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Predicting Coronary Heart Disease Events in Women: A Longitudinal Cohort Study

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Abstract

Background—Over 240,000 women die in the U.S. from coronary heart disease (CHD) annually. Identifying women's symptoms that predict a CHD event such as myocardial infarction (MI) could decrease mortality.

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Objective—For this longitudinal observational study, we recruited 1097 women, who were either clinician or self-referred to a cardiologist and undergoing initial evaluation by a cardiologist, to assess the utility of the prodromal symptoms (PS) section of the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) in predicting the occurrence of cardiac events in women.

Methods and Results—Seventy-seven women experienced events (angioplasty, stent placement, coronary artery bypass, MI, death) during the two-year follow up. The most common events were stents alone (38.9%) or in combination with angioplasty (18.2%). Ten women had MIs; 4 experienced cardiac death. Cox proportional hazards was used to model time to event. The prodromal score was significantly associated with risk of an event (HR = 1.10, 95% CI = 1.06–1.13), as was the number of PS endorsed by each woman per visit. After covariate adjustment, five symptoms were significantly associated with increased risk: discomfort in jaws/teeth, unusual fatigue, arm discomfort, shortness of breath and general chest discomfort (HR = 3.97, 95% CI = 2.32–6.78). Women reporting >1 of these symptoms were 4 times as likely to suffer a cardiac event as women with none.

Conclusions—Both the MAPMISS PS scores and number of PS were significantly associated with cardiac events, independent of risk factors, suggesting there are specific PS that can be easily assessed using the MAPMISS. This instrument could be an important component of a predictive screen to assist clinicians in deciding the course of management for women.

Keywords

Women; Coronary disease; Myocardial Infarction; Cardiovascular disease

Although cardiovascular disease (CVD) mortality rates are declining for women, as they are for men, women's CVD mortality rates continue to exceed those of men.¹ Coronary heart disease (CHD), a subset of CVD, is responsible for over 240,000 deaths among women in the United States each year.² For many years, there has been a consensus that under-recognition of women's symptoms and difficulty in diagnosing CHD in women contribute to their greater disability and mortality following a CHD event. In response to the challenges in diagnosing CHD in women, the Agency for Healthcare Research and Quality commissioned a review of the accuracy of noninvasive technologies for diagnosis of CHD in women.³ Although this is a seminal review, only studies of women with chest pain syndrome were included. Yet, numerous studies have reported that chest pain is not present in a significant number of women with CHD and many women report little or no chest pain prior to or with myocardial infarction (MI).^{4–7}

Thus, it is vital to identify symptoms other than chest pain that are associated with risk of progressing to a CHD event such as MI, so that women experiencing non-chest pain symptoms may undergo appropriate diagnostic testing. Several risk score calculators, such as the Framingham and Reynolds scores, are useful in predicting long-term risk for CVD.^{8,9} However, these instruments do not assess the prodromal symptoms, other than angina, that women frequently experience prior to MI.^{10,11} The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) assesses the presence of a broad range of prodromal symptoms (PS) among women. However, although the MAPMISS has been

used in several studies^{10,12,13} all have been retrospective. As a result, we know little about the predictive utility of symptoms in the PS section of the MAPMISS.

The aim of this longitudinal observational study therefore was to assess the utility of the MAPMISS PS scores and PS counts in predicting the occurrence of cardiac events in women over a 2-year period. Our goal was to identify the most parsimonious subset of PS data predictive of angioplasty, stent placement, coronary artery bypass, MI or death attributed to CHD.

METHODS

Setting and Sample

We recruited women who were either clinician- (n=903, 82.32%) or self-referred (n=194, 17.68%) to cardiology practices for initial cardiology evaluation. We recruited women from three sites in Arkansas and one in Kentucky. The sites were either associated with academic centers or large state-wide private practices with multiple satellite clinics in urban, suburban, and rural areas. To be eligible for the study, women had to a) have been referred or self-referred to a cardiologist for initial CHD evaluation and have no current or previous CHD diagnosis, b) identify themselves as African American/Black or Caucasian/White, c) be at least 21 years old, d) be cognitively intact, e) have access to a telephone, and f) be able to read or spell out medication information from their prescriptions or designate a family member to perform this task.

