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Exercise Capacity and Mortality in Patients With Ischemic Left Ventricular Dysfunction Randomized to Coronary Artery Bypass Graft Surgery or Medical Therapy

An Analysis From the STICH Trial (Surgical Treatment for Ischemic Heart Failure)

Ralph A.H. Stewart, MBChB, MD,* Dominika Szalewska, MD,† Lilin She, PhD,‡ Kerry L. Lee, PhD,§ Mark H. Drazner, MD, MSc,‖ Barbara Lubiszewska, MD, PhD,¶ Dragana Kosevic, MD,# Permyos Ruengsakulrach, MD, PhD,** José C. Nicolau, MD, PhD,†† Benoit Coutu, MD,‡‡ Shiv K. Choudhary, MCh,§§ Daniel B. Mark, MD, MPH,‖‖ John G.F. Cleland, MD, PhD,¶¶ Ileana L. Piña, MD, MPH,## Eric J. Velazquez, MD,‖‖ Andrzej Rynkiewicz, MD,*** Harvey White, DSc*

ABSTRACT

OBJECTIVES The objective of this study was to assess the prognostic significance of exercise capacity in patients with ischemic left ventricular (LV) dysfunction eligible for coronary artery bypass graft surgery (CABG).

BACKGROUND Poor exercise capacity is associated with mortality, but it is not known how this influences the benefits and risks of CABG compared with medical therapy.

METHODS In an exploratory analysis, physical activity was assessed by questionnaire and 6-min walk test in 1,212 patients before randomization to CABG (n = 610) or medical management (n = 602) in the STICH (Surgical Treatment for Ischemic Heart Failure) trial. Mortality (n = 462) was compared by treatment allocation during 56 months (interquartile range: 48 to 68 months) of follow-up for subjects able (n = 682) and unable (n = 530) to walk 300 m in 6 min and with less (Physical Ability Score [PAS] >55, n = 749) and more (PAS ≤55, n = 433) limitation by dyspnea or fatigue.

RESULTS Compared with medical therapy, mortality was lower for patients randomized to CABG who walked ≥300 m (hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.59 to 0.99; p = 0.038) and those with a PAS >55 (HR: 0.79; 95% CI: 0.62 to 1.01; p = 0.061). Patients unable to walk 300 m or with a PAS ≤55 had higher mortality during the first 60 days with CABG (HR: 3.24; 95% CI: 1.64 to 6.83; p = 0.002) and no significant benefit from CABG during total follow-up (HR: 0.95; 95% CI: 0.75 to 1.19; p = 0.626; interaction p = 0.167).

CONCLUSIONS These observations suggest that patients with ischemic left ventricular dysfunction and poor exercise capacity have increased early risk and similar 5-year mortality with CABG compared with medical therapy, whereas those with better exercise capacity have improved survival with CABG. (Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease [STICH]; NCT00023595) (J Am Coll Cardiol HF 2014;2:335–43)

From the *Green Lane Cardiovascular Service, Auckland City Hospital, and University of Auckland, Auckland, New Zealand; †Medical University of Gdansk, Department of Rehabilitation, Gdansk, Poland; ‡Duke Clinical Research Institute, Clinical Trial Biostatistics, Durham, North Carolina; §Duke Clinical Research Institute, Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina; ‖University of Texas Southwestern Medical Center, Dallas, Texas; ¶National Institute of Cardiology, Warsaw, Poland; #Dedinje Cardiovascular Institute, Belgrade, Serbia; **Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand; ††Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; ‡‡Hotel-Dieu du CHUM, Montreal, Canada; §§All India Institute of Medical Sciences, New Delhi, India; ‖‖Duke Clinical Research

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery

CCS = Canadian Cardiovascular Society

ECG = electrocardiogram

HR = hazard ratio

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricular

NYHA = New York Heart Association

PAS = Physical Ability Score

Impaired exercise or functional capacity has been associated with increased mortality in healthy general populations (1), in the elderly (2,3), and in patients with coronary artery disease (4) and heart failure (5–8). Most of these studies have assessed exercise capacity by treadmill, bicycle ergometry, or corridor walking speed over various distances. In patients with heart failure, the 6-min walk test has been commonly used to evaluate functional capacity, and a low 6-min walk distance has been associated with increased total mortality and more hospital admissions for heart failure (5–8). Impaired functional capacity assessed by questionnaire has also been associated with mortality in heart failure populations (9–12).

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Although the long-term prognostic importance of exercise capacity is well known, it is not certain whether assessing the level of exercise limitation provides useful prognostic information in patients with ischemic left ventricular (LV) dysfunction considered for either coronary artery bypass graft surgery (CABG) or medical therapy only. It is also unclear whether exercise limitation is best assessed by a formal test of functional capacity or by a health status questionnaire in this setting. The Society for Thoracic Surgeons risk score does not include any objective measure of exercise capacity (13,14). The EuroSCORE 2 includes a category called "poor mobility," but this is not defined by objective testing (15).

