Transcript of Dr. Fuster'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 very much, P.K. and Dr. Naghavi. Well, this is an interesting time since in the prevention field. The role of imaging is coming very rapidly and obviously is a question of economics. My talk today is going to be entitled CT MRI and CRP calcium score in the risk of stratified pyramid. Actually, it's almost similar as was presented by Dr. Braunwald with the same figures. This is my pyramid. And this is --

Chairman Dr. PK Shah: Valentin that's a three dimensional triangle!

All right. This is an intermediate risk, asymptomatic patient who may have one or two risk factors from Framingham and this is the high risk asymptomatic patient. We would like to look at whether they're developing subclinical atherosclerotic disease. So, these are all primarily prevention in a way, which is -- just give me a second to switch this off (beeper sounded). Thank you. So, we are talking about below this line. And these are the two groups that I'm going to be concentrating on. Now, what is an intermediate risk, asymptomatic patient? If you go to Framingham, here is the group between five and twenty percent events, hard events of coronary disease over a ten-year period. And if you go backwards, how do you get this risk looking at the score, as you know these factors. They give you a score. Well, basically, if your age is over 54 in a single risk factor, it puts you into the category of an intermediate risk score and that is where we have to be very careful because most of us sitting here might be in that range.

Therefore, we are not going to start doing imaging on everybody to see what is going on. I'm just presenting this just to start as an introduction. I think this is critical. This comes through the NHANES study where if you have a prediction from Framingham from five to twenty percent events over a period of ten years, this is the intermediate risk, which is about forty percent of the population. The question is, if you now test the patient with all the stress tests that we do and even angiography you find that actually a large number of these patients are at lower risk or higher risks than you might have predicted. This has made the thought that maybe this is the patient -- the group of patients that we have to test. I tend to agree partially, but I wouldn't use imaging in the way we are going to describe today because this is a very significant population. It's 40 percent of the population. What I would do is to use a marker like CRP and we might consider calcium scoring.

And this is what I want to present in the next two or three years' life. This is a letter from the women's heart study, Paul Ridker, and I have actually had four other studies showing the same thing. This is the intermediate risk of patients at Framingham, from five to at least twenty percent. If you now have a CRP, which is more than three, you can see how you can make patients from intermediate risks to go towards a higher risk. So, a reasonable marker. Now, if you look now at calcium score and this is the intermediate risk patients, from five percent to twenty percent over a ten-year period, if the calcium score is below 80, no problem. You're really almost in the low risk. But if the calcium score is above 80, you really jump into a high risk very rapidly, regardless of the score of Framingham. And what this is saying is, the calcium score is very good to really tell you where you are in the intermediate risk with Framingham as well as the CRP. And this is all the data from the calcium scoring from Greenland just published three weeks ago where you can have the Framingham score intermediate here from 10 to 20 percent and now you have a calcium score of more than 300 in over a 7-year period. You are already moving towards a high risk patient.

So, my conclusion here in talking about intermediate group of patients, between five and twenty percent per year, it seems to me that this is a group that may do more than the conventional risk factor profile of Framingham. We might add CRP. Maybe we might add calcium score and we could tell whether the patient is in the high risk category or not, which we might have missed. So, this is the first point I want to make.

Now, I'm going to move into the high risk population. The high risk population is a group of people who have more than 20 percent risk of a coronary event over a 10-year period following Framingham. And these patients have two or three or four risk factors and the question is, are they developing the disease? We are not interested in markers so much. We're interested in seeing the anatomy, whether they're developing the

disease or not. And this is where we're going now to expose -- to at least present to you an update on the technology that is evolving to assess whether or not a high risk patient has coronary disease.

