Ten-Year Outcomes After Coronary Artery Bypass Grafting According to Age in Patients With Heart Failure and Left Ventricular Systolic Dysfunction

An Analysis of the Extended Follow-Up of the STICH Trial (Surgical Treatment for Ischemic Heart Failure)

BACKGROUND: Advancing age is associated with a greater prevalence of coronary artery disease in heart failure with reduced ejection fraction and with a higher risk of complications after coronary artery bypass grafting (CABG). Whether the efficacy of CABG compared with medical therapy (MED) in patients with heart failure caused by ischemic cardiomyopathy is the same in patients of different ages is unknown.

METHODS: A total of 1212 patients (median follow-up, 9.8 years) with ejection fraction ≤35% and coronary disease amenable to CABG were randomized to CABG or MED in the STICH trial (Surgical Treatment for Ischemic Heart Failure).

RESULTS: Mean age at trial entry was 60 years; 12% were women; 36% were nonwhite; and the baseline ejection fraction was 28%. For the present analyses, patients were categorized by age quartiles: quartile 1, ≤54 years; quartile, 2 >54 and ≤60 years; quartile 3, >60 and ≤67 years; and quartile 4, >67 years. Older versus younger patients had more comorbidities. All-cause mortality was higher in older compared with younger patients assigned to MED (79% versus 60% for quartiles 4 and 1, respectively; log-rank P=0.005) and CABG (68% versus 48% for quartiles 4 and 1, respectively; log-rank P<0.001). In contrast, cardiovascular mortality was not statistically significantly different across the spectrum of age in the MED group (53% versus 49% for quartiles 4 and 1, respectively; log-rank P=0.388) or CABG group (39% versus 35% for quartiles 4 and 1, respectively; log-rank P=0.103). Cardiovascular deaths accounted for a greater proportion of deaths in the youngest versus oldest quartile (79% versus 62%). The effect of CABG versus MED on all-cause mortality tended to diminish with increasing age ($P_{interaction}$=0.062), whereas the benefit of CABG on cardiovascular mortality was consistent over all ages ($P_{interaction}$=0.307). There was a greater reduction in all-cause mortality or cardiovascular hospitalization with CABG versus MED in younger compared with older patients ($P_{interaction}$=0.004). In the CABG group, cardiopulmonary bypass time or days in intensive care did not differ for older versus younger patients.

CONCLUSIONS: CABG added to MED has a more substantial benefit on all-cause mortality and the combination of all-cause mortality and cardiovascular hospitalization in younger compared with older patients. CABG added to MED has a consistent beneficial effect on cardiovascular mortality regardless of age.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00023595.

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Clinical Perspective

What Is New?

- The 10-year follow-up of the STICH trial (Surgical Treatment for Ischemic Heart Failure) demonstrated a reduction in all-cause mortality in patients with heart failure who received coronary artery bypass grafting (CABG) added to guideline-directed medical therapy compared with medical therapy alone.
- In the present analyses, we report that the reduction in all-cause mortality with CABG was most pronounced in younger patients. The impact of CABG on all-cause mortality and the combination of all-cause mortality and cardiovascular hospitalization is diminished in older patients.
- The benefit of CABG on cardiovascular mortality is consistent across all ages in the trial.

What Are the Clinical Implications?

- Patients presenting with heart failure who are potential candidates for CABG should be investigated to establish if they have coronary heart disease amenable to surgical revascularization.
- Cardiologists and cardiac surgeons can offer appropriate patients CABG in addition to optimal medical therapy with the knowledge that cardiovascular mortality is reduced across all age groups included in the trial.
- When considering older patients for surgical revascularization, clinicians should be aware that the reductions in all-cause mortality and the combination of all-cause mortality and cardiovascular hospitalization seen in younger patients are diminished with increasing age.

Older patients with heart failure (HF) more commonly have coronary artery disease (CAD) as the cause of their HF than younger patients.[1] With improving survival, the prevalence of patients living with both ischemic heart disease and HF who potentially require coronary revascularization has risen.[2] Management of these patients is difficult; many have angina or evidence of ischemia or myocardial viability and are considered for coronary revascularization. Because there have been no randomized trials of coronary percutaneous intervention in populations with HF, the benefits or harms of this approach are unknown. However, results from the STICH trial (Surgical Treatment for Ischemic Heart Failure; including the extended follow-up study)[3,4] demonstrated improved clinical outcomes after coronary artery bypass grafting (CABG); over a median of 9.8 years, the risk of all-cause death, death resulting from cardiovascular causes, and all-cause death or hospitalization for cardiovascular causes was significantly lower in those randomized to receive CABG and guideline-directed medical therapy compared with patients randomized to medical therapy alone.[4]

Increasing age is associated with worse short- and long-term outcomes after CABG in general populations of patients with CAD.[5,6] Because increasing age is associated with higher mortality in patients with HF,[7] clinicians may be reluctant to recommend older patients for revascularization with CABG as a result of uncertainty about its benefits. We examined the effect of CABG and guideline-directed medical therapy compared with guideline-directed medical therapy alone according to age in the STICH trial.

METHODS

The STICH trial[3] (http://www.clinicaltrials.gov. Unique identifier NCT00023595) and extended follow-up[4] have been described in detail previously. The median follow-up time was 9.8 years (interquartile range, 9.1–11.0 years). Patients ≥18 years of age with CAD that was amenable to treatment with CABG and an ejection fraction of ≤35% as determined at each enrolling site (measured by cardiac magnetic resonance ventriculogram, gated single-photon emission computed tomography ventriculogram, echocardiography, or contrast ventriculogram within 3 months of trial entry) were enrolled. Patients were randomized to CABG with guideline-directed medical therapy versus medical therapy alone. Trial sites were prompted by the STICH team to implement guideline-recommended optimal medical therapy in both randomized arms. Patients were eligible for randomization only if they did not have a coronary stenosis of ≥50% of the diameter of the left main coronary artery and if they did not have Canadian Cardiovascular Society class III or IV angina while receiving medical therapy. The extended follow-up study was a prespecified extension of the STICH trial with follow-up extended an additional 5 years. The study complied with the Declaration of Helsinki, and the locally appointed ethics committee approved the research protocol. Informed consent was obtained from the subjects or their legally authorized representatives.

Outcomes

The primary outcome was all-cause death, and the 2 key secondary outcomes were cardiovascular death and a composite of all-cause death or cardiovascular hospitalizations. All deaths were classified by a blinded clinical events committee according to prespecified criteria.

Statistical Analysis

The randomized population was divided according to age into quartiles: quartile 1, ≤54 years; quartile 2, >54 and ≤60 years; quartile 3, >60 and ≤67 years; and quartile 4, >67 years. Baseline characteristics are presented by quartile of age. Continuous variables are presented as medians with 25th and 75th percentiles and categorical variables as counts with percentages. The distribution of continuous variables was tested with the Jonckheere-Terpstra trend test (Spearman correlation *P* values are presented in the online-only Data Supplement) and of categorical variables with the Cochran-Armitage trend test. Kaplan-Meier rates were computed for each age group by randomized treatment.[8] The relationship between age as a continuous variable and outcomes was examined and graphed with

Table 1. Baseline Characteristics by Age

Variable	Baseline Age Quartiles				*P* Value for Trend
	Quartile 1 (Age ≤54 y) (n=330)	Quartile 2 (54<Age≤60 y) (n=295)	Quartile 3 (60<Age≤67 y) (n=279)	Quartile 4 (Age>67 y) (n=308)	
Age, y	50 (47, 53)	57 (56, 58)	64 (62, 65)	72 (69,75)	
Women, n (%)	35 (11)	26 (9)	37 (13)	50 (16)	0.011
White race, n (%)	187 (57)	189 (64)	200 (72)	251 (82)	<0.001
BMI, kg/m^2	27 (24, 31)	27 (24, 30)	27 (24, 30)	26 (24, 29)	0.180
Medical history, n (%)					
Diabetes mellitus	103 (31)	121 (41)	124 (44)	130 (42)	0.003
Hypertension	178 (54)	177 (60)	159 (57)	214 (70)	<0.001
PVD	36 (11)	40 (14)	42 (15)	66 (21)	<0.001
Renal insufficiency	10 (3)	16 (5)	25 (9)	43 (14)	<0.001
Stroke	23 (7)	14 (5)	21 (8)	34 (11)	0.028
Atrial flutter/fibrillation	19 (6)	25 (9)	42 (15)	67 (22)	<0.001
Previous MI	250 (76)	229 (78)	208 (75)	247 (80)	0.320
Hyperlipidemia	190 (58)	174 (59)	181 (65)	185 (60)	0.286
Depression	24 (7)	17 (6)	15 (5)	20 (7)	0.646
Current smoker	104 (32)	64 (22)	50 (18)	34 (11)	<0.001
Previous PCI	45 (14)	38 (13)	38 (14)	35 (11)	0.465
Previous CABG	8 (2)	10 (3)	11 (4)	7 (2)	0.974
CCS angina class, n (%)					
No angina	106 (32)	97 (33)	91 (33)	148 (48)	<0.001
I	42 (13)	44 (15)	52 (19)	49 (16)	0.145
II	169 (51)	141 (48)	119 (43)	96 (31)	<0.001
III	10 (3)	12 (4)	15 (5)	11 (4)	0.551
IV	3 (1)	1 (<1)	2 (1)	4 (1)	0.583
NYHA class, n (%)					
I	35 (11)	50 (17)	22 (8)	32 (10)	0.276
II	185 (56)	134 (45)	157 (56)	150 (49)	0.318
III	100 (30)	106 (36)	93 7 (33)	113 (37)	0.152
IV	10 (3)	5 (2)	7 (3)	13 (4)	0.315
Median systolic BP, mm Hg	120 (110, 130)	120 (110, 130)	120 (110, 130)	122 (110, 136)	<0.001
Median heart rate, bpm	76 (68, 84)	75 (68, 82)	74 (66, 82)	71 (63, 80)	<0.001
Median 6-min walk distance, m	352 (259, 434)	360 (273, 415)	340 (270, 400)	321 (250, 385)	<0.001
Laboratory measures					
Hemoglobin, g/dL	14.3 (13.2, 15.4)	13.9 (12.7, 14.9)	13.7 (12.6, 14.8)	13.6 (12.3, 14.6)	<0.001
Creatinine, mg/dL	1.02 (0.90, 1.18)	1.10 (0.97, 1.23)	1.10 (0.94, 1.30)	1.17 (1.00, 1.40)	<0.001
Sodium, mEq/L	139 (137, 142)	140 (137, 142)	140 (138, 142)	140 (137, 142)	0.143
BUN, mg/dL	22 (15, 37)	21 (16, 34)	21 (16, 36)	24 (18 ,39)	0.031

