Chronic and long-lasting inflammation is the beginning of the endothelial dysfunction process and atherosclerosis. Thus, C-reactive protein (CRP) initially described as an acute phase protein is a marker of cardiovascular disease but not so early on and specific. The association between CRP and the development of hypertension and cardiovascular disease has been revealed, but not completely understood, since the cause-effect relationship and the reduction of them has not been consistently demonstrated.

Despite the established cut-off points in the healthy adult population, high sensitivity CRP (hsCRP) needs new thresholds due to the wide variability among individuals by genetic and behavioral factors. The CRP levels should be taken into account the accumulation of conditions such as obesity, diabetes mellitus, old age and hypertension. Nevertheless, clinical evidence supports a modest benefit in cardiovascular risk prediction in the intermediate risk group by the Framingham risk score.

This article approaches the applicability of hsCRP in clinical practice looking for the capacity to stratify and to refine cardiovascular risk assessment. We searched if there is any hsCRP utility on driving CV risk treatment. Some favorable evidence about the association between CRP and the development of hypertension were checked over. However, CRP could not be separate of dietary and metabolic factors, namely obesity. Finally, analysis of the prospective studies of CRP as a prognostic factor in hypertension were done including high-normal blood pressure person, hypertensive’s and resistant hypertensive’s.
>3.0 mg/l) correspond to approximate tertiles of hsCRP in the adult population. These thresholds are based on distributions of hsCRP samples in over 40 thousand persons gathered, however it is extremely unlikely that CRP modify the stratification such as low-risk people (<10% per 10 years) to have a high risk (>20% risk over 10 years).

Within reason, who are at high risk or with established atherosclerotic disease generally should be treated intensively regardless of their hsCRP levels [6]. To date, the hsCRP utility as a public health remains in doubt and guidelines recommends against screening of the entire adult population [7-9]. Some of the reasons for this issue are: 1- the main studies were carried out in European and American (Asians tend to have lower CRP values) [10]; 2- consistent differences between men and women favoring mostly evidences about higher values in men; 3-wide variability among individuals and in the same person [11]; 4- need for age stratification [11]; 5- influence of other factors such as aspirin and statin use, smoking, visceral obesity [12], diabetes and metabolic syndrome [13].

Thereafter, some researchers plead that association between hsCRP and CV diseases is due to a strong correlation with traditional risk factors. Thus, this biomarker did not allow us to discriminate CV events in all people independently of conventional risk assessment because of relative collinearity within Framingham risk score (FRS) variables. The Reynolds risk score (RRS) adds hsCRP level and CHD family history to conventional parameters considered in the FRS. Although both scores are predictive of CV risk, the RRS has been shown as additional predictive power in atherosclerosis progression. In spite of a small amount contribution of CHD family history and even less of hsCRP, the RRS seemed to be better and useful when discordance exists between the two scoring systems [14].

The CRP advantages are: firstly, the substance is easily dosed showing quantitative differences in patients with and without coronary artery disease; secondly, CRP levels behave to be stable over time in the same individual to the same extent as other biochemical and physical attributes [15]. Clinical evidence supports a modest benefit in cardiovascular risk prediction in a specific group (intermediate risk by the FRS). Notwithstanding the proven association between elevations of CRP levels and CV diseases, measurement of protein should not be used to exclude disease (low negative predictive value), either, for driving treatment [9].

Concerning the benefit effect on cardiovascular events and hsCRP under statin treatment, Server et al., researched baseline and on-treatment hsCRP levels with cardiovascular events among hypertensive patients in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm) [6]. Again, baseline hsCRP levels predicted incident CV diseases, even though no difference was detected in the relative effect of statin therapy on tertiles of CRP. Although achieving LDL-C levels below the median at 6 months was associated with lower CV diseases risk, a clear risk reduction was not seen for hsCRP levels below the median in fully adjusted models.

Previously, Bödder et al., suggested that baseline hsCRP levels distinguished which patients with relatively low LDL-C levels have benefited from statin therapy [16]. In the JUPITER study, post hoc analysis better powered for on-treatment analysis, proposed that lower hsCRP levels may indicate greater degrees of success with statin treatment [17]. Moreover, in the Heart Protection Study with over twenty thousand at-risk individuals bridging the primary and secondary prevention phases, statin therapy conferred a 29% relative risk reduction even if baseline hsCRP was <1.25 mg/l [18].

A previous meta-regression analysis found that the degree of risk reduction conferred by statins is completely compatible with the degree of LDL-C lowering rather than additional pleiotropic effects [19]. In brief, there is inconsistent evidence regarding the utility of hsCRP measurements for targeting statin therapy for primary prevention.

