Acute Ischemic Heart Disease

Global inflammation predicts cardiovascular risk in women: A report from the Women's Ischemia Syndrome Evaluation (WISE) study

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Background Measurement of C-reactive protein (CRP), a marker of inflammation, is recommended to improve cardiovascular disease (CVD) risk stratification. However, no studies have collectively evaluated how inflammatory markers cluster empirically and relate to angiographic coronary artery disease and CVD events.

Methods From the WISE study, 580 women with fasting plasma samples of inflammatory markers (interleukin [IL]-6, IL-18, tumor necrosis factor α, transforming growth factor β, CRP, serum amyloid A [SAA], and intercellular adhesion molecules) were analyzed over a median of 4.7 years follow-up. All women were referred for coronary angiography (1996-2000) to evaluate suspected myocardial ischemia.

Results In factor analysis, a "proinflammation" factor (cluster) loaded on IL-6, CRP, and SAA (r = 0.63-0.87); a "proinflammation and anti-inflammation" cluster loaded on IL-18 and tumor necrosis factor α (r = 0.72, 0.77); and an "immunosuppressive" factor loaded singly on transforming growth factor β (r = 0.96). No cluster was independently associated with angiographic coronary artery disease. However, quartile increases of the "proinflammation" cluster (IL-6, CRP, and SAA) yielded death rates of 2.6%, 7.2%, 13.1%, 26.6%, respectively ($P < .0001$). Women with $\geq$2 of 3 proinflammation markers in the upper quartile had an adjusted relative risk of death of 4.21 (95% CI 1.91-9.25), a higher conferred risk than any single marker alone, all of which were roughly equally predictive.

Conclusions Although IL-6, CRP, and SAA all predict CVD risk in women, development of global measures of inflammation and simply counting the number of markers with high levels improve CVD risk stratification. In addition, results indicate that the adverse impact of inflammation may be largely through other mechanisms than promotion of atherogenesis (ie, destabilization of vulnerable plaques). (Am Heart J 2005;150:900-6.)

Cardiovascular disease (CVD) is the leading cause of death in both men and women in the United States. Traditional scoring methods to predict CVD risk are based on established risk factors including age, total/low-density lipoprotein/high-density lipoprotein (HDL) cholesterol, systolic/diastolic blood pressure, diabetes, and smoking status.[1] Recently, adjunctive measurement of C-reactive protein (CRP), a sensitive circulating marker of low-grade inflammation, has been suggested for improved risk stratification[2] because of its independent relationship with CVD in general and high-risk populations,[3,4] and because many CVD-related deaths occur in persons without conventional risk factors or preexisting obstructive coronary artery disease (CAD).[5] Possible mechanisms proposed for the independent association between an inflammatory state and incident CVD include up-regulation of expression of matrix metalloproteinases involved in vascular remodeling and destabilization/disruption of preexisting atherosclerotic plaques.[6,7]

The relative predictive value of individual inflammatory markers (ie, CRP, serum amyloid A [SAA], interleukin [IL] 6, tumor necrosis factor [TNF] α, and

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doi:10.1016/j.ahj.2005.02.002

transforming growth factor [TGF] β) as modulators/markers of an acute inflammatory state and in relation to CVD has received considerable attention yet remains a matter of uncertainty and scientific inquiry.[8-14] Investigators have sought to quantify the unique contribution of CVD risk attributed to specific inflammatory markers individually and, more recently, in combination.[14-16] However, to our knowledge, we know of no prior attempt to evaluate how inflammatory markers cluster empirically, and how these clusters relate to angiographic CAD and risk of CVD events.

Accordingly, by use of exploratory factor analysis, a variable reduction approach, we empirically grouped inflammatory markers into factors (clusters) in women with chest pain and suspected myocardial ischemia who were evaluated by coronary angiography. We then evaluated how these clusters, as well as their individual components, relate to extent of angiographic CAD and risk of CVD events.

