It is really an honor to come to this session for several years in a row now, it’s just fantastic to see such a great attendance and such fantastic lectures that I’ve listened to earlier today. So I guess I’m now down to 30 minutes instead of 40 but what I’d like to do today is – I’ve been tasked with this topic, use of markers to guide decision making and so I’m going to set some ground rules just because of the time limitations.

Since you’re heard, I’m kind of interested in prevention so I’m not going to talk a lot about markers of acute myocardial infarction, congestive heart failure and how they guide our management. You probably have some sessions a little later for some of that so I’d like to stick a little bit into the prevention realm. What markers are there out there that help us identify individuals who are risk for cardiovascular disease.

At last check there’s probably over 150 and in 40 minutes I’ve decided to limit that to what I think are four clinically relevant markers. So my goal for you today is to hopefully walk away with some tangible information that might help you in clinical practice, on some of the tools that are out there, some of the markers that might help us identify individuals at risk. So in my disclosure information and I will focus on number three, I’ve been accused of blatantly being lipocentric, I have this unshakeable conviction that you can see there, it’s all in the abnormal lipoprotein concentration folks and hopefully I’ll be able to sell you on my conviction.

I also, those of you who’ve suffered through my lectures before understand that I show this picture a
lot and that is because I kind of, you know, as a _____ maniac in the clinical training that all of us in this room have received, focusing on the patient, there is no better marker of someone at risk than this picture by Frank Nutter of clinical obstructive coronary artery disease. And I always kind of like to ground ourselves, we’re going to talk about some fancy markers and we’re going to talk about some fancy tests. But you know even if we all agree to do a better job on the patients that we know have obstructive coronary vascular disease at least as far as aggressive lipid management, aggressive blood pressure control, aggressive respect to modification that we’ve all learned about, we’re going to continue to make an impact in this disease. We’re making an impact, unfortunately coronary artery disease, disease of the vessels supplying profusion to the muscle, the heart, remains the number one killer of men and women in this country. Has so since 1900, except for 1918 of course which was the influenza epidemic.

But none the less, so I always like to ground ourselves a little bit with that but let’s talk a little bit about this atherosclerotic process and again kind of define some ground rules. Because we understand that obviously this is a disease that takes time to develop but it starts in many of us very early in life. So this is a timeline, this is a slide that was given to me by John Rumberger who’s now at the Princeton Longevity Center, I think it’s a beautiful depiction of the atherosclerotic timeline. The fact here is that this just as I said a timeline, we get the idea, you know, that when coronary artery disease develops it develops overnight and it doesn’t, obviously. Certainly plaque rupture, acute myocardial infarction from atherothrombosis, obstructive coronary artery disease, the late stage processes may become clinically evident overnight, but this is a disease process that we all
work on probably for those who are going to develop it beginning in our second decade of life. And, in fact, if we look at this gross anatomic picture of a left anterior descending coronary artery that has been splayed open in the pericardial sac you can see first of all that it’s always a poor prognosis indicator to have your coronary artery on a slide in a lecture. And secondly that unfortunately, this is a 20-year old individual who had an automobile accident and during the autopsy was found to have not obstructive but certainly early coronary artery disease. And so this person had already started early in life developing atherosclerosis and then as that continues to fall through this timeline, we see that the atherothrombosis depicted in this slide, someone who did unfortunately die of a coronary atherothrombosis we see a significant plaque ___ and the obstruction of the atherothrombosis that caused sudden demise.

And then we all are aware of those who may survive that phenomenon but go on to develop the obstructive coronary artery disease, the flow limitation that can become very symptomatic as the Frank Nutter depiction that I showed you.

This is an incredibly complex process as we know, as I’d like to kid my invasive colleagues and I think Dr. Lee is on right after me, you know, it doesn’t take much to know when the plumbing is blocked but identifying you know which toilet it is in the house that’s going to have the problem is really, really something.