**Association between CRP and hypertension**

Despite the great number of factors and conditions associated with CV disease and elevated CRP levels, high blood pressure (BP) are well established as a cardiovascular risk factor. CRP could be not only a marker of atherothrombosis process, but also a mediator of this mechanism. Although CRP has emerged as a predictor of future cardiovascular events, the mechanism in which the protein and hypertension promotes atherogenesis remains obscure [20]. The question remains open: What is the role of hypertension in vascular inflammation?

In order to explain this mechanism, a large cohort study followed around 15,000 apparently healthy women for eight years [21]. In summary, after adjustment of known variables as risk factors (age, BMI, diabetes, smoking, LDL and HDL cholesterol), the authors showed that increased categories of BP levels was related to higher CRP values. In prospective analyses, both elevated CRP levels (≥3 mg/l) and increasing BP categories were independent determinants of future cardiovascular events, and CRP had incremental prognostic value at all BP levels. One possibility would be a direct effect of the pressure in the vessels through known routes of adhesion of inflammatory cells promoting vasoconstriction. Meanwhile, the reverse thinking can be postulated: the vascular inflammation and CRP could provide hypertension. It should to be noted that in the aforementioned study, CRP increased along with the BP levels hindering cause-effect relationship.

Sesso et al., followed more than 5,000 women who developed hypertension from more than 20,000 people enrolled for almost 8 years. Those in the highest CRP quartile had twofold risk of developing hypertension than women in the lowest quartile. The inclusion of CRP only marginally improved the prediction of incident hypertension [22]. Back then, two other studies found associations between CRP and the risk of hypertension development [23,24].

Recently, nested case-control studies showed association between baseline CRP levels [25] or increasing CRP levels [26] and risk of hypertension, losing significance after adjustment for body mass index (BMI). However, CRP has been associated with the risk of hypertension even after adjustment for abdominal obesity in two other cohorts of middle-aged men and women [27,28].
All these studies [21-28] that showed whether or not any risk prediction between CRP and hypertension have been concerned with traditional confounders. There is also a concern with serial measurements of inflammatory markers, and rightly to the type of population studied. It is impossible to assess and to compare so heterogeneous populations regarding the risk of developing hypertension, even if they have similar prevalence of risk factors.

Comprehensive adjustments for major risk factors for hypertension were done, while residual confounding by unavailable dietary and metabolic factors may persist. Additionally, it is important to discuss about changing lifestyle and routine use of medications, changing the CRP values but not necessarily reducing the inflammatory state. One of these questions is whether high fitness attenuates the likelihood of developing hypertension in subjects with elevated inflammatory markers [29]. Of 2,475 normotensive men, 266 (10.7%) developed hypertension during an average of 4 years’ follow-up. The association of CRP and incident hypertension was shown in those in the upper tertile versus lower tertile, losing significant after adjusting for BMI. Cardio respiratory fitness was analyzed for same multivariate adjustment decreasing 27% of the risk of incident hypertension compared fit to unfit participants. In the joint analysis, unfit men with upper CRP had 1.81 times greater risk of hypertension development compared to fit men with low CRP, even though this risk did not significantly increase in comparison fit men with upper CRP. It was argued that endothelial dysfunction, oxidative stress and arterial stiffness were previously mitigated with cardio respiratory fitness. Somehow, high-fitness subjects provide vascular protection by enhanced autonomic function and by reduced cardio metabolic risk factors, including body fat and insulin resistance, independently of elevated inflammatory markers [29].

Based on these latest articles [25,29] we can hypothesize that something happens in endothelial level by promoting inflammation, and hence, rising CRP in younger individuals until middle age. These people would be in jeopardy for developing hypertension if endothelial inflammation persists due to the emergence of a pro-atherogenic metabolic status, particularly obesity. We do not know which the triggers are and we did not clarify the obscure interrelationship among CRP, endothelial dysfunction and hypertension. Whether by genetic mechanisms, acquired conditions or both, some individuals are more susceptible to progression and complications of atherosclerosis, called higher CRP responders [30].

C-reactive protein as a prognostic factor in hypertension

On one hand, the risk analysis between CRP and hypertension is complex; on the other, the prediction of adverse outcomes arising from this association is necessary. However, few prospective studies concluded about the prognosis of patients with hypertension, considering the CRP as a marker of the fates. (Table 1) As described before, Blake et al. [21], evaluated 15,215 women followed prospectively for 8 years, divided in 4 categories based on CRP and BP levels. The risk factor-adjusted hazard ratios, using low CRP/low BP as reference, increased linearly as follows: high CRP/low BP, 1.86; low CRP/high BP, 2.46, and high CRP/high BP, 2.94.