The STICH (Surgical Treatment for Ischemic Heart Failure) trial randomized 1,212 patients with ischemic LV dysfunction and coronary artery disease suitable for bypass grafting to either medical therapy or CABG (16). The aim of this exploratory analysis was to determine whether low 6-min walk distance or more limiting dyspnea or fatigue assessed by questionnaire (17) predicted increased mortality in the STICH study population. In addition, we evaluated whether either measure of physical limitation provided useful information on the balance of benefits and risks of CABG compared with medical treatment in these patients.

METHODS

STUDY POPULATION. Eligible patients had coronary artery disease amenable to CABG and an ejection fraction of 35% or less, as determined at each enrolling site. All patients provided written informed consent. The current analysis included 1,212 subjects randomized to medical therapy or medical therapy plus CABG. Patients were eligible for medical therapy alone if they did not have ≥50% left main coronary artery stenosis or Canadian Cardiovascular Society (CCS) grade III or IV angina.

During the initial evaluation, information was obtained on demographic variables, clinical characteristics, diagnostic investigations, and cardiovascular procedures. Clinical variables recorded at baseline included age, sex, history of renal impairment (defined as serum creatinine >1.5 mg/dl), diabetes mellitus, peripheral vascular disease, number of diseased coronary arteries with diameter stenosis >75%, LV ejection fraction, LV end-systolic volume index, degree of mitral regurgitation, heart rate, history of stroke, CCS angina grade, New York Heart Association (NYHA) functional class, and physician diagnosis of depression. Quality of life was assessed from the 5-item European Quality of Life questionnaire, with a higher score indicating better quality of life (18). The baseline characteristics of the study population have been reported in detail elsewhere (19).

THE 6-MIN WALK TEST. The study protocol included a 6-min walk test for all study participants. Instructions to patients included, "Walk for 6 minutes around this course, covering as much ground as possible during that time. Keep going continuously, if possible, but don't worry if you have to slow down

Institute, Department of Medicine-Cardiology, Duke University School of Medicine, Durham, North Carolina; ¶¶Castle Hill Hospital/Hull Royal Infirmary, Kingston-upon-Hull, United Kingdom; ##Albert Einstein College of Medicine, Montefiore Medical Center, New York, New York; and the ***University of Waria and Mazury, Department of Cardiology and Cardiosurgery, Olsztyn, Poland. The STICH trial was funded by grants U01HL69015 and U01HL69013 from the National Heart, Lung, and Blood Institute. Dr. Nicolau is a consultant for AstraZeneca, Sanofi, and Bayer; has received grants from Sanofi, GlaxoSmithKline, Bayer, and Novartis; and has received lecture fees from Sanofi, Daiichi-Sankyo, AstraZeneca, Bayer, and Bristol-Myers Squibb. Dr. Rynkiewicz has received consulting fees, lecture fees, and grant support from Amgen, AstraZeneca, Boehringer Ingelheim, Pfizer Inc., Servier, Bristol-Myers Squibb, and Sanofi-Aventis. Dr. White has received research grants from Sanofi-Aventis, Eli Lilly, The Medicines Company/National Institutes of Health, Pfizer Inc., Roche, Johnson & Johnson, Schering-Plough, Merck Sharpe & Dohme, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo Pharma Development, and Bristol-Myers Squibb; and has served on advisory boards for Merck Sharpe & Dohme, Roche, and Regado Biosciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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and rest." If the patient did not attempt the test, "patient unable" was recorded in the case report form.

PHYSICAL ABILITY ASSESSMENT BY QUESTIONNAIRE. The Kansas City Cardiomyopathy Questionnaire (KCCQ) (17), a health-related quality-of-life instrument, evaluated the effect of heart failure symptoms on quality of life at baseline. For this analysis, the severity of physical limitation was assessed from the following 6 KCCQ questions. Subjects were asked, "Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks: 1) showering or bathing; 2) dressing yourself; 3) walking one block on level ground; 4) doing yard work, housework, or carrying groceries; 5) climbing a flight of stairs without stopping; 6) hurrying or jogging (as if to catch a bus)." Possible responses to each question were "extremely limited" (score = 1), "quite a bit limited" (score = 2), "moderately limited" (score = 3), "slightly limited" (score = 4), "not limited at all" (score = 5), or "limited for other reasons or did not do the activity" (scored as missing). The Physical Ability Score (PAS) was calculated for each patient by averaging his or her nonmissing responses to the 6 questions, transforming that number to a 0 to 100 scale by subtracting the lowest possible score and dividing by the range of the scale, and then multiplying by 100. If fewer than 3 of the 6 questions were answered, the score was considered missing. A PAS of 100 indicates no limitation by fatigue or dyspnea during any activity.

FOLLOW-UP AND OUTCOMES. After the baseline assessment, patients were randomly assigned to medical therapy only or to medical therapy plus CABG (16). The primary outcome of the STICH trial was all-cause mortality. Median follow-up of the patients was 56 months (interquartile range: 48 to 68 months).