An issue here is that this process as I said not only begins early but incredibly complex in so far as
the vulnerability factor for each individual in this room to kick off that atherosclerotic cascade. So we all understand and these are all—I use this slide really as review for you. These are the factors that we deal with everyday in clinical practice that contribute to the vulnerability of the blood vessels, so the hyperinsulinemia, the diabetes, the hypertension, I don’t have tobacco use up here for some strange reason, the genetic disposition predisposition. We understand that those are all vulnerability factors that place our endothelium at risk and we’ll go through that a little bit because therein lies some of the markers that we can use. But make no mistake that this is a process that is driven by the dyslipidemia that results. And so one of the factors I will talk about is a marker of dyslipidemia that goes beyond LDL cholesterol.

If we take a look at the pathobiology it’s worthy to, it’s worthwhile just going through that and this is a nice depiction of the normal coronary or cerebral or peripheral or other arterial vessel in our body and it is characterized by a normal endothelium, it is not a passive barrier. We all understand that endothelium plays a very active role with these factors that you can see here. And it is the first stage of atherosclerosis that is defined by endothelial dysfunction. Endothelial dysfunction may be a physical disruption of this barrier or may be even just a functional disruption of this barrier. But when that endothelial function occurs and again in the absence of any obstructive process we now really set the stage for vulnerability and development of atherosclerosis. So now we have again in my lipocentric vein, we have the lipoprotein, notice I don’t have this labeled as LDL, I don’t have this labeled as a triglyceride molecule, I have this unlabeled. This is a lipoprotein and we’re going to talk about that because one of the markers as I said, we’ll talk about it, how do we recognize how
many of these lipoproteins are in our circulation to take advantage of this vulnerability. Realize that the initiation of atherosclerosis and moving on to the formation of this fatty streak that I showed you in that gross anatomic specimen is really not a complex receptor mediated phenomenon. The more lipoproteins you have circulating over the dysfunctional epithelium, the higher your risk of getting those lipoproteins into the subendothelial space and developing this atherosclerotic process.

As we move on and develop this plaque formation, now perhaps in a minimally obstructive, the so-called minimal irregularity, we realize that there is a complex phenomenon of inflammation. So you frequently will hear about markers of inflammation that may or may not be helpful to you and we’ll talk about that. But it is this inflammatory cascade that is essentially either initiated by or the initiator of the atherosclerotic formation that really kind of – I like to use the analogy of throws flame on the fire or gasoline on the fire. It really flares this atherosclerotic process. And in a subcellular way we now understand where some of our markers of inflammation may play a role in identifying individuals who are at least at risk for this process because of what’s going on in their vessel wall. So this is a very strong magnification obviously of one of these activated macrophages that continues to take up by way of the scavenger receptors, the oxidized lipoprotein and this slide labeled LDL, that doesn’t have to be low density lipoprotein, could be very low density lipoprotein remnants, could be ___ micron remnants.

These then activate this macrophage and this activated macrophage pours out if you will cytokines and we’re all familiar with one of these inflammatory markers, C reactive protein. And we’re going
to talk about that as one of the markers that may be helpful for us, but this inflammation and this inflammatory process and this cytokine generation really does make this a very unstable process and leads to fibrous cap weakening that is trying to protect this lipid gruel if you will from the exposure to the blood.

So if you step back and talk about the first marker and that is an inflammatory marker, we had a lot of markers to choose from in the inflammation but again I’m going to focus on the prevention realm and not talk about troponin and CTK and these other markers, not even going to get into some of the basic science of the VCAM, ICAM, all of these other cytokines. Why because you’re not going to really be able to walk away today and use that in your clinical practice. And I think that’s important, that we give you some information that you can. But we will focus on CV active protein today and I’ll focus a little bit on LP PLAT the lipoprotein-associated phospholipase A2. Why did I choose those two, those are two things that you can order in your office today and we’ll see that information and what that data suggests.

