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Sex Difference in Patients with Ischemic Heart Failure Undergoing Surgical Revascularization: Results from the STICH Trial

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Abstract

Background—Female sex is conventionally considered a risk factor for coronary artery bypass grafting (CABG) and has been included as a poor prognostic factor in multiple cardiac operative risk evaluation scores. We aimed to investigate the association of sex and the long-term benefit of CABG in patients with ischemic left ventricular (LV) dysfunction enrolled in the prospective Surgical Treatment for Ischemic Heart Failure Study (STICH) trial.

Methods—The STICH trial randomized 1212 patients [148 (12%) women and 1064 (88%) men] with CAD and LV ejection fraction (EF)≤ 35% to CABG + medical therapy (MED) versus MED alone. Long-term (10-year) outcomes with each treatment were compared according to sex.

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Results—At baseline, women were older (63.4 vs 59.3, p=0.016) with higher BMI (27.9 vs 26.7, p=0.001). Women had more CAD risk factors (diabetes 55.4% vs 37.2%, hypertension 70.9% vs 58.6%, hyperlipidemia 70.3% vs 58.9%) except for smoking (13.5% vs 21.8%), and had lower rates of prior CABG (0% vs 3.4%, all p<0.05) than men. Moreover, women had higher New York Heart Association (NYHA) class (Class III/IV 66.2% vs 57.0%), lower 6-min walk capacity (300m vs 350m) and lower Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores (51 vs 63) (all p<0.05). Over 10-years of follow up, all- cause mortality (49.0% vs 65.8%, adjusted HR 0.67, CI 0.52–0.86, p=0.002) and CV mortality (34.3% vs 52.3%, adjusted HR 0.65, CI 0.48–0.89, p=0.006) were significantly lower in women compared to men. With randomization to CABG + MED vs. MED treatment, there was no significant interaction between sex and treatment group in all-cause mortality, CV mortality, or the composite of all-cause mortality or CV hospitalization (all p>0.05). In addition, surgical deaths were not statistically different (1.5% vs 5.1%, p=0.187) between sexes among patients randomized to CABG per protocol as initial treatment.

Conclusions—Sex is not associated with the effect of CABG + MED vs. MED on all-cause mortality, CV mortality, the composite of death or CV hospitalization, or surgical deaths in patients with ischemic LV dysfunction. Thus, sex should not influence treatment decisions regarding CABG in these patients.

Keywords

heart failure; women; coronary artery bypass grafting

Introduction

Sex-specific differences have been recognized with respect to prevalence, etiology and prognosis of coronary artery disease (CAD) and ischemic heart failure (HF).[1–4] Despite having lower burden of obstructive CAD by coronary angiography and better left ventricular ejection fraction (LVEF) compared to men, women with CAD and ischemic HF are usually more symptomatic, have lower functional capacity, worse quality of life, higher rate of ischemia, and possible higher mortality rate post myocardial infarction, all of which could lead to higher health costs associated with frequent office visits and hospitalization.[4–12] In fact, CAD is the leading cause of death and HF is the leading cause of hospitalization in women over the age of 65.[13, 14] Despite these facts, studies have suggested that physicians are less likely to pursue an aggressive approach to CAD in women than in men.[15, 16] In addition, female sex is conventionally considered a risk factor for open-heart surgery, and has been included as a poor prognostic factor in multiple cardiac operative risk scores, e.g. EuroScore II, STS score, modified Parsonnet's score, New York's Cardiac Surgery Reporting System score, and Northern New England Cardiovascular Disease Study Group score.[17–21]

The STICH trial provides a unique opportunity to examine sex differences in the baseline characteristics and clinical outcomes of a high-risk group of patients with severe ischemic LV dysfunction, treated with contemporary guideline directed medical therapy with or without surgical revascularization. Furthermore, the long-term follow-up for mortality in STICHES can provide additional information based on sex.[22] Therefore, the objective of this

study was to investigate the association of sex on the long-term benefit of CABG in patients enrolled in the prospective STICH trial.

