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Clinical implications of the Women’s Ischemia Syndrome Evaluation: inter-relationships between symptoms, psychosocial factors and cardiovascular outcomes

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Cardiovascular disease remains the leading cause of death in the USA and is associated with several modifiable (hypertension, diabetes, high cholesterol, tobacco use, physical inactivity, obesity and unhealthy diet) and nonmodifiable (age, gender and family history) risk factors. The role of psychosocial risk factors in the development of cardiovascular disease has a growing body of literature, and differences in men and women have been identified. The Women’s Ischemia Syndrome Evaluation provides insight into psychosocial risk factors in a cohort of women presenting with chest pain who had a comprehensive battery of psychosocial assessments and long-term follow-up. This review focuses on symptom presentation for chest pain and its relationship to cardiovascular disease morbidity and mortality, quality of life, healthcare costs and psychosocial predictor variables, including anxiety, depression, hostility and social networks. In the Women’s Ischemia Syndrome Evaluation, persistent chest pain was associated with an increased rate of adverse events and relatively high rates of depression and anxiety, with reduced functional capacity and impaired quality of life, over a median of 6 years of follow-up. More research is needed to better understand the relationships between symptoms and negative emotions and to determine whether psychological (pharmacologic and/or cognitive) interventions might impact both psychological and cardiovascular outcomes.

Cardiovascular disease (CVD) remains the most prevalent life threatening disease for men and women in the USA, despite tremendous improvements in care and the resulting reductions in overall mortality that have taken place over the past 20 years [1]. Multiple conditions are associated with CVD and progress has been made for the treatment of diabetes, hypertension, hypercholesterolemia and other biomedical risk factors for CVD. While psychosocial stress is generally considered to have a negative impact on cardiovascular (CV) health, our understanding of the relationships between psychosocial risk factors and CVD risk, particularly among women, is not as robust as that for more traditional risk factors. The link between CVD and psychological risk factors has been explored in many studies, with negative emotional states, psychological stress and lack of social support consistently associated with adverse CVD outcomes [2–4]. A 2010 review specific to women suggested that depression, anxiety disorders, anger suppression and stress related to relationships or family responsibilities are associated with elevated CVD risk, and supportive social relationships and positive psychological factors, such as optimism and emotional vitality may be associated with reduced risk [4]. Compared with men, general anxiety, hostility and work-related stress are less consistently associated with CVD among women.

The Women’s Ischemia Syndrome Evaluation (WISE) is a National Heart, Lung, and Blood Institute-funded project whose purpose was to optimize symptom evaluation and diagnostic testing for ischemic heart disease in women. WISE was a prospective cohort study of women aged 18 years or older who were undergoing a clinically indicated coronary angiogram for chest pain symptoms or suspected myocardial ischemia. WISE explored mechanisms for chest pain symptoms, myocardial ischemia and downstream

Keywords
• anxiety • chest pain • coronary artery disease • depression • nonobstructive disease • women
major adverse clinical events in women with and without epicardial coronary artery stenoses. Unique to WISE was the comprehensive CV and psychosocial assessment approach used to provide insight into the long-term CV risk as well as the relationship of psychosocial characteristics with CV outcomes in these women [5]. The goal of this review is to summarize 17 years of WISE research. This review will focus on symptom presentation for chest pain and its relationship to CV morbidity and mortality, healthcare costs and psychosocial predictor variables including anxiety, depression, hostility and social networks.

Key findings from WISE
Psychosocial assessment
A psychosocial battery of questionnaires was developed by investigators with expertise in psychological assessment and is summarized in Table 1. Psychosocial assessment included measures of hostility/cynicism [6,7], depression [8], trait anxiety and anger [9,10], panic scale [11], social networks [12], quality of life (QoL) [13] and symptom questionnaires [14,15]. The Beck Depression Inventory (BDI) [8] was added at a baseline of 6 months after initiation of patient recruitment, while the Spielberger State-Trait Anxiety Inventory Subscale was initiated after 1 year [9].