Measures

The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) has three sections: (1) the Acute Symptom section which is administered following a cardiac event (e.g., MI, angioplasty), (2) the 30 question Prodromal Symptom (PS) section administered in the absence of a known cardiac event, and (3) a Background section that addresses demographic characteristics, comorbid conditions, other risk factors, and current medications.^{10,14} The analyses reported here are based on data from the PS and Background sections. In the PS section, women are asked about the occurrence of each of 30 PS in the preceding 3 months. For each of the symptoms reported, they are then asked to specify the intensity and frequency with which it occurred. Categorical response options for intensity are mild, medium or severe, scored 1–3, respectively. Categorical response options for frequency are daily, several times/week, > 1/week, >2/month, monthly and <monthly, scored 7, 3.5, 1, 0.5, 0.25, 0.167 days per week, respectively. A PS not reported for the period is scored 0 for intensity and 0 for frequency. Individual PS scores are calculated as the product of intensity and frequency (range 0–21, where 0 indicates the absence of the symptom).¹⁴ A cumulative PS score is calculated as the sum of individual symptom scores (range 0–630). The MAPMISS has been shown to have content validity and solid test/re-test reliability with both African American/Black and Caucasian women ($r=0.91$).^{14,15}

The Short Blessed Test (SBT) assesses for cognitive impairment and was administered at baseline and again at 12 months to assure that participants were sufficiently cognitively intact to provide meaningful information. The SBT includes six weighted items that evaluate

orientation and memory and has established reliability and validity.^{16–18} Each item is scored 0–5, and lower scores indicate better cognitive function.¹⁷ Women who scored 16 or higher at baseline were not eligible to participate in the study.

Procedures

Institutional Review Board approval was obtained at each site prior to recruitment. At all sites, new female patients received a flyer describing the study as part of the packet of forms completed by new patients at the site. Interested women returned the flyer to office staff along with their names and telephone numbers and completed a *Health Insurance Portability and Accountability Act* (HIPAA) authorization permitting the clinic to disclose their names and medical history (reason for clinic visit) to the research team. A research assistant (RA) collected the forms, telephoned interested women, explained the study, answered questions, and for interested women, obtained verbal consent and authorization to review their medical records. The RA then administered the SBT; if the woman scored <16, the RA scheduled a telephone interview to administer the MAPMISS. Participants completed follow-up telephone interviews at 3-month intervals that asked about symptoms experienced during the previous 3-month period, for 2 years or until a CHD event occurred.

If a woman reported a CHD event (angioplasty, stent placement, coronary artery bypass surgery, or MI) during the previous 3 months, the woman completed the acute section of the MAPMISS questions, and an RA audited the woman's medical records from the cardiology clinic, emergency department, and/or hospital where she received treatment to verify occurrence of the event. Once an event occurred, a woman's participation in the study was complete and no further follow-up assessments were conducted. If a woman died, family members were asked about her hospitalization and cause of death. We also obtained a death certificate to confirm cause of death. The first author and other team members evaluated whether a CHD event had occurred and whether the death was cardiac-related. A cardiologist adjudicated all disagreements and made the final determination.

All interviews were administered by RAs located at the site using a computer-assisted telephone interview system that allowed them to enter data directly into a computer program while conducting the interviews. The baseline assessment covered PS in the previous 3 months, demographic characteristics, cardiovascular risk factors including comorbidities and CHD family history, and currently prescribed medications. It took approximately 60 minutes to complete. Follow-up assessments included only the MAPMISS PS section with respect to the previous 3-month period. Follow-up interviews took approximately 20–30 minutes. Women received a \$40 gift certificate for completing the baseline interview, \$15 for each subsequent 3-month follow-up interview, and \$30 for the final interview.

Statistical Methods

MAPMISS data were analyzed to generate PS symptom counts (present/absent; 0–30), individual PS symptom scores (0–21) and cumulative PS symptom scores (0–630). As described earlier, individual scores for each of the 30 PSs were calculated for each woman at each visit based on the frequency (0–7 days/week) and intensity (0–3) she reported for each

symptom in the preceding 3 months. A cumulative PS score was also computed for each woman at each visit as the sum of her 30 individual PS scores.

We had two main analytic goals: (1) to assess the utility of PS scores in predicting study outcomes (angioplasty, stent placement, coronary artery bypass, MI or death attributed to CHD), and (2) to identify the most parsimonious subset of PS data predictive of cardiac events. We used the cumulative PS score to address the first goal because it is the most information-rich MAPMISS measure, incorporating symptom count, intensity and frequency. To this end, we estimated hazard ratios (HR) and corresponding 95% confidence intervals (CI) for experiencing an adverse cardiac event using multivariable Cox proportional hazards regression modeling, including cumulative PS scores as a time-dependent covariate. The model was first adjusted for age and race only. To determine whether cumulative PS scores contributed independently to prediction after accounting for the variables included in existing risk measures, we repeated the analysis adjusting the model for BMI, education, income, marital status, physical activity, family history of CHD, smoking status, diabetes, hypertension and hypercholesterolemia, in addition to age and race.