So first of all we understand that as we start talking about these markers there are certainly markers that help us identify a population at risk. And I’m going to continue to make the distinction between analyzing a population at risk or looking at inflammatory markers and others in that population and the fact that that is very different than the individual at risk. And applying population statistics to the individual who walks in your office can be a tricky game. And as clinicians we treat, we treat individuals. The epidemiologist treats the population and so it’s going to be important for us to
Certainly make that distinction as we go along. But what I have listed here from the Physicians Health Study, it’s a list of various markers and again I’m going to talk a little bit about high sensitivity C reactive protein. And the first thing that I’d like to do, I did not want to just focus on the male gender of the Physician Health Study which of course was predominantly male but even in the women’s health study we can see that inflammatory markers such as C reactive protein, those who have the highest quartile of C reactive protein are indeed at the highest level of risk. So as a marker of a population who is at risk for atherosclerotic events, it may be a very, very helpful – sorry about that, a very, very helpful marker.

Can I have the next slide please. Thank you. So this is some interesting data that you’ve heard about C reactive protein. And Dr. Ricker has been prolific in his publication in his group in New England about C reactive protein and I chose this slide because I think it really gets to the crux of the matter. Should we be checking C reactive protein rather than lipid levels? And this is the PROVE IT TIMI 22 study, this is a study that essentially looked at the difference between very intensive high dose statin therapy versus a little less intensive moderate dose therapy. And the bottom line was that if you looked at the cumulative rates of recurring myocardial infarction or coronary deaths, heart end points, heart clinical end points that I think are clinically relevant to us. And compared those individuals who were treated aggressively to achieve LDL cholesterol levels less than 70 milligrams per deciliters versus those who were left on moderate therapy, we can see a significant improvement in that end point rate. But we also see the same thing in those individuals who’s C reactive protein levels ended up being very low, less than 2 milligrams per deciliters compared to those who were
left with C reactive protein greater than 2 milligrams per deciliter. So the thinking is, well gee is this, in this population a better marker than treating even their cholesterol levels. Should I treat C reactive protein, hold that in the back of your mind.

This is probably the graph that you all saw in your articles, in your review articles and this was the New England Journal of Medicine paper from a couple of years ago. ___ gathered some steam with C reactive protein because what it showed was in this particular large study, the outcome, the recurrent MI or coronary death rate for individuals who were treated to LDL cholesterol less than 70 milligrams per deciliter, but whose C reactive proteins remained elevated, had a higher event rate than those who had the LDL cholesterol less than 70 and the C reactive protein less than 2. And probably the important distinction here was even those who achieved LDL cholesterol of less than 70 milligrams per deciliters but still had high C reactive proteins, they even had higher event rates than the latter group that I just mentioned.

So the question really is again, is this marker, is C reactive protein a marker that I should be checking on everyone. And if the C reactive protein remains elevated, should I gear up my therapy. Remember, we don’t have a C reactive protein specific therapy. We don’t have an intervention that specifically tagged for C reactive protein. Because the data for C reactive protein being biologically involved in that atherosclerotic process that I showed you is not ready for prime time. But the recommendations are that, well, if C reactive protein remains high maybe I ought to gear up my lipid lowering, hence my lipocentricity.
Let’s look a little bit at some of the perhaps pitfalls of C reactive protein and why in my opinion it’s not quite ready for prime time. First of all, where do we see elevated C reactive protein levels? Or you’ll be reminded by this slide that C reactive protein elevation is unfortunately a common, common an issue with those who struggle with obesity. And as we all struggle with a patient and metabolic syndrome which we’ll talk a little bit more about, obesity is prevalent. And so to simply go out and screen for C reactive proteins to identify those individuals who have markers that might help us identify them at risk, may be casting a very large net and catching the same individuals that you would catch if you put them on a scale.

The other issue is you know I’m frequently asked and I mentioned this a little bit, well what’s a great therapy for C reactive protein? And a great therapy for C reactive protein is weight loss. This is an interesting study in the Journal of Clinical Endocrinology Metabolism, it showed if you really wanted to lower C reactive protein in individuals – put them on a very low calorie diet and get a reduction in their body mass index. Interesting.

