Hostility Scores Are Associated With Increased Risk of Cardiovascular Events in Women Undergoing Coronary Angiography: A Report from the NHLBI-Sponsored WISE Study

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Objective: To evaluate hostility-related personality traits assessed by the Cook Medley Hostility Inventory and to relate these to the occurrence of adverse cardiac events in women with suspected myocardial ischemia. **Methods:** The cohort included 506 women with suspected coronary artery disease from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. We examined individual components of the Cook Medley Hostility Score (CMHS) measuring cynicism, hostile affect, and aggressive responding, and a total CMHS (sum of these three) and associations with adverse events (defined as hospitalization for angina, nonfatal myocardial infarction, stroke, congestive heart failure (CHF) other vascular events and death) during 3 to 6 years follow-up using Cox proportional hazard modeling. **Results:** Women with adverse events had higher total CMHS (10.6 ± 5.5) than women without any of these events (9.2 ± 5.1) $p = .02$. They also had poorer survival by Kaplan-Meier analysis (log-rank $p < .05$). Unadjusted Cox models showed that the individual scores of cynicism and aggressive responding and the total CMHS were associated with more adverse events (all $p < .05$). Women with total CMHS above the median had a 35% increase risk of an adverse event in comparison to women with lower scores. In a risk-adjusted Cox model, the hazard ratio for an adverse event was 1.5 ($p = .03$) for women with total CMHS above the median. **Conclusion:** In this cohort of women with suspected myocardial ischemia, higher Cook Medley scores reflecting cynicism, hostile affect, and aggressive responding were associated with poorer 3 to 6 year event-free survival and a higher risk of adverse events. After adjusting for risk factors and CAD, the association with risk for adverse events increased. **Key words:** hostility, cardiovascular events, women.

CAD = coronary artery disease; **CHF** = congestive heart failure, **HT** = hormone therapy; **WISE** = Women's Ischemia Syndrome Evaluation; **CHD** = coronary heart disease; **MI** = myocardial infarction; **HERS** = Heart and Estrogen/Progestin Replacement Study; **NHLBI** = National Heart, Lung, and Blood Institute; **CMHS** = Cook Medley Hostility Score.

INTRODUCTION

Early studies, including MRFIT (Multiple Risk Factor Intervention Trial) showed that measures of hostility or its correlates were associated with coronary heart disease (CHD) and adverse outcomes (myocardial infarction (MI), all cause mortality) in men (1–6). Later studies, also in men, suggested that the association of hostility with MI was age-dependent such that hostility was only a risk indicator for first MI in men younger than 50 years of age (7). Studies with both men and women found that hostility was associated with long-term risk of hypertension, CHD and was also predictive of all cause mortality (8–12). Although other studies have shown little or inconsistent associations between hostility measures and CHD or events (13,14), overall the results indicate that hostility is an independent risk factor for CHD (15,16).

Many of these early studies on the association of psychosocial risk factors with coronary heart disease and events have been done in exclusively male cohorts (1–7,17) or in datasets that included few women (18–20). Psychosocial risk factors for heart disease in women have not been well investigated, and many of the studies have been inconclusive (21). In postmenopausal women, the hostile affect subscale of the Cook Medley was linearly associated with a 20% excess risk for MI (22). Similarly, in the HERS (Heart and Estrogen/Progestin Replacement Study), hostility was found to be an independent risk factor for recurrent events in postmenopausal women with coronary heart disease (23). We investigated the association of hostility and risk of adverse events in women with symptoms suggesting suspected coronary artery disease and myocardial ischemia. As part of this evaluation, we examined associations of hostility scores with traditional coronary risk factors and coronary artery disease (CAD).