Methods

Study population

The study population consisted of 580 (61%) of 944 women enrolled in the WISE study (December 1996 to March 2000), ages 31 to 85 years, in whom fasting plasma samples collected at study entry were assayed for multiple inflammatory markers. The primary reason for study exclusion was inadequate plasma sample available for all markers. By study protocol, all women were clinically referred for coronary angiography to evaluate suspected myocardial ischemia at 1 of 4 sites (University of Alabama at Birmingham; University of Florida, Gainesville; University of Pittsburgh; Allegheny General Hospital, Pittsburgh, Pa).[17] Exclusion criteria included pregnancy, cardiomyopathy, New York Heart Association class IV angina, congestive heart failure (CHF), recent myocardial infarction or revascularization, and any contraindications to provocative testing. All subjects provided informed consent and completed research forms approved by the institutional review board at their local WISE clinical site. Upon enrollment in the study, each woman had a baseline evaluation that included collection of demographic information, traditional CVD risk factors, medication use, medical and reproductive history, symptom and psychosocial evaluation, a physical examination with blood pressure and physical measurements, and sampling of blood in the fasting state for lipid, glucose, insulin, and reproductive hormones measured in core laboratories.

Measurement of inflammatory markers

Plasma sampled at baseline was frozen at −70°C for subsequent measurement of inflammatory markers. Levels of IL-6, IL-18, TNF-α, TGF-β, and intercellular adhesion molecule (ICAM) were measured from plasma collected at study entry using a commercially available enzyme-linked immunosorbent assay kit (Quantikine hs human IL-6, R&D Systems, Minneapolis, Minn). Levels of high-sensitivity CRP (hsCRP) and SAA were measured by a high-sensitivity method on the Hitachi 911 analyzer using reagents from Denka Seiken (Niigata, Japan). All samples were assayed at a core laboratory (Brigham and Women's Hospital, Boston, Mass) using previously validated techniques.[18]

Assessment of angiographic CAD

Quantitative analysis of coronary angiograms was performed off-line at the WISE Angiographic Core Laboratory (Rhode Island Hospital, Providence, RI) by investigators blinded to all other subject data.[19] Luminal diameter was measured at all stenoses and at nearby reference segments using an electronic cine projector-based "cross-hair" technique (Vanguard Instrument Corporation, Melville, NY). The presence of 1 or more stenoses ≥50% in diameter was considered "obstructive" CAD; maximum diameter stenosis 20% to 49% was considered "minimal" CAD, and <20% stenosis in all coronary arteries was considered "no" CAD.

Ascertainment of cardiovascular events

Follow-up for the occurrence of untoward cardiovascular events was obtained by annual telephone and/or mail contact. The primary clinical outcomes of interest were death or the composite end point of major adverse cardiovascular event (MACE; death, nonfatal myocardial infarction, stroke, or CHF). The median length of follow-up for ascertainment of survival was 4.7 years (interquartile range 2.9-5.5 years), and among the 536 women who did not die during follow-up, 76% had ≥3 years of follow-up.

Statistical methods

Distributions of inflammatory markers were positively skewed. Therefore, the Spearman correlation was used to estimate correlation coefficients between markers. To investigate the underlying factor (cluster) structure of the markers assayed, exploratory factor analyses were conducted using orthogonal and oblique rotations and ranked distributions of each marker. Briefly, exploratory factor analysis is a mathematical model used to explain variation in a large set of observed variables (in this analysis, inflammatory markers) in terms of a smaller set of unobserved "latent" variables (clusters). For each cluster identified, a factor score (inflammation cluster score) was derived from a linear combination of the individually measured markers.[20,21] Specifically, the observed value of each inflammatory marker within the cluster was multiplied by a specific weight and then summed to obtain a theoretical (unobserved) cluster score. Importantly, naming and interpretation of the clusters are arbitrary. In the analysis, scree plots were inspected, and clusters with a minimum eigenvalue of 1.0 were retained.[20] For each cluster identified, subjects were grouped into quartiles based on respective cluster scores. Analysis of covariance was then used to compare adjusted mean numbers of lesions ≥20% stenosis and ≥50% stenosis by quartiles of cluster scores. The Kaplan-Meier method was used to estimate incidence rates of death and MACE by quartiles of the cluster scores. Similarly, Cox regression analysis was used to estimate hazard ratios of death and MACE associated with increasing quartiles of cluster scores, with statistical adjustment for age; lipid-lowering statin use; history of diabetes, CHF, and smoking; and extent of angiographic CAD. Participants who did not experience the clinical outcome of interest were censored at their last known date of follow-up. The proportional hazards assumption of

