CME / CE Information

CME/CE Released: 06/15/2009; Valid for credit through 06/15/2010

This activity has expired.

The accredited provider can no longer issue certificates for this activity. Medscape cannot attest to the timeliness of expired CME activities.

Target Audience

This educational activity is designed for physicians and nurses who treat patients with hypertension and arthritis.

Goal

The prevalence of atherosclerotic coronary artery disease and related adverse outcomes is increased in chronic inflammatory diseases affecting connective tissues, particularly in patients with arthritis. Many such patients require NSAIDs but these agents may increase blood pressure and have also been associated with arrhythmias, congestive heart failure, myocardial infarction, and stroke. Endothelial dysfunction, characterized by impaired vascular nitric oxide (NO) bioavailability is a key component of cardiovascular disease. This program will review and discuss the current research and therapeutic strategies to increase or preserve NO availability, which may have an important role in the development of new drugs for the treatment of arthritis patients with hypertension.

Learning Objectives

Upon completion of this activity, participants should be able to:

1. Evaluate the cardiovascular effects of non-steroidal anti-inflammatory drugs (NSAIDs) and the subsequent consequences of NSAID treatment for patients with cardiovascular disease
2. Examine the role of nitric oxide in cardiovascular biology and vascular function and the effects of endothelial dysfunction on cardiac function
3. Summarize the mechanism of action of nitric oxide donating agents at the vascular level and the benefits of nitric oxide donating agents in hypertensive patients
4. Discuss the pre-clinical and clinical studies on the effects of CINODs on blood pressure

Credits Available

Physicians - maximum of 1.50 *AMA PRA Category 1 Credit(s)*™

Nurses - 1.50 *ANCC Contact Hour(s)*

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

Physicians should only claim credit commensurate with the extent of their participation in the activity.

Accreditation Statements

For Physicians

MEDICAL EDUCATION RESOURCES, INC.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Medical Education Resources (MER) and Innovations Consulting Group, LLC (ICG). MER is accredited by the ACCME to provide continuing medical education for physicians.

Medical Education Resources designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Contact This Provider

For Nurses

Medical Education Resources is an approved provider of continuing nursing education by the Colorado Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

This CE activity provides 1.5 contact hours. Provider approval expires July 31, 2010.

Provider approved by the California Board of Registered Nursing, Provider #CEP 12299, for 1.5 contact hours.

Contact This Provider

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This activity is supported by an educational grant from

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Speakers Bureau: Boehringer Ingelheim, Forest.
Grants/Research Support: NIH, Novartis.

New Options for Cardiovascular Safety in Patients With Osteoarthritis

Carl J. Pepine, MD, MACC, Chair; Andrew Whelton, MD, FACP; William B. White, MD

CME/CE Released: 06/15/2009; Valid for credit through 06/15/2010

This CME activity is based on the slides and lectures presented by the faculty at the symposium "New Options for Cardiovascular Safety in Patients with Osteoarthritis" on March 31, 2009, at the Peabody Hotel, Orlando, Florida.

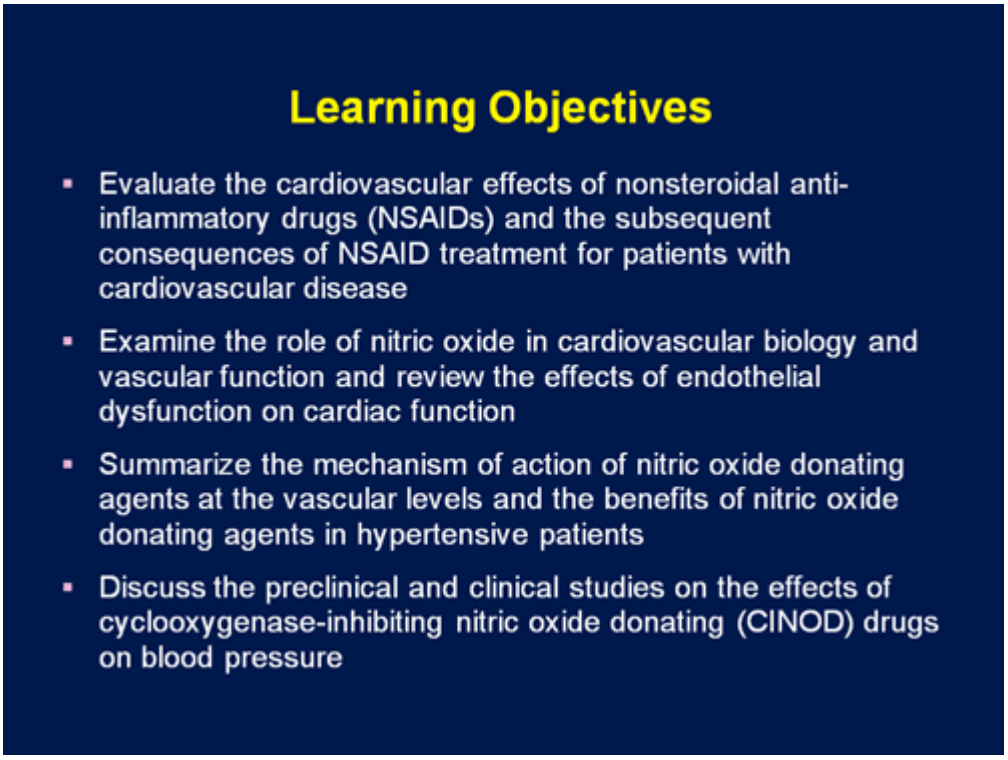
New Options for Cardiovascular Safety in Patients With Osteoarthritis

Slide 1.

Carl Pepine, MD, MACC: The topic is centered around a new class of compounds, which are compounds that release nitric oxide (NO) while blocking cyclooxygenase. We have put these compounds into this symposium, which we have entitled New Options for Cardiovascular Safety in Patients With Osteoarthritis. We have assembled the faculty this morning to present some of the various aspects of this problem of osteoarthritis and its management amongst patients with cardiovascular disease. I hope that you will find this program enlightening

Slide 2.

The agenda for this symposium is summarized here. The first speaker in this program on this topic is Dr. Andrew Whelton. Andrew will deal with the topic of Clinical Challenges With Hypertension Patients who have Arthritis and Pain. I am sure if you are practicing that we are seeing larger and larger and larger numbers of patients who have osteoarthritis as our population ages as well as our population becomes more obese. In addition the epidemic of increased blood pressure continues to result in an expanding prevalence of hypertension.

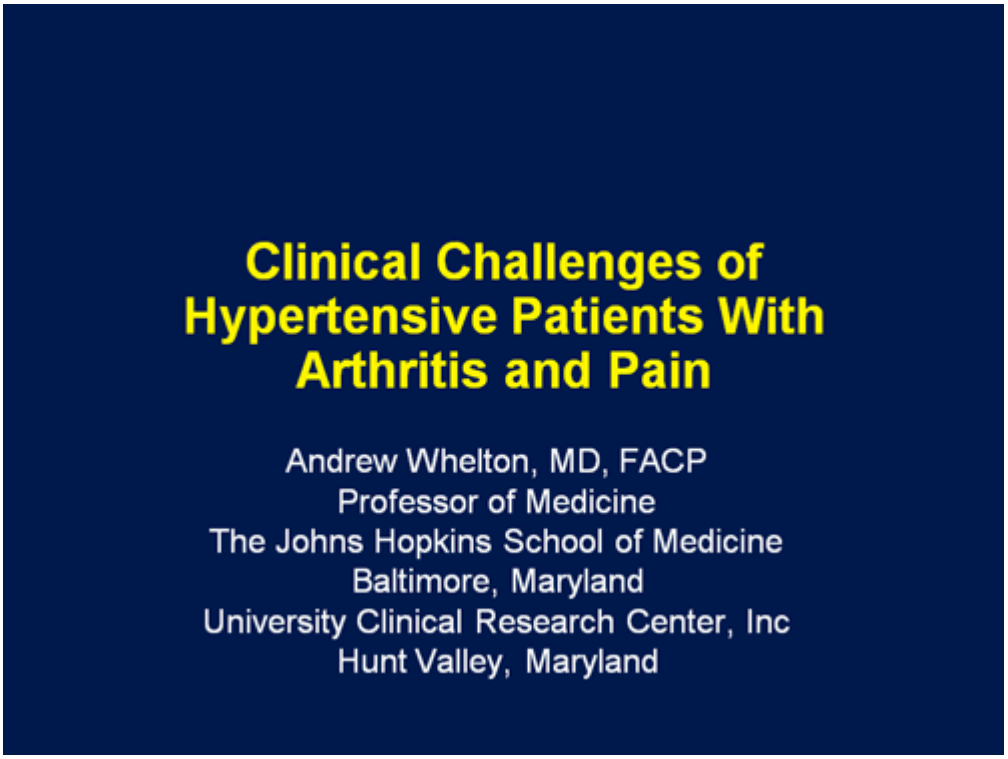


Slide 3.

The overall learning objectives for this program are summarized here. We intend to evaluate the cardiovascular effects of non-steroidal anti-inflammatory drugs, so-called NSAIDs, and the subsequent consequences of NSAID treatment for patients with cardiovascular disease. Also the attendees here will examine the role of NO in cardiovascular biology and vascular function and also we will review the effects of endothelial function on cardiac function in general. We will summarize the mechanism of action of NO donating agents at the vascular levels and the benefits of nitric oxide donating agents in patients with hypertension. Finally we will discuss the pre-clinical and clinical studies on the effects of cyclooxygenase-inhibiting nitric oxide donating drugs on blood pressure.

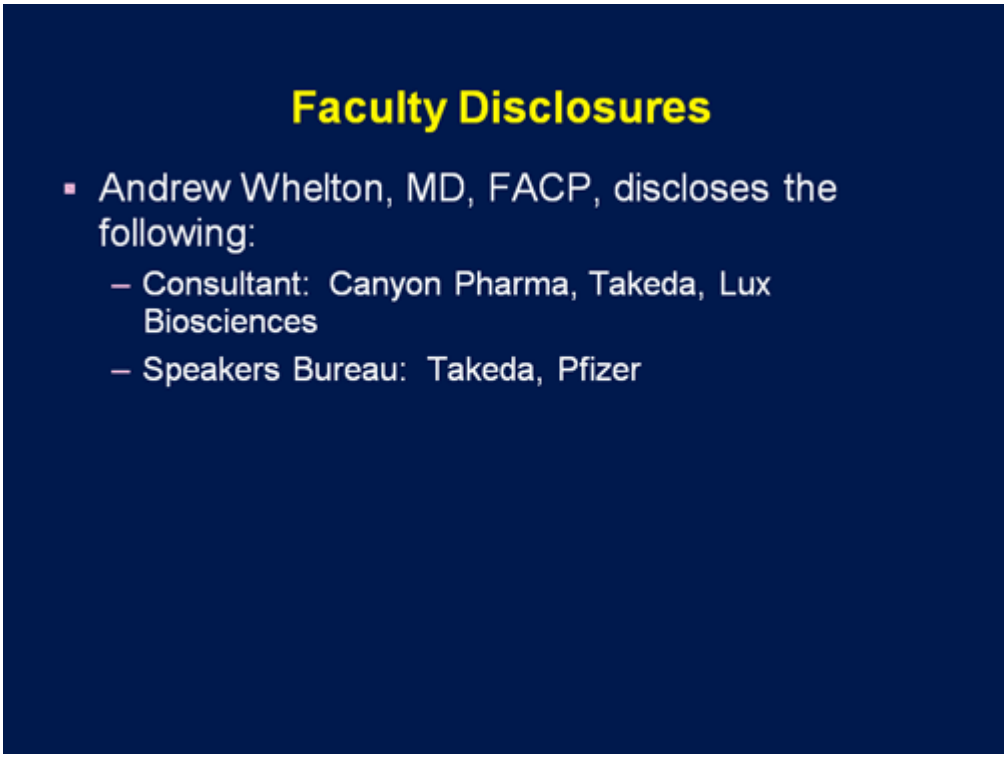
I want to introduce you to our first speaker, Dr. Andrew Whelton. He is professor of medicine at Johns Hopkins School of Medicine in Baltimore. His topic is Clinical Challenges of Hypertensive Patients With Arthritis and Pain. Andrew.

Clinical Challenges of Hypertensive Patients With Arthritis and Pain



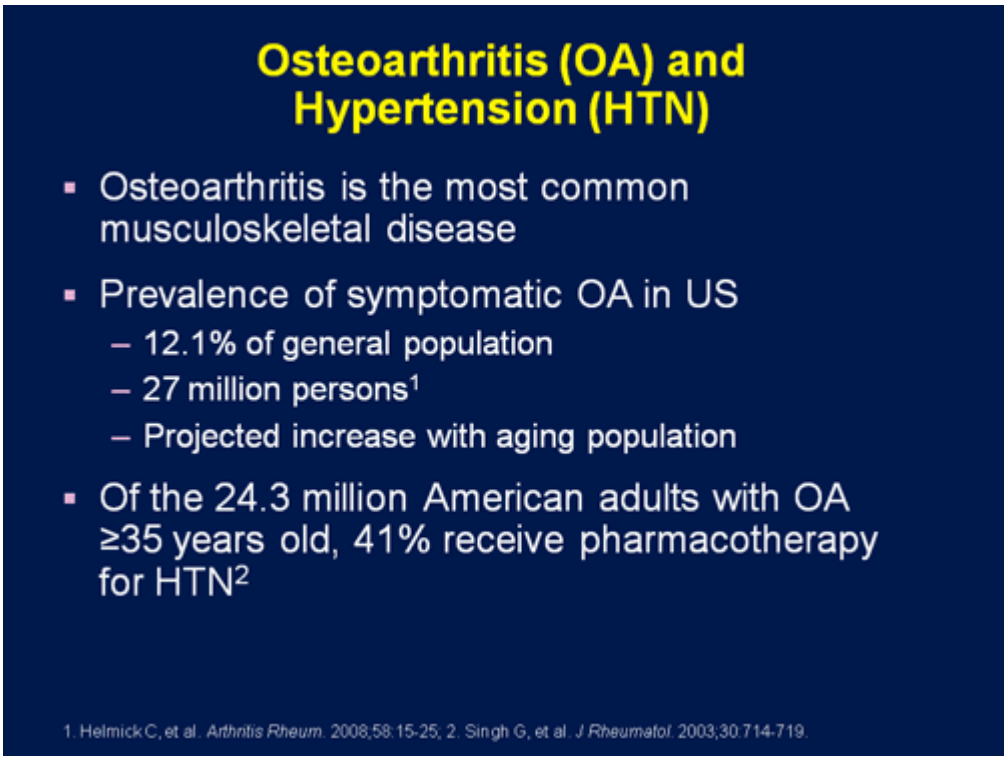
Slide 4.

Andrew Whelton, MD, FACP: Well, Dr. Pepine, Carl thank you very much, number one, for including me in your symposium and for the very kind words of introduction. As you have heard for a start I am going to do a general overview of some of the issues inherent and the cardiovascular issues that emerge during the use of NSAIDs.



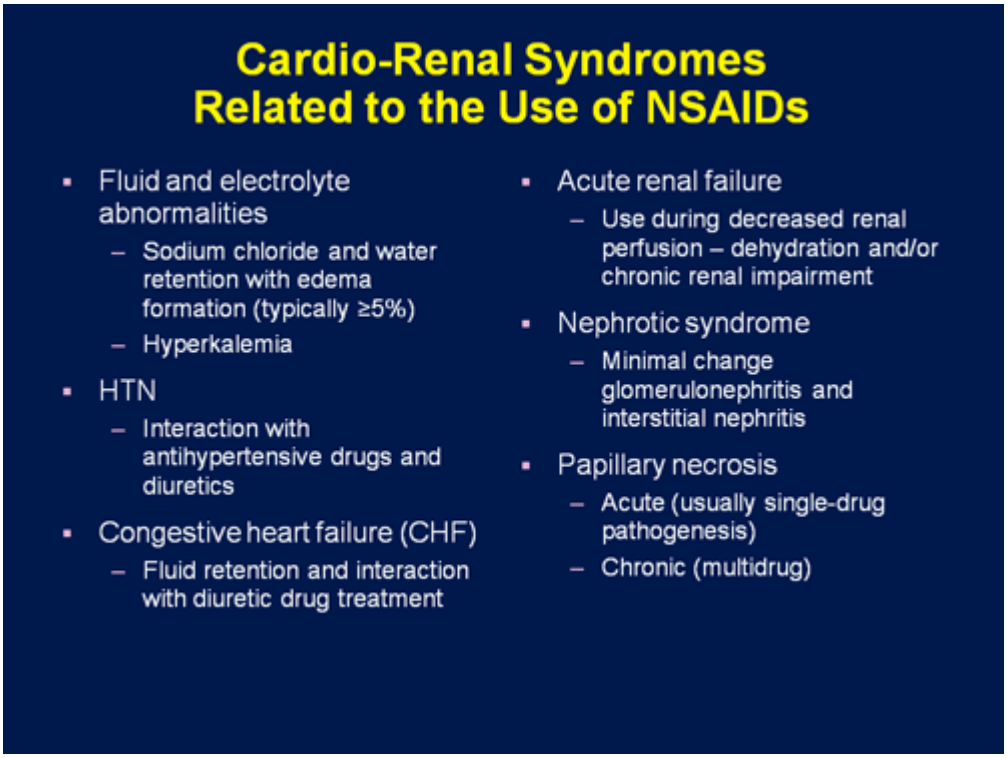
Slide 5.

I have put up the disclosure slide and we will move on.



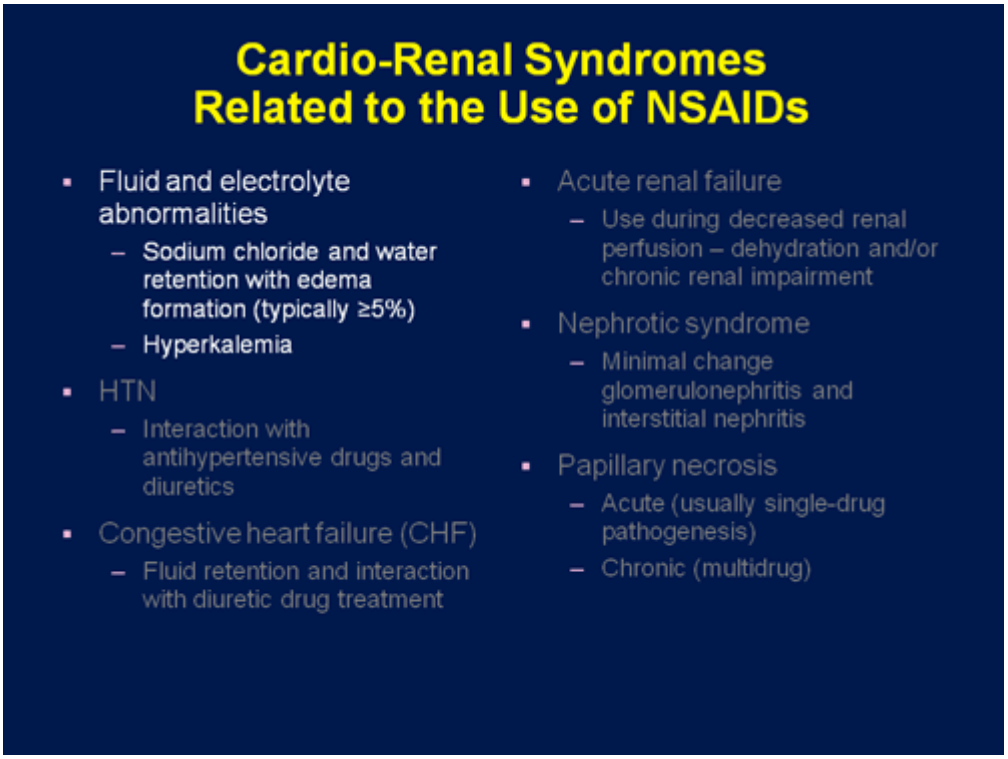
Slide 6.

I start by echoing what Dr. Pepine has said and that is that from the point of view of arthritis, osteoarthritis as you know so well, is the most common form of musculoskeletal disease. And with the aging population that we keep on talking about, clearly we know that the increase in prevalence is really quite remarkable. If you then turn your attention to those who are currently receiving pharmacotherapy at a cut point of >35 years, it is a whopping 41%. This puts it in the realm of approaching 24 million people who are receiving pharmacotherapy for osteoarthritis. If you scale forward to a cut point of age 65, 60% of all such individuals will have the comorbid events of arthritis and hypertension. That then is the large pool in the general population that we have to be concerned with, with regard to these cardiovascular NSAID issues.



Slide 7.

