Inflammatory Markers of Cardiovascular Disease in the Elderly

Adriane M. Ramos, Lucia Campos Pellanda, Iseu Gus, Vera L. Portal

Instituto de Cardiologia/Fundação Universitária de Cardiologia; Programa de Pós-Graduação em Ciências da Saúde da Fundação Universitária de Cardiologia, Porto Alegre, RS - Brasil

Summary

Most information on the role of inflammatory markers as cardiovascular disease predictors concerns only middle-aged individuals.

This review aims at evaluating the role of inflammatory markers as cardiovascular disease predictors in the elderly.

The Medline (Pubmed) and Cochrane databases were used in the search, using the key words. After adding the following filters: Limits: Aged 65+ years, Humans, Randomized Controlled Trial, Meta-Analysis, Review, Clinical Trials, 554 studies were identified. Of these, 120 were selected and evaluated regarding their power of evidence (classification of the Oxford Centre for Evidence-Based Medicine).

In studies with patients older than 65 years, interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) showed to be good predictors of cardiovascular events. Regarding C-reactive protein (CRP), the data are inconsistent, as it appears to have lower power of prediction in the elderly when compared to middle-aged individuals. Fibrinogen levels seem to be predictors of mortality, although they are non-specific predictors, i.e., not solely of cardiovascular mortality. Additionally, the inflammatory markers are also indicative of functional decline and mortality, regardless of the presence of cardiovascular disease.

The current evidence is not sufficient to allow the routine use of inflammatory markers in the elderly, as there are few studies in this age range and most of them are short-term ones with a small number of inflammatory markers. The routine request for these markers must be decided on an individual basis.

Introduction

Cardiovascular diseases are the main cause of morbi-mortality in Brazil and in the world[1]. Their clinical manifestations generally occur as acute myocardial infarction (AMI), cerebral vascular accident (CVA), angina or sudden death between 50 and 60 years in men and 60 and 70 years in women, progressively increasing with age[2,3].

Key words

Biological markers; cardiovascular diseases; aged.

Mailing Address: Vera Lucia Portal •
Av. Princesa Isabel, 370 - Epidemiologia - 90620-001, Porto Alegre, RS - Brazil
E-mail: veraportal@via-rs.net
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The elderly population is the fastest increasing population segment in the world. The prevalence of coronary artery disease (CAD) is very high in this group. Considering the North-American data, 61% of the AMI occur in individuals older than 65 years and 36% in those older than 75 years. Additionally, the mortality markedly increases with age, reaching 85% in the acute phase of AMI among individuals older than 65 years[2-6].

Studies have demonstrated that inflammation participates in all phases of the development of atherosclerosis[7-9]. Several inflammatory markers such as cytokines, total leukocyte count, C-reactive protein (CRP), among others, are being assessed. However, CRP has been the most frequently used marker[7-10]. The methods used to measure other markers such as cytokines are, in general, inadequate for routine clinical use and these proteins have a very short half-life. The laboratory procedures to assess fibrinogen are not well established, despite the consistent population data. Total leukocyte count and globular sedimentation rate have a questionable value regarding their clinical applicability. On the other hand, there are well-established methods to measure ultrasensitive CRP (us-CRP). Additionally, this is a stable marker that has a long half-life (18 to 20 hours) and its measurement can be performed in either frozen or fresh plasma, without the need for special collection procedures[10,11].

In 2002, the American Heart Association and the US Center for Diseases Control and Prevention (CDC) recommended the request for inflammatory markers, especially CRP, as it has a higher availability of measurement methods, to improve prediction of coronary events among patients at intermediate risk at the Framingham Risk Score[12]. This recommendation was important for elderly patients, considering that a large number of American women older than 65 years would already present the necessary criteria to be classified as presenting intermediate risk[13]. However, none of these recommendations were based on studies carried out with the elderly population. The extrapolation of data obtained with middle-aged individuals for the elderly can be inadequate for several reasons. One example is what occurs with lipid levels and its association with CAD risk. The incidence of CAD is higher in the population older than 65 years and the same is true regarding mortality rates. The risk or relative risk rate decreases with age due to the natural decrease in lipid levels[14]. However, as the disease is more prevalent in this age range, there is an increase in the attributable or absolute risk, i.e., a higher absolute benefit is observed with CAD treatment in this population[14,15]. In the 90's, some observational studies questioned the validity of total cholesterol (TC) as a predictor of cardiovascular risk in the elderly, whether the approach for its control should be the same for younger individuals and if the decrease in TC levels below a certain value would not be harmful.

