European Heart Journal (2006) **27**, 1408–1415
doi:10.1093/eurheartj/ehl040

Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study

B. Delia Johnson[1]*, Leslee J. Shaw[2], Carl J. Pepine[3], Steven E. Reis[4], Sheryl F. Kelsey[1], George Sopko[5], William J. Rogers[6], Sunil Mankad[7], Barry L. Sharaf[8], Vera Bittner[6], and C. Noel Bairey Merz[2]

[1] *Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA;* [2] *Division of Cardiology, Department of Medicine, Cedars-Sinai Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA;* [3] *Division of Cardiovascular Medicine, University of Florida, Gainesville, FL, USA;* [4] *Cardiovascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA;* [5] *National Heart, Lung and Blood Institute, NIH, Bethesda, MD, USA;* [6] *Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA;* [7] *Division of Cardiology, Department of Medicine, Allegheny University of the Health Sciences, Pittsburgh, PA, USA; and* [8] *Division of Cardiology, Rhode Island Hospital, RI, USA*

Received 21 October 2005; revised 14 April 2006; accepted 4 May 2006; online publish-ahead-of-print 23 May 2006

See page 1387 for the editorial comment on this article (doi:10.1093/eurheartj/ehi758)

KEYWORDS
Chest pain;
Prognosis;
Women;
Myocardial ischaemia

Aims Women with chest pain but without obstructive coronary artery disease (CAD) are considered at low risk for cardiovascular (CV) events, but half continue to experience debilitating chest pain over many years. This study compared CV outcomes in women with persistent chest pain (PChP) vs. those without PChP.

Methods and results We studied 673 Women's Ischaemia Syndrome Evaluation (WISE) participants with chest pain undergoing coronary angiography for suspected myocardial ischaemia and at least 1 year of follow-up. PChP was defined as self-reported continuing chest pain after 1 year. Events occurring after that year were recorded for a median of 5.2 years. We compared CV event rates for women with and without PChP in subgroups with and without obstructive CAD. The median age was 58 years, 20% were racial minorities, 45% had PChP, 39% had obstructive CAD. Among women without CAD, those with PChP had more than twice the rate of composite CV events ($P = 0.03$), that included non-fatal myocardial infarctions ($P = 0.11$), strokes ($P = 0.03$), congestive heart failure ($P = 0.38$), and CV deaths ($P = 0.73$), compared with those without PChP. In women with CAD, there was no difference in composite CV events in those with and without PChP ($P = 0.72$).

Conclusion Among women undergoing coronary angiography for suspected myocardial ischaemia, PChP in women with no obstructive CAD predicted adverse CV outcomes. Such women might benefit from additional evaluation and aggressive risk factor modification therapy.

Introduction

In clinical practice, chest pain in the absence of obstructive coronary artery disease (CAD) remains a baffling problem that primarily affects women. More than half of women with chest pain undergoing coronary angiography in the U.S. are found to have normal or near-normal coronaries, as compared with only 15% of men.[1–2] This high 'false-positive' rate for severe coronary artery stenosis among symptomatic women has not declined since it was first reported.[3–4] Today, among the over half million angiograms performed annually in U.S. women, the cost related to lack of specific diagnosis in the presence of normal angiographic findings is estimated around $300 million.[5]

About 50% of women sent home with normal coronaries continue to experience disabling symptoms that are often unresponsive to conventional anti-ischaemic therapy[4,6] and return for repeat evaluations, adding to the economic and human costs in terms of lost productivity and need for continuing evaluation and care. Although the constellation of angina and normal coronary angiograms may have multiple aetiologies, recent evidence suggests that an ischaemic mechanism may play a role due to coronary microvascular or macrovascular endothelial dysfunction[7–11] that in many cases appears to be female-specific.[11–14]

* Corresponding author. Tel: +1 412 624 7256; fax: +1 412 624 3775.
E-mail address: djohnson@edc.pitt.edu.

The prognosis in women with chest pain and normal coronary angiograms is said to be excellent.[15–18] However, in a recent study of women with chest pain and normal appearing coronaries, 59% who additionally displayed an abnormal vasomotor response to acetylcholine continued to experience chest pain and developed CAD at up to 10 years.[19] The women with normal vasomotor response, by contrast, had a complete resolution of their symptoms at follow-up. Although the study was small (42 women), the findings suggest that persistent chest pain (PChP) in women with angiographically normal coronaries may forecast downstream development of obstructive CAD and cardiovascular (CV) events. The aims of the present study were (i) to evaluate systematically the clinical status and prognosis of women referred for coronary angiography who have PChP or symptoms suggestive of ischaemia and (ii) to evaluate the prognostic significance of PChP in women without obstructive CAD.

Methods

Study population

The study population consisted of 673 participants in the Women's Ischaemia Syndrome Evaluation (WISE) study who reported chest pain symptoms at baseline, who had at least 1 year of follow-up that included a symptom/chest pain assessment necessary for the definition of PChP, and for whom follow-up information was available beyond the 1 year follow-up. WISE is a National Heart, Lung, and Blood Institute-sponsored 4-center study of 936 women undergoing clinically ordered coronary angiography for suspected myocardial ischaemia.[20] Exclusion criteria included emergency referral, pregnancy, cardiomyopathy (as defined in the patients' medical records), New York Heart Association class IV congestive heart failure (CHF), acute ischaemic syndrome (defined as acute myocardial infarction (MI) or unstable angina) within one month prior to study entry, coronary revascularization by either CABG or PTCA within 6 months prior to study entry, conditions other than ischaemic heart disease likely to be fatal or requiring frequent hospitalization within 4 years (such as severe lung, renal or hepatic disease, or surgically uncorrected significant congenital or valvular heart disease), any contraindication to provocative myocardial stress testing, and any condition likely to affect study retention (alcoholism, drug abuse, or severe psychiatric illness). Of the consecutive women screened and those who met the WISE eligibility criteria, 50% agreed to participate in the study. This study complies with the Declaration of Helsinki. All women provided signed informed consent for baseline evaluations and follow-up by using forms and procedures in accordance with institutional guidelines and approved by the institutional review board at each WISE clinical site.