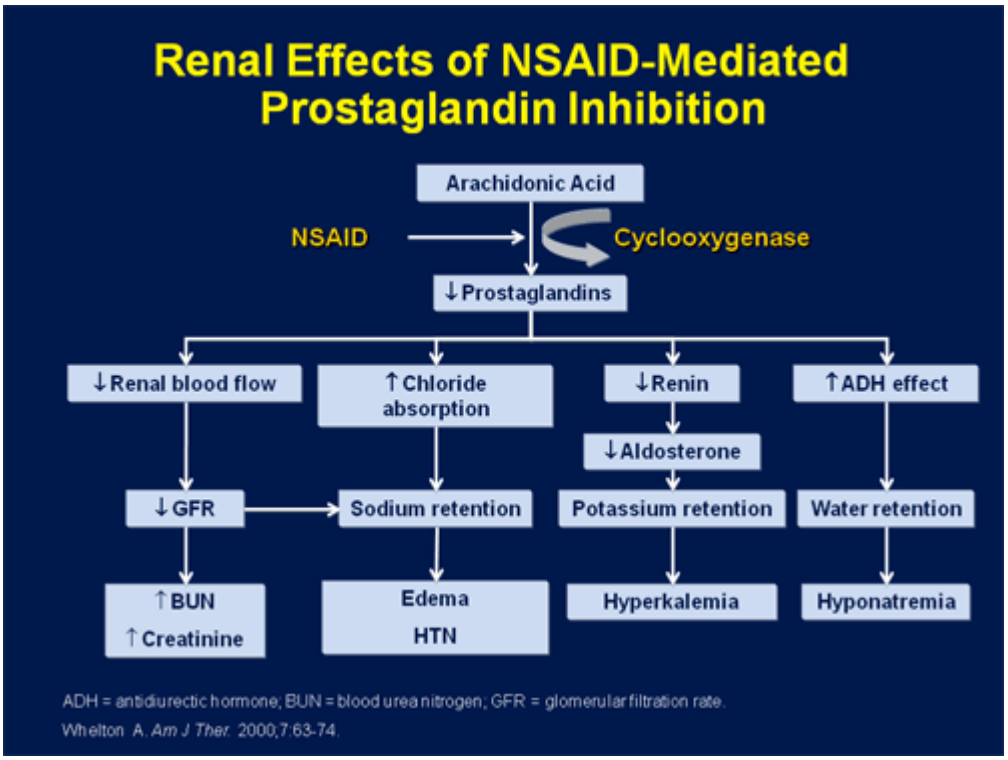
Several years ago, my goodness, almost decades ago, it became apparent that with respect to side effects clinically of NSAIDs you really could begin to package these, cardiorenal side effects in particular, into relatively distinct syndromes and going from the most common one, which would be disorders of salt and water, particularly salt and water retention and the development of peripheral edema, that across the board in general day-to-day clinical operations about 5% of all people who take an NSAID will manifest edema. Then you can go through the cascade to the least common and that would be the development of papillary necrosis. For our purposes, I am going to take the first 3 syndromes on the list here, the salt and water issues and the mechanisms by which edema are formed, secondly the whole issues of disruption of blood pressure control in particular turning the intracurrent use of anti-hypertensives and NSAIDs, and then a word about the development of congestive heart failure in the population that is taking both NSAIDs and diuretics.



Slide 8.

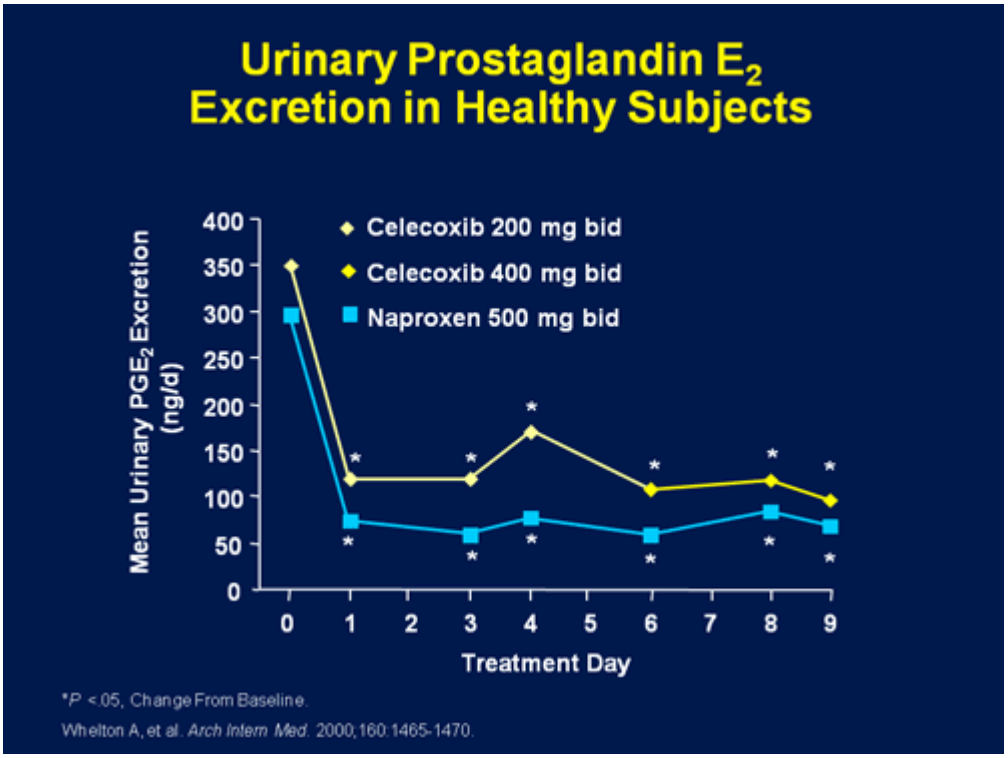
Taking the salt and water part of the story let me first identify, you will recall, that it was the seminal description by our

colleague now deceased, Sir John Vane, 1971. You remember in *Nature*, he published that article entitled: The Mechanism of Action of Aspirin and Aspirin-like Drugs.



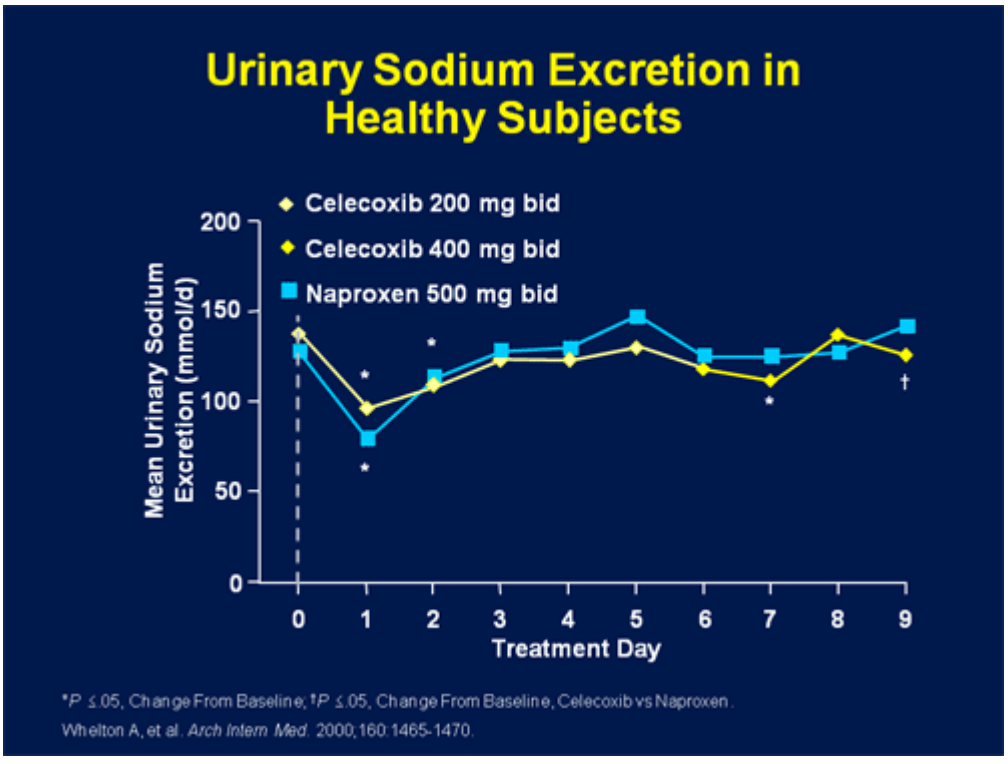
Slide 9.

It was really a revelation because what John pointed out to us was that the biologic target site of all NSAIDs, aspirin, and everything else that was at that time conceived as a bit of a hodge podge is the enzyme system cyclooxygenase. All of the sudden, it made sense as to why we have cardiorenal side effects, because by inhibiting prostaglandin production then there are a series of cascades by which you and I doing this in our patients could induce cardiovascular problems ranging from increases in BUN and creatinine, ergo reduction of glomerular filtration rate, the edema issue, which is central to our discussion at the start this morning, problems with electrolytes, etc. So the gist of it is, it now became mechanistically apparent as to why some of these things would develop. Along the way when the COX-2 drugs started into major development at the very end of the 1980s to the early 1990's we thought well now from the work of Phil Needleman and colleagues, who had told, as you will recall, that cyclooxygenase is composed of two isoenzymes and COX-2 is purely pain and inflammation and needs to be induced. Lo and behold it seemed very reasonable to conceive that the new development of NSAIDs, the COX-2s, would be devoid of impact on the cardiorenal axis, after all our basic scientist colleagues kept on saying COX-2 is pain and inflammation, COX-2 is pain and inflammation.



Slide 10.

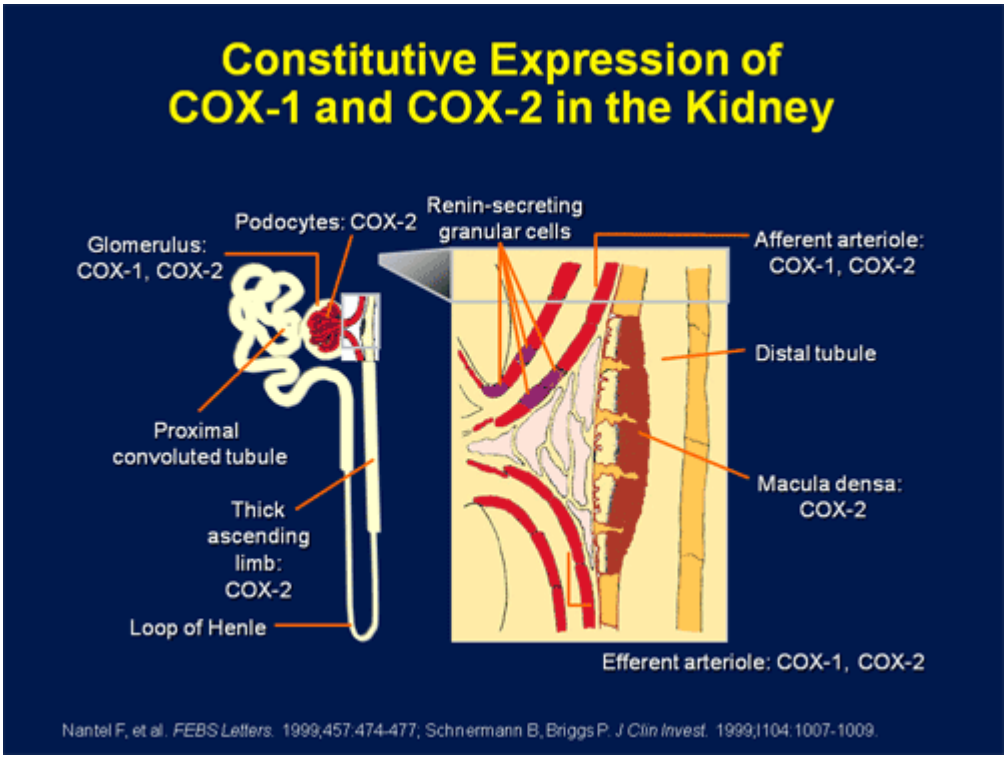
Let me share with you that when we did the first studies in humans and here simply taking celecoxib as a model of the COX-2 development in the NSAIDs, rofecoxib being basically the same, we frankly were astonished to find that in otherwise healthy individuals when we started tracking the issue of renal prostaglandin production, that indeed with these new drugs in a healthy kidney we saw almost the same degree of suppression of renal prostaglandin production as we saw with a comparable, we might say traditional NSAID. In this instance, the NSAID naproxen. Why I will tell you, being involved in doing these studies, when I first saw those results I said it has got to be a lab error. We were so convinced by the biology, so we went back and did it again and found that no this is absolutely reproducible. Then the question was what is the antecedent consequence of this.



Slide 11.

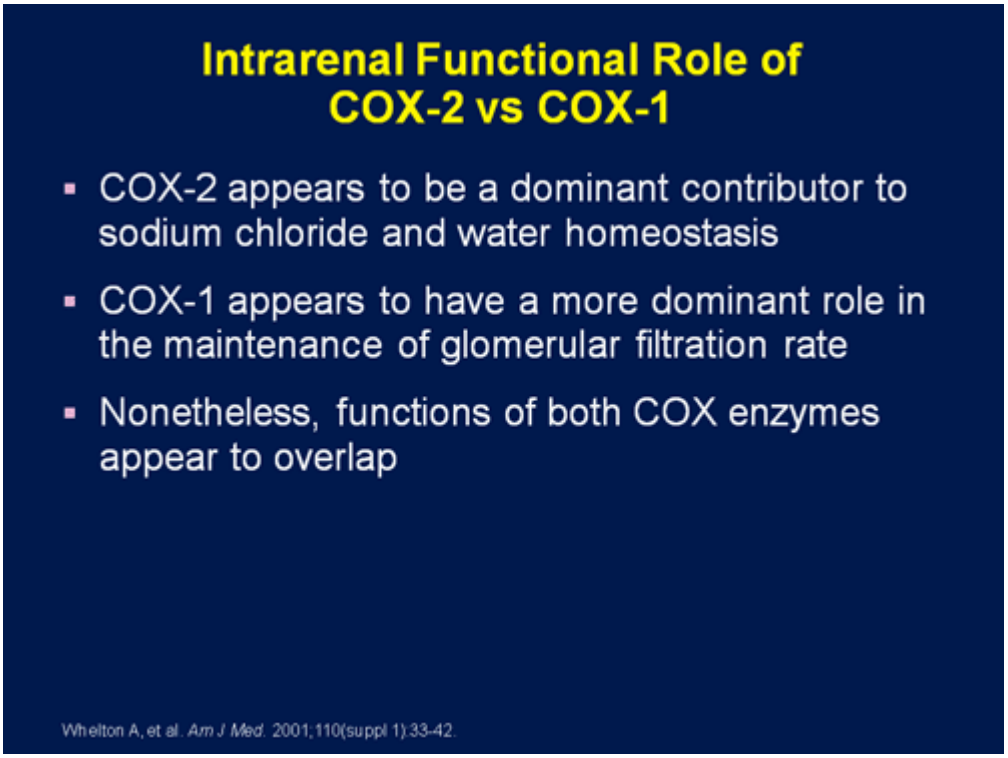
It is the following. It became apparent that by suppressing the COX-2 enzyme in the kidney either with, shall we say the selective suppressors or the non-selective, that what happens across the board in all of us, every single one of us here

this morning and that is that we all undergo a modest retention of salt and water. It is transient, the first 24 or 48 hours, it is about a kilo or a kilo and a half, so it is really not enough to detect in yourself development of peripheral edema. Then the kidney begins to compensate. I just showed you our very first studies on this and that by day 3 or 4 we begin to see in essence a dumping of the retained salt and water in the urine. We subsequently characterized this more carefully, but this was the first finding. It also then became apparent that if you and I were dealing with an individual with pre-existing renal problems or perhaps pre-existing cardiac or hormonal problems, that predisposes one to edema that what we found is that the retention of salt and water took place, continued and that by the end of 1 week typically 80% of all people who were going to develop edema would have it manifest. So edema, if it is going to occur, is a quickly manifesting phenomenon, 80% by the end of 1 week. That really was a bit astonishing.



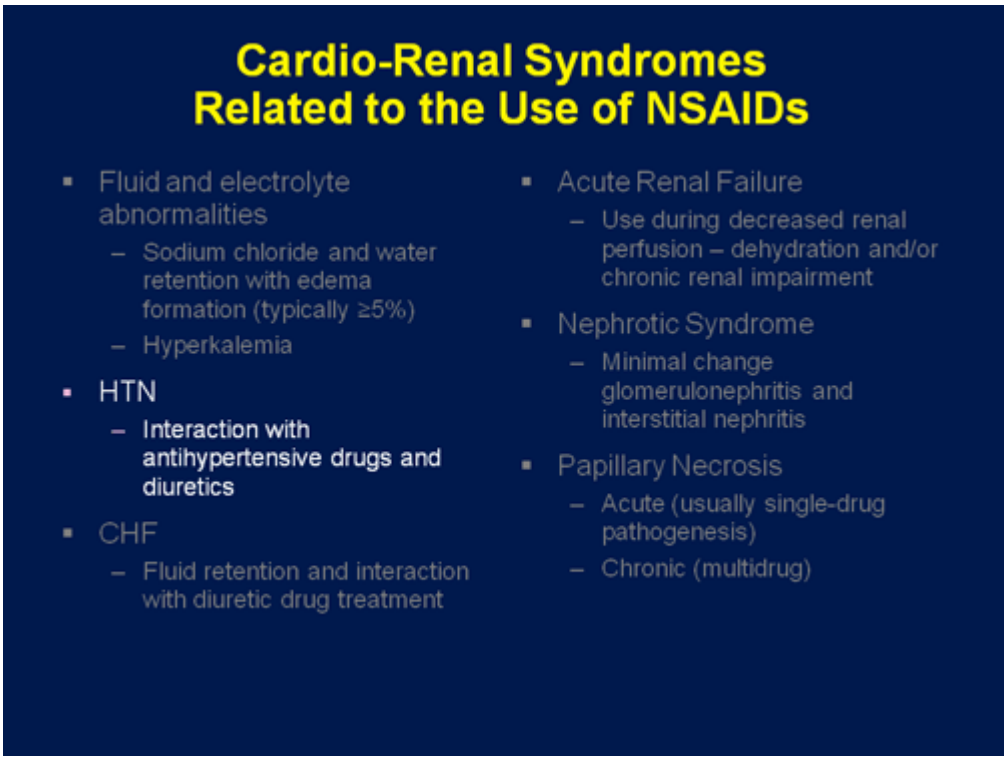
Slide 12.

Then I would just share that the next part in the step, of course, was the identification that, yes indeed, in the healthy kidney you and I express the COX-2 isoenzyme in the podocytes of the glomerulus. If you have forgotten the anatomy of the glomerulus, those would be the epithelial outside cells covering the capillary loops that make up the glomerular filtration apparatus. Indeed in the thick ascending limb of the loop of Henle, over here, COX-2 is also expressed.



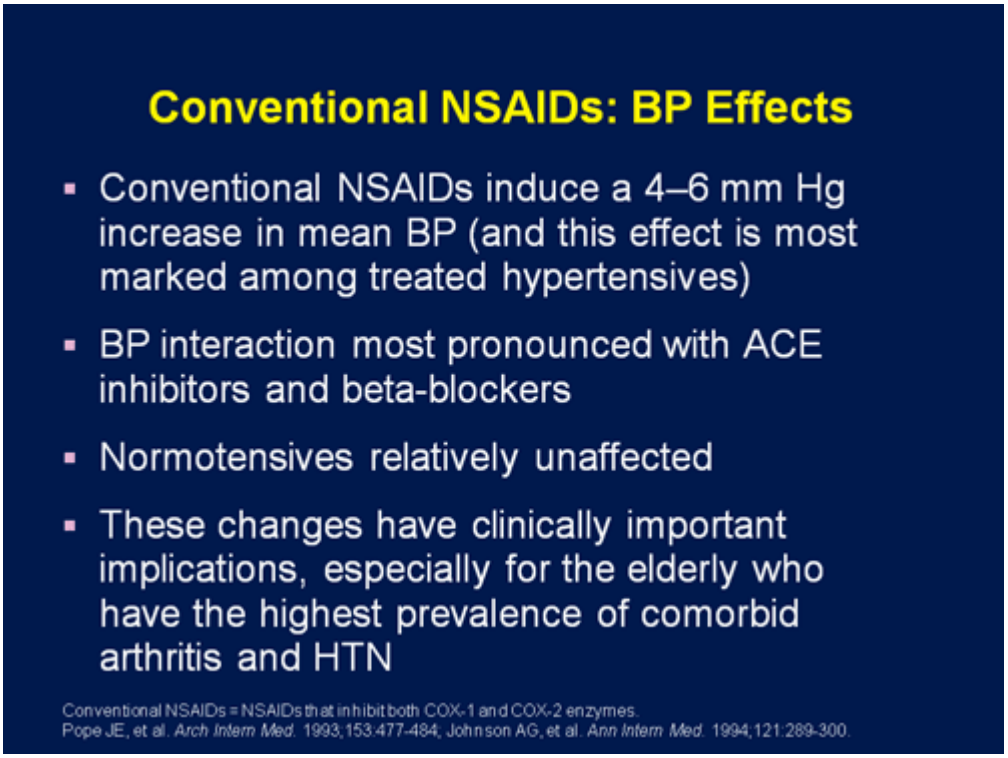
Slide 13.

The end of the story when it comes to these isoenzymes and NSAIDs is that it appears that COX-2 is dominantly related to salt and water homeostasis. You could almost conceive of COX-2 as a mild diuretic. If we inhibit it with an NSAID, obviously the consequence is going to be some degree of salt and water retention. On the other hand, on balance the COX-1 isoenzyme looks to have a greater impact on maintenance of glomerular filtration rate, but I would just say clearly the functions of both of the isoenzymes tend to overlap.



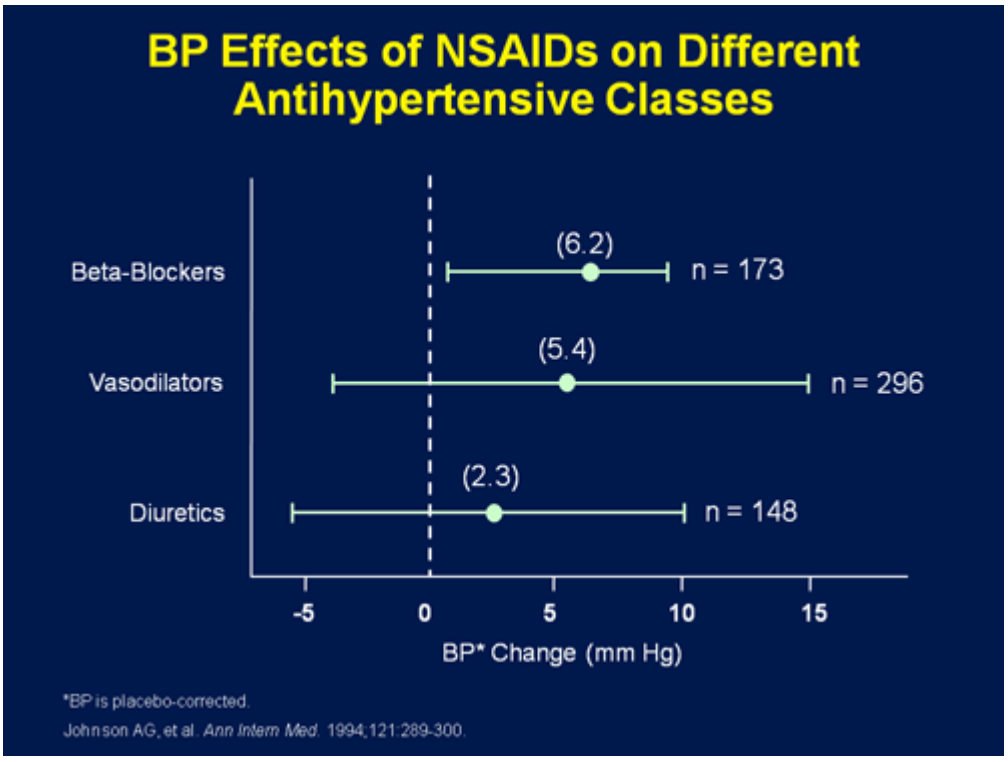
Slide 14.

