



Transcript of Dr. Maseri's presentation at the 2nd Vulnerable Patient Symposium held by AEHA on March 6th in conjunction with the Annual Conference of American College of Cardiology 2004 New Orleans, LA



Thank you for the invitation and for the title, which I didn't choose because the title has some implications so far what I know very difficult to address because in pre-symptomatic vulnerable patients, it means patients that did not have coronary disease before. So, it's talking about primary prevention. And in this, there is nothing that I know that can tell whether one patient -- whether it be a different type from another in terms of what is described by traditional risk factors. So, I'm a clinician. I'm used to seeing patients. I still see patients. I still keep being surprised about how patients present to me and I try to learn from what they are trying to teach me. Not necessarily do I succeed, but I try.

So, you see one of the problems that we are confronted when we have used risk stratification and we hear of the Framingham score, plus CRP, or LDL cholesterol plus CRP from this review from Paul Ridker, we are facing the fact that we see a very remarkable stratification of risks from these patients with low CRP and low Framingham score. It's about 1% risk in 10 years to these two with high CRP and high Framingham score. There's more than 20%. However, there are two points that to a clinician are

very embarrassing. The first is that these have had events in 10 years. There was no way that I could predict who was going to have it within one month or within one year or within nine years or within ten. The second is that after all what I've done here, about 80% of patients in 10 years have absolutely nothing, which is remarkable. If you think that these are the highest risks we can stratify. So, you see the problem is that in these patients, if we had anything, it will be difficult to identify those apparent risks in this low risk group because of the Bayesian theory. It's very difficult to identify those risks. So, we can hope to identify here some of these that are a greater risk.

And now how are we going to do it? You heard before that some of these people that get the first heart attack don't have clinical stenosis. So, if we have the coronary angiogram the day before, we could not have predicted that they were going to have a heart attack. Now, if we can find plaques that are going to become unstable, now that is a problem because we have difficulty in distinguishing a number of things when we see something. We have difficulties in finding what is a mountain which we will never erupt which is a volcano that sometimes may erupt. And we only are good at identifying volcanos when they are erupting because we see them. They have trembles on top. They create trouble. They give symptoms for the patient most of the time. But if they don't erupt and they erupted in the past, then it becomes difficult again. It's like recoining some volcano which has erupted 100 years ago, or 500 years ago, and we don't know what it's going to do next. So, we have a difficult problem; however, if we try to learn from what these patients try to tell us, maybe we can very humbly take a new track, you know, change the sails according to the wind. And the problem is we're talking about that atheroma and atherosclerosis and identify the total atherosclerotic risks. Well, I'm impressed as a physician that some patients have a lot of atheroma and yet they didn't have an infarction and others had very little atheroma and they have an infarction. I'm even more impressed by the fact that some patients have an infarction, have that atheroma and then for years and years have absolutely nothing with the same atheroma staying there, the same atheromatic burden.

So, I think that on average, we go on what we've always learned, but if we want to move ahead, we have to start thinking along different lines and try to understand what triggers an acute coronary syndrome: Unstable angina, heart attack. If this is not linearly related with that atheroma because it's not, with these alternations no it's not, from others, yes, but in clinical practice it's not. So, in other conditions, a subtle difference in clinical presentation and phenotypic features may provide clues suggestive of specific causes of clinical syndrome. In anemic patients, clinical history and red cell features can provide useful information of specific causes of anemia, which you wouldn't have if you're measuring the hemoglobin. And we do this most of the time with patients with systemic heart disease because in epidemiology, we only measure heart attacks or coronary death. When we do a geography, we measure stenosis, but it's only one thing. And I ask myself, could this be the case also of a patient presenting with acute coronary syndrome? And always listening to patients, this could be the case because there's spectrum of clinical presentations for patients that come in with acute coronary syndrome with heart attacks. And one extreme, you must have seen patients like this. Is the present patient presented with an infarction, out of the blue sky, preceded and followed by complete stability? If patient denies having had anything before, you can always say that the patient doesn't know, that he's stupid because he doesn't tell me what the book stuff are telling me that he should teach me. But that's not the case. And it's followed by convinceability. The patient may not have anything for the next 10 years, 20 years.

At the other extreme end of the spectrum of presentation, you have this other patient, Type 2. Patient has unstable angina, followed by infarction and followed by recurrent acute coronary syndrome, post infarction angina and new infarction and you must have seen these patients and you know unstable angina is -- angina is defined unstable if it happens up to two months before admission and then can remain stable for a few months later. And if you look at the Duke database, you see that mortality following infarction or acute -- or unstable angina decreases gradually following this chart for the first six months and reaches that of stable patients only after six months. So, there is a

transient, prolonged period of instability in patients that have had an acute coronary syndrome, but is period of instability equally affecting all the patients both Type 1 and Type 2, well it does not appear to be like that because these patients, Type 1 and Type 2, appear to have also some biological difference, not only clinical difference of presentation, but also some biological differences. Here, for example, if you'll look at patients -- of course, the patients have to be very well characterized, these are patients with Braunwald classification 3-B unstable angina, 65% of these patients have elevated levels of CRP, but of course if patient was persisting unstable angina like in Braunwald classification 3B. Now, a compliment to this is that patient that have an infarction, but the infarction was proceeded by unstable angina, in practically 100% had levels of CRP on admission higher than three milligram per liter. But if you compare patients that have infarction, not proceeded by unstable angina, only 45% had elevated values of CRP and interleukin 6 on admission and this was published by in this paper, Giovanna in '94 in the New England and repeated in another study published on JACC in '99.

