C-reactive protein in cardiovascular risk prediction. *Zooming in* and *zooming out*

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Over the last 5 years the number of reports on the relationship between blood levels of C-reactive protein (CRP) and cardiovascular risk found annually in Medline, is growing exponentially; it was only one until 1994 and gradually reached 58 during the year 2000 (Fig. 1). As the positive correlation between CRP blood levels and cardiovascular atherothrombotic events appears largely independent of traditional lipid and coagulation factors, this previously unsuspected relationship is opening intriguing avenues for research, screening and prevention, not even imaginable only few years ago[1].

In order to lay the basis for a rational and speedy introduction of the measurement of this novel cardiovascular risk indicator into routine clinical practice, it is useful to *zoom in* on the reported predictive role of CRP in primary and secondary prevention, on the assessment of its normal, "habitual" blood levels and of their determinants, on the cost-effectiveness of its measurement and, finally on its possible direct cardiovascular pathogenetic mechanisms and potential new pharmacological treatments. The articles presented in this minisymposium, of which Cornelis Kluft is the Guest Editor, go a good way in this direction.

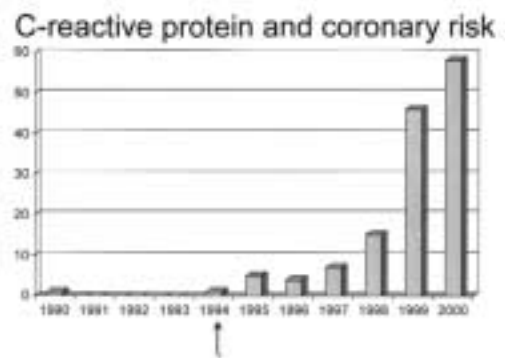

Figure 1. *The number of publications on the relationship between C-reactive protein blood levels and prognosis increased exponentially following the report by Liuzzo et al.[2] in 1994 that in patients with unstable angina C-reactive protein levels > 3 mg/l had an adverse prognostic value independently of signs of myocardial necrosis.*

In his review of the studies on risk stratification of individuals without known cardiovascular diseases, Wolfgang Koenig concludes that the evidence of an important predictive role of CRP for cardiovascular events is strong and convincing, a conclusion shared by Luigi Biasucci and co-workers in their review of the studies performed in patients with various ischemic syndromes. In general the discriminating cut-off CRP values which best separate low and high risk groups appear to be higher in patients (> 3 or < 10 mg/l) than in individuals without known cardiovascular diseases at least in the American health Physicians and Nurses studies (> 1 mg/l) and seem to vary in different syndromes as well as according to the endpoints (recurrent instability, myocardial infarction or death) considered.

Cornelis Kluft and Moniek de Maat report on the reproducibility of the measurements, the normal values of CRP and on their "habitual" variations with time, and they conclude that the accuracy of high sensitivity methods is quite satisfactory and, when low values are found, a single measurement is sufficient to classify patients in a low risk group. Conversely, when the value of the first test sample is elevated multiple blood samples should be taken over time, in order to obtain representative "habitual" blood levels that most correctly predict an increased cardiovascular risk.

Silvia Ess and Thomas Szucs provide evidence for a substantial potential cost-effectiveness of CRP measurements in a theoretical economic model in which long-term statin administration is limited to patients with elevated CRP values. As at present it

might be controversial to not treat all patients with high cholesterol levels, this intriguing hypothesis needs to be particularly validated.

Moniek de Maat and Cornelis Kluft indicate some chronic inflammatory diseases as well as other conditions apparently unrelated to inflammatory states such as sex, age, race, diet, physical training and some drugs which may affect CRP blood levels.

Finally Mark Pepys, a long established authority in the field of CRP, in his article with Gideon Hirschfield, does not find surprising "the recent torrent of reports demonstrating a powerful predictive relationship between CRP production and atherothrombotic events". The binding affinity of CRP for low density lipoproteins (LDL), modified LDL and for damaged or dead cells coupled with the capacity of bound CRP to activate complement represent potential pathogenetic mechanisms of cardiovascular damage and provide scope for developing drugs to block CRP binding.

Collectively, the information presented in this minisymposium does not stress enough the intriguing possibility that low CRP blood levels, possibly below 1 mg/l for primary prevention and, possibly, below 3 mg/l for secondary prevention, are predictive of a very low cardiovascular risk, possibly independent of elevated traditional risk factors. Thus at one end of the spectrum, a single high sensitivity measurement could be sufficient to reassure large number of worried persons and patients when they are found to have very low CRP levels. At the other end of the spectrum, patients with known cardiovascular diseases and persistently elevated CRP values are at high risk and should be carefully followed with appropriate risk reduction strategies. Above which cut-off value individuals without known disease should be considered at elevated risk and below which cut-off value patients with various atherothrombotic syndromes should be considered at low risk, requires further evaluation and a consensus, since the available evidence suggests that, both in normals and in patients, the gradient of risk is continuous.

To put this novel cardiovascular risk factor into clinical and research perspectives it is useful to *zoom out* on a broader scenario. CRP values > 3 mg/l are found in only about 65% of patients with unstable angina, Braunwald class IIIB and in nearly 100% of patients with myocardial infarction preceded by unstable angina, but in only 45% of patients with myocardial infarction not preceded by unstable angina[2,3], and only in a tiny minority of patients with chronic stable angina and severe coronary atherosclerosis[2] and of those with variant angina and severe ischemia[4]. Conversely, in other vascular disorders CRP levels may remain elevated for years without ever leading to unstable angina, myocardial infarction or stroke[5].

It also remains to be investigated: 1) the multiple possible triggers of inflammation and whether or not they all contribute to risk, 2) the enhanced responsiveness to inflammatory stimuli found in nearly all patients with CRP levels persistently above 3 mg/l[3,6,7] suggesting that mildly elevated habitual levels are a marker of responsiveness[1], and 3) the mechanisms responsible for the acute, occasional, transient or prolonged coronary localization of inflammation in the presence of a very variable severity of atherosclerosis[3].

Therefore, inflammation appears an important, common but not a necessary or a sufficient component of acute atherothrombosis and hence the predictive accuracy of CRP measurement can only be limited, just like it is the case for isolated traditional risk factors. Moreover, it is likely that, the prevalence of an inflammatory component in acute atherothrombotic syndromes as well as in normal individuals may vary according to age, sex and environmental condition, as well as in different ethnic groups[8].

Meanwhile, in my opinion, the standardization of the high sensitivity assays and the assessment of the "habitual" blood levels of CRP at present available do set the stage for the routine inclusion of CRP measurements among the other short- and long-term prognostic indicators of cardiovascular risk. However, CRP measurements should be included according to the standardized protocols and reported on appropriate registries together with patient outcome. These registries will provide the presently lacking information and will gradually improve the prognostic information obtainable from CRP measurements according to age, sex populations as well as according to clinical syndromes and to selected clinical endpoints.

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