ORIGINAL RESEARCH

Sex Differences in Clinical Characteristics, Psychosocial Factors, and Outcomes Among Patients With Stable Coronary Heart Disease: Insights from the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) Trial

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***Background*—**Greater understanding of differences between men and women with coronary heart disease is needed.

***Methods and Results*—**In this post hoc analysis of the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial, we described psychosocial factors, treatments, and outcomes of men versus women with stable coronary heart disease and explored the association of sex with psychosocial characteristics and cardiovascular risk. Cox proportional hazards models were used to assess the relationship between sex and outcomes. Interactions among sex, psychosocial factors, and the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke were tested. Of 15 828 patients, 2967 (19%) were women. Among women, 21.2% felt often or always stressed at home (versus 9.8% of men), and 19.2% felt often or always sad or depressed (versus 10.1% of men; all $P<0.0001$). The median duration of follow-up was 3.7 years (25th–75th percentiles: 3.5–3.8 years). Use of evidence-based medications for coronary heart disease at baseline and 24 months was similar between sexes, as were event rates for all outcomes analyzed. In the multivariable model including psychosocial measures, female sex was associated with lower cardiovascular risk. There was a statistically significant interaction ($P=0.03$) such that the lower risk in women varied by depressive symptom frequency, whereby women who were more depressed had a risk similar to men.

***Conclusions*—**Female sex was independently associated with better long-term clinical outcomes, although this was modified by frequency of depressive symptoms. This suggests that emotional state may be an important target for improving outcomes in patients with coronary heart disease, specifically in women.

***Clinical Trial Registration*—**STABILITY ClinicalTrials.gov number (NCT00799903). **(*J Am Heart Assoc*. 2017;6:e006695. DOI: 10.1161/JAHA.117.006695.)**

Key Words: cardiovascular disease • depression • psychosocial factors • risk • sex

Sex differences in the prevalence, presentation, management, and prognosis of coronary heart disease (CHD) have been described frequently.[1–3] Female patients have more complex signs and symptoms of ischemia, and the variation in reproductive hormone levels may play a role in CHD pathophysiology and response to treatment. In both acute and chronic settings, several studies have shown that women, compared with men, are less aggressively treated with evidence-based therapies and less often undergo invasive procedures.[4–8] However, less is known about the relationship of

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Accompanying Tables S1 through S5 are available at http://jaha.ahajournals.org/content/6/9/e006695/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Women with coronary heart disease had more comorbidities and reported stress and depressive symptoms more frequently in this large trial.
- There were no differences between women and men regarding rates of coronary revascularization procedures during study follow-up or use of evidence-based medications, perhaps indicating improvements in clinical practice.
- Female sex was independently associated with better long-term clinical outcomes; this association was modified by frequency of depressive symptoms, such that as depressive symptoms became more frequent, the cardiovascular risk of women became similar to that of men.

What Are the Clinical Implications?

- Our results suggest that emotional state may be an important target for improving outcome in patients with coronary heart disease, particularly in women.

psychosocial factors, sex, and clinical outcomes among patients with CHD.[9–13] Greater understanding of clinical and psychosocial characteristics and their relationship with treatment and outcomes of men and women with stable CHD may provide insights into opportunities to improve care.

The STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial compared darapladib, an oral inhibitor of lipoprotein-associated phospholipase A_2, with placebo in patients with high-risk stable CHD.[14] This secondary analysis was planned to describe baseline characteristics, psychosocial factors, and treatments for CHD of men and women enrolled in this contemporary trial. We also aimed to explore the association of sex and clinical outcomes as well as the relationship among sex, psychosocial characteristics, and cardiovascular risk.

Methods

Study Design and Participants

The design and main findings of the STABILITY trial were published previously.[14] Briefly, STABILITY was a randomized, double-blind, controlled trial that enrolled patients with a history of CHD, including previous myocardial infarction (MI), previous percutaneous coronary intervention or coronary artery bypass grafting, or multivessel coronary disease confirmed by angiography, and on statin therapy unless contraindicated or not tolerated. In addition, at least one of the following risk factors was required for enrollment: age ≥60 years, diabetes mellitus requiring pharmacotherapy, moderate renal impairment, smoking ≥5 cigarettes per day at study entry or within the past 3 months, polyvascular arterial disease, poorly controlled hypertension, or high-density lipoprotein cholesterol <40 mg/dL. Patients were excluded if they had liver disease, severe renal dysfunction, history of nephrectomy or kidney transplantation, heart failure with New York Heart Association class III or IV, or severe asthma or if they had a percutaneous coronary intervention, coronary artery bypass grafting, or a major surgical procedure planned. Study participants were randomized to receive either a 160-mg oral dose of darapladib daily or placebo. The median duration of follow-up was 3.7 years (25th–75th percentiles: 3.5–3.8 years). The study was approved by the institutional review committee in each participating country, and all patients provided written informed consent.

