High-Sensitivity C-Reactive Protein: To Measure or not to Measure?

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Abstarct: Based on evidence that inflammatory processes play a fundamental role in the development of cardiovascular disease, high sensitivity C-reactive protein (hsCRP) is considered a powerful risk marker for cardiovascular events. Irrespective of a potential role in risk prediction, recent evidence implicates a direct involvement of CRP *per se* in the pathogenesis of atherosclerotic cardiovascular disease. In the present article we review the literature concerning clinical studies assessing the association between hsCRP concentration and cardiovascular disease. Measurement of hsCRP levels may help guiding medical treatment initiation and adjustment in certain groups of subjects both in the primary and secondary prevention.

Keywords: C-reactive protein, inflammation, atherosclerosis, cardiovascular disease, atherogenesis.

INTRODUCTION

Recent research indicates that C-reactive protein (CRP) plays an important role in the development of atherosclerotic cardiovascular disease (CVD) [1-3]. CRP may not only be a biomarker of inflammation as it has been found in atherosclerotic plaques and shown to cause endothelial cell dysfunction, oxidant stress and intima hypertrophy in experimental models [4-6]. Understanding the underlying mechanisms of CRP effect on atherosclerosis development may provide insight into potential new prevention strategies and therapeutic interventions.

METHODS

We performed a PubMed search up to July 2009 using combinations of the following key words: atherogenesis, coronary heart disease, CRP, high sensitivity CRP (hsCRP), atherosclerosis, inflammation, inflammatory markers, cardiovascular disease, atherothrombosis and myocardial infarction. We also searched data from reference lists of original papers, case reports and review articles as well as from randomized clinical trials and meta-analyses

C-REACTIVE PROTEIN POLYMORPHISMS

CRP is an acute-phase protein, which is released in the circulation in response to inflammation and tissue damage [7,8]. CRP is synthesized by hepatocytes under the transcriptional control of inflammatory cytokines, particularly interleukin 6 (IL-6) [7]. CRP reaches maximum concentration in plasma in approximately 50 hours and falls after the removal of inflammatory stimulus, having a half life of 18 h [9]. The human CRP gene is located on chromosome 1 [10]. The CRP gene in hepatocytes is predominantly under transcriptional control by IL-6 and, to a lesser degree, by interleukin 1b (IL-1b) and tumor factor necrosis factor a (TNFa).

Recent studies have established that alterations in serum CRP levels are not only a response to changes in the environment, but also are a consequence of genetic variation in the CRP gene [11-13]. In a recent study, 4 tag single-nucleotide polymorphisms (SNPs) (1919A/T, 2667G/C, 3872G/A, 5237A/G) were genotyped in 3941 white (European American) participants and 5 tag SNPs (addition of 790A/T) were genotyped in 700 black (African American) participants, aged 65 years or older, all of whom did not have myocardial infarction (MI) or stroke before study entry [14]. The 1919T and 790T alleles were associated with higher CRP levels in white and black participants, respectively. The 3872A allele was associated with lower CRP levels in both populations, and the 2667C allele was associated with lower CRP levels in white participants only. There was no association between carotid intima-media thickness (CIMT) and any CRP gene polymorphism in either population. In white participants, the 1919T allele was associated with increased risk of stroke (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.06-1.87) and CVD mortality (HR, 1.40; 95% CI, 1.10-1.90). In black participants, homozygosity for the 790T allele was associated with a 4-fold increased risk of MI compared with homozygosity for the 790A allele (95% CI, 1.58-10.53). The minor alleles of the 2 SNPs associated with lower plasma CRP concentration in white participants (2667C and 3872A) were associated with decreased risk of CVD mortality. Therefore, this study showed that genetic variation in the CRP gene is associated with plasma CRP levels and CVD risk.

However, other studies indicated that genetically controlled CRP elevations by CRP SNPs do not contribute to CVD risk [15,16]. In the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study cohort neither CRP haplotypes nor individual SNP genotypes were associated with IMT of the common carotid or internal carotid artery or the bifurcation of the carotid arteries [15]. Similarly, in a

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1874-2416/10

cohort of 504 white and 244 African-American incident dialysis patients no association was detected between CRP gene variation and CVD risk in either whites or African Americans [16].

A recent study showed that polymorphisms in 5 genetic loci were strongly associated with CRP levels [17]. Notably, this is the largest genome-wide association study aiming to indentify genetic loci associated with plasma CRP concentrations and examine their effect on CVD risk. A significant association of CRP variants with CRP levels and CRP levels with CVD was observed, but not CRP variants with CVD. The variants included in this study were associated with approximately 20% lower CRP levels, corresponding to a 6% reduction in CVD risk as predicted by the meta-analysis of observational studies of CVD risk. The lack of association of genetic variants in the CRP locus with CVD suggests that the observational data linking CRP levels and CVD may be confounded by association with other CVD risk factors, or reflect a secondary inflammatory response associated with atherosclerosis (reverse causation), rather than indicate a causal relationship [17].

Additionally, two recent studies regarding the association between CRP genetic polymorphisms and CVD concluded that no CRP gene polymorphism is associated with increased risk of CVD. Zacho J *et al.* gathered data from 4 genetic studies (45,000 patients) and showed that genotype combinations of 4 CRP polymorphisms were associated with an increase in CRP levels of up to 64%, resulting in a theoretically predicted increased risk of up to 32% for ischemic heart disease and up to 25% for ischemic cerebrovascular disease. However, these genotype combinations were not associated with an increased risk of ischemic vascular disease [18]. Similarly the Luric Study including 3250 patients reported that none of the genetic variants affecting circulating CRP was consistently associated with the prevalence of angiographic coronary artery disease [19].

In conclusion, the most large and reliable studies on the association between CRP genetic loci and CVD risk show that CRP gene polymorphisms may influence CRP levels but not CVD risk.

MEASUREMENT OF CRP

As CRP has prognostic value in patients with acute coronary syndromes and in apparently healthy people [20], various hsCRP methods have been introduced [21]. Regardless of the assay procedure being used the CRP molecule measured is the same [22]. Most traditional CRP tests designed to monitor acute and chronic inflammation have inadequate sensitivity for risk stratification of CVD [23]. Assays for hsCRP have been used by research laboratories for 30 years [8]. We can mention IMMULITE and BNA hsCRP methods, the Beckman Synchron LX20 CRP method and a hsCRP method for the Beckman Coulter IMMAGE [24]. Because an individual's CRP concentration will be interpreted according to fixed cut-points, issues related to the pre-analytic and analytic components of CRP measurement must be considered and standardized where possible to avoid potential misclassification of CVD risk [23].The new development into clinical practice is the introduction of commercial and automated CRP immunoassay systems with greater sensitivity than before. HsCRP levels less than 1 mg/L are considered "low," levels from 1 to 3 mg/L are considered "average," and levels greater than 3 mg/L are considered "high" [25]. Levels greater than 10 mg/L are usually seen only with active inflammatory processes, such as infection, major trauma or chronic inflammatory diseases [26-28]. Because CRP can fluctuate over time, most experts recommend measuring two hsCRP levels a few weeks apart and average the two values.

