Sex and Gender Discrepancies in Health-Related Quality of Life Outcomes Among Patients With Established Coronary Artery Disease

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Background—Although eradicating discrepancies in health is of unquestioned importance, there are few studies examining health-related quality of life (HRQOL) among men and women with coronary artery disease (CAD), a highly prevalent and morbid condition among industrialized nations. This study compares the HRQOL outcomes of men and women in Alberta, Canada, 1 year after the documentation of coronary artery disease by cardiac catheterization.

Method and Results—Patients’ disease-specific HRQOL was assessed 1 year after angiography using the Seattle Angina Questionnaire, whereas their generic health status, burden of depressive symptoms, and social support were respectively quantified with the EuroQol EQ-5D, the Center for Epidemiological Studies Depression Scale (short form), and the Medical Outcomes Study social support scale. The latter 2 instruments were used to adjust Seattle Angina Questionnaire outcomes for potential confounding characteristics hypothesized to be associated with sex and gender. General linear modeling and a change in Seattle Angina Questionnaire scores from baseline to 1 year were used to compare the HRQOL outcomes of men and women, after adjusting for demographics, clinical factors, depressive symptoms, and social support differences between groups. A total of 2394 (60% of those eligible) patients responded to the baseline and the 1-year follow-up survey. The adjusted mean 1-year Seattle Angina Questionnaire scores were significantly higher in men when compared with women, even after adjustment for all clinical factors, social support, depressive symptoms, and baseline HRQOL scales. Not only were women noted to have worse health status at the time of angiography, but despite adjusting for these differences, residual discrepancies in 1-year health status persisted.

Conclusions—Women with coronary artery disease report worse HRQOL 1 year after coronary angiography when compared with men, and the discrepancies observed are only partially accounted for by sex differences in depression and social support. As a result, the measurement of gender roles and perceptions may be the best place to persist on the quest to identifying and understanding the noted discrepancies in cardiac recovery and HRQOL outcomes.

Key Words: atherosclerosis ▪ women ▪ gender ▪ sex differences ▪ outcomes research ▪ health-related quality of life

Early in the 20th century, Sir William Osler stated that “it is more important to know what kind of patient has the disease than to know what kind of disease the patient has.” Those words continue to ring true today as we seek to understand the differences in outcomes between men and women with coronary artery disease (CAD). A previous investigation by our group1 identified important sex differences (“sex” refers to biology and anatomy) in the health-related quality of life (HRQOL) outcomes of patients treated for CAD in Alberta, Canada, where women were observed to consistently report poorer HRQOL when compared with men. Taking into consideration that the data had been adjusted for all known cardiac-related risk factors, it was postulated that the HRQOL outcomes might have been confounded by sex and gender discrepancies in psychological sequelae (“gender” refers to the behavioral, cultural, or psychological traits typically associated with one sex). A review of the literature, however, indicated that although HRQOL outcome measures are increasingly being used as primary outcomes in clinical trials,2 a paucity of reported HRQOL outcome data describing or comparing HRQOL in men and women persists; particularly, sex-associated discrepancies in patients undergoing treatment for CAD was evident. Given the prevalence of ischemic heart disease, and that it is the leading cause of

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death for both men and women in developed countries, it is critically important to address these gaps in knowledge about the discrepancies in HRQOL outcomes between men and women with angiographically confirmed CAD.

There is conflicting evidence in the literature surrounding the nature of the association between sex, psychosocial factors, and HRQOL outcomes in patients with CAD. Studies have identified the prevalence of major depression in patients with cardiovascular disease to be between 16% and 23%,\textsuperscript{3–6} whereas 65% of patients manifest symptoms of major or minor depression after myocardial infarction.\textsuperscript{7} Furthermore, depression has been demonstrated to be strongly associated with women’s overall poorer recovery from cardiac events.\textsuperscript{5,8–12} Although an association between depressive symptoms and poorer HRQOL outcomes has been identified,\textsuperscript{13,14} the relationship between sex and HRQOL outcomes after controlling for depression status requires more definitive results to improve clinical practice.

An additional emerging risk factor for adverse HRQOL outcomes is lack of social support. Acting as a buffer between psychological distress and subsequent health outcomes, social support enhances physical recovery and reduces psychological distress and mortality. In women and in men, lack of social support is related to poorer CAD outcomes after a coronary event.\textsuperscript{15–18} Finally, social support is associated with depression, medical treatment compliance, medication adherence, and other factors directly related to health, although it is not clear whether these variables are confounders or mediators by which social support affects disease.\textsuperscript{11,19–21}

The purpose of this study was to extend our previous work comparing HRQOL outcomes after cardiac catheterization to determine whether a sex difference continues to exist after controlling for baseline HRQOL, established risk factors, depressive symptomatology, and social support in a cohort of men and women with CAD. Furthermore, this study examined the association between sex, depressive symptoms, and social support as they relate to HRQOL outcomes and explored whether these factors explain potential sex discrepancies in HRQOL.