Three other large studies were conducted in Asian countries evaluating CRP in hypertensive patients [31-33]. Firstly, in order to assess the risk of ischemic stroke, 2,589 individuals from rural villages in China were followed for 9.2 years on average (total follow-up of 15 years) [31]. The subjects were stratified into four groups, considering the presence or absence of hypertension and

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients enrolled (n)</th>
<th>Mean age (years)</th>
<th>Mean follow-up (months)</th>
<th>Number of events</th>
<th>Outcome</th>
<th>Parameter evaluated</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake 2003 [22]</td>
<td>15,215</td>
<td>54.28</td>
<td>97</td>
<td>321</td>
<td>Cardiac death, Nonfatal MI, nonischemic stroke, coronary revascularization</td>
<td>CRP ≥ 3 mg/L and BP 120-129/75-84</td>
<td>1.44 †</td>
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<td></td>
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<td></td>
<td></td>
<td>BP 130-139/85-89</td>
<td>1.38*</td>
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<td></td>
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<td></td>
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<td>BP 140-159/90-94</td>
<td>2.40*</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>BP 160/95</td>
<td>2.45*</td>
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<tr>
<td>Wang 2014 [32]</td>
<td>2,589</td>
<td>&gt; 20y</td>
<td>110</td>
<td>76</td>
<td>Ischemic stroke</td>
<td>NT/Low CRP</td>
<td>0.84 (0.28-2.52)</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td>HT/Low CRP</td>
<td>1.41 (0.74-2.68)</td>
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<td></td>
<td></td>
<td>HT/High CRP</td>
<td>2.66 (1.29-5.47) †</td>
</tr>
<tr>
<td>Tanaka 2010 [33]</td>
<td>22,676</td>
<td>40-80 yr</td>
<td>59 ± 10</td>
<td>62 ± 30</td>
<td>Ischemic stroke</td>
<td>LVH / CRP &lt; 1 mg/L</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>NT-7,625</td>
<td>62 ± 30</td>
<td>32</td>
<td>103</td>
<td></td>
<td>LVH / CRP ≥ 1 mg/L # 2</td>
<td>1.72 (0.93-3.18)</td>
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<td>PreH-T - 5,721</td>
<td></td>
<td></td>
<td>16</td>
<td>30</td>
<td></td>
<td>2.86 (1.65-4.95)*</td>
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<tr>
<td></td>
<td>HT-9,330</td>
<td></td>
<td></td>
<td>97</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Iwashima 2007 [34]</td>
<td>629</td>
<td>62 ± 6.0</td>
<td>32</td>
<td>52</td>
<td>MI, stroke, PAD, HF</td>
<td>LVH / CRP &lt; 1 mg/L</td>
<td>2.21 (1.29-4.57) †</td>
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<tr>
<td></td>
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<td></td>
<td>LVH / CRP ≥ 1 mg/L</td>
<td>2.65 (1.55-5.46)*</td>
</tr>
<tr>
<td>Cortez 2016 [36]</td>
<td>476 RH</td>
<td>70 ± 11</td>
<td>108</td>
<td>103</td>
<td>Fatal and nonfatal CV events: MI, stroke, HF, PAD</td>
<td>CRP &gt; 3.0 mg/L</td>
<td>1.49 (0.95-2.34)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>CRP &gt; 3.8 mg/L (median)</td>
<td>1.99 (1.29-3.06) †</td>
</tr>
</tbody>
</table>

**Abbreviations**: NT: Normotension; PreH: Pre Hypertension; HT: Hypertension; RH: Resistant Hypertension; MI: Myocardial Infarction; PAD: Peripheral Artery Diseases; HF: Heart Failure; LVH: Left Ventricular Hypertrophy
*ρ < 0.001, †ρ < 0.01, ‡ρ < 0.05

Multivariate Cox proportional hazard model was used to determine the hazard ratios (HRs) in all studies.
elevated CRP or not (>1.06 mg/l log CRP). The risk of ischemic stroke according to BP and CRP levels was 2.66 times higher for the group with both high conditions, compared to the group with low CRP levels and normal BP levels. In the multivariate Cox model, hypertensive patients with high CRP had the highest risk of incident ischemic stroke among the 4 subgroups. Nonetheless, normotensive with high CRP or hypertensive patients with low CRP levels were not associated with the risk of ischemic stroke, in comparison with normotensive and low CRP levels, suggesting that the unique combination of hypertension and elevated CRP levels would be an important prognostic marker of cerebrovascular event.