HsCRP AND CARDIOVASCULAR DISEASE

A number of studies demonstrated a strong predictive association between elevated hsCRP levels and future atherothrombotic events (coronary events, stroke and peripheral arterial disease) [29-36].

The Role of hsCRP in Coronary Heart Disease

A meta-analysis of all published studies up to 2000, comprising of 1953 coronary events, showed a relative risk of 2.0 for a future coronary event in subjects with a single initial baseline hsCRP value in the upper third compared with those in the lower third of the distribution in the general population [37]. However, a recent study demonstrated that for short-term prediction of CVD outcomes in an Iranian population, measurement of hsCRP has no additional value when traditional cardiovascular risk factors are known [38]. The age-and sex-adjusted relative risk of CVD for subjects in the highest quartile of the population distribution of hsCRP compared with the lowest quartile was 2.6 (95% CI=1.4-5.1, p=0.006). However, after additional adjustment for traditional cardiovascular risk factors the odds ratio decreased to non significant levels (0.8, 95% CI=0.3-1.9). Addition of hsCRP did not improve the area under receiver operating characteristic curve of risk functions that was based on traditional cardiovascular risk factors or Framingham coronary risk score [38].

A cohort study including 5067 participants evaluated the utility of CRP levels for predicting CVD risk when added to conventional risk factors [39]. This study reported a modest effect of CRP in CVD risk prediction. CRP may be used to predict future CVD events, but the gains over conventional risk factors are minimal. Risk classification improved in intermediate-risk individuals, mainly through the identification of those unlikely to develop events [39].

A post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) demonstrated that statin therapy may be effective in the primary prevention of coronary events among subjects with relatively low lipid levels but with elevated hsCRP concentration [40]. In this trial the rates of coronary events increased significantly with increases in the baseline levels of hsCRP [40].

Moreover, serum hsCRP levels may predict outcome after myocardial infarction and reflect infarct size [41-44]. In a case-control analysis of post-myocardial infarction patients randomly assigned to pravastatin or placebo in the Cholesterol and Recurrent Events (CARE) trial, those with elevated hsCRP levels at baseline exhibited an increased risk of recurrent coronary events (RR=1.77, p=0.02) [45].

A substudy of the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial demonstrated that increased hsCRP levels, even >1 mg/L, were

associated with a significantly greater risk of cardiovascular death MI, or stroke in patients with stable coronary artery disease (hsCRP 1 to 3 mg/L: adjusted HR 1.39; 95% CI 1.06 to 1.81; p=0.016; hs-CRP >3 mg/L: adjusted HR 1.52; 95% CI 1.15 to 2.02; p=0.003) [46].

There is evidence that the elevation of hsCRP can be a useful predictor for restenosis and other major cardiac events (MACE) after percutaneous coronary intervention (PCI). [47,48]. Maruszewski L *et al.* showed that in patients with MACE the mean hsCRP concentration was significantly higher (median 4.8 mg/L; 1.9-11.4) in comparison with the control group (median 2.2; 1.3-4.3), p<0.05 [48]. Another study showed that post-procedural hsCRP levels higher than 3 mg/L measured in the third month after stent implantation can predict angiographic in-stent restenosis [49]. An elevated hsCRP concentration (≥24 mg/L) on the second day after stent implantation was found to be higher in patients with restenosis [50]. However, in another study such a correlation was not found. In this study pre-and post-procedural hsCRP concentrations were similar in restenotic and non-restenotic patients [51]. Another recent study showed that an increase in hsCRP levels after PCI predicts long-term major adverse cardiac events in patients with stable angina pectoris [52]. Moreover, in patients who undergo coronary artery bypass grafting, high pre-operative hsCRP levels were associated with increased long-term risk of CVD events independently of other cardiac risk factors [53]. In this study the relative risk of CVD events for hsCRP above the median was 3.9 (95% CI 1.1 to 13.9, p<0.05).

A prespecified analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study revealed an independent association between hsCRP reduction and risk of recurrent coronary events and between LDL cholesterol reduction and risk of CVD events. Specifically, PROVE IT compared outcomes in 4162 patients with acute coronary syndrome receiving atorvastatin 80 mg/day or pravastatin 40 mg/day. Patients with hsCRP levels reduced to <2 mg/L had fewer recurrent events regardless of LDL cholesterol level achieved by statin therapy [54]. The patients at highest risk were those in whom both LDL cholesterol and hsCRP levels remained elevated despite statin therapy. Patients whose LDL cholesterol was lowered to <70 mg/dL but hsCRP levels remained elevated (≥2 mg/L) had similar recurrent event rates compared with those whose hsCRP levels were reduced to <2 mg/L but LDL cholesterol levels remained ≥70 mg/dL. Patients with both low hsCRP (<2 mg/L) and LDL cholesterol (<70 mg/dL) had the lowest risk [55,56].

Two cohort studies generated controversy on the risk prediction of CRP levels. In the Framingham Heart Study the age- and sex-adjusted relative risk of a CRP level greater than 3 mg/L for major CVD events was 1.60 (95% CI, 1.19-2.14), but with evidence of attenuation (RR 1.22; 95% CI, 0.90-1.66) in multivariable models [57]. Moreover, in multivariable models that included traditional risk factors the C-statistic (a measure of the discriminatory capability of the prediction models) was 0.78, a value that remain unchanged with the addition of CRP to the multivariable model [57]. In the Reykjavik Heart Study CRP was a relatively moderate predictor of CVD [58]. In this study, after adjustment for baseline values for established risk factors the odds ratio for CVD was 1.45 (95% CI, 1.25-1.68) for participants in the top third compared with those in the bottom third. Similar overall findings were observed in an updated meta-analysis involving a total of 7068 patients with coronary heart disease [58].

The Role of hsCRP in Ischemic Stroke

A recent study showed that hsCRP levels were significantly elevated in patients with progressive carotid stenosis and associated with the occurrence of a first future CVD event [59]. Similarly, in another study hsCRP concentration was significantly associated with cerebral arteries stenosis >70% [60]. Mullenix PS *et al.* recently showed that hsCRP levels were independently associated with carotid stenosis (odds ratio [OR] 1.2, 95% CI 1.1-1.5, p=0.04), while LDL cholesterol levels were not (OR 1.0, 95% CI 0.98-1.01, p=0.8) [61].

In the Atherosclerosis Risk in Communities (ARIC) study hsCRP improve the stratification of ischemic stroke risk [62]. In a model using traditional risk factors alone, the area under the receiver operator characteristic curve was 0.732, whereas adding hsCRP improved it to 0.743 [62]. Elevated hsCRP has been shown to correlate with increased CIMT [63] and has been discussed as a possible marker for plaque instability in carotid territories [64,65].

Moreover, the Carotid Atherosclerosis Progression Study showed that hsCRP levels were significantly associated with baseline CIMT in all carotid segments, but this association was no longer significant after controlling for age, gender and CVD risk factors [66]. Also, hsCRP was not related to individual CIMT progression. In the Cardiovascular Health Study there was no association between CIMT and any CRP gene polymorphism [14]. Dziedzic T *et al.* recently showed that elevated hsCRP levels in patients with acute ischemic stroke are associated with increased risk of recurrent stroke or other CVD events [67].