BMI indicates body mass index; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease. Values in parentheses are 25th and 75th percentiles.

the mfpi command in Stata as a fractional polynomial.[9,10] The effect of randomized therapy (CABG with guideline-directed medical therapy versus medical therapy alone) by age was examined in a Cox proportional hazards model with an interaction term of randomized therapy and age as a continuous variable. All models were unadjusted, and analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC) and Stata version 14 (StataCorp, College Station, TX), with values of $P<0.05$ considered statistically significant.

RESULTS

Baseline Characteristics by Age

The 1212 patients were split into 4 quartiles. Patients in the oldest quartile (age >67 years) tended to more often be female and white (Table 1 and the online-only Data Supplement). Older patients had a higher prevalence of comorbidities except for hyperlipidemia and depression. The proportion of patients with no or Canadian Cardiovascular Society class I angina was highest in the oldest age group. Older patients had a shorter 6-minute walk test distance. Systolic blood pressure was higher and heart rate was lower in the older group. Hemoglobin was lower and kidney function was worse in the older age groups. Within the oldest quartile, 75 (6%) were >75 years of age and 15 (1%) were >80 years of age (online-only Data Supplement)

Baseline medical therapy and device therapy were similar across ages (Table 2) except for greater use of warfarin (owing to more atrial fibrillation) and loop or thiazide diuretics in older patients. The proportion on guideline-directed medical therapy fell in the older compared with younger patient groups over time (online-only Data Supplement). In each age quartile, there was no difference in medical therapies between the CABG and medical therapy groups (online-only Data Supplement).

Echocardiographic Measures and Coronary Anatomy According to Age

Left ventricular ejection fraction was similar over the age range, although end-diastolic volume indexed to body surface area was lower in the oldest age group (Table 3). The E-wave velocity and E/A ratio were lower in the older group than younger groups, but there were no significant

Table 2. Baseline Medical and Device Therapies by Age

Variable	Baseline Age Quartiles, n (%)				*P* Value for Trend
	Quartile 1 (Age ≤54 y) (n=330)	Quartile 2 (54<Age≤60 y) (n=295)	Quartile 3 (60<Age≤67 y) (n=279)	Quartile 4 (Age >67 y) (n=308)	
β-Blocker	282 (86)	247 (84)	250 (90)	257 (83)	0.946
ACE inhibitor	267 (81)	248 (84)	233 (84)	248 (81)	0.879
ARB	27 (8)	23 (8)	23 (8)	42 (14)	0.023
ACE or ARB	288 (87)	263 (89)	252 (90)	282 (92)	0.068
Statin	271 (82)	242 (82)	230 (82)	240 (78)	0.216
Digoxin	68 (21)	62 (21)	55 (20)	60 (20)	0.651
Aspirin	273 (83)	250 (85)	232 (83)	247 (80)	0.348
Warfarin	25 (8)	23 (8)	35 (13)	44 (14)	0.001
Clopidogrel	57 (17)	57 (19)	47 (17)	47 (15)	0.387
Diuretic					
Loop/thiazide	200 (61)	190 (64)	184 (66)	217 (71)	0.008
Potassium-sparing	161 (49)	137 (46)	136 (49)	122 (40)	0.042
Loop/thiazide or potassium sparing	233 (71)	222 (75)	216 (77)	241 (78)	0.020
Nitrate	166 (50)	154 (52)	162 (58)	164 (53)	0.232
Insulin	42 (13)	54 (18)	49 (18)	52 (17)	0.191
Oral antihyperglycemic agent	62 (19)	70 (24)	84 (30)	70 (23)	0.089
Antidepressant	16 (5)	17 (6)	17 (6)	15 (5)	0.938
Cardiac resynchronization therapy	3 (1)	0 (0)	1 (<1)	3 (1)	0.871
Pacemaker	3 (1)	3 (1)	4 (1)	8 (3)	0.073
ICD	11 (3)	6 (2)	8 (3)	4 (1)	0.161

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and ICD, implantable cardioverter-defibrillator.

differences in the E/e′ ratio. The presence and severity of mitral regurgitation did not vary significantly. Older patients had more vessels with a coronary stenosis but less proximal left anterior descending artery stenosis. The Duke CAD severity index increased with age.

Procedural Details and Complications of CABG by Age

In the CABG group, there was no difference in the number of conduits used by age, but the older group was more likely to have more distal anastomoses performed (Table 4). There was no difference in time on bypass or length of stay in the intensive care unit by age. The proportions who had to return to the operating room, developed mediastinitis, had intubation for pulmonary edema, or experienced a cardiac arrest were not different by age. New-onset atrial fibrillation rose with increasing age, as did the need for inotropes for low cardiac output.

Effect of Age on 10-Year Outcomes

All-cause mortality increased with increasing age in both the medical therapy (60% versus 79% for quartiles 1 and 4, respectively; log-rank P=0.005) and CABG (48% versus 68% for quartiles 1 and 4, respectively; log-rank P<0.001) groups. Cardiovascular mortality was higher in the older quartiles compared with the younger quartiles, but this difference was not statistically significant in either the medical therapy group (49% versus 53% in quartiles 1 and 4, respectively; log-rank P=0.338) or the CABG group (35% versus 39% in quartiles 1 and 4, respectively; log-rank P=0.103; Figure 1). Cardiovascular deaths accounted for a greater proportion of all deaths in the young (79% in the youngest quartile versus 62% in the oldest quartile).

Table 3. Baseline Left Ventricular Structure and Function and Coronary Anatomy by Age

Variable	Baseline Age Quartiles				*P* Value for Trend
	Quartile 1 (Age ≤54 y) (n=330)	Quartile 2 (54<Age≤60 y) (n=295)	Quartile 3 (60<Age≤67 y) (n=279)	Quartile 4 (Age >67 y) (n=308)	
Structure and function					
LVEF, %	28 (22, 33)	28 (23, 35)	26 (21, 33)	28 (22, 34)	0.496
ESVI	81 (62, 103)	81 (61, 98)	77 (60, 105)	77 (61, 98)	0.179
EDVI	117 (92, 144)	113 (90, 139)	109 (87, 141)	108 (87, 135)	0.012
E velocity, m/s	0.70 (0.30, 0.90)	0.70 (0.50, 0.90)	0.70 (0.50, 0.90)	0.60 (0.50, 0.85)	<0.001
A velocity, m/s	0.60 (0.40, 0.80)	0.70 (0.50, 0.80)	0.73 (0.60, 0.90)	0.70 (0.60, 0.90)	<0.001
E/A ratio	1.00 (0.75, 2.25)	1.00 (0.71, 1.78)	0.80 (0.63, 1.57)	0.75 (0.57, 1.33)	<0.001
E/e′ ratio (septal)	14 (11, 20)	17 (12, 23)	15 (12, 24)	17 (11, 23)	0.183
E/e′ ratio (lateral)	11 (8, 15)	12 (9, 16)	13 (9, 17)	12 (8, 17)	0.192
Anterior akinesia or dyskinesia, %	43 (30, 57)	43 (20, 50)	43 (29, 57)	40 (14, 57)	0.155
MR severity, n (%)					
None or trace	123 (37)	110 (37)	106 (38)	96 (31)	0.145
Mild	149 (45)	130 (44)	128 (46)	147 (48)	0.456
Moderate	43 (13)	47 (16)	38 (14)	53 (17)	0.240
Severe	14 (4)	8 (3)	7 (3)	10 (3)	0.460
Coronary anatomy					
No. of vessels with stenosis ≥50%, n (%)					
1	46 (14)	24 (8)	24 (9)	18 (6)	<0.001
2	101 (31)	94 (32)	87 (31)	84 (27)	0.362
3	183 (56)	177 (60)	168 (60)	205 (67)	0.006
Stenosis of proximal LAD ≥75%, n (%)	242 (73)	200 (68)	185 (66)	199 (65)	0.020
Duke CAD severity index	52 (39, 65)	65 (39, 77)	65 (39, 77)	65 (39, 77)	0.030

A indicates atrial contraction-induced diastolic filling velocity wave; CAD, coronary artery disease; e′, early diastolic myocardial velocity; E, early diastolic filling velocity; EDVI, end-diastolic volume indexed; ESVI, end-systolic volume indexed; LAD, left anterior descending; LVEF, left ventricular ejection fraction; and MR, mitral regurgitation.