Methods

The STICH/STICHES data, analytic methods, and study results are available for review online.[23] The raw datasets and analysis datasets have been deidentified and submitted to NHLBI and will be published at the NHLBI BioLinCC website in the future.[24]

Study Population

The design of the STICH trial has been described previously.[25] In brief, STICH was a prospective, multicenter, randomized controlled trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) that recruited 1212 patients with CAD and LVEF ≤35% from 99 sites in 22 countries between 2002 and 2007. The STICH Hypothesis 1 examined the question whether CABG with optimized medical therapy (MED) improves long-term survival compared with MED alone. The primary results of Hypothesis 1 have been published.[26] Detailed inclusion and exclusion criteria have also been previously described. The NHLBI and the ethics committee at each participating institution approved the study protocol. All patients provided written informed consent.

Statistical Analysis

Baseline characteristics for women and men were summarized by the median and interquartile range for continuous variables and by the frequency and percentage for categorical variables. Comparisons of baseline characteristics between men and women were assessed using the Wilcoxon rank-sum test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Cumulative event rates of clinical outcomes (all-cause mortality, cardiovascular mortality, mortality or cardiovascular hospitalization, sudden cardiac death, and heart failure death) were calculated for different patient groups using the method of Kaplan and Meier. The event rates per-person years for each patient group were obtained by dividing the total number of events by the total number of years of follow-up among all patients in the group. For the composite endpoint of mortality or CV hospitalization, the numerator in the event rate per-person year includes only the first event a patient experienced. The effects of treatment as randomized (CABG + MED vs. MED alone) on clinical outcomes were statistically assessed in male and in female patients using the log-rank test and summarized using hazard ratios and 95% confidence intervals generated from the Cox proportional hazards regression model. The Cox model was also used to assess whether the effect of CABG + MED vs. MED was different in women compared to men by examining the interaction between treatment and sex for each clinical endpoint. For comparing men vs. women directly with respect to clinical outcomes, the Cox model was used, adjusting for key prognostic baseline characteristics (including age, race, HF class at baseline, history of MI, previous revascularization, number of diseased vessels, ejection fraction, chronic renal insufficiency, history of atrial flutter/fibrillation, mitral regurgitation, history of stroke, hemoglobin and hyperlipidemia) and randomized treatment (CABG + MED vs. MED). Quality of life measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score over the first 36 months of follow-up was compared

between men and women using the repeated measures analysis in the PROC MIXED procedure in SAS. The least-square means of KCCQ Overall Scores and their 95% CIs were obtained for men and women at each time point. All calculations were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics and Baseline Parameters

The baseline characteristics of men (n=1064, 88%) and women (n=148, 12%) in the Hypothesis 1 group are listed in Table 1. Women were older than the men (median 63.4 vs. 59.3 years, p=0.016), more likely to be White, and had a higher body mass index (BMI) (median 27.9 vs. 26.7, p=0.001). More risk factors for CAD were reported in women except for smoking (diabetes 55.4% vs. 37.2%, p<0.001, hypertension 70.9% vs. 58.6%, p=0.004, hyperlipidemia, 70.3% vs. 58.9%, p=0.008), while women were less likely to have had prior CABG (0% vs. 3.4%, p=0.017). In addition, women were more likely to report depression and had worse baseline renal function (glomerular filtration median rate 83.8 vs. 91.2 mL/min/1.73m^2, p<0.001).

Baseline Left Ventricular Function and Coronary Anatomy

Table 2 details the baseline LV function and the coronary anatomy by sex. Clinical values are the best available data reported by participating sites and/or core labs. The rates of triple vessel disease, left main stenosis ≥ 50% and proximal left anterior descending stenosis ≥ 75% were not statistically different. The median LVEF (30.0% vs 27.0%, p =0.0001) was higher in women.

Symptoms

There was no significant difference in symptoms of angina between sexes by the CCS angina score (Table 1). The percentage of patients with advanced HF class (by highest NYHA class during the 3-month period prior to randomization) was higher in women than men (66.2% vs. 57.0%, p=0.034). In addition, women had a lower functional capacity as noted by the 6 min walk distance (median 300 vs. 350 meters, p<0.0001, Table 1). Health status (HRQoL) measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score was lower in women at baseline (51 vs. 63, p<0.0001).

Medical Therapy

More men than women were on ACE inhibitors (83.5% vs. 73.0%, p= 0.002), However, a higher proportion of women were receiving ARBs, thus making the use of ACEI or ARBs relatively similar between sexes (Table 1). Beta-blocker use was also not statistically different between the two groups. While digoxin was more commonly used in men (21.1% vs. 13.5%, p=0.030), more women were on insulin treatment (27.0% vs. 14.8%, p<0.0001).