The observational study EPESE, which evaluated 4,056 men and women after adjusting the cardiovascular risk factors and health quality indicators such as serum iron and albumin levels, demonstrated that TC was a predictor of mortality risk due to CAD, with decrease in risk with the control of TC levels (p=0.005)[16]. Some studies have already demonstrated a reduction in clinical or substitute outcomes, in secondary as well as primary prevention with the use of statins in elderly individuals[17-21]. The predictive value of the traditional risk factors changes with age. For instance, among the elderly, TC and low-density lipoprotein cholesterol (LDL-C) levels represent lower-power risk predictors[22-24]. Additionally, the prevalence of the subclinical disease is elevated in this same age range. Among the participants of the Cardiovascular Health Study (≥65 years) with no evidence of clinical disease, the prevalence of cardiovascular disease was around 61%[24]. It is also not clear whether the power of association of risk factors is the same among the subclinical disease cases[25]. Elderly individuals have, in general, a higher number of comorbidities and many of them could already be associated with inflammation[26,27].

Finally, the physiopathology of the cardiovascular diseases can change with aging. Burke *et al*, reviewing cases of sudden death, found a higher proportion of acute thrombosis among young individuals than among the elderly[28]. For all these reasons, it would be inaccurate to generalize the information or to define procedures on inflammatory markers for the elderly based on evidence obtained from middle-aged patients. Therefore, it is important to evaluate the evidence on this issue concerning individuals older than 65 years.

C-Reactive Protein

The C-reactive protein (CRP) is synthesized by the liver after a stimulus such as tissue injury, inflammation and/or infection. Its production also occurs in atherosclerotic lesions by smooth muscle cells and macrophages, kidneys, neurons, pulmonary alveoli and adipose tissue[8,29].

As the methods traditionally employed to measure CRP do not have good sensitivity, it is recommended to measure us-CRP to evaluate atherothrombotic disease, which usually presents lower CRP levels than the other inflammatory processes[7,9,10,11,30].

Several prospective studies have indicated that slightly elevated CRP levels are present in individuals with stable and unstable angina at risk for AMI, elderly individuals at risk for symptomatic CAD, smokers and apparently healthy middle-aged men at risk for AMI or cerebrovascular accident (CVA). Additionally, the predictive value of us-CRP as a biochemical marker for CAD risk was higher when compared to that of traditional risk factors such as TC, LDL-C or newer risk factors such as lipoprotein (a), homocysteine, and apoproteins A and B[8,9,23]. Among women, for instance, the us-CRP was the strongest risk predictor for future cardiovascular events[31,32]. Furthermore, many studies have also demonstrated that the measurement of us-CRP at hospital admission as well as at hospital discharge of patients with acute coronary syndromes has a prognostic value for complications or new events and that it can be an isolated risk stratifier or in association with troponin[33-36].

The levels of CRP seem to increase slightly with aging in men, but not in women. There is little evidence to support the affirmation that its levels increase after 70 years of age[10,11].

Tracy *et al*.[37] carried out a case-control study based on a sample of elderly individuals (≥ 65 yrs) from the Cardiovascular Health Study (cohort with 5,201 elderly individuals, followed for 2.4 yrs). The cases (n=146) were elderly individuals with angina, AMI or who had died. The elevated CRP levels presented a stronger association with AMI, mainly among women with subclinical disease, odds ratio (OR) = 4.5 (95% CI: 0.97-20.8). However, these associations must be considered with caution, as they did not undergo adjustment for risk factors[37].

Cushman *et al*[38] evaluated the CRP levels in 3,971 elderly individuals, without previous cardiovascular disease. The patients were followed for 10 years. After adjustment for confounding factors, the RR of CAD was 1.45 (95%CI, 1.14-1.86), when the group with CRP levels > 3 mg/L was compared to the one with CRP levels < 1.0 mg/L and the attributable risk of the population with increased CRP levels was 11%. The study demonstrated that CRP was associated with a higher risk of CAD in 10 years, in both male and female elderly individuals, regardless of other risk factors. A single measurement of CRP offered additional risk information, especially for men with intermediate scores and women with high scores at the Framingham Risk Score[38].