Table 2 compares the characteristics of all WISE women, with women not undergoing the full battery of psychosocial testing due to delays in implementation. In the full WISE cohort (n = 936), the mean age was 58 ± 12 years, 80% had completed high school and 19% were nonwhite, primarily African–American. Almost all of the women (94%) reported pain or discomfort above the waist during the prior 12 months, with the remainder presenting with shortness of breath or other angina equivalents. Although the majority (67%) had three or more major CVD risk factors, most had no obstructive coronary artery disease (CAD). Only 39% had obstructive CAD defined as ≥50% diameter stenosis in one or more epicardial arteries. Those completing the full psychosocial testing were more likely to be white, had a lower prevalence of obstructive CAD and fewer risk factors.

Evaluation of chest pain
Perhaps the most complex issue in the assessment of women for CVD is the impact characteristics of chest pain and other presenting symptoms play in referral for further diagnostic testing and treatment. Given the lack of a clear understanding of the etiology of symptoms (e.g., cardiac vs noncardiac) and their relationship to ischemia, the WISE protocol had an extensive symptom evaluation that included two instruments. The Diamond and Forrester Prediction Model is a traditional chest pain assessment validated in large female and male populations for CAD prediction [14] and was used to classify symptoms as typical angina (substernal, precipitated by physical exertion or emotional stress, and relieved within 10 min by rest or nitroglycerin), atypical angina (having only two of these characteristics), nonanginal (having only one of these characteristics), and asymptomatic (having none of these characteristics). A second symptom checklist, developed by the WISE investigators, explored other common presenting symptoms, which were also characterized by including location, intensity, duration, remedies and symptom triggers [15].

Chest pain findings in WISE
Typical angina & obstructive CAD
In a pilot sample of 449 WISE participants without history of myocardial infarction (MI) or...
revascularization, typical angina had a sensitivity of 35% and specificity of 77% for predicting obstructive CAD, suggesting a high rate of false negatives or underdiagnosis of CAD. This classification, known to be highly predictive for obstructive CAD in men, was only weakly related in the WISE women. However, when stratified by age, no association was noted in women aged 35–55 years, while only a mild association became evident in the 55–65 years age group, and the association became more robust among those older than 65 years [16]. These findings were later replicated in the final WISE cohort. They confirm prior data that women experience symptoms of obstructive CAD differently from men and suggest that with increasing age, CAD symptoms become more similar to those reported by men. The finding of a lack of association between symptoms and obstructive CAD differently from men and suggest that with increasing age, CAD symptoms become more similar to those reported by men. The finding of a lack of association between symptoms and obstructive CAD differently from men and suggest that with increasing age, CAD symptoms become more similar to those reported by men. The finding of a lack of association between symptoms and obstructive CAD differently from men and suggest that with increasing age, CAD symptoms become more similar to those reported by men. The finding of a lack of association between symptoms and obstructive CAD differently from men and suggest that with increasing age, CAD symptoms become more similar to those reported by men.

Persistent chest pain & nonobstructive CAD
The persistence of symptoms, particularly in women with nonobstructive disease, who are generally perceived as low risk, starts a cycle of frustration for both patients and clinicians. Many clinicians believe that such women have no significant CV risk and they are frequently referred back to either primary care providers or other specialists for further evaluation (gastroenterology or psychiatry), or are dismissed from care. Among the entire WISE cohort, 45% had chest pain persisting at the 1-year follow-up evaluation. This rate was 46% in those without obstructive CAD. In this group, those with persistent chest pain (PChP) had more than twice the rate of adverse CV events (p = 0.03), including nonfatal MI, stroke, heart failure and CV-related deaths, compared with those without PChP [19]. From the entire cohort there were 72 women categorized as dying from any cause; 53 from CV causes, 24 nonfatal MIs, 44 hospitalized for congestive heart failure, 33 had a stroke, 189 were hospitalized for chest pain and 196 underwent coronary angiography. The rate of events for nonobstructive disease and PChP versus no PChP was: 5.3 vs 1.6% (p = 0.11) for nonfatal MI; 7.5 vs 2.0% (p = 0.03) for strokes; 7.55 vs 3.75 (p = 0.38) for congestive heart failure hospitalizations. There were 30% more CV deaths in those with PChP.