First of all, we don't -- I don't like the term "vulnerable plaque." and I'm not going to discuss it any longer. We go high risk plaque, high risk blood and burden of disease to start with. Regardless of what you design here, we are talking about a systemic disease. In fact, if we just look at the CAPRI registry and the TASC registry in Europe and in the United States, it's very interesting how the disease advances systemically with time. In fact, today, any patient over the age of fifty-five that presents with one of the three systems affected has a twenty-five percent chance that has a manifestation of a second of the three systems and actually about seven percent chance of having the three regions involved. The disease is really systemic and I will show this to you with imaging. Very rarely you just see coronary disease. You know, this is a systemic disease. And if you have complications, you are not going to die of complications, but you will die of a heart attack. It has the same risk factor profile in itself as if you have angina. So, the whole issue here is we have to really take into account the whole arterial system when we talk about risks of a particular patient.

Now, let me move into the second issue of these imaging technologies. I really feel very compulsive to say the following. We cannot find the vulnerable plaque. There are meetings and meetings and meetings. Let's find the vulnerable plaque. Forget it. This is my view. There are too many. And once you go with imaging, you see them. And which one is going to explode? Any patient with a coronary event has already 12 plaques that you would call vulnerable, if you look at the coronary system. A patient with claudication -- I will show you these in a moment -- so, the issue of "let's go to find the vulnerable plaque" to me is a complete dream of a poet, because perspectively, you know, I don't see how you can. That plaque exploded and this was vulnerable. This is only perspective, but perspectively good luck with imaging technology, you will tell me which plaque is going to make it back in the future. Anyway, I have said enough about this. There are too many. And actually this slide was going to point out this.

Let's move into the next. Why I like the term "high risk" and why I don't like the term "vulnerable plaque"? Because the term "vulnerable plaque" implies fat -- fat. Fat is there when the plaque breaks. The term "high risk plaque" is telling you that 50 percent of the cardiovascular events leaves no plaque rupture. Therefore, that plaque that is very stenotic and very fibrotic and is in your carotid artery, it doesn't have plaque will lead to a stroke and you will need -- it's like saying it's not a vulnerable plaque. It is a vulnerable plaque, but in a different sense that fat is very fibrotic qualification. There is no literature at all that an inclusion in the leg relates to plaque rupture with a high

content of fat. All the inclusions in the leg that you've seen the literature, very fibrotic plaque that a clot takes place on top of that plaque.

I want to make this point very clear. If we talk about vulnerable plaque, it's fine to me, but then be sure that we are not talking only about fat and plaque ruptures. And I'm not going to be discussing this in detail, but this is all the work we have done in the last three or four years and I'd just like to summarize by telling that from the coronary plaques, two-thirds are plaque ruptures of a lipid pool. We believe that one-third is a very stenotic plaque, very fibrotic. It is a hypercoagulable state. We find very high tissue factor activity in blood in these patients which I'm not going to discuss now. In the carotid arteries in green means most of the plaques actually that lead to stroke are very stenotic and very fibrotic. And this is actually a dissection. The ejection of blood during systolic in passing to a plaque that vibrates because it's narrowed, and then you have there a dissection very different than a plaque rupture is a spontaneous rupture because it is a significant compilation of fat. It's a hemodynamic problem with a vibration that is worse. As Glagov pointed out many years ago, as the plaque is more stenotic.

Plaques in the thoracic aorta are very important. We see lots of them with MRI leading to strokes. This is a plaque in general, very lipid reach that really fulfills the concept of vulnerable plaque if you tell vulnerable, meaning a significant content of fat in plaque rupture. And in the peripheral circulation as I mentioned, most of these patients are diabetics, cigarette smokers, or hypercholesterol limit. There is no plaque rupture there. This is a clot on top of a very stenotic lesion. And we believe that these risk factors: diabetes, hypercholesterolemic, and cigarette smoking can create a hypercoagulable state in aplaque by venturi effect, is very stenotic, but is pulled the endothelium out, plaque that otherwise would not have a clot, with a hypercogulable state you have a clot. One-third of the coronary events belong to this category and most of the events in claudication.