Clinical Outcomes

Over a median follow up of 9.8 years, women had significantly lower all-cause mortality compared to men (73/148, 49.3% vs. 684/1064, 64.3%, adjusted HR 0.67, 95% CI 0.52–

0.86, p=0.002) and CV mortality (48/148, 32.4% vs. 496/1064, 46.6%, adjusted HR 0.65, 95% CI 0.48–0.89, p=0.006, Table 3). With randomization to CABG vs MED treatment, there was no significant interaction between sex and treatment group in all- cause mortality (p=0.495, Figure 1), CV mortality (p=0.386), mortality or CV hospitalization (p=0.176). For both women and men, CABG + MED patients had lower event rates than MED patients (Table 4) on all-cause mortality (32/73, 43.8% vs. 41/75, 54.7% for women; 327/537, 60.9% vs. 357/527, 67.7% for men), CV mortality (19/73, 26.0% vs. 29/75, 38.7% for women; 228/537, 42.5% vs. 268/527, 50.9% for men), and mortality or CV hospitalization (50/73, 68.5% vs. 62/75, 82.7% for women; 417/537, 77.7% vs 462/527, 87.7% for men). The same pattern of results was also observed on the event rates for sudden cardiac death and heart failure death (Table 3 and Table 4). Moreover, surgical deaths were not statistically different for both sexes among patients randomized to CABG and received CABG per protocol as initial treatment (men 25/488, 5.1% vs. women 1/67, 1.5%, p = 0.187). In addition, both sexes had significant improvements in HRQoL as measured by the KCCQ Overall Score, lasting up to 36 months of follow up (p<0.0001, Figure 2), but remained lower in the women.

Discussion

The STICH trial is the first and only contemporary randomized clinical trial designed to compare CABG plus intensive HF medical therapy with intensive HF medical therapy only in patients with severe LV dysfunction, in an era with the availability of an evidence-based HF medical regimen. Historically, due to limited numbers of women, data based on predominantly male subjects in cardiovascular clinical trials have been extrapolated to women in practice. This is the first sub-analysis of a contemporary trial to suggest that despite having more cardiovascular comorbidities and worse functional status at baseline, female sex is not associated with the effect of CABG on all-cause mortality, CV mortality or surgical death rates in these patients. Furthermore, women had significantly lower rates of long-term all-cause mortality and CV mortality than men.

Baseline Clinical Characteristics

In light of these findings, a brief review of baseline demographics in comparison to other HF studies is relevant. Baseline characteristics of the STICH Hypothesis 1 cohort are similar to other studies such as CASS, CABG Patch, CHARM and MERIT-HF with a higher prevalence of comorbidities in the women compared to the men.[1, 3, 27, 28] In addition, in the STICH trial, women were more likely to experience depression and had lower KCCQ Overall scores. In comparison, the HF-ACTION and BEST trials showed that women were younger and had a lower or same prevalence of hypertension and diabetes.[2, 8] Moreover, in HF-ACTION, the scores on the Beck Depression Inventory II (8 vs. 8) and the KCCQ (68 vs. 69) were similar, and the history of depression (21% vs. 22%) was similar as well in both men and women.[8] It was speculated that this seeming inconsistency could be due to the recollection of a history of hypertension or diabetes in a younger cohort, who may not have these comorbidities yet manifest.[8] In addition, these medical and exercise therapy trials included a large portion of patients with non-ischemic heart failure; in contrast, the STICH

trial focused on ischemic heart failure, which may explain the high prevalence of cardiovascular comorbidities in the STICH population.

Ischemic Heart Failure Medical Therapy

The STICH trial is a contemporary trial in which participants were well medicated with evidence based heart failure medical therapy. More than 80% of patients in the STICH trial were treated with beta-blocker, ACE inhibitor or ARB, lipid-reducing therapy and antiplatelet therapy. Additionally, more than 45% of patients received potassium-sparing diuretics. Overall, there was no significant sex difference in the medical therapy for ischemic HF at baseline. Our results showed that a lower proportion of women received ACE inhibitor, while a higher proportion of women received ARB. However, the combined proportion receiving ACE inhibitor or ARB was similar between sexes. This pattern is consistent with observations from prior trials, probably related to the higher prevalence of ACE inhibitor-induced cough in women than in men.[1, 8]