Table 2. Characteristics of The Women’s Ischemia Syndrome Evaluation women with and without psychosocial assessments.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All WISE (n = 936)</th>
<th>Limited psychosocial battery (n = 279)</th>
<th>Complete psychosocial battery (n = 657)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 12</td>
<td>59 ± 12</td>
<td>58 ± 11</td>
<td>0.20</td>
</tr>
<tr>
<td>White (%)</td>
<td>81</td>
<td>75</td>
<td>84</td>
<td>0.002</td>
</tr>
<tr>
<td>Completed high school (%)</td>
<td>80</td>
<td>76</td>
<td>82</td>
<td>0.06</td>
</tr>
<tr>
<td>Obstructive CAD (%)</td>
<td>39</td>
<td>51</td>
<td>34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain/discomfort above waist (%)</td>
<td>94</td>
<td>95</td>
<td>93</td>
<td>0.24</td>
</tr>
<tr>
<td>≥2 CVD risk factors† (%)</td>
<td>86</td>
<td>90</td>
<td>85</td>
<td>0.050</td>
</tr>
<tr>
<td>≥3 CVD risk factors† (%)</td>
<td>67</td>
<td>74</td>
<td>64</td>
<td>0.007</td>
</tr>
<tr>
<td>Obese, BMI ≥30 (%)</td>
<td>41</td>
<td>50</td>
<td>38</td>
<td>0.0007</td>
</tr>
<tr>
<td>Hx of diabetes (%)</td>
<td>25</td>
<td>30</td>
<td>23</td>
<td>0.012</td>
</tr>
<tr>
<td>Hx of hypertension (%)</td>
<td>59</td>
<td>64</td>
<td>57</td>
<td>0.036</td>
</tr>
<tr>
<td>Hx of dyslipidemia (%)</td>
<td>55</td>
<td>60</td>
<td>53</td>
<td>0.06</td>
</tr>
<tr>
<td>Family Hx of CAD (%)</td>
<td>66</td>
<td>62</td>
<td>68</td>
<td>0.08</td>
</tr>
<tr>
<td>Hx of smoking (%)</td>
<td>53</td>
<td>56</td>
<td>52</td>
<td>0.23</td>
</tr>
<tr>
<td>Prior Hx of CAD (%)</td>
<td>28</td>
<td>29</td>
<td>28</td>
<td>0.72</td>
</tr>
</tbody>
</table>

†CVD risk factors include obesity, diabetes, hypertension, dyslipidemia, family Hx, smoking and prior Hx of myocardial infarction or revascularization.

CAD: Coronary artery disease; CVD: Cardiovascular disease; Hx: History; WISE: Women’s Ischemia Syndrome Evaluation.
likely to use antidepressants and anti-anxiety medications than women without PChP. The findings indicate that PChP without obstructive CAD is clearly not benign in terms of QoL, functional capacity and adverse outcomes [19]. In women with CAD, on the other hand, there were no differences in CV event rates among those with versus without PChP. While WISE found a strong association between PChP and evidence of depression or anxiety, it is possible that depression and anxiety may be normal and expected reactions to severe, debilitating, and persistent symptoms of undetermined etiology.

**Psychosocial characteristics**

**Anxiety**

A growing body of literature has established links between anxiety symptoms and disorders, higher rates of cardiac risk factors [20,21] and increased risk of CV events [22,23], signaling a need to better understand the role of anxiety in CVD patients. The prevalence of anxiety disorders in women exceeds that of men [24], raising concerns that anxiety symptoms may introduce further bias into the process of diagnosing and treating CAD in women. Understanding how anxiety may affect the diagnosis and treatment of CAD, however, is complex and controversial. In some reports, higher levels of anxiety among women have been associated with less aggressive treatment [25,26], whereas lower levels of anxiety among men may result in overly aggressive treatment [27].

**Anxiety & CAD in WISE**

The WISE protocol included three distinct measures of anxiety: the ten-item trait anxiety subscale from the Spielberger State-Trait Anxiety Inventory [9]; self-reported use of anxiolytic medication in the week prior to the baseline assessment; and a self-reported history of treatment for an anxiety disorder. WISE reports have examined relationships between anxiety and CV risk factors, cardiac symptoms, CVD severity, and CV and mortality events [28–32]. Among these cardiac variables, higher anxiety measures (Spielberger State-Trait Anxiety Inventory scores and anxiety disorder treatment history) predicted more severe cardiac symptoms (e.g., night time angina, shortness of breath and greater angina frequency); whereas anxiolytic use predicted higher rates of night time angina and nitroglycerin use. A history of treatment for an anxiety disorder was associated with less severe maximum stenosis on coronary angiography, lower global CAD severity scores and lower rates of obstructive CAD overall. Anxiety was not an independent predictor of adverse CVD events or mortality, but did interact with depression (BDI scores and antidepressant use) suggesting that anxiety can improve the prediction of CVD events indirectly when combined with knowledge of depression status.

