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

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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

	Baseline Age Quartiles				
Variable	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)	*P* Value for Trend
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

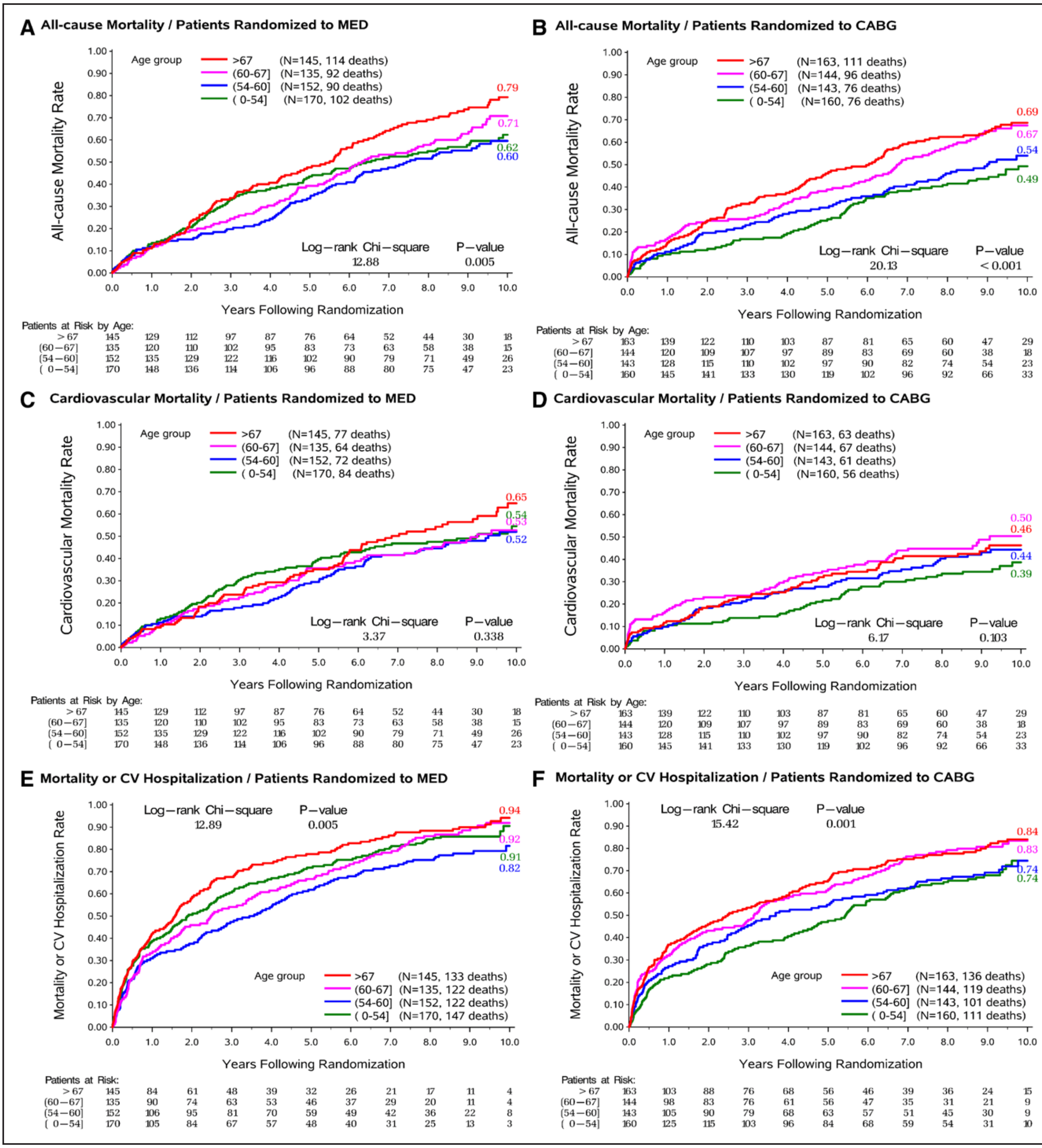

Figure 1. Kaplan-Meier rates of all-cause death, cardiovascular death, and all-cause death or cardiovascular (CV) hospitalization as a function of time from randomization by quartiles of age in patients randomized to coronary artery bypass grafting (CABG) and patients randomized to medical therapy (MED).