A recent meta-analysis of studies with long follow-up (>8 years) regarding the predictive role of CRP in stroke showed that the risk for stroke in healthy individuals with the highest quartile of CRP concentrations increased nearly 70% compared with those with the lowest quartile [68]. Also, high concentrations of CRP were predictive of cognitive decline and dementia [68].

According to published guidelines there is not sufficient evidence to recommend measurement of CRP in the routine evaluation of cerebrovascular disease risk in primary prevention, because there is insufficient evidence as to whether early detection or intervention based on detection improves health outcomes [69]. In secondary prevention of stroke elevated CRP adds to existing prognostic markers, but it remains to be established whether specific therapeutic options can be derived from this [69].

The Role of hsCRP in Peripheral Arterial Disease (PAD)

A recent cross-sectional study in 1611 participants without CVD, diabetes or hypertension showed that higher hsCRP levels were positively associated with PAD independently of smoking, waist circumference, body mass index, blood pressure, serum total cholesterol and other confounders [70]. Multivariable OR (95% CI) comparing quar-

tile 4 of hsCRP (>0.54 mg/L) to quartile 1 (<0.09 mg/L) was 6.38 (1.77-22.96, p=0.005). In the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg (INVADE) study, the pathological ankle-brachial index (ABI) (p<0.001) and prediagnosed PAD (p=0.002) were significantly higher in patients with elevated hsCRP [71]. However, a recent study showed that hsCRP is not independently associated with peripheral subclinical atherosclerosis [72]. Hs-CRP levels were associated with major CVD risk factors, 10-year CVD risk, lower ABI, and higher CIMT values. In a logistic model, after adjustment for significant covariates, the association of hsCRP levels with ABI and IMT was no longer significant [72].

According to a meta-analysis of 13 prospective trials regarding the predictive ability of CRP for PAD, CRP appears to be a strong predictor and marker of severity of PAD and may also predict the risk of restenosis after angioplasty [73].

Statins reduce plasma hsCRP levels and this decrease is independent of LDL cholesterol reduction [74,75]. Statins have pleiotropic effects, including anti-inflammatory actions. The anti-inflammatory effects of statins seem to be dose-dependent [76-79].

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study demonstrated that lowering hsCRP levels in addition to lowering LDL cholesterol concentration in patients with CVD by intensive statin therapy attenuated atherosclerotic lesion progression as measured by intravascular ultrasonography [80]. Nissen *et al.* reported that statin treatment decreased hsCRP levels, which were inversely correlated with the rate of disease progression in patients with angiographically documented coronary artery disease [80].

HsCRP and Primary Prevention

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study is the first prospective study which demonstrated that statin therapy lowers CVD risk in patients with at-goal LDL cholesterol but elevated hsCRP levels. JUPITER was a large multinational, long-term, double-blind, placebo-controlled, randomized clinical trial designed to assess whether statin therapy could benefit apparently healthy individuals with at goal LDL cholesterol levels (<130 mg/dL) but elevated hsCRP levels (≥2 mg/dL) [81]. Asymptomatic individuals (men >50 years and women >60 years, n=17,802) who had no history of MI, stroke or myocardial revascularization and who on screening were found to have LDL cholesterol levels <130 mg/dL and hsCRP≥2 mg/L were randomized to either rosuvastatin 20 mg/day or placebo. All participants were then observed over a period of 3 to 4 years for the development of a first CVD event. The primary end point was defined as MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CVD causes.

The trial was stopped prematurely, with only a median 1.9 years of follow-up, when the data and safety monitoring committee noted a significant reduction by 44% in the primary end point among participants assigned to rosuvastatin (142 primary events vs 251 in the placebo group, HR 0.56; 95% CI, 0.46-0.69, p<0.00001) [82]. Rosuvastatin was associated with significant reductions in rates of the individual components of the primary trial end point. Specifically, there was a 55% decrease in the fatal or nonfatal MI (HR 0.46; 95% CI, 0.30-0.70; p = 0.0002) and a 48% decrease in fatal and non fatal stroke (HR 0.52; 95% CI, 0.34-0.79; p = 0.002). The combined end point of nonfatal MI, nonfatal stroke, or death from CVD causes was reduced by 47% (HR 0.53; 95% CI, 0.40-0.69; p < 0.00001) [82]. Importantly, the rates of death from any cause were reduced by 20% (HR 0.80; 95% CI, 0.67-0.97; p = 0.02).

Similar reductions were seen for both women (46%) and men (42%) and in every other subgroup evaluated, including subgroups according to age, race or ethnic group, region of origin, status with regard to traditional risk factors and Framingham risk score. Groups typically assumed to be at very low risk also benefited. For participants who had elevated levels of hsCRP but who were nonsmokers, did not have the metabolic syndrome, had a calculated Framingham risk score of 10% or less, or had an LDL cholesterol level of 100 mg/dL or lower, the observed relative reductions in the HR associated with rosuvastatin for the primary end point was similar to those in higher risk groups. For subjects with elevated hsCRP levels but no other major risk factor other than increased age, the benefit of rosuvastatin was similar to that for higher risk subjects (HR 0.63; 95% CI, 0.44-0.92; p = 0.01) [82].

Previous statin trials (most of which used LDL cholesterol level criteria for enrolment) have generally reported a 20% reduction in vascular risk for each 1 mmol/L (38.7 mg/dL) of absolute reduction in the LDL cholesterol level [83], an effect that would have predicted a proportionate reduction in the number of events in JUPITER study of approximately 25%. However, the reduction in the HR seen in JUPITER, in which enrolment was based on elevated hsCRP levels rather than on elevated LDL cholesterol levels, was almost twice this magnitude and revealed a greater relative benefit than that found in most previous statin trials [82].

Of note, symptomatic venous thromboembolism occurred in 94 participants: 34 in the rosuvastatin group and 60 in the placebo group. This corresponds to a reduction of 43% (HR 0.57; 95% CI 0.37-0.86; p = 0.007) [84]. Pulmonary embolism was reduced by 23% (HR 0.77; 95% CI, 0.41-1.45; p = 0.42), whereas deep-vein thrombosis was reduced by 55% (HR 0.45; 95% CI, 0.25-0.79; p = 0.004) [84].

An analysis from the JUPITER trial showed a 65% reduction in vascular events in participants allocated to rosuvastatin who achieved both LDL cholesterol less than 70 mg/dL and hsCRP less than 2 mg/L (adjusted HR 0.35; 95% CI, 0.23-0.54) vs a 33% reduction in those who achieved one or neither target (HR 0.67; 95% CI, 0.52-0.87) (p across groups <0.0001) [85]. Moreover, a 79% reduction (HR 0.21; 95% CI, 0.09-0.52) in vascular events was noticed in participants who achieved LDL cholesterol less than 70 mg/dL and hsCRP less than 1 mg/L [85].