The interpretation of anxiety–CAD relationships from WISE, and comparison of these relationships to anxiety–CAD associations from other cohorts, requires caution. First, the WISE cohort consisted of women presenting with symptoms and/or signs suggestive of ischemic heart disease warranting coronary angiography. The demographic characteristics of the WISE sample separate the results from previous mixed-gender anxiety–CAD studies and from other studies focused exclusively on women, but with dissimilar sample characteristics [33].

A second distinguishing feature of the WISE cohort was the relatively low rate of significant CAD [5]. Compared with some other large cohort studies examining anxiety–CAD relationships among women, obstructive CAD prevalence and severity in WISE were low. For example, Watkins and colleagues studied patients with a high rate (90%) of angiographic disease [34]. However, the WISE CAD rate was higher than the approximately 3% self-reported history of CAD in the Women’s Health Initiative [33]. The low-to-moderate disease rate among WISE women also limits comparisons of findings to anxiety–CAD relationships reported in a 2010 meta-analysis that focused on post-MI populations [35].

A third distinction was the type of anxiety measures included. For example, other recent cohort studies of women quantified anxiety only in the form of phobic anxiety, which refers to intense fears of specific objects or circumstances [33,35]. This anxiety definition differs considerably from the use of anxiolytics, reported treatment history and trait anxiety captured in WISE. Thus, due to methodological considerations, sample characteristics and measurement strategies, WISE is distinct from other previous studies describing anxiety–CAD relationships among women.

WISE has produced some important findings of anxiety–CAD relationships in women. These findings suggest that the anxiety–CAD relationships are much broader than simply the prediction of adverse CV events as suggested in previous studies [34–37]. Presence of anxiety can also contribute to predictions of clinically relevant features of CAD, such as CAD severity (less severe) and CAD symptoms [28–32]. Based on
prior WISE findings [28,30,32], anxiety, combined with depression, can better predict outcomes such as CAD event risk. Lastly, WISE focused on brief measures of anxiety that could potentially be applicable in clinical settings. The three anxiety measures included the ten-item trait sub-scale, single-item anxiolytic use and treatment history measures, tools that are individually or in aggregate could be incorporated into clinical exams at minimal cost and low patient and staff burden and potentially yield a wide array of clinical insights.

Depression
The prevalence of depression among women with CVD is approximately twice as high as in men [4]. Depression has been found to be a consistent predictor of both incident and recurrent CVD among women [4]. The effect of depression on CV risk may be related to both psycho-physiological and behavioral mechanisms, and the impact of psychological-based treatment of depression on CV outcomes is still not clear. The relationship of depression in women with non-obstructive CAD and ischemia is even less clear and provided an opportunity for WISE to add new information.

Depression–CVD findings from WISE
Relationships between depression and CVD outcomes were a focus in 11 WISE publications [28,30,32,37–44]. The baseline data included three measures of depression: depressive symptoms using the BDI [8]; use of antidepressant medications; and self-reported depression treatment. Previous WISE reports used these measures of depression separately [37,38] and in combination [42–44] to examine depression associated with CV outcomes including CV risk factors, cardiac symptoms, cardiac disease severity and adverse CV events. The body of published WISE evidence overwhelmingly supported relationships between higher depression status and increased rates of CV risk factors, CV events and greater CVD healthcare costs.

In the WISE cohort, depression was a prominent comorbid feature. At baseline, 17.3% reported use of antidepressants, 24.4% endorsed a history of treatment for depression and 45.3% scored ≥10 on the BDI, the latter score a common threshold for indicating the presence of clinically significant depressive symptoms [42]. These relatively high rates of indicators of depression are consistent with previous evidence supporting higher rates of depression among women versus men in CAD populations [45]. Although there was evidence of statistical overlap between the depression measures, the magnitude of this overlap ranged from mild to moderate (correlations ranged from $r = 0.18$, between BDI scores and antidepressant use, to $r = 0.57$, between antidepressant use and depression treatment history). Presence of depression among WISE similarly overlapped with demographic factors, with depression rates higher among women who were younger, disabled, unmarried and unemployed.