And now we are going to be discussing in some detail the last two points which is what I consider we should be perhaps less ambitious in going through what we call the burden of disease; that is, where the disease from a systemic point of view, how significant it is and can we score it? So, let me talk about from the diagnostic point of view the so-called burden of artherothrombosis disease which is called BAD. I'd like to tell you it's bad. It's very bad. Here we now go back to the pyramid and to the Framingham. The high risk population is in yellow. This is for women, this is in men, and this is the age. Altogether, when you see people over the age of 50, it's about 40 -- it's about 25 percent of the population. I think Gene (Dr Euegen Braunwald) said a little bit higher. I believe it's at 25, 30 percent of the population. This is people at the high risk with a high

risk score. And this is what we are doing and this is a study we began sometime ago that is now getting better and better as we move on. This is a high risk asymptomatic patient. The layer I was mentioning, I'm going to be discussing.

Four technologies are being applied. First, calcium score. We are doing it because we do all the ultrafast CT. Otherwise, the calcium's score would be for the intermediate group, but we take advantage. The second issue is systemic MRA, injection of gadolonium in the vein and to see the systemic circulation. Third, ultra fast CT, injection in the vein and to see the coronary arteries. And, fourth, to look with MR tissue characterization the plaques that are identified in the systemic circulation with MRA or in the coronary circulation by CT.

Now, I'm going to present to you sensitivity, specificity and the things that we need to know about these technologies as we are moving on and learning. Ultra fast CT, before you inject anything, you can see calcium. What about calcium? Well, you have great experts in this room that will talk later. We already said that after the Framingham. But what about the sensitivity and the specificity of calcium? Well, here it is. If you have a hundred patients with coronary disease, 91 will have a calcium score that is abnormal. If you have a hundred people without coronary disease, you are going to find that 36 have an abnormal calcium score. Therefore, the sensitivity's high. The specificity's not good at all. How do you improve in specificity? By quantifying the calcium score, which is what I presented to you before. More than anything, more than a hundred, then the specificity gets much better. And I think that to me is a summary of the present situation.

We are now beginning to be interested in looking at the calcium score in the whole body and in the whole arterial system. And this is fascinating to find out a patient or an individual who is asymptomatic over the age of 70. Look at this. About 95 percent have significant calcium somewhere and infact with MR, they have disease, arteriosclerotic disease. And I'm pointing this out to you because this is a systemic problem, that the older you are, significant it's more significant. Now, we go to the second technology, MRA, which is basically to look at to the computer after you have done this, you can look at the different systemic arteries. The question that I'd like to answer today, is there any future for MRA to the coronary arteries? And I'd like to give the answer, and the answer is no. I may be wrong. I may not be wrong. CT will much better. However, if you want to characterize tissue in the coronary arteries, CT is not good. MRI is very good. So, let's be sure that we distinguish between where the narrowings are and what less characterize the lesion. From the point of view of MRA, I'm not entirely sure it is going to make it in the coronary circulation with injection into the vein, or without injection, but certainly in the systemic circulation, will.

Second that I said, calcium score. MRA for the systemic circulation now CT for the coronary circulation. Well, let's go into the data and it's very interesting. If you pull Jack this week, you will be stunned by a paper that says the sensitivity of ultra fast CT is 37 percent. Everybody's buying machines and you read that paper and you begin to question what in the world are we doing? Well, you have to read the paper very carefully because the patients were not made bradycardy. The heart was beating at 80 per minute. You can see nothing. It's all a blur. Second, they didn't the 16 that we use now today, and therefore, you really have to understand what you are doing before you buy a machine and how you apply it. I think this is very important.

The sensitivity and specificity is pretty high for this particular technology, but I'd like to present to you two problems. The first problem is radiation in that this ultra fast CT carries a radiation that is higher than a coronary angiogram. The question is whether in the next few years, it will be lower. And there is a lot of hope that it will, but that's one issue. The second issue is the calcification. You do -- you have a patient at the high risk, and you have a high risk score, and the next question is if this patient has coronary stenosis. And you're in trouble, because the calcium overshadows the artery. You do not see anything there in terms of the narrowing. This is like when you go to catch an airplane and you carry your computer. They'll take the computer out. Sure, you have to take it out; otherwise, these people cannot see what is behind the computer. This is what happened with calcium. However, technology's advancing very rapidly. I see Dr. Ruis here. He has done fantastic work on the so-called angioscopy in that we saw something in the coronary arteries that appeared to be like a plaque with a high content of fat.