STATISTICAL ANALYSIS. Continuous demographic and baseline variables were summarized with the median and the first and third quartiles and categorical variables by frequency and percentage. Between-group comparisons for baseline continuous and ordinal variables were performed with the Kruskal-Wallis test (comparing 3 groups) and the Wilcoxon rank sum test (comparing 2 groups). Categorical variables were compared between groups with the chi-square test or Fisher exact test.

Univariate relationships of 6-min walk distance and PAS with all-cause mortality were examined with the Cox proportional hazards model. The 6-min walk distance and PAS were analyzed as both continuous variables and categorical variables. Whether or not patients were able to walk ≥300 m in the 6-min walk test was used to categorize patients, because a 6-min walk distance <300 m has been associated with increased mortality or cardiovascular hospitalization in populations with heart failure or LV systolic dysfunction (5,20,21). There is no prior literature that relates PAS and mortality. To dichotomize PAS, a threshold of 55 was chosen, because mortality risk decreased with increasing levels of PAS up to approximately 55, with no further gradient of risk for PAS >55. Relative risks were derived from the Cox model and expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs).

The Cox model was also used to assess the incremental prognostic value of the 6-min walk and PAS beyond other clinical predictors of mortality identified in previous multivariable analyses using the STICH database. Independent predictors of mortality in these analyses ($p < 0.05$) were LV end-systolic volume index, creatinine, moderate or severe mitral regurgitation, age, heart rate, history of stroke, and treatment received.

TABLE 1 Baseline Characteristics of Study Population by 6-Min Walk Distance Group

Variable	Unable to Walk (n = 168)	Walk <300 m (n = 362)	Walk ≥300 m (n = 682)	p Value
6-min walk distance (m)	–	225 (162, 270)	390 (348, 440)	–
Age at randomization (yrs)	62 (54, 69)	60 (54, 68)	59 (53, 66)	0.005
Male	144 (86)	303 (84)	617 (90)	0.004
Region*				<0.001
Poland	21 (7)	73 (23)	225 (70)	
United States/Canada	63 (26)	82 (34)	98 (40)	
West Europe†	28 (25)	20 (18)	64 (57)	
Other countries†	56 (10)	187 (35)	295 (55)	
Hispanic/Latino/nonwhite	62 (37)	162 (45)	197 (29)	<0.001
CCS angina grade ≥ II	73 (44)	206 (57)	304 (45)	<0.001
NYHA HF class ≥ III	82 (49)	189 (52)	176 (26)	<0.001
Heart rate (beats/min)	75 (66, 83)	75 (68, 83)	72 (64, 80)	0.020
LV ejection fraction (%)	28 (21, 33)	27 (22, 34)	28 (23, 34)	0.128
LV end-systolic volume index	80 (65, 99)	77 (59, 102)	80 (61, 101)	0.614
Atrial flutter or fibrillation	24 (14)	48 (13)	81 (12)	0.638
Mitral regurgitation (moderate/severe)	32 (19)	70 (20)	118 (17)	0.651
3-Vessel CAD with ≥75% stenosis	68 (41)	150 (42)	224 (33)	0.011
Body mass index (kg/m^2)	26 (24, 30)	27 (24, 30)	27 (24, 30)	0.212
Chronic renal insufficiency	36 (21)	26 (7)	32 (5)	<0.001
Diabetes mellitus	78 (46)	149 (41)	251 (37)	0.053
History of stroke	18 (11)	27 (8)	47 (7)	0.244
Peripheral vascular disease	44 (26)	71 (20)	69 (10)	<0.001
Depression	26 (16)	21 (6)	29 (4)	<0.001
Quality of life EQ-5D score	0.65 (0.52, 0.81)	0.69 (0.52, 0.85)	0.79 (0.66, 1.00)	<0.001

Values are median (first, third quartiles) or n (%). *Percentage of patients in each walking group within a region. †West European countries here include Austria, Germany, Italy, Sweden, Norway, and United Kingdom. "Other countries" include other European, Asia-Pacific, and South American countries.

CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; EQ-5D = 5-item European Quality of Life Questionnaire; HF = heart failure; LV = left ventricular; NYHA = New York Heart Association.

