There is a great deal of physiopathological and epidemiological data that have identified the beginning and the course of atherosclerotic disease as being related to a chronic inflammatory process. Thrombosis added to erosion, fissure, or rupture of the atherosclerotic plaque produces the acute coronary syndromes (ACS) that are the clinical manifestation of this disease.

At the present time, a significant percentage of investigation being done on atherothrombosis is focused on the identification of inflammatory cells, cytokines, and reactant and adhesion molecules in the acute phase of the disease, among other inflammatory markers, whether at the cellular level, in vascular tissue, or in the blood, both in the initial phase of the disease and in the more chronic stages.

While our knowledge of inflammation as the instigator of atherosclerosis continues to increase, C-reactive protein (CRP), which is produced by the liver in response to chronic inflammatory phenomena, has been described as having prognostic value in patients with ACS. The FRISC and TIMI 11A studies, among others, have provided data in this respect.\(^1\),\(^2\)

Similarly, in population studies it has been shown that elevated PCR values have prognostic value with regard to the development of future cardiovascular complications — like vascular mortality — and for this reason are even more powerful than other classic and universally recognized risk factors such as total or LDL cholesterol levels.\(^3\),\(^5\)

In the AFCAPS/TexCAPS study it was found that in healthy subjects with normal cholesterol but above average CRP levels treatment with lovastatin reduced the relative risk of vascular complications;\(^6\) in the same manner, the findings of the PRINCE study showed that it was possible to significantly reduce CRP levels via the administration of 40 mg of pravastatin in a group of subjects without a history of cardiovascular disease.\(^7\) The decrease of CRP concentrations has also been observed with the administration of simvastatin, atorvastatin, and cerivastatin.\(^8\),\(^9\) Thus, the benefit of the statins appears to go beyond the mere reduction of total and LDL cholesterol levels and the consequent stabilization of vulnerable plaques. One of the pleotropic effects attributed to these products is an anti-inflammatory effect, independent of the lipid changes.

Nevertheless, the routine determination of markers of inflammation has not been incorporated into daily practice for the care of patients with ACS, as we still do not know which inflammation marker is the one with the greatest prognostic value, and we also do not know when to measure it, the method to use, and what it adds to other well-established clinical, electrical, and biochemical parameters, such as the presence of prolonged pain at rest, electrocardiographic changes in the form of ST segment depression, and an increase in troponins. We also do not have, at the moment, cost-efficiency studies for the determination of markers of inflammation for either primary or secondary prevention.

An important and paradoxical aspect that has been observed in the countries of Southern Europe is the decreased incidence of heart disease in comparison with the Nordic countries or North America, taking into account the cholesterol levels of the general population. For example, the average cholesterol levels in population studies in Minnesota (United States) are lower than those of Gerona (REGICOR); nevertheless, the incidence of cardiovascular disease in Minnesota is much higher than that recorded in Catalonia.\(^10\) Therefore, we always wonder if data obtained from Anglo-Saxon populations are applicable to our reality and, in that way, the initiation of the study "The Systemic Inflammation Evaluation in Patients with Non-ST-Segment Elevation Acute
Coronary Syndromes (SIESTA) study is welcomed. The SIESTA study has 3 important objectives:

1. To evaluate the prognostic value of CRP, pro- and anti-inflammatory cytokines, adhesion molecules, fibrinogen, leukocytes, and amyloid A serum protein, among other markers of inflammation in patients with ACS.

2. To compare the value of these markers with those already known to be useful (ECG changes and troponins).

3. To establish the prognostic value of a single determination in comparison with the serial measurement of various markers. Samples will be collected upon admission, discharge, at 1 month, and at 6 and 12 months.

The sample is calculated on a 20% possibility of presenting with new cardiovascular episodes. This number is realistic and a little lower than that recorded in the DESCARTES registry, performed by the Ischemic Cardiopathy Section of the Spanish Cardiology Society, to study the therapeutic and prognostic management of non-ST segment elevation acute coronary syndrome (NSTEACS) in Spain. In a sample of 2058 patients, preliminary data from the DESCARTES study indicate that complications at the time of admission were: mortality, 2.2%; infarct/re-infarct, 4.7%, and recurrent angina/post infarct angina, 20.1%. These numbers are slightly higher than those reported by the Euro Heart Survey, also on NSTEACS, in which the mortality rate was 2.4%, infarct-re-infarct 1.4%, and recurrent angina/post-infarct angina 13.5%. These differences clearly show the need for having suitable data available regarding the real situation in our practice and to propose measures that will improve treatment of our patients. The data from the DESCARTES register have been collected from Spanish hospitals that care for more than 5 patients per month, after randomization according to patient care characteristics. It is most likely that the percentage of episodes reported by the SIESTA study more closely approximates that in the Euro Heart Survey, as the majority of participating hospitals had a hemodynamic department available and, therefore, were able to offer coronary revascularization more quickly which would, without doubt, reduce short- and long-term ischemic complications in high-risk patients. Nevertheless, the SIESTA protocol has chosen an interval of 48 hours from initiation of the pain to admission; this prolonged interval will increase the inclusion of lower risk patients, which may potentially reduce the occurrence of ischemic complications and, therefore, the number of events may be lower than expected.

It is important that patient recruitment continue until the number of complications defined in the sample calculation (313) has been reached, as if the population included is at lower risk, the total number of patients needed to obtain the expected number of events will be higher.

One solid aspect of the project is the centralization of samples in 2 laboratories that specialize in the analysis of lipids and inflammatory factors, as well as the judgment of the occurrence of events by an independent committee.

Nevertheless, the project does not describe what technique it will use to determine the various markers of inflammation, and also does not use the body mass index as 1 of the variables to be included. This data, together with others that they are going to acquire, would allow the determination of the percentage of patients with a metabolic syndrome that, in addition to atherosclerosis, appears to share the same inflammatory mechanisms. Another point on which they do not provide details is the composition of the committee that will judge the occurrence of events and decide when patients will cease to be included in the study upon achievement of the predetermined number of complications. The protocol also does not explain how data will be collected (on paper or directly in an electronic database) or what center will coordinate the study and process the data.

We Spanish cardiologists are going to know if the inflammatory profile of our patients is similar to that of other countries and the added value of CRP (and perhaps of other parameters that the SIESTA study identifies as valid) in the prognosis of death, re-infarct, and angina following NSTEACS will be confirmed. It will be very important to know what determination this prognosis is going to give us: upon admission? upon discharge? during followup? How will this marker of inflammation vary according to treatment received (aspirin alone or a combination of other antithrombotic agents, aggressive treatment with statins, etc.), and does invasive treatment have any relevance in comparison with that guided by ischemia with regard to inflammatory parameters?

One important aspect that the study does not cover is economics. It would be extraordinarily useful if the researchers could identify the best prognostic marker and, perhaps, identify whether it is necessary to measure markers only in some subgroups of patients (with normal cholesterol? non-smokers?) and determine what the economic impact would be of their routine use.

There is no doubt that the researchers of the SIESTA study have an important task ahead of them because recruitment of patients, acquisition and processing of samples, and one-year followup of the patient population requires exquisite organization and the availability of very dedicated personnel at each hospital center. The acronym of the SIESTA study strongly identifies the study with the country performing it, but its objectives have nothing to do with a peaceful nap.
after a pleasant meal. For this reason the name «SIESTA», although proper, does not do justice to the ambitious objectives of the project.

Thanks to this project and others already underway, such as the FORTIAM study, our epidemiological, clinical, and prognostic knowledge about patients with NSTEACS will be increasingly more complete.

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