Tice *et al*.[39] carried out a case-control study, selecting elderly Caucasian women who participated in the Osteoporotic Fracture Cohort (cohort of 9,704 elderly women with a mean follow-up of 6 years). Of the 492 Caucasian patients, 150 died, with 52 of them due to cardiovascular death. After the adjustment for confounding factors, women with us-CRP levels > 3.0 mg/L had an 8-fold higher risk (95%CI: 2.2-29) of cardiovascular mortality, when compared to those that had us-CRP levels ≤ 1.0 mg/L. The levels of us-CRP were not associated with other causes of mortality (RR= 0.92; 95% CI: 0.4-2.1)[39].

Ridker *et al*.[40] evaluated the CRP levels in a sample of 543 patients from the Physician's Health Study (cohort of apparently healthy male individuals aged 40-84 years, followed for a period > 8 years). The men whose CRP levels were at the higher quartiles had a RR=2.9; p<0.001 for AMI and RR=1.9; p=0.02 for CVA, compared to men at the lower quartiles. These findings were not altered after adjustment for smoking and other risk factors[40].

Several studies have analyzed the association between CRP and ischemic CVA. Rost *et al*.[41] followed a sample of 591 men and 871 women from the Framingham cohort, with a mean age of 69.7 years that had not presented previous vascular events. A total of 196 events (CVA and transient ischemic episodes) occurred during 12-14 years of follow-up. Regardless of age, men with CRP levels at the higher quartiles had a 2-fold higher risk of events (RR=2; p=0.027) and women had an almost 3-fold higher risk of events (RR=2.7; p=0.0003), when compared to those with CRP levels at the lower quartiles. After the adjustment for smoking, TC/HDL ratio, systolic arterial pressure and diabetes, this risk association remained unaltered for both men (p=0.0365) and women (p=0.0084)[41].

Cao *et al*[42] studied the association between the carotid intimal-medial thickening and CRP with CVA in a sample of 5,017 elderly individuals, without cardiovascular disease, from the Cardiovascular Health Study. Durante 10.2 years of follow-up, 469 ischemic CVA occurred. After the adjustment for the carotid intimal-medial thickening, there was an important modification in the association between CRP and CVA. Such association remained only among the individuals with elevated carotid intimal-medial thickening[42].

The Honolulu Heart Study is the study that offers the longest and most comprehensive follow-up to evaluate the association between CRP and CVA. A total of 259 apparently healthy Japanese-American men were identified, which presented CVA during a 20-year follow-up and compared with 1,348 controls. CRP levels were measured in these patients (aged 48-70 years). After the adjustment for risk factors, the men with 48-55 years with CRP > 1.0 mg/L presented OR=3.0; 95% CI: 1.4-6.4 for thromboembolic CVA, compared to men with CRP levels ≤ 1.0 mg/L[43]. This association was not observed among the participants aged 56-70 years (OR=1.3; 95%CI: 0.8-2.0). The same apparent reduction in the age-related power of association was found in the Quebec Cardiovascular Study. This study evaluated 105 cases of acute ischemic syndromes without previous cardiac disease, which were followed for 5 years. The study demonstrated that the us-CRP was a predictor independent of other risk factors for acute ischemic syndromes only among individuals aged ≤ 55 years[44].

Interleukins

The IL-6 is an important immune cell activator and can participate in the destabilization of the atherosclerotic plaque[45-47]. The IL-6 also reflects the cardiovascular risk factors in a model that is similar to that of CRP and its levels increase with age[45-49].

Jenny *et al*[50], in a case-control study, evaluated the levels of IL-6 in a sample of elderly individuals (mean age of 73 years) from the Cardiovascular Health Study. IL-6 levels were more elevated among the elderly individuals with subclinical cardiovascular disease[50].

Volpato S *et al*[51], evaluated the association of IL-6 levels with general mortality in 620 elderly women that were followed for 03 years. After the adjustment for confounding factors, the elderly women with cardiovascular disease and elevated IL-6 levels presented a 4-fold higher risk of death (RR=4.6; 95%CI: 2.0-10.5), when compared to those whose levels were at the lower terciles. Among the women without cardiovascular disease, this association was much lower and had no statistical significance (RR=1.8; 95%CI: 0.7-4.2)[51].

The IL-10 is an anti-inflammatory cytokine that inhibits the production of several inflammatory cytokines, such as IL-2 and IFN-gamma and is strongly associated with a better prognosis among those patients with acute ischemic syndromes[52,53]. Van Excel *et al*[54] evaluated the association of IL-10 with CVA in 599 elderly individuals (85 years) from the city of Leiden. The RR for CVA was 2.94 (95%CI: 1.01-8.53), when comparing the participants with low or intermediate IL-10 levels with those with elevated levels[54].