Until now, on the basis of Current National Cholesterol Education Program/Adult Treatment Panel III (NCEP ATP III) guidelines ≈ 58% of the middle-aged to older adult population have an indication for statin therapy. On the basis of JUPITER's findings ≈ 80% of older persons may now have

an indication for statin therapy [86]. In the United States 6.5 million adults with LDL cholesterol <130 mg/dL and hsCRP ≥2 mg/L not currently on therapy met the "older" age requirement for the JUPITER study and, thus, might now be considered statin candidates [87]. In addition, 6.7 million older adults with elevated hsCRP ≥2 mg/L have LDL cholesterol levels that exceed their NCEP ATP III goals [87].

The results of JUPITER raise two important questions about the primary prevention of CVD. Should indications for statin treatment be expanded? And how should measurements of hsCRP be used?

The design of JUPITER means that the study provides only limited and indirect information about the role of hsCRP protein testing in clinical management, since the trial did not compare subjects with and those without hsCRP measurements, nor did it compare the use of hsCRP with the use of other markers of CVD risk. It also did not ascertain whether subjects with CRP level of less than 2 mg/L would benefit from treatment [88].

There remains much confusion within the medical community as to when it may be appropriate to measure hsCRP levels and what to do about them when found to be elevated. It is not yet known whether hsCRP is a risk factor or merely a marker of increased CVD risk. More importantly, it is not known if reducing only hsCRP levels also decreases CVD risk. The American Heart Association (AHA) recommends measuring hsCRP levels in patients who have a moderately elevated risk of CVD events according to traditional CVD risk factors and specifically in individuals with Framingham risk score between 10% and 20% [89]. In these patients, an elevated hsCRP measurement would indicate that the risk may be much greater than "moderate." For patients who are already known to have high risk, measuring hsCRP levels does not have additional clinical value; the risk is high whatever the hsCRP levels. Thus, given our current level of knowledge in high risk patients there is little to be gained by measuring hsCRP levels.

JUPITER provides more evidence about the effectiveness of statin therapy in reducing CVD risk, even among persons who would not currently be considered for pharmacotherapy. Guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but statin therapy depends on the balance between the benefits of treatment and its long-term safety and cost.

A novel biomarker, the lipoprotein-associated phospholipase A_2 (Lp-PLA_2), is competitive to hsCRP regarding CVD risk prediction [62,90,91]. Lp-PLA_2 is a proinflammatory enzyme secreted by macrophages that is primarily bound to LDL in the circulation. It hydrolyzes oxidized phospholipids to generate lysophosphatidylcholine and oxidized fatty acids, which have proinflammatory properties, and its activity is increased in small, dense LDL [92]. Moreover Lp-PLA_2 may be a novel target for therapy to reduce CVD risk and an agent that inhibits Lp-PLA_2 is currently in phase 3 testing [93]. In the Atherosclerosis Risk in Communities (ARIC) study individuals with high levels of both hsCRP and Lp-PLA_2 were at the highest risk after adjusting for traditional risk factors compared with individuals with low levels of both, whereas others were at intermediate risk [62].

THE ROLE OF CRP IN THE PATHOGENESIS OF ATHEROSCLEROSIS

CRP has been detected in atherosclerotic lesions of human coronary arteries as well as heart, kidney and adipose tissue [94-96]. In patients with acute coronary syndrome CRP is localized in the vessel wall and its levels are higher in the coronary sinus than in the aorta, suggesting a cardiac source of CRP [97,98].

Many possible mechanisms of a direct action of CRP on vascular cells have been reported. CRP induces the expression of adhesion molecules by the endothelial cells, such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [99,100], which play a crucial role in the migration of monocytes and T-leukocytes into the vessel wall and thus in atherosclerosis development [101,102]. Moreover, in a recent study CRP stimulated superoxide anion release and tissue factor activity not only *in vitro*, but also *in vivo* [103]. Furthermore, CRP may induce plasminogen activator inhibitor-1 (PAI-1) expression and activity in human endothelial cells [104,105], which is a marker of impaired fibrinolysis and atherothrombosis [106,107]. Additionally, CRP may induce apoptosis in human coronary vascular smooth muscle cells, thus promoting atherogenesis [108]. Finally, CRP may also increase the susceptibility of endothelial cells to destruction by cell lysis [109], a mechanism that could lead to plaque erosion or rupture and precipitate acute coronary syndrome.

CONCLUSIONS

On the basis of JUPITER trial hsCRP measurement may be considered in asymptomatic people older than 50 years of age with an LDL cholesterol of <130 mg/dL. If it is found elevated (>2 mg/L on two separate occasions), then initiation of a powerful statin may be needed.

Future studies are needed to investigate if hsCRP should also be considered as a target of treatment. Both JUPITER and PROVE-IT showed that the reduction of both LDL cholesterol and hsCRP results in greater decrease in CVD events compared with the reduction of only LDL cholesterol. It should further be studied if an on treatment measurement of hsCRP is warranted and whether adjusting lifestyle measures and power of lipid-lowering treatment to achieve hsCRP targets is associated with improved outcomes.

ABBREVIATIONS

IL-6 = Interleukin 6

IL-1b = Interleukin 1b

TNFa = tumor factor necrosis factor a

SNPs = single-nucleotide polymorphisms

CIMT = carotid intima-media thickness

IMT = intima-media thickness

CRP = C-reactive protein

HsCRP = high sensitivity C-reactive protein

HR = hazard ratio

OR = odds ratio

CVD = cardiovascular disease

MI = myocardial infarction

LDL = low-density lipoprotein cholesterol

RR = relative ratio

PCI = percutaneous coronary intervention

PAD = peripheral artery disease

ABI = ankle-brachial index

$Lp\text{-}PLA_2$ = lipoproteinassociated phospholipase A_2

ICAM = intracellular adhesion molecule-1

VCAM = vascular cell adhesion molecule-1

PAI-1 = plasmonogen activator inhibitor-1

REFERENCES

[1] Ridker, P.M.; Glynn, R.J.; Hennekens, C.H. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation*, **1998**, *97*, 2007-2011.

[2] Ridker, P.M.; Buring, J.E.; Shih, J.; Matias, M.; Hennekens, C.H. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*, **1998**, *98*, 731-733.

[3] Ridker, P.M.; Rifai, N.; Rose, L.; Buring, J.E.; Cook, N.R. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N. Engl. J. Med.*, **2002**, *347*, 1557-65.

[4] Wilson, M.W.; Marno, C.R.; Andrew, J.B. The novel role of C-reactive protein in cardiovascular disease:risk marker or pathyogen. *Int. J. Cardiol.*, **2006**, *106*, 291-297.

[5] Libby, P. Inflammation in atherosclerosis. *Nature*, **2002**, *420*, 868-74.

[6] Yasojima, K.; Schwab, C.; McGeer, E.G.; McGeer, P.L.; Generation of C-reactive protein and complement components in atherosclerotic plaques. *Am. J. Pathol.*, **2001**, *158*, 1039-1051.

[7] Pepys, M.B.; Baltz, M.L. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv. Immunol.*, **1983**, *34*, 141-212.

[8] Gabay, C.; Kushner, I. Acute-phase proteins and other systemic responses to inflammation. *N. Engl. J. Med.*, **1999**, *340*, 448-454.

[9] Blake, G.J.; Ridker, P.M. C-reactive protein: a surrogate risk marker or mediator of atherothrombosis? *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2003**, *285*, R1250-1252.