Psychosocial Evaluation

In the STABILITY trial, psychosocial characteristics were collected at baseline using a questionnaire, including marital and work status, whether patients were living alone, and level of education. Information about frequency of stress at home and at work and depressive symptoms (feeling sad; low in spirits; depressed; or loss of interest in hobbies, work, or activities that previously gave pleasure) was also collected, with patients responding never/rarely, sometimes, often, or always.

Outcomes

The study's primary outcome was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Other outcomes of interest were cardiovascular death, stroke, nonfatal MI, all-cause death, urgent revascularization for myocardial ischemia, hospitalization for heart failure, and the composites of major coronary events (death from CHD, nonfatal MI, or urgent revascularization for myocardial ischemia) and total coronary events (death from CHD, nonfatal MI, hospitalization for unstable angina, or any coronary revascularization procedure). A clinical events classification committee, blinded to study assignment, adjudicated all end points according to prespecified criteria.

Statistical Analysis

Continuous variables are described as medians and 25th and 75th percentiles, whereas categorical variables are presented as frequencies and percentages. Baseline characteristics were compared between men and women, using the Wilcoxon rank sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Kaplan–Meier event rates by sex for each prespecified cardiovascular outcome are reported using the log-rank test for comparisons. An association between sex and feeling down or depressed with each

prespecified outcome was assessed using a Cox proportional hazards model. All modeling assumptions were tested, and transformations were performed when necessary. The interaction of sex, feeling down or depressed, and clinical outcomes was tested, and the results are presented both unadjusted and adjusted for age. An association between sex and cardiovascular outcomes was explored, adjusting for feeling down or depressed. Modeling assumptions of proportional hazards and linearity were tested. To assess linearity for continuous factors, linear models and models with cubic splines were generated. These models were assessed visually to explore whether transformation was needed. If the measurement was not linearly related, then a linear spline was modeled. The Akaike information criterion and the log likelihood χ^2 values of the linear and cubic splines were assessed to see whether the latter was reasonable to use. Schoenfeld residuals were assessed to confirm whether the assumption of proportional hazards was met. The χ^2 value is reported along with the degrees of freedom and *P* values as well as the hazard ratio (HR) for women versus men, with 95% confidence intervals (CIs). The relationship between several risk factors and the primary composite outcome (cardiovascular death, MI, or stroke) was explored in multivariable models. Three Cox proportional hazards models were generated. Model 1 included the qualifying criteria for entering in the trial, such as age, current smoking, history of polyvascular disease, diabetes mellitus, renal dysfunction, low high-density lipoprotein cholesterol, and randomized treatment. Model 2 included model 1 plus geographic region, and model 3 further included psychosocial characteristics (marital and work status, whether patients were living alone, frequency of stress at work and financial stress, and frequency of depressive symptoms). The *P* values and χ^2 values with degrees of freedom are reported to assess sex contribution to the multivariable model, compared with the other risk factors. HRs with 95% CIs were reported for the final multivariable model. Analyses were performed using SAS software, version 9.4 (SAS Institute). All tests were 2-sided, and $P<0.05$ was considered statistically significant, with no adjustment for multiple comparisons. All analyses were performed at the Duke Clinical Research Institute (Durham, NC).

Results

Clinical and Psychosocial Characteristics

Of the 15 828 participants in the STABILITY trial, 2967 (19%) were women. Of those, 77.5% were postmenopausal, 19.3% were of child-bearing age and unable to have children, and 3.2% were able to potentially bear a child. Baseline characteristics by sex are presented in Table 1. Women were older, had a higher body mass index, and were more likely to have a history of diabetes mellitus, hypertension, chronic kidney disease, and/or congestive heart failure than men. Men were more frequently current smokers and were more likely to have a history of prior MI or revascularization than women. Women had higher levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, and high-sensitivity C-reactive protein but lower levels of lipoprotein-associated phospholipase A_2 activity and a lower estimated glomerular filtration rate than men.