Clinical Outcome of Coronary Bypass Grafting Surgery

Given the distinct differences in sex hormones and their effects on cardiovascular disease process, women and men may respond to therapies differently, including revascularization.[4, 7, 29–31] Some studies have shown higher rates of mortality and complications in women compared to men after coronary revascularization; however, after multivariable adjustment, female sex was often deemed not an independent predictor of poor outcome.[27, 32–37]

The data on the effect of female sex on CABG outcomes have been controversial in both clinical trials and registries. Women participants were more likely to be older, had significantly greater pre-operative comorbidities (including hypertension, hyperlipidemia, diabetes mellitus, unstable angina, congestive heart failure, and peripheral vascular disease), and were more likely to undergo urgent CABG.[27, 28, 32, 36, 38–43] Thus, the association or potential impact of female sex as an independent predictor on the poor outcome of isolated CABG surgery has long been debated. The CASS registry showed that women had worse surgical mortality (4.5% vs 1.9%, p=0.02) and 1-year survival than men despite risk variable adjustment, but there was no significant difference between sexes with regard to long-term 6-year mortality (8.7 vs. 7.9%, p=0.41).[27, 44] A meta-analysis of 20 studies reported a higher mortality in women post CABG not only at short term, but also at mid- and long-term follow up.[42] Recent studies from the 1990's and 2000's attributed this elevated mortality to the higher prevalence of pre-operative risk factors at baseline and later referral bias in women.[32, 35, 41, 43, 45] Furthermore, a retrospective analysis of patients undergoing CABG in 1999–2000 suggested that female sex was an independent predictor of increased perioperative mortality, even after adjusting for all comorbidities.[39] Despite this seemingly high perioperative mortality, a number of studies suggest that long-term survival (2.6 to 10 years) was reported similar between sexes after risk variable adjustment, but nevertheless women were likely to remain symptomatic from angina and subsequent heart failure.

On the other hand, one subset analysis from the BARI registry (patients enrolled from 1988 to 1991 and majority with preserved EF) reported better outcome in women.[38] The in-hospital mortality was similar between sexes, and female sex was an independent predictor

of better 5-year survival in both of the CABG and PTCA groups, after adjusting for multiple risk variables.[38] Whether an improvement in surgical technique has added to a better survival has not been examined but could account for differences across time.

Data on patients with impaired ventricular function undergoing CABG have been quite limited, as most patients in previous trials or retrospective cohorts had preserved EF. In the CASS trial, only 160 patients (20.5%) had EF 34–50% and of those only 5% were women.[46] The CABG Patch trial included 900 patients with an EF≤35%, and of those 15.7% were women. The 2-year all-cause mortality was higher in CABG Patch (22%) than STICH (15.1% in women, 20.9% in men), as well as re-hospitalization rates. This could be a result of better underlying HF medical therapy and possible advances in surgical technique over time. For example, the CABG Patch cohort was sub-optimally medicated for HF with beta-blocker, ACEI and lipid-lowering agents in comparison to STICH. Both of these studies showed that female sex was not associated with increased mortality.

Limitations

This analysis of the STICH Hypothesis 1 study by sex has several limitations including its post hoc nature. Women and men had markedly different baseline characteristics. The sex difference on clinical outcomes was assessed by Cox model after adjusting for key baseline characteristics. Moreover, the number of women represented was small. Some patients may have been excluded or never offered the study due to symptoms or the inherent bias by their providers or from the literature available at the time STICH was initiated. Some of these biases can include older data showing a higher mortality in women after revascularization and concern about the background comorbidities making these women worse candidates as a “fait accompli”. Additionally, there was an exclusion criterion that if angina symptoms were Class III–IV, the clinician could decide against randomization in Hypothesis 1. This inclusion/exclusion may have also precluded more symptomatic women from being enrolled. In STICH, the inclusion and exclusion criteria added to a protocolized application of medical therapy may have made the women more similar to their male counterparts and received better medical therapy when compared to cohort studies without those stipulations. Others have reported a lower use of medical therapy in women with CAD with less CVD risk stratification.[47] Nonetheless, the value of the data is the prospective inclusion of patients with a solid protocol and collection of large amounts of baseline characteristics allowing comparisons between sexes. In addition, the proportion of women with CAD and reduced LV function enrolled in more contemporary coronary revascularization trials remained very low 1–2 % (FREEDOM, BEST, EXCEL).[48–50] While the number of women enrolled in the STICH trial was low (n=148, 12%), it is comparable to more recent trials and provides probably the largest cohort for analysis.