[10] Whitehead, A.S.; Bruns, G.A.; Markham, A.F.; Colten, H.R.; Woods, D.E. Isolation of human C-reactive protein complementary DNA and localization of the gene to chromosome 1. *Science*, **1983**, *221*, 69-71.

[11] Kathiresan, S.; Larson, M.G.; Vasan, R.S.; Guo, C.Y.; Gona, P. Contribution of clinical correlates and 13 C-reactive protein gene polymorphisms to interindividual variability in serum C-reactive protein level. *Circulation*, **2006**, *113*, 1415-23.

[12] Kivimäki, M.; Lawlor, D.A.; Smith, G.D.; Eklund, C.; Hurme, M. Variants in the CRP gene as a measure of lifelong differences in average C-reactive protein levels: the Cardiovascular Risk in Young Finns Study, 1980-2001. *Am. J. Epidemiol.*, **2007**, *166*, 760-4.

[13] Crawford, D.C.; Sanders, C.L.; Qin, X.; Smith, J.D., Shephard, C. Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey. *Circulation*, **2006**, *114*, 2458-65.

[14] Lange, L.A.; Carlson, C.S.; Hindorff, L.A.; Lange, E.M.; Walston, J. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. *JAMA*, **2006**, *296*, 2703-11.

[15] Wang, Q.; Hunt, S.C.; Xu, Q.; Chen, Y.E.; Province, M. Association study of CRP gene polymorphisms with serum CRP level and cardiovascular risk in the NHLBI Family Heart Study. *Am. J. Physiol. Heart Circ. Physiol.*, **2006**, *291*, H2752-7.

[16] Zhang, L.; Kao, W.H.; Berthier-Schaad, Y.; Plantinga, L.; Fink, N. C-Reactive protein haplotype predicts serum C-reactive protein levels but not cardiovascular disease risk in a dialysis cohort. *Am. J. Kidney Dis.*, **2007**, *49*, 118-26.

[17] Elliott, P.; Chambers, J.; Zhang, W.; Clarke, R.; Hopewell, J.C.; Peden, J.F.; Erdmann, J.; Braund, P.; Engert, J.C.; Bennett, D.; Coin, L.; Ashby, D.; Tzoulaki, I.; Brown, I.J.; Mt-Isa, S.; McCarthy, M.I.; Peltonen, L.; Freimer, N.B.; Farrall, M.; Ruokonen, A.; Hamsten, A.; Lim, N.; Froguel, P.; Waterworth, D.M.; Vollenweider, P.; Waeber, G.; Jarvelin, M.R.; Mooser, V.; Scott, J.; Hall, A.S.; Schunkert, H.; Anand, S.S.; Collins, R.; Samani, N.; Watkins, H.; Kooner, J.S. Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. *JAMA*, **2009**, *302*, 37-48.

[18] Zacho, J.; Tybjaerg-Hansen, A.; Jensen, J.S.; Grande, P.; Sillesen, H.; Nordestgaard, B.G. Genetically elevated C-reactive protein and ischemic vascular disease. *N. Engl. J. Med.*, **2008**, *359*, 1897-908.

[19] Grammer, T.B.; März, W.; Renner, W.; Böhm, B.O.; Hoffmann, M.M. C-reactive protein genotypes associated with circulating C-reactive protein but not with angiographic coronary artery disease: the LURIC study. *Eur. Heart*, **2009**, *30*, 170-82.

[20] Rifai, N.; Ridker, P.M. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. *Clin. Chem.*, **2001**, *47*, 403-11.

[21] Burnett, J.R.; Watts, G.F.; Vasikaran, S.D. C-reactive protein: a new cardiovascular risk factor? *Med. J. Aust.*, **2000**, *173*, 117-8.

[22] de Ferranti, S.D.; Rifai. N. C-reactive protein: a non-traditional serum marker of cardiovascular risk. *Cardiovasc. Pathol.*, **2007**, *16*, 14-21.

[23] Ledue, T.B.; Rifai, N.; Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clin. Chem.*, **2003**, 49, 1258-71.

[24] Rothkrantz-Kos, S.; Schmitz, M.P.; Bekers, O.; Menheere, P.P.; van Dieijen-Visser, M.P. High sensitivity C-reactive protein methods examined. *Clin. Chem.*, **2002**, *48*, 359-62.

[25] Pearson, T.A.; Mensah, G.A.; Alexander, R.W.; Anderson, J.L.; Cannon, R.O 3rd.; Criqui, M.; Fadl, Y.Y.; Fortmann, S.P.; Hong, Y.; Myers, G.L.; Rifai, N.;Smith, S.C.; J.r.; Taubert, K.; Tracy, R.P.; Vinicor, F. Centers for disease control and prevention; american heart association markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for health-care professionals from the centers for disease control and prevention and the american heart association. *Circulation*, **2003**, *107*, 499-511.

[26] Yasojima, K.; Schwab, C.; McGeer, E.G.; McGeer, PL. Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer's disease. *Brain Res*, **2000**, *887*, 80-89.

[27] Black, S.; Kushner, I.; Samols, D. C-reactive protein. *J. Biol. Chem.*, **2004**, *279*, 48487-48490.

[28] Davey, S.G.; Timpson, N.; Lawlor, D. C-reactive protein and cardiovascular disease risk: Still an unknown quantity? *Ann. Intern. Med.*, **2006**, *145*, 70-72.

[29] Kuller, L.H.; Tracy, R.P.; Shaten, J.; Meilahn, E.N. Relation of C-reactive protein and coronary heart-disease in the MRFIT nested case control study. *Am. J. Epidemiol.*, **1996**, *144*, 537-547.

[30] Ridker, P.M.; Cushman, M.; Stampfer, M.J.; Tracy, R.P.; Hennekens, C.H. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N. Engl. J. Med.*, **1997**, 336, 973-979.

[31] Koenig, W.; Sund, M.; Fröhlich, M.; Fischer, H.G.; Löwel, H.; Döring, A.; Hutchinson, W.L.; Pepys, M.B. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation*, **1999**, *99*, 237-242.

[32] Danesh, J.; Whincup, P.; Walker, M.; Lennon, L.; Thomson, A.; Appleby, P.; Gallimore, J.R.; Pepys, M.B. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ*, **2000**, *321*, 199-204.

[33] Morrow, D.A.; Ridker, P.M. C-reactive, inflammation, and coronary risk. *Med. Clin. North Am.*, **2000**, *84*, 149-161.

[34] Ridker, P.M.J.; Hennekens, C.H.; Buring, J.E.; Rifai, N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N. Engl. Med.*, **2000**, *342*, 836-843.

[35] Ridker, P.M.; Stampfer, M.J.; Rifai, N. Novel risk factors for systemic atherosclerosis: A comparison of C-reactive protein, fibrinogen, homocystein, lipoprotein (a), and standard cholesterol screen-

ing as predictors of peripheral arterial disease. *JAMA*, **2001**, *285*, 2481-2485.

[36] Nakou, E.S.; Liberopoulos, E.N.; Milionis, H.J.; Elisaf, M.S. The role of C-reactive protein in atherosclerotic cardiovascular disease: an overview. *Curr. Vasc. Pharmacol*., **2008**, *6*, 258-70.

