Transcript of Dr. Vogel's presentation at the 2nd Vulnerable Patient Symposium held by AEHA
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Thank you for asking me to discuss the use of endothelial function assessment for determining cardiovascular risk. The good news is that endothelial function is very predictive of future cardiovascular events. The bad news is that we don't yet adequate clinical tests for assessing endothelial function.

On this first slide, I have outlined my understanding of the atherosclerotic process in broad strokes. It starts with risk factors, such as hypercholesterolemia. A genetic predisposition is also very important. All people do not develop atherosclerosis, even with overt risk factors. There is a great deal of information to be learned from those you don't get atherosclerosis under these circumstances. My mother is an example. At 96 years old, she has no evidence of atherosclerosis despite a total cholesterol of 350 and an LDL of 250. She clearly has no genetic predisposition. So she does not and I hope that I do not have any genetic predisposition to risk factors such as hypercholesterolemia – so the risk factors, you know, are not the same as disease. There may be other issues with regard to genetic predisposition, the first true gene for myocardial infarction was recorded last year, the MAF2 transcription factor gene. It is not a risk factor, if you have that gene, you will have a myocardial infarction. The

penetration is essentially 100% without fasting, but if you have risk factors and you have a genetic predisposition, then you injure your endothelium, minimally you decrement your availability to nitrous oxide, you certainly produce a pro-inflammatory state and you also increase markers from thrombogenesity. Example perhaps of information might be CRP and we've been hearing that if you then proceed through what the vascular biology destination of endothelial dysfunction is, then you develop atherosclerosis and one of the markers might be coronary artery calcification. I think it is short-sighted to look at any one of these four quadrants and say that's how we're going to evaluate the vulnerable patient, because I think there are all helpful, even if you knew a patient was headed in this direction, you might have to go back over here or back over here or some place else to find out what the appropriate therapy would be.

And so, I think when the dust settles in this field, we will still have risk factors, gene, vascular biology and imaging diagnostic. Now the one that I want to concentrate on for the next 15 minutes is endothelial function and as all you know, the concept of endothelial function is a misnomer because there are many endothelial function. The endothelium if healthy makes many molecules, nitric oxide, tPA, are examples which are vasodilatory, thrombolytic, disaggregant for platelets, anti-smooth muscle cell proliferative and lipolythic but if activated the endothelium makes a whole other host of molecules which vasconstrictive, thrombotic, adhesive for platelets and white cells producing smooth muscle cell growth and certainly hallmark of inflammation. Now, you can't just look at one of these. If for no other reason that a specific intervention may changes these in opposite direction. What am I talking about? Estrogen. Estrogen you'll learn at least temporarily improves nitrous oxide availability but at the same time, increases inflammation and so you couldn't even predict from that what the result of giving a woman estrogen would do because of the complexity of endothelial function.

Having said that, there is some general relationships which hold -- if you look at CRP and you look at endothelium mediated basal dilations, in general, these have an inverse relationship. Individuals with low CRP robust responses to acetylcholine whereas those

with high CRP have good responses to acetylcholine. And it is reasonable to think of nitric oxide as one of the major mediators of endothelial dependent basal dilation as being conducted with progression of atherosclerosis. In experimental animals, if you inhibit nitric oxide synthase with a specific synthase inhibitor, atherosclerosis increases, if you make more nitrous oxide available by giving the precursor, atherosclerosis increases. And so availability of nitric oxide, one of the endothelial functions might be interpreted as a way of measuring the rate of progression of atherosclerosis. Well, what techniques do we have? Well, I'd like to stand up here and tell you we have many clinically applicable techniques for measuring endothelial functions that are helpful. My first large message tonight is we don't. The techniques that we have for measuring endothelial function at least flow mediated dilation are a fatality of vascular biology that is going on at any one time.

Now, this concept that won the Nobel Prize for medicine in 1998 by Furchgott picked up by others, is applicable for coronary artery -- you can look at endothelium mediated agonist such as acetylcholine and infuse 'em down coronary arteries and you may get just as you do in rabbit aorta preparation, vasoconstrive responses or vasodilative responses and those mean something for cardiovascular events. If you have a vasoconstrive responses to acetylcholine your subsequent over seven year frequency of cardiovascular events is dramatically increased, but it's not only with regard to acetylcholine -- if you look at it with regards to cold pressor, or you look at with regard to flow mediated dilation, although you're always looking at something a little bit different, you still get a substantial discrimination in cardiovascular risk rate, those are patients with coronary artery disease. There are patients without coronary disease and yet, the vascular biology predicts exactly the same thing whether you're looking at resistant changes or diameter changes to acetylcholine -- still, a 3, 4, 5 time prediction of increased risks. Moreover, in getting back to the central concept of a vulnerable patient, if you look at coronary blood flow responses to acetylcholine, you actually can predict the risk of stroke and TIA. There is nothing different going on in the head than in the

heart and that's a very, very nice concept where we see cross-talks between the different vascular.