At study entry, 84.5% of men and 59.4% of women were married or living with a partner (Table 2). More women were widowed, divorced, or single. Overall, 22.4% of women and 11.3% of men were living alone. Men were more likely to have higher levels of education than women. Work status also differed, with 82.4% of women and 64.3% of men not currently working, with most being retired. Women were more likely to feel often or always stressed at home and to be more often under financial stress than men. In addition, women felt more often low in spirits or depressed than men.

Treatment of CHD

At baseline and after 24 months of follow-up, the rates of use of aspirin, $P2Y_{12}$ inhibitors, statins, beta blockers, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers did not differ significantly between men and women (Tables S1 and S2). Overall, 10.9% of men and 9.9% of women had undergone coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass grafting) by 3.7 years of follow-up ($P=0.11$).

Clinical Outcomes

Kaplan–Meier event rates of clinical outcomes among men and women are presented in Table 3, and Kaplan–Meier curves for the primary outcome among men and women are presented in Figure 1. There were no differences between sexes for any outcomes analyzed. In the model adjusted for frequency of feeling down or depressed, women had a lower risk of cardiovascular death (HR: 0.79; 95% CI, 0.65–0.98), all-cause death (HR: 0.81; 95% CI, 0.69–0.95), and total coronary events (HR: 0.90; 95% CI, 0.80–0.99) than men (all $P<0.05$; Table S3). By multivariable analysis, we observed in models 1 and 2 that several risk factors were associated independently with the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke, whereas female sex was not (Tables S4 and S5). In the full model (model 3), including psychosocial factors, we observed that female sex was associated with a lower risk of cardiovascular death, MI, or stroke (HR: 0.83; 95% CI, 0.71–0.96; $P=0.013$; Table 4).

A significant interaction of sex, frequency of feeling down or depressed, and the primary composite outcome was seen

Table 1. Baseline Characteristics

Characteristic	Men (n=12 861)	Women (n=2967)	*P* Value
Age, y	64.0 (58.0–71.0)	66.0 (61.0–72.0)	<0.001
Current smoker	2439 (19.0)	419 (14.1)	<0.001
Diabetes mellitus	4836 (37.6)	1300 (43.8)	<0.001
Hypertension	9011 (70.1)	2307 (77.8)	<0.001
Chronic kidney disease	3637 (28.3)	1152 (38.8)	<0.001
Congestive heart failure	2691 (20.9)	691 (23.3)	0.005
Prior MI	7654 (59.5)	1669 (56.3)	0.001
Prior revascularization	9756 (75.9)	2107 (71.0)	<0.001
Any history of prior stroke	790 (6.1)	185 (6.2)	0.85
Prior peripheral artery disease	440 (3.4)	111 (3.7)	0.39
Multivessel CHD	1913 (14.9)	477 (16.1)	0.10
Polyvascular disease	1912 (14.9)	460 (15.5)	0.381
Body mass index, kg/m^2	28.2 (25.6–31.5)	28.6 (25.3–32.6)	<0.001
Region of enrollment			<0.001
Asia/Pacific	2526 (19.6)	563 (19.0)	
Eastern Europe	2757 (21.4)	774 (26.1)	
North America	3330 (25.9)	693 (23.4)	
South America	937 (7.3)	262 (8.8)	
Western Europe	3311 (25.7)	675 (22.8)	
Baseline systolic blood pressure, mm Hg	131 (120–142)	130 (119–143)	0.57
Baseline LpPLA$_2$, μmol/min/L	177.2 (148.8–208.6)	150.4 (125.4–180.7)	<0.001
Baseline hs-CRP, mg/L	1.3 (0.6–2.9)	1.6 (0.8–3.8)	0.002
Baseline HDL cholesterol, mmol/L	1.1 (1.0–1.3)	1.3 (1.1–1.6)	<0.001
Baseline LDL cholesterol, mmol/L	2.1 (1.6–2.6)	2.2 (1.7–2.8)	<0.001
Baseline HbA1c,* %	7.0 (6.3–8.0)	7.2 (6.5–8.4)	<0.001
Baseline eGFR, mL/min/1.73 m^2	78.0 (66.0–90.0)	66.0 (60.0–78.0)	<0.001

Data provided as median (25th–75th percentiles) or n (%). CHD indicates coronary heart disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LpPLA$_2$, lipoprotein-associated phospholipase A$_2$; MI, myocardial infarction.*Among patients with diabetes mellitus.