Table I. Spearman correlations between inflammatory markers (N = 580)

Marker	IL-6	IL-18	TNF-α	TGF-β	hsCRP	SAA	ICAM
IL-6 (pg/mL)	1.0 (n/a)	–	–	–	–	–	–
IL-18 (pg/mL)	0.13 (.002)	1.0 (n/a)	–	–	–	–	–
TNF-α (pg/mL)	0.27 (<.0001)	0.19 (<.0001)	1.0 (n/a)	–	–	–	–
TGF-β (pg/mL)	0.12 (.004)	0.06 (.14)	−0.01 (.72)	1.0 (n/a)	–	–	–
hsCRP (mg/dL)	0.42 (<.0001)	0.07 (.11)	0.15 (.0003)	0.05 (.27)	1.0 (n/a)	–	–
SAA (mg/dL)	0.32 (<.0001)	0.09 (.04)	0.07 (.10)	0.07 (.09)	0.58 (<.0001)	1.0 (n/a)	–
ICAM (pg/mL)	0.14 (.001)	0.05 (.21)	0.26 (<.0001)	−0.08 (.07)	0.22 (<.0001)	0.11 (.01)	1.0 (n/a)

P values are listed in parentheses. The effective N for ICAM correlations is 572.

Table II. Factor (cluster) loadings of exploratory factor analysis of inflammatory markers (n = 580)

	Orthogonal rotation			Oblique rotation*		
Marker(s) and higher-level cluster identified	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
Cluster 1: Proinflammation						
IL-6	0.63	0.37	0.11	0.59	0.34	0.10
hsCRP	0.87	0.04	−0.03	0.88	0.00	−0.03
SAA	0.84	−0.05	0.04	0.85	−0.10	0.04
Cluster 2: Proinflammation and anti-inflammation						
IL-18	−0.02	0.72	0.20	−0.10	0.72	0.19
TNF-α	0.14	0.77	−0.20	0.07	0.78	−0.21
Cluster 3: Immunosuppressive						
TGF-β	0.06	0.02	0.96	0.02	−0.03	0.97

*The correlation between cluster 1 and clusters 2 and 3 was 0.16 and 0.06, respectively; the correlation between clusters 2 and 3 was 0.07.

invariant relative risk (RR) over follow-up was assessed and found to be satisfactory.

Statistical power

With a sample size of 580 women, the study had 80% power to detect hazard ratios of 1.94 and 1.69 or higher assuming cumulative mortality and MACE rates of 7.0% and 12.0%, respectively, in the reference group (ie, low inflammation), balanced subgroups, 2-sided type I error rate of 0.05, and 5% loss to follow-up.

Results

Baseline characteristics of study population

The mean age of the study population was 58 ± 12 years, mean body mass index (BMI) was 29.7 ± 6.8, 81% were white, 26% had a history of diabetes, 30% were on lipid-lowering statin therapy within the week before study entry, and 20% were current smokers. In addition, mean systolic and diastolic blood pressures were 136 ± 21 and 76 ± 11 mm Hg, respectively; mean total cholesterol was 192 ± 43 mg/dL, and 39% of all women were classified with no CAD, 26% with minimal CAD, and the remaining 35% with significant CAD. Compared with the 364 nonstudy participants, the 580 study participants were more often on lipid-lowering statin therapy, had lower total and HDL cholesterol levels, and had less obstructive angiographic CAD.

