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Review

Clinical relevance of high sensitivity C-reactive protein in cardiology

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ABSTRACT

Coping with cardiovascular diseases (CVD), which are of the main causes of death worldwide, has influenced investigation of high sensitivity CRP (hsCRP) and its role in pathogenesis, prognosis and prevention of CVD. hsCRP can be synthesized in vascular endothelium, atherosclerotic plaques, and theory of inflammatory origin of atherosclerosis is being more widely debated, raising questions, whether higher hsCRP plasma concentration might be the cause or the consequence. Summing up controversial data from multiple studies, guidelines recommend hsCRP testing for both, primary (stratifying CVD risk groups, selecting patients for statin therapy) and secondary CVD prevention (prognosis of CVD and its treatment complications, evaluation of treatment efficacy in moderate CVD risk group). hsCRP testing also has role in heart failure, atrial fibrillation, arterial hypertension, valve pathology and prognosis of coronary stent thrombosis or restenosis. Medications (the well-known and the new specific – CRP binding) affecting its concentration are being investigated as well.

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1. Introduction

Cardiovascular diseases remain the leading cause of death worldwide [1], making it essential to realize the causes,

pathogenesis of these diseases and improve their diagnostic and treatment capabilities as well as prophylactic programs.

Inflammation is thought to be the key mechanism in the pathogenesis of atherosclerosis, from the formation and progression of the plaque till its rupture, and stent restenosis

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[2–5]. The process of inflammation is also significant in development of arterial hypertension, heart failure, valvular disease and atrial fibrillation [6–8].

Since vascular inflammatory changes can hardly be evaluated using cardiac imaging methods, the role of inflammation biomarkers testing in peripheral blood is increasing, with the hsCRP being the most profoundly studied in cardiovascular diseases [1,3]. It remains stable in samples over long periods of time and can be quite simply, rapidly and cheaply tested [1].

Multiple prospective cohort studies have shown the association between increased CRP levels and increased CVD event risk in patients with established disease, and the incidence of first cardiovascular events in individuals at risk for atherosclerosis [9]. It makes hsCRP testing valuable in both, primary and secondary CVD prophylaxis. And for those, who already suffer from CVD, this test is useful in evaluation of disease severity, treatment efficacy and outcome prognosis [1,10,11].

What is more, a number of drugs used in the treatment of CVD reduce serum CRP, therefore possibly contributing to its therapeutic effects [12–14]; the issue is being discussed in the article as well.

1.1. CRP qualities, detection

CRP belongs to the pentraxin protein family and is synthesized in hepatocytes and some extrahepatic tissues, such as vascular smooth muscle, atherosclerotic plaques, intracardial tissues [1–3,12]. The idea about CRP being synthesized intracardially is confirmed by measuring CRP concentration gradient in the sinus venosus, peripheral blood and coronary arteries (proximally and distally to the atherosclerotic plaque) after percutaneous angioplasty [3]. There are two CRP types with different qualities: pCRP (pentamer) and mCRP (monomer). mCRP evolves when the pentamer is dissociated and is synthesized by the cells which are activated by the pathological process (tissue necrosis, trauma, infection and related mediators: interleukins IL-1, IL-2, IL-17 and tumor necrosis factor alpha [TNF α]). mCRP has proinflammatory and prothrombotic qualities [12]. Metabolism among the healthy and the diseased does not differ and the rate of synthesis depends on the intensity of pathological process. The half-life is ~19 h and the majority is eliminated through liver. CRP concentration in blood serum in healthy individuals usually does not exceed 10 mg/L (mean 0.8 mg/L) [1,3,12]. If stimulated, synthesis can increase over 1000 times. The concentration doubles every 8 h and reaches its maximum in 36–50 h [1,2,4]. The basal CRP concentration depends on the following factors: patient's age, sex, ethnicity, race, hormonal condition, smoking status, obesity, alcohol consumption, eating habits, infectious agent, duration of the disease, co morbidities, drugs, genetic polymorphism; therefore, the average of two measurements should be used [1,2,12]. Blood plasma concentration is estimated using qualitative, semi-qualitative latex agglutination and quantitative methods (immunoenzyme, immunoluminometric, immunoturbidimetric, nephelometric), the latest being the most popular [1]. CRP values lesser than 0.8 mg/L are hard to accurately access using regular methods that is why a more accurate (less than 0.3 mg/L), cheaper and faster

(15–30 min) method has evolved, i.e., high sensitivity CRP, which is used in experimental cardiology [1–3].

1.2. CRP in CVD pathogenesis

Inflammation is considered to be an essential factor in atherosclerosis and acute coronary syndromes (ACS) development by stimulating atheroma formation, destabilization of damaged atherosclerotic plaques and formation of occlusive thrombi [3,4].