TABLE 2 Baseline Characteristics of Study Population by Physical Ability Score

Variable	Physical Ability Score ≤55 (n = 433)	Physical Ability Score >55 (n = 749)	p Value
6-min walk distance (m)	300 (220, 372)	361 (285, 427)	<0.001
Age at randomization (yrs)	60 (54, 67)	60 (54, 67)	0.621
Male	358 (83)	680 (91%)	<0.001
Region*			<0.001
Poland	101 (32)	215 (68)	
United States/Canada	101 (42)	138 (58)	
West Europe†	38 (37)	65 (63)	
Other countries†	193 (37)	331 (63)	
Hispanic/Latino/nonwhite	151 (35)	262 (35)	0.970
CCS angina grade ≥II	245 (57)	325 (43)	<0.001
NYHA HF class ≥III	258 (60)	177 (24)	<0.001
Heart rate (beats/min)	76 (68, 84)	72 (65, 80)	<0.001
LV ejection fraction (%)	26 (21, 33)	28 (23, 34)	<0.001
LV end-systolic volume index	81 (63, 104)	77 (60, 99)	0.076
Atrial flutter or fibrillation	69 (16)	79 (11)	<0.001
Mitral regurgitation (moderate/severe)	77 (18)	138 (18)	0.803
3-vessel CAD with ≥75% stenosis	164 (38)	264 (35)	0.350
Body mass index (kg/m^2)	27 (24, 31)	27 (24, 30)	0.198
Chronic renal insufficiency	41 (10)	50 (7)	0.084
Diabetes mellitus	182 (42)	286 (38)	0.192
History of stroke	41 (10)	46 (6)	0.035
Peripheral vascular disease	88 (20)	89 (12)	<0.001
Depression	40 (9)	33 (4)	<0.001
Quality of life EQ-5D score	0.62 (0.52, 0.73)	0.81 (0.69, 1.00)	<0.001

Values are median (first, third quartiles) or n (%). *Percentage of patients in each physical ability score group within a region. †West European countries include Austria, Germany, Italy, Sweden, Norway, and United Kingdom; "Other countries" include other European, Asia-Pacific, and South American countries.

Abbreviations as in Table 1.

Event rate plots were created with the Kaplan-Meier method for the following groups: unable to perform the 6-min walk test, walked <300 m, or walked ≥300 m; and for PAS ≤55 and >55. To evaluate the value of combining 6-min walk results and PAS, Kaplan-Meier plots were also generated for subjects who were both able to walk ≥300 m and had a PAS >55 and for subjects who did not meet both of these criteria. The log-rank test was used to examine the randomized treatment comparisons (CABG vs. medical therapy) with respect to all-cause mortality among patients in different exercise capacity groups. The interaction of exercise capacity and randomized treatment with respect to mortality was assessed with the Cox model. Kaplan-Meier plots for all subjects suggested increased mortality for subjects randomized to CABG during the first ~60 days and lower mortality after 2 years (16). In exploratory analyses to evaluate possible differences in early versus later mortality by treatment allocation and exercise group, HRs for mortality <60 days, 60 days to 2 years, and >2 years after randomization were calculated.

RESULTS

BASELINE ASSESSMENTS. Clinical characteristics for all patients at baseline are summarized by 6-min walk distance groups in Table 1. Subjects unable to perform the 6-min walk test were compared with those who walked <300 m or ≥300 m. Patients who walked ≥300 m were younger, more likely to be male, and more likely to be white. Patients from Poland were most likely to do well on the test, and those from the United States or Canada were the least likely to do well. Patients unable to perform the 6-min walk test were more likely to have chronic renal insufficiency, peripheral vascular disease, depression, and lower quality of life. Subjects who walked ≥300 m were less likely to have NYHA functional class ≥III or have 3-vessel coronary artery disease.

Baseline characteristics for the 1,182 (97.5%) patients who completed the baseline questionnaire are displayed by PAS groups in Table 2. Patients reporting greater physical ability (PAS>55) did significantly better on the 6-min walk test and were more likely to be male. Patients from Poland tended to report less physical limitation than patients from the United States/Canada. Patients with more physical limitations on average were more likely to have NYHA heart failure functional class III or greater, CCS angina grade II or greater, lower LV ejection fraction, higher resting heart rate, and a higher rate of atrial flutter or fibrillation, but other markers of severity of cardiac disease were similar. Patients with poorer physical capacity were more likely to have a history of stroke, peripheral vascular disease, or depression and lower quality of life.

MORTALITY BY WALK DISTANCE. During follow-up for a median of 56 months (interquartile range: 48 to 68 months), there were 462 deaths (38%). The majority of deaths were of cardiovascular causes (n = 369, 80%). Figure 1 displays the Kaplan-Meier estimated mortality rates and HRs by three 6-min walk distance groups: unable to walk, walked <300 m, and walked ≥300 m. Patients who walked ≥300 m tended to have lower mortality than patients who were not able to walk (HR: 0.83; 95% CI: 0.64 to 1.08) and patients who walked <300 m (HR: 0.82; 95% CI: 0.67 to 1.01). Because mortality rates were similar for subjects who were not able to walk or who walked <300 m in 6 min (Fig. 1), these 2 groups were combined for further analysis. The association between mortality and 6-min walk distance analyzed as a continuous variable was of borderline statistical significance (p = 0.051),

excluding patients unable to walk, with p = 0.045 if patients unable to walk were included with their walking distance set as 0. This association was not significant after multivariable adjustment for other prognostic clinical factors (Table 3).

MORTALITY BY PAS. PAS (0 to 100) was first analyzed as a continuous variable (Table 3). Each increase in PAS of 1 standard deviation (25 U) was associated with a decrease in total mortality risk when PAS changed from 0 to 55 (HR: 0.73; 95% CI: 0.62 to 0.85; p < 0.001), but there was no further decrease in mortality as PAS increased above 55. Patients with a PAS >55 compared with ≤55 had lower mortality risk (HR: 0.77; 95% CI: 0.64 to 0.93; p = 0.008) (Fig. 2), and this association remained significant after adjustment for other prognostic factors in the multivariable model (Table 3).