Baseline evaluation

On enrolment, baseline evaluation by site physicians and study nurses included the collection of demographic information, risk factors for CAD, medication use, medical and reproductive history, detailed symptom history and psychosocial evaluation, a physical examination, activity status assessment, and sampling of blood. All WISE women also received an ECG that was evaluated by the WISE ECG core laboratory for rhythm, rate, LVH, conduction abnormalities, ST-T wave changes, and Q-Waves.

Quantitative angiographic assessment of CAD

In order to maintain uniformity of methodology and interpretation, all coronary angiograms obtained at enrolment were analysed quantitatively and qualitatively offline at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI, USA) by investigators masked to all other WISE clinical data.[21] Luminal diameter was measured at all stenoses with a cine projector-based 'cross hairs electronic caliper' method for all angiograms recorded onto cine film and with a computer-based edge detection method for all angiograms recorded onto CD-ROM. The inter-observer variability for this lab was 0.196 mm with a 6.3% coefficient of variation.[21] The presence of obstructive CAD was defined as $\geq$50% stenosis in $\geq$1 major epicardial coronary artery. An angiographic CAD severity index was calculated based on the stenosis severity weighted by proximal lesion.[21]

Definition of chest pain and PChP

Both at baseline and 1 year follow-up, all WISE women were questioned by site physicians and nurses about their experience of pain or discomfort above the waist over the prior year. When asked, 'In the last 12 months have you had pain or discomfort above the waist?' 94% had experienced such symptoms at baseline. The 57 asymptomatic women were excluded from the current analysis. PChP was defined as symptoms at 1 year follow-up as assessed by the same question. Symptoms were considered not persistent (no PChP) if not present at the 1 year follow-up. Consistent with prior WISE findings,[22] the characterization of symptoms was not limited to 'pain' or location in the chest but included other descriptors and locations (e.g. shortness of breath, discomfort, shoulder location).

At baseline and follow-up, all women also completed a brief symptom questionnaire to assess the presence of typical angina, defined as pain that is substernal, precipitated by exertion or emotional stress, and relieved within 10 min by rest or nitroglycerin.[23] Additionally, at baseline, the women completed an extensive symptom checklist regarding specific symptom types (e.g. chest tightness, nausea), locations (e.g. chest, stomach, arm), severity, frequency, triggers (e.g. lower body exertion, during or after meals), and relievers (e.g. rest, heartburn medications), with instructions to check all the relevant items. In addition to specific items, we also assessed the number of items checked in the various categories (e.g. number of locations, triggers, etc.).

Follow-up procedures

Follow-up was conducted by site nurses and physicians through telephone and/or mail contact at 6 weeks and then yearly thereafter. Follow-up consisted of a scripted interview by an experienced nurse or physician. Each woman was queried about symptoms, medication use, CV events since last contact, hospitalizations, and diagnostic or revascularization procedures. In the event of death, a death certificate was obtained. Classification of deaths as CV was performed by WISE investigators masked to angiographic findings. Besides individual events, two composite outcomes were assessed: (i) CV death or MI and (ii) CV event (defined as CV death, MI, CHF, or stroke). As PChP was defined at the 1 year follow-up, only CV events occurring after the 1 year follow-up evaluation were included (*Figure 1*) in the present analysis in order to maintain the predictive nature of PChP.

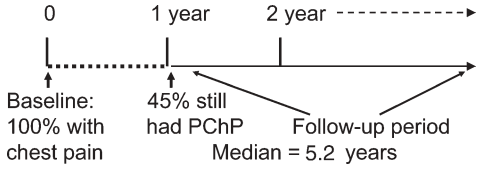


Figure 1 Definition of follow-up period.

Statistical methods

Baseline data are reported as means ± SD. We compared four groups of women (no CAD/no PChP, no CAD/PChP, CAD/no PChP, CAD/PChP), and the major comparisons were between women with PChP vs. those without PChP within the CAD and no CAD subgroups. Because we found a strong relationship between PChP and age, and because age is also a major correlate in WISE of demographic characteristics and CAD risk factors, all *P*-values in *Table 1* (with the exception of age and menopausal status) were adjusted for age using logistic regression.

Because of differing follow-up times due to censoring, we estimated the 6-year CV event rates, beginning after the first year, by using the Kaplan–Meier method. The statistical significance of differences in event rates between women with and without PChP was derived using the log rank statistic for subgroups of those with and without obstructive CAD. The Cox proportional hazards method was used to generate separate hazard ratios and 95% confidence intervals for women with and without CAD. We developed a multivariable Cox proportional hazards model based on the major risk factors for CV events (using Framingham risk criteria) in addition to PChP. We then added specific chest pain and diagnostic parameters, such as ECG results, that provided incremental predictive information. All analyses were performed using the SAS 8.12 software (Cary, NC, USA).