Today, the resolution is much better. It's 270 micros here, and you can distinguish it slide by slide. The most interesting thing is the molecular MR. Now, we are able to see a single clot of one and a half milliliters with MR by targeting the MR with the specific antibodies. For example, this is just one and a half millimeter clot here. Okay. This is in the rabbit model. But also the fat, look how beautiful. In other words, what I really see here is that molecular MR is going to provide incredible information, not only at the molecular level but on the diagnostic level from the point of view of tissue characterization. And that's the way we are doing. However, even the plaques without injecting anything are becoming much more reliable in terms of sensitivity and specificity. Let me give you an example. We are now studying the whole aorta. About a year ago, it took 24 hours -- a couple of hours where the patient is scanning and 24 hours of processing. Today, you can do everything in one hour, just a year of how you process the images with MRI, simply working on the software. Give thanks to Dr. Zahi Fayad. And this is when we do burden of disease quantification.

I'd like to summarize what I said about the high risk patient. What I said is that the disease is systemic. There are too many vulnerable high risk plaques. The composition of the plaque leading to an event is different, dependent of the region, not necessarily a plaque rupture. And then I mentioned to you the combination of four technologies: ultra fast with CT, MRA of the systemic circulation, ultra fast of the coronaries, and then tissue characterization with MRI. Where is the state of the art? And I'd like to finish, but what in the world is going on in the myocardium? Because the question is the ischemia has an impact and it's very important and I'd like just to finish by making a few comments, because this technology is going to give an answer to something we do not have the answer, the assessment of the microcirculation. If you really look at the epicardial stenosis, here it could be vascular tone, in the microcirculation could be increase in tone, could be hibernation, could be stunning.

We just reviewed the whole subject and I'm now going to talk about nonviability or hyper enhancement of viability. How good MR is for this? But just to concentrate on systemic, I think this is critical when we use all this testing today to figure out the PET is the best because here's the highest sensitivity in the specificity. ECHO is a stress test. It has very high specificity, but you miss many patients' low sensitivity, for example. MR is like PET on all the studies that had been reviewed. And I don't have to go into the details in terms of profusion, sensitivity, and specificity. Dobutamine MR is actually much better than Echo stress testing. I'm saying this for you, because at the moment that we do all the studies with MR, we can collateralize the tissue and do this at the same time. And what is really happening here is that technologies are evolving in a unified fashion. And this is the summary of my presentation today and this is what we are now doing in our laboratories. And that if you have a patient with an intermediate risk, I will say we need markers and CRP in classification can be very helpful in putting this patient up in the scale or down in the scale. If you have a patient as I defined, with a high risk profile, our goal is to have a single machine that will have CT and MR capabilities and will do everything in one hour. And basically we're beginning to do this, but with two different machines and that here you have CT for the coronaries. Here, you have tissue collateralization with MR. Here, you have the adenosin stress test profusion with MR. This is really what you need in the high risk patient. Then you have all the things you can do for the patient with myocardium disease, hyper enhancement, and so forth. That is not what we are discussing today.

So, in summary, the way the field is evolving in my own view is that this intermediate risk patient population, which is about 40 percent of the population in this country over the age of 50, maybe new markers, CRP in classification today, are really giving you a good hand. If you have a patient and you are concerned whether he's developing the disease or not, I think the technology that I've presented to you today, not only in terms

of the coronary arteries with CT as a road map and then followed with MR to look at the lesions, but also in the myocardium, these techniques are so powerful that I don't think we will have to send the patient here and there in the future. I think probably we'll be able to do it in a single place where all these technologies will be combined on a single machine. And that is basically how I see at least from my point of view the future on the high risk patient. Thank you very much. (Applause.)