In case of chronic low-intensity inflammation CRP damages the glycocalyx of vascular endothelium, causing its dysfunction and making it more susceptible to proatherogenic factors [4]. Moreover, the processes of endothelium-dependent vasodilatation, endothelial stem cell migration and adhesion are disturbed and apoptosis is induced [4]. Infiltration of vascular wall with inflammatory cells, neutral lipid deposition in arterial intima is stimulated and macrophages use up plasma low-density lipoproteins (LDL) easier, forming foam cells [1,4,6]. Vascular smooth muscle cells proliferate faster, migrate to the intima and synthesize more extracellular matrix. Inflammatory cells boost up metabolic activity in vascular walls making the medium more acidic, which in turn promotes faster smooth muscle cell apoptosis [1,4,6,15]. By activating the angiotensin-aldosterone system, angiotensin-1 and angiotensin-2 receptors, CRP promotes proatherogenic activity of angiotensin, directly and indirectly stimulates structural and functional modification of arterial walls, heart and vascular remodeling, vascular stiffening, increment of peripheral vascular resistance, interferes with arterial blood pressure (ABP) regulation mechanisms [4]. CRP induces activation of metalloproteinases (MMP) (which cause collagen destruction) in endothelial cells and macrophages and suppresses tissue MMP inhibitors. All of it increases the probability of atherosclerotic plaque remodeling, destabilization and rupture [15]. Prothrombotic status can be described as activation of the complement system, formation of thrombin, release of tissue factor from the endothelium, mononuclear cells and smooth muscle cells; endothelium is covered with more adhesion molecules which then prompt thrombocyte adhesion. Fibrinolysis is diminished, because CRP stimulates plasminogen activator inhibitor-1, which in turn decreases the fibrinolytic abilities of plasminogen activator [1,4,6]. Oxidative stress takes place since CRP stimulates certain vascular cells to synthesize reactive oxygen radicals more rapidly [15]. Vicious circle develops: foam cells create and maintain proinflammatory medium in the subintima layer of atherosclerotic vessels, therefore stimulating cytokine and CRP synthesis and production, whereas CRP itself maintains inflammation by stimulating the release of various cytokines (IL-1, IL-2, TNF α) from macrophages and foam cells and promoting self-production [6]. CRP pathogenesis is depicted in Figure.

However it remains unclear, whether CRP is truly related to vascular damage, since the majority of proof comes from research done in vitro and with animals, where CRP is obtained from *Escherichia coli* and can possibly be polluted with bacterial lipopolysaccharide remains and sodium azide (which is used as a preservative). What is more, the pathogenetic relation between proatherogenic, proinflammatory and prothrombotic effects of CRP and CVD development was not confirmed by

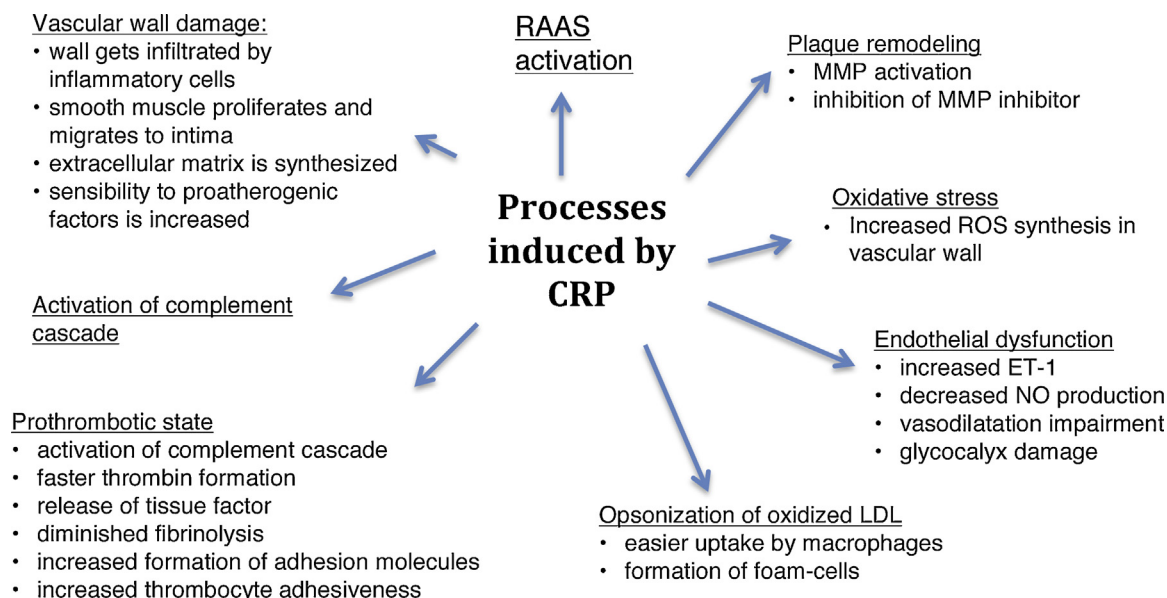


Figure – C-reactive protein pathogenesis. CRP, C-reactive protein; ET-1, endothelin-1; NO, nitric oxide; MMP, matrix metalloproteinase, ROS, reactive oxygen species; RAAS, renin-angiotensin-aldosterone system.

research with transgenic (human CRP gene hyperexpression) rabbits and mice or research of CRP gene polymorphism [1,4,12,16]. So it is unknown if higher CRP concentration is simply an epiphenomenon or one of the causes of atherosclerosis, or perhaps – both?

