Sex Difference in Patients With Ischemic Heart Failure Undergoing Surgical Revascularization
Results From the STICH Trial (Surgical Treatment for Ischemic Heart Failure)

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 dysfunction enrolled in the prospective STICH trial (Surgical Treatment for Ischemic Heart Failure Study).

METHODS: The STICH trial randomized 1212 patients (148 [12%] women and 1064 [88%] men) with coronary artery disease and left ventricular ejection fraction ≤35% to CABG+medical therapy (MED) versus MED alone. Long-term (10-year) outcomes with each treatment were compared according to sex.

RESULTS: At baseline, women were older (63.4 versus 59.3 years; \(P=0.016\)) with higher body mass index (27.9 versus 26.7 kg/m\(^2\); \(P=0.001\)). Women had more coronary artery disease risk factors (diabetes mellitus, 55.4% versus 37.2%; hypertension, 70.9% versus 58.6%; hyperlipidemia, 70.3% versus 58.9%) except for smoking (13.5% versus 21.8%) and had lower rates of prior CABG (0% versus 3.4%; all \(P<0.05\)) than men. Moreover, women had higher New York Heart Association class (class III/IV, 66.2% versus 57.0%), lower 6-minute walk capacity (300 versus 350 m), and lower Kansas City Cardiomyopathy Questionnaire overall summary scores (51 versus 63; all \(P<0.05\)). Over 10 years of follow-up, all-cause mortality (49.0% versus 65.8%; adjusted hazard ratio, 0.67; 95% confidence interval, 0.52–0.86; \(P=0.002\)) and cardiovascular mortality (34.3% versus 52.3%; adjusted hazard ratio, 0.65; 95% confidence interval, 0.48–0.89; \(P=0.006\)) were significantly lower in women compared with men. Over 10 years of follow-up, all-cause mortality (49.0% versus 65.8%; adjusted hazard ratio, 0.67; 95% confidence interval, 0.52–0.86; \(P=0.002\)) and cardiovascular mortality (34.3% versus 52.3%; adjusted hazard ratio, 0.65; 95% confidence interval, 0.48–0.89; \(P=0.006\)) were significantly lower in women compared with men. With randomization to CABG+MED versus MED treatment, there was no significant interaction between sex and treatment group in all-cause mortality, cardiovascular mortality, or the composite of all-cause mortality or cardiovascular hospitalization (all \(P>0.05\)). In addition, surgical deaths were not statistically different (1.5% versus 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 versus MED on all-cause mortality, cardiovascular mortality, the composite of death or cardiovascular hospitalization, or surgical deaths in patients with ischemic left ventricular dysfunction. Thus, sex should not influence treatment decisions about CABG in these patients.


Key Words: coronary artery bypass ■ heart failure ■ women

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Surgical Revascularization

Clinical Perspective

What Is New?

- Studies have shown sex-specific differences for coronary artery disease and heart failure.
- Whether these differences affect the benefit of coronary artery bypass grafting (CABG) in patients with ischemic left ventricular dysfunction has not been studied prospectively.
- Our study examined the association of sex and the long-term benefit of CABG in patients enrolled in the prospective STICH trial (Surgical Treatment for Ischemic Heart Failure).
- 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, cardiovascular mortality, cardiovascular hospitalization, or surgical deaths in patients with ischemic left ventricular dysfunction.
- In the assessment of revascularization strategy in a patient with ischemic heart failure with left ventricular dysfunction, although women may appear to have seemingly high preoperative risks, sex should not influence treatment decisions about CABG in these patients.
- Clinicians should base their decision to recommend CABG to women not on their baseline risk factors or perceptions of poor outcome, but on the data presented here.

Ex-specific differences have been recognized with respect to prevalence, pathogenesis, and prognosis of coronary artery disease (CAD) and ischemic heart failure (HF). Despite having a lower burden of obstructive CAD by coronary angiography and better left ventricular (LV) ejection fraction (EF) compared with men, women with CAD and ischemic HF are usually more symptomatic and have lower functional capacity, worse quality of life, a higher rate of ischemia, and possibly a higher mortality rate after myocardial infarction, all of which could lead to higher healthcare costs associated with frequent office visits and hospitalization. In fact, CAD is the leading cause of death and HF is the leading cause of hospitalization in women >65 years of age. Despite these facts, studies have suggested that physicians are less likely to pursue an aggressive approach to CAD in women than in men. 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—for example, the EuroScore II, the Society of Thoracic Surgeons score, the modified Parsonnet score, New York’s Cardiac Surgery Reporting System score, and the Northern New England Cardiovascular Disease Study Group score.