While the knowledge in people with high CRP has been structured on the risk of CV events, and possibly the risk of developing hypertension, comes the interest in patients classified as pre-hypertensive (PreHT) patients or high-normal BP (systolic BP between 120 to 139 mmHg and diastolic BP between 80 and 89 mmHg) in whom are indicated changes in lifestyle to prevent disease progression. Thus, the Iwate-Kenko Study Group prospectively followed individuals with high-normal BP, normotensive, and hypertensive, relating them to the CRP levels and the incidence of ischemic stroke [32]. Of the more than 22,000 subjects from 40 to 80 years with out previous CV diseases but with a great variety of risk factors, only 143 had stroke (mean follow-up 2.7 years). The bivariate analysis of the population showed a statistically significant difference between the groups, and the greater the number of known risk factors for CV diseases the higher the BP by separate groups. As expected, CRP was higher in the hypertensive group compared to normotensive, and also higher in the PreHT group compared to normotensive group. In the model with multivariate survival analysis considering the BP standard (high, pre-hypertensive and normal) and CRP levels dichotomized by the median were formed 6 subgroups. Pre-hypertensive individuals with elevated CRP levels presented greater risk of stroke than the entire normotensive group and similar risk to those with hypertension and low CRP (2.63 and 2.64, respectively; p < 0.03), while hypertensive patients with high CRP have had ischemic stroke risk increased by 3.5 times.

Two findings indicate that hsCRP is a relatively short-term marker for cerebrovascular risk in PreHT. The first point is the risk of ischemic stroke was not significantly increased in the total PreHT group, but was increased in the PreHT subgroup with elevated hsCRP levels. Secondly, the known relationship between pre-hypertensive patients and subclinical atherosclerosis, such as increased coronary atherosclerosis, carotid and brachial intima-media thickness and microalbuminuria increasing the risk for any cardiovascular event compared to individuals with normotension [32].

Iwashima et al., studied prospectively 629 asymptomatic hypertensive patients associating CRP levels and the presence or absence of LVH [33]. The concomitant presence of left ventricular hypertrophy (LVH) and CRP above 1 mg/l was an independent predictor of cardiovascular risk, being superior as a method of risk detection compared to measurement of either biologic marker alone. Despite the smaller number of subjects, they have used CRP levels near literature.

These associations among subclinical organ damage namely, left ventricular hypertrophy and albuminuria, were extensively described in resistant hypertension [34]. Patients with uncontrolled hypertension have higher incidence of target organ damage and poorer prognosis. Recently, it was published a Brazilian study that analyzed 476 individuals with resistant hypertension towards prognostic value of CRP [35]. The protein values were substantially higher, as expected by the concomitance of several risk factors and morbidities. After a follow up reached up 10 years, elevated CRP levels (>3.8 mg/l) predicted major fatal and nonfatal cardiovascular outcomes over and beyond traditional CV risk factors, including ambulatory BP monitoring parameters. Moreover, the usually recommended cutoff value for CRP (3.0 mg/l) had no prognostic value in this population. This is the first prospective study that evaluated the prognostic importance of CRP levels in resistant hypertension highlighting different CRP thresholds in the dependence of sex, age, ethnicity, socioeconomic status, lifestyle, metabolic profile, morbidities, others inflammatory biomarkers, and genetic predisposing.

CONCLUSION

In conclusion, currently, CRP levels should not be used to guide therapy in any cardiovascular disease, including hypertension, but it is useful to stratify and to refine subgroups of patients at CV risk. It is well known that high hsCRP levels may precede or rise together with BP levels. However, we are unable to clearly determine whether this biomarker is a guilty or just taking part of inflammatory processes involved in others associated cardiometabolic factors such as obesity.

There are strong evidence regarding prognostic value of hsCRP in patients with hypertension and also in pre-hypertensives, despite this last one presents CRP levels below than previously established (3 mg/dl). Moreover, higher blood pressures are related to higher CRP levels, and both are predictors of CV events in patients with resistant hypertension.

Despite all these evidences, it is necessary to validate this marker in other populations and conditions, allowing its use in clinical practice. Furthermore, new interventional studies could identify if the hsCRP reduction with use of statins or any other drug may reduce the cardiovascular risk, beyond the well-established BP and other CV risk factors control.

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