Method

Study Design

We used a comprehensive, prospective, longitudinal inception cohort of all adult residents in the province of Alberta, Canada, undergoing catheterization for CAD captured through the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry. The APPROACH project began data collection in 1995 and has been previously described.\textsuperscript{22} Briefly, the APPROACH database contains detailed clinical information, including the results from catheterization, and is merged bimonthly with mortality data from the Vital Statistics Registry. Individuals in the APPROACH registry are followed longitudinally after catheterization, thus allowing for assessment of subsequent procedures (ie, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]), as well as the outcomes of mortality and quality of life in patients who consent to follow-up. The authors had full access to and take full responsibility for the integrity of the data and all authors have read and agree to the manuscript as written.

Study Population

Eligible subjects included all Alberta residents over the age of 18 years with \( \geq 1 \) vessel CAD (Duke Coronary Index between 3 and 15)\textsuperscript{23} and without a previous catheterization who were undergoing catheterization between November 2, 2004 and November 30, 2005, and consented to be enrolled in the APPROACH cohort. All eligible patients were approached consecutively for consent at the time of catheterization.

Collection of Data

Data collected at catheterization included sociodemographic characteristics (sex, age, address, and postal code), clinical comorbidities (renal insufficiency, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, smoking status, pulmonary disease, liver/gastrointestinal disease, and malignancy), disease severity variables (congestive heart failure, prior myocardial infarction, prior thrombolytic therapy, Canadian Cardiovascular Society angina class, and results of noninvasive tests), and coronary angiography results (coronary anatomy, extent of coronary stenosis, and left ventricular ejection fraction). These data were collected in the catheterization laboratory from the patient’s charts and input by nurses, residents, and cardiologists into the APPROACH registry. Similarly, subsequent interventions and catheterizations data were collected in and retrieved from the APPROACH registry.

Patients were provided with 2 options for completing the baseline and 1-year follow-up questionnaires, which were mailed within 1 week of the initial catheterization and 1 year later, respectively. Subjects could either complete the questionnaire and mail it back in a stamped addressed envelope or call and respond to a verbally administered questionnaire using a toll-free line, which was recorded and transcribed daily. The questionnaire included information on employment status, income level, and race; the Seattle Angina Questionnaire (SAQ), a 19-item disease-specific HRQOL instrument; the EuroQol EQ-5D, a generic 5-item HRQOL instrument; the Center for Epidemiological Studies Depression Scale, short form (CES-D-10); and the Medical Outcomes Study (MOS) social support scale. Follow-up questionnaire data were entered into the APPROACH registry by the APPROACH data entry clerk.

Measures

The SAQ is a 19-item self-administered questionnaire on 5 dimensions of HRQOL assessed over the past 4 weeks. Five dimensions of CADs are measured, generating 5 independent scales, including physical limitation, anginal stability, anginal frequency, quality of life, and treatment satisfaction. The SAQ has been shown to be a valid, responsive, and reliable instrument.\textsuperscript{24} The EQ-5D is a generic scale for measuring HRQOL over the past 4 weeks. It expresses health status using a single index score based on societal based utility theory. The EQ-5D covers 5 dimensions of health, including mobility, self-care, family and leisure activities, pain, and mood. A unique health state is defined by combining 1 level from each of the dimensions. The CES-D is a 10-item self-reported measure of depressive symptoms observed over the past week. Each item provides a statement representing a symptom characteristic of depression followed by a 4-point Likert-type response scale ranging from “rarely or none of the time” (<1 day) to “most all of the time” (5 to 7 days). The CES-D is scored by summing all of the highest ratings for each of the 10 items. Scores range from 0 to 40, with higher scores indicating a higher frequency of current depressive symptoms experienced during the past week. Investigators have used a validated cutoff score of 10 to differentiate clinically depressed from nondepressed patients.\textsuperscript{25,26} The MOS social support scale was developed as an instrument to measure the present day level of social support for patients in the MOS, a 2-year survey of patients with chronic conditions.\textsuperscript{27} This 19-item self-administered questionnaire covers 5 dimensions, including emotional support, informational support, tangible support, positive social interaction, and affection. MOS subscale scores sum the responses checked for the relevant items; these scores are rescaled to

\( \text{EQ-5D} \times \text{CES-D} \times \text{MOS} \).
a 0 to 100 range for each subscale, with higher scores indicating more support. A total score is calculated from the mean of the subscale scores.