Results

Population characteristics

Overall, 673 out of the 936 (72%) women enrolled in WISE were included in this analysis. Not included were women who were asymptomatic at baseline ($n = 57$) and women without a 1-year symptom assessment ($n = 206$). Compared with the study population, the 57 asymptomatic

Table 1 Demographic and risk factor characteristics by presence/absence of obstructive CAD and presence/absence of PChP. Means ± SD for continuous variables, percentages for frequencies

Characteristics	No obstructive CAD		Obstructive CAD		*P*-Values (no PChP vs. PChP)[a]	
	No PChP $n = 223$	PChP $n = 189$	No PChP $n = 145$	PChP $n = 116$	Within no CAD	Within CAD
Age (years)	58 ± 11	54 ± 10	63 ± 11	59 ± 12	0.0002	0.006
CAD severity score	7.0 ± 3.8	7.4 ± 3.9	27.5 ± 15.7	25.2 ± 16.0	0.05	0.36
Normal coronary arteries (no lesion)	130 (59%)	104 (56%)	–	–	0.15	–
Post-menopausal	165 (74%)	136 (72%)	125 (87%)	87 (76%)	0.65	0.02
Non-white minority	40 (18%)	30 (16%)	38 (26%)	28 (24%)	0.37	0.39
Current smoker	35 (16%)	35 (18%)	32 (22%)	27 (23%)	0.95	0.52
Ever smoked	104 (47%)	95 (50%)	78 (54%)	76 (66%)	0.47	0.17
Diabetes	38 (17%)	32 (17%)	59 (41%)	35 (30%)	0.94	0.06
History of dyslipidaemia	95 (47%)	86 (48%)	85 (63%)	78 (74%)	0.55	0.05
History of hypertension	127 (57%)	104 (55%)	92 (64%)	78 (68%)	0.86	0.64
Family history of CAD	142 (64%)	125 (68%)	88 (65%)	83 (73%)	0.64	0.20
Number of co-morbidities	2.7 ± 1.8	3.1 ± 1.8	3.1 ± 2.0	3.5 ± 2.0	0.01	0.10
Obese (BMI ≥ 30)	94 (43%)	78 (41%)	51 (36%)	46 (40%)	0.46	0.85
Beck depression	8.8 ± 6.8	12.2 ± 8.4	9.3 ± 7.5	12.9 ± 8.7	0.001	0.02
Spielberger Anxiety	18.0 ± 5.2	20.1 ± 6.4	17.7 ± 5.0	20.1 ± 5.4	0.04	0.06
DASI	24.4 ± 15.0	19.7 ± 16.2	17.7 ± 11.9	13.7 ± 11.9	0.002	0.004
Typical angina	67 (30%)	62 (33%)	46 (32%)	47 (40%)	0.65	0.14
Symptom intensity rating (range 1–5)	2.3 ± 1.0	2.6 ± 1.0)	2.6 ± 1.1	2.6 ± 1.0	0.01	0.94
Symptoms almost every day or more	68 (30%)	93 (49%)	49 (34%)	57 (39%)	0.0004	0.01
Number of symptom locations (range 1–11)	3.9 ± 2.4	4.9 ± 2.4	3.5 ± 2.3	4.9 ± 2.0	0.0006	0.0004
Perceived QOL	7.3 ± 1.9	6.6 ± 2.2	7.1 ± 2.2	6.6 ± 2.3	0.003	0.08
History of HRT	126 (57%)	119 (63%)	58 (40%)	63 (56%)	0.04	0.02
Lipid-lowering medications	53 (24%)	46 (24%)	49 (34%)	54 (46%)	0.45	0.01
Anti-hypertensive medications	107 (48%)	80 (42%)	78 (54%)	65 (56%)	0.57	0.67
Psychotropic medications	56 (25%)	79 (42%)	35 (24%)	39 (34%)	0.002	0.11
1-year lipid-lowering[b]	16 (9%)	12 (8%)	37 (39%)	21 (34%)	0.75	0.57
1-year anti-hypertensive[b]	15 (13%)	17 (16%)	20 (30%)	20 (40%)	0.57	0.28

CAD, obstructive CAD, defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery; BMI, body mass index; HRT, hormone replacement therapy; QOL range 1–10, with 10 = best. In addition, no differences were found for education, marital status, environmental stress, current HRT use, hormone levels, BMI, systolic or diastolic blood pressure, presence or absence of metabolic syndrome, positive vs. negative exercise stress test, anaemia, lipids (total cholesterol, LDL-C, HDL-C, triglycerides), inflammatory markers (C-reactive protein, interleukin-6), haemoglobin, specific symptom types, use of anti-ischaemic medications (nitrates, beta blockers, calcium channel blockers), anticoagulant or antiplatelet medications, or baseline ECG characteristics.

[a]All *P*-values reflect comparisons between women with and without PChP: within no CAD: among women without CAD, adjusted for age (except age and post-menopausal, no age adjustment); within CAD: among women with CAD, adjusted for age (exceptions see above).

[b]Percentage of women initiating lipid-lowering or anti-hypertensive medication use between baseline and 1-year follow-up among those not taking these therapies at baseline.

women were much older (mean age 66 vs. 58 years, $P < 0.0001$), and sicker (54 vs. 39% with obstructive CAD, $P = 0.01$; CAD severity score 22.4 vs. 14.3, $P = 0.007$). However, they were less depressed ($P < 0.0001$), had less anxiety symptoms ($P = 0.04$), and reported a better quality of life (QOL) than those with chest pain at baseline ($P < 0.0001$). Most (60%) of these women listed an abnormal stress test as their primary reason for referral to coronary angiography.

Among the 206 women without a 1-year symptom assessment, 18 women died during the first year, 38 chose not to participate in any follow-up, 117 had a 6-week follow up only, and 33 did not receive their 1-year follow-up but were re-contacted for later follow-ups. These women were slightly but significantly younger (56 vs. 58 years, $P = 0.009$) but did not differ significantly in any other baseline characteristics when compared with the study population.