The STICH trial (Surgical Treatment for Ischemic Heart Failure Study) 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 the STICHES trial (Surgical Treatment for Ischemic Heart Failure Extension Study) can provide additional information based on sex. Therefore, the objective of this study was to investigate the association of sex and the long-term benefit of coronary artery bypass grafting (CABG) in patients enrolled in the prospective STICH trial.

Methods

The STICH/STICHES data, analytical methods, and study results are available for review online (URL: ClinicalTrials.gov. Unique identifier: NCT00023595). The raw data sets and analysis data sets have been deidentified and submitted to the National Heart, Lung, and Blood Institute and will be published on the National Heart, Lung, and Blood Institute’s BioLINCC website in the future.

Study Population

The design of the STICH trial has been described previously. In brief, STICH was a prospective, multicenter, randomized controlled trial sponsored by the National Heart, Lung, and Blood Institute that recruited 1212 patients with CAD and LVEF ≤35% from 99 sites in 22 countries between 2002 and 2007. The STICH hypothesis examined the question of whether CABG with optimized medical therapy (MED) improves long-term survival compared with MED alone. The primary results of hypothesis 1 have been published. Detailed inclusion and exclusion criteria have also been previously described. The National Heart, Lung, and Blood Institute 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 with the Wilcoxon rank-sum test for continuous variables and the chi² test or Fisher exact test for categorical variables. Cumulative event rates of clinical outcomes (all-cause mortality, cardiovascular mortality, mortality or cardiovascular hospitalization, sudden cardiac death, and HF death) were calculated for different patient groups with the Kaplan-Meier method. 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
end point of mortality or cardiovascular hospitalization, the numerator in the event rate per person-year includes only the first event that a patient experienced. The effects of treatment as randomized (CABG+MED versus MED alone) on clinical outcomes were statistically assessed in male and female patients with the log-rank test and summarized with hazard ratios (HRs) and 95% confidence intervals (CIs) generated from the Cox proportional hazards regression model. The Cox model was also used to assess whether the effect of CABG+MED versus MED was different in women compared with men by examining the interaction between treatment and sex for each clinical end point. For comparing men and women directly with respect to clinical outcomes, the Cox model was used, with adjustment for key prognostic baseline characteristics (including age, race, HF class at baseline, history of myocardial infarction, previous revascularization, number of diseased vessels, EF, chronic renal insufficiency, history of atrial flutter/fibrillation, mitral regurgitation, history of stroke, hemoglobin, and hyperlipidemia) and randomized treatment (CABG+MED versus 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 with 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 with SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

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 men (median, 63.4 versus 59.3 years; P=0.016), were more likely to be white, and had a higher body mass index (median, 27.9 versus 26.7 kg/m²; P=0.001). More risk factors for CAD were reported in women (diabetes mellitus, 55.4% versus 37.2%, P<0.001; hypertension, 70.9% versus 58.6%, P=0.004; hyperlipidemia, 70.3% versus 58.9%, P=0.008) except for smoking, whereas women were less likely to have had prior CABG (0% versus 3.4%; P=0.017). In addition, women were more likely to report depression and had worse baseline renal function (median glomerular filtration rate, 83.8 versus 91.2 mL-min⁻¹·1.73 m²; P<0.001).

Baseline LV 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 laboratories. The rates of triple-vessel disease, left main stenosis ≥50%, and proximal left anterior descending stenosis ≥75% were not statistically different. The me-

### Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>Women (n=148)</th>
<th>Men (n=1064)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63.4 (54.4, 66.4)</td>
<td>59.3 (53.5, 66.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>White, %</td>
<td>71.6</td>
<td>67.8</td>
<td>0.345</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9 (24.6, 32.5)</td>
<td>26.7 (23.9, 29.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.79 (1.64, 1.92)</td>
<td>1.93 (1.79, 2.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>75.7</td>
<td>77.3</td>
<td>0.668</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>55.4</td>
<td>37.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>8.1</td>
<td>7.5</td>
<td>0.800</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.9</td>
<td>58.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>70.3</td>
<td>58.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13.5</td>
<td>21.8</td>
<td>0.020</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>14.9</td>
<td>15.2</td>
<td>0.909</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>7.4</td>
<td>7.8</td>
<td>0.873</td>
</tr>
<tr>
<td>Atrial flutter/fibrillation</td>
<td>8.8</td>
<td>13.2</td>
<td>0.133</td>
</tr>
<tr>
<td>Depression</td>
<td>10.8</td>
<td>5.6</td>
<td>0.015</td>
</tr>
<tr>
<td>Performed 6-min walk test</td>
<td>83.8</td>
<td>86.9</td>
<td>0.303</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>0</td>
<td>3.4</td>
<td>0.017</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>16.9</td>
<td>12.3</td>
<td>0.119</td>
</tr>
<tr>
<td>ICD</td>
<td>1.4</td>
<td>2.5</td>
<td>0.567</td>
</tr>
<tr>
<td>Mitral valve repair or replacement</td>
<td>0</td>
<td>0.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Pacemaker for heart rate</td>
<td>1.4</td>
<td>1.5</td>
<td>1.000</td>
</tr>
<tr>
<td>Pacemaker for resynchronization</td>
<td>0</td>
<td>0.7</td>
<td>1.000</td>
</tr>
<tr>
<td>CCS angina class, %</td>
<td></td>
<td></td>
<td>0.514</td>
</tr>
<tr>
<td>No angina</td>
<td>33.1</td>
<td>36.9</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>18.2</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>42.6</td>
<td>43.4</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4.7</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Highest NYHA heart failure class, %</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>I</td>
<td>5.4</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28.4</td>
<td>37.2</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>43.9</td>
<td>44.6</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>22.3</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>Advanced HF (class III/IV), %</td>
<td>66.2</td>
<td>57.0</td>
<td>0.034</td>
</tr>
<tr>
<td>Distance walked in 6-min walk test, m</td>
<td>300 (220, 370)</td>
<td>350 (270, 410)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KCCQ overall summary score</td>
<td>51 (33, 69)</td>
<td>63 (46, 80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Laboratory/biomarker values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.6 (11.6, 14.0)</td>
<td>14.0 (12.9, 15.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

(Continued)
dian LVEF (30.0% versus 27.0%; P=0.0001) was higher in women.

**Symptoms**

There was no significant difference in symptoms of angina between sexes by the Canadian Cardiovascular Society angina score (Table 1). The percentage of patients with advanced HF class (by highest New York Heart Association class during the 3-month period before randomization) was higher in women than men (66.2% versus 57.0%; P=0.034). In addition, women had a lower functional capacity as noted by the 6-minute walk distance (median, 300 versus 350 m; P<0.0001; Table 1). Health status–related quality of life measured by KCCQ overall summary score was lower in women at baseline (51 versus 63; P<0.0001).

**Medical Therapy**

More men than women were on angiotensin-converting enzyme inhibitors (ACEIs; 83.5% versus 73.0%; P=0.002). However, a higher proportion of women were receiving angiotensin II receptor blockers (ARBs), thus making the use of ACEI or ARBs relatively similar between sexes (Table 1). β-Blocker use was also not statistically different between the 2 groups. Although digoxin was more commonly used in men (21.1% versus 13.5%; P=0.030), more women were on insulin treatment (27.0% versus 14.8%; P<0.0001).

**Clinical Outcomes**

Over a median follow-up of 9.8 years, women had significantly lower all-cause mortality compared with men (73 of 148 [49.3%] versus 684 of 1064 [64.3%]; adjusted HR, 0.67; 95% CI, 0.52–0.86; P=0.002) and cardiovascular mortality (48 of 148 [32.4%] versus 496 of 1064 [46.6%]; adjusted HR, 0.65; 95% CI, 0.48–0.89; P=0.006; Table 3). With randomization to CABG + MED versus MED treatment, there was no significant interaction between sex and treatment group in all-cause mortality (P=0.495; Figure 1), cardiovascular mortality (P=0.386), or mortality or cardiovascular hospitalization (P=0.176). For both women and men, patients receiving CABG+MED had lower event rates than patients receiving MED (Table 4) for all-cause mortality (32 of 771 [4.2%] versus 135 of 1064 [12.7%]; adjusted HR, 0.33; 95% CI, 0.21–0.52; P<0.0001).
tus at baseline, female sex is not associated with the cardiovascular comorbidities and worse functional status. This is the first subanalysis of a contemporary trial based on predominantly male subjects in cardiovascular clinical trials have been extrapolated to women in practice, historically, because of 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 subanalysis of a contemporary trial to suggest that, despite the fact that women have more cardiovascular comorbidities and worse functional status at baseline, female sex is not associated with the effect of CABG on all-cause mortality, cardiovascular mortality, or surgical death rates in these patients. Furthermore, women had significantly lower rates of long-term all-cause mortality and cardiovascular mortality than men.