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-

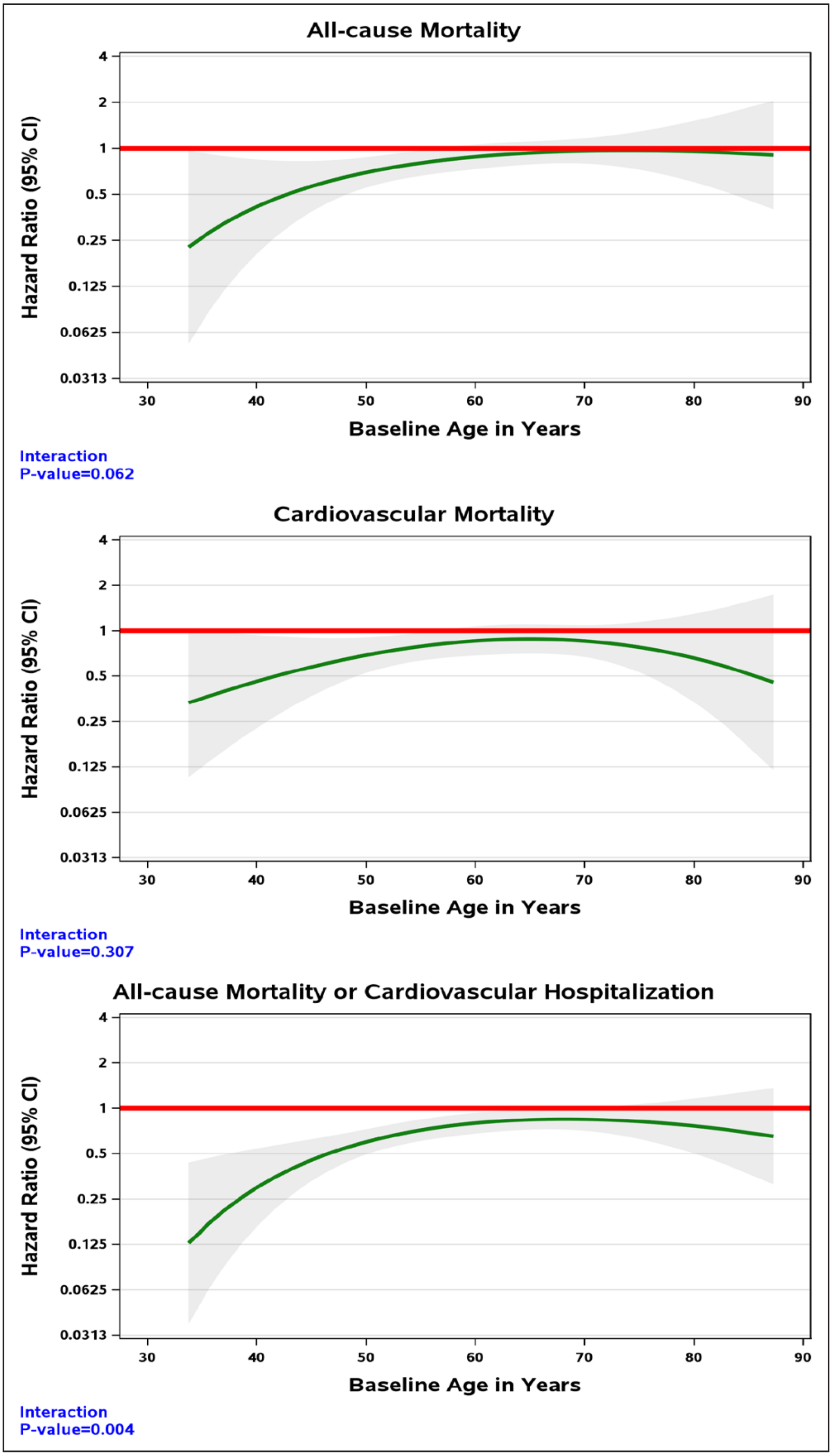

Figure 2. Hazard ratio (solid line) and 95% confidence interval (CI; gray area) for the effect of coronary artery bypass grafting vs medical therapy across the range of ages.

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.

ORIGINAL RESEARCH ARTICLE

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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