(Figure 2). As the frequency of feeling down or depressed increased, the cardiovascular risk advantage in women was lost (*P*=0.03 for interaction). Consequently, in women feeling depressed more frequently, adjusted cardiovascular outcomes were similar in women and men. The same pattern was observed after adjusting for age and in the full model. Female patients had a statistically significant increase in cardiovascular risk as the frequency of depressive symptoms increased (HR of 1.21 [95% CI, 1.04–1.41] for increase in the frequency of depressive symptoms by 1 degree; HR of 1.47 [95% CI, 1.09–1.99] for increase in the frequency of depressive symptoms by 2 degrees; and HR of 1.79 [95% CI, 1.14–2.80] for the comparison between never/rarely feeling depressed and always feeling depressed; *P*=0.04 for interaction). The same association was not observed for men (HR of 1.02 [95% CI, 0.93–1.12] for increase in the frequency of depressive symptoms by 1 degree; HR of 1.05 [95% CI, 0.87–1.26] for increase in the frequency of depressive symptoms by 2 degrees; and HR of 1.07 [95% CI, 0.82–1.41] for the comparison between never/rarely feeling depressed and always feeling depressed).

Discussion

In a large contemporary CHD trial, we observed that women presented with more comorbidities and stress or depressive symptoms than men at study entry. Approximately 40% of women were widowed, divorced, or single, whereas the majority of men were married. In addition, more women were living alone and not currently working. Similar rates of use of

Table 2. Psychosocial Characteristics

Characteristic	Men (n=12 861)	Women (n=2967)	*P* Value
Marital status			<0.001
Married or living with a partner	10 701 (84.5)	1725 (59.4)	
Widowed	580 (4.6)	717 (24.7)	
Divorced or separated	771 (6.1)	284 (9.8)	
Single	606 (4.8)	176 (6.1)	
Lives alone	1423 (11.3)	648 (22.4)	<0.001
Not currently working	8124 (64.3)	2378 (82.4)	<0.001
Retired	6634 (52.5)	1781 (61.7)	
Education			<0.001
<9 y	2601 (20.6)	964 (33.4)	
≥9 y	10 026 (79.4)	1921 (66.6)	
"Have you felt stress at work?"*			0.24
Never/rarely	2015 (32.5)	289 (34.8)	
Sometimes	2694 (43.5)	333 (40.1)	
Often	1173 (18.9)	159 (19.2)	
Always	311 (5.0)	49 (5.9)	
"Have you felt stress at home?"			<0.001
Never/rarely	5505 (44.6)	873 (31.2)	
Sometimes	5630 (45.6)	1335 (47.7)	
Often	996 (8.1)	464 (16.6)	
Always	215 (1.7)	129 (4.6)	
"Have you been under financial stress?"			<0.001
Never/rarely	6360 (51.6)	1323 (47.2)	
Sometimes	4017 (32.6)	918 (32.8)	
Often	1364 (11.1)	391 (14.0)	
Always	576 (4.7)	169 (6.0)	
"Have you felt down/depressed?"			<0.001
Never/rarely	5594 (45.3)	906 (32.2)	
Sometimes	5504 (44.6)	1364 (48.5)	
Often	1056 (8.6)	423 (15.0)	
Always	183 (1.5)	119 (4.2)	
"Have you lost interest in hobbies?"			<0.001
Never/rarely	7206 (58.6)	1488 (53.3)	
Sometimes	3808 (30.9)	894 (32.0)	
Often	983 (8.0)	287 (10.3)	
Always	310 (2.5)	125 (4.5)	

*Among patients who worked within the past year.

evidence-based medications were recorded at baseline and after 2 years of follow-up among women and men. Unadjusted rates of major clinical outcomes were similar for women and men. In multivariable analysis, several clinical risk factors and psychosocial characteristics were associated independently with the composite primary outcome of cardiovascular death, nonfatal MI, or nonfatal stroke. Female sex was associated with lower rates of the composite primary outcome but only after controlling for psychosocial factors. Interestingly, there was an interaction between frequency of

Table 3. Kaplan–Meier Event Rates at 3.7 Years After Randomization

Outcomes	Men	Women	*P* Value
Cardiovascular death/ nonfatal MI/nonfatal stroke	1294 (10.2)	294 (10.1)	0.88
Cardiovascular death	608 (4.8)	124 (4.3)	0.21
Nonfatal stroke	248 (2.0)	58 (2.0)	0.92
Nonfatal MI	610 (4.9)	156 (5.4)	0.23
All-cause death	964 (7.2)	195 (6.3)	0.10
Urgent revascularization for myocardial ischemia	242 (2.0)	55 (2.0)	0.91
Hospitalization for heart failure	276 (2.2)	74 (2.5)	0.25
Major coronary events	1270 (10.0)	281 (9.7)	0.57
Total coronary events	2002 (16.0)	426 (14.8)	0.14