METHODS

The WISE is a National Heart, Lung, and Blood Institute (NHLBI) sponsored four-center study that aims to improve diagnostic testing in the evaluation of ischemic heart disease in women. Details of the protocol and design of the WISE have been published (24). Briefly, a total of 954 women aged 18 years and older were enrolled between 1996 and 2000. Each center obtained institutional review board approval and participant consent before the initiation of testing. Women had clinically indicated angiograms based on chest pain and/or suspected myocardial ischemia. Baseline evaluation included a physical exam and the collection of demographic and psychosocial data. Major exclusion criteria included comorbidity that could compromise 1-year follow-up, pregnancy, cardiomyopathy, and New York Heart Association class IV congestive heart failure. Data collection for the Cook Medley

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This study 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; National Institutes of Health Grants U01-HL64829, U01-HL64914, and U01-HL64924; General Clinical Research Center Grant MO1-RR00425 from the National Center for Research Resources. Also supported by grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, New Jersey; The Women's Guild of Cedars-Sinai Medical Center, Los Angeles, California; and The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, Pennsylvania.

Received for publication July 4, 2004; revision received March 5, 2005.

DOI: 10.1097/01.psy.0000170830.99263.4e

0033-3174/05/6704-0546

began about 6 months after the start of recruitment for the overall study, resulting in a smaller sample size ($n = 506$) for this component of the project.

Psychological Measures

The CMHS used in the WISE study consisted of 27 items from the larger 50-item version of the Cook Medley Hostility Inventory. These 27 items are defined as the total Cook Medley (CMHS) and included the sum of the subscales of cynicism, hostile affect, and aggressive responding. Scores range from 0 to 27. Higher scores indicate bitterness, mistrust, and cynicism (25). Cynicism often refers to "the belief that others are motivated by selfish concerns, and mistrust is the often co-occurring expectation that others are likely to be provoking or hurtful" (16). Aggressive responding can take the form of "verbal assault including insult, sarcasm, rudeness, or direct physical assault" (16). This subset of the Cook Medley (cynicism, aggressive responding, and hostile affect) has been found to be a better predictor of health outcomes than the full scale (26). When these factors are considered together they constitute a general trait of hostility that encompasses "a devaluation of worth and motives of others" as well as "a relational view of being in opposition to others and a desire to inflict harm" (16).

Quantitative Angiography

A core laboratory at Rhode Island Hospital analyzed all coronary angiograms. Measurements included quantitative assessment as to the presence, severity, and complexity of epicardial artery stenoses, using previously published methods (27). Obstructive coronary artery disease (CAD) was defined as ≥50% stenosis in ≥1 epicardial coronary artery. A severity score (modified Gensini index), defined as an aggregate of percent luminal stenosis, extent and location of stenosis, and degree of collateral vessels was also assigned (27). And we also defined CAD severity by maximum percent stenosis in any vessel.

Follow-up

At 6 weeks and yearly for 3 to 6 years (depending on the year of intake into the study), follow-up data were collected either in person or by a scripted telephone interview by an experienced nurse, physician, or both. Participants were queried for the occurrence of adverse events requiring hospitalization, and referring physicians were contacted for confirmation dates and documentation. Deaths were captured from patient records. In the event of death, a death certificate was obtained, and a WISE event committee reviewed available information to determine the likelihood of a cardiovascular etiology, the latter included as a study outcome.

Statistical Methods

Data are presented as means and the SD for continuous variables and frequencies for categorical variables. Spearman rank correlations were used to assess relationships of the individual components and the total CMHS with cardiovascular risk factors and with each other. χ^2 (discrete variables) and Wilcoxon tests (continuous variables) were used to compare risk factors of women with scores above and below the median for the total CMHS and the individual components. Comparisons of scores of women with events to those without events were also done using Wilcoxon tests. Standard Kaplan-Meier techniques were used to estimate cumulative incidence rate of adverse events, with the log-rank statistic to assess differences between those above and below the median cutpoint of the total CMHS. Unadjusted and adjusted Cox proportional hazards models were used to assess risk of an adverse outcome. Univariate predictors of events as well as those variables that were associated with differences in the Cook Medley scores were entered into a forward step Cox proportional hazards model. Variables were chosen for entry into the model based on prior relevant literature, investigator experience, and significant univariate and multivariate analysis. The following variables were entered into the model: age (per 10 years), education (high school versus less than high school), HDL-C, history of diabetes, CAD (yes/no), history of dyslipidemia (yes/no), race, waist circumference (in inches), ever smoked, current hormone therapy (HT), and a variable that defines the median split of the total CMHS. Criterion for entry into the model was 0.05. Separate models were also run with the three components (cynicism, aggressive responding, and hostile affect) entered in the model as continuous variables instead of the median of the total CMHS. All tests were two-sided, and $p < .05$ were considered statistically significant. Analyses were performed using SAS software release 8.2 (SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

