LV ejection fraction, median (25th, 75th), %	29 (23, 35)	27 (21, 33)	25 (20, 32)	<0·001
ESVI, median (25th, 75th), mL/m^2	72 (57, 93)	81 (61, 101)	88 (65, 121)	<0·001
Six-minute walk test				
Able to perform, no. (%)	339 (85)	436 (88)	168 (87)	0·310
Distance walked, median (25th, 75th), m	350 (290, 420)	340 (356, 409)	333 (255, 400)	0·040

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; ESVI, end-systolic volume index; LAD, left anterior descending; MED, medical therapy; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Supplemental table 2: Baseline Characteristics of 1089 Patients who received their assigned treatment by Mitral Regurgitation Severity and Randomized Treatment Assignment

Characteristic	None or Trace MR		Mild MR		Moderate-Severe MR	
	MED (n=203)	CABG (n=198)	MED (n=227)	CABG (n=266)	MED (n=104)	CABG (n=91)
Age, median (25th, 75th), yrs	59 (63, 66)	60 (54, 67)	59 (54, 68)	60 (53, 68)	59 (53, 69)	62 (55, 69)
Male, no. (%)	185(91)	179 (90)	198 (87)	228 (86)	87 (84)	81 (89)
Previous MI, no. (%)	160(79)	146 (74)	180 (79)	204 (77)	78 (75)	71 (78)
Hyperlipidaemia, no. (%)	132(65)	129 (65)	138 (61)	151 (57)	57 (55)	54 (60)
Hypertension, no. (%)	131 (65)	124 (63)	142 (63)	156 (59)	61 (59)	50 (55)
Diabetes, no. (%)	88 (43)	82 (41)	87 (38)	100 (38)	42 (40)	36 (40)
Chronic renal disease, no. (%)	15 (7)	17 (9)	16 (7)	17 (6)	11 (11)	7 (8)
Previous stroke, no. (%)	11 (5)	21 (11)	17 (8)	19 (7)	8 (8)	8 (9)
Previous PCI, no. (%)	19 (9)	23 (12)	29 (13)	29 (11)	18 (17)	18 (20)
Previous CABG, no. (%)	4 (2)	6 (3)	5 (2)	6 (2)	4 (4)	4 (4)
Current CCS angina class, no. (%)						
0	84 (41)	78 (39)	84 (37)	87 (33)	41 (39)	36 (40)
1	36 (18)	28 (14)	26 (12)	51 (19)	21 (20)	8 (9)
2	74 (37)	82 (41)	110 (49)	117 (44)	37 (36)	40 (44)
3	9 (4)	7 (4)	4 (2)	11 (4)	5 (5)	5 (6)
4	0 (0)	3 (2)	3 (1)	0 (0)	0 (0)	2 (2)
Highest NYHA class in last 3 months, no. (%)						
I	16 (8)	12 (6)	15 (7)	12 (5)	6 (6)	4 (4)
II	88 (43)	82 (41)	74 (33)	101 (38)	30 (29)	27 (30)
III	82 (40)	76 (38)	106 (47)	121 (46)	46 (44)	44 (48)

IV	17 (8)	28 (14)	32 (14)	132 (12)	22 (21)	16 (18)
Region, no. (%)						
Europe	100 (49)	91 (46)	138 (61)	160 (60)	55 (53)	48 (53)
US and Canada	46 (23)	42 (21)	45 (20)	58 (22)	16 (15)	17 (19)
Other	57 (28)	65 (33)	44 (19)	48 (18)	33 (32)	26 (29)
Risk at randomization, median (25th, 75th)	8 (3, 16)	8 (3, 16)	12 (5, 20)	11 (6, 19)	17 (9, 24)	17 (11, 23)
CAD distribution, no. of vessel stenosed ($\geq$ 75%), no. (%)						
1	50 (25)	52 (26)	64 (28)	61 (23)	25(24)	21 (23)
2	86 (42)	77 (39)	78 (34)	101 (38)	41 (39)	35 (39)
3	67 (33)	69 (35)	85 (37)	104 (39)	38 (37)	35 (39)
Left main ($\geq$ 50% stenosis), no. (%)	4 (2)	3 (2)	5 (2)	10 (4)	3 (3)	3 (3)
Proximal LAD ($\geq$75% stenosis), no. (%)	150 (74)	144 (73)	153 (67)	179 (67)	63 (61)	55 (60)
Duke CAD index, median (25th, 75th), 0–100	65 (39, 77)	52 (39, 77)	65 (39, 77)	65 (39, 77)	52 (39, 77)	59 (39, 77)
LV ejection fraction, median (25th, 75th), %	30 (24, 35)	27 (22, 34)	26 (21, 34)	27 (22, 32)	25 (20, 32)	26 (20, 31)
ESVI, median (25th, 75th), mL/m2	72 (57, 90)	71 (57, 99)	83 (57,108)	80 (64, 98)	90 (67,122)	85 (63,121)
Six-minute walk test						
Able to perform, no. (%)	178 (89)	161 (81)	203 (89)	233(88)	93 (89)	75 (83)
Distance walked, median (25th, 75th), m	350 (291, 423)	350 (280, 417)	330 (255, 412)	350 (259, 401)	340 (255, 400)	333 (255, 399)

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; ESVI, end-systolic volume index; LAD, left anterior descending; LV, left ventricular; MED, medical therapy; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Supplemental table 3 Therapies at baseline in patients with moderate/severe MR as randomized.