[37] Danesh, J.; Whincup, P.; Walker, M.; Lennon, L.; Thomson, A.; Appleby, P.; Gallimore, J.R.; Pepys, M.B. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ*, **2000**, *321*, 199-204.

[38] Tohidi, M.; Hadaegh, F.; Harati, H.; Azizi, F. C-reactive protein in risk prediction of cardiovascular outcomes: Tehran Lipid and Glucose Study. *Int. J. Cardiol.*, **2009**, *132*, 369-74.

[39] Melander, O.; Newton-Cheh, C.; Almgren, P.; Hedblad, B.; Berglund, G.; Engström, G.; Persson, M.; Smith, J.G.; Magnusson, M.; Christensson, A.; Struck, J.; Morgenthaler, N.G.; Bergmann, A.; Pencina, M.J.; Wang, T.J. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA*, **2009**, *302*, 49-57.

[40] Ridker, P.M.; Rifai, N.; Clearfield, M.; Downs, J.R.; Weis, S.E.; Miles, J.S.; Gotto, A.M.Jr. Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N. Engl. J. Med*., **2001**, *344*, 1959-65.

[41] de Beer, F.C.; Hind, C.R.; Fox, K.M.; Allan, R.M.; Maseri, A.; Pepys, M.B. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br. Heart J.*, **1982**, *47*, 239-243.

[42] Pietilä, K.O.; Harmoinen, A.P.; Jokiniitty, J.; Pasternack, A.I. Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. *Eur. Heart J*., **1996**, *17*, 1345-1349.

[43] Ueda, S.; Ikeda, U.; Yamamoto, K.; Takahashi, M.; Nishinaga, M.; Nago, N.; Shimada, K. C-reactive protein as a predictor of cardiac rupture after acute myocardial infarction. *Am. Heart J*., **1996**, *131*, 857-860.

[44] Anzai, T.; Yoshikawa, T.; Shiraki, H.; Asakura, Y.; Akaishi, M.; Mitamura, H.; Ogawa, S. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. *Circulation*, **1997**, *96*, 778-784.

[45] Ridker, P.M.; Rifai, N.; Pfeffer, M.A.; Sacks, F.M.; Moye, L.A.; Goldman, S.; Flaker, G.C.; Braunwald, E. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation*, **1998**, *98*, 839-844.

[46] Sabatine, M.S.; Morrow, D.A.; Jablonski, K.A.; Rice, M.M.; Warnica, J.W.; Domanski, M.J.; Hsia, J.; Gersh, B.J.; Rifai, N.; Ridker, P.M.; Pfeffer, M.A.; Braunwald, E. PEACE Investigators. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. *Circulation*, **2007**, *115*, 1528-1536.

[47] Markuszewski, L.; Rysz, J.; Makowski, M.; Debska, A.; Pietruszynski, R. C-reactive protein as a predictor of major adverse cardiac events (MACE) after percutaneous coronary intervention? *Arch. Med. Sci.*, **2005**, *1*(3), 152-156.

[48] Gaspardone, A.; Crea. F.; Versaci. F.; Tomai, F.; Pellegrino, A.; Chiariello, L.; Gioffrè, P.A. Predictive value of C-reactive protein after successful coronary-artery stenting in patients with stable angina. *Am. J. Cardiol.*, **1998**, *82*, 515-518.

[49] Karaca, I.; Aydin, K.; Yavuzkir, M.; Ilkay, E.; Akbulut, M. Predictive value of C-reactive protein in patients with unstable angina pectoris undergoing coronary artery stent implantation. *J. Int. Med. Res.*, **2005**, *33*, 389-396.

[50] Iarlykova, E.I.; Kuchkina, N.V.; Vorob'eva, E.I. C-reactive protein as possible early prognostic marker of restenosis development in coronary artery stents. *Kardiologiia*, **2002**, *42*, 11-13.

[51] Yip, H.K.; Hung, W.C.; Yang, C.H.; Chen, Y.H.; Cheng, C.I. Serum concentrations of high-sensitivity C-reactive protein predict progressively obstructive lesions rather than late restenosis in patients with unstable angina undergoing coronary artery stenting. *Circ. J*., **2005**, *69*, 1202-1207.

[52] Gach, O.; Legrand, V.; Biessaux, Y.; Chapelle, J.P.; Vanbelle, S.; Pierard, L.A. Long-term prognostic significance of high-sensitivity C-reactive protein before and after coronary angioplasty in patients with stable angina pectoris. *Am. J. Cardiol.*, **2007**, *99*, 31-35.

[53] van der Harst, P.; Voors, A.A.; Volbeda, M.; Buikema, H.; van Veldhuisen, D.J.; van Gilst, W.H. Usefulness of preoperative C-reactive protein and soluble intercellular adhesion molecule-1 level for predicting future cardiovascular events after coronary artery bypass grafting. *Am. J. Cardiol.*, **2006**, *97*, 1697-1701.

[54] Ridker, P.M.; Cannon, C.P.; Morrow, D.; Rifai, N.; Rose, L.M.; mCcABE, ch.; Pfeffer, M.A.; Braunwald, E. C-reactive protein levels and outcomes after statin therapy. *N. Engl. J. Med*., **2005**, *352*, 20-28.

[55] Ridker, P.M.; Morrow, D.A.; Rose, L.M.; Rifai, N.; Cannon, C.P.; Braunwald, E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. *J. Am. Coll. Cardiol*., **2005**, *45*, 1644-1648.

[56] Mega, J.L.; Morrow, D.A.; Cannon, C.P.; Murphy, S.; Cairns, R.; Ridker, P.M.; Braunwald, E. Cholesterol, C-reactive protein, and cerebrovascular events following intensive and moderate statin therapy. *J. Thromb. Thrombolysis*, **2006**, *22*, 71-76.

[57] Wilson, P.W.; Nam, B.H.; Pencina, M.; D'Agostino, R.B.Sr.; Benjamin, E.J.; O'Donnell, C.J. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. *Arch. Intern. Med.*, **2005**, *165*, 2473-8.

[58] Danesh, J.; Wheeler, J.G.; Hirschfield, G.M.; Eda, S.; Eiriksdottir, G.; Rumley, A.; Lowe, G.D.; Pepys, M.B.; Gudnason, V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N. Engl. J. Med*., **2004**, *350*, 1387-97.

[59] Schlager, O.; Exner, M.; Mlekusch, W.; Sabeti, S.; Amighi, J.; Dick, P.; Wagner, O.; Koppensteiner, R.; Minar, E.; Schillinger, M. C-reactive protein predicts future cardiovascular events in patients with carotid stenosis. *Stroke*, **2007**, *38*, 1263-1268.

[60] Flegar-Mestric, Z.; Vrhovski-Hebrang, D.; Preden-Kerekovic, V.; Perkov, S.; Hebrang, A.; Grga, A.; Janus, D.; Vidjak, V. C-reactive protein level in severe stenosis of cerebral arteries. *Cerebrovasc. Dis.*, **2007**, *23*, 430-434.