1.3. CRP and primary CVD prevention

In order to decrease CVD caused morbidity and mortality and its economic burden for the community, it is relevant to develop primary and secondary prevention programs. This is why individualized CVD risk prognostication becomes important.

There is a bunch of CVD risk calculation tools: Framingham, PROCAM, SCORE, Reynolds, VILCAD, QRISK [4]. Though the Framingham Heart Study (FHS)-based prognostic algorithms significantly improved CVD risk evaluation, one third of patients with coronary events have none or one CVD risk factor, moreover, 40% of patients who died due to CVD had blood cholesterol concentration lower than average [12]. So it becomes relevant to search for new and more accurate risk factors helping classify the patients. Though more and more evidence-based guidelines recommend measuring CRP concentration to assess CVD risk, the data about its benefit remain controversial.

In absence of synthesis stimuli, the individual CRP concentration (the same as with cholesterol concentration or ABP) remains constant and correlates with the 10 year CVD risk (using FRS calculation) [17]. A strong relation between individual (with no CVD) basal CRP concentration and cardiovascular events (myocardial infarction (MI), ischemic stroke, peripheral artery disease, sudden cardiac death) risk in the future is based on the data of abundant prospective studies [3]. According to the Physician's Health Study, patients with higher basal hsCRP concentration have twice higher stroke

risk, three times higher MI risk and four times higher risk to suffer from severe peripheral artery disease [18]. The Women's Health Study claim hsCRP to be a better prognostic factor for cardiovascular events compared to lipids or homocysteine. This data prove that with every increased quartile of hsCRP concentration adjusted relative risk of cardiovascular events increases by 26% in men and 33% in women [19]. Salazar et al. in their review have reported that after adjustment for other risk factors, patients with hsCRP 1–3 mg/L have 50% higher risk of CVD, compared to those with hsCRP < 1 mg/L, while hsCRP > 3 mg/L is associated with a double CVD risk [1]. According to the meta-analysis by Kaptoge et al. (2010; 54 prospective studies, 160,309 patients), hsCRP is a more accurate CVD prognostic factor (RR 1.37) than increased ABP (RR 1.35) or cholesterol concentration (RR 1.28) [20]. HsCRP, when combined with lipid concentration, metabolic syndrome and FRS, provides additional prognostic information, and newer CVD calculation algorithms that use hsCRP and family history (Reynolds scale) can classify patients to higher and lower risk groups more accurately. This way over 40%–50% of women and 15%–20% of men who belong to the heterogeneous intermediate CVD risk group, can be reclassified [3,17].

However, a great share of scientists doubts the benefit of hsCRP on making CVD risk prognosis more accurate [3,12,16,17,21,22]. According to the Heart Protection Study (2011), the relation of hsCRP concentration and CVD risk can be explained by the influence of other risk factors (age, smoking, obesity, body mass index [BMI], physical activity, ABP, diabetes, alcohol consumption, hormone replacement therapy, fibrinogen and lipid concentrations, other markers of thrombosis and inflammation) [20]. Silva et al. have reported that hsCRP directly correlates with BMI, smoking, systolic ABP, total cholesterol and triglyceride concentration, heart rate, fasting glycaemia, prior CVD and stroke and indirectly correlates with diastolic ABP and high density lipoprotein

cholesterol concentration [3]. Hingorani et al. showed that average hsCRP concentration differed among various patients' ethnicities and these differences could not be explained by the influence of other CVD risk factors [16]. According to Calabro et al., hsCRP compared to traditional risk factors has little or no input evaluating CVD risk [12], while Corrado et al. proposed that hsCRP only slightly specified the risk, already calculated using FRS. In the highest and lowest FRS risk groups the accuracy of risk evaluation does not differ, while in the group of average risk, hsCRP concentration higher than 3 mg/L is related to higher CVD risk and the need for more intense preventive therapy [17].

Shah et al. investigated the prognostic value (discrimination expressed by sensitivity, specificity, AUC, calibration, calibration, reclassification) of hsCRP as the CVD risk factor in these prospective studies: NPHS-II and EAS. Later the systematic review of prospective studies (31 studies, population of 84,063, 11,252 coronary events), investigating hsCRP and CVD relations, has been done. Multifactorial analysis models prove additional clinical benefit of hsCRP to be minimal [22]. A systematic review by Schnell-Inderst et al. has analyzed the prognostic value, effectiveness and costs-benefit ratio of hsCRP together with traditional CVD risk factors and shown that there were not enough data that

additional hsCRP testing would improve assessment of CVD risk and patient outcomes. Though a prognostic value of such combined models increases, it remains unclear, whether the increment is clinically relevant. Concerning the costs-benefit ratio, hsCRP evaluation becomes significant when selecting asymptomatic patients with increased hsCRP and normal LDL cholesterol for treatment with statins [23]. HsCRP cannot be used to rule out the disease due to low sensitivity, low negative prognostic value [12] and individual variability [3]. The studies on primary CVD prevention are summarized in Table 1.

1.4. CRP and secondary CVD prevention

For those with CVD, hsCRP is used to assess the severity of disease, treatment effectiveness and to forecast the outcomes (recurrence of CV events, death).