Because assessing intensity and frequency is clinically time-consuming and perception of symptom-intensity may vary by individual, we next looked at the predictive utility of the PS count, following the same two-step procedure used for cumulative PS scores. Lastly, we explored whether predictive utility might be retained if data (scores or counts) were collected on a specific subset of symptoms. In identifying the most parsimonious predictive models, we first fit separate score and count models for each PS individually. In each case (scores and counts), we then evaluated all PS together and the simplest models with the smallest number of PS and the greatest explanatory power were selected using a strategy which combined stepwise regression, Akaike information criteria, and the best subset selection method, as suggested by Shtatland et al.^{19,20} This strategy was designed to retain the best qualities of each of these three model building methods.

The predictive ability of the final models was assessed by computing Harrell's concordance or C-statistic and the corresponding bootstrapped 95% confidence interval.^{21,22} Harrell's C-statistic is analogous to the area under the receiver operating characteristic (ROC) curve for survival data and it is an estimate of the probability that for 2 randomly selected individuals, the risk of failure predicted from the model will be higher for the individual that fails first. Thus the C-statistic is interpreted the same way that the area under the ROC is interpreted. Specifically, if C=1, then the model has perfect prediction, whereas if C=0.5, the model's predictive ability is no better than a coin flip. Data analysis was performed using Stata® version 12²³ and SAS 9.3.²⁴

RESULTS

A total of 1114 women were enrolled in the study who were either clinician or self-referred to cardiology practices for initial evaluation. Referrals occurred for a variety of reasons including initial evaluation of symptom(s) (n=469, 42.75%), to establish a relationship with a cardiologist (n=286, 26.07%), or other reasons such as for clearance prior to surgery. Of

the 1114 women, 3 of these were found ineligible and 14 did not complete the study (missed a total of 3 interviews or could not be located). Among the remaining 1097 (98.5%) women, a total of 77 women (7%) experienced cardiac events during the 2 years of follow up (see Table 1). The majority (57.1%) of cardiac events were stent placements, either alone (38.9%) or in combination with angioplasty (18.2%). Ten of the 77 women had MIs, and 4 women suffered cardiac-related death.

Characteristics of the 1097 women who completed the study are summarized in Table 2, stratified by the occurrence of a cardiac event. Briefly, the majority of women were White (86.5%), more than 50 years of age (61.1%), with more than a high school education (64%) and married (60.8%). Most of the women were overweight or obese (74.3%) and nearly all reported a family history of CHD (98.1%). The 77 women (7%) who experienced events during the 2-year follow-up were generally older, had less education, lower incomes, and more chronic conditions than those who did not experience a cardiac event.

Predictive utility of cumulative MAPMISS PS scores and PS counts

To determine whether cumulative MAPMISS PS scores and total PS counts were significantly associated with the occurrence of cardiac events, controlling for known clinical and sociodemographic risk factors, we first entered the cumulative PS score, computed as the sum of individual PS scores (range: 0–630), as a predictor. Results were similar whether we adjusted for race and age only or for all the covariates listed in Table 2. After adjusting for all covariates, the HR for subsequent occurrence of a cardiac event increased by 10% for every 10-unit increase in the cumulative prodromal score (HR = 1.10, 95% CI = 1.06–1.13). The total PS count, that is, the number of PS endorsed by each woman at each visit (range: 0–30), was also significantly associated with risk of a subsequent cardiac event. After adjusting for all covariates, the HR increased by approximately 17% for every additional PS reported (HR = 1.17, 95% CI = 1.13–1.21).

The most predictive PS subsets

Since both the MAPMISS cumulative PS scores and total PS counts were predictive of subsequent cardiac events, we explored individual PS data to identify the most parsimonious models for predicting cardiac events. We again began by examining PS scores incorporating symptom intensity and frequency, and then looked at the simpler measures of symptom presence/absence.

PS scores—We looked at the relationships between each of the 30 individual PS scores and the risk of a cardiac event, first adjusted for age and race only, and then for all covariates. The HRs and 95% CIs from these analyses are shown in Table 3. Estimates obtained after adjusting for all covariates were similar to those obtained after adjusting for age and race only. Figure 1 illustrates the adjusted HRs and CIs for the 10 PS with the highest HRs based on individual PS scores.

We then constructed a parsimonious model taking the individual PS scores for all symptoms into consideration and retaining all covariates listed in Table 2. The adjusted HRs and the corresponding 95% CIs estimated from this Cox proportional hazards model are shown in

Table 4. Three symptoms were significantly associated with increased risk of a cardiac event whether we adjusted for all covariates or for age and race only: general chest discomfort, shortness of breath and unusual fatigue. The C-statistics and thus the predictive ability of these models were high (0.78 when adjusted for age and race only and 0.82 when adjusted for all covariates).