Having identified some of that biology and the simple mechanism by which edema can form, lets then turn our attention to the next issue on the docket, so to speak. That is the issue of hypertension. I will tell you I was one, probably like some in the group here, who by the early to mid 1990s was kind of astonished to see that taking large meta-analyses, it became apparent that looking at such populations, heaven's above, NSAIDs do increase blood pressure.



Slide 15.

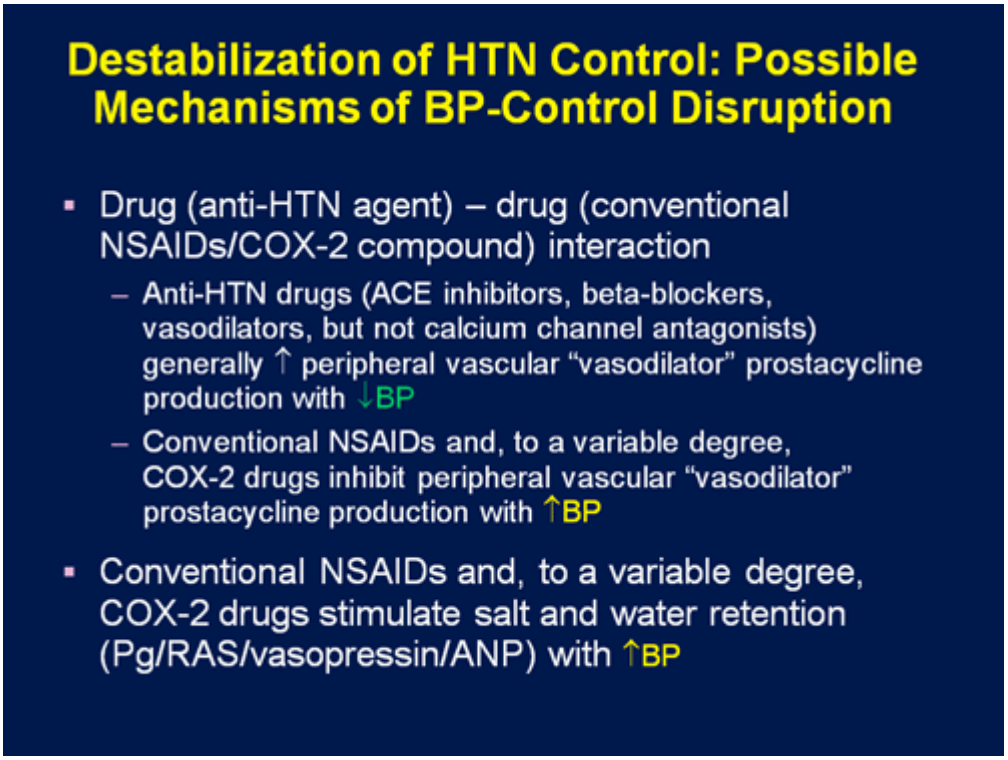
It emerged in these data that largely it was treated hypertensives that had the greatest increase in blood pressure. I would emphasis normotensives, yes it can occur in them, but certainly they are a lot less affected.



Slide 16.

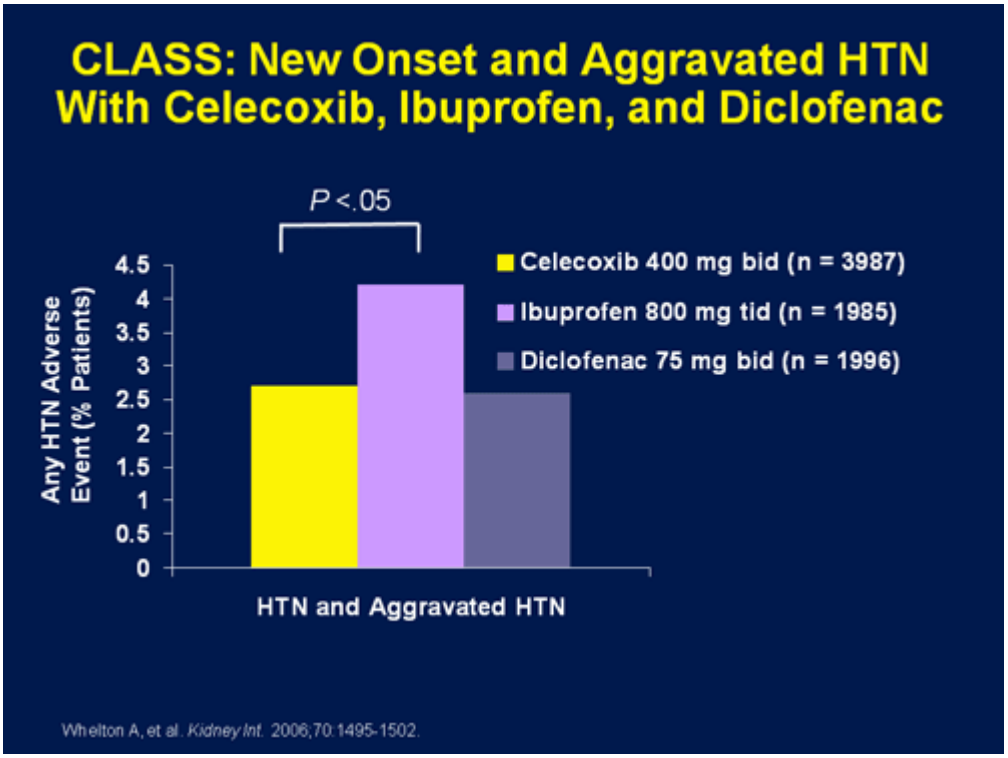
The other curious observation was that this impact seemed to be particularly pronounced with vasodilators such as ACE inhibitors, beta-blockers and not calcium channel antagonists. That was interesting and curious. Then, of course, you would say the clinical conclusion from all of these findings in the early '90s was that indeed this is important in terms of particularly the aging population and I am in it myself now, who have the comorbid events of hypertension and osteoarthritis. Then from these very early studies, just looking at the quantitative increase in blood pressure you say yes, this really would get your attention, 5 to 6 mm Hg with beta blockers and ACE inhibitors as I show you here, even thiazide diuretics edging up the blood pressure. So then the question was why does this occur? Is there any reasonable explanation for this issue of blood pressure destabilization in treated hypertensives? Well the answer is yes, there is a

reasonable clinical explanation.



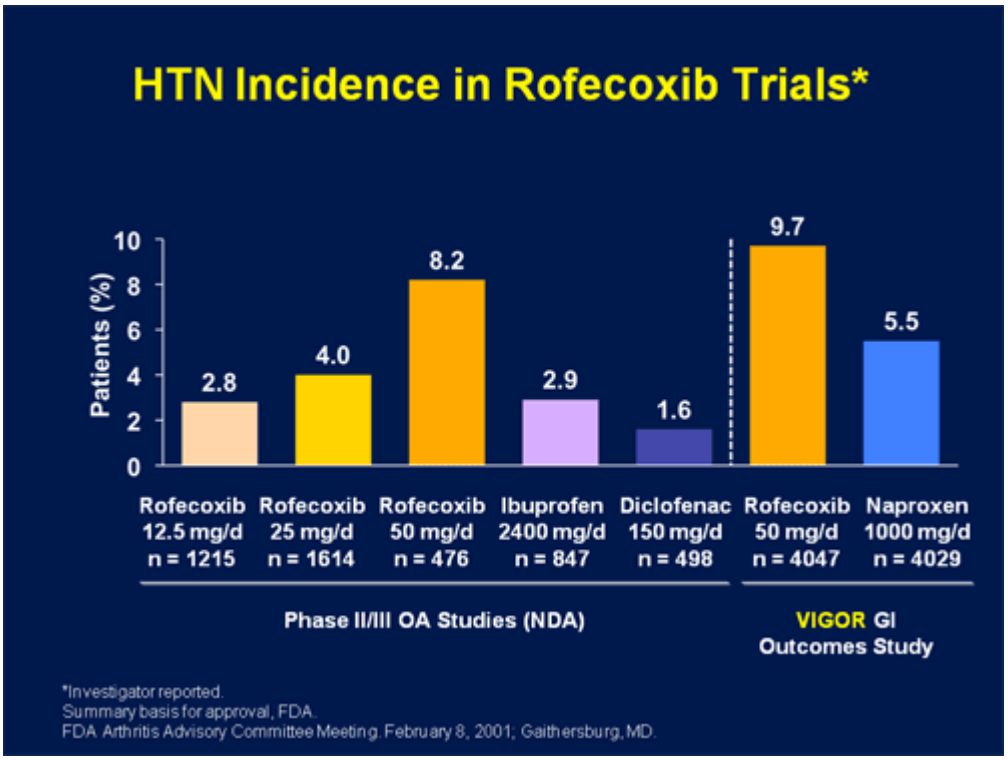
Slide 17.

First, I would say that as I have pointed out and as Dr. Pepine said in the introductory remarks, there is such a commonality between the use of NSAIDs and osteoarthritis. This drug-drug interaction, the interaction of an anti-hypertensive with an NSAID, be it the traditional NSAIDs or the COX-2s, this is one of the most common day-to-day clinical drug interactions. In a very brief summary of the mechanism, all of you will recall that part of the mechanism by which ACE inhibitors and beta blockers produce a reduction in blood pressure is by coming to the wall of blood vessels and stimulating a prostaglandin, and in this instance prostacyclin, which is, as you recall, a potent vasodilator and hence blood pressure falls. One of the medications, calcium channel blockers is not, of course, dependent on prostaglandin, an independent mechanism. Then the issue of concern about destabilization of blood pressure is that when you or I are treating a patient and we give them an NSAID to suppress prostaglandin in a bad hip or a bad knee, for example — and you recall that by suppressing prostaglandin you lose that as a transmitter of the sensation of pain. You also lose the continued prostaglandin effect in enhancing inflammation, so the patient will get clinical benefit at the hip or the knee, but if they are intercurrently being managed for hypertension with an ACE or a beta blocker then unfortunately, almost as a bystander, at the vascular smooth muscle level, the vasodilator effect of prostacyclin is inhibited and blood pressure tends to go up. Combine that then with the salt and water retention I mentioned earlier and we have a perfectly plausible explanation for this increase in blood pressure.



Slide 18.

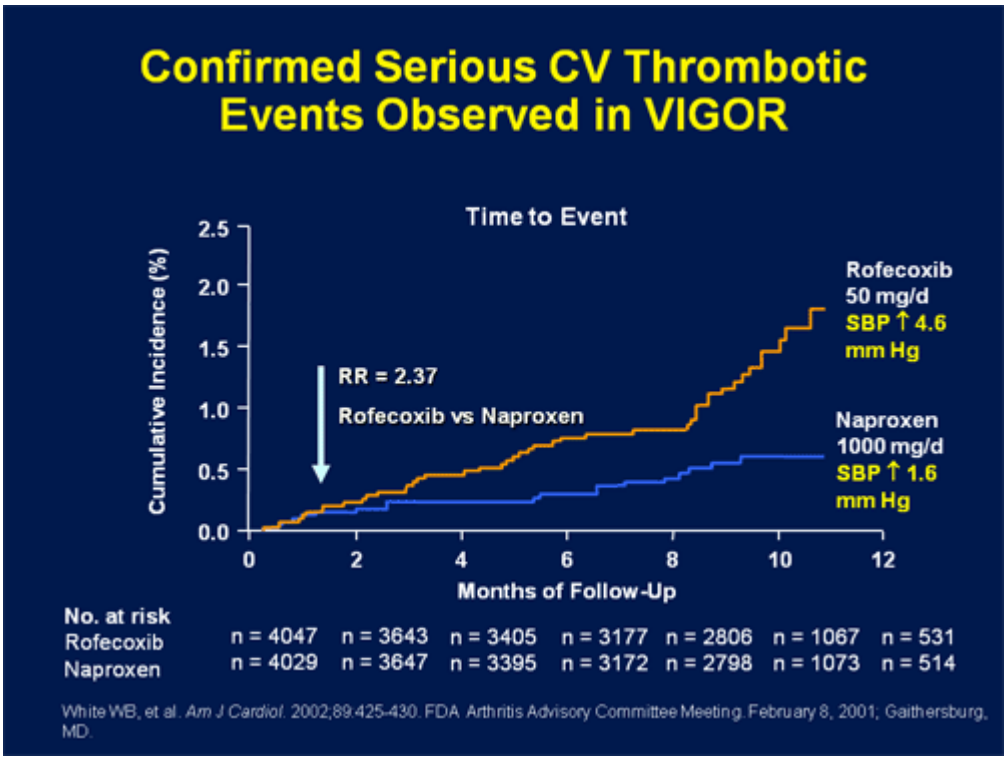
I show you here an example of just tracking a large osteoarthritis population, usual day-to-day management. These are some 8000 patients in the GI safety study we did with one of the COX-2s, in this instance celecoxib, and it is tracking them for a median exposure time of 10 months. The simple thing that I would bring to your attention is even in the best of control in a trial, we still saw nonetheless, look at this, the most commonly used NSAID over the counter, ibuprofen, producing in that setting a significant increase in either new-onset hypertension or an aggravation of existing hypertension. So it is just to say that, yes, it does emerge and drugs that are available OTC are absolutely potent potentially in doing this also.



Slide 19.

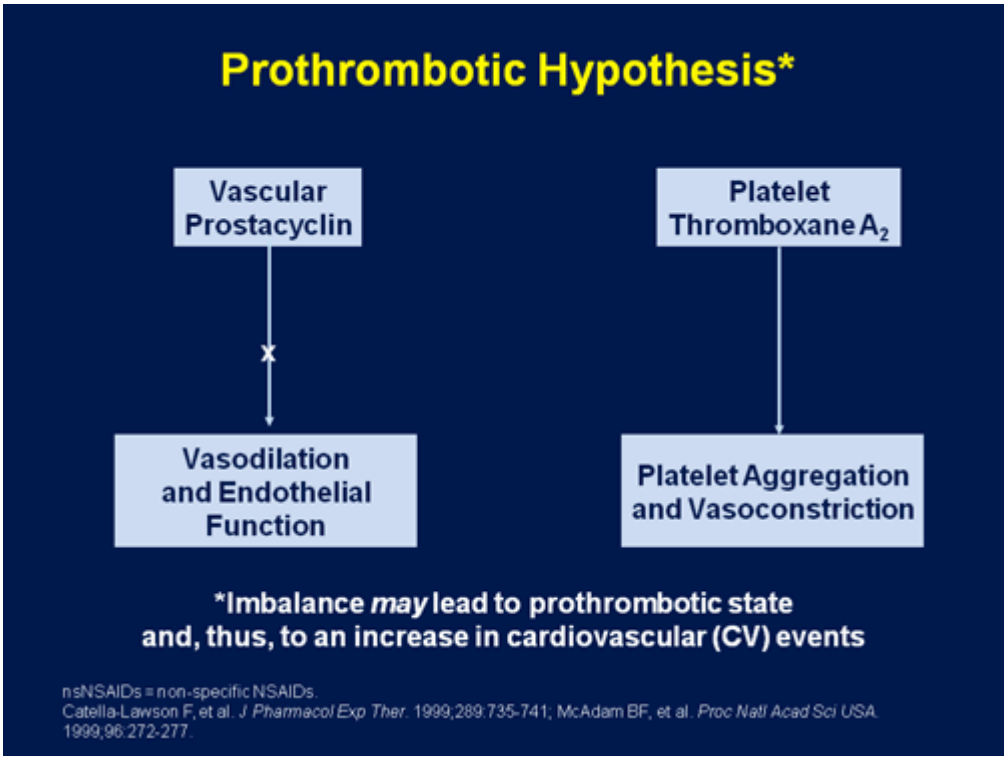
We knew at the outset with the COX-2s, as I mentioned originally, I think we all shared that they were not going to impact on the cardiorenal access and we were all completely wrong. For example, take the instance of rofecoxib or many will recall it as *Vioxx*. Even in the early development, phase II or phase III, we saw that there was a very tight correlation in dose between the increase in the appearance of hypertension. Then in the seminal GI safety study, the study that first

brought the whole cardiovascular story to our attention with NSAIDs, it became apparent that there was a whopping 10% or so of people developing new or aggravated hypertension. Let me then go on and bring back to your memories perhaps a couple of issues that you did hear about gosh almost a decade ago now, but this was a big surprise I think for all of us.



Slide 20.

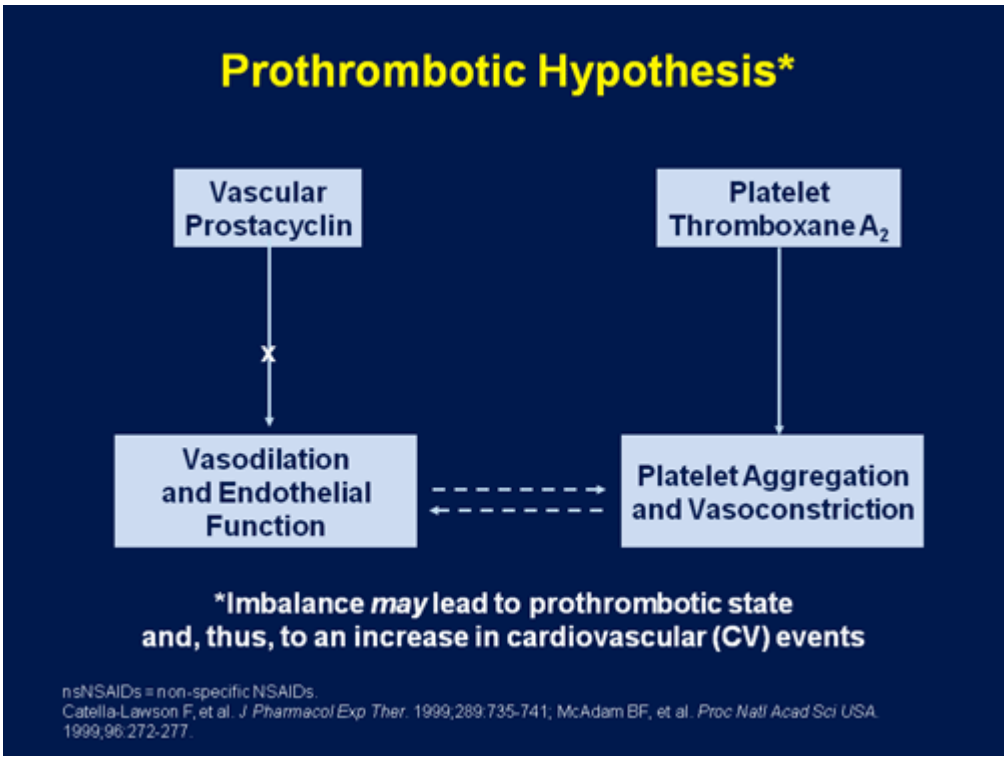
Now this study was *Vioxx* Gastrointestinal Outcome Research (VIGOR). First, I should tell you that the aim and object of it looking for safety and the answer is yes, absolutely safer in the GI tract. The big finding at the end, as I show you here approximately at 12 months, was the finding of a significant difference in cardiovascular events, particularly myocardial infarction, a 5-fold difference between these 2 drugs. One of the issues not really appreciated at that time was the evolution of significant differences in blood pressure between naproxen and rofecoxib in this trial.



Slide 21.

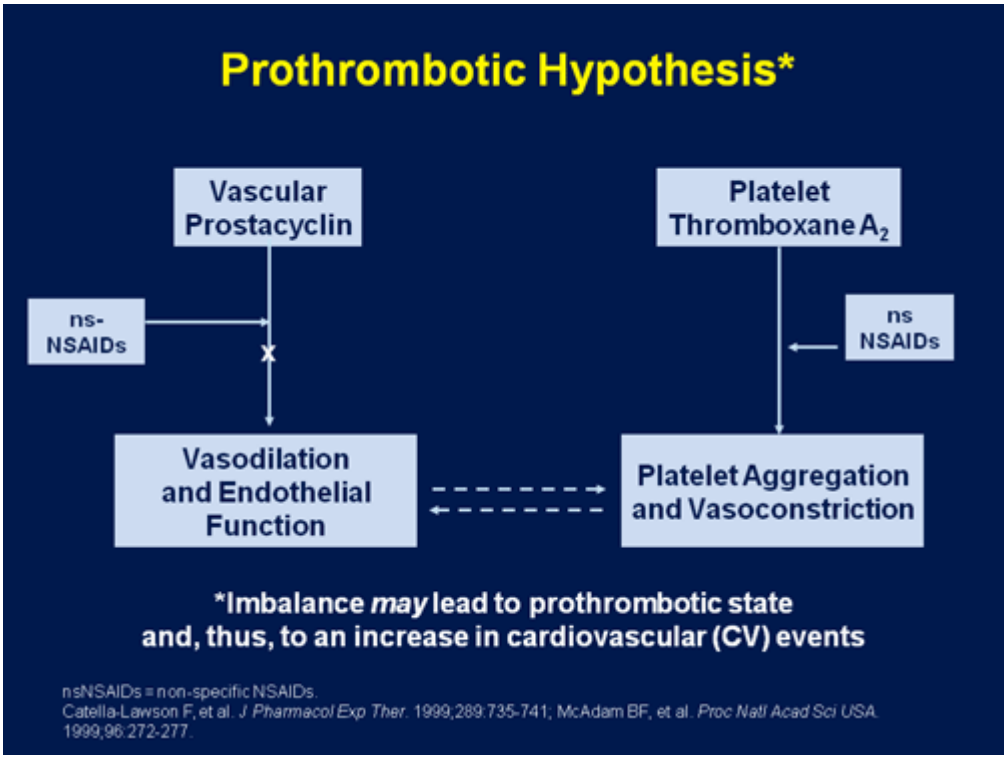
If you cast your memories back, you will remember the tremendous interest about the mechanism here, the suggestion

that, in fact, the new COX-2 drugs may have a prothrombotic effect. Our colleague, Dr. Garrett Fitzgerald, very carefully brought this to our attention. Of course, we will all recall that on a day-to-day basis we kind of oscillate between a degree of platelet thromboxane production producing aggregation potentially and vasoconstriction.