So we take a population marker and now try to understand whether that population marker is really applicable to this individual. Is this individual C reactive protein elevated because of their body mass index? That’s one example. Not only that, we have other effects on C reactive protein, here’s the effect of hormone therapy, so conjugated estrogens with various formulations for progesterone, all of which can raise C reactive proteins. So you see, I’m kind of muddying the waters here a little
bit. When you have a patient that comes in to your office and your clinical question is, am I doing a job that’s good enough for that patient to prevent atherosclerotic vascular disease events. Is measuring that C reactive protein really what I want to do?

The other issue is the variability in C reactive protein is well known. And this study that was published a couple of years ago, if you just take a group of patients and measure the C reactive protein and one month later measure the C reactive protein again and unfortunately, have a dilemma. And that is the dilemma that about a third of those folks who had any ___ at all moved to a higher risk C reactive protein. About a third of the folks moved to a lower risk C reactive protein. You had about 10 percent who moved to a very low risk of C reactive protein and about 50 percent moved to a higher C reactive protein. What do you do with that clinically?

So I’m not so sure C reactive protein as a marker right now, to go out and screen your patients, all comers, for vascular disease prevent rates is ready for prime time. And in fact if we look at the American Heart Association and the CDC panel recommendations for the use of C reactive protein in clinical practice you see here, this is an independent marker of cardiovascular disease risk in a population, I have no argument with that whatsoever. In patients at intermediate risk, you know, maybe this would be a helpful marker if you have difficulty deciding that you want to gear up aggressively.

Certainly, you have stable coronary disease and acute coronary syndrome patients where this may be
a useful and independent marker for prognosis then you talk about that data. So C reactive protein may be helpful in clinical situations but for screening the general population I’m not sure it’s ready for prime time. So the clinical recommendation that you should walk away with today is that if you’re going to check C reactive protein, you need to do it at least twice, 2 weeks apart. You’re going to average those results, doesn’t matter whether you’re fasting or not fasting. If you got a C reactive protein greater than 10 milligrams per deciliter, you’re got something else going on. And it’s worthwhile considering that. And then the relative risk categories for populations are listed here. So C reactive protein a helpful marker but not a marker in my opinion to go out and start screening the general population.

Let me move to the second of four markers and this is the last inflammatory marker that I will show you because I think Lp-PLA 2 has some interesting data behind it. Some of you may be checking Lp-PLA 2, the so-called plaque test because the labs have it available to us in various places. This is another depiction of a vessel lumen, here’s the endothelium here. This is the depiction of the oxidized low density lipoprotein or other lipoproteins becoming entrapped in the – if you have a ___ endothelium space, Lp-PLA 2 is an enzyme that sits on lipoproteins and that enzyme takes phospholipids and essentially produces oxidized fatty acids that can be very thrombogenic. And those fatty acids themselves will then contribute to the turning on if you will, the throwing of gasoline on the fire with the cytokine and other adhesion molecules that really ramp up the atherosclerotic process.
We can measure this, we can measure how much of this enzyme is present, we can measure the activity of this enzyme - what’s very interesting in the basic science is that this Lp-PLA 2 which is the reddish-brown stain seems to be very specific for rupture prone or ruptured plaque and that’s what this brown staining here is showing us.

So there is some anatomic and pathologic association with rupture or vulnerable plaque and there is a slew of trials that have shown an association with Lp-PLA 2 with risk of cardiovascular disease. So again the population risk can be identified by checking this – this particular marker.

What is very interesting is that probably you have some additive effect with C reactive protein and this is data from Christy Valentine in Texas in his group and showed very nicely that if we look at these various risk ratios, we take individuals in the top risk group for C reactive protein and the top risk groups for this inflammatory marker, in this trial these were the individuals holding steady for everything else, that had a very, very high risk for cardiovascular events.

And this was for those who had LDL cholesterols less than 130 milligrams per deciliters for coronary heart disease and these are individuals who had similar risk for stroke, again, those who had the highest risk in both C reactive protein and Sp-PLA 2. Really in this population with very high risk for clinical event.