In case of stable coronary artery disease (SCAD), hsCRP is useful for prognosticating the velocity of disease progression and outcomes. According to Silva and Pais de Lacerda, hsCRP concentration has a direct correlation with coronary artery remodeling grade, atherosclerotic plaque content (assessed using intravascular ultrasound) and an indirect correlation with collateral coronary circulation, left ventricle ejection fraction [3]. It is also related to progression of coronary artery

Table 1 – HsCRP in primary CVD prevention.

Authors	Sample	Point of interest	Results
Ridker et al., 1998 [18]	PHS 14,916 healthy men	Does hsCRP measurement increase the predictive value of cholesterol when estimating future risk of MI?	Baseline hsCRP level evaluation adds to the predictive value of lipid parameters in determining risk of first MI
Ridker et al., 2000 [19]	WHS 28,263 healthy postmenopausal women	Measurement of inflammation markers and improvement of cardiovascular events risk prediction	The additional hsCRP measurement together with lipid screening may improve identification of those at risk for cardiovascular events
Kaptoge et al., 2010 [20]	Meta-analysis, 54 studies, 160,309 patients without history of CVD	Evaluation of predictive value, clinical effectiveness and cost-effectiveness when hsCRP screening is added to traditional CAD risk factor screening in healthy persons	Addition of hsCRP to traditional risk factor screening improves risk prediction but the clinical relevance and cost-effectiveness of such improvement remain unclear
Heart protection study collaborative group, 2011 [21]	Heart protection study, 20,536 patients of high vascular events risk	Hypothesis, that statins might be more beneficial in those with increased hsCRP concentrations, and might even be ineffective in those with low concentrations of both hsCRP and LDL-C	Baseline hsCRP concentration does not modify the vascular benefits of statin therapy economically
Shah et al., 2009 [22]	NPHS-II and the EAS, 3441 people Systematic review, 31 study, 84,063 individuals	Evaluation of hsCRP predictive performance in the NPHS-II and the EAS comparing discrimination by AUC, calibration and reclassification	HsCRP does not perform better than the Framingham risk equation for discrimination. The improvement in risk stratification or reclassification when hsCRP is added to models based on established risk factors is small and inconsistent
Schnell-Inderst et al., 2010 [23]	Systematic review, 11 studies	Evaluation of predictive value, clinical effectiveness and cost-effectiveness when hsCRP screening is added to traditional CAD risk factor screening in healthy persons	Addition of hsCRP to traditional risk factor screening improves risk prediction but the clinical relevance and cost-effectiveness of such improvement remain unclear

PHS, Physicians Health Study; CRP, C-reactive protein; MI, myocardial infarction; WHS, Women Health Study; CVD, cardiovascular diseases; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; NPHS-II, Northwick Park Heart Study; EAS, Edinburgh Artery Study; AUC, area under the ROC curve.

disease (CAD) [24] and heart failure (HF) [3]. According to substudy PEACE, higher than 1 mg/L hsCRP concentration, independently of primary patient characteristics and treatment, is significantly related to higher risk of cardiovascular death, MI and stroke [3,25]. However, the relation of hsCRP concentration and coronary artery stenosis grade is controversial. Kojuri et al. reported that it did not correlate with angiographically defined stenosis grade [26]. On the other hand, a subsequent study by Choi et al. showed that in cases of coronary artery stenosis greater than 50%, hsCRP concentration was found to be higher [27]. Overall, 2013 ESC guidelines on SCAD do not recommend a routine assessment of hsCRP concentration on the basis of systematic review and meta-analysis of 83 studies by Hingorani et al., since the publication bias makes it uncertain, whether there is a reliable independent relation between hsCRP and prognosis in SCAD patients [9].

The method, duration and intensity of treatment of patients with acute coronary syndromes (ACS) depend on the risk of death or recurrence of cardiovascular event. Instability of atherosclerotic plaque in the setting of ACS is related to exacerbated inflammation [28]. It was thought that hsCRP concentration might be used as a prognostic marker of cardiovascular events (MI, need for urgent revascularization, restenosis following percutaneous coronary intervention [PCI], cardiac death) [3].

Troponin concentration (used in short term risk assessment scales, such as PURSUIT, TIMI, GRACE, in patients with MI) does not always allow classifying patients with ACS, since increasing troponin concentration does not necessarily reflect bad outcomes [29].