Among the depression findings from WISE, several are noteworthy with regards to women and depression–CAD. For example, three publications categorized women using multiple depression markers into groups with no evidence of depression, evidence of one depression marker, or evidence of two or more depression markers [41,43,44]. We observed that the latter group had relatively higher rates of CV risk factors and levels of inflammatory markers and, more importantly, were more likely to experience CV events during follow-up. Hazard ratios were significant in the unadjusted model (hazard ratio: 2.58; 95% CI: 1.47–4.51; $p = 0.009$) and remained significant after adjustment for demographics, CV risk factors, CAD severity score and C-reactive protein (hazard ratio: 2.43; 95% CI: 1.26–4.67; $p = 0.008$) [43]. These findings suggest that evidence of prolonged, treatment resistant, or repeated episodes of depression could help to identify those with potentially the highest risk for adverse outcomes. We have also built upon prior evidence of the overlap between anxiety and depression to examine interactions between these mood dimensions in the prediction of adverse CV events. We first noted that BDI-measures of severity of depression independently predicted adverse CV events, but also interacted with trait anxiety symptoms [30]. This showed that depression predicted events more strongly among women with lower rather than higher anxiety symptoms. Second, we examined depression and anxiety in the form of antidepressant and anxiolytic use [28]. Again we found an independent association between antidepressant use and higher CV event risk, as well as evidence that event risk was higher among women jointly using antidepressant and anxiolytic agents. Finally, we used factor analysis to examine the BDI questionnaire as a CV event predictor in the cohort. We found that the BDI was best conceptualized as comprising three factors (somatic, appetitive and cognitive) among WISE women, with the somatic symptoms of depression showing the strongest relationship with CV events [38]. Several subsequent
analyses have also observed a pattern of somatic symptoms, compared with cognitive symptoms, showing stronger relationships with CV outcomes [46]. A recent factor analysis of WISE psychosocial measures found that depression and anxiety symptoms formed a single ‘negative affect’ factor that correlated with CV risk factor status [32]. The latter findings are among the first empirical tests of the negative affect hypothesis: the hypothesis that known correlations between depression, anxiety and other distress measures are indicative of an underlying negative affect dimension. This negative affect dimension could provide more robust prediction of CV events as compared with separate measures of these affective dimensions.

An underlying rationale to the WISE recruitment methodology was that its results would have direct application to the clinical setting. In retrospect, the enrollment strategy of including symptomatic women with suspected myocardial ischemia offered both advantages and disadvantages for studying relationships between CAD and psychosocial features of depression. Depression may have been a cause or consequence (or both) of cardiac symptoms. Identifying mechanisms that potentially might explain the relationship between depression and CV events also proved beyond the methodology of WISE, as separate reports showed that depression–CV events relationships were largely robust to adjustment for CV risk factors, demographic characteristics, and physiological mechanisms such as inflammatory markers. Identifying and understanding specific biobehavioral pathways that may link depression and CAD processes is a critical objective for advancing the current knowledge in this field. Finally, despite the array of depression measures collected in WISE, no data were collected on important information, such as duration of treatment, success of treatment, specific types or names of antidepressants, antidepressant doses or measurement of depression at any point other than baseline. Thus, the WISE findings represent an important milestone in the study of depression and CAD among women, but as with most cohort studies, the findings have limitations that may influence the direction of future research.

Despite these limitations, we believe that there are at least three clear implications from the WISE depression findings for clinicians. First, among women with suspected myocardial ischemia, clinically significant depression is present in a significant proportion (e.g., 20–50%) of cases, with the highest rates observed based on questionnaire measures of symptom severity. Second, depression correlates with multiple dimensions of CAD relevant to the clinical care of women, including risk factors, inflammation markers and CV events. Third, evidence from WISE suggests that assessment of depression may only require minimal diagnostic interviews in order to obtain clinically useful information; brief measures of depressive symptoms and treatment status appear effective for predicting clinically significant outcomes.

**Quality of life**

QoL is a multidimensional construct comprised of physiological, psychological, emotional and social components. It is assessed with validated questionnaires that target one or all of these domains to assess QoL at different points in time in order to categorize current status and/or changes across time. Patients with chest pain or angina have a worse QoL, and their QoL is directly related to the frequency and severity of symptoms and their interference with activities of daily living [47–50]. The data are less robust in women with symptoms and nonobstructive CAD who repeatedly access healthcare resources in search of a cause for their symptoms.