The trouble that I have with these markers is that I don’t think we have a good understanding yet of
their role in cardiovascular disease in so far as are these factors, risk factors for sure or are they risk markers. And that really is the crux of the matter. Are these markers that actually contribute to the atherosclerotic process or are these factors simply those that along with traditional risk factors, mark and individual population that may be at risk. For the true biologic relationship, is not quite yet well defined, at least not well enough for clinical practice. So if we’re going to use inflammatory markers I think we need to be very careful about fishing with inflammatory markers. You’re going to pick up a lot of individuals who may not have that individual increase risk for vascular disease just because they have an elevated inflammatory marker.

I think this sign puts it best. Really, it’s all in the presentation.

So let me go back to my, my kind of construct here of the various contributors to this atherosclerotic process. We understand inflammatory markers certainly are that, they’re markers. But if you’re going to use them for clinical practice, I gave you my caution. The other way to look at this and again kind of I think argues toward my lipocentricity is that we need to think about what atherosclerosis is. Atherosclerosis, the development of plaque, is a common source epidemic. That’s what it is, right. This is a lipid storage disorder, this is a disease of the endocrinologist. Just so happens that a cardiologist developed a little catheters to put down there and opened it up but this is a lipid storage disorder that is driven as I alluded to earlier by abnormal lipoprotein deposits in the vessels. And this is, you know, the common source in this disease, I think you know not so arguably is high cholesterol primarily, especially in industrialized countries from dietary saturated
fatty acid and cholesterol. If you go to places in the world that don’t consume the diet that industrialized countries do then you will not see many ______. And the issue here is that we measure kind of the exposure to this common source various ways, LDL cholesterol, Apolipoprotein which is the third marker that I’d like to talk about and even lipoprotein particle concentration. Again, things you can measure in clinical practice but now have some data behind us.

Now why do I make this analogy, it’s the epidemiology blood in me I guess, because you know in Pittsburgh there’s a great story about a common source epidemic. You’ll probably recognize this word, I always like to kid, Dr. Jim Shaver who’s a fantastic college mentor of mine, I think that was him as a house officer right there. We don’t see to many of these wards in our hospitals any more because the Salk team right here in Pittsburgh has essentially helped us eradicate this disease from the face of the earth. But how did he do it? How did they decide the right approach to a common source epidemic. Well they didn’t do more expensive braces, crutches or other accoutrements for these patients. As a matter of fact they didn’t even need to spend million of dollars on the genetic markers of susceptibility. All they really needed to do was control the common source. And if we step back and think of atherosclerosis as a common source epidemic, what we as a society need to do is control the common source. Now that’s a complex issue, society, political, personal and it gets to the difference between primordial prevention - not even letting someone get into that atherosclerotic cascade. So that’s the approach to our children and to the youngsters in our society.

This is primary prevention of heart attack and stroke. So we need to focus on the common source.
What’s the common source? The common source is deposition of cholesterol in saturated fats. So I’m going to give you your five second review of cholesterol metabolism. Here is your endogenous cholesterol metabolism, sorry, and this is your exogenous cholesterol metabolism. Now – there will not be a quiz on that. But I show it to you to remind you that what drives atheroma formation, the process that we’re talking about, is the abnormal concentration of lipoprotein. Certainly low density lipoprotein is one of them. But intermediate density lipoprotein, a relatively transitory form of lipoprotein and our ability to carry cholesterol around is atherogenic. VLDL, very low density lipoprotein, the product of the liver that helps us package cholesterol and triglycerides, remnants are atherogenic. So when in excess not just LDL, even chylomicron remnants in excess from the exogenous arm of lipid metabolism can contribute to atheroma. So why do we think that just measuring LDL cholesterol is going to identify everyone who’s at risk for atherosclerosis. So now you’re thinking about your patients who had LDL cholesterol of 80 or 90 and still had a coronary event.