PS presence/absence—Again, we first modeled each of the 30 PS individually, adjusting for age and race only and then for all covariates. The HRs and 95% CIs from these analyses are shown in Table 5. Estimates adjusted for all covariates were similar to estimates adjusted for age and race only. Figure 2 shows the HRs and CIs for the 10 PS with the highest HRs based on individual symptom occurrence (presence/absence).

We then constructed a parsimonious model taking all symptoms into consideration and retaining all covariates listed in Table 2. The adjusted HRs and corresponding 95% CIs for the retained PSs estimated from this parsimonious Cox proportional hazards model are presented in Table 6. When we adjusted for race and age only, four symptoms were significantly associated with increased risk of a cardiac event: discomfort in jaws/teeth, unusual fatigue, discomfort in arms, and shortness of breath. Women reporting one or more of these symptoms were over 4 times as likely to suffer an adverse cardiac event as women with none of these four symptoms (HR = 4.19, 95% CI = 2.63–7.44). When we added the other Table 2 covariates to the model, general chest discomfort was significantly associated with increased risk, along with the other four symptoms. Women reporting one or more of these symptoms were almost 4 times as likely to suffer an adverse cardiac event as women with none of these five symptoms (HR = 3.97, 95% CI = 2.32–6.78). The C-statistics and thus the predictive ability for these models was also high (0.81 when adjusted for age and race only and 0.84 when adjusted for all covariates).

In order to better understand the nature of the chest discomfort reported by some of the women, we examined the sensations/descriptors associated with this discomfort (Table 7). Of the 1097 women in the study, 620 (57%) endorsed having chest discomfort in any one of the four chest symptom locations at any time during follow-up. The four chest locations were left chest, general chest, right chest, and centered high in the chest. Interestingly, although the difference was not statistically significant, women with subsequent events endorsed having chest discomfort less frequently (49%) than women without subsequent events (57%) ($p=0.19$). Among women who did not experience an event but who endorsed chest discomfort as a symptom, the majority described the discomfort as pressure (45%), tightness (29%) or sharpness (28%). In contrast, the women who experienced an event and reported chest discomfort described it primarily as either pressure (47%) or tightness (26%). We also examined discomfort in the back, between the shoulder blades. Back discomfort at any time during follow-up was endorsed by 526 of the 1097 women in the study (48%). Women without subsequent events endorsed back discomfort more often (49%) than women with subsequent events (39%) ($p=0.10$).

DISCUSSION

Models for prediction of heart disease have been in use for many decades, but they lack specificity and sensitivity for women, making it difficult for clinicians to know which risk model to use for routine screening. A recent article examined the accuracy of the most commonly used prediction models in women in the United States and concluded that many questions remain and it is unclear how to use these models to make treatment decisions.²⁵ Models such as Framingham^{9,26} and the Reynolds Risk score have been useful in calculating long-term risk, and current efforts are underway to add additional biomarkers to improve cardiovascular risk prediction.^{9,26–31} However, the *10 Q Report: Advancing Women's Heart Health through Improved Research, Diagnosis and Treatment*, and others, concluded that lack of sufficient numbers of women and gender-specific analysis in clinical trials make it difficult for clinicians to know how to adequately assess a woman's risk of CHD or to modify this risk.^{32,33} This report also emphasized the need to identify symptoms other than chest pain that may be suggestive of CHD in women. Our study identified specific symptoms that were predictive of progression to a cardiac event in a sample of women followed over a 2-year period who did not have a CHD diagnosis at the time of enrollment into the study.

This study demonstrated the predictive utility of the PS section of the MAPMISS instrument. Both MAPMISS cumulative PS scores and total PS counts were significantly associated with subsequent development of a cardiac event among women, independent of traditional risk factors. After adjustment for clinical and socio-demographic characteristics, the risk of a cardiac event increased approximately 10% for every 10-unit increase in the cumulative MAPMISS PS score and approximately 17% for every additional PS reported. The latter finding may be especially useful in the clinical setting because it is quicker and easier to count symptoms endorsed than to score and sum PS intensity and frequency. Further, presence/absence reports are also likely to be less vulnerable than estimates of symptom intensity to individual differences, including symptom tolerance. This is important since it is unlikely that additional assessments will be incorporated into a clinical practice or prediction rule unless they minimally increase workload and do not bring additional expense.³⁴ Assessment of individual symptoms included in the MAPMISS is easy to administer (yes/no) and adds minimal time and expense during a clinical encounter.