Baseline characteristics of these women are summarized in Table 1. The women were mostly postmenopausal (mean age 58 years), with approximately 50% taking hormone therapy. A history of hypertension and dyslipidemia were the most prevalent risk conditions. One-third had angiographic evidence of CAD defined as ≥50% stenosis in one or more epicardial arteries. About 40% were obese (body mass index ≥30), one-third of the women reported use of lipid-lowering medication (mainly statins) and 39% beta-blockers.

Overall Psychosocial Scores

The total CMHS and the individual components appear in Table 2. The group had a median total score of 9, and we used this as the cut point for much of the analyses.

Association of Cook Medley Scores with Demographic Characteristics and Risk Factors

There was an inverse association between age and total CMHS ($r = -.12$, $p = .01$), and both the aggressive responding ($r = -.11$, $p = .02$) and the hostile affect ($r = -.13$, $p = .003$) subscores. Of the risk factors listed in Table 1, there was also a significant negative association of total scores with HDL-C ($r = -.15$, $p < .001$), positive association of total CMHS with waist circumference ($r = .15$, $p < .001$) and diastolic blood pressure ($r = .10$, $p = .02$). Categorical analyses resulted in similar findings. Women with scores above the median were somewhat younger (57 years versus 59 years, $p < .05$), less educated, and more likely to be nonwhite (both $p < .001$). Similarly those with scores above the median were likely to have lower HDL-C levels, larger waist circumferences, higher diastolic blood pressures (all $p < .001$), and to be current smokers (26% versus 12%, $p < .001$), but less likely to use hormone therapy (42% versus 58%, $p = .003$). The Cook Medley cynicism is correlated with both the CM hostile affect of $r = .52$, $p = .0001$, and the CM aggressive responding of $r = .36$, $p = .0001$. Similarly, the CM aggressive responding is correlated with the hostile affect component of $r = .36$, $p = .0001$.

Medication Use

No differences were noted in use of lipid-lowering medication or anti-hypertensive drug use (ACE or beta blockers) comparing the use of medication for women with scores above and below the median of the total CMHS.

Association With Coronary Artery Disease at Baseline

We examined the association of hostility scores, both total score and the individual components with several measures of coronary artery disease at baseline (study intake). There was no association of scores with CAD as defined by the dichot-