Fibrinogen as an inflammatory marker

Fibrinogen is a component of coagulation and a determinant of blood viscosity. Elevated fibrinogen levels also increase platelet reactivity[55]. During the acute phase of inflammation, its levels can increase 100 to 200%. There is a strong interaction between the inflammatory and the hemostatic systems[56,57].

Prospective studies with healthy individuals have demonstrated a direct and independent association between the plasma fibrinogen levels and the risk of coronary events, of total and cardiovascular mortality[58]. Among the elderly, it also seems to be a risk factor for general and cardiovascular mortality, ischemic CVA and deep venous thrombosis[59-62].

Yano *et al*[63] evaluated the association between fibrinogen and mortality due to different causes in a cohort of Japanese-American individuals (aged 71-93 years) that were followed for 4.4 years. Of the 728 deaths, 37% were due to cardiovascular disease and 27% to cancer. During the first year of follow-up, the RR adjusted for age for general mortality was 4.3 (p<0.0001), when comparing the highest quintile (>3.51 g/dL) with the lowest one (<2.57 g/dL). The RR was reduced to 1.7 in the second year, but remained elevated in the subsequent years. After the adjustment for age and confounding factors, the RR (95% CI) associated with the increase of a standard-deviation of fibrinogen (0.64 g/dL) for general mortality, cardiovascular disease, cancer and other causes of mortality was 1.3; 1.2; 1.3 and 1.3, respectively. The presence of previous diseases did not influence the association between fibrinogen and mortality[63].

Other inflammatory markers

TNF-α is an important triggering factor of the inflammatory response. However, it has been scarcely assessed in epidemiological studies[64].

Cesari *et al*[65] found a stronger association of TNF-α with CAD (RR=1.67, 95%CI: 1.23-2.26) than CRP (RR=1.33, 95%CI: 0.98-1.80) in elderly individuals (70-79 years) without previous cardiovascular disease, followed for 3.6 years. Nevertheless, there was no association between TNF-α and CVA (RR=1.18, 95%CI: 0.69-2.03), considering the same group and time of follow-up[65].

Elkind *et al*[66] evaluated the association between TNF-α and/or receptor type 1 and 2 with carotid atherosclerotic disease in 279 individuals (mean age of 67.6 ± 8.5 years). After the adjustment for gender, ethnicity, hypertension, diabetes, LDL-cholesterol, smoking and body mass index (BMI), there was an association for individuals younger than 70 years between the receptors type 1 and 2 of the TNF-α and the increase in the carotid intimal-medial thickening. However, such association was not observed with participants aged ≥ 70 years[66].

Value of the combined inflammatory marker evaluation

Due to the complexity of the inflammatory process, of the interrelations with cytokines and the response of acute-phase proteins, it is likely that no single marker can detain all the important risk information[62].

Cesari *et al*[65] evaluated the levels of CRP, IL-6 and TNF-α in 2,225 elderly individuals (70 to 79 years), without previous cardiovascular disease that were selected from the Health, Aging, and Body Composition study (cohort with 07 years of follow-up that evaluated the functional and psychological impact of age-related modifications in body composition and health status).

The evaluated outcomes were new episodes of cardiac disease, CVA and congestive heart failure. The mean period of follow-up was 3.6 years. After adjustment for confounding factors, the IL-6 was associated with all outcomes, TNF–α with CAD and heart failure and CRP only with heart failure. The combination of the 03 markers presented the strongest risk prediction for CAD (RR=2.13; 95%CI: 1.27-3.55), compared to only one elevated marker (RR=1.17; 95%CI: 0.79-1.73)[65].

Harris *et al*[67] followed for 4.6 years a sample of 1,293 healthy elderly individuals from the Rural Health Study. The IL-6 was a better predictor of mortality than CRP among the elderly. Levels of IL-6 ≥ 3.19 pg/dL were associated with a two-fold higher risk of death (RR=1.9 95%CI: 1.2-3.1) and CRP ≥ 2.78 mg/L was also associated with a higher risk of death (RR=1.6 95%CI: 1.0-2.6). The elderly that presented elevated CRP and IL-6 levels had a 2.6-fold higher risk of mortality during follow-up, when compared to those with lower levels of the two markers. The results were similar for cardiovascular or total mortality and independent from age, gender, BMI, smoking, diabetes, cardiovascular disease, fibrinogen, albumin and leukocyte levels. These authors observed a synergy between IL-6 and CRP in the prediction of mortality in healthy elderly individuals that presented elevated levels of both markers[67].