In the present study, we also looked at which symptoms and symptom scores were most predictive of a subsequent cardiac event. Even after adjusting for known clinical and socio-demographic risk factors, women who reported one or more of the following symptoms were approximately 4 times as likely to suffer an adverse cardiac event as women reporting none of the symptoms (HR = 3.97, 95%CI = 2.32–6.78): discomfort in jaws/teeth, unusual fatigue, discomfort in arms, general chest discomfort, and shortness of breath. This suggests that a subset of MAPMISS PS items may provide a useful screen for primary care clinicians considering whether to refer women for additional cardiac work-up and provide key information to inform clinical management decisions. However, it is essential that this subset undergo further testing in primary-care samples to confirm its usefulness in identifying women with early symptoms most indicative of CHD in need of further evaluation. The literature highlights the importance of identifying symptoms predictive of

CHD in women.^{32,33} Only future research in primary-care populations can determine whether the subset of MAPMISS symptoms identified in this study can meet this need.

Historically, chest pain has been considered the signature indicator of CHD. Interestingly, in our study, women who did not experience a cardiac event were more likely to report chest discomfort or pain in one or more sites (right, left, high, general) than women who had such an event. This highlights the need for clinicians to consider a wider spectrum of symptoms than just chest pain or discomfort, especially unusual fatigue, discomfort in jaws/teeth and shortness of breath, when evaluating women for risk of progressing to a CHD event. Although, there is increasing awareness that women commonly experience symptoms other than or in addition to chest pain or discomfort, this study is the first to identify specific PS that are predictive of subsequent cardiac events. The results indicate these symptoms might precede an acute MI by weeks or months and should be useful to both clinicians and women. Earlier recognition of symptoms should contribute to decreasing MI-associated mortality rates in women.

Limitations

In addition to its many strengths (sample size, sample diversity, two-year longitudinal design), the study had several limitations. Data were based on self-report, making them vulnerable to recall bias. To minimize the risk of recall bias, we employed a short (3-month) follow-up interval, worded questions simply, and, if the RA noted any hesitation in the participant's response(s), re-phrased the question. Also, throughout the interview, the RAs frequently verified participants' understanding of MAPMISS items. Additionally, the SBT cognitive screen was administered at baseline and again at 12 months in order to decrease the influence of change in cognitive status. None of the participants scored >16 (i.e., positive for cognitive impairment) on the SBT at 12 months. Individuals may also differ in their perceptions of symptom severity and, consciously or unconsciously, could exaggerate or minimize their reports of symptom severity or frequency. Therefore, with the participants' informed consent, we audited their medical records over the 2-year period, to verify the information they provided. No discrepancies were noted. Finally, although we had sufficient overall power, subgroup analysis was limited by the relatively small number of events observed. Future studies with a greater number of events would enable additional subgroup analyses.

Conclusions

The devastating impact of CHD is largely preventable if the condition is diagnosed early in the disease process. Instruments to facilitate early identification of high-risk individuals are vitally important. This need is especially great for women who often present with a variety of symptoms. This study demonstrated that a valid and reliable symptom instrument, the MAPMISS, can be used by clinicians in assessing women's CHD risk. Using the MAPMISS, this study identified specific PS that are predictive of future cardiac events. We observed that women who reported one or more of five of the MAPMISS PS items: 1) discomfort in jaws/teeth, 2) unusual fatigue, 3) discomfort in arms, 4) general chest discomfort, or 5) shortness of breath, were four times as likely to suffer an adverse cardiac

event as women reporting none of those symptoms. Informing clinicians and women of the implications of these symptoms could contribute to early detection and initiation of treatment to prevent or delay progression to a cardiac event. This in turn could assist in reducing the high disability and mortality rates in women associated with acute MI.

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What's New?

- Over 240,000 women die from coronary heart disease annually in the U.S.
- Identifying symptoms that predict coronary heart disease events in women could decrease mortality
- The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) may be useful in predicting coronary events in women

Figure 1.

Adjusted hazard ratios and 95% confidence intervals (CI) for the 10 prodromal symptoms with the highest HRs based on individual prodromal symptom scores. Hazard ratios adjusted for all covariates in Table 2

Figure 2.

Adjusted hazard ratios and 95% confidence intervals (CI) for the 10 prodromal symptoms with the highest HRs estimated from data on presence/absence of symptom. Hazard ratios adjusted for all covariates in Table 2.