The median age of the study population ($N = 673$) was 58 years (range 21–86), and 20% were racial minorities, primarily black. Sixty-eight percent of the women had at least two CAD risk factors [including diabetes (24%), history of dyslipidemia (55%), history of hypertension (60%), current smoking (19%), and obesity (BMI $\geq$ 30, 40%)]. Obstructive CAD was present in 39% of the women, and 45% had PChP. Notably, there was no difference in the prevalence of PChP (44 vs. 46%) comparing women with and without obstructive CAD.

Tabulation of demographic and risk factor variables by PChP within the CAD subgroups (*Table 1*) shows that women with PChP but no obstructive CAD were younger ($P = 0.0002$), and had lower functional capacity as measured by the Duke Activity Status Index (DASI) ($P = 0.002$). They had a slightly but statistically higher ($P = 0.05$, age adjusted) mean angiographic CAD severity score (7.4 ± 3.9 vs. 7.0 ± 3.8) as compared with those without PChP. They rated their symptoms at baseline as more intense ($P = 0.01$), more frequent ($P = 0.0004$), and occurring in more body locations ($P = 0.0006$), however, no differences were found for typical angina. They also had a higher prevalence of co-morbidities ($P = 0.01$) and psychological problems, such as depression ($P = 0.001$) and anxiety ($P = 0.04$), were more likely to be using antidepressant or anti-anxiety medications ($P = 0.002$), and rated their overall QOL as lower ($P = 0.003$). No differences were found for ECG characteristics. Notably, 57% of the women without obstructive CAD were found to have angiographically normal coronary arteries (no lesions), but this did not differ by the presence or absence of PChP.

These differences were found to a lesser extent in women with obstructive CAD. PChP was not associated with CV risk factors, typical angina, baseline ECG characteristics, or baseline lipid-lowering or anti-hypertensive medication use. Change in the use of these therapies at 1 year did not differ by PChP. However, among women diagnosed with obstructive CAD who were not receiving lipid-lowering or anti-hypertensive therapies at baseline, 37 and 34% had initiated these respective therapies at 1 year follow-up. In contrast, among those diagnosed as having no CAD, only 9 and 14% initiated these therapies. No differences were observed between women with and without PChP. Interestingly, regardless of CAD, women with PChP were more likely at baseline to report chest, neck, back, shoulder, arm, hand, and throat pain but not jaw, oesophagus, or stomach pain, and the number of sites was highly associated with PChP ($P = 0.0006$ and $P = 0.0004$).

Prediction of CV events

The median follow-up period, beginning after the first year, among surviving patients was 5.2 years [ranging from 5.0 to 5.5 years ($P = 0.39$) among the four groups]. Among the 673 women, 72 died of any cause, 53 died from CV causes, 24 suffered a non-fatal MI, 44 were hospitalized for CHF, and 33 had a stroke. A total of 189 women were hospitalized for chest pain not associated with any of the above events, and 196 underwent repeat angiography.

Women without obstructive CAD also experienced major CV events, although at a far lower rate than the subgroup with obstructive CAD (*Figure 2*). However, in the former, those with PChP had more than three times the 6-year rate of non-fatal MI (5.3 vs. 1.6%, $P = 0.11$), more than three times the rate of strokes (7.5 vs. 2.0%, $P = 0.03$), twice the rate of CHF events (7.5 vs. 3.7%, $P = 0.38$), and 30% more CV deaths ($P = 0.73$). No appreciable differences were observed for all-cause mortality. Women with obstructive CAD had about the same rate of MIs as those without obstructive CAD, and those with PChP had almost twice the rate of MIs (7.7 vs. 4.2%, $P = 0.34$) and the same rates of CHF, stroke, CV deaths, and all-cause mortality. The 6-year incidence of all combined CV events was twice as high in women with PChP in the non-obstructive CAD subgroup (20.5 vs. 10.1%, $P = 0.03$) but not in the obstructive CAD subgroup (38.2 vs. 36.8%, $P = 0.72$). When predicting composite CV events, the hazard ratio for PChP was 1.89 (1.06, 3.39), $P = 0.03$ in women without and 1.17 (0.76,1.80), $P = 0.49$ in those with obstructive CAD (*Figure 3*).

In both subgroups of women, those with PChP underwent repeat coronary angiography at a higher rate than those without PChP (34.5 vs. 21.2%, $P = 0.01$ in those without obstructive CAD; 64.3 vs. 39.8%, $P = 0.0006$ in those with obstructive CAD). In women with obstructive CAD, 39.8% with and 23.2% without PChP underwent a revascularization procedure over 6 years ($P = 0.02$) (not tabulated).

In order to evaluate the potential confounding role of minimal lesions in women without obstructive CAD, we repeated the same analyses in women with normal coronary angiograms (57% of the women without obstructive CAD). The same higher 6-year rates for MI, CHF, and stroke were observed in women with vs. without PChP (composite CV events 16.6 vs. 5.1%, $P = 0.03$).

