AEHA
ASSOCIATION FOR ERADICATION OF HEART ATTACK

Transcript of Dr. Rumberger'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, George, I'm excited to actually -- now here I am listening to the likes of Dr. Braunwald, Dr. Fuster, talking about CT in coronary calcium when I can remember giving speeches when there were three people in the room -- Rob Schwartz, myself and some drunk who got lost stumbling into the wrong ACC AHA session. So, we've come a long way and let's try to talk about this and I'm going to try and blend. A lot of this stuff is philosophy. That's what we do. And this is really my current philosophy on the situation. We really can't exploit the proper way to define individuals without having a proper method of separating people from high and low risks. If we mis-classify people, then many higher risk people would not be identified denying them what we now consider to be considerably advantageous therapy and conversely, many lower risk individuals are subject to over treatment with a variety of medications that still have, as far as I'm concerned, some long-term consequences regarding safety.

Coronary heart disease in a given person is a complicated thing and it's due to a variety of factors which we all know that are related largely to genetics and metabolism, modified by your habits, modified by your lifestyle, and modified by your environment as well as your individual suspectability to inflammation. How good is current NCEP

designation for traditional things? We've heard Dr. Braunwald talk about that; we've heard Dr. Fuster and even Dr. Zipes indicate that it's very difficult to do that. Here's a very interesting study that was published last year and looked at 222 patients who had their first myocardial infarction. And the real question was: If I had seen them in the office yesterday, how would I have felt about it? Today, they have a myocardial infarction. Now, these are people on the red that would have qualified for therapy and the people in yellow that would not have qualified for therapy. That is, they would have been at considered goal. High risk individuals, Dr. Braunwald's explained that to you, we consider by the NCEP criteria that if you're above 2% per year or 20% per decade, we call you high risk. Well, if you look at these people, then they should be considered to have an NCEP LDL goal less than 100, probably less than that, clinically but that's been the guideline. Six percent would not have qualified for that; that is, they already had an LDL less than 100, and 6% would have qualified for a whopping 12% of these individuals.

People that were considered to be intermediate risks, again, I'm seeing them the day before their infarction in the office and I'm trying to characterize them. Their goal would have been less than 130 for an LDL. Eight percent would not have qualified -- they would have already been below that -- and 10% would have qualified for therapy for an additional 18% of individuals. What about the people that I see in the office and I say, You know what? You look terrific. Your risk is low, you're absolutely just doing great and I want to get your LDL down, but the NCEP tells me that if it's below 160, I guess we're doing pretty well. Sixty-one percent would not have qualified, 9% would have qualified and 70% of the total people that had the MI yesterday that I saw in the office I would have totally blown it. So, 88% of these relatively young people who suffered their first infarction were in the low to intermediate risk category according to Framingham Risk and would have been missed as truly being high risk as modified by the fact that they came in the next day with a heart attack.

So, let's put up the vulnerable plaque pyramid, or triangle as you wish, and look at these individual situations. We have the low risk population that we define and then they are

modified by individuals that have a family history, intermediate risk, sub-clinical atherosclerosis fits in here and then true cardiovascular disease. We certainly can see the modulation that as we increase and we find people that are low risk that fall into the positive family history, we increase them a little bit up into intermediate risk. Some intermediate risk people, as we've talked about, are appropriate for further imaging and should be looked at for subclinical atherosclerosis. After we find or don't find subclinical atherosclerosis, we can re-categorize them. Many of them are categorized to truly having cardiovascular disease.

People talk about risk -- this is from Leslie Shaw's paper --is Leslie here? Leslie just walked in. Thank you. All right. Anyway, this is a large study looking at 10,377 individuals from Nashville, Tennessee with Dr. Kalister and looking at them down the road and what they did as they looked at the National Death Registry. How do I know you're dead? I look at your Social Security number and if it's retired, then I guess you're dead, unless you're living in the south of France. So, they found again that diabetes, smoking and hypertension all produced the kinds of risk that we do. So, when a patient comes into our office and we say, Listen, you're a smoker. You have twice to three times the risk of the guy who doesn't smoke. Same kind of thing. We also found that when you looked at the coronary calcium scores, you could also characterize them using this sort of characterization where you see an incremental increase in the relative risks. Furthermore, they found it to be incremental and independent of the conventional risk factors.