	MED (n = 116)	CABG Only (n = 55)	CABG + MVRep (n = 49)
ICD	3 (2.6%)	3 (5.5%)	2 (4.1%)
Pacemaker for heart rate	5 (4.3%)	0 (0%)	1 (2.0%)
Pacemaker (CRT)	1 (0.9%)	0 (0%)	0 (0%)
Beta-Blocker*	103 (89%)	42 (76%)	44 (90%)
ACE Inhibitor	93 (80%)	45 (82%)	43 (88%)
ACE Inhibitor or ARB	103 (89%)	50 (91%)	46 (94%)
Statin	97 (84%)	43 (78%)	43 (88%)
Aspirin	96 (83%)	42 (76%)	38 (78%)
Aspirin or Warfarin*	106 (91%)	45 (82%)	39 (80%)
Clopidogrel*	25 (22%)	15 (27%)	5 (10%)
Digoxin	34 (29%)	19 (35%)	18 (37%)
Diuretic	99 (85%)	44 (80%)	45 (92%)
Nitrate	58 (50%)	29 (53%)	28 (57%)

Abbreviations: ACE, angiotensin converting enzyme, ARB, aldosterone receptor blocker, CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MED, medical therapy; MR, mitral regurgitation.
*$0.05 < p < 0.10$. $P > 0.10$ for all other comparisons

Supplemantal table 4 Therapies at baseline in patients with moderate/severe MR per protocol.

|	MED (n = 104)	CABG Only (n = 42)	CABG + MVRep (n = 49)
ICD	3 (2.9%)	2 (4.8%)	2 (4.1%)
Pacemaker for heart rate	5 (4.8%)	0 (0%)	1 (2.0%)
Pacemaker (CRT)	1 (1.0%)	0 (0%)	0 (0%)
Beta-Blocker	91 (88%)	32 (76%)	44 (90%)
ACE Inhibitor	84 (81%)	35 (83%)	43 (88%)
ACE Inhibitor or ARB	94 (90%)	39 (93%)	46 (94%)
Statin	87 (84%)	33 (79%)	43 (88%)
Aspirin	85 (82%)	32 (76%)	38 (78%)
Aspirin or Warfarin*	95 (91%)	34 (81%)	39 (80%)
Clopidogrel*	23 (22%)	12 (29%)	5 (10%)
Digoxin	31 (30%)	16 (38%)	18 (37%)
Diuretic	88 (85%)	35 (83%)	45 (92%)
Nitrate	52 (50%)	25 (60%)	28 (57%)