Table 1

Type and distribution of cardiac events/interventions in 77 women

Cardiac event	N	%
<i>Non-fatal events</i>		
Angioplasty	4	5.2
Stent placement	30	38.9
Stent placement with angioplasty	14	18.2
Bypass surgery	15	19.5
MI		
Alone	4	5.2
With angioplasty	2	2.6
With angioplasty and stent placement	4	5.2
<i>Cardiac deaths</i>	4	5.2
Total	77	

Table 2

Selected characteristics of the 1097 women at baseline interview

No. (%) of women				
Characteristic	All (N = 1097)	Event (N=77)	No Event (N = 1020)	p-value*
Race				
African American	148 (13.5)	6 (7.8)	142 (13.9)	0.1290
Caucasian	949 (86.5)	71 (92.2)	878 (86.1)	
Age				
Age <= 50yrs	427(38.9)	8 (10.4)	419 (41.1)	<0.0001
Age > 50yrs	670 (61.1)	69 (89.6)	601 (58.9)	
Education				
High school or less	394 (35.9)	43 (55.8)	351 (34.4)	0.0007
College/vocational school	571 (52.1)	29 (37.7)	542 (53.1)	
Post graduate studies	132 (12.0)	5 (6.5)	127 (12.5)	
Income				
Less than or equal to \$30,000	637 (58.1)	55 (71.4)	582 (57.1)	0.0012
More than \$30,000	431 (39.3)	17 (22.1)	414 (40.6)	
Don't know/Refused	29 (2.6)	5 (6.5)	24 (2.3)	
Marital status				0.0315
Never Married	83. (7.6)	3 (3.9)	70 (7.8)	
Currently Married	667 (60.8)	41 (53.2)	626 (61.4)	
Divorced/Separated	232 (21.1)	18 (23.4)	214 (21.0)	
Widowed	115 (10.5)	15 (19.5)	100 (9.8)	
BMI				
Under weight	8 (0.7)	0 (0.0)	8 (0.8)	0.2247
Normal weight	274 (25.0)	14 (18.2)	260 (25.5)	
Over weight	317 (28.9)	29 (37.7)	288 (28.2)	
Obese	498 (45.4)	34 (44.1)	464 (45.5)	
Diabetes				
No	753 (68.6)	42 (54.5)	711 (69.7)	0.0057
Yes	344 (31.4)	35 (45.5)	309 (30.3)	

No. (%) of women				
Characteristic	All (N = 1097)	Event (N=77)	No Event (N = 1020)	p-value*
High blood pressure				
No	343 (31.3))	23 (29.9)	320 (31.4)	0.7839
Yes	754 (68.7)	54 (70.1)	700 (68.6)	
High cholesterol				
No	415 (37.8)	21 (27.3)	394 (38.6)	0.0476
Yes	682 (62.2)	56 (72.7)	626 (61.4)	
Smoker				
No	880 (80.2)	61 (79.2)	819 (80.3)	0.8197
Yes	217 (19.8)	16 (20.8)	201 (19.7)	
Exposed to second hand smoke				
No	276 (25.2)	22 (28.6)	254 (24.9)	0.4743
Yes	821 (74.8)	55 (71.4)	766 (75.1)	
Physical activity				
No	554 (50.5)	48 (62.34)	506 (49.6)	0.0312
Yes	543 (49.5)	29 (37.7)	514 (50.4)	
Menopause				
No	622 (56.7)	34 (44.2)	588 (57.7)	0.0212
Yes	475 (43.3)	43 (55.8)	432 (42.3)	
Family History				
No	19 (1.7)	1 (1.3)	18 (1.8)	0.0563
Yes	1076 (98.1)	75 (97.4)	1001 (98.1)	
Don't know	2 (0.2)	1 (1.3)	1 (0.1)	

* Comparison of characteristics of women who experienced a cardiac event and of those who did not.

Table 3

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for individual prodromal symptom scores modeled independently