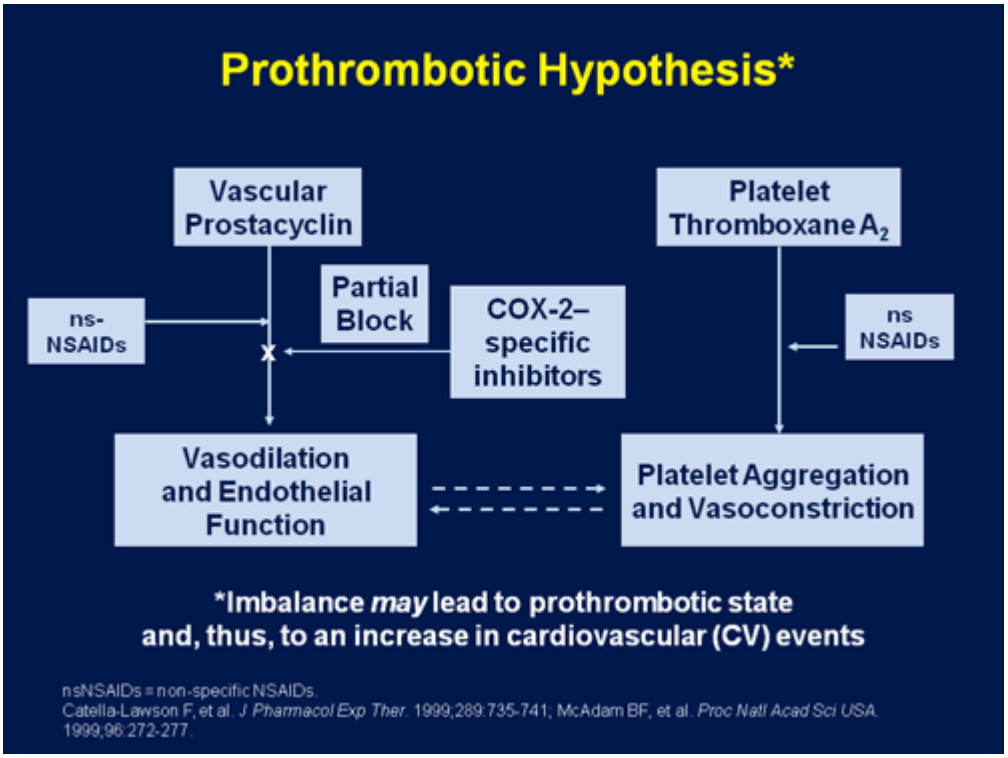
Slide 22.

This is counterbalanced during the day by vascular production by prostacyclin, vasodilatation and also actually an impact on platelet aggregation —



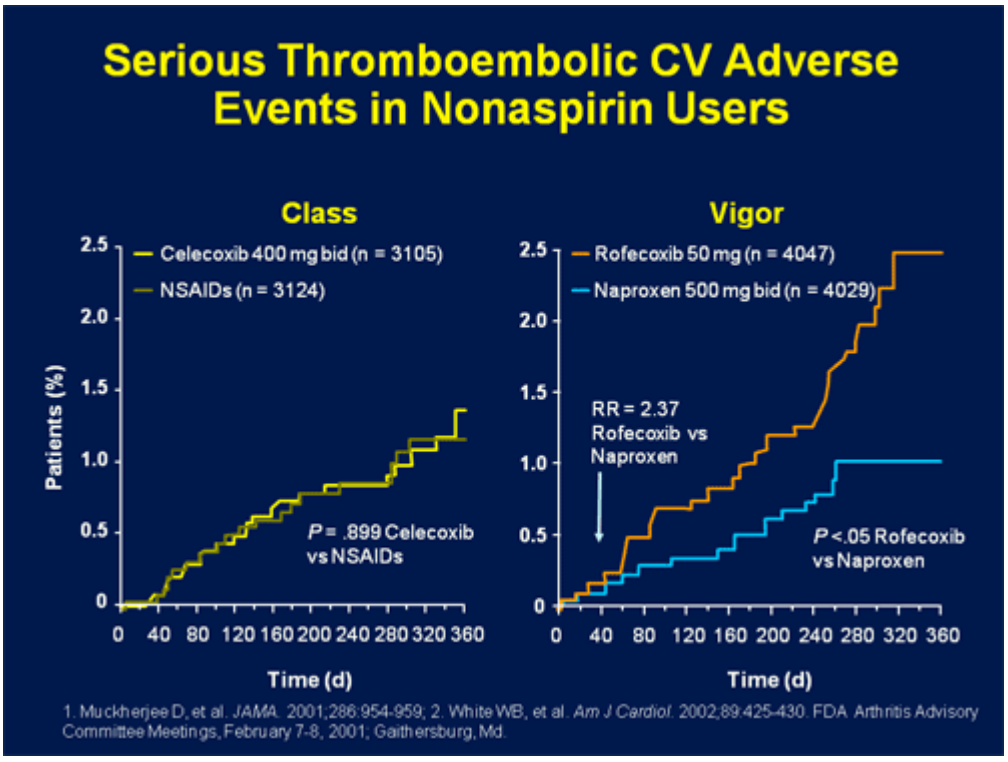
Slide 23.

— and that if you gave one of the older NSAIDs, be it *Indocin*, ibuprofen or naproxen, that both of these limbs were pretty much equally inhibited so that there was not a change in the balance —



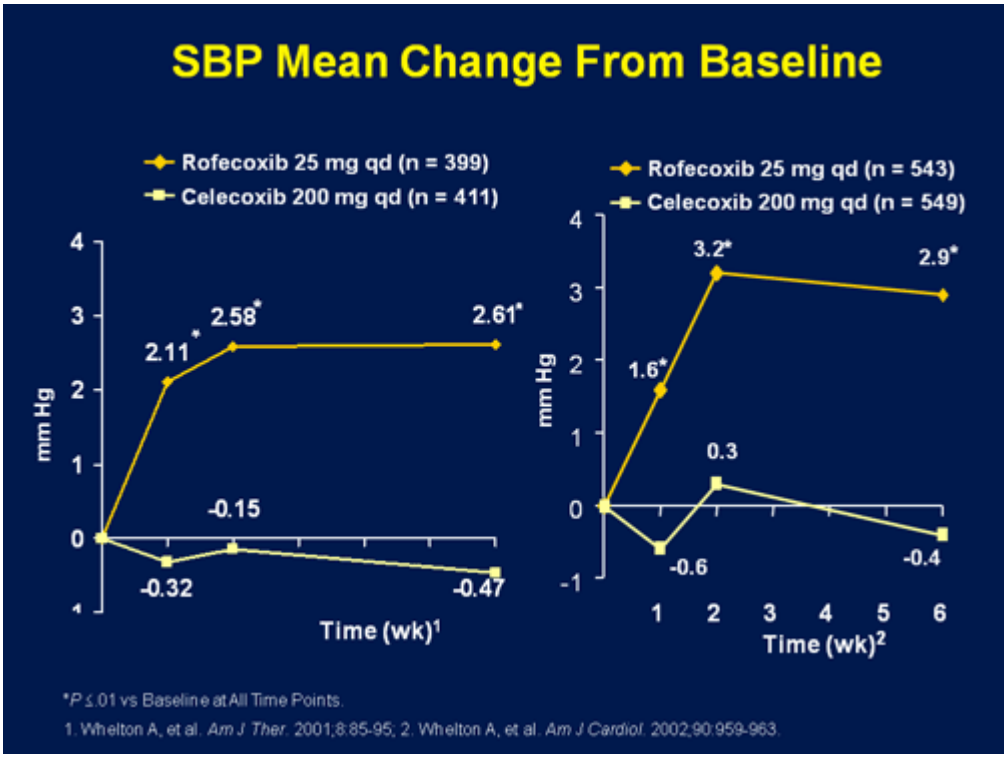
Slide 24.

— but that it appeared the COX-2 drugs had a partial impact on just this prostacyclin limb alone. The issue then being that you tilt this balance towards a prothrombotic state. That seemed terrific.



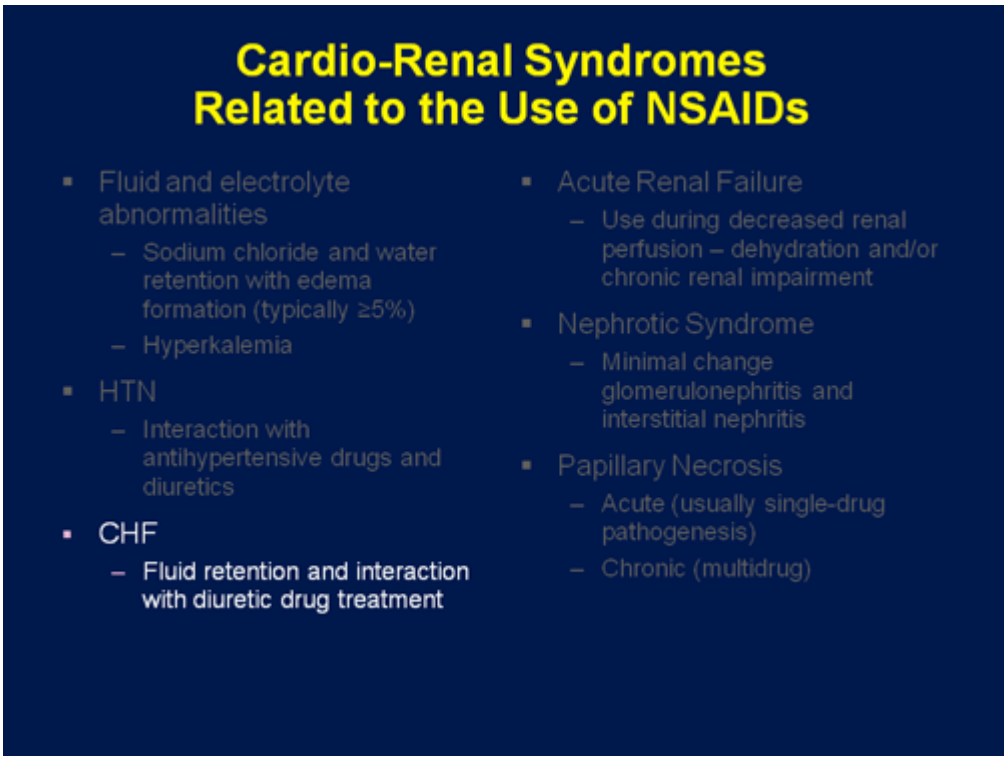
Slide 25.

You say then that should explain cardiovascular events with all of the new COX-2s, but actually that did not happen because shortly after the rofecoxib GI safety trial, a comparable one done with the other COX-2 available at that time, celecoxib, it showed celecoxib and ibuprofen and diclofenac cardiovascularly had exactly the same outcome events in that setting and subsequent COX-2s the same story. So the prothrombotic hypothesis indeed may be a contributor, but it absolutely is not the full explanation.



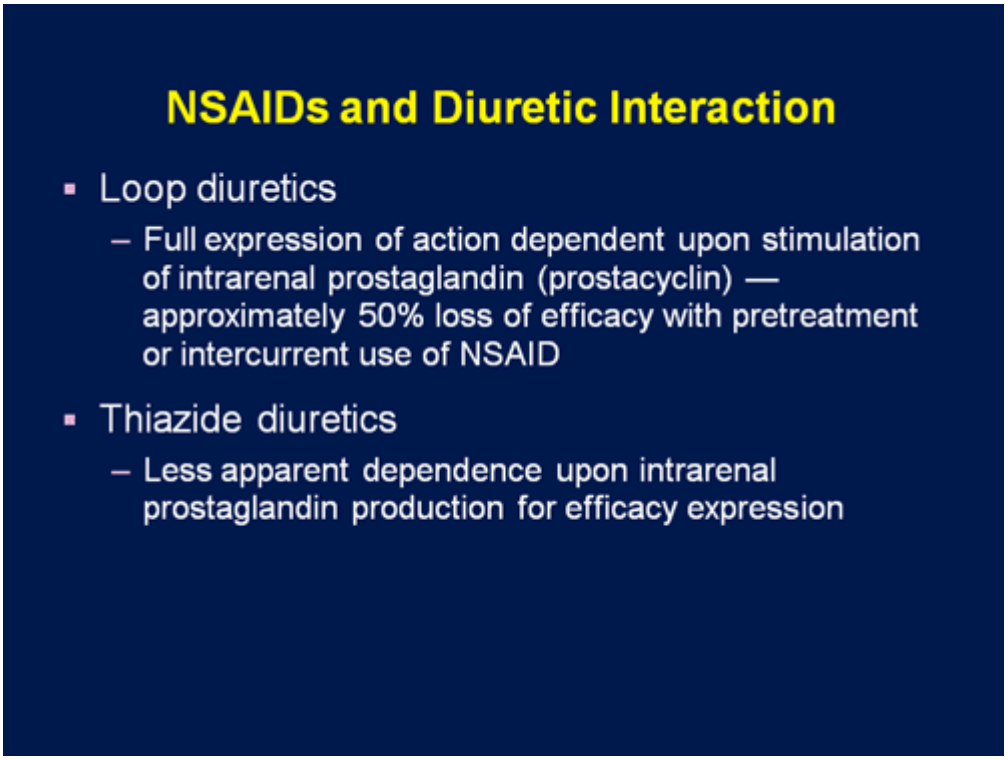
Slide 26.

As I move along to tell you that the next step in the scientific story was taking these drugs, exactly the same category of NSAID, but showing that yes molecularly there are differences in blood pressure destabilization. Now these are 2 studies here, populations of people who had stable blood pressure entering into the trials. We had about 800 in the first trial. It simply shows that, yes, if this is going to occur it discloses itself early. So you are going to see it at the end of 1 week or 2 weeks and that is our general recommendation nowadays. If you are starting somebody on an NSAID, who is being treated for hypertension, get them back to the clinic or the office in about 2 weeks to see what has happened to their blood pressure. We were not sure at this stage that if pressure did go up was there some degree of compensation, would it go back to baseline, but the bottom line is that is not so. If it goes up, all things staying the same clinically, it will remain up. So we just went back and recharacterized that and, yes, that indeed was a solid issue. So blood pressure, if it is going to occur, occurs early, so take a look at patients at the end of 2 weeks.



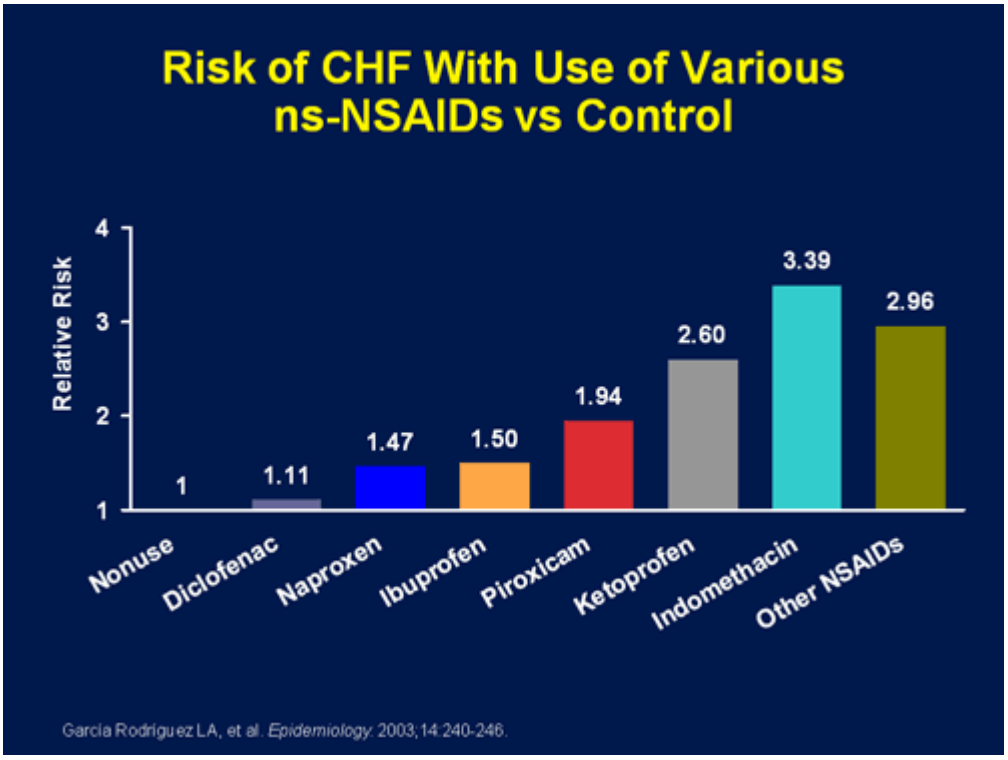
Slide 27.

What about the congestive heart failure part of the story. This is kind of interesting also.



Slide 28.

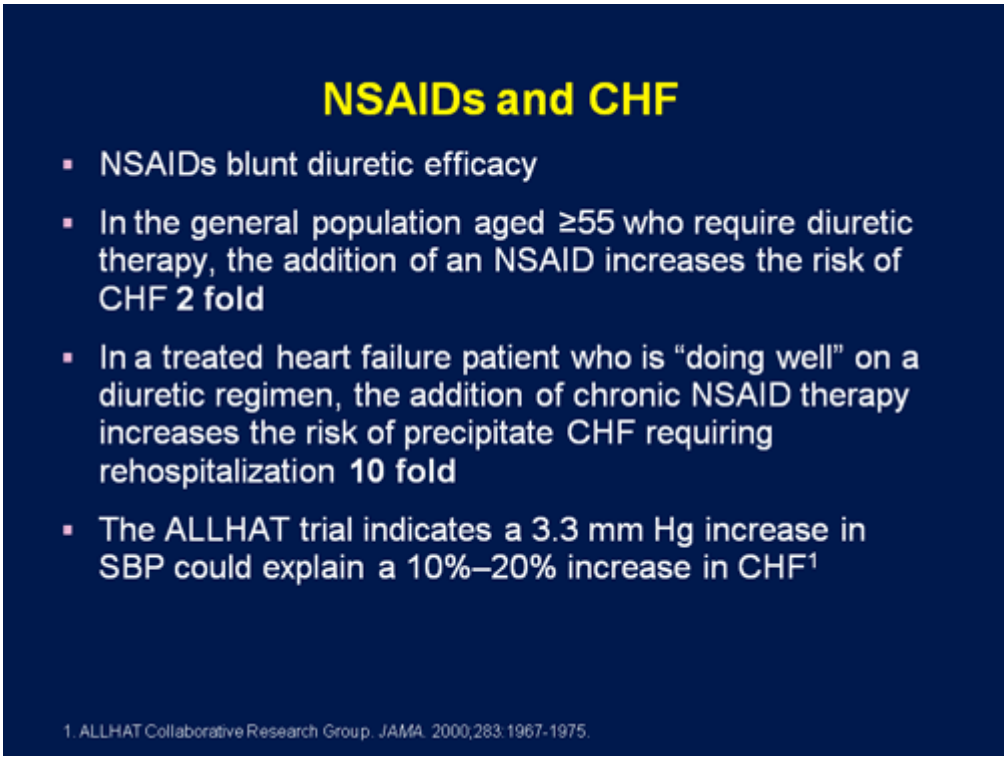
One of the things that we did not really appreciate until some wonderful work coming from Dr. Craig Brater, who pointed out to us that, in particular, loop diuretics require intrarenal prostaglandin. There is the link once again, production for the full description or full manifestation of their effect and that, in fact, about 50% of the action of a loop diuretic is related to prostaglandin production in the kidney. Ergo, if you inhibit it either by pretreatment with an NSAID before giving a diuretic or somebody on a stable regimen of diuretic that then gets an NSAID, we destabilize the effectiveness of the loop diuretic. We see it with the thiazides also, but not quite as dramatically.



Slide 29.

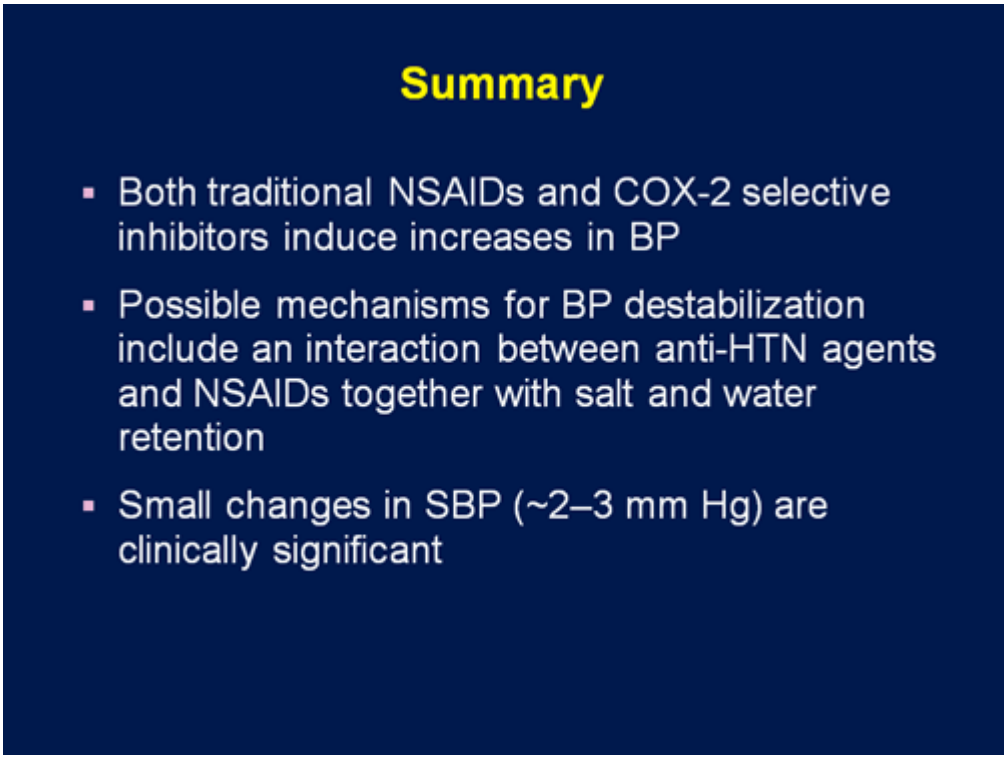
Then if you take a look at the general population in terms of development of congestive heart failure, yes this does manifest itself. You can see there is a cascade between different NSAIDs, but the bottom line being that on average we

see about a 2- to 3-fold increase in hospitalization for congestive heart failure across the board in the general population when an NSAID is added to a diuretic regimen.