Abbreviations: ACE, angiotensin converting enzyme, ARB, aldosterone receptor blocker, CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MED, medical therapy; MR, mitral regurgitation.
*$0.05 < p < 0.10$. $P > 0.10$ for all other comparisons
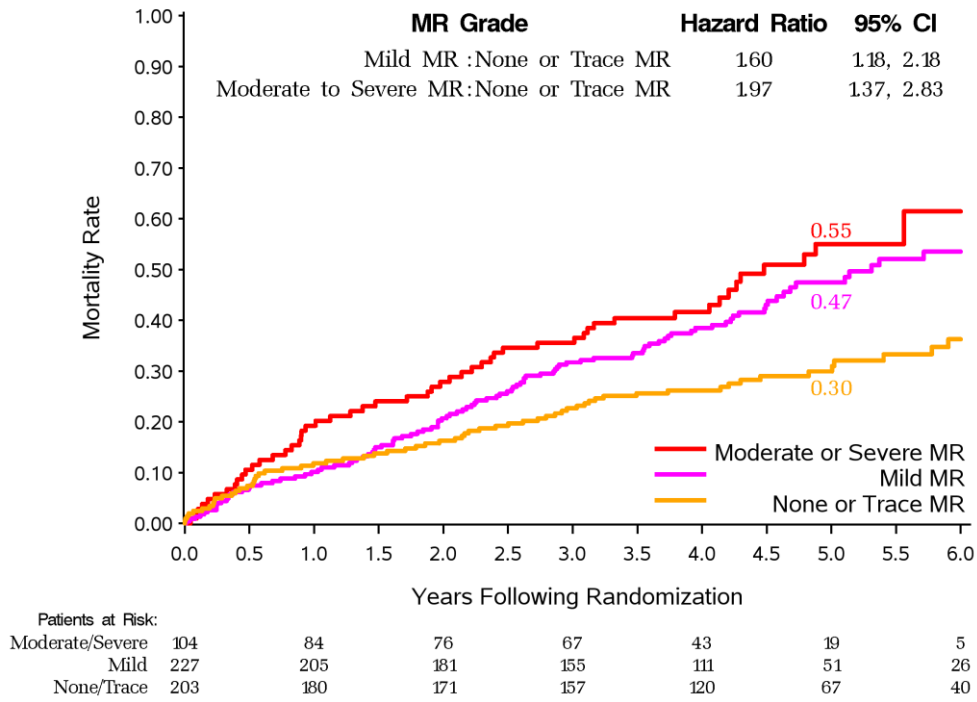
Figure 1. Kaplan-Meier estimates of death from any cause among patients assigned to and treated with MED. Separate curves for patients with site-reported none or trace, mild, and moderate-severe MR are presented.
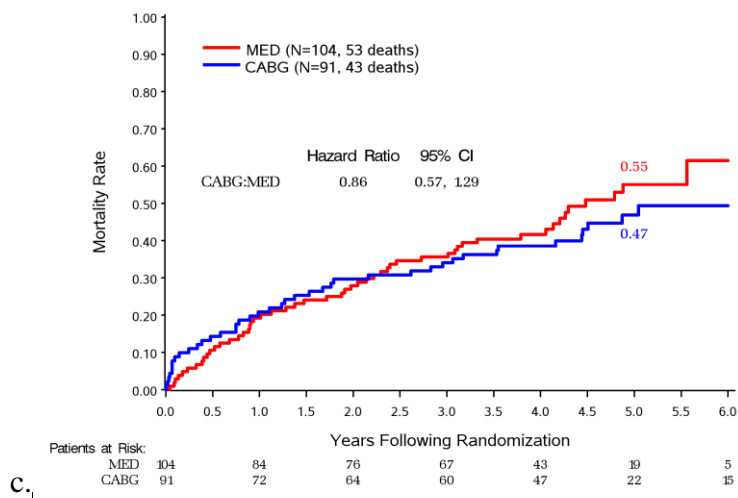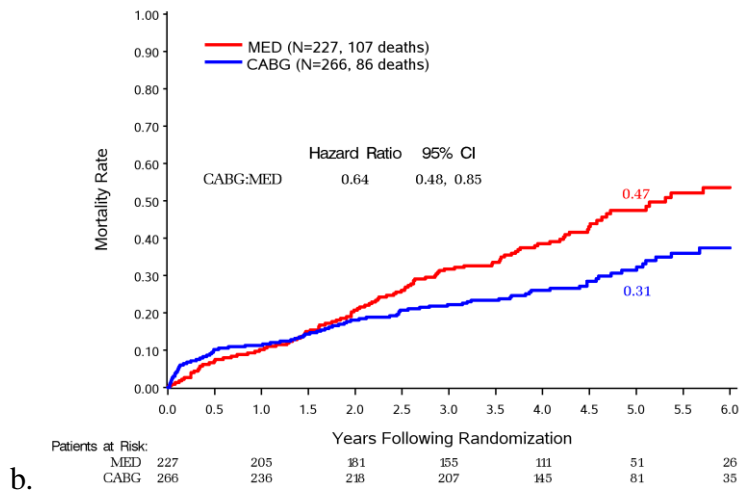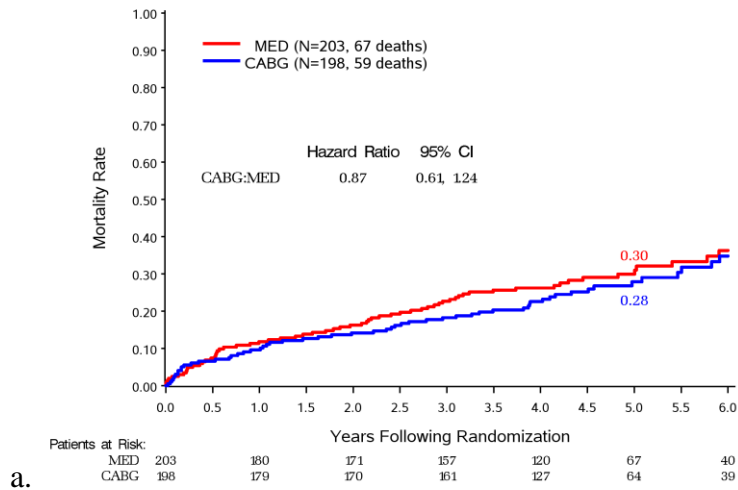
Figure 2. Kaplan-Meier estimates of death from any cause in patients assigned to and treated with MED or MED and CABG with site-reported none or trace MR at baseline (a), mild MR at baseline (b), moderate-severe MR at baseline (c).