Values are number of patients with an event during follow-up (Kaplan–Meier event rates at 3.7 years). MI indicates myocardial infarction.

depressive symptoms and cardiovascular outcome according to sex. For patients not feeling down or depressed, women had better outcomes than men; however, when women often or always felt down or depressed, they had outcomes similar to men. This finding is consistent with conventional wisdom that the cardiovascular health of women, compared with men, seems to be more closely related to emotional state.[15]

Sex and CHD

Women often present with clinical manifestations of CHD later in life than men.[2,3] It has been hypothesized that estrogens have protective effects on the vascular endothelium, thus women require more time and risk factor load to develop coronary disease.[1] Compared with men, women also have less atherosclerotic burden, with lower prevalence of obstructive lesions, and more often have MI with no obstructive CAD.[16,17] And indeed, we observed that women with stable CHD enrolled in the STABILITY trial were older and had more risk factors, such as hypertension, diabetes mellitus, and chronic kidney disease, than men.

In both stable and unstable CHD settings, several studies have shown that women, compared with men, undergo invasive procedures less often and are less aggressively treated with evidence-based medications.[4–6] A study of 3779 patients with stable angina showed that in women with proven coronary disease, revascularization procedures were used less frequently than in men.[7] Meanwhile, at 1 year of follow-up, the combination of antiplatelet and lipid-lowering therapies was prescribed less for women than for men. Likewise, another study with 8817 patients with previous coronary events showed that women, compared with men, were treated less frequently with beta blockers and statins.[8] In contrast, a recent analysis of the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, in 8966 stable patients with suspected coronary ischemia, showed no sex-related differences in revascularization rates and prescription of aspirin and statins.[18] Similarly, in our study, there were no differences between women and men regarding rate of coronary revascularization procedures during study follow-up and the use of evidence-based medications at baseline and at 2 years of follow-up. Our findings, coming from a large, contemporary, multinational trial, might suggest an improvement in the healthcare systems and/or in doctors' behavior that has reduced the sex-based gap in the management of CHD.

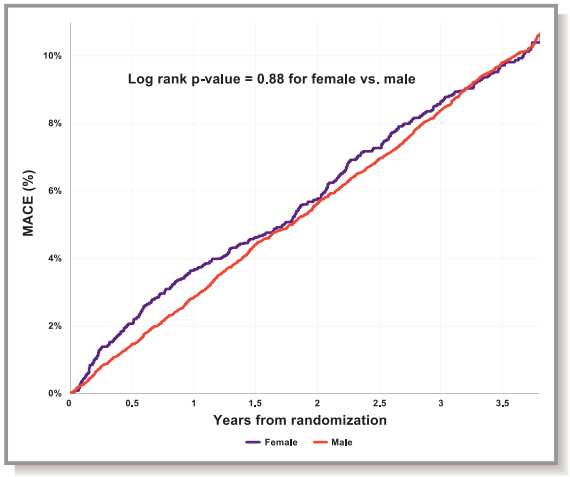

Figure 1. Kaplan–Meier curves for the primary outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke among women and men. MACE indicates major adverse cardiac events.

Sex and Psychosocial Factors

Xu et al showed that among patients with acute MI, women were working less frequently and presented with higher psychological stress than men.[19] Similarly, in our analysis, more women than men were living alone, were not working, and had more perceived psychological stress and depressive symptoms.

Several studies have proposed an association between psychosocial stress or marital status and cardiovascular disease.[20,21] High levels of marital or job stress were associated with progression of coronary stenosis in women with a previous coronary event.[22] A study including >700 000 middle-aged women, recruited as part of the breast screening program in the United Kingdom, showed that women who were married or living with a partner, compared with

Table 4. Relationship Between Risk Factors and the Primary Composite Outcome (Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke) in the Full Model (Model 3)