Correlations between markers

Among the set of markers assessed, the strongest rank correlations were observed between hsCRP and SAA (r_s = 0.58) and hsCRP and IL-6 (r_s = 0.42) (Table I). More modest, yet highly statistically significant, correlations were also observed between IL-6 and SAA (r_s = 0.32), IL-6 and TNF-α (r_s = 0.27), ICAM and TNF-α (r_s = 0.26), ICAM and hsCRP (r_s = 0.22), and TNF-α and IL-18 (r_s = 0.19). Overall, TGF-β correlated the weakest with all other markers (r_s range −0.08 to 0.12).

Exploratory factor (cluster) analysis

Consistent with the results of the correlation analysis, a 3-cluster solution best fit the data. A dominant higher-level cluster, deemed as "proinflammation," was represented by individual measures of IL-6, hsCRP, and SAA (r = 0.63-0.87); a second higher-level cluster, deemed as "proinflammation and anti-inflammation," was represented by IL-18 and TNF-α (r = 0.72, 0.77), and a third cluster, deemed as "immunosuppressive," was represented singly by TGF-β (r = 0.96) (Table II, orthogonal rotation). Results were consistent in both the orthogonal (forces independence of each cluster to aid in interpretation) and oblique rotation (does not force independence of the clusters). ICAM, which is a marker of endothelial cell activation, was not represented by any cluster and thus was removed from the final

Table III. Relationship of inflammation cluster scores and angiographic CAD (N = 580)

Derived inflammation cluster score	Lesions ≥20% stenosis		Lesions ≥50% stenosis	
	Unadjusted (mean ± SD)	Adjusted* (mean)	Unadjusted (mean ± SD)	Adjusted* (mean)
Proinflammation cluster				
Lower quartile	2.0 ± 2.5	2.0	0.9 ± 1.7	0.9
Second quartile	1.7 ± 2.1	1.7	0.7 ± 1.2	0.8
Third quartile	1.9 ± 2.2	2.0	0.7 ± 1.4	0.7
Upper quartile	2.4 ± 2.5	2.4	0.9 ± 1.4	0.9
P for trend	.12	.10	.82	.79
Proinflammation and anti-inflammation cluster				
Lower quartile	1.4 ± 1.8	1.7	0.6 ± 1.1	0.7
Second quartile	2.0 ± 2.1	2.0	0.6 ± 1.1	0.7
Third quartile	2.4 ± 2.7	2.3	1.1 ± 1.7	1.0
Upper quartile	2.3 ± 2.5	2.1	1.0 ± 1.6	0.9
P for trend	.0004	.08	.002	.07
Immunosuppressive cluster				
Lower quartile	1.9 ± 2.3	1.9	0.8 ± 1.3	0.7
Second quartile	2.2 ± 2.4	2.1	0.8 ± 1.3	0.7
Third quartile	2.0 ± 2.4	2.1	0.7 ± 1.4	0.8
Upper quartile	1.8 ± 2.2	1.9	0.9 ± 1.6	1.0
P for trend	.54	.90	.42	.15

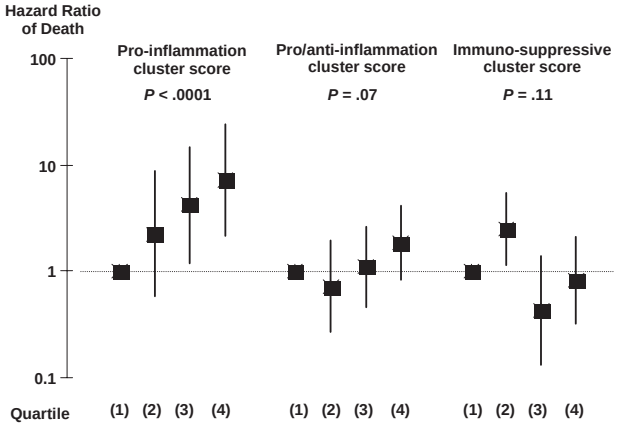
*Adjusted for age, BMI, history of diabetes, triglycerides (log), and lipid-lowering statin use: effective N = 565 because of missing cases.

solution. The 6 markers included in the final solution belonged to only 1 cluster with the exception of IL-6 which was best represented by the "proinflammation" cluster (r = 0.63) and was represented to a lesser degree by the "proinflammation and anti-inflammation" cluster (r = 0.37). These data indicate that IL-6, hsCRP, and SAA represent a common biologic construct (ie, proinflammation); IL-18 and TNF-α represent a different biologic construct (ie, proinflammation and anti-inflammation), and TGF-β represents a third biologic construct (ie, immunosuppressive).