In 2003 American Centers of Disease Control and Prevention (CDC) as well as American Heart Association (AHA) have recommended implementing hsCRP as an independent prognostic factor in patients with ACS. It is estimated that a CRP value of greater than 10 mg/L prognosticates the risk of ACS recurrence [30]. The prognostic value of hsCRP does not depend on troponin concentration, hence can be a useful risk evaluation tool for those without signs of myocardial necrosis. Moreover, when used together, these markers can help prognosticate more accurately: when the concentration of only one marker rises, the risk is moderate, whereas the rise of both, hsCRP and troponin, indicates a very high risk of adverse events [29]. Though studies show hsCRP concentration to be related to early and late adverse CV events recurrence following ACS, hsCRP has different prognostic value for short, moderate and long term outcomes for patients with non-ST-elevation ACS. The data regarding short-term prognosis are controversial. According to Schiele et al., patients who belong to the highest hsCRP tertile group have higher 30-day mortality risk. Moreover, when hsCRP is being evaluated together with GRACE scale components, the applicability, discrimination and calibration of GRACE scale increase. However, patients with inflammatory diseases were not excluded and ethnic subgroups were left unanalyzed [31]. According to a systemic review by Correia and Esteves (2011), which included 15 studies on an hsCRP prognostic value in patients hospitalized with non-ST-elevation ACS, data on hsCRP relation to short-term 30-day mortality are controversial: 9 studies support this relation, 6 denies it. The latter studies had much lesser sample,

which could have influenced the results. Regarding study data controversies, authors do not recommend routine hsCRP evaluation in patients hospitalized with ACS [28]. According to the meta-analysis by He et al. (20 studies, 17,442 patients), early rise of hsCRP (within 72 h from the start of ACS) is moderately associated with long term cardiovascular event recurrence or death risk. In ACS sufferers, hsCRP concentration of 3.1–10.0 mg/L is related to 1.4, and >10 mg/L is related to 2.18 times higher adverse event risk. Moreover, higher hsCRP concentration is related to greater myocardial damage, and the intensity of early inflammatory response is related to ventricular function and remodeling, ischemic and reperfusion damage, all of which can be significant for long-term outcomes [32]. The drawbacks of meta-analysis are as follows: insufficient number of proper studies, different values of hsCRP (expressed by logarithmic or categorical values), not all the studies evaluated the influence of significant risk factors (drugs, damage extent), articles analyzed were only in English. The 2011 ESC guidelines on non-ST-elevation ACS draw attention that the hsCRP concentration of >0.1 mg/L in patients with normal troponin concentration is related to long-term (from 6 months to 4 years) mortality [33]. In order to estimate moderate and long term risk, hsCRP estimation can be done after the episode of ACS [1].

In patients with ST-elevation MI, rise in hsCRP concentration is related to myocardial damage extent, outcomes and complication risk. According to Chan and Ng, early postinfarction-related rise in hsCRP is significantly and independently from other prognostic markers related to higher risk of cardiac (heart rupture, ventricular aneurysm, thrombus formation) and early mechanical complications, but does not prognosticate reinfarction [15]. However, new coronary events after MI should be prognosticated only after hsCRP concentration returns to basal level (in 12 weeks), since primary rise in hsCRP concentration reflects acute inflammatory reaction to myocardial damage [3,15].

If percutaneous coronary intervention (PCI) is performed, hsCRP can be useful to evaluate the risk of postprocedural complications (stent restenosis, thrombosis). It is relevant to select patients with lesser complication risk, because up to 30% of cases when metal stents are implanted and 7%–13% of cases with drug eluting stents end in restenosis. For those with higher risk, drug eluting stents or anti-inflammatory drugs are recommended to deal with inflammation – the main pathogenetic mechanism of restenosis [5]. hsCRP is thought to prognosticate the risk of restenosis more accurately if a metal stent was implanted versus a drug eluting one. In the latter case, thrombosis is prognosticated better [34]. However, it remains unclear whether preprocedural or postprocedural hsCRP concentration should be tested to prognosticate outcomes.

Ndrepepa et al. in 2014 analyzed the prognostic value of preprocedural hsCRP and LDL cholesterol concentration for those with SCAD, who were treated with statins and PCI, and proved that mortality higher than 1 year is associated to >3 mg/L hsCRP concentration, but not with LDL cholesterol concentration. When additionally hsCRP is being evaluated, discriminating capacity of multifactorial mortality prognostic models increases [35]. In 2011, Schoos et al. have analyzed the relations among preprocedural hsCRP concentration, stent

type and outcomes of patients who had PCI performed for ST-elevation MI, and found that hsCRP concentration is independently related to death, MI, revascularization of culprit vessel. In patients, who had drug eluting stents implanted not in the case of ACS, hsCRP concentration is related to death, MI and stent thrombosis. The authors recommend to choose metal stent if hsCRP is <2 mg/L and drug eluting stent if hsCRP is higher in order to reduce the number of long term adverse events [36]. However, since this study had a small sample, data from larger clinical studies are needed to support the present evidence. According to a review by Nicoli et al., both preprocedural and postprocedural hsCRP concentrations are related to metal stent thrombosis, whereas preprocedural hsCRP concentration is not relevant in prognosis when drug eluting stent is implanted [34]. A meta-analysis by Li et al. found that higher cardiovascular event risk was related to an increased hsCRP concentration only if this increment persisted longer than 48 h after a successful stent implantation, and higher preprocedural concentration was related to restenosis risk only in statin-naïve patients [37]. The studies are summarized in Table 2.

1.5. Heart failure

CRP has been correlated with the severity and prognosis of HF, as well as with response of HF patients to treatment.