Conclusions

In summary, this subset analysis of the STICH Hypothesis 1 population suggested that while women appeared to have higher preoperative risk profiles at baseline, when randomized to CABG + MED vs. MED alone treatment, there was no significant interaction between sex and treatment group in all-cause mortality, CV mortality, CV hospitalization or surgical

deaths in patients with ischemic LV dysfunction. Mechanisms responsible for this observation are speculative. However, regardless of mechanisms, these findings carry significant implications for clinical practice in the future. Sex should not influence treatment decisions regarding CABG in these patients.

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Clinical trial registration: ClinicalTrials.gov#NCT00023595; www.stichtrial.org

Abbreviations

ACEI	angiotensin-converting-enzyme inhibitor
ARB	angiotensin II receptor blocker
BARI	bypass angioplasty revascularization investigation
BEST	beta-blocker evaluation in survival trial
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CASS	Coronary Artery Surgery Study
CS	Canadian Cardiovascular Society
CI	confidence interval
CHARM	candesartan in heart failure - assessment of mortality and morbidity
CV	cardiovascular
EDVI	end diastolic volume index
EF	ejection fraction
ESVI	end systolic volume index
eGFR	estimated glomerular filtration rate
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training

HFrEF	heart failure with reduced ejection fraction
HRQoL	health status related quality of life
HR	hazard ratio
ICD	Implantable cardioverter defibrillator
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAD	left anterior descending artery
LV	left ventricle
MED	medical therapy
MERIT-HF	metroprolol CR/XL randomized intervention trial in congestive heart failure
MI	myocardial infarct
NHLBI	National Heart, Lung, and Blood Institute
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
STICH	Surgical Treatment for Ischemic Heart Failure Trial

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Clinical Perspective

What is new?

- Studies have shown sex-specific differences regarding CAD and heart failure.
- Whether these differences affect the benefit of CABG in patients with ischemic LV dysfunction has not been studied prospectively.
- Our study examined the association of sex on the long-term benefit of CABG in patients enrolled in the prospective Surgical Treatment for Ischemic Heart Failure Study (STICH) trial.
- This is the largest prospectively collected group of women with impaired ventricular function and coronary artery disease enrolled in a protocol-driven trial.

What are the clinical implications?

- Sex is not associated with the effect of CABG on all-cause mortality, CV mortality, CV hospitalization or surgical deaths in patients with ischemic LV dysfunction.
- When assessing revascularization strategy in a patient with ischemic heart failure with LV dysfunction, although women may appear to have seemingly high preoperative risks, sex should not influence treatment decisions regarding CABG in these patients.
- Clinicians should base their decision to recommend CABG to women not based on their baseline risk factors or perceptions of poor outcome, but on the data presented here.