Table 4. Procedural Details and Perioperative Complications by Age

Variable	Baseline Age Quartiles				*P* Value for Trend
	Quartile 1 (Age ≤54 y) (n=149)	Quartile 2 (54<Age≤60 y) (n=127)	Quartile 3 (60<Age≤67 y) (n=131)	Quartile 4 (Age >67 y) (n=148)	
No. of conduits, n (%)					
1	26 (17)	10 (8)	15 (12)	18 (12)	0.284
2	49 (33)	37 (29)	42 (32)	47 (32)	0.958
3	60 (40)	60 (47)	52 (40)	64 (43)	0.894
≥4	14 (9)	20 (16)	22 (17)	19 (13)	0.362
No. of arterial conduits, n (%)					
0	11 (7)	9 (7)	12 (9)	18 (12)	0.123
1	123 (83)	104 (82)	104 (79)	115 (78)	0.249
≥2	15 (10)	14 (11)	15 (12)	15 (10)	0.957
No. of distal anastomoses, n (%)					
0	2 (1)	2 (2)	2 (2)	1 (1)	0.631
1	23 (15)	10 (8)	14 (11)	16 (11)	0.319
2	41 (28)	27 (21)	30 (23)	30 (20)	0.185
3	57 (38)	55 (43)	50 (39)	59 (40)	0.982
4	22 (15)	23 (18)	22 (17)	31 (21)	0.211
≥5	4 (3)	10 (8)	12 (9)	11 (7)	0.090
Off-pump surgery, n (%)	40 (27)	24 (19)	25 (19)	27 (18)	0.083
Total time on cardiopulmonary bypass, min	83 (63, 110)	92 (72, 125)	93 (66, 110)	89 (70, 126)	0.425
Cross-clamp time, min	50 (33, 67)	55 (41, 79)	54 (35, 72)	56 (39, 80)	0.203
Intensive care unit length of stay, h	52 (43, 87)	61 (42, 94)	49 (27, 97)	65 (40, 112)	0.337
Perioperative complications, n (%)					
Return to operating room	7 (5)	9 (7)	7 (5)	12 (8)	0.326
Mediastinitis	3 (2)	4 (3)	2 (2)	2 (1)	0.516
Other infection	9 (6)	10 (8)	8 (6)	19 (13)	0.061
New-onset atrial fibrillation	10 (7)	20 (16)	22 (17)	38 (26)	<0.001
Worsening renal impairment	2 (1)	4 (3)	12 (9)	16 (11)	<0.001
Intra-aortic balloon pump	25 (17)	22 (17)	24 (18)	18 (12)	0.335
Inotrope use	45 (30)	44 (35)	56 (43)	71 (48)	<0.001
Cardiac arrest requiring cardiopulmonary resuscitation	3 (2)	3 (2)	10 (8)	7 (5)	0.079
Pulmonary edema requiring intubation	3 (2)	3 (2)	4 (3)	4 (3)	0.640
Mortality within 30 d after CABG, n (%)	3 (2)	5 (4)	10 (8)	8 (5)	0.081

CABG indicates coronary artery bypass grafting.

Effect of Age on the Impact of CABG

There was a trend toward a greater reduction in all-cause mortality with CABG compared with guideline-directed medical therapy in younger compared with older patients (hazard ratio [HR] in those ≤54 years of age, 0.66; 95% confidence interval [CI], 0.49–0.89; HR in those >67 years of age, 0.82; 95% CI, 0.63–1.06; $P_{interaction}$=0.062). The efficacy of CABG in reducing cardiovascular mortality was consistent across all age groups (HR in those ≤54 years of age, 0.61; 95% CI, 0.43–0.85; HR in those >67 years of age, 0.70; 95% CI, 0.50–0.97; $P_{interaction}$=0.307; Figure 2 and the online-only Data Supplement). CABG resulted in a greater reduction in all-cause death and cardiovascular hospitalizations compared with medical therapy alone, and

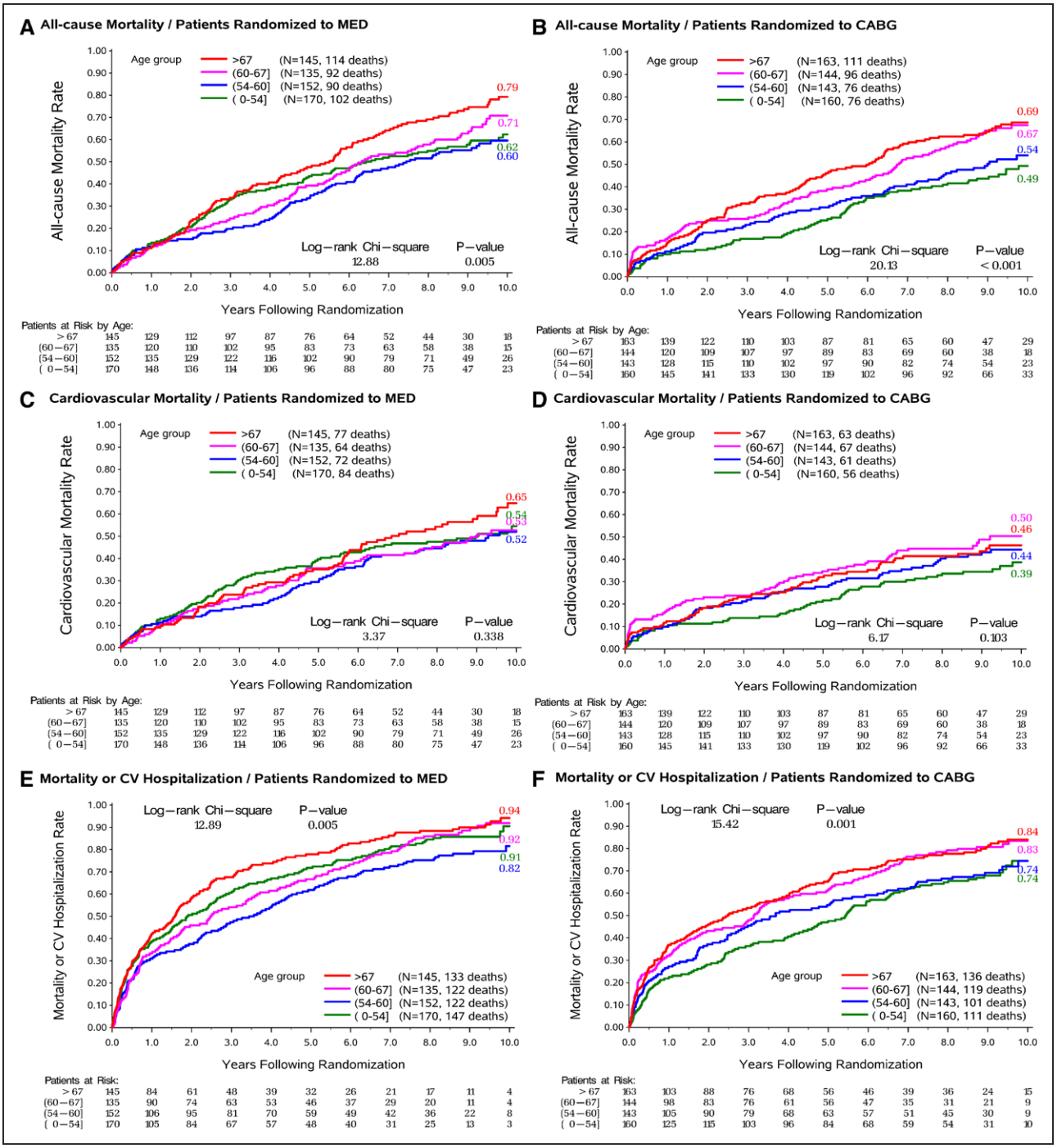

Figure 1. Kaplan-Meier rates of all-cause death, cardiovascular death, and all-cause death or cardiovascular (CV) hospitalization as a function of time from randomization by quartiles of age in patients randomized to coronary artery bypass grafting (CABG) and patients randomized to medical therapy (MED).

the effect was greater in the young (HR in those ≤54 years of age, 0.55; 95% CI, 0.43–0.71; HR in those >67 years of age, 0.73; 95% CI, 0.57–0.92; $P_{interaction}$=0.004). Noncardiovascular deaths were not statistically different in the group randomized to CABG and the group randomized to medical therapy and did not vary by age (Table 5).