	χ^2	*df*	*P* Value	HR (95% CI)
Characteristics				
Polyvascular disease	58.243	1	<0.001	1.62 (1.43–1.84)
Age (as continuous variable)				
Per 5 y, when age >65 y	55.186	1	<0.001	1.25 (1.18–1–32)
Per 5 y, when age ≤65 y	0.810	1	0.368	1.03 (0.97–1.09)
Renal dysfunction	46.275	1	<0.001	1.47 (1.32–1.64)
Diabetes mellitus	35.465	1	<0.001	1.40 (1.25–1.54)
Smoking (current vs never)	27.079	2	<0.001	1.48 (1.26–1.73)
HDL cholesterol (as continuous variable)				
Per 0.5 mmol/L, when HDL <1.4 mmol/L	8.815	1	0.003	0.81 (0.71–0.93)
Per 0.5 mmol/L, when HDL ≥1.4 mmol/L	3.228	1	0.072	1.16 (0.99–1.37)
Female sex*	6.199	1	0.013	0.83 (0.71–0.96)
Region of enrollment (ref. Western Europe)	8.226	4	0.084	
Asia/Pacific				1.05 (0.88–1.24)
Eastern Europe				1.14 (0.98–1.33)
North America				0.99 (0.85–1.15)
South America				1.26 (1.03–1.54)
Randomized treatment (darapladib vs placebo)	2.285	1	0.131	0.92 (0.83–1.02)

CI indicates confidence interval; *df*, degress of freedom; HDL, high-density lipoprotein; HR, hazard ratio; ref., referent; χ^2, chi-square.
*In addition to the variables listed in the table, this model also included psychosocial characteristics (marital and work status; whether patients were living alone; frequency of stress at work and financial stress; and frequency of depressive symptoms). For all variables except sex, the results are from a multivariable model including the interaction between sex and feeling down/depressed (p-value for that interaction = 0.041). The results for sex are from the same multivariable model excluding the interaction term. The interaction between sex and feeling down or depressed with respect to the primary outcome is displayed in Figure 2.

unpartnered women, were at lower risk of death due to ischemic heart disease over a mean follow-up of 8.8 years.[23] Patients with a harmonious relationship with a partner may have more social support, healthier habits, better medical adherence, and less psychological stress. Meanwhile, a group-based stress-reduction intervention program for women with previous MI or revascularization procedures was associated with improved survival compared with usual care.[24] In the general population, the impact of stress on cardiovascular risk factors, specifically high blood pressure, might be mediated by the type of occupation; namely, higher stress levels are associated with high blood pressure in people with low occupational status but with lower blood pressure in those with a higher occupational status.[25] This interaction with type of occupation is not likely to have mattered in the present study because many patients were past retirement age, and there was no difference between men and women regarding stress at work.

A key finding of our study was an interaction between cardiovascular risk and emotional state in women versus men. Among patients who never/rarely or sometimes felt sad, low in spirits, or depressed, women had substantially lower cardiovascular risk compared with men; however, as the frequency of depressive symptoms increased, the cardiovascular risk in women became similar to that of men. This interaction was found in the model adjusted for clinical and psychosocial features. Previous investigations have reported an association between depression and adverse outcomes in patients with heart disease.[26–28] A study in >22 000 patients with a new diagnosis of stable angina observed that female sex was a predictor of developing depression after coronary angiography. Furthermore, in this cohort, the frequency of depressive symptoms was independently associated with a higher risk of death and admission for MI.[29] Similarly, a study in 988 women referred for coronary angiography observed that women with a history of depression were hospitalized more often over 2.3 years of follow-up than those without a history of depression. In addition, the risk of death increased with increasing depression severity, even after adjusting for cardiovascular risk factors.[1] The possible explanations for this relationship include both biological pathways and health behaviors, such as medication adherence, dietary habits, and physical activity.