TABLE 1. Characteristics of the Study Population

Characteristic	Total	>Total Median	≤Total Median
Number	506	247	259
Age (yrs) mean ± SD*	58 ± 11	57 ± 11	59 ± 11
Education (High school or higher)**	43%	32%	53%
White (%)**	83%	77%	89%
Postmenopausal (%)	73%	72%	73%
Current HT* (Postmenopausal only)	50%	42%	58%
Hx. Hypertension	58%	61%	55%
Hx. Diabetes	23%	26%	21%
Hx. Dyslipidemia	56%	56%	56%
Current smoker**	19%	26%	12%
Ever smoked	51%	52%	49%
Obese (body mass index ≥ 30)	40%	42%	37%
CAD (≥50% stenosis in ≥1 epicardial artery	33%	32%	34%
Total cholesterol (mg/dl) mean ± SD	194 ± 44	197 ± 46	194 ± 42
LDL-C (mg/dl) mean ± SD	112 ± 38	114 ± 42	109 ± 35
HDL-C (mg/dl) mean ± SD**	54 ± 13	52 ± 12	56 ± 13
Triglycerides (mg/dl) mean ± SD	194 ± 44	197 ± 46	194 ± 42
Severity score	13 ± 13	13 ± 12	14 ± 14
Maximum stenosis (%)	36 ± 35	36 ± 36	35 ± 34
Body mass index (kg/m^2)	29 ± 7	30 ± 7	29 ± 6
Waist circumference (in)**	36 ± 7	37 ± 8	35 ± 6
Systolic blood pressure (mm Hg)	136 ± 20	138 ± 20	134 ± 19
Diastolic blood pressure (mm Hg)**	77 ± 10	78 ± 10	76 ± 11
Medication			
Lipid-lowering medication	35%	34%	35%
ACE inhibitors	26%	27%	26%
Beta blockers	39%	38%	41%

Hx. = history; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ACE = angiotensin-converting enzyme. Comparison of characteristics above and below the median; * $p < .05$; ** $p < .001$.

TABLE 2. Psychosocial Characteristics: Cook Medley Scores

Characteristics	Mean ± SD	Median	Range
Total score	9.7 ± 5.3	9	0–27
Cynicism	4.9 ± 3.5	5	0–13
Aggressive responding	2.8 ± 1.7	3	0–9
Hostile affect	1.9 ± 1.3	2	0–5

omous variable (CAD/no CAD). CAD is defined as ≥50% stenoses in one or more epicardial artery. Of the group with total Cook median hostility scores greater than/equal to median, the 34% of women had angiographic CAD in comparison to 32% of women with scores below the median. There were no significant correlations of individual scores or the total score with maximum percentage of stenoses. The correlations ranged from 0.006 to 0.04 with corresponding $p = .89$ to .36. A similar pattern was observed with the severity score. Women with total scores greater than/equal to the median had severity scores of 12.8 (±12.4) in comparison to values of 14.1 (±13.9) for women with lower scores. The correlations of severity scores with total and individual scores (as a continuous measure) ranged from −0.001 to −0.02 and p values from .98 to .69 with the exception of the hostile affect score. There was a weak inverse association of the hostile affect score and the severity score ($r = -.09$, $p < .04$). These data are consistent with earlier analyses in this WISE cohort that focused specifically on differences in the individual component scores in women with CAD (defined as above) versus those without. Women with angiographic coronary artery disease had cynicism scores of 5.3 (±3.5) versus 4.9 (±3.4) in those with no CAD. Aggressive responding scores (2.8 ± 1.7) were the same for both groups. The hostile affect scores were lower in women with CAD (1.8 ± 1.3) than in those without angiographic disease (2.0 ± 1.3). None of these results were statistically significant (28).

Association of Hostility Scores with Adverse Events

Among the 506 women, there were 169 women with 223 adverse events defined as hospitalization for angina, nonfatal myocardial infarction, stroke, other vascular events, congestive heart failure (CHF), and death. The median length of follow-up for this cohort was 3.9 years with a range of 0 to 6 years. About 96% of the women had a 6-week follow-up or longer. Among these 223 adverse events, there were 115 anginal hospitalizations, 18 nonfatal myocardial infarctions, 17 women with CHF, 15 stroke and 31 other vascular events (including carotid endorectomy, transient ischemia attacks, blood clots, uncontrolled hypertension, pulmonary emboli, and deep vein thrombosis), and 27 deaths. Among the 27 deaths, 15 (56%) were of cardiovascular etiology. Even in those cases where the underlying cause of death was not classified as cardiovascular, these women often had anginal

hospitalizations and other adverse events (within the study time frame) before death from other causes.