The numbers of patients crossing from medical therapy to CABG and from CABG to medical therapy were low, and there was no difference in either by age (P_{trend}=0.25 and 0.62, respectively). The as-treated analysis demonstrated similar findings with perhaps an even greater impact of age on the effects of CABG versus medical therapy on 10-year outcomes (ie, greater ben-

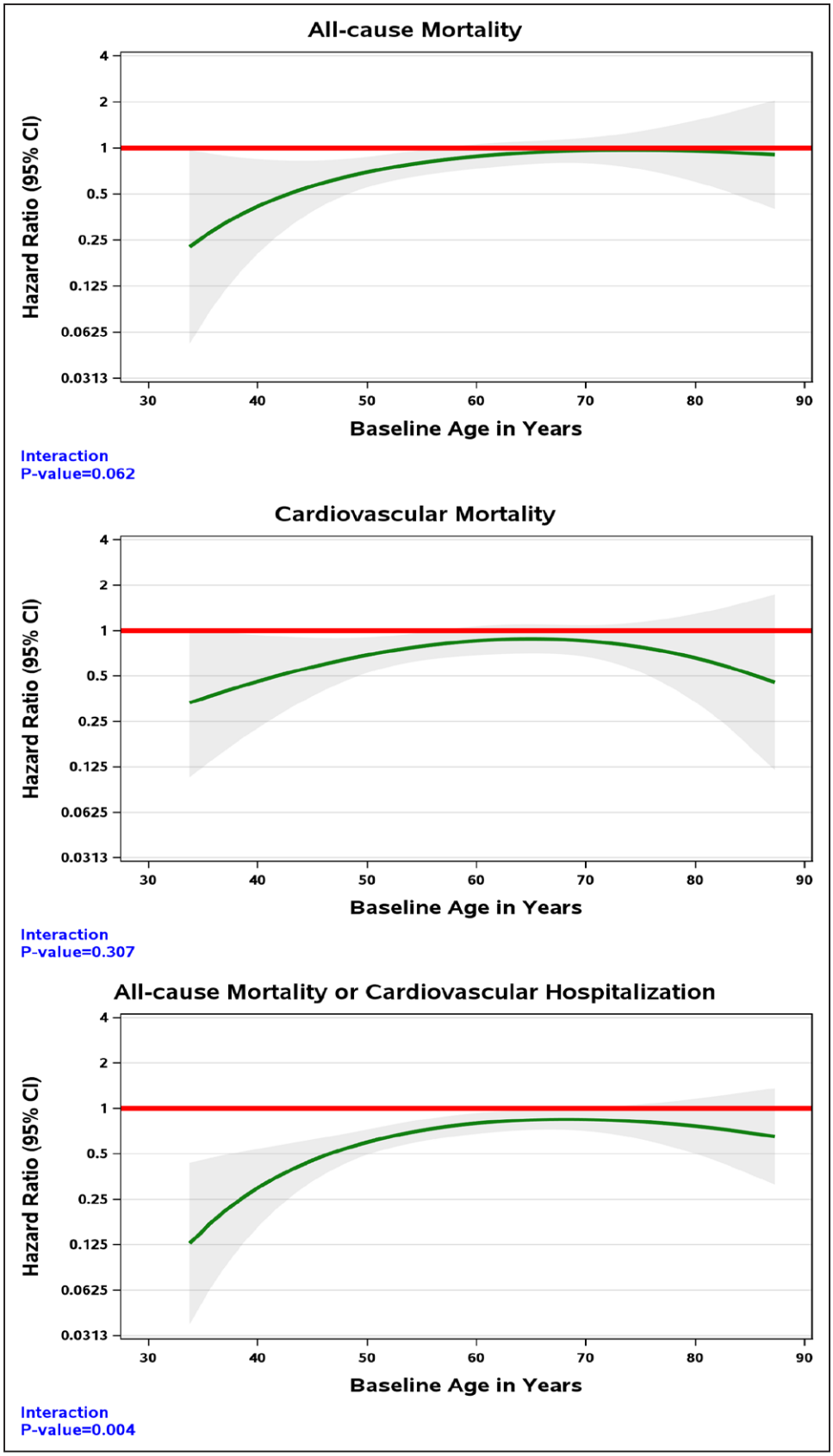

Figure 2. **Hazard ratio (solid line) and 95% confidence interval (CI; gray area) for the effect of coronary artery bypass grafting vs medical therapy across the range of ages.**

Table 5. All Deaths; Deaths Resulting From Cardiovascular, Noncardiovascular, and Unknown Causes; and All-Cause Mortality or Cardiovascular Hospitalizations by Quartiles of Age

Cause of Death	Randomized Treatment	Baseline Age Quartiles, n/N (%)				Total (n=1212)	*P* Value*
		Quartile 1 (Age ≤54 y) (n=330)	Quartile 2 (54<Age≤60 y) (n=295)	Quartile 3 (60<Age≤67 y) (n=279)	Quartile 4 (Age >67 y) (n=308)		
All-cause	CABG	76/160 (47.5)	76/143 (53.1)	96/144 (66.7)	111/163 (68.1)	359/610 (58.9)	0.004
	MED	102/170 (60.0)	90/152 (59.2)	92/135 (68.1)	114/145 (78.6)	398/602 (66.1)	
Cardiovascular	CABG	56/160 (35.0)	61/143 (42.7)	67/144 (46.5)	63/163 (38.7)	247/610 (40.5)	0.002
	MED	84/170 (49.4)	72/152 (47.4)	64/135 (47.4)	77/145 (53.1)	297/602 (49.3)	
Noncardiovascular	CABG	10/160 (6.3)	8/143 (5.6)	21/144 (14.6)	32/163 (19.6)	71/610 (11.6)	0.714
	MED	9/170 (5.3)	9/152 (5.9)	20/135 (14.8)	33/145 (22.8)	71/602 (11.8)	
Unknown	CABG	10/160 (6.3)	7/143 (4.9)	8/144 (5.6)	16/163 (9.8)	41/610 (6.7)	0.205
	MED	9/170 (5.3)	9/152 (5.9)	8/135 (5.9)	4/145 (2.8)	30/602 (5.0)	
All-cause death or cardiovascular hospitalization	CABG	111/160 (69.4)	101/143 (70.6)	119/144 (82.6)	136/163 (83.4)	467/610 (76.6)	<0.001
	MED	147/170 (86.5)	122/152 (80.3)	122/135 (90.4)	133/145 (91.7)	524/602 (87.0)	

CABG indicates coronary artery bypass grafting; and MED, medical therapy.
**P* values are from the Cochran-Mantel-Haenszel test, which does not account for time to event.

efit in younger patients and less benefit in older patients across all end points) compared with the intention-to-treat analysis (online-only Data Supplement).

DISCUSSION

This analysis of the long-term follow-up of the STICH trial demonstrates that the benefit of CABG compared with guideline-directed medical therapy on all-cause mortality and the combination of all-cause mortality and cardiovascular hospitalizations is greater in younger compared with older patients. In contrast, the benefit of CABG on cardiovascular mortality is similar across all age groups. The discrepancy between the effect of CABG across ages as it relates to cardiovascular mortality and all-cause mortality likely results from the greater proportion of noncardiovascular deaths in older patients, deaths that are less likely to be avoided by CABG.

An understanding of the efficacy of CABG in patients of different ages is needed to help inform clinical decision making.[11] In the STICH trial, older patients had higher all-cause mortality compared with younger patients, whether they were randomized to medical therapy or CABG. This result is consistent with recent HF trials[12] and previous surgical trials in patients without severe left ventricular dysfunction.[11] It is not surprising because in STICH older patients had more comorbidities and were more likely to die of noncardiovascular causes than younger patients.

In the present analyses, although cardiovascular mortality increased with age, it was not statistically significantly higher in the older compared with younger patients, suggesting that in patients such as those in STICH, with CAD, HF, and an ejection fraction ≤35%, the risk associated with their cardiovascular disease somewhat attenuates the risks associated with age and the comorbidities that go along with age. The efficacy of CABG over medical therapy on cardiovascular mortality persisted across all ages despite more comorbidities and slightly higher early postoperative mortality in older patients. A further explanation for the finding may be the excellent medical therapy received by STICH patients regardless of age. Medical therapies used in the treatment of HF are similarly effective across the spectrum of age.[12,13] Use of guideline-recommended medical therapies was lower in the older patients but not different between the randomized groups in any age group and is unlikely to have biased our findings. The use of implantable cardioverter-defibrillators (ICDs) was low at baseline (the population was recruited from 2002–2007 and the benefit of primary prevention ICDs was reported in 2004–2005). Greater use of ICDs might have reduced the risk of cardiovascular death in STICH. Because the rate of ICD use was similarly low across the age range and in both treatment groups, we do not believe underuse of ICDs biased our results. However, the rate of sudden death in our cohort may have been higher than in contemporary real-world cohorts; therefore, the potential benefit of CABG may be lower. Because STICH is the only contemporary CABG trial of patients with HF and significant left ventricular dysfunction, there are no trials with which to compare these findings.