[61] Mullenix, P.S.; Steele, S.R.; Martin, M.J.; Starnes, B.W.; Andersen, C.A. C-reactive protein level and traditional vascular risk factors in the prediction of carotid stenosis. *Arch. Surg.*, **2007**, *142*, 1066-1071.

[62] Nambi, V.; Hoogeveen, R.C.; Chambless, L.; Hu, Y.; Bang, H. Lipoprotein-associated phospholipase A2 and high-sensitivity C-reactive protein improve the stratification of ischemic stroke risk in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*, **2009**, *40*, 376-381.

[63] Magyar, M.T.; Szikszai, Z.; Balla, J.; Valikovics, A.; Kappelmayer, J.; Imre, S.; Balla, G.; Jeney, V.; Csiba, L.; Bereczki, D. Early-onset carotid atherosclerosis is associated with increased intima-media thickness and elevated serum levels of inflammatory markers. *Stroke*, **2003**, *34*, 58-63.

[64] Cao, J.J.; Thach, C.; Manolio, T.A.; Psaty, B.M.; Kuller, L.H. C-reactive protein, carotid intima-media thickness, and incidence of ischemic stroke in the elderly: the Cardiovascular Health Study. *Circulation*, **2003**, *108*, 166-170.

[65] Di Napoli, M.; Schwaninger, M.; Cappelli, R.; Ceccarelli, E.; Di Gianfilippo, G. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP Pooling Project members. *Stroke*, **2005**, *36*, 1316-29.

[66] Lorenz, M.W.; Karbstein, P.; Markus, H.S.; Sitzer, M. High-sensitivity C-reactive protein is not associated with carotid intima-media progression: the carotid atherosclerosis progression study. *Stroke*, **2007**, *38*, 1774-1779.

[67] Dziedzic, T. Clinical significance of acute phase reaction in stroke patients. *Front Biosci.*, **2008**, *13*, 2922-2927.

[68] Kuo, H.K.; Yen, C.J.; Chang, C.H.; Kuo, C.K.; Chen, J.H.; Sorond, F. Relation of C-reactive protein to stroke, cognitive disorders and depression in the general population: systematic review and meta-analysis. *Lancet Neurol.*, **2005**, *4*, 371-380.

[69] Di Napoli, M.; Schwaninger, M.; Cappelli, R.; Ceccarelli, E.; Di Gianfilippo, G.; Donati, C.; Emsley, H.C.; Forconi, S.; Hopkins, S.J.; Masotti, L.; Muir, K.W.; Paciucci, A.; Papa, F.; Roncacci, S.; Sander, D.; Sander, K.; Smith, C.J.; Stefanini, A.; Weber, D. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care pro-

fessionals from the CRP Pooling Project members. *Stroke*, **2005**, *36*, 1316-1329.

[70] Shankar, A.; Li, J.; Nieto, F.J.; Klein, B.E.; Klein, R. Association between C-reactive protein level and peripheral arterial disease among US adults without cardiovascular disease, diabetes, or hypertension. *Am. Heart J.*, **2007**, *154*, 495-501.

[71] Schulze, H.C.; Ilg, R.; Sander, K.; Bickel, H.; Briesenick, C. High-sensitivity C-reactive protein at different stages of atherosclerosis: results of the INVADE study. *J. Neurol.*, **2009**, *256*, 783-791.

[72] Bo, M.; Corsinovi, L.; Brescianini, A.; Sona, A.; Astengo, M. High-sensitivity C-reactive protein is not independently associated with peripheral subclinical atherosclerosis. *Angiology*, **2009**, *60*, 12-20.

[73] Abdellaoui, A.; Al-Khaffaf, H. C-reactive protein (CRP) as a marker in peripheral vascular disease. *Eur. J. Vasc. Endovasc. Surg.*, **2007**, *34*, 18-22.

[74] Kardys, I.; Knetsch, A.M.; Bleumink, G.S.; Deckers, J.W.; Hofman, A.; Stricker, B.H.; Witteman, J.C. C-reactive protein and risk of heart failure: The Rotterdam Study. *Am. Heart J.*, **2006**, *152*, 514-520.

[75] Ridker, P.M.; Rifai, N.; Lowenthal, S.P. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation*, **2001**, *103*, 1191-1193.

[76] Albert, M.A.; Danielson, E.; Rifai, N.; Ridker, P.M. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*, **2001**, *286*, 64-70.

[77] Jialal, I.; Stein, D.; Balis, D.; Grundy, S.M.; Adams-Huet, B.; Devaraj, S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation*, **2001**, *103*, 1933-1935.

[78] Liberopoulos, E.N. ; Daskalopoulou, S.S. ; Mikhailidis, D.P. ; Wierzbicki, A.S. ; Elisaf, M.S. A review of the lipid-related effects of fluvastatin. *Curr. Med. Res. Opin.*, **2005**, *21*, 231-244.

[79] Okura, H.; Asawa, K.; Kubo, T.; Taguchi, H.; Toda, I.; Yoshiyama, M.; Yoshikawa, J.; Yoshida, K. Impact of statin therapy on systemic inflammation, left ventricular systolic and diastolic function and prognosis in low risk ischemic heart disease patients without history of congestive heart failure. *Intern. Med.*, **2007**, *46*, 1337-1343.

[80] Nissen, S.E.; Tuzcu, E.M.; Schoenhagen, P.; Crowe, T.; Sasiela, W.J.; Tsai, J.; Orazem, J.; Magorien, R.D.; O'Shaughnessy, C.; Ganz, P. Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N. Engl. J. Med.*, **2005**, *352*, 29-38.

[81] Mora, S.; Ridker, P.M. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)-can C-reactive protein be used to target statin therapy in primary prevention? *Am. J. Cardiol.*, **2006**, *97*, 33A-41A.

[82] Ridker, P.M.; Danielson, E.; Fonseca, F.A.; Genest, J.; Gotto, A.M. Jr.; Kastelein, J.J.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; Nordestgaard, B.G.; Shepherd, J.; Willerson, J.T.; Glynn, R.J. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.*, **2008**, *359*, 2195-2207.

[83] Baigent, C.; Keech, A.; Kearney, P.M.; Blackwell, L.; Buck, G.; Pollicino, C.; Kirby, A.; Sourjina, T.; Peto, R.; Collins, R.; Simes, R. Cholesterol Treatment Trialists' (CTT) Collaborators.Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*, **2005**, *366*, 1267-1278.

[84] Glynn, R.J.; Danielson, E.; Fonseca, F.A.; Genest, J.; Gotto, A.M. Jr.; Kastelein, J.J.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; Nordestgaard, B.G.; Shepherd, J.; Willerson, J.T.; Ridker, P.M. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N. Engl. J. Med.*, **2009**, *360*, 1851-1861.

[85] Ridker, P.M.; Danielson, E.; Fonseca, F.A.; Genest, J.; Gotto A.M. Jr.; Kastelein, J.J.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; Macfadyen, J.G.; Nordestgaard, B.G.; Shepherd, J.; Willerson, J.T.; Glynn, R.J. JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet*, **2009**, *373*, 1175-1182.