Relationship between inflammatory cluster scores and angiographic CAD

Scores (quartiles) of the proinflammation cluster (IL-6, hsCRP, and SAA) were not associated with the extent of angiographic CAD, defined as number of lesions ≥20% stenosis or ≥50% stenosis (Table III). In contrast, there was a strong univariate relationship between the proinflammation and anti-inflammation cluster scores (IL-18, TNF-α) and the mean number of lesions ≥20% stenosis, which generally increased from the lower to upper quartiles (1.4 to 2.0 to 2.4 to 2.3, P for trend <.0001). However, after statistical adjustment for age, BMI, history of diabetes, triglycerides, and lipid-lowering statin use, this association became marginal (1.7 to 2.0 to 2.3 to 2.1, P for trend = .08). Similar results were observed when considering lesions ≥50% stenosis. Immunosuppressive cluster scores (TGF-β) were not associated with angiographic CAD. Thus, none of the higher-level clusters of inflammatory markers were independently associated with extent of angiographic CAD.

Figure 1



Hazard ratios of death over a median of 4.7 years of follow-up by quartiles of higher-level cluster scores (see Results for individual markers that correlated with each cluster). Rectangles depict hazard ratio estimates; vertical lines depict 95% CIs. Quartile 1 is the reference category with RR of 1.0 (hence no CIs are displayed). P values are tests of trend by increasing quartile level.

Relationship between inflammatory cluster scores and CVD events

A total of 44 women died, and 92 experienced a MACE during follow-up. Proinflammation cluster scores were strongly associated with risk of death over a median of 4.7 years of follow-up. Specifically, quartile

Table IV. Adjusted RRs of death and MACE by quartiles of IL-6, hsCRP, SAA, and all markers combined

	Death				MACE			
Inflammatory marker(s)	**N**	**Incidence**	**RR***	**95% CI**	**N**	**Incidence**	**RR†**	**95% CI**
IL-6 (model 1)								
Quartile 1 (<1.68 pg/mL)	145	6.4%	1.0	–	145	11.7%	1.0	–
Quartile 2 (1.68 to <2.93 pg/mL)	145	7.7%	1.88	0.63-5.63	145	19.5%	1.43	0.71-2.89
Quartile 3 (2.93 to <5.28 pg/mL)	145	4.8%	1.06	0.32-3.50	145	20.6%	1.13	0.55-2.32
Quartile 4 (≥5.28 pg/mL)	145	30.1%	3.74	1.39-10.05	145	43.9%	2.31	1.20-4.44
hsCRP (model 2)								
Quartile 1 (<0.17 mg/dL)	145	5.6%	1.0	–	145	16.5%	1.0	–
Quartile 2 (0.17 to <0.37 mg/dL)	145	9.1%	1.33	0.47-3.76	145	21.4%	1.07	0.54-2.13
Quartile 3 (0.37 to <0.84 mg/dL)	145	8.1%	1.32	0.45-3.88	145	18.4%	1.18	0.60-2.32
Quartile 4 (≥0.84 mg/dL)	145	27.2%	3.00	1.19-7.55	145	41.1%	1.92	1.04-3.54
SAA (model 3)								
Quartile 1 (<0.31 mg/dL)	146	6.5%	1.0	–	146	17.2%	1.0	–
Quartile 2 (0.31 to <0.55 mg/dL)	148	4.7%	0.81	0.24-2.70	148	11.5%	0.61	0.30-1.26
Quartile 3 (0.55 to <0.97 mg/dL)	142	14.2%	2.51	0.95-6.60	142	27.1%	1.18	0.63-2.19
Quartile 4 (≥0.97 mg/dL)	144	24.4%	2.61	1.03-6.65	144	40.7%	1.69	0.96-2.97
All 3 markers combined (model 4)								
0 in upper quartile	322	3.9%	1.0	–	322	16.3%	1.0	–
1 in upper quartile	134	15.7%	2.98	1.30-6.83	134	24.8%	1.54	0.89-2.66
2 or 3 in upper quartile	124	29.5%	4.21	1.91-9.25	124	44.6%	2.45	1.48-4.06