Slide 30.

I would summarize the NSAID and congestive heart failure part of the story and say that diuretic efficacy is blunted across the board by NSAIDs. If you take a cut of the population age 55 and older who are on a stable regimen of diuretics and add an NSAID, there is a 2-fold increase in their need for hospitalization for CHF. On the other hand, if it is a patient of yours who has had CHF, been hospitalized and now doing well back into the community and an NSAID is added, either purchased over the counter or by prescription, it is extraordinary, a whopping 10-fold increased risk of rehospitalization for CHF. I might just bring back to your attention, and Dr. White will particularly talk about it more, small changes in blood pressure. You know this story, you know it so well, small changes in blood pressure in large populations have a very important increase in cardiovascular events shown here in particular CHF.

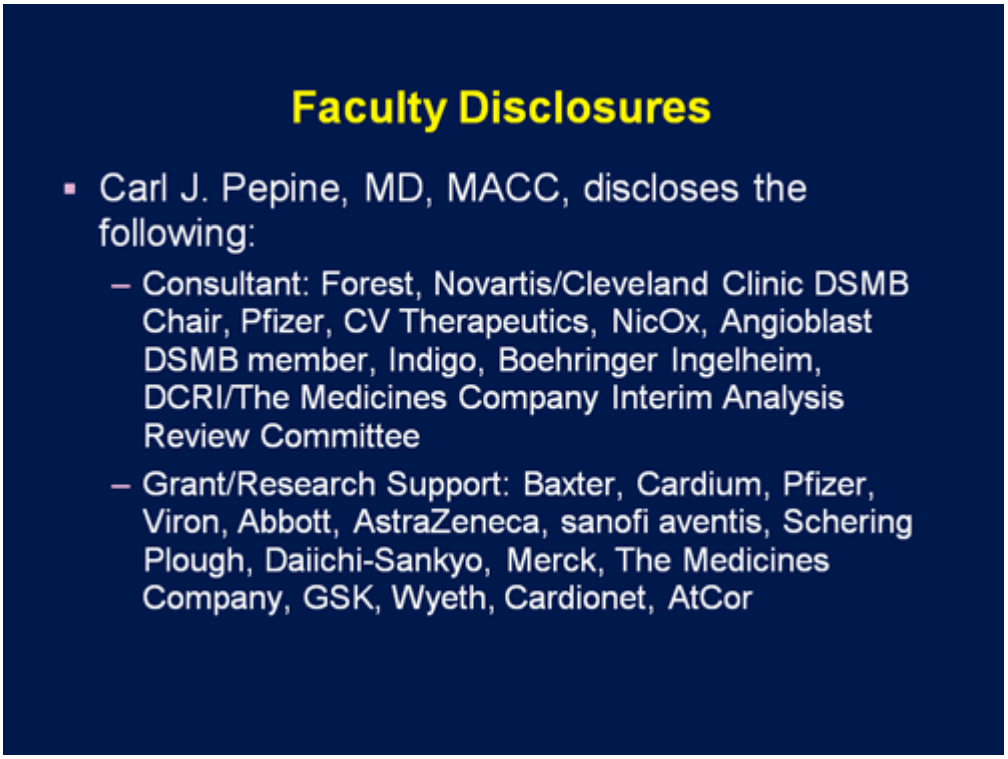


Slide 31.

If I wind up my initial presentation, I would say that all of the NSAIDs, the traditional and the COX-2s, do have an impact to a variable degree in destabilization of blood pressure. The mechanisms are potentially an interaction between the NSAIDs and anti-hypertensive agents combined with salt and water retention. And again emphasizing that in this business, small changes in systolic blood pressure are clinically significant. So, Dr. Pepine, I will pass it back to you now if I may.

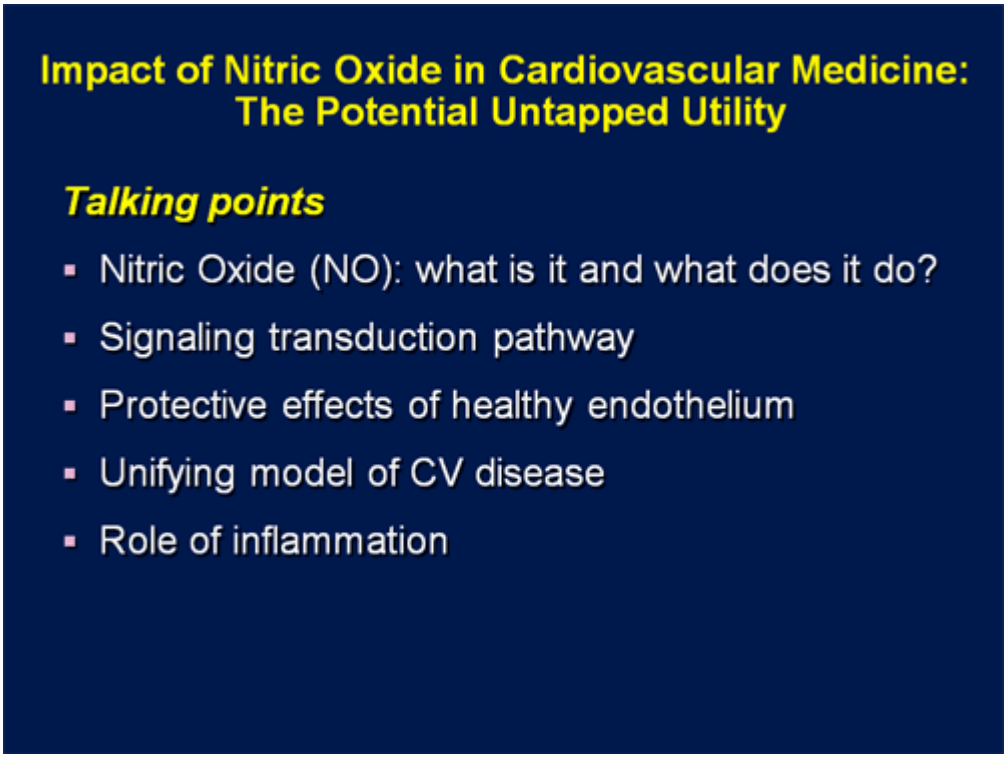
Impact of Nitric Oxide in Cardiovascular Medicine: The Potential Untapped Utility

Slide 32.



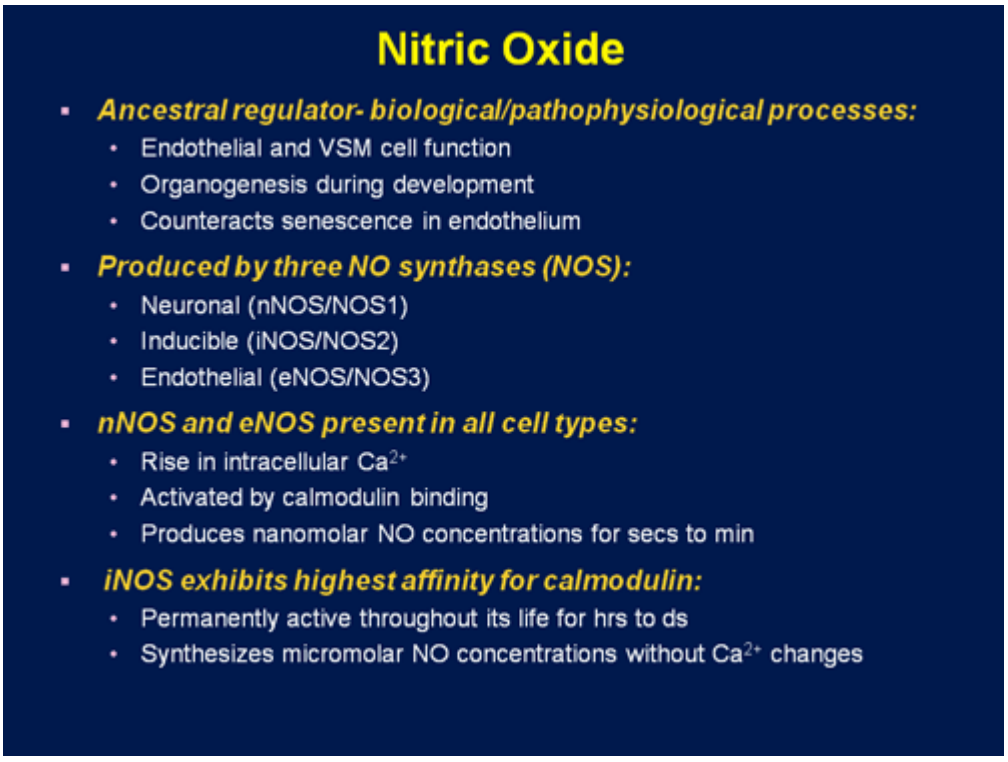
Slide 33.

Dr. Pepine: Well thank you, Andrew.



Slide 34.

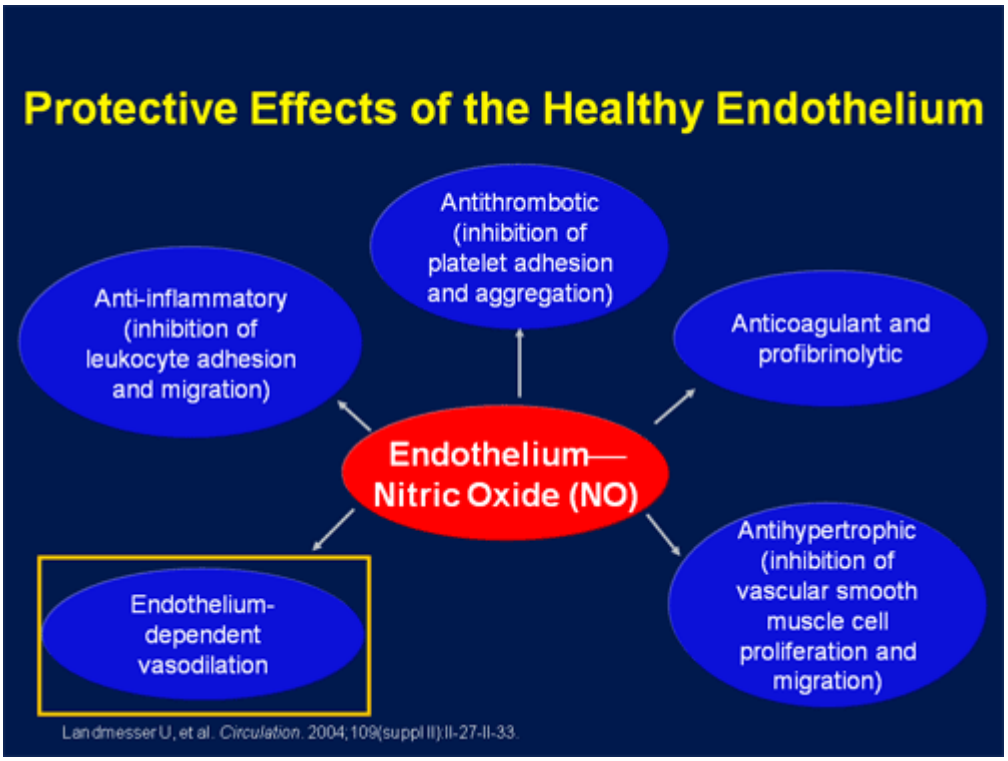
In this next talk, I will deal with the impact of nitric oxide (NO) in cardiovascular medicine and what a potential untapped utility NO is. Over this next 20 minutes, I would like to deal with NO, what it is, what it does; review its signaling transduction pathway; talk about the protective effects on healthy endothelium; and then some of the effects when the endothelium becomes dysfunctional or diseased and put this into a unifying model for cardiovascular disease; and then briefly wind up with some comments about inflammation and its effect on both NO and endothelium.



Slide 35.

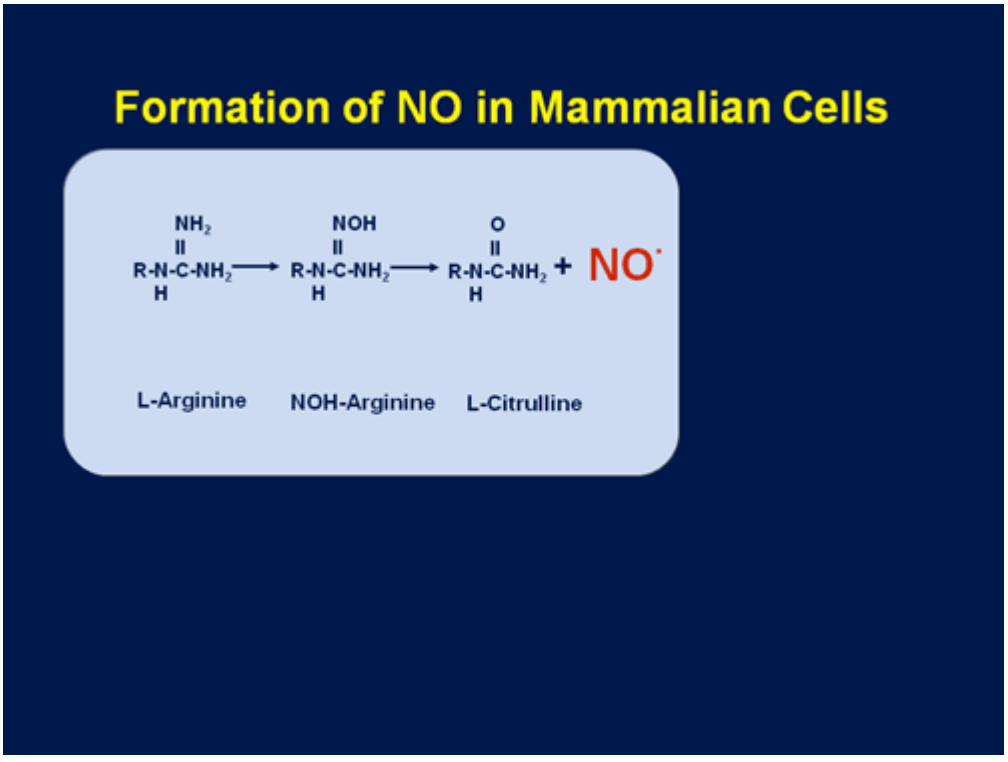
I need to remind you that nitric oxide is an ancestral regulator of vascular function. This molecule has been preserved throughout millennia. It is critically important for maintenance of biological processes and a fundamental problem in the pathogenesis of vascular disease. Its actions in the vasculature are at the endothelial and vascular smooth muscle level. It is also involved in organogenesis in the embryo and more recently has been shown to prevent or counteract senescence in endothelium. It is produced by 3 NO synthases, neuronal, which is found in neurons, inducible, which is found principally

in mononuclear macrophages, and also endothelial, which is found in virtually all organs. Neuronal and endothelial NO synthases are present in all organ and cell types. This enzyme is responsive to a rise in intracellular Ca^{2+} and it is activated by calmodulin binding. It then produces nanomolar amounts of NO. The NO concentrations persist for only seconds to at most a minute. On the other hand, inducible NO synthase exhibits the highest affinity among all 3 enzymes for calmodulin. It is permanently active throughout its life and, hence, generates NO for hours to days. It synthesizes, in contrast to both the neuronal and endothelial varieties, micromolar concentrations of NO without changes in calcium signaling.



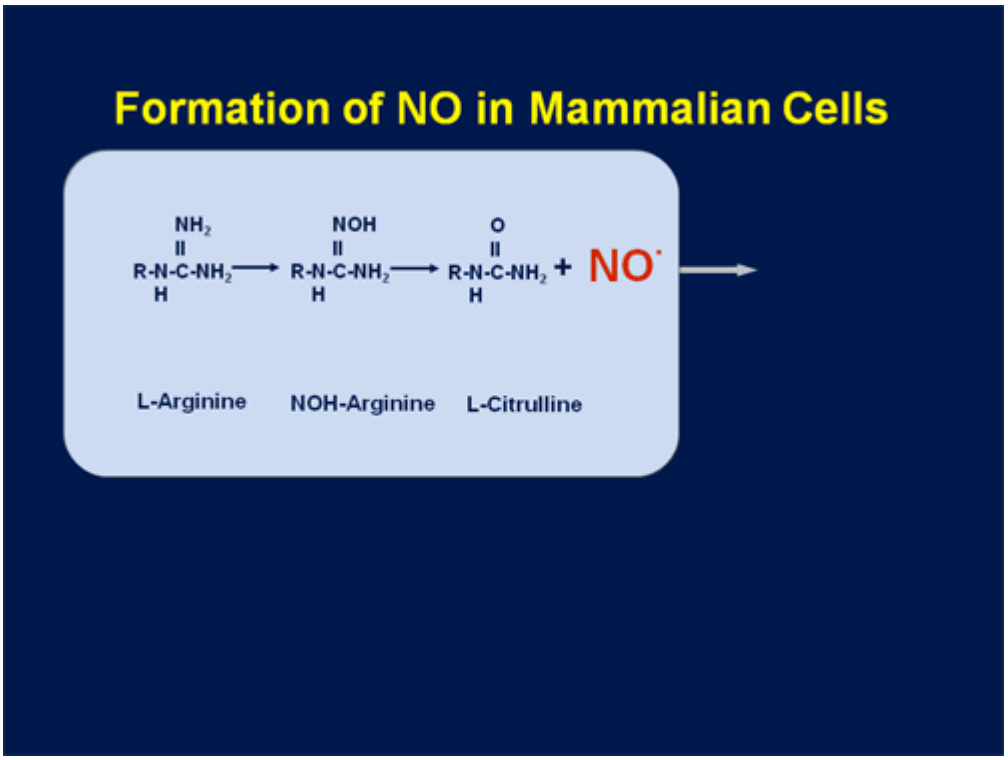
Slide 36.

The endothelium produces NO and this is responsible for protecting us in health. First, it provides a constant state of relaxation for blood vessels at both the large vessels and perhaps more importantly at the microvascular level. It provides an anti-inflammatory effect through its action to inhibit the adhesion of mononuclear cells and also their migration. It provides an anti-thrombotic effect by inhibition of platelet adhesion and aggregation. It provides an anticoagulant effect. It is also a potent inhibition of cell division and cell growth, so that vascular smooth muscle proliferation is suppressed.



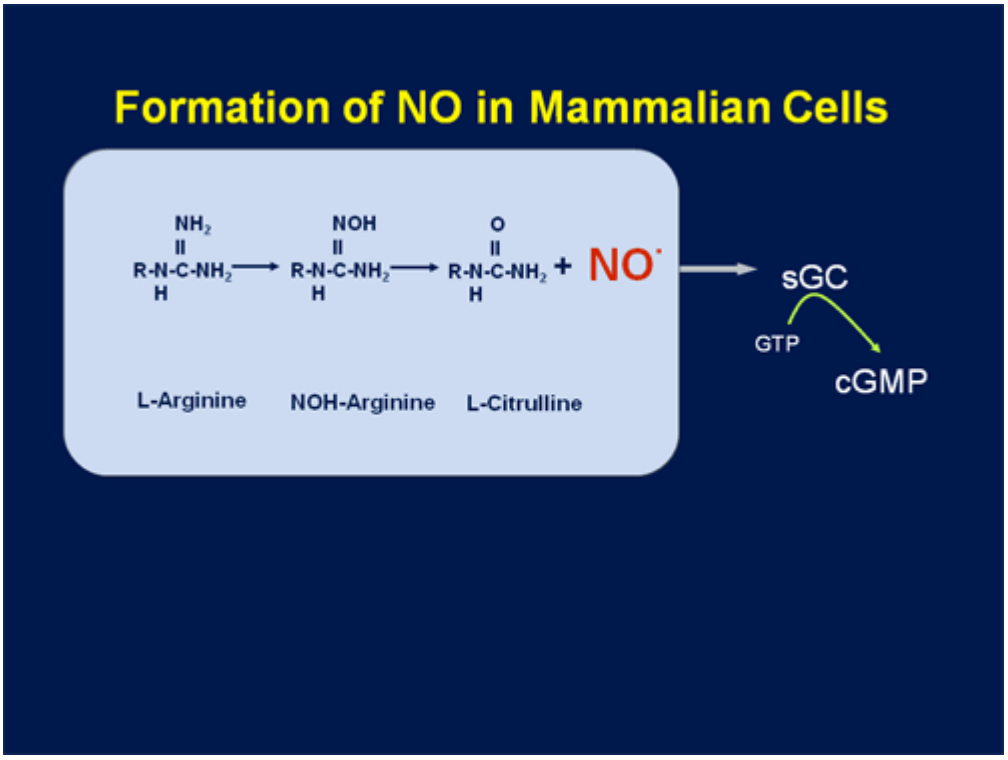
Slide 37.