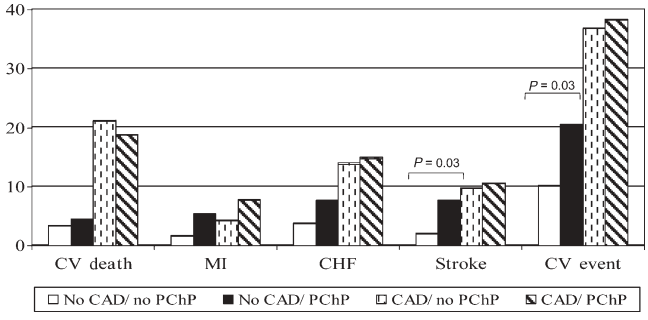
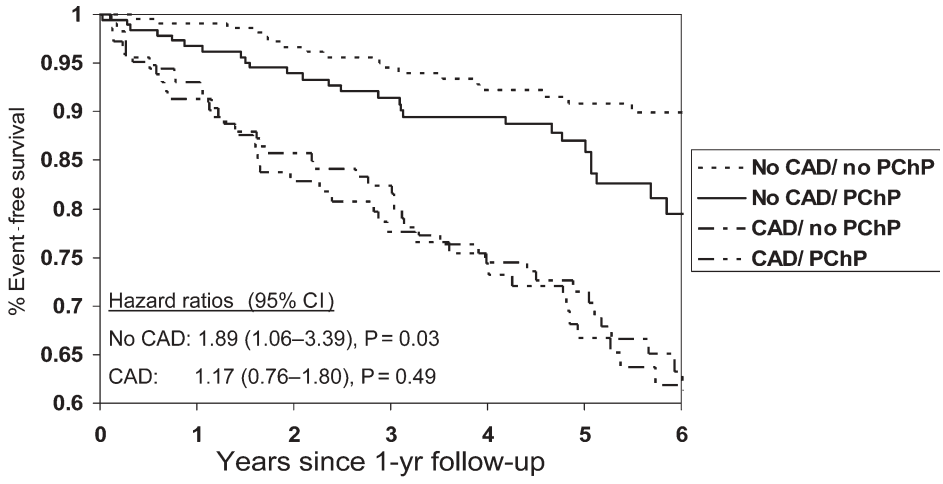


Figure 2 Six-year CV event rates by CAD and PChP. CV events defined as CV death, MI, CHF, or stroke. Six-year event rates were estimated by Kaplan–Meier method.



Number at Risk:

No CAD/no PChP	223	215	190	173	154	109	65
No CAD/PChP	189	179	157	139	128	80	38
CAD/no PChP	145	129	110	96	82	60	33
CAD/PCh P	116	103	82	73	67	46	22

Figure 3 Event-free survival from CV events by CAD and PChP. CV events defined as CV death, MI, CHF, or stroke.

Multivariable prediction of CV outcomes

In order to determine whether PChP was an independent predictor of CV events, a multivariable Cox proportional hazards model was calculated for all women without obstructive CAD. *Table 2* gives the multivariable risk model for predicting CV events in such women. Notably, smoking, CAD severity, diabetes, and increased QT_c interval were significant independent predictors of CV events. PChP added to this model remained a statistically significant ($P = 0.049$) predictor of CV events. In this group of women without obstructive CAD, age, history of hypertension or dyslipidemia, and use of anti-hypertension medications did not predict CV events.

Discussion

Women without obstructive CAD at coronary angiography have been considered a low risk population,[4,17,24–31] and indeed, these women in our study had a lower overall CV event rate compared with women with obstructive CAD. However, our data suggest that PChP in the absence of obstructive CAD is not a benign condition. These women experienced major CV events such as MI and stroke at approximately double the rate found in women with neither PChP nor CAD. This association between PChP and adverse CV events was not found in women with obstructive CAD.

Although prior studies address the issue of chest pain in the absence of obstructive CAD,[4,30,32,33] very little is known about chronic chest pain in such patients with regard to adverse CV outcomes. Prior work has demonstrated a high prevalence of PChP in patients without obstructive CAD, noting it as a typical outcome in about half of the patients.[4,30,32,33] However, to our knowledge, PChP *per se* has not been studied as a predictor of CV outcome. The need for investigating the risk associated with chronic chest pain syndromes has recently been discussed in detail in an NHLBI/AHA/WISE workshop.[34]

One possible explanation for our findings may be that these women have atherosclerosis that is relatively diffuse and not apparent as focal stenosis by angiography (B. Sharaf, submitted for publication). In support of this possibility was the finding of a mildly elevated CAD severity score in those with vs. without PChP, and that severity score was an independent predictor of adverse events. Against this possibility, we found that PChP was predictive of adverse events even among the subgroup (57%) of women with completely normal coronary angiograms.

A major difference between women with and without PChP was that the former were experiencing a higher prevalence and severity of psychological symptoms, including depression, anxiety, and panic disorder. Ever since Freud's description of hysteria in women, 'non-cardiac chest pain' has often been ascribed to such psychological symptoms and the two are often shown to correlate.[31,35] Moreover, psychological problems worsen the CV prognosis in women.[36,37] However, such evidence does not necessarily prove the causal direction between unexplained PChP symptoms and psychological problems. It has been suggested that depression and anxiety may in fact be a normal and expected reaction to severe, debilitating, and persistent symptoms of undetermined aetiology,[38,39] i.e. can also be considered an outcome of persistent and unexplained symptoms rather than vice versa. The current results support this, in that adjustment for psychosocial variables in our multivariable model did not significantly alter our results. More study is needed to resolve this issue.