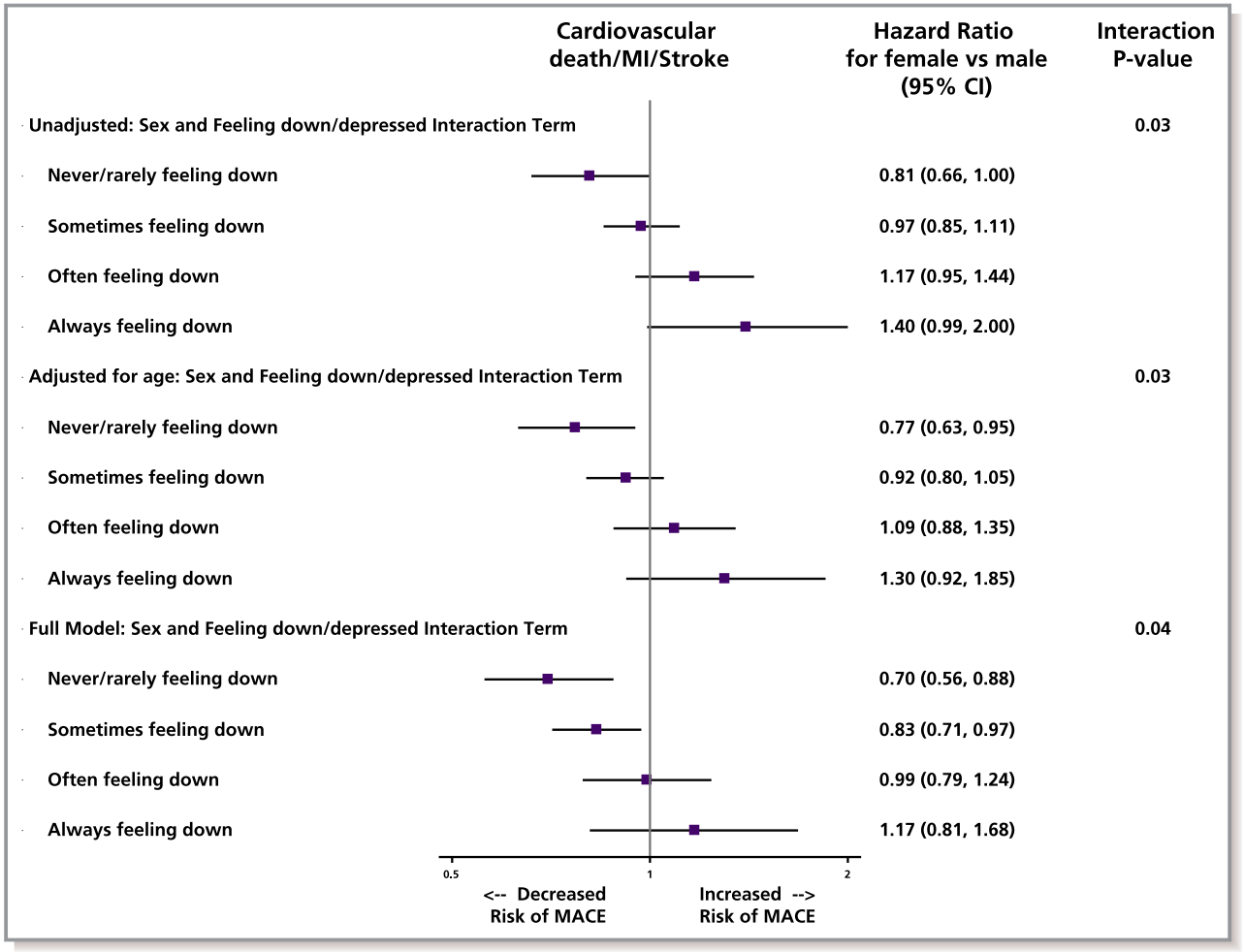

Figure 2. The composite primary outcome of cardiovascular death, nonfatal MI, or nonfatal stroke among women and men, according to status of baseline symptoms of depression and feeling down. CI indicates confidence interval; MACE, major adverse cardiac events; MI, myocardial infarction.

Strengths and Limitations

This study reports findings in a large contemporary cohort of patients with established stable CHD. The patients had intensive follow-up, and evidence-based therapy was well documented. The proportion of women enrolled was smaller than that of men, but there was still a considerable number of women. Our study is a post hoc analysis of a clinical trial, and unmeasured confounders exist. In addition, as in all randomized controlled trials, strict selection criteria were applied for inclusion and exclusion of patients, and thus the population may not be fully representative of patients with stable CHD. It is likely that the high level of use of appropriate medications and interventions in this population exceeds that seen in clinical practice. Psychosocial health was evaluated using a self-reported questionnaire and did not depend on rigorous psychological evaluation. The questionnaire used for the STABILITY trial was in part based on the psychosocial questionnaire used in INTERHEART and in part developed by the (lifestyle and) psychosocial study group for the STABILITY trial, both of which had experience in psychosocial measurements. Because this trial did not primarily address psychosocial outcomes, the included questionnaire was generated to assess a general pattern of psychosocial features rather than being a diagnostic validated instrument.