Heeschen C *et al*[53] evaluated 547 patients from the CAPTURE study (clinical trial with 1,265 patients that presented acute ischemic syndrome). The evaluated outcomes were death and non-fatal AMI during a six-month follow-up.

The levels of IL-10 were not associated with the levels of troponin, but presented an inverse relation with the CRP levels (p<0.001). Patients with higher levels of IL-10 (>3.5 pg/mL) had a lower risk of presenting the evaluated outcomes when compared to those who presented lower levels of this marker (RR=0.33, 95%CI: 0.25-0.76; p=0.002). The predictive value of IL-10 was independent from myocardial necrosis, but interacted significantly with the CRP levels. Patients with increased CRP levels and IL-10 >3.5 pg/mL were protected against a higher cardiac risk, when compared to those with elevated CRP and low IL-10 levels (RR= 0.25; 95%CI: 0.10-0.63; p=0.003)[53].

In a meta-analysis, Danesh *et al*[68], after evaluating 18 studies with 4,018 cases of CAD, estimated that the RR for CAD, among those presenting fibrinogen levels at the upper tercile (> 350 mg/dL) was 80% higher when compared with those at the lower terciles (< 250 mg/dL). That was a stronger association than the one observed for CRP (RR= 1.7; 95%CI: 1.4-2.1)[68]. There are at least two studies that demonstrated a decrease in the association of CRP with cardiovascular events when both CRP and fibrinogen were included in the same model of multivariate analysis, indicating that fibrinogen could be a better predictor for cardiovascular risk[68,69].

Tracy *et al*[70] followed 5,888 elderly individuals of both sexes from the Cardiovascular Health Study for 05 years. Fibrinogen, factor VIII and factor VII levels were measured in these patients. The evaluated outcomes were total mortality and new cardiovascular events. After adjustment for risk factors and subclinical cardiovascular disease, fibrinogen was significantly associated with men presenting CAD (RR=2.1), CVA or transient ischemic episode (RR=1.3), as well as with mortality (RR=5.8) during the 2.5-year period of follow-up and late mortality (RR=1.7). Factor VIII was also significantly associated, in men, with coronary events (RR=1.5) and mortality (RR=1.8) and in women, with CVA and/or transient ischemic episode (RR=1.4). Factor VII, in general, was not consistently associated with cardiovascular events in this population[70].

Yano *et al*[63] observed an interaction between fibrinogen and leukocyte count when evaluating a sample of 3,571 Japanese-American elderly individuals (71-93 years). Individuals with high levels of both markers had a higher probability of death during follow-up[63].

Jenny *et al*[71] evaluated the association between the combination of CRP and fibrinogen with early death (03 years) and later death (04 to 08 years) in 5,828 elderly individuals. For the men who presented both markers at the higher quartiles, the RR for early death was 9.6 (95% CI: 4.3-21.1) and 13.5 for early cardiovascular death (95% CI: 3.2-56.5). These associations were attenuated in the following years. For women, there was an association only between CRP and early general or cardiovascular death, with a RR of 2.3 (95% CI: 1.4-3.9)[71].

Penninx *et al*[72], after evaluating 2,979 elderly individuals of both sexes (70-79 years) for 30 months, showed an association of inflammatory markers with the onset of mobility limitation. The RR of the onset of mobility limitation was 1.19 (95%CI: 1.10-1.28) for IL-6, 1.2 (95%CI: 1.12-1.29) for TNF-α and 1.4 (95% CI: 1.18-1.68) for CRP[72].

According to the aforementioned studies, the markers evaluated in elderly individuals represent only part of the knowledge and it is likely that the importance of their combination has yet to be fully elucidated[64].

Another aspect to be considered is that, although there is great interest in the study of inflammatory markers as cardiovascular risk predictors in elderly individuals, these markers are as good as, or even better predictors of all causes of mortality in relation to the first. This is due to the fact that inflammation participates in the physiopathological process of several chronic conditions, such as depression, osteoporosis, arthritis, periodontal disease, chronic obstructive pulmonary disease and cognitive impairment, which can reduce its impact on the prediction of cardiovascular risk[73-78].

Conclusion

The influence of inflammatory markers on the development of atherosclerotic disease is well-established and they are useful in the prediction of elevated cardiac risk among middle-aged individuals. Studies including only elderly individuals

showed that CRP and fibrinogen may not be so useful as IL-6 and TNF-α. The current evidence is not sufficient, as there are few studies in this age range and most of them are short-term ones with a small number of inflammatory markers. Considering that, the routine assessment of inflammatory markers in the elderly cannot be justified in clinical practice. The routine request for these markers must be decided on an individual basis.