Symptom	HR (95% CI) [*]	HR (95% CI) [†]	p value [†]
Shortness of breath	1.12 (1.08, 1.15)	1.10 (1.07, 1.14)	<.0001
Unusual fatigue	1.09 (1.06, 1.12)	1.08 (1.05, 1.11)	<.0001
Left breast discomfort	1.13 (1.07, 1.18)	1.13 (1.07, 1.19)	<.0001
Back discomfort	1.10 (1.06, 1.14)	1.10 (1.05, 1.14)	<.0001
Jaw/teeth discomfort	1.14 (1.08, 1.21)	1.14 (1.07, 1.21)	<.0001
Heart racing	1.09 (1.05, 1.14)	1.09 (1.05, 1.14)	<.0001
General chest discomfort	1.11 (1.05, 1.18)	1.13 (1.06, 1.19)	<.0001
Centered high in chest discomfort	1.13 (1.07, 1.19)	1.12 (1.06, 1.19)	<.0001
Ache in arms	1.10 (1.05, 1.14)	1.08 (1.04, 1.13)	<.0001
Arm(s) discomfort	1.09 (1.05, 1.14)	1.08 (1.04, 1.13)	0.0003
Arms tingling	1.08 (1.03, 1.13)	1.07 (1.02, 1.12)	0.0063
Cough	1.08 (1.03, 1.13)	1.07 (1.02, 1.11)	0.0067
Neck/throat discomfort	1.07 (1.01, 1.12)	1.07 (1.02, 1.13)	0.0083
Hands tingling	1.07 (1.02, 1.11)	1.06 (1.01, 1.10)	0.0090
Arms weak/heavy	1.07 (1.03, 1.12)	1.06 (1.02, 1.12)	0.0094
Headaches frequency change	1.08 (1.03, 1.13)	1.06 (1.01, 1.11)	0.0252
Top of shoulder discomfort	1.06 (1.00, 1.12)	1.06 (1.00, 1.12)	0.0402
Sleep disturbance	1.05 (1.01, 1.08)	1.03 (1.00, 1.07)	0.0541
Legs aching	1.05 (1.01, 1.09)	1.04 (1.00, 1.08)	0.0578
Difficulty breathing at night	1.09 (1.03, 1.16)	1.07 (1.00, 1.14)	0.0586
Vision blurry, changes	1.05 (0.99, 1.11)	1.06 (1.00, 1.12)	0.0639
Change in thinking	1.06 (1.02, 1.11)	1.04 (1.00, 1.09)	0.0643
Arms numb	1.06 (1.01, 1.12)	1.05 (1.00, 1.11)	0.0690
Frequent indigestion	1.06 (1.02, 1.10)	1.04 (0.99, 1.08)	0.1032
Headaches intensity change	1.06 (1.01, 1.12)	1.04 (0.99, 1.10)	0.1222
Dizziness	1.05 (1.00, 1.11)	1.04 (0.98, 1.10)	0.1844
Anxious	1.12 (1.08, 1.15)	1.03 (0.98, 1.08)	0.2093
Abdominal discomfort/pain	1.09 (1.06, 1.12)	1.02 (0.95, 1.09)	0.5990
Loss of appetite	1.13 (1.07, 1.18)	1.01 (0.95, 1.08)	0.7134
Right side chest discomfort	1.10 (1.06, 1.14)	0.95 (0.68, 1.32)	0.7491

* Adjusted for age and race only

† Adjusted for all variables listed in Table 2.

Table 4

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for retained symptoms and significant covariates in the parsimonious model based on individual prodromal symptom scores

	HR (95% CI) [*]	HR (95% CI) [†]	p value [†]
Symptom			
General chest	1.08 (1.01, 1.14)	1.09 (1.03, 1.16)	0.0058
Shortness of breath	1.08 (1.04, 1.12)	1.07 (1.03, 1.11)	0.0015
Unusual fatigue	1.06 (1.02, 1.09)	1.05 (1.01, 1.08)	0.0091
Significant covariates			
Age	1.05 (1.04, 1.07)	1.07 (1.05, 1.10)	<0.0001
BMI			
18.5–24.9	Reference		
25–29.9		2.05 (1.04, 4.03)	0.0374
30		2.01 (1.01, 3.98)	0.0469
Hypertension		0.52 (0.31, 0.90)	0.0190
Diabetes		1.78 (1.10, 2.89)	0.0193
Harrell's C (95% C.I)	0.78 (0.73, 0.83)	0.82 (0.77, 0.86)	

* Adjusted for age and race only

† Adjusted for all variables listed in Table 2

Table 5

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for presence/absence of each prodromal symptom modeled independently