**QoL & healthcare utilization in WISE**

Two measures of QoL and functional capacity were utilized in the WISE: a general QoL rating taken from the Medical Outcomes Study [13], “Overall, how would you rate your quality of life?” This question has possible responses ranging from 0 (worst) to 10 (best); and the Duke Activity Status Index (DASI) [49], a 12-item self-administered measure of functional status that can be expressed in metabolic equivalents [49]. In WISE, women who were Caucasian, older and had more than a high school education had higher QoL [15]. Women with a history of hypertension, dyslipidemia or who were current smokers had worse QoL and DASI scores. Predictors of higher QoL scores in this group of women included current hormone replacement therapy use and a greater number of social ties. Hormone replacement therapy use was also related to higher functional status (DASI scores). Women with cardiac ischemia rated their QoL higher and had significantly fewer depressive symptoms (BDI) than women without myocardial ischemia, which seems paradoxical. Further analysis of women without ischemia found that these women had less functional capacity (inability to complete an exercise stress test) and so were more symptomatically impaired than...
those with ischemia. Presence of obstructive CAD was related to lower functional status and a higher prevalence of depressive symptoms. The number and severity of cardiac symptoms were independent predictors of lower QoL scores. A combination of socioeconomic factors placed women at higher risk for worsening CV prognosis, including being non-Caucasian, unmarried and having less than a high school education. These characteristics were also consistent predictors of reduced QoL [35].

WISE found a complex inter-relationship between low socioeconomic status, worse health outcome and QoL, among women presenting with symptoms of myocardial ischemia. Among the array of socioeconomic factors measured (ethnicity, marital status, highest level of education, retirement status, employment, vocational status, disability, income and health insurance coverage), low income was the strongest predictor of CV morbidity and mortality [51]. Those at highest risk included women with an annual household income of < US$20,000 versus women earning ≥ US$50,000. In a multivariable model, income (p = 0.001) and education (9–12 grade, GED or < ninth grade vs post-high school; p = 0.012) were the greatest predictors of CV death or MI. The relative risk ratio was 4.91-fold higher for women with an annual household income < US$20,000. When controlled for CAD, symptoms, BMI and risk factors; income remained a significant predictor (p = 0.006). This is consistent with prior findings that low socioeconomic factors contribute to higher CAD risk [37,40]. More than half of the low income women perceived their health status, as fair/poor versus only 10% of higher-income women. This lower-income group also reported higher functional disability. One distinguishing factor of the WISE follow-up was the ability to capture the status of physical capabilities in metabolic equivalents over time using the DASI, which showed lower physical status among lower-income women. The DASI score correlated very well with treadmill exercise capacity and long-term outcomes [52]. Other findings support its relationship with low socioeconomic status and worse health outcomes (p < 0.001). Lower-income women reported more sick days, which may have reduced their salaries and job satisfaction. Together, these factors may have increased the likelihood of nonadherence to medical therapy. WISE yielded important new findings regarding inter-relationships of QoL, lower socioeconomic status and health outcomes, including morbidity and mortality. Women who are disadvantaged economically and socially experience greater symptom burden, poorer QoL and decreased survival rates compared with women with higher SES status [51].

**Psychological & socioeconomic impact on CVD healthcare costs**

The combination of CV and mental health conditions, such as depression, results in greater disability than either one alone [53], and results in increased use of healthcare resources. Despite the growing body of research demonstrating increased medical expenses in chronic disease populations [54–56], little is known about CVD healthcare costs in women with symptoms and signs of ischemia and no obstructive CAD.