So remember that a lipoprotein is, this is low density lipoprotein, simply a sphere, right, with all of its phospholipid shell that is a carrier of the cholesterol and triglycerides because neither of those are soluble in blood, we need lipoproteins to transport our cholesterol and our triglycerides to where it needs to go. The problem is – is that this kind of incredibly complex slide tells a story of what’s happening to lipoprotein in a segment of our population that is taking up more and more of our waiting rooms and that are those with insulin resistance and prediabetes as well as diabetes. I’ll just walk you through this because in talking about lipoproteins and the fact that each lipoprotein is
labeled by an Apo lipoprotein B, each lipoprotein that contributes to plaque, we can see that even though we are not necessarily measuring the cholesterol concentration of each one of these lipoproteins. If I measured the lipoprotein, Apo lipoprotein B, Apo B100 in endogenous metabolism, Apo B48 in exogenous metabolism, again, a really nice count of how many particles are circulating. Kind of like the bicycle flag on the bicycle when the kid is riding down the street. You need a quick survey of how many bikes are there. Well, remember it is the number of particles that drive that cholesterol into the wall of the blood vessel and what we know is that in this individual with insulin resistance and mobilization of free fatty acids, we now have outpouring of triglycerides, the VLDL containing Apo lipoprotein B. And in a triglyceride rich milieu, not the triglyceride of a 1000 or 2000 perhaps but even that patient walks in with a triglyceride of 500 or maybe even just 250, his LDL cholesterol may still be within your treatment goal, why are they at risk? Because that triglyceride is being exchanged, it’s being handed off by way of cholesterylster transfer protein to HDL. So now that triglyceride rich HDL undergoes the action of hepatic lipase, it becomes dissociated. The Apo lipoprotein A1 that’s the marker of HDL becomes excreted. That’s the low HDL cholesterol phenomenon in our insulin resistant patients. It’s what makes HDL, let alone fill it with cholesterol because of this dissociation that occurs, the effects of hepatic lipase.

Same thing with LDL. LDL that’s triglyceride rich becomes very small and very dense. So the small dense particles that we talked about can be very atherogenic. Here’s a nice example of the Quebec Cardiovascular Study data, it takes, you know, a nice cartoon of a blood vessel and divides it into four quadrants. All of the individuals in this observational trial on the left side of this line had
LDL cholesterol levels greater than 130 mg per deciliter. The individuals on the right had LDL cholesterol less than 130 mg per deciliter. So what you’ll notice is the individuals in this quadrant who had the highest odds ration for ischemic heart disease regardless of the fact that they had similar LDL choles terols as these individuals who had about a twofold increase, these folks carried small dense particles. Each one of those particles labeled by an Apo B, Apo lipoprotein B. So that’s why looking at particle size is, actually particle number even more than particle size is a very good way for us to perhaps go beyond just LDL cholesterol in identifying those individuals at risk.

Now we all understand the story of statins. And we all understand that as we treat individuals who have elevated LDL cholesterol levels down to that – I’ll call it physiologic range as you’re born with an LDL cholesterol around 40. Those populations that I talked about without cath labs, their LDL is around 70 and as we manipulate and this is just a summary of the statin trials that are out there. As we get these patients LDL cho lesterols down to the physiologic range we see a decrease in this event rate for cardiovascular disease. The game is not to get to zero although many people accuse me of trying to do that in my patients. The issue is to get down into physiologic range. But the challenge is are we using the right marker when we just measure LDL cholesterol to identify those individuals.

Now this is an interesting kind of slide, this is a slide of patients. Each dot on this slide is an individual and let’s just take the individuals here who have an LDL cholesterol of 90 mg per deciliter, perhaps someone we would be very satisfied that their LDL was 90 if they had vascular disease. But we go up to this line and I’m not going to be exactly on probably, but here’s an
individual with an LDL of 90 who’s Apo Lipoprotein B is about 60. And all up that line, here is an individual all the way up here who’s LDL is the same but whose Apo Lipoprotein B is significantly higher. They’re carrying much more particles around and potentially are atherogenic.