When we examined the individual components of the CMHS, there were differences in scores for women with events in comparison to those without events for the cynicism and aggressive responding subscores. Cynicism scores for women with all adverse events and composite events that included deaths of cardiovascular etiology were higher (both $p < .01$) as were events limited to the composite of nonfatal MI, CHF, stroke, and other vascular ($p < .01$). Additional associations of scores with composite events are shown in Table 3. The hostile affect portion of the CMHS did not differ for any of the composite events and the aggressive responding section differs for some of the composites. In regard to total CMHS, women with all adverse events (angina, nonfatal MI, CHF, stroke, other vascular, and death) had higher total CMHS (10.6 ± 5.5) than women without any of these events (9.2 ± 5.1) $p = .02$. We then repeated the analyses using deaths of cardiovascular etiology. There were 162 women with 211 events (cardiovascular mortality, angina, nonfatal MI, CHF, stroke, and other vascular). Women with these composite cardiovascular events had total CMHS that were significantly higher than scores of women without events ($p < .02$). When we examined the composite data for women with events other than anginal hospitalizations, the trend was similar. Women with nonanginal events (nonfatal MI, CHF, stroke, other vascular and death) had higher CMHS than women who did not have an event. The respective scores were 10.7 ± 5.4 versus 9.4 ± 5.2, $p = .05$ as shown in Table 3.

Event-free survival using all adverse events by Kaplan-Meier method (Figure 1) shows that women with scores above the median had poorer event-free survival than those with scores below the median ($p < .05$). When we repeated the analyses, limiting it to cardiovascular deaths and more severe events (nonfatal MI, CHF, vascular events, stroke) we got similar results. Women with total CMHS above the median had worse survival than those with scores below ($p < .05$).

Associations With Adverse Events (Cox Models)

Univariate Cox models identified CAD, diabetes, hypertension and dyslipidemia, race, waist circumference, and ever smoking as significant predictors of adverse events (all $p < .02$). Among the psychosocial scores, the total CMHS and individual Cook Medley scores of cynicism and aggressive responding were also significantly associated with the risk of an adverse event both as continuous variables and as the total CMHS median split (all $p < .05$). Women with total CMHS above the median had 35% increased risk of having an adverse event. In a multivariable Cox model, significant predictors of adverse events included total CMHS, CAD, age, and hypertension. Women with Cook Medley scores above median had 50% increased risk of an adverse event (Table 4). Results were very similar for cynicism and aggressive responding components in separate models. With each point increase in cynicism scores, there was a 7% excess risk of an adverse event (risk-adjusted $p = .007$). With each point increase in the aggressive responding score, there was a 16% excess risk of an adverse event (risk-adjusted $p = .003$). However, the hostile affect component was not a significant independent predictor of events when entered into a separate multivariable model. Multivariable models using only cardiovascular events and cardiovascular disease deaths had similar outcomes. Women with scores above the median had a 64% increase in the risk of an adverse event (risk adjusted $p < .01$).

DISCUSSION

In this population of women with complete demographic, psychosocial and angiographic data, we observed a cross-sectional association of CMHS with lower HDL-C level, larger waist circumference, and higher diastolic blood pressure. Women with higher total CMHS were somewhat younger, less educated, more likely to be nonwhite, current cigarette smokers, and less likely to use hormone therapy. These data generally replicated patterns found in healthy individuals indicating an association of the CMHS with tradi-

TABLE 3. Mean and SD for Total Hostility Scores and Cynicism Scores for Women With and Without Adverse Events