Our finding that CABG had a consistent effect in all ages on the outcome that it is most likely to influence, cardiovascular death, is of clinical relevance. Cardiologists and surgeons can recommend surgical revascularization for patients with CAD amenable to CABG and HF knowing that a reduction in cardiovascular death is seen across the spectrum of ages of those included in the STICH trial. The lack of effect of CABG on all-cause mortality in older patients is a consequence of 2 findings. First, cardiovascular deaths accounted for a greater proportion of all deaths in the younger compared with older patients (79% of deaths in the youngest quartile but 62% of deaths in the older quartile). Second, it may be unreasonable to expect CABG to reduce noncardiovascular deaths. Of more concern in older patients was that CABG may in fact increase noncardiovascular deaths through a greater burden of comorbidities, which in turn lead to a greater risk of postoperative complications and noncardiovascular deaths. In this surgical trial, it was important to analyze all causes of death to ensure no harm. This is in contrast to trials of medical therapies in which cardiovascular death is often the primary mortality end point, because there is less concern about increasing noncardiovascular deaths. Although the numbers were small, we observed no difference in the numbers of noncardiovascular deaths in the 2 treatment arms in the oldest quartile. Thus, our finding that CABG did not reduce all-cause mortality in the older group was not entirely unexpected. It was reassuring that CABG in addition to guideline-directed medical therapy did not result in an iatrogenic increase in the risk of all cause death.

This study has a number of limitations. Because of the relatively small numbers of women, we were unable to examine potential interactions of sex with age and assigned strategy.[14] This was a post hoc, subgroup analysis and thus was not included in the power calculations for the original trial. Therefore, our findings should be considered exploratory rather than confirmatory. The patients and outcomes in the STICH trial may not be entirely representative of real-world populations because of the selection bias that occurs when any trial is conducted. The outcomes may also have been better because sites were selected on the basis of their surgical expertise (they had to demonstrate a 30-day mortality of ≤5% for patients with a profile similar to those meeting the STICH inclusion criteria). There were few patients in the truly older age groups (75 [6%] were >75 years of age and 15 [1%] were ≥80 years of age). In older patients, the true rate of complications and potential for long-term benefit may be different.

CONCLUSIONS

The consistent benefit of CABG on cardiovascular mortality regardless of age supports the recommendation of surgical revascularization to reduce cardiovascular death in patients with severe left ventricular dysfunction across all ages studied. Because cardiovascular deaths accounted for more deaths in the younger age group, they tend to gain a greater reduction in all-cause mortality. Careful assessment of competing mortality risk is important before pursuing revascularization in older patients.

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FOOTNOTES

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Ten-Year Outcomes After Coronary Artery Bypass Grafting According to Age in Patients With Heart Failure and Left Ventricular Systolic Dysfunction: An Analysis of the Extended Follow-Up of the STICH Trial (Surgical Treatment for Ischemic Heart Failure)

STICH Trial Investigators, Mark C. Petrie, Pardeep S. Jhund, Lilin She, Christopher Adlbrecht, Torsten Doenst, Julio A. Panza, James A. Hill, Kerry L. Lee, Jean L. Rouleau, David L. Prior, Imtiaz S. Ali, Jyostna Maddury, Krzysztof S. Golba, Harvey D. White, Peter E. Carson, Lukasz Chrzanowski, Alexander Romanov, Alan B. Miller and Eric J. Velazquez
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Dr. Carolyn Lam: Welcome to Circulation On The Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, Associate Editor from The National Heart Center and Duke National University of Singapore. Our interview today comes to you live from Rome at the European Society of Cardiology, where I talk to authors of The STICH Trial, about their ten year outcomes that help to answer the question, "Is there such a thing as being too old for coronary artery bypass surgery in heart failure?" But first, here's your summary of this week's journal:

The first paper provides experimental evidence that hypertension may be a bone marrow disease. In this paper, first author Dr. Wang, corresponding authors Dr. Li and [Sia 00:00:50] from The First Affiliated Hospital of Dalian Medical University in China, recognize that recruitment of leukocytes from the bone marrow to the vascular wall is a key step in the development of hypertension. Numerous factors stimulate this leukocyte migration during inflammation, including chemokines, which are low molecular weight proteins of the cytokine family which activate g-protein coupled receptors and induce migration of neutrophils, monocytes, and macrophages to the damaged vascular wall.

In this study the authors focus on chemokine receptor CXCR2. Using mouse models with hypertension they found that aortic MRNA levels of CXCR2 and its ligand CXCL1 are elevated in these mice with hypertension. They elegantly demonstrated that mice lacking CXCR2 are protected from blood pressure elevation, vascular inflammation of inflammatory cells, fibrosis, reactive oxygen species formation, NADPH activation and vascular dysfunction in response to either angiotensin 2 or [dolcasalt 00:02:01].

These results were recapitulated using a novel, allosteric inhibitor of CXCR2. Importantly, they also showed in 30 hypertensive patients compared to 20 normatensive controls that hypertensive patients have increased numbers of circulating CXCR2-positive cells and that there is a correlation between blood pressure and the number of CXCR2-positive cells in the circulation.

In summary, these findings that CXCR2 inhibition prevents and reverses hypertension and vascular dysfunction in response to multiple hypertensive stimuli really help us to understand the mechanisms involved in CXCR2 action, but also point to a potential clinical use of CXCR2 inhibition for the treatment of hypertension. This is discussed in a beautiful accompanying editorial by Drs. [Montenel 00:02:56] and Harrison.

The next study suggests that the eyes provide a window to long-term cardiovascular risk. In this paper from first author Dr. [Seidelman 00:03:12], corresponding author Dr. [Solomon 00:03:13] and colleagues from the Brigham and Women's Hospital, authors investigated whether retinal vessel calibers are associated with cardiovascular outcomes in long-term follow-up, and whether they provide incremental value over the 2013 ACCAHA pooled cohort equations in predicting atherosclerotic cardiovascular disease events. They studied 10, 470 men

and women from the [Eric 00:03:41] or Atherosclerosis Risk in Community Study who underwent retinal photography at their third visit, which occurred in 1993-1995.

During a mean follow-up of sixteen years, narrower retinal arterials, but wider retinal venules were associated with long-term risk of mortality and ischemic stroke in both men and women. Coronary heart disease in women was also related to narrower retinal arterials and wider retinal venules independent of the the pooled cohort equation variables. In fact, retinal vessel caliber reclassified 21% of low-risk women as intermediate-risk for atherosclerotic cardiovascular disease events.

In discussing the clinical implications of these findings, the authors noticed that identification of coronary heart disease is frequently delayed in women and this under-recognition may party be due to the fact that non-obstructive coronary artery disease is more prevalent in women and micro-vascular dysfunction may largely contribute to myocardial ischemia in women. Since the retinal vessels offer an insight into micro-vasculature, adding retinal imaging may be of incremental value to current practice guidelines in risk prediction in low-risk women. This, of course, deserves further study.

The next study challenges the traditional focus on macro-vascular disease in Type 2 diabetes, namely myocardial infarction, strokes, and peripheral artery disease, and causes us to focus on micro-vascular disease instead. In this paper from first author Dr. [Sorrenson 00:05:33], corresponding author Dr. [Stiehauer 00:05:36], and colleagues from the Maastricht University Medical Center in the Netherlands, authors hypothesized that micro-vascular dysfunction occurs in pre-diabetics, which may explain the increased risk of complications of micro-vascular origin in pre-diabetes and early Type 2 diabetes.

They studied 2,213 individuals in the Maastricht study, which is population-based cohort study enriched with Type 2 diabetes, and they determined micro-vascular function, measured as flicker-light-induced retinal arterial[inaudible 00:06:12] percentage dilatation, as well as heat-induced skin percentage hyperemia. They found impaired retinal and skin micro-vascular function in pre-diabetics with further deterioration in patients with Type 2 diabetes. Inverse linear associations were found between micro-vascular function and measures of glycemia such as HBA1C, fasting and two-hour post-op glucose levels. All associations were independent of cardiovascular risk factors.

The clinical implications are that micro-vascular dysfunction in pre-diabetes may at least partially explain the increased risk of complications that are known to be of micro-vascular origin such as retinopathy and albuminuria but also diseases such as heart failure and cognitive decline. The take-home message is that both early hyperglycemia and micro-vascular dysfunction may be considered potential targets for early preventive intervention.

Well, those were your summaries! Now, let's on to Rome.

Hello, I'm Dr. Carolyn Lam, associate editor of Circulation, and I am so delighted to be reporting from Rome this time at the European Society of Cardiology. We are discussing the 10-year followup paper on STICH that includes an age analysis that is being featured as a hotline session of clinical trials update. I'm here with the distinguished guest, the first author, Dr. Mark Petchey, from University of Glasgow, the corresponding author Dr. Eric [Moleskus 00:07:51] from Duke University, and the associate editor who managed this paper, Dr. Nancy [Scheitzer 00:07:56] from University of Arizona. Welcome! [crosstalk 00:07:59]

Right, let's get straight into this. Eric, remind us what it first showed and why there's a need to look at the effective age.

Dr. Eric M. : Thank you Carolyn. Thanks to Circulation and to both of you for really helping us work through this paper. We are very excited that we're being able to feature this work in Circulation. So, a STICH trial is a reminder. Surgical treatment of ischemic heart failure trial has been a 15-year effort actually that started with the first patient enrolled in 2002, enrollment ending in 2007 and at the ACC with the simultaneous fabrication in the journal, we published the 10-year results of the STICH trial, combining medical therapy vs. cabbage plus medical therapy in patients with ischemic cardiomyopathy defined as an EF less than 35%. Coronary disease [inaudible 00:08:51] to cabbage was over 90% having class 2 or greater heart failure systems.