Independently of HF etiology (ischemic heart disease, idiopathic dilated cardiomyopathy, valvular heart disease), a higher hsCRP concentration is related to a more severe disease course, decreased left ventricle ejection fraction, worse quality of life and treatment effect, higher New York Heart Association HF class, more activated neurohormones (brain natriuretic peptides, noradrenaline, aldosterone), higher rate of rehospitalization, in case of acute HF – hospitalization to intensive care units, higher mortality in hospital and long term mortality [10,38].

According to a systemic review by Araujo (2009), hsCRP concentration is a strong and independent prognostic factor for heart failure (short and long term) development in both general and high risk (SCD, ACS) populations; and for those, who already have acute or chronic HF – hsCRP can help predict outcomes [6,10]. Majority of studies, analyzed by Araujo et al., have used higher cut-off hsCRP concentrations (5–10 mg/L) to predict adverse outcomes in chronic HF, and this could have had a significant influence on the results [10].

The Val-HeFT study investigated the significance of hsCRP in HF morbidity and mortality in a vast population of over 4000 HF patients with a median hsCRP of 3.23 mg/L. Patients with higher hsCRP values were more likely to have HF with low left ventricular ejection fraction and III or IV class of New York Heart Association, worse quality of life and higher BNP, norepinephrine and aldosterone levels. HsCRP could prognosticate independently of BNP and HF cause [39].

To stratify patients with acute HF it is recommended to simultaneously evaluate concentrations of troponin (myocyte damage), hsCRP (inflammation), brain natriuretic peptide (volume overload): troponin and hsCRP are significant for hospitalization, while brain natriuretic peptide is also important during discharge, because it reflects treatment efficacy better and helps to plan intensity of outpatient observation

[38]. A study by Sabatine et al. proved that hsCRP, brain natriuretic peptide (BNP) and troponin I, when measured simultaneously in patients presenting with non-ST-elevation ACS, were a good tool helping stratify the HF risk. The cutoff hsCRP value was 15 mg/L. Having all three blood markers elevated pointed out an 8-fold increase in the risk of HF development by 6 months [25]. To predict heart failure in patients with acute MI, a cut-off CRP concentration during first 48 h within the onset of symptoms is proposed to be higher than in the general population – up to 10–15, or even 20 mg/L. In case of SCAD or following the acute MI period (1 month), it remains 3 mg/L [10].

Inflammation mediates myocardial fibrosis and predisposes the development of diastolic dysfunction, which in turn causes HF. Such a hypothesis was supported by a study involving young Afro-Americans (107 patients; mean age, 48 ± 10 years), having no heart or kidney diseases and consuming no alcohol. More than half (52%) of the patients had diastolic dysfunction, which was independently associated with hsCRP [40].

HsCRP assessment prior to cardiac resynchronization therapy helps prognosticate treatment response and cardiac mortality for those with severe HF (NYHA class III–IV). Patients with higher initial hsCRP values had no positive treatment effect (left ventricle end systolic volume was not reduced by 15%). What is more, hsCRP level of 3 mg/L was identified as a cut-off value for cardiac mortality [41]. The studies are summarized in Table 2.

1.6. Atrial fibrillation (AF)

Independently of ischemic heart disease morbidity, rise in hsCRP concentration is related to AF development risk and its type (permanent/paroxysmal) [8]. When AF is already present, hsCRP is associated to success rate of nonpharmacological treatment (cardioversion, catheter ablation). Prior to cardioversion, this test can be useful predicting relapse rate, since higher basal hsCRP concentration is related to short, moderate and long term relapse risk in those with either paroxysmal, or permanent AF [8,42]. The studies are summarized in Table 2.

1.7. Arterial hypertension (AH)

HsCRP concentration in healthy adults correlates with arterial blood pressure and independently of gender predicts the risk of AH development in men and women: hsCRP > 3.0 mg/L is related to 3 times higher risk of AH development, compared to those with hsCRP < 1.0 mg/L [6]. In case when AH is already present, hsCRP is associated to vascular stiffness, development of atherosclerosis, target organ damage, cardiovascular event risk [43] and correlates with systolic, diastolic and mean blood pressure [6]. Moreover, hsCRP concentration together with echocardiographically evaluated epicardial fat thickness in patients with known untreated AH, was found to independently prognosticate development of diastolic dysfunction [44]. The studies are summarized in Table 2.

1.8. Valve pathology

In case of valvular heart disease, basal hsCRP concentration is related to disease severity, progression rate, complications,

Table 2 – CRP and various pathologies.