Associations between both PAS and 6-min walk distance and cardiovascular and noncardiovascular mortality are reported in Online Table 1.

MORTALITY BY TREATMENT ALLOCATION. All baseline characteristics were similar by treatment allocation to CABG or medical therapy (16). For patients who were able to walk ≥300 m, mortality risk was lower if they had been randomized to CABG compared with medical treatment (HR: 0.77; 95% CI: 0.59 to 0.99; p = 0.038) (Fig. 3). However, for patients who were not able to walk 300 m, mortality was not significantly different for the CABG treatment group and the medical therapy group (HR: 0.98; 95% CI: 0.75 to 1.27; p = 0.871, p for interaction = 0.207) (Fig. 3).

A similar difference in mortality by treatment was observed by PAS (Fig. 4). For subjects with PAS >55, there was a trend for lower mortality if they were randomized to CABG (HR: 0.79; 95% CI: 0.62 to 1.01; p = 0.061). In contrast, patients with more limiting symptoms (PAS ≤55) had a similar mortality risk when randomized to CABG than to medical therapy (HR: 0.94; 95% CI: 0.70 to 1.25; p = 0.652, p for interaction = 0.406) (Fig. 4).

Combined information from the walk test and the PAS are presented in Figure 5. For subjects who walked ≥300 m and had a PAS >55 (n = 486),

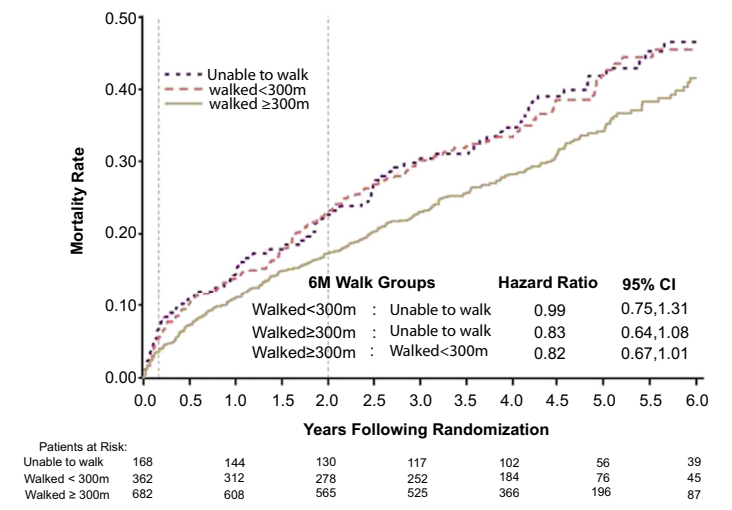

FIGURE 1 Mortality by 6-Min Walk Distance for All Subjects

Kaplan-Meier estimates of total mortality for patients unable to perform the walk test, patients who walked <300 m in 6 min, and those who walked ≥300 m in 6 min at baseline. CI = confidence interval; 6M = 6 min.

TABLE 3 Hazard Ratios for Mortality by Physical Ability Score and by 6-Min Walk Distance Assessed at Baseline

	Number of Patients*	Number of Events*	HR (95% CI) Unadjusted	p Value	HR (95% CI) Adjusted for Clinical Covariates†	p Value
Physical Ability Score (continuous)‡§‖¶	1,182	450	0.73 (0.62-0.85)	<0.001	0.79 (0.67-0.94)	0.006
Physical Ability Score >55 (yes/no)¶	1,182	450	0.77 (0.64-0.93)	0.008	0.81 (0.67-0.98)	0.026
6-min walk distance (continuous; not including patients unable to walk)‖	1,044	388	0.91 (0.82-1.00)	0.051	0.94 (0.85-1.04)	0.233
6-min walk distance (continuous; impute 0 if unable to walk)‖	1,212	462	0.94 (0.88-0.99)	0.045	0.97 (0.90-1.03)	0.318
Able to perform 6-min walk test (yes/no)	1,212	462	0.89 (0.69-1.14)	0.336	0.96 (0.75-1.24)	0.771
Able to walk ≥300 m in 6-min walk test (yes/no)	1,212	462	0.82 (0.69-0.99)	0.036	0.93 (0.77-1.12)	0.440

*Number of events refers to the number with an event during follow-up. Information on the 6-min walk test was available for all 1,212 subjects (including 1,044 who could perform the walk test and 168 who were unable), and physical ability score was available for 1,182 subjects at baseline, which explains the different number of events. †Clinical covariates included in the adjusted analyses were left ventricular end-systolic volume index, serum creatinine, moderate or severe mitral regurgitation, age, heart rate, history of stroke, and treatment (coronary artery bypass surgery vs. medical treatment) received. ‡Physical Ability Score >55 indicates less limiting symptoms of fatigue or dyspnea during daily activities. §Risk decreases as Physical Ability Score increases up to a value of 55, beyond which the risk is level. ‖The hazard ratios represent the decrease in risk for a 1-SD increase in Physical Ability Score (25 U) or 6-min walk distance (117 m). ¶Hazard ratios and p values for 6-min walk groups were similar when analyses were repeated excluding subjects who did not have Physical Ability Score data.