**Table 3. Clinical Event Rate and Hazard Ratio for Women Versus Men**

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Women (n=148)</th>
<th>Men (n=1064)</th>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events (%)</td>
<td>10-y KM Rate* (95% CI), %</td>
<td>Event Rate per Person-Year</td>
<td>No. of events (%)</td>
<td>10-y KM Rate* (95% CI), %</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>73 (49.3)</td>
<td>49.0 (40.8–57.3)</td>
<td>0.073</td>
<td>684 (64.3)</td>
<td>65.8 (62.7–68.8)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>48 (32.4)</td>
<td>34.3 (26.3–42.3)</td>
<td>0.048</td>
<td>496 (46.6)</td>
<td>52.3 (48.9–55.8)</td>
</tr>
<tr>
<td>Mortality or cardiovascular hospitalization</td>
<td>112 (75.7)</td>
<td>76.6 (68.5–84.6)</td>
<td>0.111</td>
<td>879 (82.6)</td>
<td>85.2 (82.2–88.2)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>21 (14.2)</td>
<td>17.6 (10.7–24.5)</td>
<td>0.021</td>
<td>249 (23.4)</td>
<td>30.2 (26.8–33.7)</td>
</tr>
<tr>
<td>HF death</td>
<td>10 (6.8)</td>
<td>7.5 (2.7–12.3)</td>
<td>0.010</td>
<td>148 (13.9)</td>
<td>21.9 (18.5–25.4)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HF, heart failure; and KM, Kaplan-Meier.

*The 10-year KM rate is the estimate of the event rate 10 years after randomization.

†The adjustment variables include treatment, age, race, HF class at baseline, history of myocardial infarction, 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.

DISCUSSION

The STICH trial is the first and only contemporary randomized clinical trial designed to compare CABG plus intensive HF MED with intensive HF MED only in patients with severe LV dysfunction in an era when an evidence-based HF medical regimen is available. Historically, because of 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 subanalysis of a contemporary trial to suggest that, despite the fact that women have more cardiovascular comorbidities and worse functional status at baseline, female sex is not associated with the effect of CABG on all-cause mortality, cardiovascular mortality, or surgical death rates in these patients. Furthermore, women had significantly lower rates of long-term all-cause mortality and cardiovascular mortality than men.

**Baseline Clinical Characteristics**

In light of these findings, a brief review of baseline demographics compared with other HF studies is relevant. Baseline characteristics of the STICH hypothesis 1 cohort are similar to those of other studies such as CASS (Coronary Artery Surgery Study), CABG Patch, CHARM (Candesartan in Heart Failure—Assessment of Mortality and Morbidity), and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), with a higher prevalence of comorbidities in women compared with men. In addition, in the STICH trial, women were more likely to experience depression and had lower KCCQ overall scores. In comparison, the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) and the BEST trial (β-Blocker Evaluation in Survival Trial) showed that women were younger and had a lower or the same prevalence of hypertension and diabetes mellitus. Moreover, in HF-ACTION, the scores on the Beck Depression Inventory II (8 versus 8) and the KCCQ (68 versus 69) were similar, as was history of depression (21% versus 22%), in men and women. It was speculated that this seeming inconsistency could be caused by the recollection of a history of hypertension or diabetes mellitus in a younger cohort, in whom these comorbidities may not have manifested yet. In addition, these medical and exercise therapy trials included a large portion of patients with nonischemic HF; in contrast, the
STICH trial focused on ischemic HF, which may explain the high prevalence of cardiovascular comorbidities in the STICH population.

Ischemic HF Medical Therapy
The STICH trial is a contemporary trial in which participants were well medicated with evidence-based HF medical therapy. More than 80% of patients in the STICH trial were treated with a β-blocker, ACEI, or ARB; lipid-reducing therapy; and antiplatelet therapy. In addition, >45% of patients received potassium-sparing diuretics. Overall, there was no significant sex difference in MED for ischemic HF at baseline. Our results showed that a lower proportion of women received ACEIs whereas a higher proportion of women received ARBs. However, the combined proportion receiving ACEIs or ARBs was similar between sexes. This pattern is consistent with observations from prior trials, probably related to the higher prevalence of ACEI-induced cough in women than in men.1,8