Author	Study, subjects	Point of interest	Results
SCAD			
Sabatine et al., 2007 [25]	PEACE substudy, 3771 patients with SCAD	The ability of hsCRP to predict outcomes in patients with SCAD and the prognostic significance of the CDC/AHA hsCRP cut points	HsCRP values > 1 mg/L were associated with significantly higher risk of cardiovascular death, MI and stroke and were independent predictor of new HF and new diabetes
Kojuri et al., 2010 [26]	105 patients with chronic SA undergoing angiography	Comparison of hsCRP and LDL-C in predicting degree of coronary stenosis in patients with chronic SA	HsCRP was not correlated with degree of coronary involvement evaluated by angiographic score
Choi et al., 2012 [27]	377 SA patients undergoing coronary angiography	The relationship between serum hsCRP level and severity of coronary atherosclerosis in patients with SA	HsCRP level ≥ 3.0 mg/L was significantly related to the severity of coronary atherosclerosis (OR 1.95)
ACS			
Schiele et al., 2009 [31]	1501 patients with ACS	The incremental predictive value of adding hsCRP to the GRACE risk score	Combined with GRACE risk score, hsCRP evaluation improves risk stratification
Correia and Esteves, 2011 [28]	Systematic review and meta-analysis, 19 studies	Verification whether the current scientific evidence justifies the inclusion of hsCRP for risk stratification of ACS patients at hospital admission	In relation to the long-term follow-up, there was a consistent association between hsCRP and cardiovascular events. Controversial results regarding the independent predictive value of hsCRP for short-term events. Routine use of hsCRP for risk stratification at admission of patients with ACS is not recommended
He et al., 2010 [32]	Meta-analysis, 20 studies, 17,442 patients with ACS	Associations of hsCRP obtained within 72 h from ACS onset with the RR of recurrent cardiovascular events or death	Greater early blood hsCRP moderately increases long-term risk of recurrent cardiovascular events or death
PCI			
Ndrepepa et al., 2014 [35]	7959 patients with SCAD treated with PCI	Prognostic value of preprocedural hsCRP and LDL-C for patients with SCAD, who were treated with statins and PCI	HsCRP but not LDL-C was independently associated with increased risk of 1-year mortality
Schoos et al., 2011 [36]	301 PCI patients	Ability of hsCRP to predict outcomes depending on implanted stent type in STEMI patients	Preprocedural hsCRP predicts outcomes after PCI in STEMI patients
Li et al., 2010 [37]	Meta-analysis, 9 studies, 1062 patients	Impact of hsCRP level on in-stent restenosis following PCI	Preprocedurally increased hsCRP level is associated with greater in-stent restenosis after stenting. This impact appears more prominent in UA patients
HF			
Araujo et al., 2009 [10]	Systematic review, 34 articles	HsCRP in the prediction of HF in general and in high-risk populations, its prognostic value in established HF	HsCRP is associated with incident HF in general and high-risk populations and provides prognostic information in HF patients
Rajaram et al., 2011 [40]	107 young African Americans without history of heart or kidney disease, or alcohol consumption	Associations of hsCRP level and DD	DD is independently associated with elevated hsCRP level
Kamioka et al., 2012 [41]	46 HF patients and CRT implantation	HsCRP ability to predict cardiac death and response to CRT in severe HF patients	HsCRP level is independently associated to the absence of response to treatment. Level of 3.0 mg/L was shown as the cut-off value for cardiac mortality
AF			
Liu et al., 2008 [42]	Meta-analysis, 6 studies, 366 AF patients after EC	Association between CRP levels and risk of recurrence of AF after successful EC	Increased CRP levels are associated with greater risk of EC failure

Table 2 (Continued)

Author	Study, subjects	Point of interest	Results
AH			
Turak et al., 2013 [44]	135 newly diagnosed and untreated hypertensive outpatients	Relation among echocardiographically measured EFT thickness, systemic inflammation, and LV diastolic dysfunction	Increased EFT thickness and hsCRP level are significantly related to impaired LV diastolic function independently from other factors
Valve pathology			
Alyan et al., 2009 [11]	132 patients with chronic rheumatic mitral stenosis and 145 controls	HsCRP and progression of chronic rheumatic mitral stenosis	Increased hsCRP levels are associated with chronic rheumatic mitral stenosis severity
HsCRP, high-sensitivity C-reactive protein; SCAD, stable coronary artery disease; CDC/AHA, American Centers of Disease Control and Prevention/American Heart Association; SA, stable angina pectoris; HF, heart failure; UA, unstable angina pectoris; LDL-C, low-density lipoprotein-cholesterol; ACS, acute coronary syndrome; GRACE, Global Registry of Acute Coronary Events; RR, relative risk; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; NYHA, New York Heart Association; DD, diastolic dysfunction; CRT, cardiac resynchronization therapy; AF, atrial fibrillation; EC, electrical cardioversion; EFT, epicardial fat tissue; LV, left ventricle.			

success in treatment, long term survival [7]. In patients with rheumatic mitral stenosis, hsCRP concentration is associated with disease severity [11] and risk of tachyarrhythmia development [45]. In those with rapidly progressing aortic stenosis, hsCRP is higher than in patients with moderate/severe stenosis, which progresses slower, and is an independent prognostic factor of severe aortic stenosis (OR 3.51) [7]. Evaluation of serial hsCRP tests could be used to monitor treatment efficacy [11]. The studies are summarized in Table 2.

1.9. Therapeutic possibilities

While developing theory of inflammatory cardiovascular disease, nonpharmacological and pharmacological methods to reduce CRP are being investigated and possibilities to correct modifiable CVD risk factors are being analyzed. It is thought, that regular physical activity, improved eating habits, weight and long term (>5 years) smoking cessation might decrease CRP concentration and endothelial dysfunction [13,46]. Foods rich in omega-3 polyunsaturated fatty acids, fiber, vitamins, microelements (especially magnesium) [47] and low in cholesterol and fat are recommended, as well as having low glycemic index [2]. What is more, alcohol consumption should be moderate [46]. It has been estimated, that in ones who manage to reduce weight by 1 kg due to physical activities and nutrition, CRP decreases by 0.13 mg/L compared to 0.16 mg/L in bariatric surgery group [12].