CI = confidence interval; HR = hazard ratio.

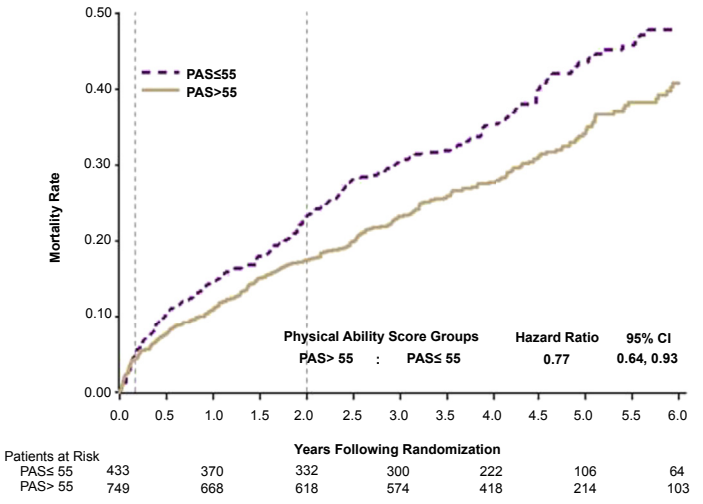

FIGURE 2 Mortality by PAS for All Subjects

Kaplan-Meier estimates of total mortality for patients with a Physical Ability Score (PAS) >55 compared with those with a score ≤55 at baseline. CI = confidence interval.

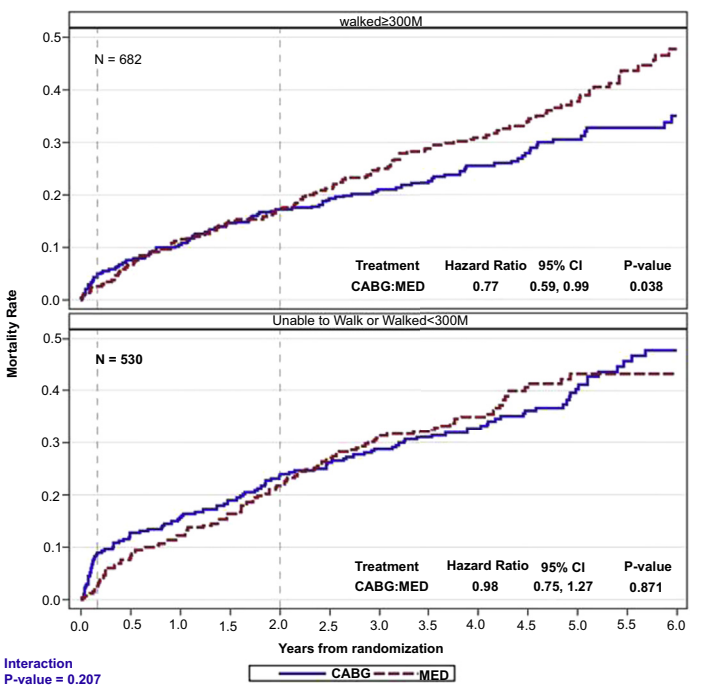

FIGURE 3 Mortality for Subjects Randomized to CABG or to Medical Treatment, Stratified by Walk Distance

Kaplan-Meier estimates of total mortality for patients randomized to coronary artery bypass graft surgery (CABG) or to medical treatment (MED) with **(top)** a 6-min walk distance ≥300 m at baseline or **(bottom)** a 6-min walk distance <300 m at baseline or who were unable to perform the walk test. CI = confidence interval.

mortality risk was lower if they were randomized to CABG than to medical therapy (HR: 0.71; 95% CI: 0.52 to 0.97; p = 0.033). In contrast, for all subjects who did not meet both of these criteria (n = 726), mortality risk was not significantly different between treatment groups (HR: 0.95; 95% CI: 0.75 to 1.19; p = 0.626, p for interaction = 0.167). The HRs for mortality by treatment allocation were similar for subjects who did not walk 300 m and had a PAS ≤55 (n = 246; HR: 0.97; 95% CI: 0.67 to 1.40; p = 0.961), those who did not walk 300 m and had a PAS >55 (n = 263; HR: 0.94; 95% CI: 0.64 to 1.40; p = 0.775), and subjects who walked 300 m and had a PAS ≤55 (n = 187; HR: 0.92; 95% CI: 0.58 to 1.44; p = 0.703). Kaplan-Meier plots for cardiovascular mortality by treatment allocation for 6-min walk and PAS groups were similar to those for total mortality (Online Figs. 1 to 3).