Clinical Outcome of CABG
Given the distinct differences in sex hormones and their effects on the cardiovascular disease process, women and men may respond to therapies, including revascularization, differently.1,7,29–31 Some studies have shown higher
rates of mortality and complications in women compared with 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. Female participants were more likely to be older, had significantly greater preoperative comorbidities (including hypertension, hyperlipidemia, diabetes mellitus, unstable angina, congestive HF, 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% versus 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% versus 7.9%; \( P = 0.41 \)).27,44 A meta-analysis of 20 studies reported a higher mortality in women after CABG not only at short-term follow-up but also at midterm and long-term follow-up.42 Recent studies from the 1990s and 2000s attributed this elevated mortality to the higher prevalence of preoperative 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 to 2000 suggested that female sex was an independent predictor of increased perioperative mortality, even after adjustment for all comorbidities.39 Despite this seemingly high perioperative mortality, a number of studies suggest that long-term survival (2.6–10 years) was reported to be similar between the sexes after risk variable adjustment. Nevertheless, women were likely to remain symptomatic from angina and subsequent HF.

On the other hand, 1 subset analysis from the BARI registry (Bypass Angioplasty Revascularization Investigation; patients enrolled from 1988–1991 and majority with preserved EF) reported better outcomes in women.38 The inhospital mortality was similar between sexes, and female sex was an independent predictor of better 5-year survival in both the CABG and percutaneous coronary angioplasty groups after adjustment 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.

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CABG+MED (n=73)</td>
<td>MED (n=75)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>32 (43.8)</td>
<td>41 (54.7)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>19 (26.0)</td>
<td>29 (38.7)</td>
</tr>
<tr>
<td>Mortality or cardiovascular hospitalization</td>
<td>50 (68.5)</td>
<td>62 (82.7)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>10 (13.7)</td>
<td>11 (14.7)</td>
</tr>
<tr>
<td>HF death</td>
<td>3 (4.1)</td>
<td>7 (9.3)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; HF, heart failure; and MED, medical therapy.

Table 4. Clinical Event Rate for Women and Men in Different Treatment Groups

Figure 2. Kansas City Cardiomyopathy Questionnaire scores by sex group.

CABG indicates coronary artery bypass grafting; CI, confidence interval; and MED, medical therapy.
Data on patients with impaired ventricular function undergoing CABG have been quite limited because most patients in previous trials or retrospective cohorts had preserved EF. In the CASS trial, only 160 patients (20.5%) had an EF of 34% to 50%, and of those, only 5% were women. 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 in STICH (15.1% in women, 20.9% in men), as well as rehospitalization rates. This could be a result of better underlying HF MED and possible advances in surgical technique over time. For example, the CABG Patch cohort was suboptimally medicated for HF with β-blockers, ACEIs, and lipid-lowering agents compared with the STICH cohort. 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 in clinical outcomes was assessed by a Cox model after adjustment for key baseline characteristics. Moreover, the number of women represented was small. Some patients may have been excluded or never offered the study because of symptoms or the inherent bias by providers or from the literature available at the time STICH was initiated. 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. In addition, there was an exclusion criterion that if angina symptoms were class III to IV, the clinician could decide against randomization to CABG+MED versus MED alone, there was no significant interaction between sex and treatment group in all-cause mortality, cardiovascular mortality, cardiovascular 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 for CABG in these patients.
REFERENCES


6. Deleted in proofs.


20. The other authors. Change; Merck & Co; New Century Health; and Novartis. The other authors.


tation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or with-


37. Park DW, Kim YH, Yun SC, Ahn JH, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Sex difference in clinical outcomes after percutaneous coro-


pitals. Circulation. 2005;112(suppl 1):I323–I327. doi: 10.1161/CIRCULA-
TIONAHA.104.525139.


42. Alam M, BandealJ, Kayani WT, Ahmad W, Shahzad SA, Ijied H, Birna-
baum Y, Kleiman NS, Coselli JS, Ballantyne CM, Lakkis N, Virani SS. Com-


44. Myers WO, Blackstone EH, Davis K, Foster ED, Kaiser GC. CASS Registry long term surgical survival: Coronary Artery Surgery Study. J Am Coll Car-

45. Khan SS, Nessim S, Gray R, Czer LS, Chaux A, MattlOJ. Increased mortal-

46. Coronary Artery Surgery Study (CASS): a randomized trial of coronary ar-

47. Shah T, Palaskas N, Ahmed A. An update on gender disparities in coro-
s11883-016-0574-5.


50. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, Kan-
Sex Difference in Patients With Ischemic Heart Failure Undergoing Surgical Revascularization: Results From the STICH Trial (Surgical Treatment for Ischemic Heart Failure)

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