In the WISE cohort, antidepressant medication use and history of depression treatment were more reliable predictors of higher costs and adverse CV outcomes than the BDI scores. Depression treatment may be a marker for more severe or enduring forms of depression. In general, women with depression had higher direct and indirect CVD healthcare costs versus nondepressed women during a median of 5.9 years follow-up. CVD healthcare costs were particularly higher in depressed, older, unmarried women with more severe CAD. Depressed women also showed adjusted annual CV costs ranging from US$1550 to 3300 higher than nondepressed women, with estimated increases in 5-year costs of 15–53%. Prior reports have demonstrated that the total healthcare costs for outpatients with depression were 50–100% higher than in patients without depression. These costs were mostly related to increased healthcare utilization rather than depression treatment [57,58]. Given that estimates for mental health treatment costs were not included, other significant pathways contributing to higher costs were considered. In accordance with other reports [4,59,60], depression within the WISE was strongly related to adverse outcomes [28]. The latter accounted for the majority of higher CVD healthcare costs in depressed women with ischemia without obstructive CAD given the high rates of depression observed in WISE – 17.3% reporting use of antidepressants at baseline, 24.4% endorsing a history of treatment for depression and 45.3% scoring ≥ 10 on the BDI; the CVD costs in this subgroup of depressed women without obstructive CAD are potentially sizable considering that more than 60% of WISE cohort had no obstructive CAD [61]. Recently, Jespersen et al. and others have also noted that the majority of symptomatic women referred to coronary angiography...
have no obstructive CAD [62]. Therefore, our economic estimates may have very important implications given this prevalence.

It is possible that the greater somatic distress associated with depression is a contributing factor to higher CVD healthcare costs [63]. WISE findings have shown higher symptom burden in depressed women [28] and emphasized the importance of physical symptoms on presentation in depressed women, concluding that somatic but not cognitive/affective depressive symptoms were associated with an increased risk of CVD-related mortality and adverse events [41]. This may partially explain the prominent symptom-driven care and subsequent higher CVD healthcare costs among depressed women in this cohort.

Other possible contributors to excess CVD costs among depressed patients are low rates of treatment adherence, poor health behavior patterns, social isolation and biological factors, such as elevations in proinflammatory markers (e.g., C-reactive protein) and hypercortisolism [42,60]. Importantly, the costs of minor depression were found to approach that of major depression in a large-scale, population-based study (49% women) [64]. In that study, costs were mostly related to production losses due to illness, which is unlike other studies reporting greater use of mental healthcare services based on patients receiving professional mental healthcare services [65,66]. Although costs for minor depression were lower at the individual level, compared with major depression, excess costs at the public level were nearly similar in both conditions due to the higher prevalence of minor depression in the population [64]. The question of whether treatment of depression reduces healthcare costs, or specifically CV-related costs, has not yet been resolved. In fact, the cost-effectiveness of treating depression associated with CAD in men and women requires testing in well designed, longer term, randomized trials [56].

Although anxiety and depression are common in both men and women with CVD, anxiety is suboptimally studied among women and may warrant greater research attention, considering that women exhibit higher rates of anxiety disorders compared with men [24]. As previously reported, women with anxiety in WISE had higher CVD healthcare costs with some variations in healthcare consumption pattern [29]. Anxiety measures predicted higher 5-year CVD costs irrespective of CAD status. This was considered an independent effect for anxiety status, as increased CVD costs in WISE were separate from mental healthcare costs including anxiety. Anxiety conditions are known to increase healthcare costs over and above the costs attributable to other comorbid diseases [67].

During follow-up in WISE, the typical angina symptom showed similar occurrence rates among women with and without obstructive CAD and hospitalization costs for symptomatic women were 1.5-times higher than those for asymptomatic women [68]. In symptomatic women, the 5-year follow-up repeat angiography rate was 13.2% for those with nonobstructive CAD, compared with 26.3% for those with three-vessel disease. Prior WISE reports also indicated that women with PChP without obstructive CAD had a higher prevalence of anxiety, depression and psychotropic medication use [19]. It is unclear whether cardiac symptoms increase anxiety or whether anxiety increases patient sensitivity to symptoms potentiating treatment-seeking behavior or whether anxiety has direct physiologic effects that impact symptom occurrence and severity, which then lead to additional medical care [29,35,69,70].

CV healthcare factors, such as income, education, employment status, insurance coverage and disability status, have shown significant associations with adverse CV outcomes including QoL and consumptions of healthcare resources. A worse CV prognosis was linked to being non-Caucasian and unmarried with limited education. However, income was the most prominent socioeconomic factor that independently contributed to worsening CV event-free survival with a fivefold increase in relative risk ratio for lower- versus higher-income women [51]. Within WISE, low income predicted mortality even after adjusting for psychosocial and behavioral variables [71].