What we showed in our 10-year results was that cabbage, when added to guideline-directed medical therapy, led to a substantial reduction in all-cause mortality, cardiovascular mortality as well as all-cause plus cardiovascular hospitalization in those patients who were randomized to the cabbage arm. This translated to about an 18 months extension in survival for the cabbage patients over that time period, a 16% relative risk reduction in mortality and nearly a 10% after the risk reduction is all-cause mortality, with the number needed to be treated of approximately 14.

With those findings, the next question that we want to address rapidly was whether there was an impact by age. This is what we're here to talk about, mostly because everyone recognizes that age is, although something we can't control ... As we age, our risk for everything increases, and clearly heart failure, which is the field that we work in clinically, patients who are older in heart failure have more risks, and worse clinical outcomes in patients who are younger. Whether there would be a benefit that would persist in terms of the treatment in younger as well as older patients was really the subject of this analysis.

Dr. Carolyn Lam: That's great. So maybe, Mark, you could tell us the highlights of the results. Give us an idea, first of all, of the age range that we're talking about, what you looked at. And then- this is definitely going to be an issue if we're talking about age- the relative risks vs. the absolute risk of the different types of outcomes.

Dr. Mark P: Sure. So, the patients in the STICH trial were similar age to a normal heart failure trial. The median age was around 61. What we did to look at the patients we had in the trial, we looked at quartiles, first of all. So the lowest quartile was aged less than 54, and the highest quartile aged more than 67. So we had a fair spread of age. We didn't have many patients, we were very elderly or very old. So 65% were above age 75 and 1% above the age of 80. When we looked at the patients we saw a similar [inaudible 00:11:18] to a usual heart failure trial. The older patients had more co-morbidities, not surprisingly, and they had more... they basically died more often as they got older as we see in every other trial.

When we started looking at the results, the treatment effects of cabbage, obviously we were very eager to know if the benefits, which Eric's talked about already were seen across all age groups. I think clinicians, when they look at patients for bypass surgery have anxieties around sending older people for bypass surgery. We were thrilled is probably the word to say that we say benefits across all age ranges. So the point has been for us in terms of all-cause mortality were all [less than one 00:11:58]. We saw consistent benefit, or certain across-the-board benefit in terms of all-cause mortality.

What we did see that we were very interested about were the younger patients got more benefit in terms of all-cause mortality, [inaudible 00:12:12] quite strikingly more. The risk reduction was over 40% for the ... We saw upper age groups having benefits with [hazard issues 00:12:24], risk reductions of, roundabout, the [teens 00:12:28], as in the major overall trial results, the younger patients got particular benefit.

We then looked at cardiovascular mortality and we saw a slightly different pattern. We saw the benefit was actually quite similar across all age groups. The older patients were getting the similar reduction in cardiovascular mortality as the younger patients. So there's the main take-home findings.

Dr. Carolyn Lam: OK, so by extrapolation then, the younger patients, a greater proportion of their deaths were probably cardiovascular, or there's a bit more of a competing risk, so to speak from non-cardiovascular deaths in the elderly, is that kind of the idea?

Dr. Mark P: Carolyn, that's exactly right. Because the cardiovascular mortality was similar across all age groups, because all people, as we know, die more commonly of non-cardiovascular events, we saw that clearly in the trial the benefits in terms of all-cause mortality weren't quite as much. Just to emphasize, the cardiovascular reduction was consistent across all age groups.

Dr. Carolyn Lam: With bypass compared to medical, yes.

Dr. Mark P: Exactly.

Dr. Eric M. : I think an important aspect to remember and I think STICH reminds us is that even in the oldest population- and although we did these analyses continuously, we

described this in quartiles for the purpose of the paper- we have to remember in heart failure patients like these who have coronary disease, cardiovascular death is the most common cause of death, regardless if you're young or old. What happens is that as we get older, there is an increasing rate of non-cardiovascular deaths. It's not surprising to us, that of the findings we found, which is that as the risk of non-cardiovascular deaths increase in the ages, the impact on all-cause mortality is mitigated slightly, while the effect on cardiovascular mortality remains consistent because it's still by far the most common cause, I think more than double the cause even in the oldest group.

Dr. Carolyn Lam: That's a great point. Now I've got to ask something though. What did you do about crossovers? Because this is a 10-year thing. The original results of STICH came out 5 years. You'd expect that there's quite a bit of crossover or no?

Dr. Eric M. : I'll just comment on the effect of crossovers in STICH in general, and then we can focus on the age analyses. What's really interesting is that in STICH approximately over time, over the time period, there was approximately an 18% rate of crossovers. That actually led to, by the intention to treat analysis, a decrease in the effect [inaudible 00:15:15] intention to treat. But when you look at crossovers, the medical therapy patients who were randomized to medical therapy but received cabbage at some point, and the patients who were randomized to cabbage but never did receive cabbage. But actually when you look at as-treated analyses, by the treatment they received, not [inaudible 00:15:36] they were randomized, the effect of cabbage actually increases. The relative risk reduction is about 25% in that group. Thankfully, the effect of crossover into different age quartiles were [inaudible 00:15:51] different. We had the same, relatively the same effect, so there were no, we were [eventually knowing 00:15:57] to make sure that there was no increase in crossover rates in the older vs. the younger and we did not find that. I started the discussion, maybe you can complete it.

Dr. Mark P: Thank you for hitting the nail on the head, Eric, that there weren't many crossovers, but if there were crossovers, if the crossover towards the cabbage, the benefits seemed the be greater and that was seen across all age groups. There was no differential between the older patients and the younger patients.

Dr. Carolyn Lam: You know then, I just want to know what's your take-home message and then I'd really like to hear from Nancy the take-home message we wanted to convey in our journal.

Dr. Mark P: I think for me the take-home message goes back to the fundamental approach to assessing a heart failure patient in a clinic. Over the years there's been a tendency for patients not to investigate and look for coronary heart disease. People tend to focus on medical therapy and device therapy but the coronary arteries have been the poorer cousin. I think we would urge people to think about revascularization by surgery, coronary artery bypass drafting's a treatment for for heart failure, so certainly, my practice, we look for coronary artery disease more than we think about the patient and weigh out the pros and cons and certainly this analysis was

done to give us [granularity 00:17:14] from the perspective of the older person and the young person and the relative benefits. Basically, it's steered me towards looking for coronary artery disease. Also you can inform the patient in the clinic and have discussions with the surgeons about the benefit in terms of the all-cause mortality across the age group, and the cardiovascular mortality as well.

Dr. Carolyn Lam: Yeah, it's consistent. That's brilliant. Nancy, speak on behalf of our journal.

Dr. Nancy S.: So at Circulation, we were very excited to get this paper because as heart failure clinicians, we all struggle with this issue in older patients in particular. When we look and find coronary disease, these tend to be patients with higher surgical risks. Our surgical colleagues are often hesitant to operate. The benefits are perhaps less apparent, and this data's very helpful to show us that in a patient in whom the heart disease is the primary morbidity, surgical revascularization has a clear benefit for these patients.

I do think that it's important to remember though, that STICH population is a selected population, and probably a little healthier than the average patient we see in clinic. As Mark rightly pointed out, the discussions with surgical colleagues I think can now occur with a greater level of data substantiation and understanding of the true benefits, and then competing risks and morbidities in this patients need to be considered with the reality that surgical revascularization benefits the patients. We're really excited to have worked with you, this fantastic group of authors to get this paper to a point where I think it's really going to have a clinical impact, and that's what we're trying to do. As you know, Carolyn, editorial board at Circ now has published really high-quality science that's going to impact the practice of clinicians seeing patients on a daily basis.

Dr. Carolyn Lam: Thanks so much for that Nancy, and actually I was going to congratulate you gentlemen. In your paper you so humbly said that these are exploratory, I think, and I was actually thinking that we're never going to have a better trial than this and it's something I am personally taking to be clinically applicable in my heart failure patients so congratulations. I'm going to switch tracks a little bit... we're actually going to a simultaneous publication in Circulation from the European Society of Cardiology and I think that's really neat for our journal, Circulation. I want to ask each of you as author perspective and as associate editor who made this happen, what do you think of these simultaneous publications? Were there challenges, what was it like, and what was your experience like?

Dr. Mark P: So I have to confess that usually when we submit papers for review, there is a mixture of trepidation, fear, generally quite negative thoughts. We submitted it, and I've got to say that it was the most interactive, positive experience I've had so far. It was quite clear that was interested in the data, and wanted to publish it in a way that informed the clinical community. They certainly worked with us to make sure the message was honed and as accurate as possible to reflect the results. We were really thrilled. It was a "breakneck pace" is also probably the best way to describe it. We worked day and night actually, but there was phone calls and emails

happening in very rapid sequence and lots of responsiveness. I could almost describe it as "fun".

Dr. Carolyn Lam: Kudos to you, Nancy! And from your point of view, was it fun?

Dr. Nancy S.: It actually was fun.