Conclusion

Women enrolled in the STABILITY trial differed from men in clinical and psychosocial profiles, with women having more comorbidities and reporting stress and depressive symptoms more frequently than men. Female sex was independently associated with better long-term clinical outcomes, although that association was modified by frequency of depressive symptoms, such that as depressive symptoms occurred more often, the advantage of being female was lost. This suggests

that emotional state may be an important target for improving outcome in patients with CHD, particularly in women.

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SUPPLEMENTAL MATERIAL

Table S1. Medications for coronary heart disease, at baseline

Medication at baseline	All patients (N=15828)	Men (N=12861)	Women (N=2967)	P-value
Aspirin	14623 (92.4%)	11877 (92.4%)	2746 (92.6%)	0.72
$P2Y^{12}$ inhibitor	5403 (34.1%)	4407 (34.3%)	996 (33.6%)	0.47
Statins	15398 (97.3%)	12525 (97.4%)	2873 (96.8%)	0.09
Beta-blockers	12508 (79.0%)	10131 (78.8%)	2377 (80.1%)	0.11
ACE inhibitor/ARB	12201 (77.1%)	9903 (77.0%)	2298 (77.5%)	0.60

ACE, angiotensin converting enzyme; ARB, angiotensin-II receptor blocker.

Table S2. Medications for coronary heart disease, at 24 months of follow-up

Medications at 24 months of follow-up	**All patients (N=15828)**	**Men (N=12861)**	**Women (N=2967)**
Aspirin	11641/12696 (91.7%)	9507/10370 (91.7%)	2134/2326 (91.7%)
$P2Y_{12}$ inhibitor	3444/12696 (27.1%)	2838/10370 (27.4%)	606/2270 (26.1%)
Statins	12332/12696 (97.1%)	10082/10370 (97.2%)	2250/2326 (96.7%)
ACE inhibitors/ ARB	10246/12696 (64.7%)	8350/10370 (64.9%)	1896/2326 (63.9%)
Beta-blockers	10070/12696 (79.3%)	8190/10370 (79.0%)	1880/2326 (80.8%)

ACE, angiotensin converting enzyme; ARB, angiotensin-II receptor blocker.

Table S3. Association between sex and cardiovascular outcomes, adjusted for feeling down/depressed

Outcomes	Wald chi-square	P-value	HR (95% CI) for women vs. men
Cardiovascular death	4.808	0.03	0.79 (0.65, 0.98)
Nonfatal stroke	0.019	0.89	0.98 (0.73, 1.32)
Nonfatal myocardial infarction	1.630	0.20	1.13 (0.94, 1.35)
All-cause death	6.362	0.01	0.81 (0.69, 0.95)
Urgent revascularization for myocardial ischemia	0.123	0.73	0.95 (0.70, 1.29)
Hospitalization for heart failure	1.675	0.20	1.19 (0.91, 1.56)
Major coronary events	1.123	0.29	0.93 (0.81, 1.06)
Total coronary events	3.995	0.04	0.90 (0.80, 0.99)

CI, confidence interval; HR, hazard ratio.

Table S4. Relationship between risk factors and primary composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in Model 1

Variables	Chi-square	Degree of Freedom	P-value
Polyvascular disease	63.275	1	<.001
Age, continuous			
For age >65 years	62.211	1	<.001
For age ≤65 years	0.332	1	0.56
Renal dysfunction	49.167	1	<.001
Diabetes	34.280	1	<.001
Current smoking	23.585	1	<.001
HDL cholesterol, continuous			
For HDL cholesterol <1.4 mmol/L	10.517	1	0.001
For HDL cholesterol ≥1.4 mmol/L	2.982	1	0.08
Randomized treatment	2.616	1	0.11
Female sex	0.270	1	0.60

HDL, high-density lipoprotein.

Table S5. Relationship between risk factors and the primary composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in Model 2

Variables	Chi-square	Degree of Freedom	P-value
Age, continuous			
For age >65 years	64.683	1	<.001
For age ≤65 years	1.064	1	0.302
Polyvascular disease	63.265	1	<.001
Renal dysfunction	49.100	1	<.001
Diabetes	38.078	1	<.001
Smoking	34.446	2	<.001
Region of enrollment	14.014	4	0.007
HDL cholesterol, continuous			
For HDL cholesterol <1.4 mmol/L	10.432	1	0.001
For HDL cholesterol ≥1.4 mmol/L	3.200	1	0.074
Randomized treatment	2.439	1	0.118
Female sex	1.463	1	0.227

HDL, high-density lipoprotein.