*Adjusted for age, history of cigarette smoking, diabetes, lipid-lowering statin use, CHF, and number of coronary lesions ≥50% stenosis (13 cases excluded because of missing data).

†Adjusted for age, history of cigarette smoking, diabetes, lipid-lowering statin use, CHF, number of coronary lesions ≥20% stenosis (13 cases excluded because of missing data).

increases from lowest to highest yielded death rates of 2.6%, 7.2%, 13.1%, and 26.6%, respectively, with corresponding hazard ratios of 1.0 (reference group), 2.25, 4.20, and 7.17 (P for trend < .0001) (Figure 1). For MACE, incidence rates were 11.0%, 17.9%, 27.9%, and 39.8%, respectively, with corresponding hazard ratios of 1.0, 1.56, 1.94, and 3.30 (P for trend <.0001). In contrast, the proinflammation and anti-inflammation cluster scores and immunosuppressive factor scores were not associated with 4-year risk of death (Figure 1) or MACE.

Given that only proinflammatory markers were associated with death and MACE, each individual marker was grouped into quartiles and in combination to assess relative contribution to adverse events. Compared with women with marker values in the lower quartile, those with values in the upper quartile for any inflammatory marker were at comparable heightened risk of death (IL-6: adjusted RR = 3.74, 95% CI 1.39-10.05; hsCRP: adjusted RR = 3.00, 95% CI 1.19-7.75; and SAA: adjusted RR = 2.61, 95% CI 1.03-6.65) and MACE (Table IV). Having 2 or 3 of the markers in the upper quartile was associated with an incremental increase in risk beyond any single marker (death adjusted RR = 4.21, 95% CI 1.91-9.25; MACE adjusted RR = 2.45, 95% CI 1.48-4.06). Of the 44 women who died, 21 (48%) had at least 2 of the 3 proinflammatory markers in the upper quartile, as compared with 103 (19%) of 536 surviving women. Alternatively, only 2 (5%) of 44 of women who died had at least 2 of the 3 proinflammatory markers in the lower quartile, as compared with 124 (23%) of 536 surviving women. These data indicate that the proinflammatory markers IL-6, hsCRP, and SAA are all predictive (roughly equally) of adverse cardiovascular events in women with suspected ischemia and that consideration of all markers in combination adds incremental predictive value.

Discussion

Measurement of inflammatory markers for risk stratification for both primary and secondary prevention of CVD has been the focus of numerous investigations and scientific debate. These efforts have been motivated by observations that inflammation is a key process in the pathophysiology of atherosclerosis and development of acute cardiovascular syndromes. At present, formal recommendation of assays of inflammatory markers for clinical risk stratification is limited to hsCRP,[2] primarily because of its consistently observed relationship with cardiovascular risk[3,4,8,10,22,23] and generally acceptable levels of precision and measurement reproducibility.[24,25] However, the incremental prognostic value of hsCRP above and beyond traditional CVD risk factors and other markers has recently been questioned,[10] further necessitating continued appraisal and evaluation of optimal risk stratification approaches.