[86] Spatz, E.S.; Canavan, M.E.; Desai, M.M. From Here to JUPITER Identifying new patients for statin therapy using data from the 1999-2004 National Health and Nutrition Examination Survey. *Circ. Cardiovasc. Qual. Outcome*, **2009**, *2*, 41-48.

[87] Michos, E.D.; Blumenthal, R.S. Prevalence of low low-density lipoprotein cholesterol with elevated high sensitivity C-reactive protein in the U.S.: implications of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study. *J. Am. Coll. Cardiol.*, **2009**, *53*, 931-935.

[88] Hlatky, M.A. Expanding the orbit of primary prevention-moving beyond JUPITER. *N. Engl. J. Med.*, **2008**, *359*, 2280-2282.

[89] Pearson, T.A.; Mensah, G.A.; Alexander, R.W.; Anderson, J.L.; Cannon, R.O. 3rd.; Criqui, M.; Fadl, Y.Y.; Fortmann, S.P.; Hong, Y.; Myers, G.L.; Rifai, N.; Smith, S.C. Jr.; Taubert, K.; Tracy, R.P.; Vinicor, F. Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for health-care professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*, **2003**, *107*, 499-511.

[90] Ballantyne, C.M.; Hoogeveen, R.C.; Bang, H.; Coresh, J.; Folsom, A.R.; Chambless, L.E.; Myerson, M.; Wu, K.K.; Sharrett, A.R.; Boerwinkle, E. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch. Intern. Med.*, **2005**, *165*, 2479-2484.

[91] Melander, O.; Newton-Cheh, C.; Almgren, P.; Hedblad, B.; Berglund, G.; Engström, G.; Persson, M.; Smith, J.G.; Magnusson, M.; Christensson, A.; Struck, J.; Morgenthaler, N.G.; Bergmann, A.; Pencina, M.J.; Wang, T.J. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA*, **2009**, *302*, 49-57.

[92] Karabina, S.A.; Liapikos, T.A.; Grekas, G.; Goudevenos, J.; Tselepis, A.D. Distribution of PAF-acetylhydrolase activity in human plasma low-density lipoprotein subfractions. *Biochim. Biophys. Acta*, **1994**, *1213*, 34-8.

[93] Mohler, E.R. 3rd.; Ballantyne, C.M.; Davidson, M.H.; Hanefeld, M.; Ruilope, L.M.; Johnson, J.L.; Zalewski, A.; Darapladib Investigators. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J. Am. Coll. Cardiol.*, **2008**, 51, 1632-41.

[94] Yasojima, K.; Schwab, C.; McGeer, E.G.; McGeer, P.L. Generation of C-reactive protein and complement components in atherosclerotic plaques. *Am. J. Pathol.*, **2001**, *158*, 1039-1051.

[95] Torzewski, M.; Rist, C.; Mortensen, R.F.; Zwaka, T.P.; Bienek, M.; Waltenberger, J.; Koenig, W.; Schmitz, G.; Hombach, V.; Torzewski, J. C-reactive protein in the arterial intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. *Arterioscler. Thromb. Vasc. Biol.*, **2000**, *20*, 2094-2099.

[96] Ouchi, N.; Kihara, S.; Funahashi, T.; Nakamura, T.; Nishida, M.; Kumada, M.; Okamoto, Y.; Ohashi, K.; Nagaretani, H.; Kishida, K.; Nishizawa, H.; Maeda, N.; Kobayashi, H.; Hiraoka, H.; Matsuzawa, Y. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation*, **2003**, *107*, 671-674.

[97] Ishikawa, T.; Hatakeyama, K.; Imanura, T.; Date, H.; Shibata, Y.; Hikichi, Y.; Asada, Y.; Eto, T. Involvement of C-reactive protein obtained by directional coronary atherectomy in plaque instability and developing restenosis in patients with stable or unstable angina pectoris. *Am. J. Cardiol.*, **2003**, *91*, 287-292.

[98] Ishikawa, T.; Imanura, T.; Hatakeyama, K.; Date, H.; Nagoshi, T.; Kawamoto, R.; Matsuyama, A.; Asada, Y.; Eto, T. Possible contribution of C-reactive protein within coronary plaque to increasing its own plasma levels across coronary circulation. *Am. J. Cardiol.*, **2004**, *93*, 611-614.

[99] Sabatine, M.S.; Morrow, D.A.; Jablonski, K.A.; Rice, M.M.; Warnica, J.W.; Domanski, M.J.; Hsia, J.; Gersh, B.J.; Rifai, N.; Ridker, P.M.; Pfeffer, M.A.; Braunwald, E. PEACE Investigators. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for car-

diovascular and other outcomes in patients with stable coronary artery disease. *Circulation*, **2007**, *115*, 1528-1536.
[100] Gaspardone, A.; Crea, F.; Versaci, F.; Tomai, F.; Pellegrino, A.; Chiariello, L.; Gioffrè, PA. Predictive value of C-reactive protein after successful coronary-artery stenting in patients with stable angina. *Am. J. Cardiol.*, **1998**, *82*, 515-518.
[101] Libby, P. Inflammation in atherosclerosis. *Nature*, **2002**, *420*, 868-874.
[102] Hulthe, J.; Wikstrand, J.; Mattsson-Hulten, L.; Fagerberg, B. Circulating ICAM-1 (intercellular cell-adhesion molecule 1) is associated with early stages of atherosclerosis development and with inflammatory cytokines in healthy 58-year-old men: the Atherosclerosis and Insulin Resistance (air) Study. *Clin. Sci. (Lond)*, **2002**, *103*, 123-129.
[103] Devaraj, S.; Dasu, M.R.; Singh, U.; Rao, L.V.; Jialal, I. C-reactive protein stimulates superoxide anion release and tissue factor activity *in vivo*. *Atherosclerosis*, **2009**, *203*, 67-74.
[104] Devaraj, S.; Xu, D.Y.; Jialal, I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. *Circulation*, **2003**, *107*, 397-403.
[105] Chen, C.; Nan, B.; Lin, P.; Yao, Q. C-reactive protein increases plasminogen activator inhibitor-1 expression in human endothelial cells. *Thromb. Res.*, **2008**, *122*, 125-133.
[106] Vaughan, D.E. PAI-1 and atherothrombosis. *J. Thromb. Haemost.*, **2005**, *3*, 1879-1883.
[107] Aso, Y. Plasminogen activator inhibitor (PAI)-1 in vascular inflammation and thrombosis. *Front Biosci.*, **2007**, *12*, 2957-2966.
[108] Blaschke, F.; Bruemmer, D.; Yin, F.; Takata, Y.; Wang, W.; Fishbein, M.C.; Okura, T.; Higaki, J.; Graf, K.; Fleck, E.; Hsueh, W.A.; Law, R.E. C-reactive protein induces apoptosis in human coronary vascular smooth cells. *Circulation*, **2004**, *110*, 579-587.
[109] Nakajima, T.; Schuttle, S.; Warrington, K.J.; Kopecky, S.L.; Frye, R.L.; Goronzy, J.J.; Weyand, C.M. T-cell mediated lysis of endothelial cells in acute coronary syndromes. *Circulation*, **2002**, *105*, 570-575.

Received: July 23, 2009 Revised: August 31, 2009 Accepted: August 31, 2009