Dr. Carolyn Lam: (laughs)

Dr. Nancy S.: You know, we've all had the experience of- on both sides- being an editor and being an author. Getting a paper, getting reviews, sending it back, getting the revision, it's not quite what you want, reviewing it again, sending it back, getting it back, it's not quite what you want, and then you feel obligated to publish a paper that's not really what you want. What we've decided to do is a much more interactive process to say "We're going to work with you to make this the paper we want to publish. We hope that as authors that's the paper you want to have written." We're doing this on a regular basis at Circulation but this was at hyperspeed, I would say.

Dr. Carolyn Lam: [inaudible 00:21:34] how long?

Dr. Nancy S.: We knew the paper was going to come in. We had been in contact with Eric. I identified reviewers before we even received the manuscript. I identified reviewers who would commit to a 72-hour turnaround. In fact, our reviewers did it in less than 24 hours. Then I looked at it, added to it, called Eric, and we talked it over. And then we sent it back with the formal replies. I think Mark then worked 24/7 to get it back to us very quickly. I worked with one of the senior associate editors; at that point we didn't involve the reviewers. We basically track-changed the paper to make the changes we really thought were necessary at the point. It wasn't a lot but I think they were critically changes. At that point, Mark and Eric were kind enough to accept those changes and the paper was on track for simultaneous publication. I do want to mention that we have simultaneous publication of five different presentations here at ESC in Circulation online which is certainly a record for Circulation and we're really proud of that.

Dr. Eric M. : First of all, I want to think the journal. Really a remarkable, wonderful experience. I've been very fortunate in my career to be in a position to submit simultaneous publications previously, and this was a wonderful- I think it was a 14-day turnaround, it was remarkable. And the responses from the reviewers were outstanding even if they were reviewed in a very short time, and I think the paper definitely improved.

A general comment about simultaneous publications as you bring it up, I think it's an area of controversy. I think my perspective as a person who does clinical trials, as well as sees a lot of patients, there's an ethical mandate that exists to... Once you have information that you're putting out there, to be in a position, if we think it's clinically impactful, and we feel that the data is mature, to get that into people's hands, all of it, as soon as possible. There's a certainly a difference between what I

can speak to in 8-10 minutes on stage with slides that will get distributed anyway across the world, and what, with Nancy's help, we are able to put into journal-wide circulation and really explain the story and give it a full [vetting 00:24:05]. I feel like, from the ethical perspective, being able to push forward with this simultaneous publication is in the best interest of our patients, and it's so exciting to see Circulation now doing this with the European Society, which is a remarkable achievement for this new editorial board, so thank you again.

Dr. Carolyn Lam: You've been listening to Circulation on the Run. Tune in next week for more.

SUPPLEMENTAL MATERIAL

Table S1: Number and percentage of patients by age category

Distribution of age	
Age<=65	820 (68%)
65<Age<=70	191(16%)
70<Age<=75	126 (10%)
75<Age<=80	60 (5%)
Age>80	15 (1%)

Table S2 Baseline Characteristics by Age

Variable	Baseline Age Quartiles				P-value for trend[1]
	Q1 (Age≤54 years) (n=330)	Q2 (54<Age≤60 years) (n=295)	Q3 (60<Age≤67 years) (n=279)	Q4 (Age>67 years) (n=308)	
Age (year)	50(47, 53)	57(56, 58)	64(62, 65)	72 (69, 75)	
Female	35 (11%)	26 (9%)	37 (13%)	50 (16%)	0.011
White race	187 (57%)	189 (64%)	200 (72%)	251 (82%)	<0.001
BMI (kg/m^2)	27 (24, 31)	27 (24, 30)	27 (24, 30)	26 (24, 29)	0.178
Medical History:					
Diabetes	103 (31%)	121 (41%)	124 (44%)	130 (42%)	0.003
Hypertension	178 (54%)	177 (60%)	159 (57%)	214 (70%)	<0.001
PVD	36 (11%)	40 (14%)	42 (15%)	66 (21%)	<0.001
Renal insufficiency	10 (3%)	16 (5%)	25 (9%)	43 (14%)	<0.001
Stroke	23 (7%)	14 (5%)	21 (8%)	34 (11%)	0.028
Atrial flutter/ fibrillation	19 (6%)	25 (9%)	42 (15%)	67 (22%)	<0.001
Previous MI	250 (76%)	229 (78%)	208 (75%)	247 (80%)	0.320
Hyperlipidemia	190 (58%)	174 (59%)	181 (65%)	185 (60%)	0.286
Depression	24 (7%)	17 (6%)	15 (5%)	20 (7%)	0.646
Current smoker	104 (32%)	64 (22%)	50 (18%)	34 (11%)	<0.001
Previous PCI	45 (14%)	38 (13%)	38 (14%)	35 (11%)	0.465
Previous CABG	8 (2%)	10 (3%)	11 (4%)	7 (2%)	0.974
CCS angina class:					
No angina	106 (32%)	97 (33%)	91 (33%)	148 (48%)	<0.001
I	42 (13%)	44 (15%)	52 (19%)	49 (16%)	0.145
II	169 (51%)	141 (48%)	119 (43%)	96 (31%)	<0.001
III	10 (3%)	12 (4%)	15 (5%)	11 (4%)	0.551
IV	3 (1%)	1 (<1%)	2 (1%)	4 (1%)	0.583
NYHA class:					
I	35 (11%)	50 (17%)	22 (8%)	32 (10%)	0.276
II	185 (56%)	134 (45%)	157 (56%)	150 (49%)	0.318
III	100 (30%)	106 (36%)	93 (33%)	113 (37%)	0.152
IV	10 (3%)	5 (2%)	7 (3%)	13 (4%)	0.315
Median systolic BP (mmHg)	120 (110, 130)	120 (110, 130)	120 (110, 130)	122 (110, 136)	<0.001
Median heart rate (bpm)	76 (68, 84)	75 (68, 82)	74 (66, 82)	71 (63, 80)	<0.001
Median 6 minute walk distance (meter)	352 (259, 434)	360 (273, 415)	340 (270, 400)	321 (250, 385)	<0.001
Lab measures:					
Hemoglobin (g/dL)	14.3 (13.2, 15.4)	13.9 (12.7, 14.9)	13.7 (12.6, 14.8)	13.6 (12.3, 14.6)	<0.001
Creatinine (mg/dL)	1.02 (0.90, 1.18)	1.10 (0.97, 1.23)	1.10 (0.94, 1.30)	1.17 (1.00, 1.40)	<0.001
Sodium (mEq/L)	139 (137,	140 (137, 142)	140 (138, 142)	140 (137,	0.086

	142)			142)	
BUN (mg/dL)	22 (15, 37)	21 (16, 34)	21 (16, 36)	24 (18, 39)	0.016

1. P-values for categorical variables are based on Cochran-Armitage Trend test. Spearman correlation test is performed to get the p-values for continuous variables and the continuous age variable.

Table S3 Baseline Left Ventricular Structure and Function and Coronary Anatomy by Age

Variable	Baseline Age Quartiles				P-value for Trend[1]
	Q1 (Age≤54 years) (n=330)	Q2 (54<Age≤60 years) (n=295)	Q3 (60<Age≤67 years) (n=279)	Q4 (Age>67 years) (n=308)	
Structure and function:					
LVEF (%)	28 (22, 33)	28 (23, 35)	26 (21, 33)	28 (22, 34)	0.518
ESVI	81 (62, 103)	81 (61, 98)	77 (60, 105)	77 (61, 98)	0.190
EDVI	117 (92, 144)	113 (90, 139)	109 (87, 141)	108 (87, 135)	0.020
E velocity (m/s)	0.70 (0.30, 0.90)	0.70 (0.50, 0.90)	0.70 (0.50, 0.90)	0.60 (0.50, 0.85)	<0.001
A velocity (m/s)	0.60 (0.40, 0.80)	0.70 (0.50, 0.80)	0.73 (0.60, 0.90)	0.70 (0.60, 0.90)	<0.001
E/A ratio	1.00 (0.75, 2.25)	1.00 (0.71, 1.78)	0.80 (0.63, 1.57)	0.75 (0.57, 1.33)	<0.001
E/e' ratio (septal)	14 (11, 20)	17 (12, 23)	15 (12, 24)	17 (11, 23)	0.129
E/e' ratio (lateral)	11 (8, 15)	12 (9, 16)	13 (9, 17)	12 (8, 17)	0.222
Anterior akinesia or dyskinesia (%)	43 (30, 57)	43 (20, 50)	43 (29, 57)	40 (14, 57)	0.146
MR severity:					
None or trace	123 (37%)	110 (37%)	106 (38%)	96 (31%)	0.145
Mild	149 (45%)	130 (44%)	128 (46%)	147 (48%)	0.456
Moderate	43 (13%)	47 (16%)	38 (14%)	53 (17%)	0.240
Severe	14 (4%)	8 (3%)	7 (3%)	10 (3%)	0.460
Coronary anatomy:					
No of vessels with stenosis ≥ 50%					
1	46 (14%)	24 (8%)	24 (9%)	18 (6%)	<0.001
2	101 (31%)	94 (32%)	87 (31%)	84 (27%)	0.362
3	183 (56%)	177 (60%)	168 (60%)	205 (67%)	0.006
Stenosis of proximal LAD ≥75%	242 (73%)	200 (68%)	185 (66%)	199 (65%)	0.020
Duke CAD severity index	52 (39, 65)	65 (39, 77)	65 (39, 77)	65 (39, 77)	0.039

1. P-values for categorical variables are based on Cochran-Armitage Trend test. Spearman correlation test is performed to get the p-values for continuous variables and the continuous age variable.