So this is interesting data from the Framingham study. This is years of followup and probability of event free survival. So we’re being optimistic in this slide right. So these individuals had the best survival and these were individuals who had low LDL cholesterol levels, over 1000 of them and low LDL particles, low Apo B. But overlapped with that best outcome are those folks who had high LDL cholesterol levels but still had low particle numbers. In other words, they carried that cholesterol around in protective particles. Their Apo B values were low. Who was at highest risk? Well, certainly those who had high LDL cholesterol and high numbers of particles but the same line essentially, the overlapping lines of those individuals who had low LDL cholesterol almost 300 of them, had high LDL particle size.

So we see how narrow as the third marker, Apo Lipoprotein B helps us understand a very nice differentiation between those who may be at risk despite what we think are perhaps safe if you will cholesterol levels. Now this is data that was given to me by Alan Snyderman at Magill who is one of the significant proponents and supporters of Apo Lipoprotein B testing and a mentor of mine. And you may be familiar with the Jupiter trial. The Jupiter trial was a trial that looked at primary prevention based on C reactive protein and intervention based on C reactive protein observed and observed interestingly – that you could get a graph that was similar to that graph that I showed you.
Individuals who had persistently high C reactive proteins had this residual risk despite their LDL cholesterol so it was an argument that C reactive protein again was something we needed to follow. It was touted as a primary prevention population. So population that all of us in the audience would say, well these, this is another reason why I ought to be screening C reactive protein. But in fact if you look at the baseline parameters from a lipid standpoint in this group, here is what they’re triglycerides, their cholesterol, their LDL seems, seemingly a low risk group.

But here is their Apo Lipoprotein B concentration. And you can see why their LDL cholesterol level for the Framingham population was in a low percentile range, their Apo Lipoprotein B was actually well above the 50th percentile. So this was not such a low risk population after all. So I’m not so sure that the interventions in that Jupiter trial and the success of those interventions were due to C reactive protein at all. I think there are a lot of folks that are skeptical about that.

So, your treatment goal, particularly for patients who have this cardiometabolic risk, that insulin resistance, those kind of things, really here they are, right. So highest risk patients that have known cardiovascular disease or diabetes, plus one or more additional risk factors, there’s your LDL cholesterol less than 70, there’s your non-HDL less than 100. But it would be very good if you’re going to use this as a marker to make sure that their Apo Lipoprotein B remains well below 80 milligrams per deciliter and there’s some who will argue that perhaps we should be even more aggressive.
Well let me end in the last couple of minutes here with some common sense. The fourth marker, and that is that you know the best test for prediction of the risk of athero is probably the demonstration of athero. Shaeffer said that and I think it’s absolutely true. And another gentleman who’s near and dear to my heart, Harvey Hecht who many of you know, people who die of an MI are just as dead whether they have no risk factor or every identifiable risk factor. So you know tongue and cheek when we look at these markers.

But nonetheless let’s go back to the demonstration of atherosclerosis. In other words, where are we in 2010, 2011, we’ve all grown up on enumerating risk factors. Right? We all understand the association in the population of all these risk factors. And I’ve talked about a couple of these up and coming risk factors. And, again, as I mentioned probably more will be coming down the pike as another inflammatory marker is investigated and show some association with a population for vascular disease.

But understanding if we are not talking about primordial prevention at this point, but prevention of clinical events it’s important to think and remember that those who are highest risk for clinical events of athero are those who have the largest athero burden. And so tests that look for in asymptomatic individuals underlying athero burdens can be very helpful to you and I’ll show you that data.

So here’s the carotid plaque intima-medial thickness at the atrophic for another session, here is
coronary calcium which is as you know we’ve been involved in for many years and many of you I know in the audience, use that for your patients. So there are markers of individuals who are at atherosclerotic risk.

Let’s talk about three that can be very clinically useful in your office. First, something that’s not very fancy but can be very effective and that’s simply the ankle brachial index. Checking the blood pressure in the arm comparing that to the blood pressure in the ankle usually with a Doppler device can be a very, very helpful test and I’ll show you the data on that. Here’s carotid ultrasonography looking for yes, intimal-media thickness when its ready for prime time, it’s getting there, the marker of individuals at risk. It’s questionable frankly, right now and arguable, whether it’s good for following progression or regression of vascular disease and then coronary calcification. So I’ll show you the data.