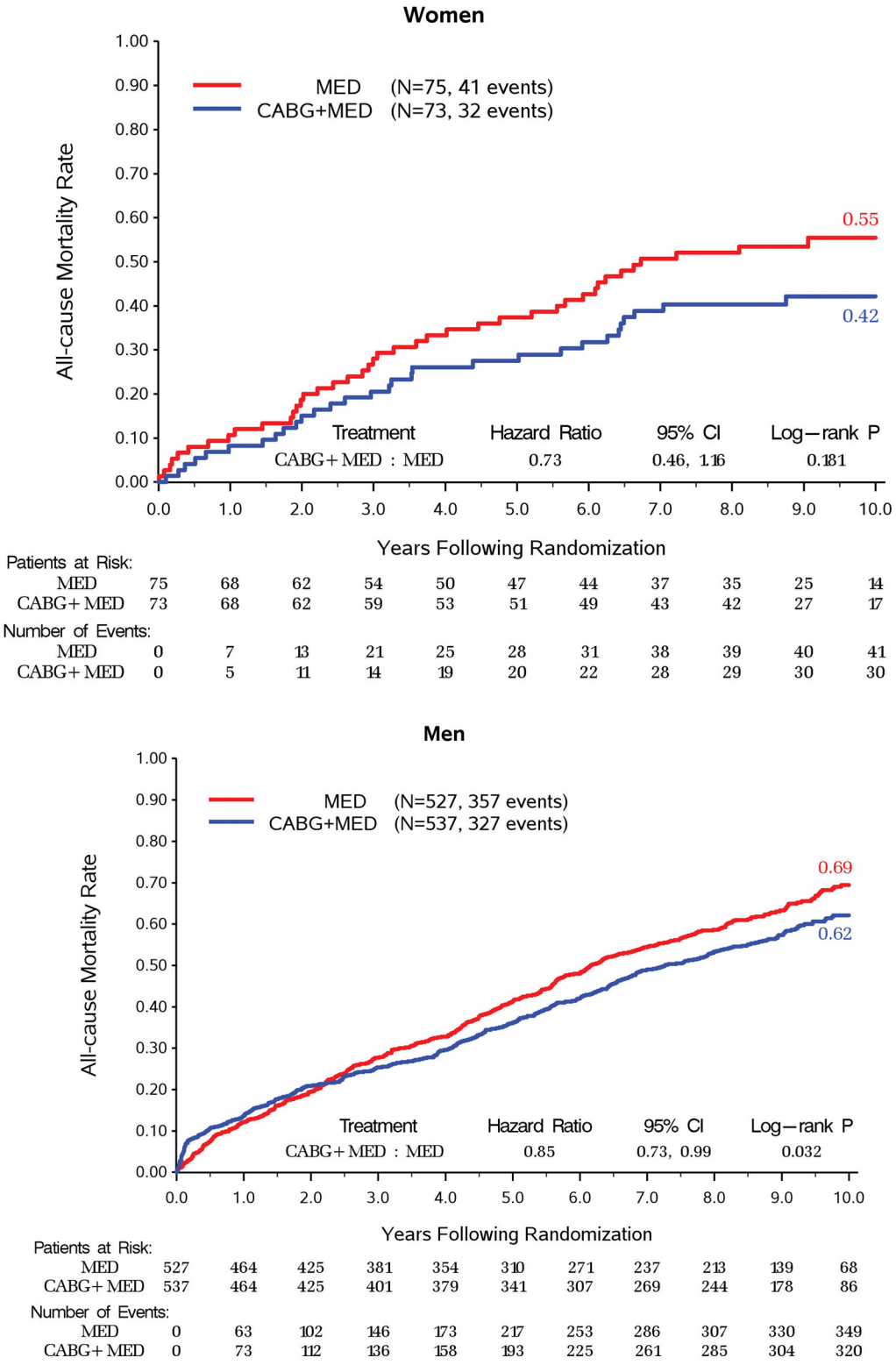

Figure 1. Kaplan-Meier Rates of All-cause Mortality by Randomized Treatment for Women and Men