NO is formed from the amino acid L-arginine —



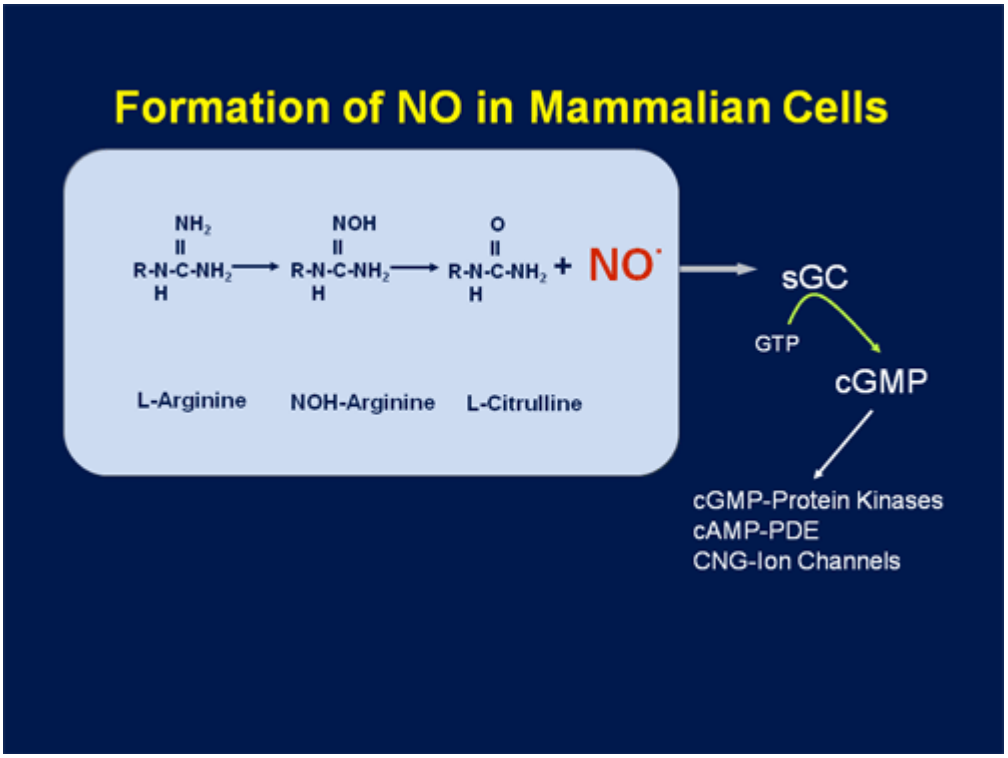
Slide 38.

— and then diffuses.



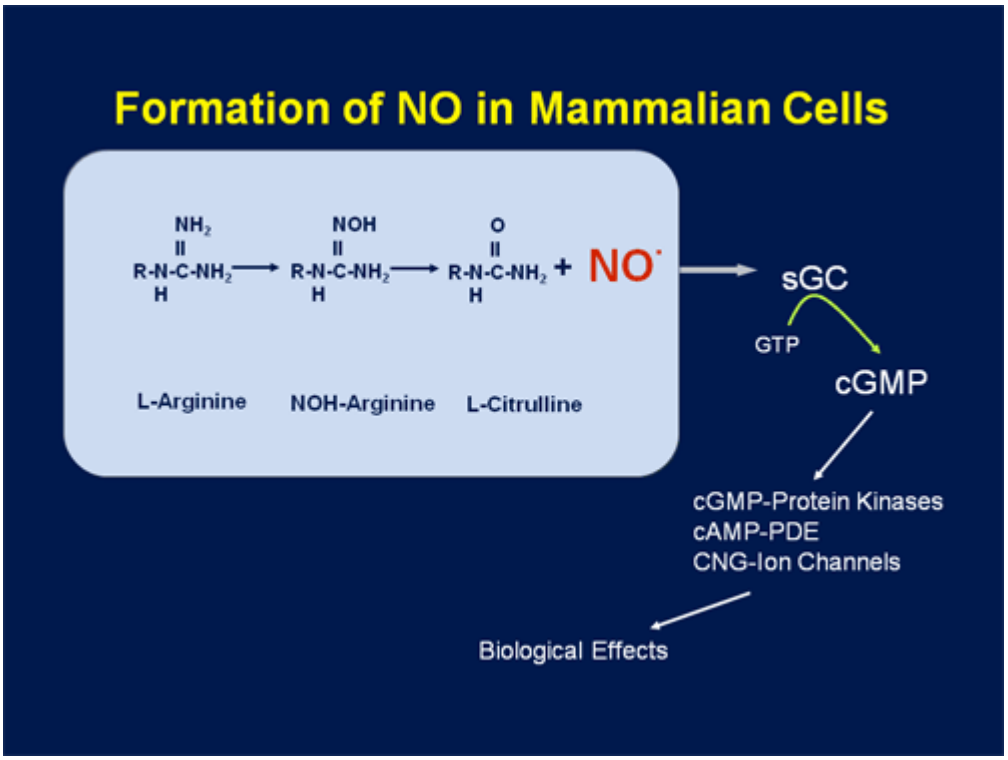
Slide 39.

This is a gas that is freely diffusible to act with soluble guanylyl cyclase — (sGC)



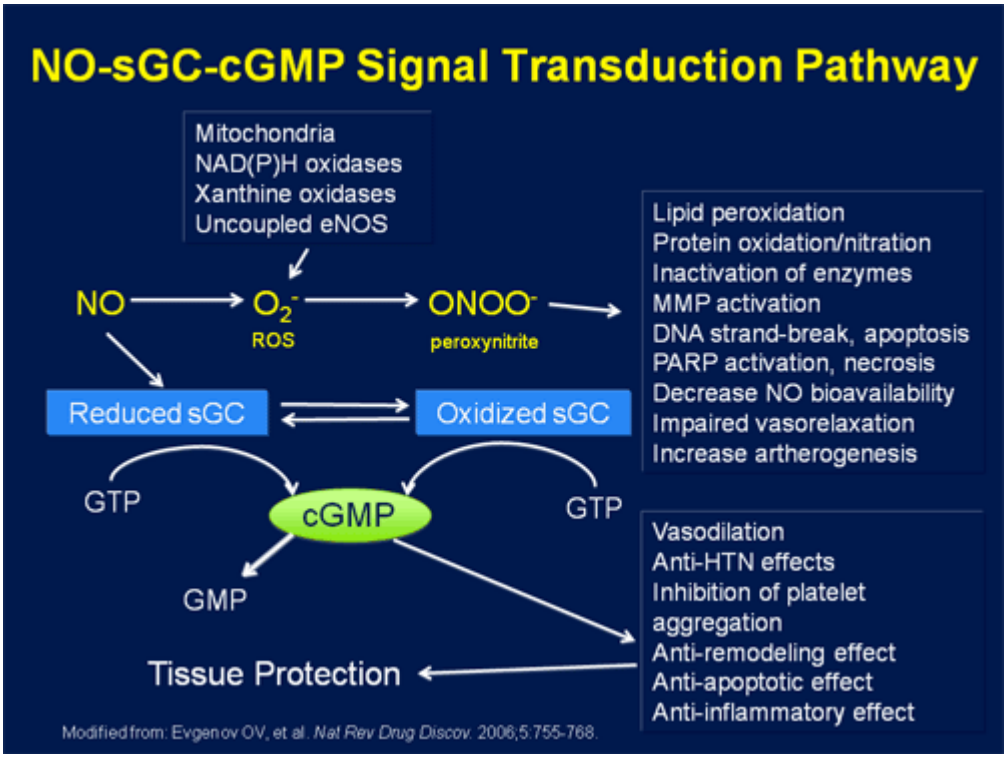
Slide 40.

— and then act at cGMP to activate a number of downstream processes —



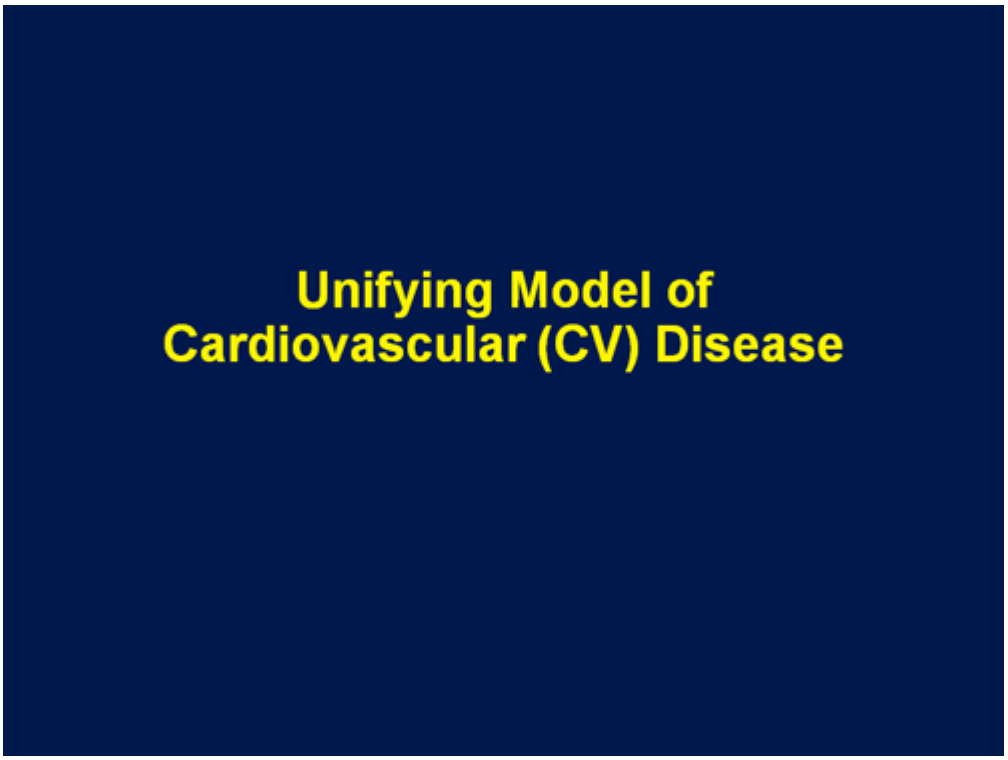
Slide 41.

— before it has biological effects.



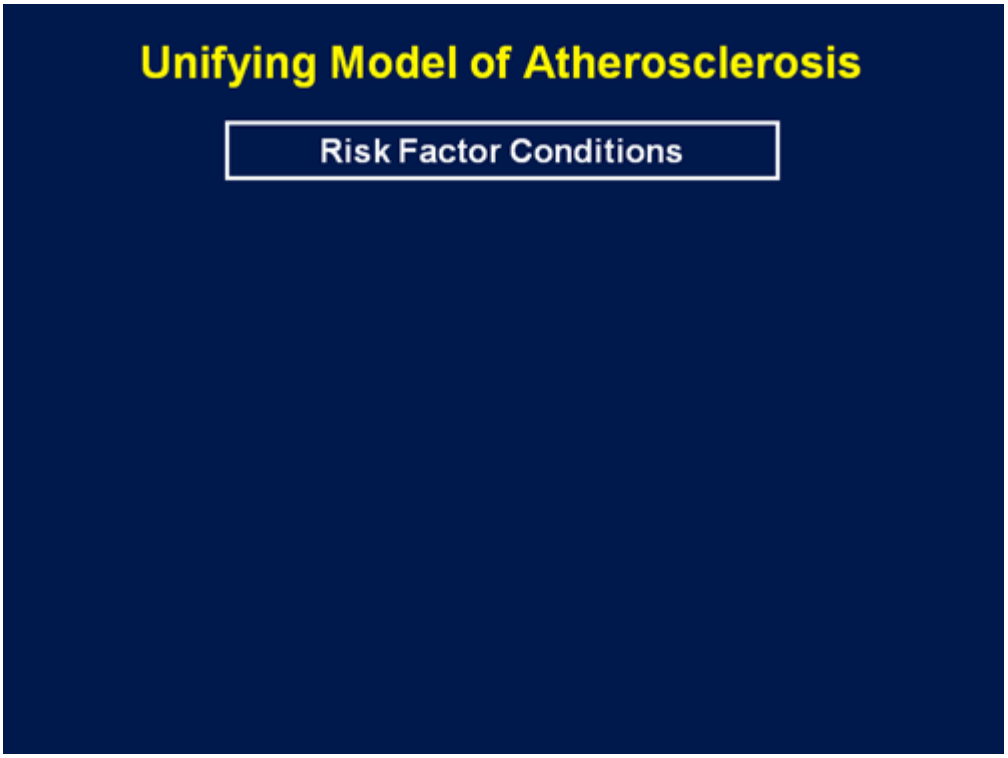
Slide 42.

In this NO sGC-cGMP transduction pathway, it is possible to understand, as you can see here, that NO is responsible for this action and its downstream effect; so that at the tissue level we have a healthy environment that is characterized by vasodilation, by anti-hypertensive effects, by inhibition of platelet aggregation, by anti-remodeling effects at both blood vessels and at the myocardial level, anti-apoptotic effects and anti-inflammatory effects. It is possible that in states where there is excess production of reactive oxygen species that NO is inactivated in the form of the peroxynitrite. This results in a host of deleterious effects, which I have summarized in this upper corner.



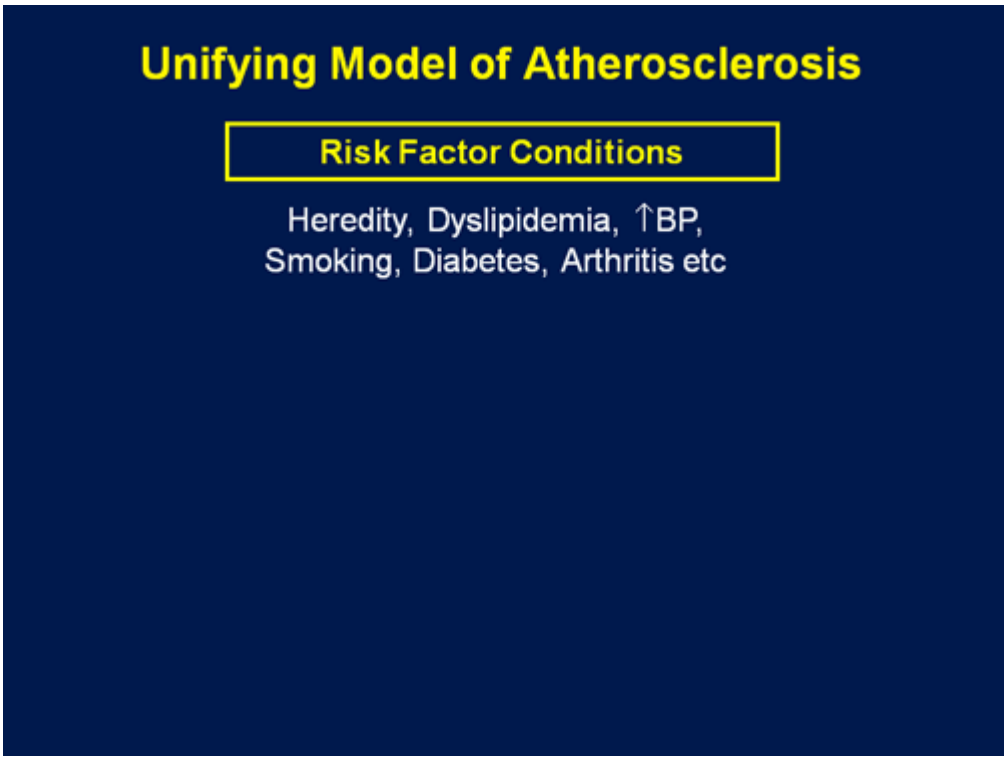
Slide 43.

If we take this information and put it into a model of cardiovascular disease —



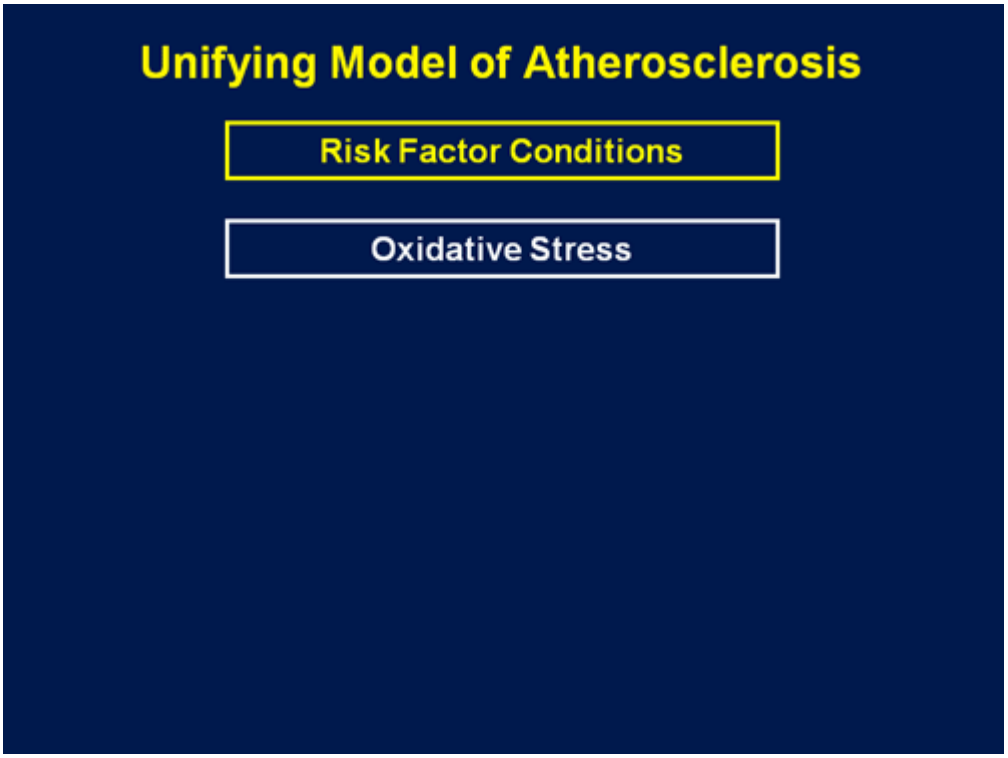
Slide 44.

— we now understand that the cardiovascular disease risk factor conditions —



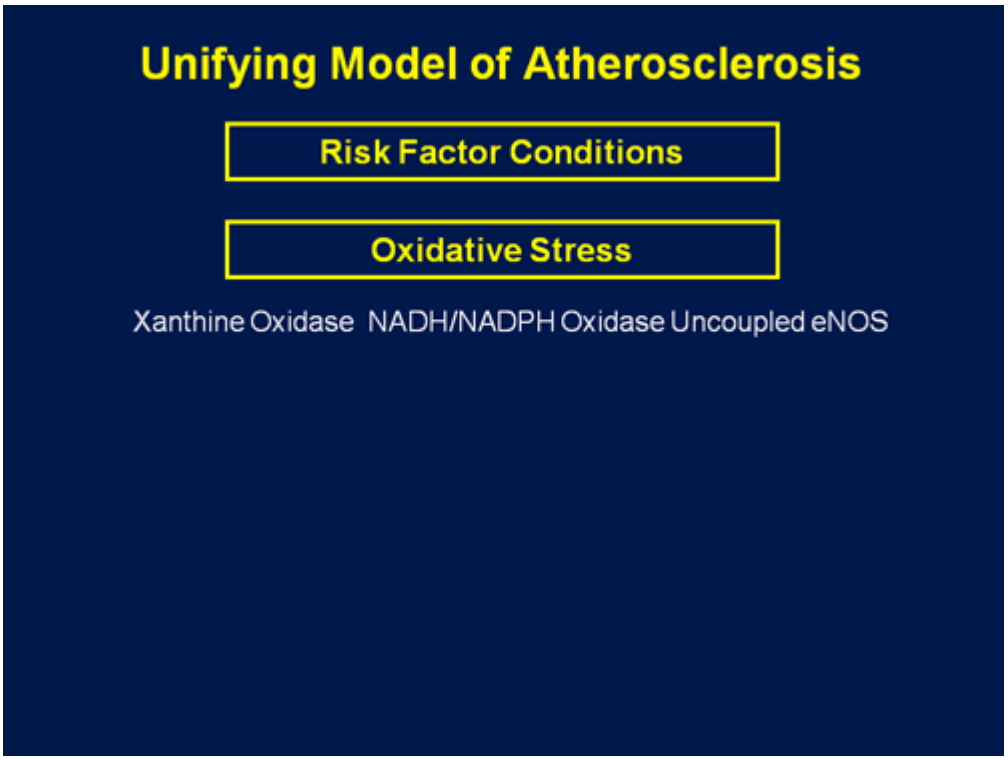
Slide 45.

— such as dyslipidemia, elevated blood pressure, smoking, diabetes, inflammatory states like arthritis and so forth —



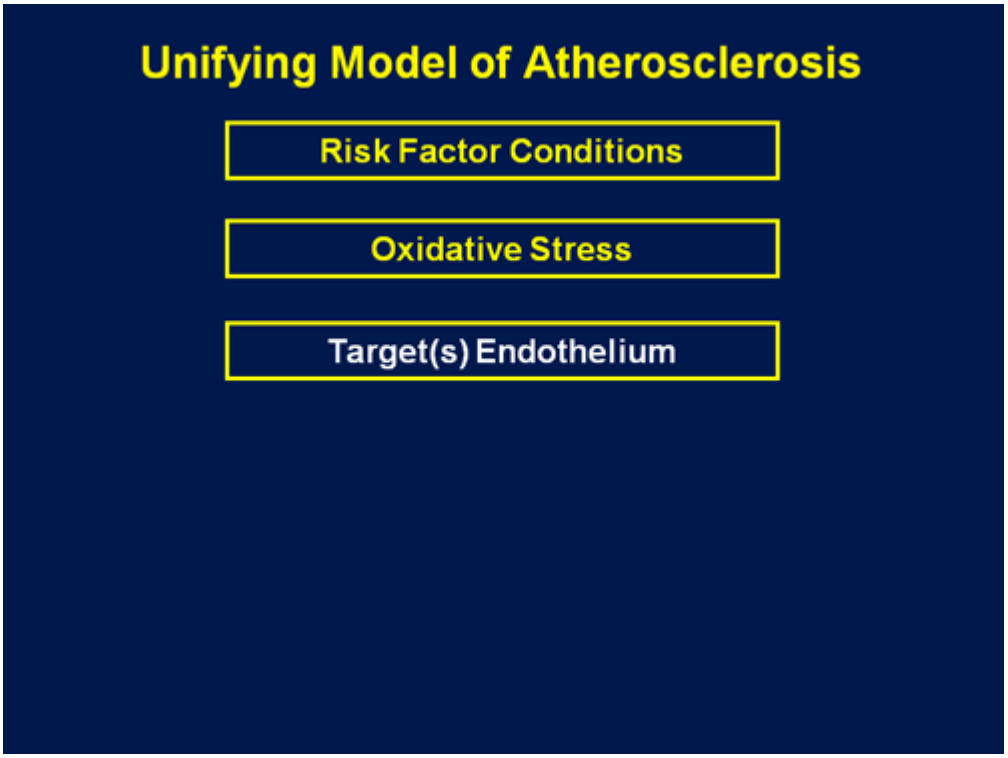
Slide 46.