LVEF – left ventricular ejection fraction, ESVI – end systolic volume indexed, EDVI - end diastolic volume indexed, E - early diastolic filling velocity, A – atrial contraction induced diastolic filling velocity wave, e′ - early diastolic myocardial velocity, MR – mitral regurgitation, LAD – left anterior descending , CAD – coronary artery disease

Table S4 Procedural Details and Perioperative Complications by Age

Variable	Baseline Age Quartiles				P-value for Trend[1]
	Q1 (Age≤54 years) (n=149)	Q2 (54<Age≤60 years) (n=127)	Q3 (60<Age≤67 years) (n=131)	Q4 (Age>67 years) (n=148)	
Number of conduits:					
1	26 (17%)	10 (8%)	15 (12%)	18 (12%)	0.284
2	49 (33%)	37 (29%)	42 (32%)	47 (32%)	0.958
3	60 (40%)	60 (47%)	52 (40%)	64 (43%)	0.894
≥4	14 (9%)	20 (16%)	22 (17%)	19 (13%)	0.362
Number of arterial conduits:					
0	11 (7%)	9 (7%)	12 (9%)	18 (12%)	0.123
1	123 (83%)	104 (82%)	104 (79%)	115 (78%)	0.249
≥2	15 (10%)	14 (11%)	15 (12%)	15 (10%)	0.957
Number of distal anastomoses:					
0	2 (1%)	2 (2%)	2 (2%)	1 (1%)	0.631
1	23 (15%)	10 (8%)	14 (11%)	16 (11%)	0.319
2	41 (28%)	27 (21%)	30 (23%)	30 (20%)	0.185
3	57 (38%)	55 (43%)	50 (39%)	59 (40%)	0.982
4	22 (15%)	23 (18%)	22 (17%)	31 (21%)	0.211
≥5	4 (3%)	10 (8%)	12 (9%)	11 (7%)	0.090
Off-pump bypass	40 (27%)	24 (19%)	25 (19%)	27 (18%)	0.083
Total minutes on bypass	83 (63, 110)	92 (72, 125)	93 (66, 110)	89 (70, 126)	0.262
Cross—clamp time in minutes	50 (33, 67)	55 (41, 79)	54 (35, 72)	56 (39, 80)	0.097
Intensive Care Unit length of stay in hours	52 (43, 87)	61 (42, 94)	49 (27, 97)	65 (40, 112)	0.124
Perioperative complications					
Return to operating room	7 (5%)	9 (7%)	7 (5%)	12 (8%)	0.326
Mediastinitis	3 (2%)	4 (3%)	2 (2%)	2 (1%)	0.516
Other infection	9 (6%)	10 (8%)	8 (6%)	19 (13%)	0.061
New onset Atrial Fibrillation	10 (7%)	20 (16%)	22 (17%)	38 (26%)	<0.001
Worsening renal impairment	2 (1%)	4 (3%)	12 (9%)	16 (11%)	<0.001
Intra-aortic balloon pump	25 (17%)	22 (17%)	24 (18%)	18 (12%)	0.335
Inotropes for low cardiac output	45 (30%)	44 (35%)	56 (43%)	71 (48%)	<0.001
Cardiac arrest requiring cardiopulmonary resuscitation	3 (2%)	3 (2%)	10 (8%)	7 (5%)	0.079
Pulmonary edema requiring intubation	3 (2%)	3 (2%)	4 (3%)	4 (3%)	0.640
Mortality within 30 days after CABG	3 (2%)	5 (4%)	10 (8%)	8 (5%)	0.081

1. P-values for categorical variables are based on Cochran-Armitage Trend test. Spearman correlation test is performed to get the p-values for continuous variables and the continuous age variable.

Table S5: Medical therapy at randomization and at 10 years in each quartile of age by randomized therapy

		Q1 (Age≤54 years) N(%)				**Q2 (54<Age≤60 years) N(%)**				**Q3 (60<Age≤67 years) N(%)**				**Q4 (Age>67 years) N(%)**			
		Overall	MED	CABG	**P**	Overall	MED	CABG	**P**	Overall	MED	CABG	**P**	Overall	MED	CABG	**P**
Betablocker	Randomization	282 (85)	148 (87)	134 (84)	**0.39**	247 (84)	135 (89)	112 (78)	**0.01**	250 (90)	124 (92)	126 (88)	**0.23**	257 (83)	122 (84)	135 (83)	**0.76**
	At 10 year follow up	280 (91)	143 (91)	137 (91)	**0.80**	246 (89)	130 (92)	116 (87)	**0.24**	228 (91)	117 (91)	111 (91)	**0.94**	223 (79)	110 (80)	113 (78)	**0.63**
ACE inhibitor or ARB	Randomization	288 (87)	149 (88)	139 (87)	**0.83**	263 (89)	132 (87)	131 (92)	**0.19**	252 (90)	121 (90)	131 (91)	**0.70**	282 (92)	129 (89)	153 (94)	**0.12**
	At 10 year follow up	269 (87)	142 (90)	127 (85)	**0.17**	233 (85)	119 (84)	114 (86)	**0.66**	226 (90)	118 (91)	108 (89)	**0.44**	211 (75)	104 (76)	107 (74)	**0.68**
Statin	Randomization	271 (82)	147 (86)	124 (78)	**0.03**	242 (82)	126 (83)	116 (81)	**0.69**	230 (82)	118 (87)	112 (78)	**0.03**	240 (78)	109 (75)	131 (80)	**0.27**
	At 10 year follow up	264 (86)	135 (85)	129 (86)	**0.89**	230 (84)	118 (83)	112 (84)	**0.80**	225 (90)	115 (89)	110 (90)	**0.79**	230 (82)	110 (80)	120 (83)	**0.59**
Aspirin	Randomization	273 (83)	145 (85)	128 (80)	**0.20**	250 (85)	129 (85)	121 (85)	**0.95**	232 (83)	116 (86)	116 (81)	**0.23**	247 (80)	123 (85)	124 (76)	**0.05**
	At 10 year follow up	272 (88)	141 (89)	131 (87)	**0.60**	237 (86)	118 (83)	119 (89)	**0.13**	203 (81)	110 (85)	93 (76)	**0.07**	203 (72)	97 (71)	106 (73)	**0.67**
Warfarin	Randomization	25 (8)	17 (10)	8 (5)	**0.09**	23 (8)	17 (11)	6 (4)	**0.03**	35 (13)	20 (15)	15 (10)	**0.27**	44 (14)	22 (15)	22 (13)	**0.67**
	At 10 year follow up	39 (13)	18 (11)	21 (14)	**0.49**	47 (17)	26 (18)	21 (16)	**0.58**	45 (18)	24 (19)	21 (17)	**0.77**	74 (26)	36 (26)	38 (26)	**0.99**
Potassium sparing diuretic	Randomization	161 (49)	84 (49)	77 (48)	**0.82**	137 (46)	70 (46)	67 (47)	**0.89**	136 (49)	67 (50)	69 (48)	**0.77**	122 (40)	55 (38)	67 (41)	**0.57**
	At 10 year follow up	173 (56)	86 (54)	87 (58)	**0.53**	147 (53)	75 (53)	72 (54)	**0.83**	150 (60)	80 (62)	70 (57)	**0.45**	127 (45)	59 (43)	68 (47)	**0.52**

Table S6: Cross overs from each treatment arm by quartile of age

Randomized Treatment	Baseline Age Quartiles				Total (n=1212)	P Value
	Q1 (Age≤54 years) (n=330)	Q2 (54<Age≤60 years) (n=295)	Q3 (60<Age≤67 years) (n=279)	Q4 (Age>67 years) (n=308)		
MED patients who crossed over to CABG	24/170 (14.1)	13/152 (8.6)	16/135 (11.9)	13/145 (9.0)	66/602 (11.0)	0.25
CABG patients who crossed over to MED	11/160 (6.9)	16/143 (11.2)	13/144 (9.0)	15/163 (9.2)	55/610 (9.0)	0.62

Table S7: Hazard ratios and 95% confidence intervals for CABG plus optimal medical therapy versus optimal medical therapy alone by quartile of age

	Q1 (Age≤54 years) (n=330)	**Q2 (54<Age≤60 years) (n=295)**	**Q3 (60<Age≤67 years) (n=279)**	**Q4 (Age>67 years) (n=308)**
All-cause death	0.66 (0.49, 0.89)	0.87 (0.64, 1.18)	1.00 (0.75, 1.33)	0.82 (0.63, 1.06)
Cardiovascular death	0.61 (0.43, 0.85)	0.88 (0.63, 1.24)	1.02 (0.73, 1.44)	0.70 (0.50, 0.97)
Death or cardiovascular hospitalization	0.55 (0.43, 0.71)	0.81 (0.62, 1.05)	0.85 (0.66, 1.09)	0.73 (0.57, 0.92)

Figure S1 Hazard ratio (solid line) and 95% confidence interval (grey area) for the effect of CABG vs medical therapy across the range of age- as treated analysis accounting for cross overs