CRP concentration can be changed by medications. Ones of the mostly investigated are statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), well known for their lipid reduction, anti-inflammatory, antihypertrophic, antifibrotic and anti-oxidative properties [12,21]. It is thought that statins reduce CRP concentration independently of the effect to lipids, that is, directly affecting hepatic mechanisms, inhibiting CRP mediated proinflammatory leukocyte activity, expression of IL-6 and TNF- α in monocytes, CRP gene transcription [13]. The JUPITER trial compared rosuvastatin to placebo and found that statin reduced LDL cholesterol concentration by 50%, CRP concentration by 37% and cardiovascular event rate by 44%. However, patients with CRP < 2 mg/L were excluded. It was thought, that statins are

useful in patients, only if they have increased cholesterol or CRP concentrations, and the higher the increase of concentrations, the higher the CVD risk. On the contrary, the Heart Protection Study proved that the risk of the first CVD event decreases independently of the initial CRP or LDL cholesterol concentration [21]. Currently, anti-inflammatory drugs (methotrexate and IL-1 β inhibitor – canakinumab), which do not affect CRP or LDL cholesterol concentration, are being investigated. And if they proved to be effective, it would support the theory that atherosclerosis has an inflammatory origin [12].

Fibrates decrease CRP concentration when hypertriglyceridemia or mixed hyperlipidemia is present, while ezetimibe is effective only when combined with statins [48]. Thiazolidinediones decrease CRP concentration as well; on the other hand, some of them increase ACS risk [13]. Non-steroidal anti-inflammatory drugs (NSAID), glucocorticoids suppress inflammation; however, they are not recommended to be used for CRP reduction, regarding adverse reactions: in case of NSAID, slight increment of ABP; in case of glucocorticoids, metabolic disturbances, progression of atherosclerosis, dyslipidemia, arterial hypertension, and insulin resistance. The effect of aspirin is dose-related and is influenced by combined drugs. CRP concentration is reduced if high doses of aspirin are given or if it is combined with clopidogrel, whereas low doses of aspirin (81–100 mg/day) do not have this effect [12,13]. CRP concentration is also reduced by anti-estrogens [13], antihypertensive drugs, some antidepressants [12,14]. A new CRP-binding medication – 1,6-bis(phosphocholine)-hexane – is currently being created. Laboratory rat studies have shown this medication to be effective in reducing infarction zone and heart dysfunction; however, its effect on humans is still unknown [49].

1.10. Guidelines

In 2002, the Adult Treatment Panel (ATP) III guidelines recommended to base on CRP concentration when choosing hyperlipidemia treatment between less and more aggressive and when evaluating treatment efficacy [15]. In 2003 AHA and CDC recommended to use hsCRP as an inflammatory marker

to evaluate the absolute risk and choose optimal treatment for those belonging to moderate CVD risk group. Risk groups are defined regarding hsCRP concentration: low risk, <1.0 mg/L; moderate risk, 0.1–0.3 mg/L; and high risk, >3 mg/L [30]. Canadian Cardiology Society guidelines of 2009, basing on JUPITER trial, recommended hsCRP assessment for moderate CVD risk patients as well [50]. 2010 AHA and CDC recommended (class IIa) hsCRP to be tested in patients without CVD symptoms in order to: (1) select patients who would benefit from statin treatment and are males older than 50 years, females older than 60 years, when LDL cholesterol concentration is <130 mg/dL, no hormonal replacement, no immunosuppressive or lipid-reductive therapy is given, no clinical signs of CVD, diabetes, severe inflammation and no contraindications for statins; (2) estimate CVD risk (higher or lower than moderate) in men older than 50 years and women older than 60 years, who belong to moderate risk group, according to FRS; (3) hsCRP is not recommended to be tested in high CVD risk patients [9].

The guidelines of ESC 2012 recommend that hsCRP may be tested in patients with moderate CVD risk (II B) and not recommended to be tested for low risk asymptomatic or high risk patients (III). Drawbacks of this test are also mentioned: (1) effects of confounding variables, (2) narrow diagnostic window regarding hsCRP concentration and CVD risk, (3) lack of causality relationship between hsCRP and CVD risk, (4) shortage of specific treatment that would decrease CVD incidence by decreasing hsCRP concentration [51].

2. Concluding remarks

Despite emerging variety of studies, the possible hsCRP role in pathogenesis of CVD remains controversial. However, recent guidelines recommend hsCRP testing for primary CVD prevention as a reliable, rapid and cheap method to stratify CVD risk groups and select patients for statin therapy. As far as secondary prevention is concerned, hsCRP can be used to prognosticate complications of CVD itself and ones caused by its treatment, to evaluate treatment efficacy; however, the test is not relevant in case of high CVD risk.

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