— contribute to increased oxidative stress and —



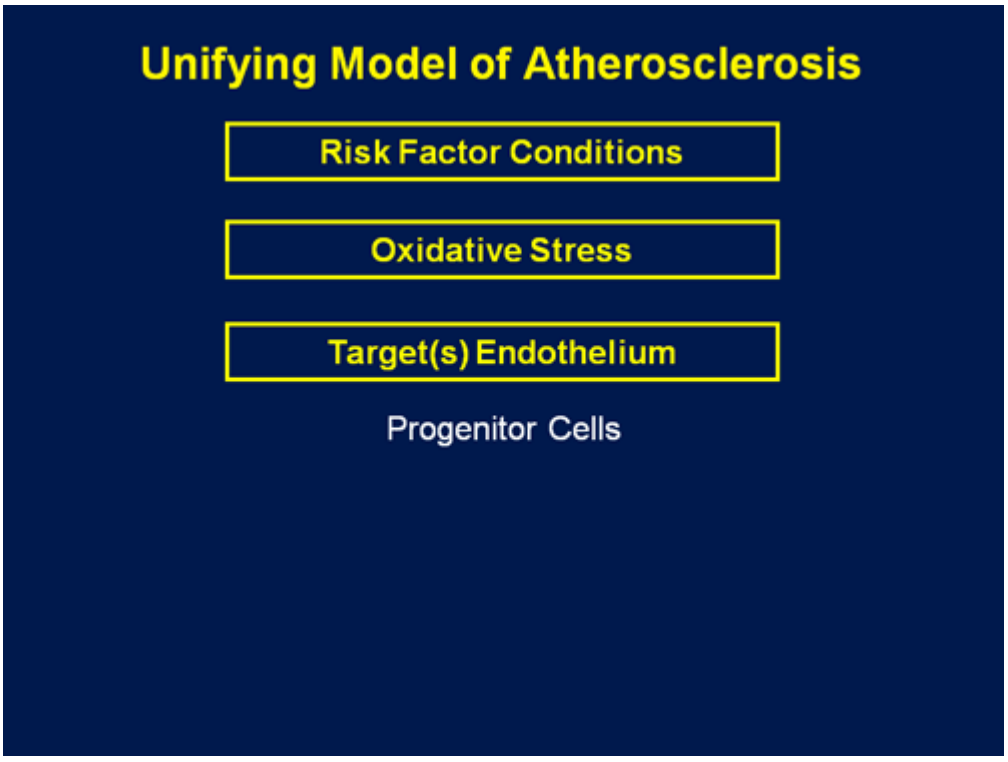
Slide 47.

— overload these naturally occurring anti-oxidase defense mechanisms.



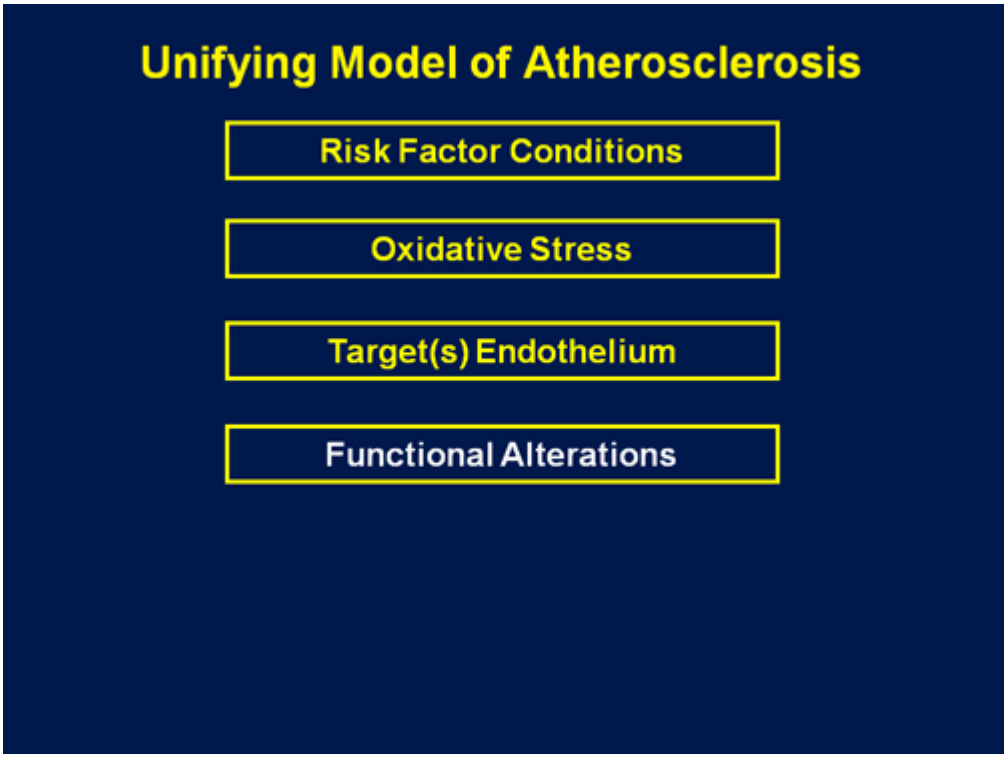
Slide 48.

At the target of the endothelial cell, they —



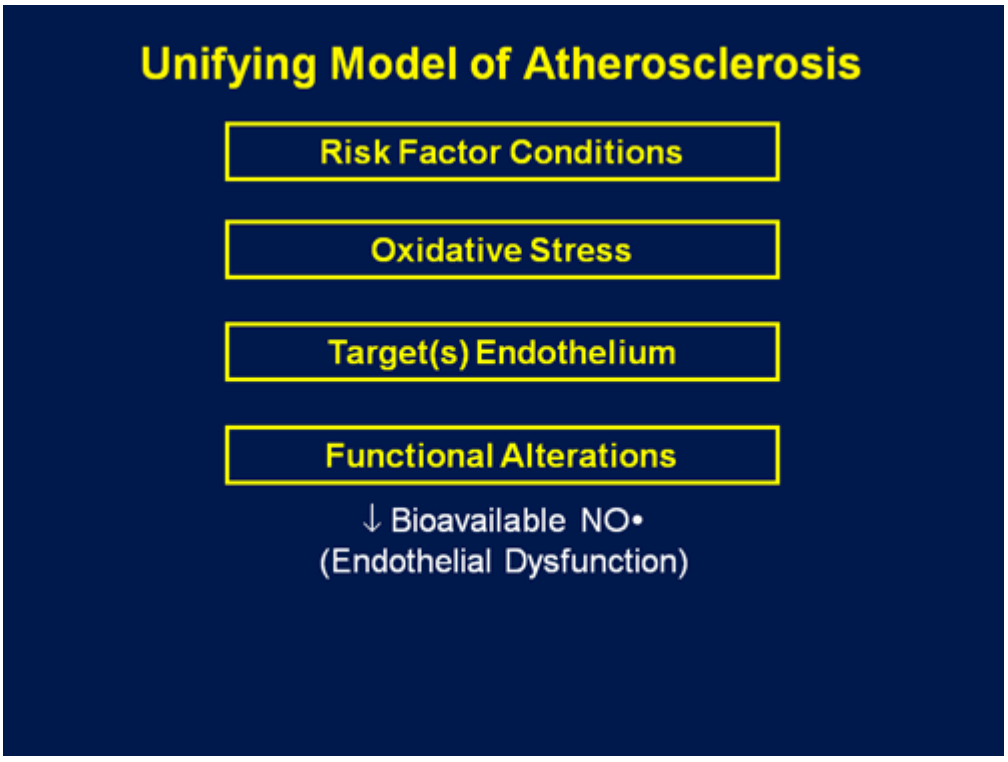
Slide 49.

— and also its progenitor cells in bone marrow and other reservoirs —



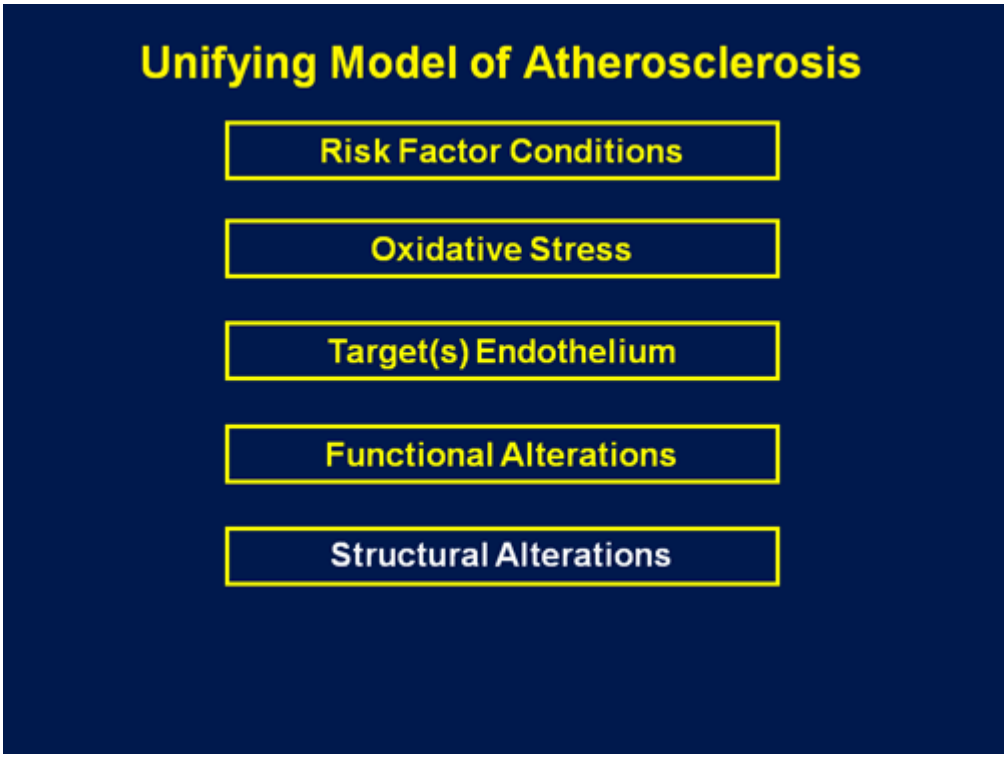
Slide 50.

— ultimately will result in functional alternations at endothelium.



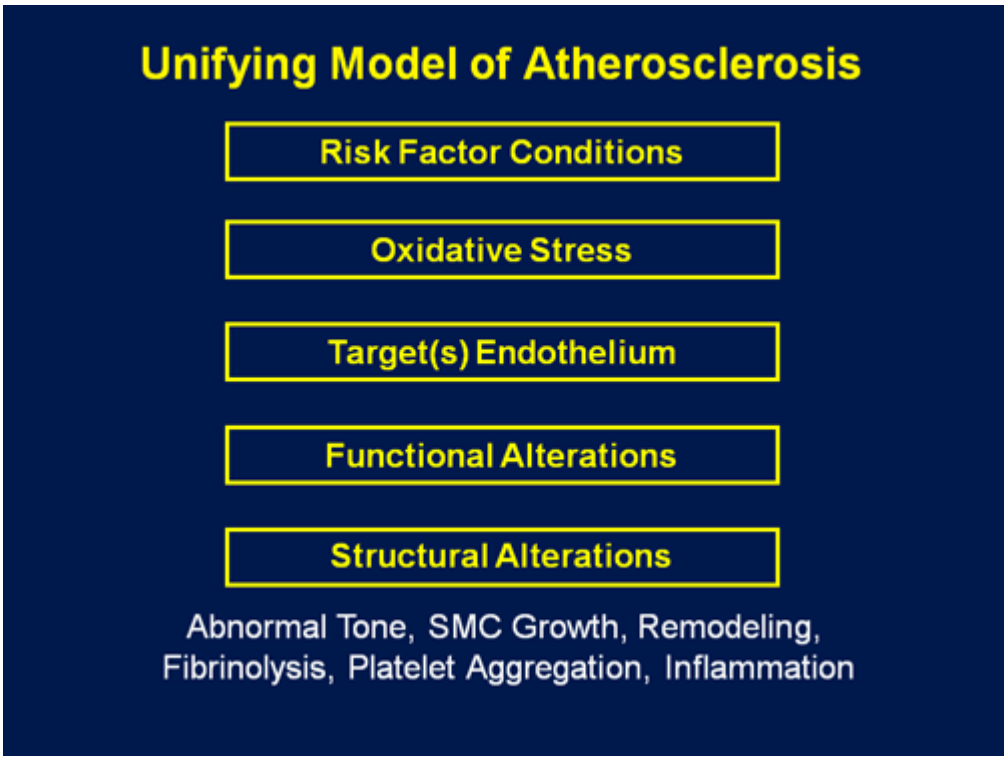
Slide 51.

This is principally due to a reduction in bioavailable NO. We term this endothelial dysfunction —



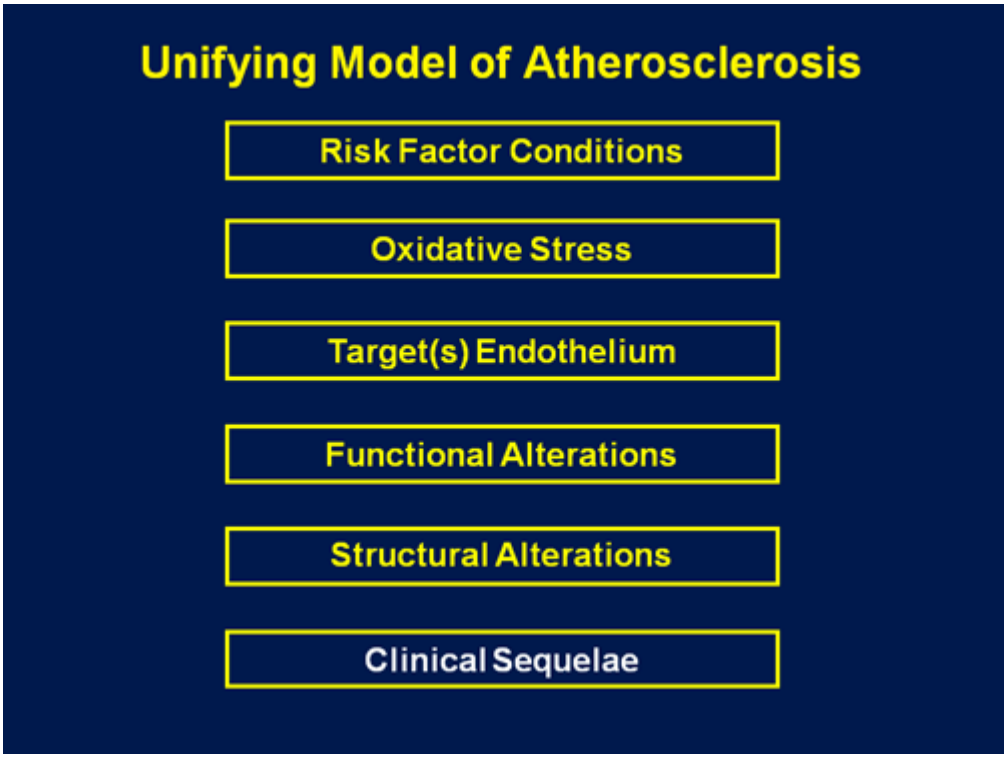
Slide 52.

— which will then result in structural alterations in blood vessels,



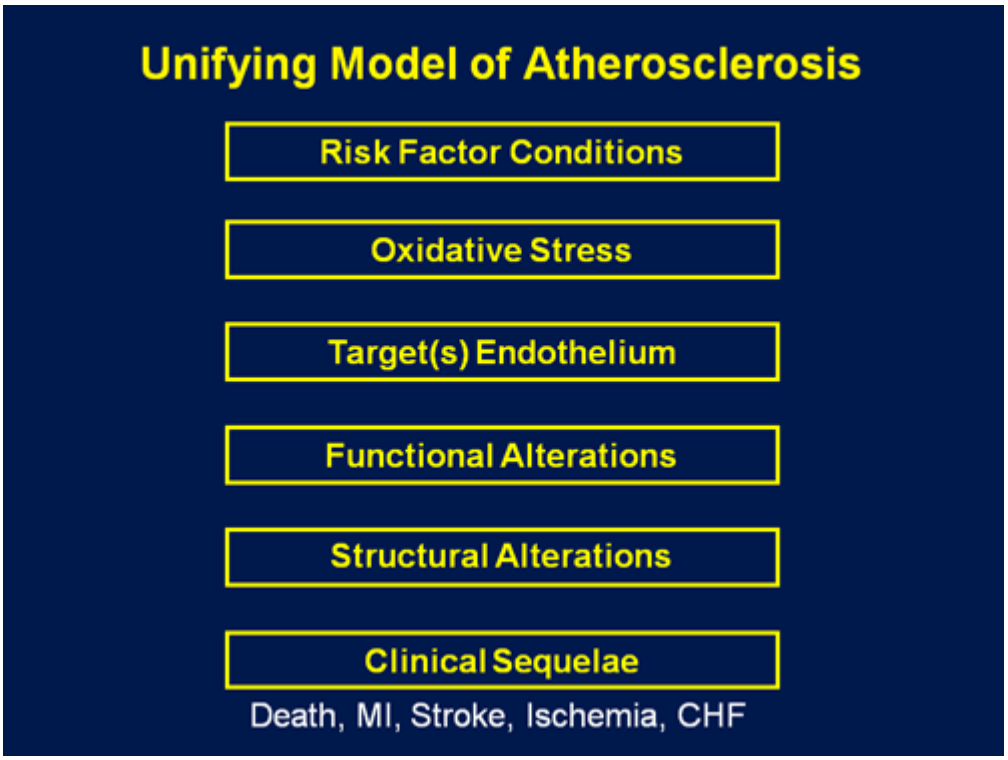
Slide 53.

characterized by abnormal tone, abnormal smooth muscle growth, remodeling of vessels, enlargement, disorders in fibrinolysis, platelet aggregation and also inflammation.



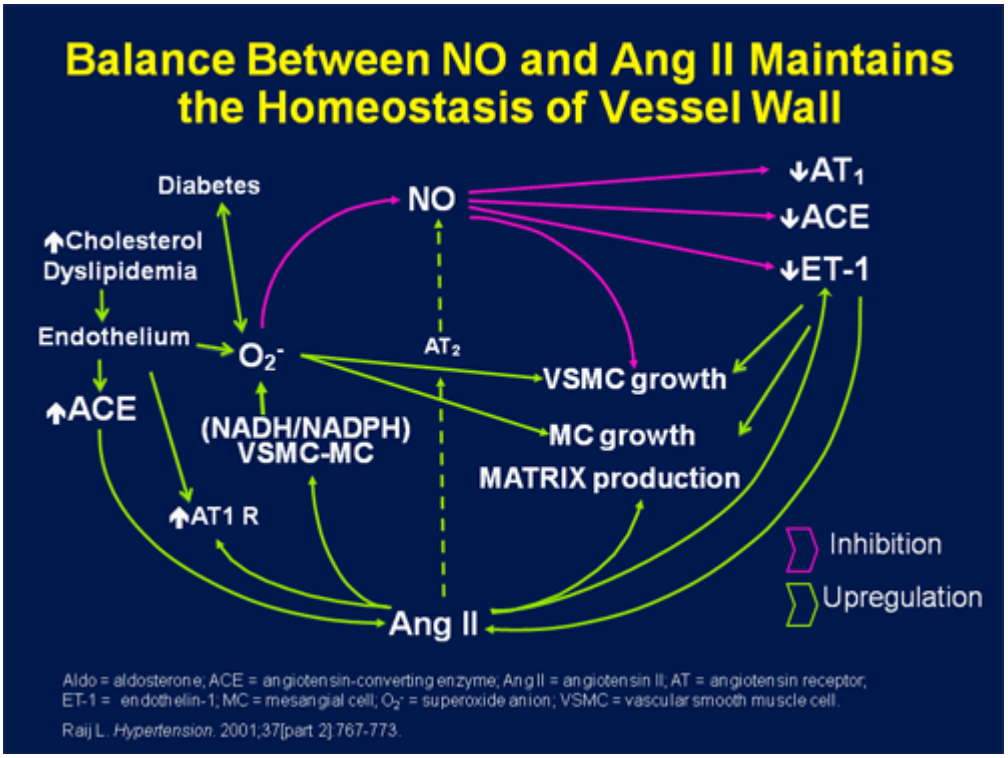
Slide 54.