Other evidence suggests that much of women's chest discomfort in the absence of obstructive CAD may be due to coronary macrovessel[40] or microvessel[25] dysfunction that limits the coronary microcirculation during stress.[41–44] Recent work from the WISE study has demonstrated a high prevalence of abnormal microvascular coronary flow

Table 2 Multivariable model of CV events among WISE women with no obstructive CAD ($n = 412$, 47 events[a])

Predictor	Hazard ratio	95% confidence intervals	*P*-value
PChP	1.95	1.004, 3.79	0.049
ECG QT_c interval[b]	1.02	1.005, 1.03	0.004
Ever smoked	2.80	1.38, 5.66	0.004
CAD severity score	1.08	1.01, 1.16	0.02
Diabetes	2.52	1.09, 5.82	0.03
Anti-hypertension medications	2.00	0.92, 4.32	0.08
History of hypertension	0.65	0.30, 1.41	0.27
History of dyslipidaemia	1.18	0.61, 2.26	0.63
Age	1.01	0.97, 1.05	0.66

Cox proportional hazards modeling was used. Non-significant predictors: non-white minority, current smoking, family history of CAD, BMI, obesity (BMI $\geq$ 30), menopausal status, co-morbid conditions, psychological distress, functional capacity, typical angina, chest pain symptom frequency, individual symptom locations, number of symptom locations, perceived QOL, other medications (HRT, lipid-lowering, anti-ischaemic), other ECG characteristics (signs of old infarcts, LVH, intraventricular conduction defects, ST-segment depression or elevation).

[a]For multivariable models, $n = 368$ due to missing ECG data; 41 events.

[b]Corrected for rate.

reserve and macrovascular endothelial dysfunction,[12,14,45,46] and resultant abnormal metabolic responses to stress consistent with myocardial ischaemia.[10,13] Additionally, a recent study[47] on men and women has demonstrated that a dipyridamole echocardiography test, diagnostic for myocardial ischaemia, performed on patients with chest pain and no obstructive CAD can identify those at higher long-term risk for CV events. Other studies have indicated that such impairment may not just be functional but may also represent structural changes in the small coronary arteries,[48,49] and appear to predict an adverse CV outcome.[7,50,51]

It is currently not known whether these structural and functional coronary abnormalities represent a distinct disease state or whether they are simply part of the spectrum of progressive atherosclerotic CAD. The recent results by Bugiardini,[19] demonstrating that coronary endothelial dysfunction predicts the development of future obstructive CAD, imply the latter. Similarly, an older study[52] reported that 27% of patients with mild disease (<50% diameter narrowing) and recurrent chest pain progressed to obstructive CAD over a mean of 42 months, whereas those patients with normal arteries did not. Our findings demonstrate an adverse association between persistent symptoms and CV outcome even in women with normal coronary arteries. While we did not evaluate repeat angiograms during the follow-up time and therefore cannot exclude the development of severe large vessel obstructive CAD as an explanation for the adverse CV events, plaque erosion with embolization in an already disordered microvasculature is also a plausible mechanism. The distribution of events in the no obstructive CAD group, relatively equal across CV death, MI, CHF, and stroke, are most consistent with a generalized atherosclerotic process potentially involving both the macro and microvascular systems.

The current results suggest that the presence of chest pain in the absence of obstructive CAD should raise concern that the patient may be at higher risk for adverse CV events. Thus, PChP may be considered a risk 'marker.' The finding of an adverse prognosis in these women may simply reflect the lack of clinical follow-up subsequent to an angiographic finding of normal or near-normal coronaries. Evidence is accumulating that women with angina and normal coronary arteries may be helped with a wide variety of therapies including nitrates, beta blockers, imipramine, statins, angiotensin-converting enzyme inhibitors, L-arginine, and exercise training.[11] Our current results show that women with no obstructive CAD did not receive more aggressive risk factor reduction, while those with obstructive CAD were more likely to have lipid-lowering and antihypertensive therapies initiated during the follow-up period. Indeed, the women with no obstructive CAD were more likely to receive sedative or hypnotic medications that are unlikely to protect against adverse outcomes. Notably, most of the WISE women had a sufficient burden of CVD risk factors to warrant aggressive risk factor modification therapy.

The major implication of this study is that women with no obstructive CAD and chronic chest pain symptoms should likely undergo additional evaluations due to their relatively higher risk of adverse CV events. Such evaluation might include provocative coronary angiographic assessment for macro and microvascular dysfunction and documentation of atherosclerosis if not evident on the coronary angiogram. The presence of CV risk factors and/or evidence of atherosclerosis or endothelial dysfunction should be treated with risk factor modification. Moreover, these patients should be closely followed and monitored for the development of infarctions, strokes, and other vascular events rather than discharged from care as 'non-cardiac.' Future research should be aimed at developing risk stratification tools, ideally non-invasive, available to practicing physicians.

Study limitations

First, low statistical power likely reduced our ability to differentiate groups with regard to individual types of CV events. However, the results showed a consistent trend throughout as well as improved significance when combining these events. We believe that low power was also a partial explanation for the attenuation of the relationship between PChP and CV events in the no obstructive CAD women when adjusting for a significant risk model. It is clear that these findings

need to be confirmed in a larger study over a longer observation period. Second, outcomes were primarily obtained from patients' information, although deaths were verified and we frequently verified other events against medical records as per our WISE protocol. However, we cannot exclude that knowledge of angiographic results and PChP may have influenced outcome reporting, choice of therapy, and actual outcomes. Moreover, we did not collect angiographic information for women undergoing repeat angiography. Third, because our study cohort was an angiographic referral population, these results may not be generalizable to the general population. However, the possible referral bias may be outweighed by the possibility that these women were already pre-screened by their referring physician for obvious non-cardiac causes such as gastro-oesophageal reflux and psychiatric disorders. Finally, even within the female angiographic population, only 50% of women eligible for WISE participation chose to enroll, and we have no further information on how the women who did not enroll differed from our study population. We further excluded 57 asymptomatic women from this analysis (who turned out to be older and sicker), thus further limiting the generalizability of our results.