Composite Event/Score	Mean Score for Women with Events (±SD)	Means Scores for Women without Events (±SD)	*p*
All cause mortality, angina, MI, CHF, stroke, vascular (total CMHS)	*n* = 169 10.6 ± 5.5	*n* = 337 9.2 ± 5.1	<.02
Cardiovascular mortality, angina, MI, CHF, stroke, vascular (total CMHS)	*n* = 162 10.6 ± 5.5	*n* = 344 9.2 ± 5.1	<.02
All cause mortality, MI, CHF, stroke, vascular (total CMHS)	*n* = 89 10.7 ± 5.4	*n* = 417 9.4 ± 5.2	.05
All cause mortality, angina, MI, CHF, stroke, vascular (cynicism only)	*n* = 169 5.5 ± 3.7	*n* = 337 4.6 ± 3.3	<.01
Cardiovascular mortality, angina, MI, CHF, stroke, vascular (cynicism only)	*n* = 162 5.6 ± 3.6	*n* = 344 4.6 ± 3.3	<.01
All cause mortality, MI, stroke, vascular (cynicism only)	*n* = 89 5.7 ± 3.5	*n* = 417 4.7 ± 3.4	<.02
All cause mortality, MI, stroke, CHF (cynicism only)	*n* = 64 5.7 ± 3.6	*n* = 442 4.8 ± 3.4	<.05
All cause mortality, MI, stroke (cynicism only)	*n* = 54 5.9 ± 3.6	*n* = 452 4.8 ± 3.4	.03

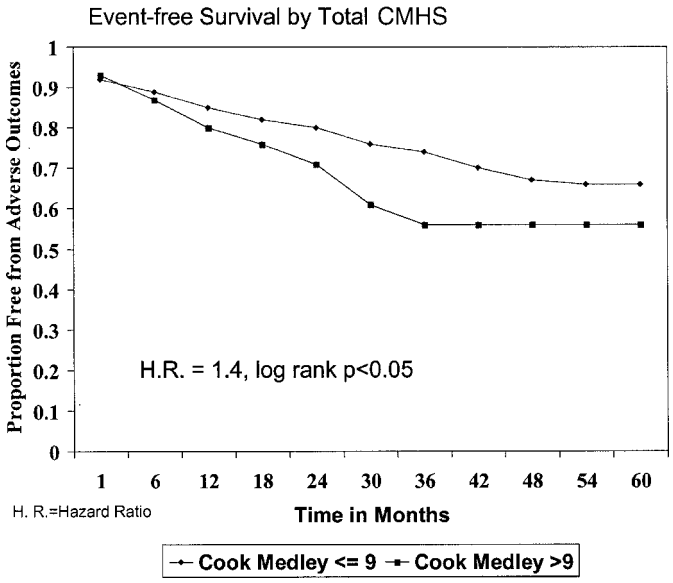

Figure 1. Survival curve of adverse events (defined as hospitalization for angina, nonfatal MI, CHF, stroke, other vascular events and death) by the median split of the total CMHS (sum of the cynicism, aggressive responding, and hostile affect portions of the Cook Medley Hostility).

TABLE 4. Significant Independent Predictors of Adverse Cardiovascular Events: Analyses of Total CMHS Scores Using Cox Proportional Hazards Regression

Risk Factor	Hazard Ratio (95% CI)	*p*
Total CMHS (scores above versus below the median)	1.50 (1.05 to 2.14)	.03
Coronary artery disease (yes/no)	3.15 (2.20 to 4.50)	.001
Age (per 10 years)	0.83 (0.71 to 0.98)	.03
Hx. Hypertension (yes/no)	1.61 (1.10 to 2.35)	.01

Forward step regression model. Variables entered into the model included total CMHS (median split), age per 10 years, CAD, history of hypertension, ever smoked cigarettes, race, waist circumference, education, HDL-C, history of diabetes, history of dyslipidemia, and use of hormone therapy.

tional cardiovascular risk factors (29). There was a very limited association of hostility scores with angiographic CAD at study intake. But women with higher hostility scores had poorer event-free survival and a higher risk of adverse cardiovascular events, even after adjustment for CAD and risk factors. When we examined only the total CMHS and adverse events, there was a 35% increase of risk in women with higher scores. This risk increased to 50% when we accounted for other factors.