A. Kaplan-Meier Rates of All-cause Mortality by Randomized Treatment for Women.

B. Kaplan-Meier Rates of All-cause Mortality by Randomized Treatment for Men. Interaction P-value = 0.495

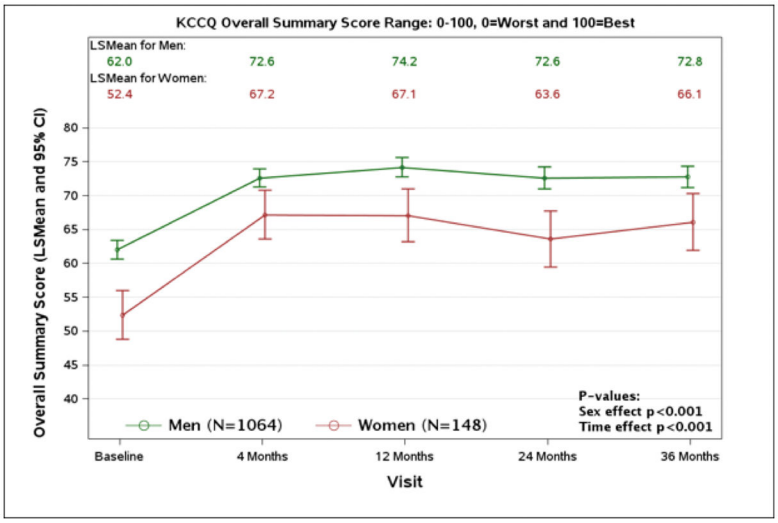

Figure 2.
Kansas City Cardiomyopathy Questionnaire Scores by Sex Group

Table 1

Baseline Characteristics of the Patients

	Women (n=148)	Men (n=1064)	P-value
Demographics			
Age, years	63.4 (54.4,66.4)	59.3 (53.5, 66.9)	0.016
White	71.6%	67.8%	0.345
BMI, kg/m^2	27.9 (24.6, 32.5)	26.7 (23.9, 29.5)	0.001
BSA, m^2	1.79 (1.64, 1.92)	1.93 (1.79, 2.07)	<0.0001
Medical History			
Previous MI	75.7%	77.3%	0.668
Diabetes	55.4%	37.2%	<0.0001
Stroke	8.1%	7.5%	0.800
Hypertension	70.9%	58.6%	0.004
Hyperlipidemia	70.3%	58.9%	0.008
Current Smoker	13.5%	21.8%	0.020
Peripheral Vascular Disease	14.9%	15.2%	0.909
Chronic Renal insufficiency	7.4%	7.8%	0.873
Atrial flutter/fibrillation	8.8%	13.2%	0.133
Depression	10.8%	5.6%	0.015
Performed 6 min walk test	83.8%	86.9%	0.303
Previous CABG	0%	3.4%	0.017
Previous PCI	16.9%	12.3%	0.119
ICD	1.4%	2.5%	0.567
Mitral valve repair or replacement	0%	0.4%	1.000
Pacemaker for heart rate	1.4%	1.5%	1.000
Pacemaker for resynchronization	0%	0.7%	1.000
CCS Angina Class			0.514
No angina	33.1%	36.9%	
I	18.2%	15.0%	

	Women (n=148)	Men (n=1064)	P-value
II	42.6%	43.4%	
III	4.7%	3.9%	
IV	1.4%	0.8%	
Highest NYHA Heart Failure Class			0.005
I	5.4%	5.7%	
II	28.4%	37.2%	
III	43.9%	44.6%	
IV	22.3%	12.4%	
Advanced HF (Class III/IV)	66.2%	57.0%	0.034
Distance walked in 6 minute walk test, m	300 (220, 370)	350 (270, 410)	<0.0001
KCCQ Overall Summary Score	51 (33, 69)	63 (46, 80)	<0.0001
Labs/Biomarkers			
Hemoglobin, g/dL	12.6 (11.6, 14.0)	14.0 (12.9, 15.0)	<0.0001
eGFR, mL/min/1.73^2	83.8 (70.0, 89.6)	91.2 (73.0, 106.4)	<0.0001
BNP, pg/mL	416 (191, 605)	310 (180, 559)	0.163
Medication Use at Baseline			
Beta blocker	85.8%	85.4%	0.905
ACE inhibitor	73.0%	83.5%	0.002
Angiotensin Receptor blocker	14.9%	8.7%	0.017
ACE inhibitor or ARB	85.1%	90.1%	0.063
Statin	81.8%	81.0%	0.829
Antiarrhythmic	7.4%	11.0%	0.186
Amiodarone	6.8%	10.2%	0.192
Digoxin	13.5%	21.1%	0.030
Aspirin	80.4%	83.0%	0.437
Warfarin	6.8%	11.0%	0.115
Clopidogrel	19.6%	16.8%	0.402
Loop diuretic	68.9%	64.8%	0.326
Potassium sparing diuretic	45.3%	46.0%	0.875

	Women (n=148)	Men (n=1064)	P-value
Nitrate	54.1%	53.2%	0.853
Insulin	27.0%	14.8%	<0.0001
Oral diabetic agent	29.1%	22.8%	0.100

Median (twenty-fifth, seventy-fifth percentiles) for continuous variables. BUN, blood urea nitrogen; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate (based on Mayo quadratic formula); ICD indicates Implantable cardioverter defibrillator; MI, myocardial infarct; PCI, percutaneous coronary intervention.