Let me describe to you a very, very brief case of two individuals. They're two prominent men, you will know them when I show you their pictures, both were smokers. Number one stopped; number two continued to smoke. Both with limited exercise. Number one became an avid runner, lost weight, became very fit. Number two continued to be inactive and obese. Both number one and number two had a family history of premature death. So, who's at greater risk to have a myocardial infarction? This little guy over here, Jim Fix died at 53 of a heart attack -- had a terrible family history, probably had

unstable angina the day he died, but regardless of that, he thought he could cure himself by exercise. This gentleman over here (Sir Winston Churchill) just did whatever the hell he wanted, had a great time and lived to be 91. Now, his father died prematurely -- I'm not telling stories out of school. Unfortunately, his father died of trcheriari syphilis, but just the same, they had premature disease in the family.

If you look at how you might use electron beam CT -- this is from our Ohio database -- 8500 middle-aged patients referred for testing. And you look at family history -- no family history, parental, sibling or both -- that's premature disease before the age of 55, men or women, just made a judgment call on that one. If you look for men and women you'll find that when you have the presence of disease, especially in both, there's a 1.4 increase in men when the calcium score is just positive and for advanced disease above the 75th percentile, it's two to one. It's even worse in women, two to one, and 2.2 to one. That is that the family history just by itself virtually doubles the risk and it needs to be considered in that situation. You also can use electron beam CT. This is compositive of nine studies or other studies out -- this doesn't include the latest one from Dr. Raggi and Dr. Budoff -- but looks at this, this is more of a concept. Don't take home the numbers, the numbers don't mean anything. It's a concept that if we are looking at disease getting worse over time, we find that in general, individuals who have subclinical atherosclerosis as defined by electron beam CT, have on average a 20 to 50% increase per year in their calcium score or their calcium burden. Individuals that were treated largely with statins were found to have on average about a 5 to 20% percent per year. Certainly, didn't stop it but again, if our goals are to slow down the progression of disease, it looks like that we have at least one test that can potentially be helpful in looking at that as a goal for determining response to therapy.

This is borrowed from Dr. Raggi's paper looking at a great individual -- group of individuals again -- that demonstrated looking at percentile ranks. When you look at percentile ranking, that's how you compare with the other kids your age and when you see here that as you go up higher and higher in your ranking, remember you don't want

to be in the high ranking like every other thing. This was like golf scores. You want to be low, you don't want to be high. You can look at individuals and notice that the annual event risk goes up considerably. In fact, these are very reminiscent of what Dr. Braunwald's divisions of low risk individuals that fall below individuals such as below the 25th percentile; intermediate risks between 25th and 75th percentile; high risks between 70th to 90th; and very high risks defined here about 6 1/2 to 7 percent per year into very high risk categories. What I'm trying to emphasize is that you need to understand the combination of taking conventional factors and adding in the subclinical imaging to try to make clinical sense of what you're doing. You cannot practice in a vacuum. You need to understand this. This is what we have been preaching for years. This is, in fact, looking at percentile ranking on adjustments to chronological age.

Age is the most powerful predictor in the Framingham Risk equations. You can have a cholesterol of 450, but if you're 20 years old, the chances of you having a heart attack in the next decade are very remote. If you have the same thing when you're 60 years old, the chances are very high because of age. Less than 25th percentile, subtract 10 years, no adjustment for being the average guy -- the average man or woman -- and if you're above that for the 90th percentile, add 10 years. And in fact, this is totally accredited to Dr. Scott Grundy, who suggested this back in the paper -- published several years ago and really got most of us thinking about how we can apply this to understanding Framingham Risks. Just like everything else, I tend to push to the next level and I felt that wasn't aggressive enough. And if you're above the 90th percentile, I'll actually make it 20 years older.