It has been suggested that psychosocial risk factors, by themselves, may not have direct effects on disease processes (30), but may interact with risk factor conditions already present (31) or contribute to mechanisms underlying cardiac events (15,32,33). The majority of studies in hostility as a psychosocial risk factor for CHD or CAD and events have been comprised mostly of male cohorts (1–7,17–20). However, our study with an all female cohort had similar findings: higher levels of hostility were observed in younger, non-Caucasian women who smoked, had higher levels of blood pressure, lower levels of "good" cholesterol, and were centrally obese. Low HDL-C levels are a well-documented and particularly potent risk factor (34) as is blood pressure (35,36) and central adiposity (37,38).

Although some studies have found measures of hostility associated with angiographic CAD (39), others have not (13,14). Our lack of association of hostility with CAD may be attributable in part to the fact that in our study, hostility was more prevalent among somewhat younger women and that ours is an exclusively female group.

Hostility and Studies in Women

There has been limited prior work examining psychosocial risk and events in female cohorts (21). One of the most recent is that of the Hostility Ancillary Study of the Heart and Estrogen Replacement Study (23). Although the HERS cohort consisted of older women (mean age 67 years) with coronary heart disease, the results are relevant to our population. Postmenopausal women with high Cook-Medley hostility scores were at a two-fold risk for recurrent nonfatal myocardial infarction. This association was independent of other cardiovascular risk factors (23). Although the primary focus of our analyses was on all adverse events, when we excluded hospitalizations for worsening anginal symptoms, total CMHS were higher for women with these adverse cardiovascular events in comparison to those without such events. In the HERS, there was the same type of association with events when the cynicism subscore was used rather than the full CMHS scale, leading the HERS authors to conclude that specific traits in the hostility construct may act independently on CHD risk (23); our results are consistent with these findings.

Mechanisms

We observed moderate correlations among CM subscores in our all female clinical sample and found similar relationships of component scores (with the exception of the hostile affect) to event outcomes. These data suggest that although individual traits may act independently, they have similar predictive relationships with clinical CAD events. Much has been reported about the wide variety of biological and structural mechanisms related to the measures of hostility. These include increased cardiovascular reactivity to stress (40) as well as increased platelet activation (41) and increased intima-media thickness (42). In addition, this study and others have observed associations of hostility with standard risk factors (8,28), and we note these relationships in an exclusively female cohort.

This is a population with chest pain indicating possible myocardial ischemia, and prior studies have demonstrated associations between hostility and ischemia in both an ambulatory and laboratory population (43,44). It is also interesting to note that in women with suspected myocardial ischemia, relationships of total CMHS to angiographic disease were, in general, not significant as opposed to significant relationships with clinical events. The lack of association may have been attributable to a recruitment strategy that focused on women

with symptoms prompting angiography and may have restricted the range of hostility scores. An alternate explanation is that hostility may play a role in triggering mechanisms such as myocardial ischemia.

Study Limitations

The WISE Study in this follow-up period is a prospective observational study design that precludes establishing definitive causal relationships between Cook Medley scores and adverse outcomes. Because the results are limited to women undergoing coronary angiography for symptoms and signs of coronary disease and suspected ischemia, they may not be generalized to all women. It should be noted that patients undergoing angiography for suspected CAD are often considered a "higher risk" population.

Clinical Implications

In 1987, an NHLBI task force on the psychological risk factors in coronary artery disease recommended additional studies in a variety of populations to assess the extent and limitations of behavioral factors as predictors of CHD (45); our study has directly responded to those needs. We found that higher hostility was independently predictive of cardiovascular events, suggesting that further work to understand mechanistic links and therapeutic options in women is indicated. These data also suggest that studies attempting to modify hostility traits in women with CAD may have important implications in preventing subsequent clinical events.

CONCLUSION

In this cohort of women undergoing coronary angiography for suspected myocardial ischemia, higher Cook Medley scores reflecting cynicism, hostile affect, and aggressive responding were associated with reduced event-free survival compared with women who had lower scores. With the exception of hostile affect, these results were robust after adjusting for atherosclerotic risk factor conditions and the presence or severity of CAD.

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