Conclusions

Our findings suggest that, contrary to popular belief, PChP in the absence of obstructive CAD is not benign and is associated with adverse CV outcomes. Women without obstructive CAD but PChP had more than twice the number of CV events, including MIs, strokes, CHF, and CV deaths compared with those without PChP. Women with no obstructive CAD and PChP should have aggressive risk factor reduction therapy designed to reduce adverse CV events as well as follow-up monitoring. Ongoing efforts should be directed at understanding the underlying pathophysiology as well as developing risk stratification tools.

Acknowledgements

This work was supported by contracts from the National Heart, Lung and Blood Institutes, nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants U0164829, U01 HL649141, U01 HL649241, a GCRC grant MO1-RR00425 from the National Center for Research Resources, and grants from the Gustavus and Louis Pfeiffer Research Foundation, Denville, New Jersey, USA, The Women's Guild of Cedars-Sinai Medical Center, Los Angeles, California, USA, The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, Pennsylvania, USA, and QMED, Inc., Laurence Harbor, New Jersey, USA.

Conflict of interest disclosure: There are no conflicts of interest to disclose by any of the co-authors.

A preliminary analysis of earlier versions of these data was previously presented as a poster at the AHA 4th Scientific Forum on Quality of Care and Outcomes Research in CV Disease and Stroke, Washington, DC, USA, 13–14 October, 2002.

References

1. Kemp HG, Elliott WC, Gorlin R. The anginal syndrome with normal coronary arteriography. *Trans Assoc Am Physicians* 1967;**80**:59–70.
2. Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 1967;**276**:1063–1066.
3. Kennedy JW, Killip T, Fisher LD, Alderman EL, Gillespie MJ, Mock MB. The clinical spectrum of coronary artery disease and its surgical and medical management, 1974–1979. The coronary artery surgery study. *Circulation* 1982;**66**:III16–23.
4. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ* 1994;**308**:883–886.
5. American Heart Association. Heart disease and stroke statistics–2005 Update **http://www.americanheart.org/downloadable/heart/1105390918119HDSStats2005Update.pdf** (2 September 2005).
6. Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM. Chest pain with angiographically insignificant arterial obstruction: clinical presentation and long-term follow-up. *Am J Med* 1980;**68**:813–817.
7. Cannon RO III, Camici PG, Epstein SE. Pathophysiological dilemma of syndrome X. *Circulation* 1992;**85**:883–892.
8. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;**346**:1948–1953.
9. Quyyumi AA, Cannon RO III, Panza JA, Diodati JG, Epstein SE. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation* 1992;**86**:1864–1871.
10. Buchthal SD, den Hollander JA, Bairey Merz CN, Rogers WJ, Pepine CJ, Reichek N, Sharaf BL, Reis S, Kelsey SF, Pohost GM. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med* 2000;**342**:829–835.
11. Bugiardini R, Bairey Merz CN. Angina with 'normal' coronary arteries. A changing philosophy. *JAMA* 2005;**293**:477–484.
12. Reis SE, Holubkov R, Smith AJC, Kelsey SF, Sharaf BL, Reichek N, Rogers WJ, Bairey Merz CN, Sopko G, Pepine CJ. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. The WISE investigators. *Am Heart J* 2001;**141**:735–741.
13. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, Doyle M, Olson MB, Pepine CJ, den Hollander J, Sharaf B, Rogers WJ, Mankad S, Forder JR, Kelsey SF, Pohost GM. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease. Results from the National Institute of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;**109**:2993–2999.
14. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, Sharaf BL, Smith KM, Olson MB, Johnson BD, Sopko G, Handberg E, Pepine CJ, Kerensky RA. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women. Results from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;**109**:722–725.
15. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. 7 years survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol* 1986;**7**:479–483.
16. Papanicolaou MN, Califf RM, Hlatky MA, McKinnis RA, Harrell FE, Mark DB, McCants B, Rosati RA, Lee KL, Pryor DB. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. *Am J Cardiol* 1986;**58**:1181–1187.
17. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol* 1995;**25**:1013–1018.
18. Pitts WR, Lange RA, Cigarroa JE, Hillis LD. Repeat coronary angiography in patients with chest pain and previously normal coronary angiogram. *Am J Cardiol* 1997;**80**:1086–1087.
19. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. *Circulation* 2004;**109**:2518–2523.
20. Bairey Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, Rogers WJ, Sharaf BL, Sopko G. The women's ischemia syndrome (WISE) study: protocol design, methodology, and feasibility report. *J Am Coll Cardiol* 1999;**33**:1453–1461.
21. Sharaf BL, Pepine CJ, Kerensky RA, Reis SE, Reichek N, Rogers WJ, Sopko G, Kelsey SF, Holubkov R, Olson M, Miele NJ, Williams DO, Bairey Merz CN. Detailed angiographic analysis of women with suspected ischaemic chest pain (pilot phase data from the NHLBI-sponsored women's ischemia syndrome evaluation [WISE] study angiographic core laboratory). *Am J Cardiol* 2001;**87**:937–941.