Let's talk about how we apply these things. We talk about conventional low to intermediate risk individuals between the ages of 35 and 65. I've given you a male who has a total cholesterol of 210, HDL borderline acceptable, no diabetes, no smoking, systolic blood pressure mildly elevated. When you look at the Framingham Risks, we divide people into low risk, intermediate risk, and high risk categories. Now, if you are to take the Framingham Risk here in red and you look at the same numbers, but you plug

in just a different age, you get this curve. This individual at 35 would have been low risk and by the time he becomes about 55, he would fall into intermediate risk. If you talk about defining calcium score throughout that whole category and let's say that they fell below the 25th percentile, then they would remain low risk throughout all of these years, where if they had had a calcium score above the 75th percentile, they would have been an intermediate risk even as young individuals and classified much earlier as high risks and then once you get above the 90th percentile, they're high risk no matter what age they fall into.

Let's look at intermediate to high risk, the same kind of situation, a male, high cholesterol, low HLD, no diabetes, no smoking, and a lot higher systolic blood pressure. Same characterization. If you look at him as a Framingham Risk, from age 35 to 65, he would have transitioned from low to intermediate to high risk with exactly the same numbers other than the fact that he's getting older. If he had a calcium score of less the 25th percentile throughout his age, throughout these ages, he would remain low risk until he got on the age of 60, where it'd be intermediate and when he's higher than that, he would be high risk both in these categories along the way. If you look at these characterizations and you try to figure out how you can incorporate these situations, you'll realize that intermediate conventional risk patients and high risk conventional risk patients frequently are misclassified. One-third or more are actually low risk; one-third or more are actually high risk; and in the high conventional risk, you can also misclassify people. So, again, we go back to what Dr. Zipes had actually said. About two-thirds of the people we actually misclassify. They could be higher; they could be lower. We get it right about 33% of the time.

So, let's go back to the concept then. The incidence of coronary disease goes up with age. We agree with that. It makes perfectly good sense. We've got tons and tons of data. But about that curve, there are highs and lows and in fact, there are areas of insecurity in terms of calculating these situations. Where I think electron B coronary calcium score comes in, in defining incremental value is within a specific age group. Now, in the simplest analysis, incremental value is merely post-test likelihood over pre-

test likelihood. Now, it could be a positive or negative number but if you just give the absolute value that it always goes up or it always goes some way and if you look at that, my interpretation is that electron beam CT has a value within these categories because the dominance of age takes over. So, if you're a 70 year old, personally, I think it probably doesn't add much incremental value to traditional factors. But within these huge loops here of insecurity, I think you can see the incremental value coming in.

So, risk increases as the calcium score and the percentile rank. And again, this is the point that we've stressed over for the years. It can't identify the vulnerable plaque but it can help you identify the vulnerable patient, which is what we're talking about today. So, at present, we've established the following: Coronary calcium is atherosclerosis. The magnitude of the score relates to the severity of the atherosclerotic disease. The calcium score as well as the percentile rank provide information in which to view risk factors rather than the other way around. The data on examining progression -- although I didn't present that fully -- are consistent with the potential to use that as the modifier of how well we're doing. It could be our report card for the individual.

So, the calcium score again, extent of disease in a given person, related to a consequence of a variety of factors, some of which we can measure and many of which we cannot measure, we can't put on a scale, we can't measure in a blood test. So, it might make more sense to use this as the additional risk factor or the risk measurer, incorporate that again with conventional assessments. So, when you're talking about again the combination of the low risk in these situations, I've now changed this to atherosclerosis imaging -- which is really where I think we should be going and in fact, you see an increase. So, EBT and other forms of atherosclerosis imaging, not just electron beam CT, take population statistics and they put them into a personal statistic situation. This is what you have as a person, not what 100 people have that look and smell the same as you. So, by measuring this, it allows you to give the extent of what I call "Pre-Symptomatic Coronary Heart Disease." Thank you. (applause)