Finally, it is likely that these inflammatory markers are predictors of the functional decline in the elderly and thus, it is important to seek interventions that aim not only at the prevention of vascular disease, but also at the preservation of the general organic function in this age range.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Table 1 - Studies on inflammatory markers and CV risk in the elderly

Author, Year of Publication	Age, Sex	Time (yrs)	Outcomes (# of events)	Statistical Adjustment	Inflammatory Markers, RR, CI		
Cushman, 2005 36	(≥ 65) Males and females	10	CAD (547)	Age, sex, ethnicity DM, SAH, BMI, WC, TC, HDL, ASA smoking	**Us-CRP#**	**CAD**	
					< 1	reference group	
					1-3	1.08 (0.86-1.35)	p<0.004
					3	1.45(1.14-1.86)	
Tice, 2003 37,	(≥ 65) Females	6	Total mortality (150) and CV (52)	Age, smoking, estrogen use	**us-CRP#**	**CV mortality**	**non-CV mortality**
					≤ 1	reference group	
					>3	8.0 (2.2-29)	0.92 (0.4-2.1)
Curb, 2003 41	48-70 Males and females	20	thromboembolic CVA (259)	TC, BMI, alcohol, SAH, DM, BMI, physical activity, smoking	**us-CRP#**	**thromboembolic CVA**	**p**
					Age		
					48-55 yrs	3.0 (1.4-6.4)	0.018
					56-70 yrs	1.3 (0.8-2.0)	0.076
Volpato, 2001 49	(≥ 65) Females	3	CV mortality (41) and non-CV (48)	Age, BMI, smoking and CRP	**IL-6 (pg/mL)**	**CV mortality**	**non CV mortality**
					≤ 1,78	reference group	
					1.79-3.10	1.08 (0.44-2.67)	1.67 (0.62-4.53)
					> 3.10	2.52 (1.21-4.55)	3.87 (1.47-10.16)
Yano, 2001 61	(71-93) Males	4,4	Total mortality (728), CV mortality (258), CA (197) and other causes (273)	Age, BMI, HDL, Ht TG, TL, SAH, DM physical activity, alcohol smoking, TC Previous diseases	**Fibrinogen (g/L) – increase of 1 SD (0.64 g/L) Mortality**		
					Mortality		
					Total	1.27 (1.18-1.38)	
					CV	1.18 (1.03-1.36)	
					Cancer	1.32 (1.14-1.52)	
					Others	1.32 (1.15-1.51)	
Cesari, 2003 63	(70-79) Males and females	3,6	CAD (188), CVA (60) CHF (92)	Age, sex, ethnicity, smoking, DM, SAH, HDL, TG, albumin, BMI	**CAD**	**CVA**	**CHF**
					IL-6* 1.27(1.10-1.48)	1.45(1.12-1.86)	1.72(1.4-2.12)
					PCR* 1.11 (0.96-1.29)	1.18(0.91-1.53)	1.48(1.23-1.78)
					TNF-α*1.22(1.04-1.43)	0,95(0.71-1.26)	1.59(1.3-1.95)
Harris, 1999 65	(≥65) Males and females	4,6	CV mortality CV (74) and other causes (102)	Age, DM, BMI, smoking, previous CVD		**Mortality**	
					Total	**males(279)**	**females(396)**
					low CRP/IL-6 $	reference group	
					elevated CRP $	1.5(0.7-3.2)	0.3(0.1-1.2)
					elevated IL-6$	1.1(0.5-2.4)	2.5(1.2-5)
					elevated CRP/IL-6$$	2.8(1.4-5.5)	2.0(0.9-4.4)

Time - time of; RR - relative risk; CI - confidence interval; TC - total cholesterol; BMI - body mass index; CV - cardiovascular; Ht - hematocrit; TL - total leukocytes; TG - triglycerides; us-CRP - ultra-sensitive C-Reactive Protein; IL-6 - interleukine-6; TNF-α - Tumor necrosis factor-alpha; WC - waist circumference; CHF - congestive heart failure; CVD - cardiovascular disease; CAD - coronary artery disease; CVA - cerebral vascular accident (stroke); DM - diabetes mellitus; SAH - systemic arterial hypertension; CA - cancer; SD - standard deviation.

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