So, it looks like a majority of patients with persistent unstable angina have elevated C-reactive protein independently from having elevated troponin because those patients were excluded. So, this was the first study where CRP was shown to be associated with persistant instability and infarction independently from elevated markers of CRP because we excluded all the patients with elevated markers of necrosis. And by conversely, all the patients in whom infarction was preceded by unstable angina have elevated CLP on admission within six hours, whereas, only 45% of patients presenting with an infarction just out of the blue, not preceded by unstable angina, had elevated CRP, but the story goes on.

Here persisting CRP elevation post discharge predicts current instability. This is the paper we published Biasucci in Circulation '99 -- and this is a similar paper follow-up study by Peter Bogarty in Canada, published in Circulation 201. So, these patients that have tended to have recurrent events tend to have elevated inflammatory markers, CRP or interleukin 6. And this is the paper of Biasucci you see that on admission, patient

with Braunwald Class 3-B, 70% had elevated CRP, but not 100. So, patients are not behaving homogeneously because probably they're not homogeneous. At discharge, 50% nearly have elevated CRP; at 3 months, over 40%, at 1 year, nearly 40% continue to have elevated CRP and interleukin 6. Now, these are patients with low levels on discharge, lower than three milligrams and these are with levels higher than three milligrams. You see the event free survival is markedly better in those with low CRP. So, these patients presenting with low CRP with unstable angina have smaller incidents of events than those that have elevated CRP.

And here, there are two interesting studies that say that those patients that have primary angioplasty for infarction -- the paper by Goldstein in New England -- and have multiple unstable coronary plaques, those that have had multiple plaques were more likely to come back within short time with a new infarction or new unstable angina. So, multiple plaques in the study by Goldstein were associated with recurrent instability. Here in the paper by Zairis in atherosclerosis, the higher number of the unstable plaques were correlated with higher levels of CRP, and in this paper that was published with Angelina Buffon in the New England in 2002, that paper showed that there is widespread information in patients that have unstable angina in Braunwald class 3-B -- unstable angina. So, that's not only the case, but this is a paper that's been just submitted and being presented last year by Antonio Lombardo from our group that shows that carotid plaques are more often complex in patients that have unstable angina and elevated CRP than simple plaques. In patients with low CRP, carotid plaques are more often simple -- or no plaques or simple plaques -- and very seldom in patient with low CRP, there are complicated plaques by echo in unstable patient with low CRP. So, it looks like there is in those patients that have persistent recurrent instability have multiple plaques in the coronaries. How can you identify which one will become the culprit lesion next time? Which one should be stented, not only but looks like they have complex plaques also in the carotids. So, it's a systemic problem, but you see, the systemic problem doesn't last forever. It's not the related to Atheroma because eventually, after three months, after six months, after two weeks, after one year, then it dies down -- yet the atheroma remains there, but this is like a storm that

happens in these patients and it's related or associated with this systemic inflammatory detectable things. I don't know whether this is related causally to CRP or that is just a mark of something. It's most likely, in my opinion, a marker.

So, the mechanism inflammation during these acute coronary syndrome, could be infectious or noninfectious agents of bacteria, viruses, oxidants, toxins stimuli as shown in these papers that we published with Giovanna Liuzzo in *Circulation* '99, 2000, with Pionna Caliguri and Goran Hansson in 2000; with Luigi Biasucci in *Circulation* 203 where we found antibodies against heat shock protein 60 of chlamydia in patient with acute coronary syndromes, but not in stable patients. And then what is common in this group of patients that have elevated CRP, persistent elevated CLP, persistent elevated interleukin 6, is that they have enhanced inflammatory responsiveness to stimuli *in vivo* like coronary arteriography, the stimulus of catheterization or to the stimulus of myocardial necrosis for the same paper, same with Giovanna Liuzzo. And here within monocytes *ex-vivo* that they respond to lipopolysaccharide but producing much more interleukin 6 than the monocytes of patients who do not have elevated CRP and interleukin 6.

So, in conclusion, in acute coronary syndromes, inflammatory response is largely independent from the global atherothrombotic burden. In some patients, but not in all, plaque instability may be prolonged in time and involve multiple vascular sites. So, you see, if we have to deal with this problem from a different angle, what do we need to do? We need to learn more. We have first to walk and then to run. We are immediately thinking how are we going to prevent these patients? We cannot prevent them before we understand what's going on. I'm only trying to tell you that there is something that goes on, but it's not necessarily the same in all patients. Inflammatory mechanisms are correlated with recurring instability. They may be multiple and not equally important in all patients. We have to admit the patient's symptoms may differ from one from another. The precise investigation of these mechanisms is required for target prevention, targeted prevention of inflammation, otherwise certainly we cannot give steroids. I

wouldn't personally. Inhibition of key inflammatory final triggers of thrombosis appears an attractive therapeutic target and patient with recurrent instability and elevated inflammatory markers are ideal candidates for pilot studies.

The problem is that if you want to explore the triggers of acute coronary syndrome, a clinical investigator should stop being lumpers and become splitters looking for distinctive rather than for common features among patients presenting with coronary atherosclerosis and acute coronary syndrome. Just to give you an idea, this is an image and what do you see there? If you look, you know, it's very confusing, but if you look at the extremes, you see clearly a bird and if you look at the other things clearly a fish. In the middle is a mess -- but if you don't start looking at the extremes, you will never understand the composition of this picture. And I think that for what goes as acute coronary syndrome, in my opinion, it may be more complex than this fish in this picture. Thank you very much. (Applause)