Our study is the first to empirically evaluate the higher-level factor (cluster) structure of multiple inflammatory markers and then assess the relationships between these cluster scores and both extent of angiographic CAD and

risk of incident cardiovascular events. Overall, we found that "proinflammation" cluster scores, derived from concurrent baseline measurement of IL-6, hsCRP, and SAA, were highly prognostic of risk of death and MACEs over a median of 4.7 years of follow-up in women with chest pain and suspected myocardial ischemia. Possible mechanisms for this finding include modulation of levels of matrix metalloproteinases and platelet adhesion and aggregation, which have deleterious properties resulting in plaque destabilization and rupture.[26,27] Overall, these data support future prospective evaluation of global proinflammation measures to be used for risk stratification in clinical practice.

We also found that the proinflammatory markers IL-6, hsCRP, and SAA, which clustered together empirically, provided roughly equal predictive value with respect to future risk of death and cardiovascular events. This finding is at odds with a recent report[14] from the Nurses Health Study in which CRP was singled out among inflammatory markers as the best predictor of incident coronary heart disease in women. Moreover, in that study, receptors of TNF-α were investigated under the premise of being proinflammatory, yet in our study, TNF-α did not empirically cluster with the conventional proinflammatory markers of IL-6, hsCRP, and SAA. The basis for these inconsistencies is not clear, although women in our study were older than those in the Nurses Health Study, as well as symptomatic for suspected myocardial ischemia.

In contrast to the association with death and cardiovascular events, we observed little evidence of an independent relationship between proinflammation cluster scores and extent of angiographic CAD. This was unexpected given prior reports that (i) IL-6 is the main hepatic stimulus for production of both CRP and SAA[2,28] and plays a critical role within the atheroma, (ii) CRP directly effects atherosclerosis by down-regulating nitric oxide release from the endothelial cells[29] and stimulating endothelin-1 and IL-6 secretion, resulting in increased expression of adhesion molecules, stimulating monocyte chemoattractant protein 1, and facilitating macrophage low-density lipoprotein uptake,[26,30,31] and (iii) SAA modulates HDL metabolism and may be involved in diminishing its atheroprotective effect.[32] Alternatively, some studies have shown poor correlations between inflammatory markers and extent of atherosclerosis,[33-35] perhaps because, in part, of limited sensitivity of angiography to detect atherosclerosis.

Strengths and limitations

Strengths of our study include a prospective multicenter design with relatively long subject follow-up and core laboratory blinded assessments of inflammatory markers and coronary angiograms. A potential limitation is the highly selective study population consisting of women with suspected myocardial ischemia who were referred for clinically indicated coronary angiography—our results may not generalize at large to women or to men. In addition, naming of the higher-level clusters from the exploratory factor analysis is arbitrary and thus should be cautiously interpreted. For example, the higher-level cluster that loaded uniquely on TGF-β was labeled "immunosuppressive" because this is its predominant systemic effect; however, TGF-β also demonstrates proinflammatory properties as a result of trauma or immune response.[36] Finally, the total of 44 deaths observed limited the number of covariates to be controlled for, as well as potential subgroup analyses.

Conclusions

In women with suspected myocardial ischemia, empirically based proinflammation cluster scores derived from baseline measurements of IL-6, hsCRP, and SAA were highly predictive of risk of death and major cardiovascular events over a median of 4.7 years of follow-up, whereas only weakly associated with extent of angiographic CAD. The predictive value of this global proinflammation measure, as well as counting the number of markers with high levels (upper quartile), exceeded that of any single marker, all of which were roughly equally predictive. Although, at present, hsCRP is the single marker endorsed for CVD risk stratification in clinical practice, as well as possible inclusion in the definition of the metabolic syndrome,[37] our data indicate that a global inflammation score may be particularly useful for cardiovascular risk stratification (ie, above and beyond direct measurement of hsCRP and other individual markers). Our data also suggest that the principal adverse contribution of the inflammatory cascade may not be the result of direct promotion of atherogenesis per se, but rather through other mechanisms such as destabilization of vulnerable plaques.

Supported by contracts from the National Heart, Lung, and Blood Institute, nos. N01-HV-68161 to N01-HV-68164, R01-HL-073412-01, and grants U0164829, U01 HL649141, and U01 HL649241.

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