EARLY AND LATE MORTALITY BY TREATMENT. HRs for total mortality at <60 days, 60 days to 2 years, and >2 years of follow-up by 6-min walk distance and PAS groups are presented in Online Figures 1 to 3. For subjects who could not walk ≥300 m or with PAS ≤55, the early mortality risk within 60 days after CABG was higher than for patients in the medical therapy group (30 deaths [8.04%] vs. 9 deaths [2.55%]; HR: 3.24; 95% CI: 1.54 to 6.83). In contrast, for subjects both able to walk ≥300 m and with higher PAS >55, there was no significant increase in mortality risk during the first 60 days for subjects randomized to CABG compared with those randomized to medical therapy (8 deaths [3.38%] vs. 7 deaths [2.81%]; HR: 1.21; 95% CI: 0.44 to 3.33) (Online Fig. 3). Similar time-dependent differences by treatment allocation were observed for cardiovascular mortality (Online Figs. 4 to 6).

DISCUSSION

In this study of patients with ischemic LV dysfunction who were candidates for CABG, poor exercise capacity assessed by the 6-min walk test and greater limitation of daily activities from fatigue or dyspnea as assessed by questionnaire were both associated with increased mortality during follow-up. These findings are consistent with many studies in which low exercise capacity predicted worse outcomes, both in general populations (1–3) and in patients with ischemic heart disease (4) and heart failure (5–8).

POSSIBLE EXPLANATIONS FOR MORTALITY DIFFERENCES BY TREATMENT. The primary results of the STICH trial (16) reported a trend toward lower mortality attributable to all causes (HR: 0.86; 95% CI:

0.72 to 1.04) and to cardiovascular causes (HR: 0.81; 95% CI: 0.66 to 1.00) for patients with ischemic LV dysfunction randomized to CABG compared with medical therapy. This result is consistent with a benefit from CABG for some patients, but it has been unclear how to identify those patients likely to have better or worse outcomes with CABG than with medical therapy. In previous analyses from STICH, neither myocardial ischemia (22) nor viability (23) predicted benefit from CABG compared with medical therapy.

In contrast to the results of this analysis, current clinical practice guidelines suggest "sicker" patients are more likely to benefit from CABG (24,25). Exploratory analyses suggested 2 reasons why patients with low functional capacity may have benefited less from CABG than from medical therapy. First, these patients had a higher early mortality risk with CABG. This increased early CABG-related risk extended for >30 days, the time usually chosen to assess surgical mortality. For this reason, a 60-day cutoff level was chosen for exploratory analysis; however, interpretation of results is not influenced by whether 30 or 60 days is used to define early mortality. Second, higher longer-term mortality risk of patients with poor functional capacity may not be reduced by CABG, especially if the increased risk is related to noncardiac factors. Both 6-min walk distance and PAS were associated with other measures of general health, depressed mood, comorbidities, and quality of life, which supports the conclusion that exercise capacity reflects overall health in addition to the severity of cardiac disease. In previous studies, poor health-related quality of life, frailty, and disability have been associated with increased mortality in patients with heart failure (9–12) and after cardiac surgery (26).

COMPARISON OF WALK TEST AND PAS. Because the focus of the current study was exercise capacity, only the 6 questions from the KCCQ on dyspnea or fatigue during common physical activities were included (17). The PAS was a stronger independent predictor of mortality than the 6-min walk distance, but this did not translate to better prediction of benefit from CABG than from medical treatment alone. The PAS provides complementary information to the 6-min walk test because it estimates self-reported severity of dyspnea and fatigue during daily activities but does not directly measure exercise capacity. Subjects able to walk ≥300 m who also had a PAS >55 had the greatest estimated benefit from CABG compared with medical therapy alone.

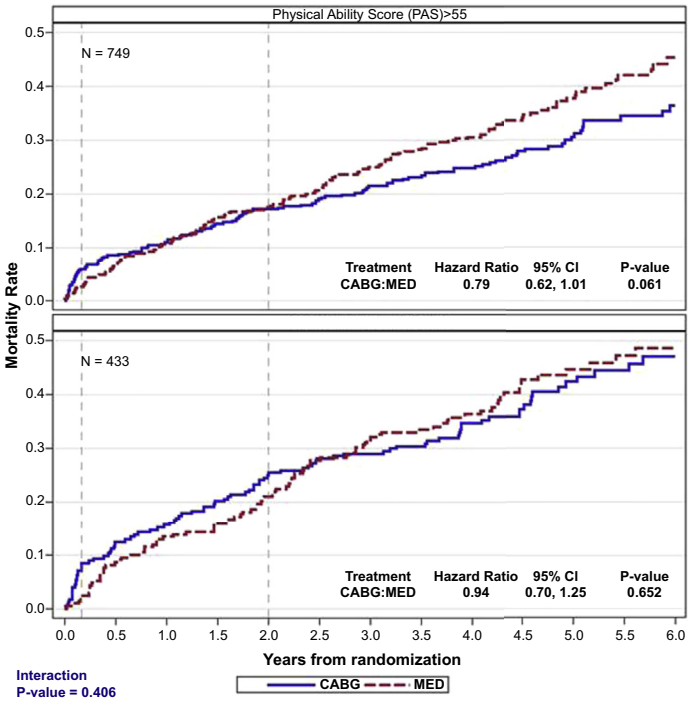

FIGURE 4 Mortality for Subjects Randomized to CABG or to Medical Treatment, Stratified by PAS

Kaplan-Meier estimates of total mortality for patients randomized to coronary artery bypass surgery (CABG) or to medical treatment (MED) with **(top)** a Physical Ability Score (PAS) >55 at baseline or **(bottom)** a PAS ≤55 at baseline.