22. Johnson BD, Kelsey SF, Bairey Merz CN. Clinical risk assessment in women: chest discomfort. Report from the WISE study. In: Shaw LJ, Redberg RF eds. *Coronary Disease in Women Evidence-Based Diagnosis and Treatment*. Totowa, NJ: Humana Press; 2003, p129–141.
23. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;**300**:1350–1358.
24. Bemiller CR, Pepine CJ, Rogers AK. Long-term observations in patients with angina and normal coronary arteriograms. *Circulation* 1979; **47**:36–43.
25. Cannon RO III, Epstein SE. 'Microvascular angina' as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988; **61**:1338–1343.
26. Day LJ, Sowton E. Clinical features and follow-up of patients with angina and normal coronary arteries. *Lancet* 1976;**1**:334–337.
27. Faxon DP, McCabe CH, Kreigel DE, Ryan TJ. Therapeutic and economic value of a normal coronary angiogram. *Am J Med* 1982;**73**:500–505.
28. Gurevitz O, Jonas M, Bayko V, Rabinowitz B, Reicher-Reiss H. Clinical profile and long-term prognosis of women $<$ or $=$50 years of age referred for coronary angiography for chest pain. *Am J Cardiol* 2000;**85**:806–809.
29. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary angiograms: a follow-up study of functional status. *N Engl J Med* 1980;**303**:1249–1252.
30. Cannan CR, Miller TD, Christian TF, Bailey KR, Gibbons RJ. Prognosis with abnormal thallium images in the absence of significant coronary artery disease. *Am J Cardiol* 1992;**70**:1276–1280.
31. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary heart disease: a behavioral phenomenon. *Am Heart J* 1984;**108**:67–72.
32. Hemingway H, Shipley M, Britton A, Page M, Macfarlane P, Marmot M. - Prognosis of angina with and without a diagnosis: 11 year follow up in the Whitehall II prospective cohort study. *Brit Med J* 2003;**327**:895.
33. Tew R, Guthrie EA, Creed FH, Cotter L, Kisley S, Tomenson B. A long-term follow-up study of patients with ischaemic heart disease vs. patients with nonspecific chest pain. *J Psychosom Res* 1995;**39**:977–985.
34. Bairey Merz CN, Bonow RO, Sopko G, Balaban RS, Cannon RO, Gordon D, Hand MM, Hayes SN, Lewis JF, Manolio TA, Maseri A, Nabel EG, Desvigne Nickens P, Pepine CJ, Redberg RF, Rossouw JE, Selker HP, Shaw LJ, Waters DD. Women's ischemic syndrome evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2–4, 2002: executive summary. *Circulation* 2004;**109**:805–807.
35. Tueth MJ. Managing recurrent nonischemic chest pain in the emergency department. *Am J Emerg Med*, 1997, 170–172. 15.
36. Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J. Depression and cardiovascular squelae in postmenopausal women. *Arch Int Med* 2004; **164**:289–298.
37. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;**99**:2192–2217.
38. Frobert O, Funch-Jensen P, Bagger JP. Chest pain and the esophagus. *Ann Int Med* 1997;**126**:740–741.
39. Johnson BD, Bairey Merz CN, Matthews K, Krantz DS, Olson MB, Kelsey SF, Pakstis D, Cornell CE, Kerensky RA. Persistent chest pain (PCP) and psychological disorders: cause or effect? The NHLBI-sponsored WISE study. (Abstract). *Circulation* 2001;**104**:II-724.
40. Maseri A, Severi S, De Nes M. 'Variant' angina. One aspect of a continuous spectrum of vasospastic myocardial ischemia. *Am J Cardiol* 1978; **42**:1019–1035.
41. Camici PG, Marraccini P, Lorenzoni R, Buzzigoli G, Pecori N, L'Abbate A, Marzilli M. Coronary hemodynamics and myocardial metabolism in patients with syndrome X: response to pacing stress. *J Am Coll Cardiol* 1991;**17**:1461–1470.
42. Chen JW, Lin SJ, Ting CT. Syndrome X: pathophysiology and clinical management. *Chin Med J (Taipei)* 1997;**60**:177–183.
43. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichek N, Rogers WJ, Walsh EG, Fuisz AR, Kerensky R, Detre KM, Sopko G, Pepine CJ. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the women's ischemia syndrome evaluation (WISE) study. *Am J Coll Cardiol* 1999;**33**:1469–1475.
44. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme a reductase in cardiac syndrome X: role of superoxide dismutase activity. *Circulation* 2004;**109**:53–58.
45. Pepine CJ, Kerensky RA, Lambert CR, Smith KM, von Mering GO, Sopko G, Bairey Merz CN. Some thoughts on the vasculopathy of women with ischaemic heart disease. *J Am Coll Cardiol* 2006;**47**:30S–35S.
46. Quyyumi AA. Women and ischaemic heart disease. Pathophysiologic implications from the women's ischemia syndrome evaluation (WISE) study and future research steps. *J Am Coll Cardiol* 2006;**47**:66S–71S.
47. Sicari R, Palinkas A, Pasanisi EG, Venneri L, Picano E. Long-term survival of patients with chest pain syndrome and angiographically normal or near-normal coronary arteries: the additional prognostic value of dipyridamole echocardiography test (DET). *Eur Heart J* 2005;**26**:2136–2141.
48. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small vessel coronary disease in patients with angina pectoris and patent large coronary arteries. *Circulation* 1986;**74**:964–972.
49. Suzuki H, Takeyama Y, Koba S, Suwa Y, Katagiri T. Small vessel pathology and coronary hemodynamics in patients with microvascular angina. *Int J Cardiol* 1994;**43**:139–150.
50. Ciavolella M, Avella A, Bellagamba S, Mangieri E, Nigri A, Reale A. Angina and normal epicardial coronary arteries: radionuclide features and pathophysiological implications at long-term follow-up. *Coron Artery Dis* 1994;**5**:493–499.
51. Radice M, Giudici V, Marinelli G. Long-term follow-up in patients with positive exercise test and angiographically normal coronary arteries (syndrome X). *Am J Cardiol* 1995;**75**:620–621.
52. Marchandise B, Bourassa MG, Chaitman BR. Angiographic evaluation of the natural history of normal coronary arteries and mild coronary atherosclerosis. *Am J Cardiol* 1978;**41**:216–220.