**Statistical Analysis**

Baseline clinical and demographic characteristics of patients who completed both the baseline and the 1-year survey (responders) and those who completed the baseline but not the 1-year surveys (nonresponders) were compared. A descriptive analysis of the variables was performed. Sex differences on all variables were examined using t test and χ² analyses. Furthermore, the relationship between 1-year CES-D scores and MOS scores and SAQ scores between men and women were examined using correlation analyses.

To determine whether depressive symptoms and social support (measured as present day states and therefore used as independent variables) had a more significant impact on HRQOL in men or women, 5 general linear models were constructed (5 SAQ dimensional scales). Using the 1-year SAQ scores and the EQ-5D score as the outcome variables, predictor variables were added one at a time to determine (1) the contribution of the variable (r²) and (2) the difference between men and women in the adjusted mean 1-year SAQ scores. Variables were incorporated in the following order: sex, age, clinical variables (including index treatment received after catheterization), baseline SAQ/EQ-5D score, 1-year CES-D score, and 1-year MOS score (total mean score of emotional support, tangible support, affectionate support, and social interactions scores). The order of the variables entered into the model was determined based on our previous work in this area and to determine the effect of each additional variable or groups of variables on the relationship between sex and HRQOL outcomes. Finally, an analysis of the changes in response from baseline to 1-year SAQ dimensional scores (ΔSAQ) was conducted. Differences between the baseline and 1-year SAQ scores were calculated. Using the SAQ change scores as the dependent variable, models were run replicating the method described above. Clinically meaningful changes (CMC) were established based on a shift of 1 to 3 responses within each scale, and corresponding transformed SAQ scores were identified. This is congruent with the strategy used by Wyrwich et al in developing intradividual estimates of significant change scores for other health status instruments and has been recently applied to the SAQ. CMC in the SAQ physical limitation scale was designated as a change of ≥8 points. For angina stability, angina frequency, treatment satisfaction, and quality of life scales, the CMC scores included scores that increased by ≥5, ≥20, ≥12.5, and ≤16 points, respectively.

**Results**

Of the 3979 (78.8% of baselines sent) patients who completed the baseline questionnaires, 329 died within the first year. Of the remaining 3683 patients, 2394 (65%) completed the 1-year follow-up questionnaire. An additional 126 respondents moved, and 180 reported that they were unable or unwilling to complete the 1-year questionnaire. The remainder did not respond to the 1-year questionnaire. Importantly, men and women were equally likely to participate in the follow-up assessments. Of the clinical variables listed in Table 1, 1-year nonresponders were younger (63.2 years versus 64.2 years) and significantly more likely to have lower ejection fractions, to have diabetes, and to be treated with medical management only after their cardiac catheterization (i.e., not revascularized) compared with the participants who responded to both questionnaires.

The clinical characteristics, comorbid conditions, treatments received, and baseline CES-D scores of the women and men in this study are presented in Table 1. Women were older and more likely to have hypertension and cerebrovascular disease. As well, a larger percentage of women underwent catheterization for unstable angina, had 2-vessel disease, were