Now, lets now turn to plethysmography and quickly show you exactly the same data. Those individuals who have the most growth spots, slow responses have over approximately three years, the smallest number of events; same thing true with acetylcholine induced flow -- blood flow responses predicting an adverse prognosis and data showing that in fact, this is free radical mediated, those with less than -- with the smallest responses to anti-oxidant have in fact, the smallest number of events. Probably the technique which is most widely used is that of brachial artery flow mediated dilation. Here is an active image of my flow mediated dilation. It's in essence a brachial artery endothelial stress test. My left brachial artery at rest one minute after five minutes of occlusion and the results in vasodilation and the reason for being happy over having more than 10% slow mediated dilation, is that it gives me about one-third the risk of having a cardiovascular event over the next five years in small and in larger studies and now, using non-invasive techniques, we can begin to screen larger and larger groups for coronary heart disease as well as cardiovascular events.

Is this technique going to be widely used to predict cardiovascular risks? I don't think so. To get the kind of pictures that I just showed you with the brachial arteries, we've had to lock our technician in the room for the past eight years who does nothing else but flow mediated dilation and that's not broadly applicable and yet, I'm still optimistic about the technique. Let me tell you why. If you have good endothelial function as measured by brachial artery flow mediated dilation, we can predict your operative technique, again, not particularly different but here is something very interesting. That is let's take us back to 1997 and that is prior to the report of the HRT Study. In 1997, most physicians were advised in HRT for post-menopausal women to reduce the incidence of cardiovascular risks and yet in 1997, we wrote that these studies were futile because they would not show any beneficial effects. Now why is that? Because of data such as this which reported that the short-term benefit on nitric oxide availability that is present

within 15 minutes of giving intravenous estradial were absent if you looked out at six months -- a finding which has held up and so there's no long-term improvement in the vascular biology on HRT for post-menopausal women and by the way, as mentioned, indices of inflammation such as CRP are impaired, indices of thrombosis are increased and many things that people forgot, you get more small dense LDL and so the entire prediction of what good would be done was based upon things like changes in LDL and HLD and that monothematic thinking that was very, very dangerous to a lot of women. Looking at the entire spectrum of vascular biology, it was very easy to predict years ago that HRT would not be beneficial. Now, here is a more challenging study published a couple of years ago. This is a study of 350 post-menopausal hypertensive women who were treated with an array of anti-hypertensives. The group started at the same blood pressure, the hypertensive level, they were all successfully treated and they were then categorized into those who had less than or more than 10% improvement in flow mediated dilation despite the fact that these two groups of women had identical blood pressure on treatment. So, it's not just blood pressure because those women who had a better improvement in vascular biology had less cardiovascular events, both of a cardiac and a cerebral nature in subsequent follow up. At the American Heart Association Meetings and recorded this week in JAMA, we found in a head to head trial of two statins in patients with coronary disease that in fact, we had greater improvement in flow mediated dilation in patients with more aggressive lipid lowering, that translated to a greater reduction in CRP, that translated to an absence of progression that was used with lower LDL therapy as compared to less LDL lowering.

Now, on Monday, at this meeting we're going -- the group is going to report the mortality and cardiovascular rate in a very similar trial using exactly the same regimen in a trial called "PROVE IT." We would predict from these that what they're going to find is what the vascular biology found, what the IVUS found and that is more LDL lowering was better. If we're correct, that substantiates the concept of using these for intermediate biomarkers to help us shorten the study and reduce the cost. So, a prediction, because what we've learned in the past 10 years is -- although these tests may not be terribly

applicable for an entire population to screen risks, they're terribly good in predicting what happens with therapy.

Well, the conclusion at this point is that both coronary and brachial arteries, endothelium dependent dilation are quite predictive of cardiovascular events whether they ever see the light of day as a clinical technique or not and probably most importantly, that we can use these in less expensive and shorter studies to predict the real therapeutic responses of an agent or in specific patients, that remains to be shown, but I think that those data will hold up. Thank you very much. (applause)