Symptom	HR (95% CI)*	HR (95% CI) [†]	p value [†]
Jaw/teeth discomfort	6.07 (3.52, 10.45)	5.98 (3.4, 10.51)	<.0001
Arm(s) discomfort	5.15 (3.20, 8.28)	4.55 (2.78, 7.44)	<.0001
Back discomfort	4.32 (2.70, 6.90)	4.32 (2.67, 6.99)	<.0001
Unusual fatigue	4.90 (3.02, 7.94)	4.53 (2.75, 7.45)	<.0001
Shortness of breath	4.22 (2.68, 6.67)	3.81 (2.37, 6.15)	<.0001
General chest discomfort	4.22 (2.27, 7.83)	4.55 (2.41, 8.57)	<.0001
Ache in arms	3.54 (2.16, 5.78)	3.26 (1.96, 5.41)	<.0001
Arms weak/heavy	3.52 (2.15, 5.76)	3.12 (1.85, 5.26)	<.0001
Neck/throat discomfort	2.88 (1.69, 4.90)	3.04 (1.76, 5.24)	<.0001
Centered high in chest discomfort	3.45 (1.93, 6.16)	3.27 (1.82, 5.88)	<.0001
Left breast discomfort	3.23 (1.93, 5.42)	2.91 (1.70, 4.97)	<.0001
Hands tingling	2.82 (1.73, 4.60)	2.66 (1.61, 4.40)	0.0001
Cough	3.06 (1.79, 5.22)	2.84 (1.64, 4.93)	0.0002
Arms tingling	2.97 (1.70, 5.17)	2.71 (1.53, 4.80)	0.0006
Anxious	2.35 (1.44, 3.81)	2.23 (1.36, 3.66)	0.0016
Change in thinking	2.60 (1.56, 4.32)	2.32 (1.37, 3.92)	0.0017
Arms numb	3.00 (1.66, 5.42)	2.56 (1.39, 4.71)	0.0024
Sleep disturbance	2.12 (1.33, 3.39)	2.09 (1.30, 3.38)	0.0025
Top of shoulder discomfort/pain	2.79 (1.55, 5.01)	2.53 (1.37, 4.67)	0.0029
Dizziness	2.55 (1.55, 4.21)	2.16 (1.28, 3.63)	0.0038
Difficulty breathing at night	3.34 (1.76, 6.35)	2.73 (1.38, 5.39)	0.0040
Legs aching	2.56 (1.51, 4.34)	2.26 (1.29, 3.95)	0.0042
Vision blurring, changes	2.31 (1.22, 4.40)	2.56 (1.32, 4.94)	0.0053
Frequent indigestion	2.42 (1.45, 4.04)	2.02 (1.18, 3.45)	0.0098
Headaches frequency change	2.40 (1.40, 4.13)	2.09 (1.18, 3.70)	0.0116
Heart racing	1.93 (1.19, 3.11)	1.75 (1.07, 2.86)	0.0267
Headaches intensity change	2.35 (1.24, 4.47)	2.05 (1.04, 4.03)	0.0372
Right side chest discomfort	2.27 (0.83, 6.22)	1.76 (0.63, 4.95)	0.2811
Loss of appetite	1.59 (0.81, 3.09)	1.36 (0.69, 2.72)	0.3755
Abdominal discomfort	1.51 (0.72, 3.14)	1.40 (0.66, 2.95)	0.3786

* Adjusted for age and race only

[†] Adjusted for all variables listed in Table 2.

Table 6

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for retained symptoms and significant covariates in the parsimonious model based on presence/absence of symptom

	HR (95% CI) [*]	HR (95% CI) [†]	p value [†]
Symptom			
Jaw/teeth discomfort	2.52 (1.40, 4.55)	2.76 (1.49, 5.11)	0.0012
Unusual fatigue	2.57 (1.47, 4.47)	2.34 (1.33, 4.14)	0.0033
Arm(s) discomfort	2.44 (1.44, 4.12)	2.15 (1.25, 3.70)	0.0057
Shortness of breath	2.00 (1.19, 3.36)	1.87 (1.11, 3.16)	0.0185
General chest discomfort		2.26 (1.15, 4.45)	0.0180
Significant covariates			
Age	1.06 (1.04, 1.08)	1.07 (1.05, 1.10)	<0.0001
BMI			
18.5–24.9		Reference	
25 –29.9		2.13 (1.08, 4.19)	0.0291
30		2.02 (1.02, 4.01)	0.0443
Hypertension		0.50 (0.29, 0.88)	0.0151
Diabetes		1.70 (1.04, 2.76)	0.0335
Physical activity		0.61 (0.38, 0.99)	0.0447
Second hand smoke		0.57 (0.34, 0.97)	0.0388
Harrell's C (95% C.I)	0.81 (0.77, 0.86)	0.84 (0.80, 0.89)	

* Adjusted for age and race only

[†] Adjusted for all variables listed in Table 2

Table 7

Counts and percentages of women experiencing specific sensations among 620 women endorsing chest discomfort during the study

Sensation	No Events (n= 582)	Events (n= 38)	Total (n=620)
Ache	170 (29.2%)	7 (18.4%)	177 (28.5%)
Burning	60 (10.3%)	5 (13.2%)	65 (10.5%)
Crushing	51 (8.8%)	4 (10.5%)	55 (8.9%)
Fullness	86 (14.8%)	5 (13.2%)	91 (14.7%)
Heat	9 (1.5%)	-	9 (1.5%)
Pressure	260 (44.7%)	18 (47.4%)	278 (44.8%)
Sharpness	164 (28.2%)	8 (21.1%)	172 (27.7%)
Soreness	47 (8.1%)	3 (7.9%)	50 (8.1%)
Spasm	49 (8.4%)	4 (10.5%)	53 (8.5%)
Tightness	169 (29.0%)	10 (26.3%)	179 (28.9%)
Tingling	41 (7.0%)	4 (10.5%)	45 (7.3%)