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women (N=522)</th>
<th>Men (N=1872)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>65.8 (11.3)</td>
<td>64.4 (10.4)</td>
<td>0.008</td>
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<tr>
<td>Pulmonary disease, %</td>
<td>14.9</td>
<td>13.5</td>
<td>0.385</td>
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<td>Cerebrovascular disease, %</td>
<td>8.4</td>
<td>5.1</td>
<td>0.004</td>
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<td>Renal disease, %</td>
<td>3.3</td>
<td>2.3</td>
<td>0.215</td>
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<td>Congestive heart failure, %</td>
<td>7.9</td>
<td>6.2</td>
<td>0.176</td>
</tr>
<tr>
<td>Dialysis, %</td>
<td>1.0</td>
<td>0.7</td>
<td>0.538</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>74.1</td>
<td>66.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>83.5</td>
<td>85.3</td>
<td>0.314</td>
</tr>
<tr>
<td>Present smoker, %</td>
<td>21.3</td>
<td>20.2</td>
<td>0.591</td>
</tr>
<tr>
<td>Malignancy, %</td>
<td>3.8</td>
<td>4.1</td>
<td>0.814</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>43.3</td>
<td>46.4</td>
<td>0.205</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>2.5</td>
<td>4.2</td>
<td>0.077</td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>3.8</td>
<td>5.2</td>
<td>0.206</td>
</tr>
<tr>
<td>Prior lytic, %</td>
<td>5.0</td>
<td>4.2</td>
<td>0.420</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>8.2</td>
<td>6.2</td>
<td>0.098</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>20.9</td>
<td>21.5</td>
<td>0.770</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, % &gt;50%</td>
<td>69.7</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td>&lt;35–49%</td>
<td>12.5</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>20–34%</td>
<td>3.1</td>
<td>4.3</td>
<td></td>
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<tr>
<td>&lt;20%</td>
<td>1.1</td>
<td>0.6</td>
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</tr>
<tr>
<td>Ventrilogram not done because of instability</td>
<td>5.0</td>
<td>7.0</td>
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<tr>
<td>Missing</td>
<td>8.6</td>
<td>6.3</td>
<td>0.005</td>
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<td>Indication for catheterization, % Stable angina</td>
<td>37.0</td>
<td>42.0</td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td>37.4</td>
<td>34.4</td>
<td></td>
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<tr>
<td>Unstable angina</td>
<td>24.3</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.3</td>
<td>1.0</td>
<td>0.197</td>
</tr>
<tr>
<td>Coronary anatomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Vessel disease, %</td>
<td>66.7</td>
<td>52.7</td>
<td></td>
</tr>
<tr>
<td>3-Vessel disease, %</td>
<td>28.7</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>Left main disease, %</td>
<td>4.6</td>
<td>10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Index treatment within 1 year of catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical management</td>
<td>48.5</td>
<td>50.7</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>8.6</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>42.9</td>
<td>36.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline SAQ physical limitation score, mean (SD)</td>
<td>62.0</td>
<td>72.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline SAQ anginal frequency score, mean (SD)</td>
<td>76.8</td>
<td>80.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline SAQ treatment satisfaction score, mean (SD)</td>
<td>87.1</td>
<td>88.1</td>
<td>0.200</td>
</tr>
<tr>
<td>Baseline SAQ quality of life score, mean (SD)</td>
<td>60.6</td>
<td>62.5</td>
<td>0.110</td>
</tr>
<tr>
<td>Baseline CES-D score, mean (SD)</td>
<td>6.30 (4.4)</td>
<td>5.25 (4.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
treated with percutaneous coronary intervention in the first year after catheterization, and reported significantly more depressive symptoms at baseline when compared with the men. Conversely, a greater percentage of men had 3-vessel or left main disease, underwent angiography for acute coronary syndromes, and were treated with coronary artery bypass surgery as the index treatment after the catheterization.

Table 2 presents the crude 1-year SAQ scores, EQ-5D scores, CESD-10 scores, and MOS scores for men and women. Women reported significantly lower mean SAQ scores and MOS scores (lower indicates worse) as compared with men. Women also reported significantly more depressive symptoms at 1 year when compared with men.

The results of the general linear modeling are presented in Figures 1 and 2. After the sequential adjustment for all of the variables, men continued to report a significantly better (P<0.001) mean physical limitation dimensional score as compared with women (83.6 versus 80.2). Although the inclusion of age and clinical variables in the model explained a small amount of the variance in physical limitation scores, the addition of the baseline physical limitation dimensional score explained 20% of the variance in the 1-year score (r² change of 0.20), and the depressive symptoms score explained a further 5.4% of the variance (r² change of 0.054). The contribution of the mean social support score in explaining the 1-year physical limitation dimensional score was minimal.

Similar to the physical limitation dimensional score, after full adjustment, men reported significantly less angina at 1 year (ie, higher angina frequency scores) when compared with women. These differences persisted after adjustment for traditional clinical variables (92.3 for men versus 89.8; P<0.001). The baseline angina frequency score explained the greatest amount of variance in the 1-year angina frequency score (r² change of 0.10% to 10% of variance) followed by the depressive symptoms score (r² change of 0.068 to 6.8% of variance).

After adjustment, men reported significantly higher treatment satisfaction when compared with women (91.5 versus 88.9; P<0.001). The baseline treatment satisfaction dimensional score explained the greatest amount of variance in the 1-year treatment satisfaction dimensional score (r² change of 0.174% to 17% of variance), followed by the depressive symptoms score (r² change of 0.04 to 4% of variance) and the social support score (r² change of 0.004 to 0.4% of variance).