Table 2

Baseline Left Ventricular Function and Coronary Anatomy

	Women (n=148)	Men (n=1064)	P-value
LV Function			
LVEF, %	30.0 (25.0, 35.6)	27.0 (22.0, 33.0)	0.0001
ESVI, mL/m^2	70.0 (53.0, 89.3)	80.2 (62.5, 102.6)	<0.0001
EDVI, mL/m^2	97.4 (79.1, 119.2)	113.9 (91.1, 141.8)	<0.0001
Anterior akinesis or dyskinesis	43.0 (29.0, 57.0)	43.0 (25.0, 57.0)	0.270
Mitral Regurgitation			0.026
None or trace	27.7%	*37.1%*	
Mild	50.7%	45.1%	
Moderate	16.9%	14.7%	
Severe	4.7%	3.0%	
Number of vessels with ≥75% stenosis			0.617
None	2.7%	2.0%	
1	29.1%	22.5%	
2	29.1%	39.4%	
3	39.2%	36.1%	
Multi-vessel disease	68.2%	75.5%	0.056
Left main stenosis ≥50%	3.4%	2.5%	0.581
Proximal LAD ≥75%	64.2%	68.8%	0.262

Median (twenty-fifth, seventy-fifth percentiles) for continuous variables. Clinical values are the best available data reported by participating sites. EDVI, end diastolic volume index; ESVI, end systolic volume index; LAD, left anterior descending artery; LVEF indicates left ventricular ejection fraction.

Table 3

Clinical Event Rate and Hazard Ratio for Women versus Men

Clinical Event	Women (N=148)			Men (N=1064)			Model	Hazard Ratio (95% CI)	P-value
	N (%) of Events	10-Year KM Rate* (%) (95% CI)	Event Rate per person-year	N (%) of Events	10-Year KM Rate* (%) (95% CI)	Event Rate per person-year			
All-cause Mortality	73 (49.3)	49.0 (40.8, 57.3)	0.073	684 (64.3)	65.8 (62.7, 68.8)	0.105	Unadjusted	0.70 (0.55, 0.89)	0.003
							Adjusted†	0.67 (0.52, 0.86)	0.002
Cardiovascular Mortality	48 (32.4)	34.3 (26.3, 42.3)	0.048	496 (46.6)	52.3 (48.9, 55.8)	0.076	Unadjusted	0.64 (0.48, 0.86)	0.003
							Adjusted†	0.65 (0.48, 0.89)	0.006
Mortality or Cardiovascular Hospitalization	112 (75.7)	76.6 (68.5, 84.6)	0.111	879 (82.6)	85.2 (82.2, 88.2)	0.135	Unadjusted	0.87 (0.72, 1.06)	0.180
							Adjusted†	0.86 (0.70, 1.05)	0.144
Sudden Cardiac Death	21 (14.2)	17.6 (10.7, 24.5)	0.021	249 (23.4)	30.2 (26.8, 33.7)	0.038	Unadjusted	0.56 (0.36, 0.87)	0.011
							Adjusted†	0.62 (0.39, 0.97)	0.038
Heart Failure Death	10 (6.8)	7.5 (2.7, 12.3)	0.010	148 (13.9)	21.9 (18.5, 25.4)	0.023	Unadjusted	0.44 (0.23, 0.83)	0.012
							Adjusted†	0.40 (0.21, 0.77)	0.007

*10-year KM Rate=Kaplan-Meier estimates of event rate at 10 years after randomization.

†The adjustment variables include treatment, age, race, HF class at baseline, history of MI, previous revascularization, number of diseased vessels, baseline ejection fraction, chronic renal insufficiency, history of atrial flutter/fibrillation, mitral regurgitation, history of stroke, hemoglobin and hyperlipidemia.

Table 4

Clinical Event Rate for Women and Men in Different Treatment Groups

	Women			Men		
Clinical Event	**CABG + MED (N=73)**	**MED (N=75)**	**Total (N=148)**	**CABG + MED (N=537)**	**MED (N=527)**	**Total (N=1064)**
All-cause Mortality	32 (43.8)	41 (54.7)	73 (49.3)	327 (60.9)	357 (67.7)	684 (64.3)
Cardiovascular Mortality	19 (26.0)	29 (38.7)	48 (32.4)	228 (42.5)	268 (50.9)	496 (46.6)
Mortality or Cardiovascular Hospitalization	50 (68.5)	62 (82.7)	112 (75.7)	417 (77.7)	462 (87.7)	879 (82.6)
Sudden Cardiac Death	10 (13.7)	11 (14.7)	21 (14.2)	106 (19.7)	143 (27.1)	249 (23.4)
Heart Failure Death	3 (4.1)	7 (9.3)	10 (6.8)	63 (11.7)	85 (16.1)	148 (13.9)