STUDY STRENGTHS AND LIMITATIONS. The STICH trial is the only large, randomized clinical trial comparing CABG with medical therapy alone in patients with ischemic LV dysfunction, and the only study that allows a comparison of outcomes for patients with poor compared with better exercise capacity for the 2 treatment options. Questionnaire and 6-min walk test data were collected by standard methods for >97% of study participants, results were consistent for the 2 methods of evaluating functional capacity, and all study participants with functional data were included in the intention-to-treat analysis.

Associations between exercise capacity and mortality could be explained in part by poorer general health or by cultural factors associated with country of residence (27). However, subjects were balanced by randomization to CABG or medical therapy, and an intention-to-treat analysis was performed, so associations between exercise capacity and demographic variables, comorbidity, general health, and quality of life would not bias the evaluation of

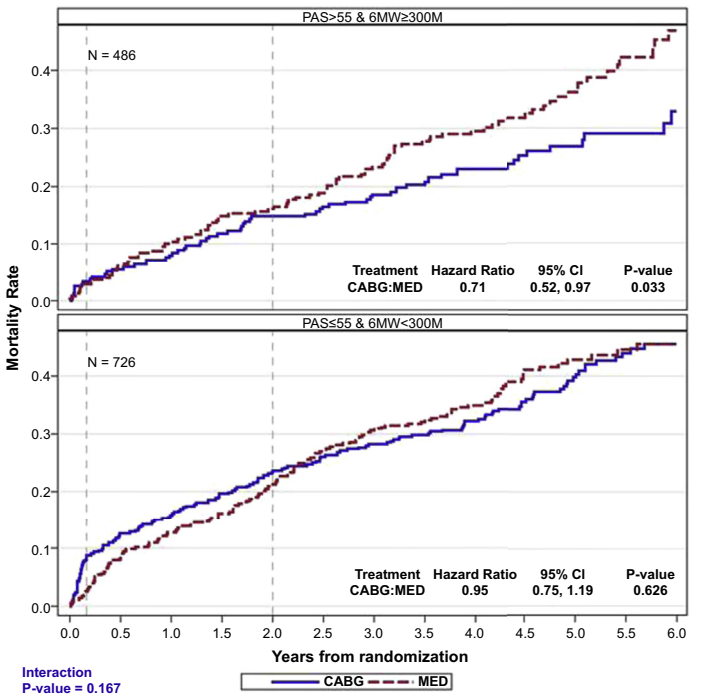

FIGURE 5 Mortality for Subjects Randomized to CABG or to Medical Treatment, Stratified by Exercise Capacity Assessed From Both Walk Distance and PAS

Kaplan-Meier estimates of total mortality for patients randomized to coronary artery bypass surgery (CABG) or to medical treatment (MED) with **(top)** a 6-min walk (6MW) distance ≥300 m and a Physical Ability Score (PAS) >55 at baseline or **(bottom)** a 6MW distance <300 m or a PAS ≤55 at baseline. CI = confidence interval.

differences in outcome by treatment allocation for subjects with lower and higher exercise capacity. The reported analyses were post-hoc, and statistical tests for interaction did not reach conventional levels of significance. It is therefore possible the observed treatment differences in mortality by exercise group occurred by chance. Time-dependent HRs were included to evaluate possible reasons for differences in mortality with CABG compared with medical treatment for each exercise group and should be considered exploratory. All-cause mortality was the primary outcome both for the STICH trial and the present analysis. Effects of CABG compared with medical therapy on symptoms and quality of life are also clinically important, but these outcomes were not the focus of this report.

CONCLUSIONS

This exploratory analysis from the large, international, randomized STICH trial suggests patients with ischemic LV dysfunction who cannot walk 300 m and those with more limiting symptoms of fatigue or dyspnea have a higher early mortality with CABG and are less likely to benefit during longer follow-up from surgery than from medical therapy. In contrast, patients with better functional capacity may have a lower mortality over ~5 years if referred for CABG.

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REPRINT REQUESTS AND CORRESPONDENCE: Prof. Ralph A.H. Stewart, Green Lane Cardiovascular Service, Auckland City Hospital, Private Bag 92024, Victoria St. West, Auckland 1142, New Zealand. E-mail: rstewart@adhb.govt.nz.

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APPENDIX For a supplemental table and figures, please see the online version of this article.