After adjustment, men also reported significantly higher quality of life scores at 1 year as compared with women (80.7 versus 74.5; P<0.001). Although the baseline quality of life score explained the greatest amount of the variance in 1-year quality of life (r² change of 0.165% to 17% of variance), the depressive symptom score also explained a substantially large percentage of the variance as well (r² change of 0.113% to 11% of variance).

The modeling of the generic EQ-5D HRQOL outcome variable is presented in Table 3. Similar to the SAQ 1-year dimensional scores, the largest change in r² occurred with the addition of the baseline EQ-5D score (r² change of 0.291% to 29% of variance). The depressive symptom score explained a further 12.3% of the variance in the 1-year EQ-5D score, and social support explained an additional 0.4% of the variance in scores.

**Discussion**

Similar to our previous study, the women in this study reported more depressive symptomatology and less social support as compared with men. However, these factors only partially attenuated the sex discrepancies in HRQOL and health status in this cohort. Baseline HRQOL and disease status scores were also major predictors of 1-year scores. Of
particular note, women reported an 11.1-point difference in the physical limitation score, suggesting that the measurement of HRQOL at catheterization may provide an opportunity to persistently follow patients who report low HRQOL. Despite the full adjustment of all these factors, however, sex remains an independent factor predicting HRQOL and disease status at 1 year.

Our study provides new insight and a more complete exploration of determinants of HRQOL and disease status in men and women with CAD. By including a broader spectrum of CAD patients, all patients with angiographically confirmed CAD, when compared with prior studies that restricted their cohorts to those with acute myocardial infarction, we have been able to extend prior insight surrounding potential gender discrepancies in HRQOL outcomes of a cohort of Canadian patients with CAD.

The major strength of our study is that we were able to collect data on a population-based cohort of patients who were catheterized for CAD in a geographically defined area. With a 65% response rate, we were able to collect both baseline and 1-year HRQOL data while simultaneously measuring depression and social support. Most notably, the comprehensiveness of the data allowed us to conduct sequential risk-adjusted models that in many ways began the process of unbundling the factors that have been suggested as contributors to sex discrepancies in HRQOL and resulted in important new insight.

Our findings highlight the fact that sex and gender are important demographic characteristics that have mechanistic and pathophysiological implications and that there are persisting unexplained factors that may be at play in understanding the outcomes of patients with CAD. We find that even after controlling for age, all known clinical factors, treatment factors, depressive symptoms, and social support variables, women continue to report worse HRQOL as compared with men. As expected, depressive symptoms continue to have a strong association with HRQOL, regardless of sex.

From a mechanistic perspective, our findings underline the fact that we have only a partial understanding of the determinants of the outcomes of heart disease in men and women and the differential factors that may underlie the sex discrepancies that are demonstrated in study after study. We have demonstrated that measured clinical factors, depression, and social support partially explain the discrepancies but also need to acknowledge that the search must continue for other biological or social factors that underlie these discrepancies.
An optimal scenario would be for there to be a full understanding of why outcomes differ in men versus women.

From a clinical perspective, meanwhile, our study findings also have important implications for practice. Our results reaffirm the fact that women have poorer quality of life outcomes at 1 year than men, such that closer follow-up of women’s health status may identify those in whom earlier treatment could further improve their symptoms, function, and quality of life. They also underline the fact that depression and social support are important mediating factors that may be part of the causal pathway producing sex and gender discrepancies. Attentiveness to psychosocial constructs, particularly depression screening and assessment of social support, is likely to be of value to the care provider in assessing prognosis of their patients for favorable clinical outcomes. Whether psychosocial interventions targeting things such as depression or inadequate social support can in turn lead to better outcomes is a whole other question that requires study, as does the potential for differential benefit in men and women.

Limitations of the study include the reality that the study population was limited to those patients who were catheterized for CAD and responded to both the baseline and the 1-year follow-up. Although there were statistically significant differences in some of the clinical/comorbid characteristics of the responders as compared with the nonresponders, a review of the significantly different variables between the responders and nonresponders suggests that the minimal percentage differences would likely not have a strong impact on the results. As well, to address the missing 1-year data, a sensitivity analysis was performed. New variables were created, whereby the lowest and highest SAQ dimensional scores were imputed into the missing 1-year responses. General linear models were run, as described above. Similar
And, from a clinical perspective, clinicians involved in cardiovascular care need to be aware that differences in HRQOL outcomes between men and women exist and are likely related to gender as opposed to sex as a biological construct. Ultimately, this research will continue the process of gaining a better understanding of the factors that contribute to overall cardiovascular HRQOL outcomes.

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Disclosures
None.

References


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