Here’s the data on ankle brachial index. If you look at just one study of many of the artery studies, if you identify individuals whose ankle brachial index, so normally your ankle blood pressure is higher than your arm blood pressure. But if your ankle brachial index becomes abnormal and in these individuals extremely abnormal, less than .7 those individuals are at very high risk compared to those with normal ankle brachial index for coronary heart disease outcomes not just peripheral vascular disease problems.

Here’s vascular ultrasound, describing and detecting very early the fatty streaks can be very
effective and then this is just some of the data showing increased relative risk of cardiovascular events associated with this carotid intimal-medial thickness. So heart attack not just stroke.

And finally then to just show you the data that many of you I know are familiar with and that is again, this ____ prognostic indicator of having your coronary artery as bright as your vertebra because there’s calcium in it. And this is indicative of disease. This is a neat slide that shows again, correlation of LDL cholesterol and calcium percentile. These are folks who had calcium scans, each circle is a patient and each patient regardless of their LDL, this is how much calcium they had based on percentile ranking. Absolutely no association.

So determining that blood cholesterol test at the time of an electron BCT scanner or other CT scans to develop calcium, same for HDL, may not be helpful for you to predict their underlying vascular burden.

I’ll just show you some of the data now that we had in thousands really of asymptomatic individuals. The fact is that if you look at the score, the calcium score, this line here compared to your ATP3 score, your Framingham risk score, a better predictor in asymptomatic individuals in those scores alone. So adding incremental benefit particularly in individuals in intermediate risk range based on your scoring algorithms doing the Framingham risk score. If you identify individuals who have the plaque as evidenced by calcium as a marker of it, you identify an individual who is at high risk. Here’s in women, over 2025 hundred asymptomatic women after
almost four years of followup, 90 percent of those women had low Framingham risk scores. We understand that women are continuously underestimated for their risk, their Framingham risk. And those individuals who had any calcification in their coronary artery, they were the ones who were having cardiovascular events and if you had a significantly high calcium score greater than 300 you were at highest risk for those clinical cardiovascular events.

And the finally, in the NIH trial, it didn’t matter, gender, ethnicity rates, this is a marker of atherosclerosis and the higher one’s coronary calcium score, this one is up to 5 years of followup, the higher the cardiovascular event rate. So Dr. Schaeffer was right, the best way to identify someone who’s at risk for atherosclerosis is to look for the atherosclerosis.

This is a scheme, the second to last slide, that we might consider. I show you a lot of EBCT data, electron BCT data, we can gather this information now with traditional CT now that scanning algorithms are allowing for lower radiation. And that is that you know if you have someone who comes from a part of the country that doesn’t get atherosclerosis, their LDL is low, their blood pressure is low. They don’t have any insulin resistance, you probably don’t need to screen them. Unfortunately that’s only about a quarter of our population. The rest of the individuals may very well be served by looking for atherosclerotic vascular disease if we can do this in a way that’s cost effective and very thoughtful in what we do with the results.

The problem is that we probably will not have a randomized controlled clinical trial to help us in
that regard. Because if I did a coronary calcium scan on you and your scan was 1000 and I said, you know, you’ve also got randomized to standard of care and placebo, you probably wouldn’t participate in the trial, it’s a problem that we have – the other problem that we have is how we’re approaching vascular disease now. Even our pharmacologic interventions for prevention pale in comparison to the secondary approach that we take for cardiovascular disease. We need to change it.

So, hopefully, I’ll summarize this way. Hopefully, what you’ll take away from this, inflammatory markers are certainly determinant to vascular disease risk in a population but not necessarily determinants of events in an individual. The debate continues over inflammatory markers, again, determinants of athero, yes, determinants of clinical events in an individual, debatable. Accurate measurement of the common source of the epidemic in atherosclerosis is important and getting that Apo B data and just hopefully broaden your horizon a little bit on there are things beyond LDL and non-HDL cholesterol to help us understand those who may be at risk. I do think that measuring atherosclerosis is the best way to predict atherosclerosis.