Nearly half of the middle-aged to elderly women reported lower-income status in the original WISE cohort. These women also suffered a greater angina burden and consumed greater healthcare resources. During the follow-up, half of the WISE participants required hospitalization, while 70% required more anti-ischemic medication. Women reporting hospitalization events and/or anti-ischemic medication use frequently had inadequate health insurance coverage, had more days of sick leave and reduced work capacity [51]. The estimated total 5-year direct CV costs exceeded US$40,000 in low-income women compared with US$23,132 for women with an income ≥US$100,000. Limited affordability and accessibility to regular healthcare is associated with under-use of both preventive
services and therapeutic interventions thus contributing to worse disease outcomes [51,72,73].

**Conclusion**
Findings from WISE have demonstrated that women presenting with chest pain and suspected myocardial ischemia have a high prevalence of nonobstructive CAD and multiple comorbid conditions. Detailed attention to chest pain has been a novel feature of the WISE study. WISE focused on the relationship between symptom typology and presence or absence of obstructive CAD, and found neither classical definitions of ‘typical angina’ highly diagnostic in men, nor the typology of symptom clusters to be diagnostic for obstructive CAD or, later, to predict adverse outcomes in women. However, the reporting of atypical symptoms may cause women to receive less diagnostic testing, which may in turn drive the continuing higher risk for adverse events in women, and particularly younger women or women of color.

WISE investigators have observed that PChP at the 1-year visit, regardless of type, is not benign. PChP was also associated with higher rates of depression and anxiety. Half of the women without obstructive CAD, the same rate as those with CAD, experienced chest pain that was persistent and debilitating and this group experienced double the rate of adverse events over a median of 6 years follow-up.

The psychosocial characteristics of these women reflect relatively high rates of depression and anxiety with reduced functional capacity and impaired QoL.. Symptom-driven care in response to ongoing refractory symptoms was considered to be a significant attribute to increase both medical resource consumption and indirect costs that reflected upon CV healthcare costs. The lack of accurate diagnostic testing and definitive diagnosis results in repeated access to healthcare resources in search for an answer to the question “why do I have chest pain?”

**Future perspective**
Importantly, the findings of WISE have demonstrated a clear relationship between depression and/or anxiety and adverse CV outcomes in this population. A simple battery of paper and pencil tests, combined with pertinent focused history questions can identify women at risk. What is not clear from WISE is the relationship and timing between the development of chest pain symptoms and pre-existing states of depression and/or anxiety or the development of these states as a response to symptoms. The majority of WISE patients reported a normal, active lifestyle until the initial development of chest pain symptoms and a negative cardiac evaluation. Given the high cost of healthcare expenditures, more research is needed to better

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**Executive summary**

**Key findings from WISE**
- Women presenting with myocardial ischemia and chest pain:
  - Presence of multiple comorbid conditions is common;
  - High prevalence of nonobstructive disease by coronary angiography;
  - Frequent utilization of healthcare resources for recurrent symptoms.
- Typical chest pain symptoms:
  - Not diagnostic for obstructive coronary artery disease;
  - Do not predict adverse outcome in these women.
- Atypical chest pain symptoms:
  - Results in less diagnostic testing;
  - Higher event rates seen in younger women and women of color.
- Persistent chest pain at 1 year:
  - Not benign – double the rate of adverse events over 6 years of follow-up;
  - Associated with higher rates of depression and anxiety;
  - Associated with worse quality of life and functional capacity.
- Psychosocial characteristics:
  - High rates of depression and anxiety overall;
  - Reduced functional capacity;
  - Impaired quality of life;
  - Symptom-driven care due to refractory symptoms leads to increased cardiovascular disease healthcare costs.
- There is a clear relationship between depression and/or anxiety and adverse outcomes in this population.
- A simple battery of paper and pencil tests with a focused history can identify women at risk.
- The relationship between symptom development and presence or development of depression and/or anxiety is unclear.
- Further research is needed to better understand the relationships between symptoms and negative emotions.
- The effect of psychological interventions on psychological and cardiovascular outcomes is unclear.
understand these relationships between symptoms and negative emotions and determine if psychological (pharmacologic and/or cognitive) interventions might impact both psychological and CV outcomes. Further research in men with nonobstructive CAD and signs and symptoms of ischemia is also warranted to determine whether the psychological factors seen in WISE are present in men.

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• Explored the impact of symptoms on cost of cardiovascular care, demonstrating the high burden of costs for this population in the presence of nonobstructive disease.