Then this will drive a number of clinical sequela in the patients that we see —



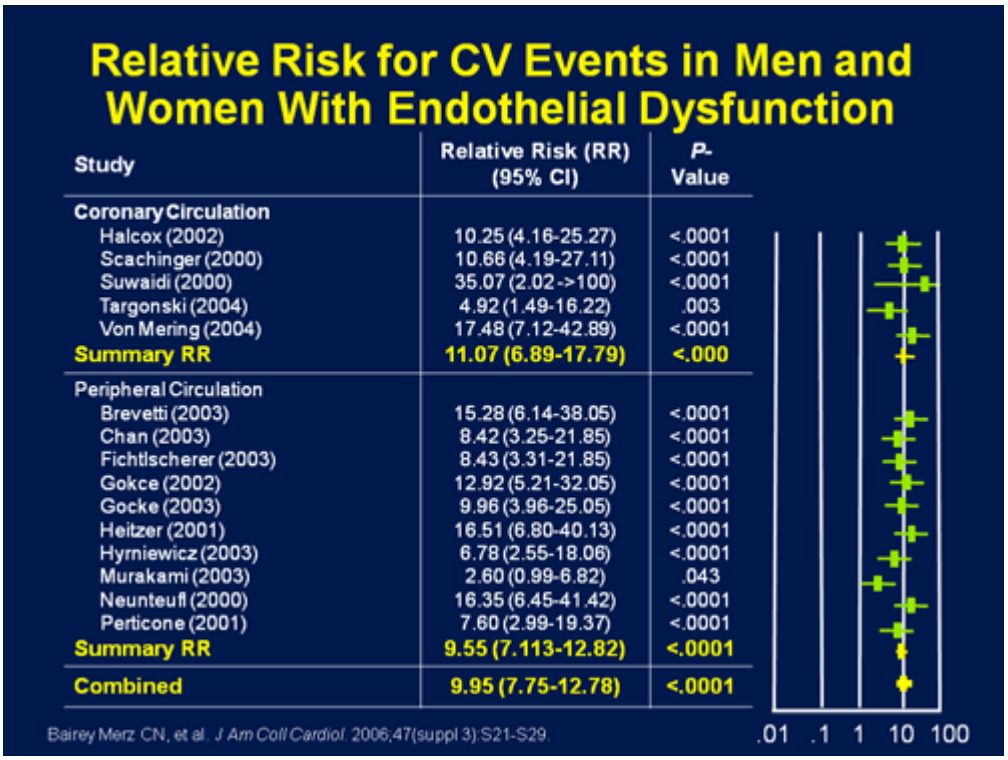
Slide 55.

— and is responsible ultimately for cardiovascular death, myocardial infarction, stroke, ischemia, heart failure, and so on.



Slide 56.

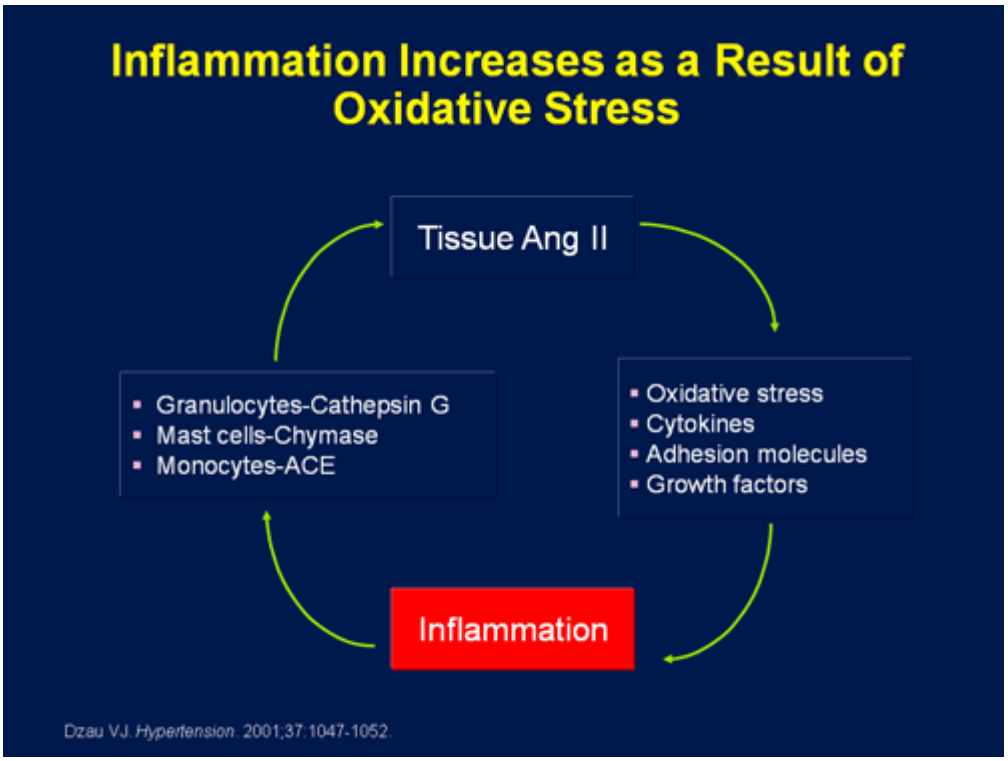
So critically at the present concept, the balance between NO and the reactive oxygen species determines the fate of the endothelium and that determines the fate of the patient. There are a number of molecules that disrupt this balance. One principal molecule is angiotensin-2 (Ang II), and Ang II has the ability to generate reactive oxygen species and basically inactivate NO. This then causes a reduction in the action of NO and all of the steps that I have outlined in the previous slides. So vascular smooth muscle growth is no longer inhibited, in fact it is stimulated. Matrix growth, likewise, becomes defective. Matrix production by the vascular smooth muscle cell is no longer maintained and it is possible that you can see abnormal remodeling.



Slide 57.

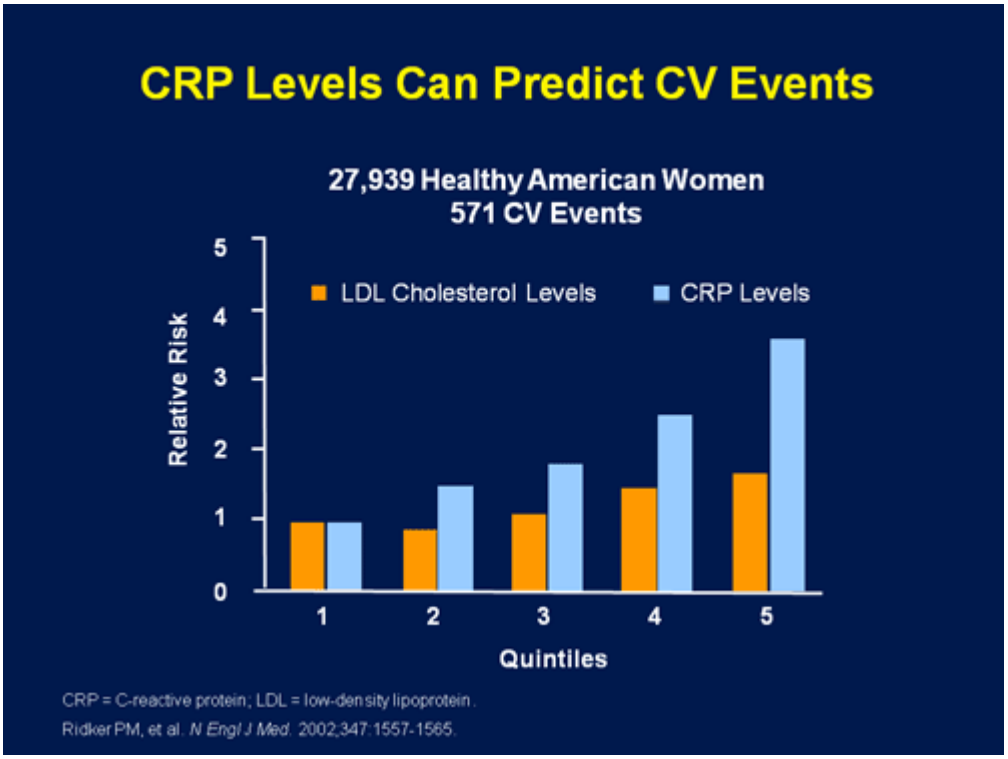
There have been a number of studies, in fact, I think I have summarized 15 or 16 on this slide, that have used endothelial dysfunction as a marker of defective NO production and then characterized patients with endothelial dysfunction over follow-up periods to examine the frequency of cardiovascular events. As you can see here, if a patient has coronary

endothelial dysfunction, the relative risk compared with patients without coronary endothelial dysfunction for a cardiovascular event is increased about 11-fold over follow-up periods that range from 1 to 5 years. The same is true for the studies that have examined endothelial dysfunction in the peripheral circulation, again an increase in risk of about 10-fold for a subsequent cardiovascular event if you have detectable endothelial dysfunction at the periphery. So clearly the risk for cardiovascular events in both sexes, men and women, amongst patients with endothelial dysfunction, hence a decrease in bioavailable NO, is elevated about 10-fold.



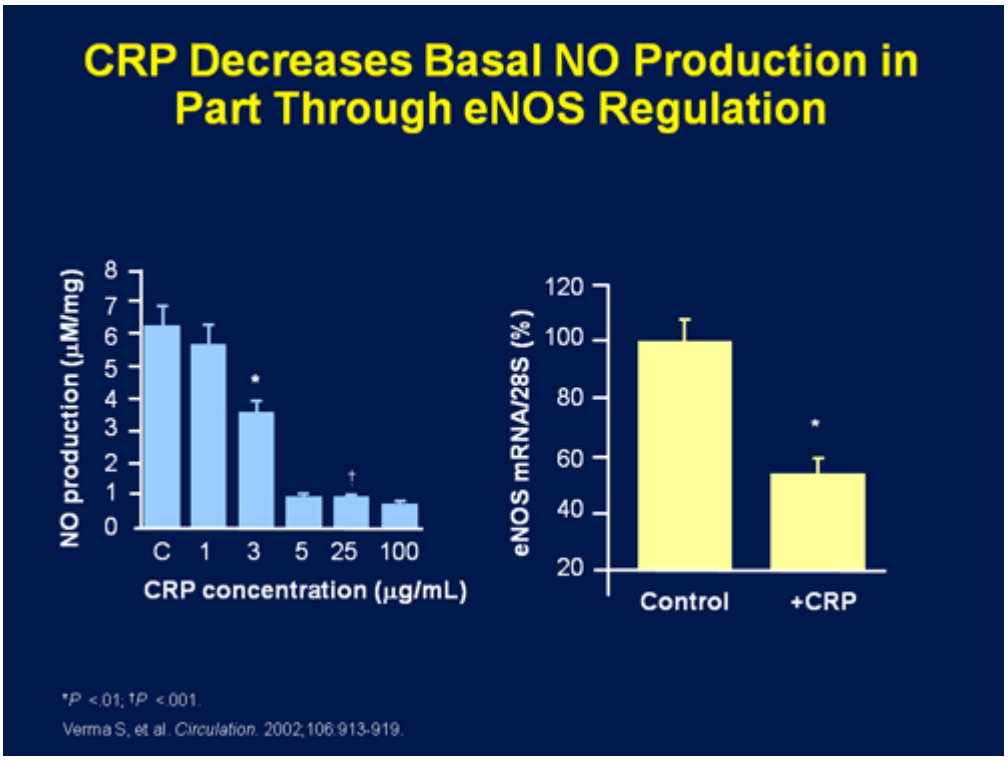
Slide 58.

We also know that inflammation increases as a result of oxidative stress. These are some of the potential mechanisms by which inflammation can result in the generation of Ang II at the tissue level, which can drive increases in oxidative stress to then inactivate NO. A number of studies have shown that markers of inflammation, such as CRP, are linked to the prediction of cardiovascular events over time.



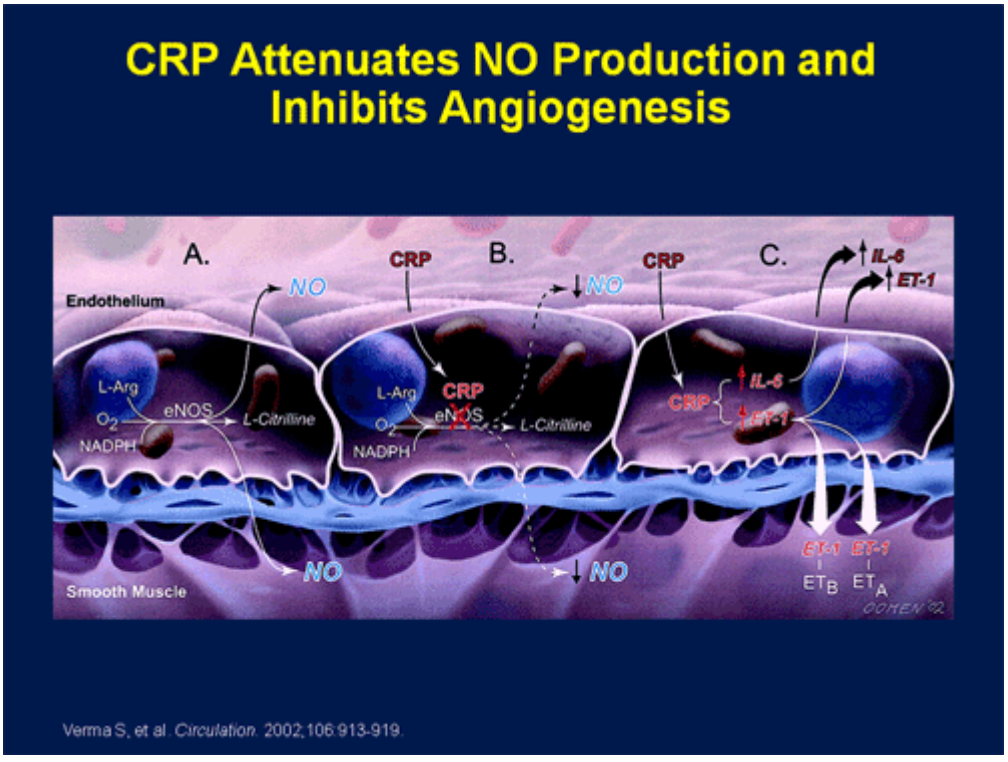
Slide 59.

In this report, which came from Paul Ridker, of over 27,000 healthy US women, it is clear that increasing levels of CRP predict subsequent risk for cardiovascular events despite only modest changes in LDL. In fact, increases in CRP at these lower levels of LDL are believed now to be predictive in models much better than other markers for cardiovascular events.



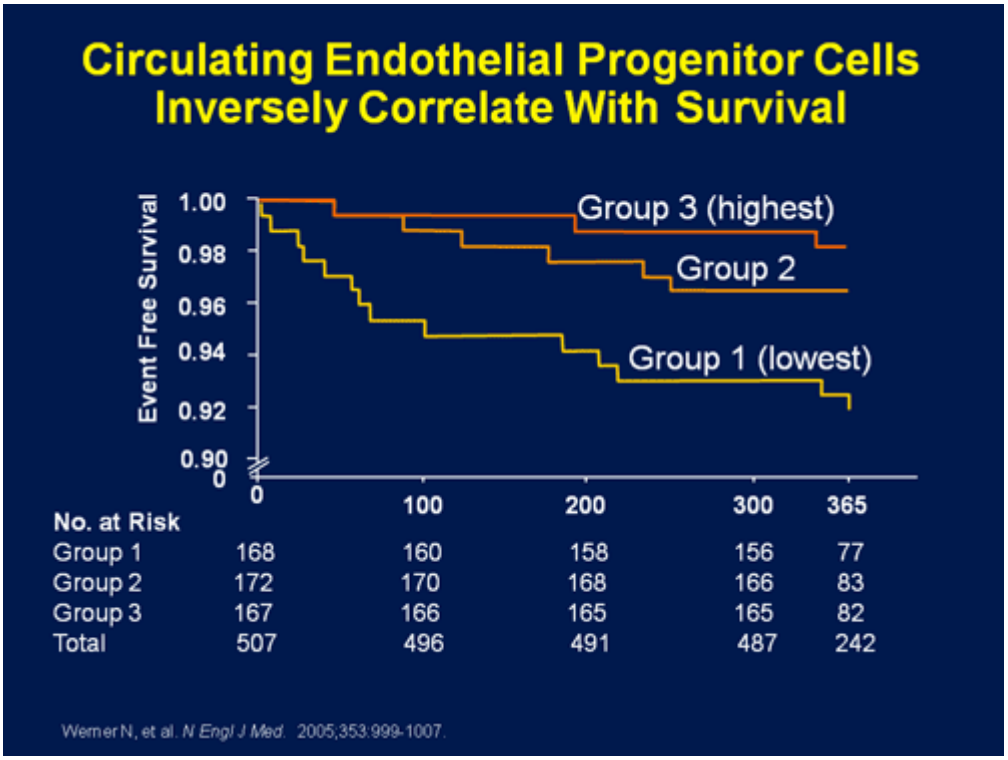
Slide 60.

Other studies have shown that CRP decreases the production of NO in endothelium partly through regulation of the enzyme eNOS. As you can see, as the CRP concentration is increased in these ex vivo models, the production of NO falls off. This is depicted visually here. It has been shown that CRP actually has the ability to uncouple the enzyme eNOS at the endothelial level, so this results in a reduction of bio-available NO and subsequently reduces the functional activity of the endothelial cell and that drives the production of a host of inflammatory cytokines to further perpetuate inflammation at the endothelial cell level.



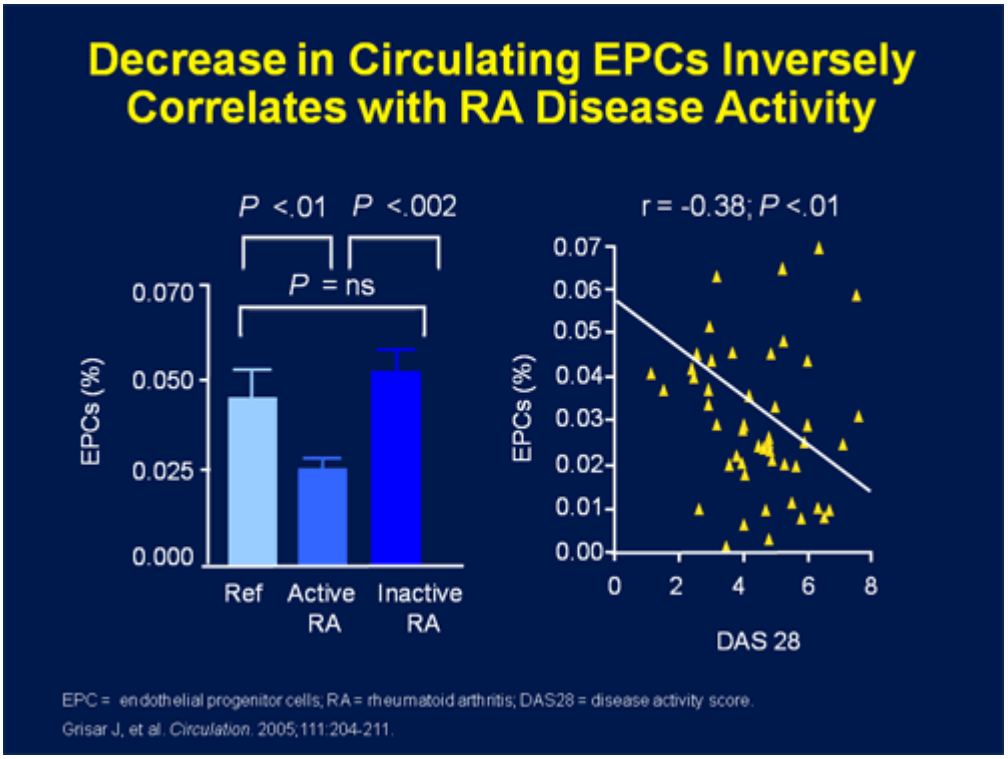
Slide 61.

It also inhibits other functions of the endothelial cell such as angiogenesis.



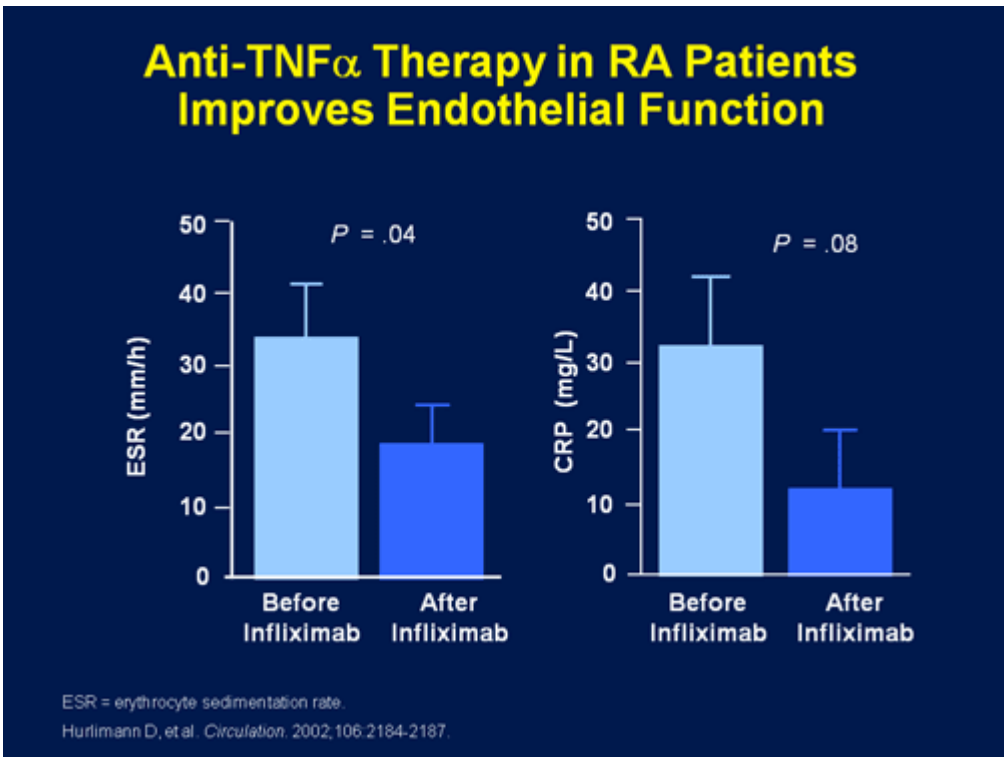
Slide 62.

A series of more recent studies has confirmed that circulating progenitor cells, which are cells produced in the bone marrow, are migrating or homing to repair defective endothelial cells, also contain NO. The number and function of these circulating progenitor cells is predictive of cardiovascular events. In this report, patients with cardiovascular disease who are in the lowest tertile of patients, just looking at the number of circulating progenitor cells, had reduced event-free survival compared with the patients in the higher tertiles. This has also been shown, not only for the number of the circulating progenitor cells, but for the function of the circulating progenitor cells. In other words, those who have the most defective function, for example, the ability for these cells to grow in cell culture, will have the highest risk for events over the subsequent year. So it is seems like defective NO production is a predictor of events even in the very earliest endothelial cell lines that are produced in bone marrow.



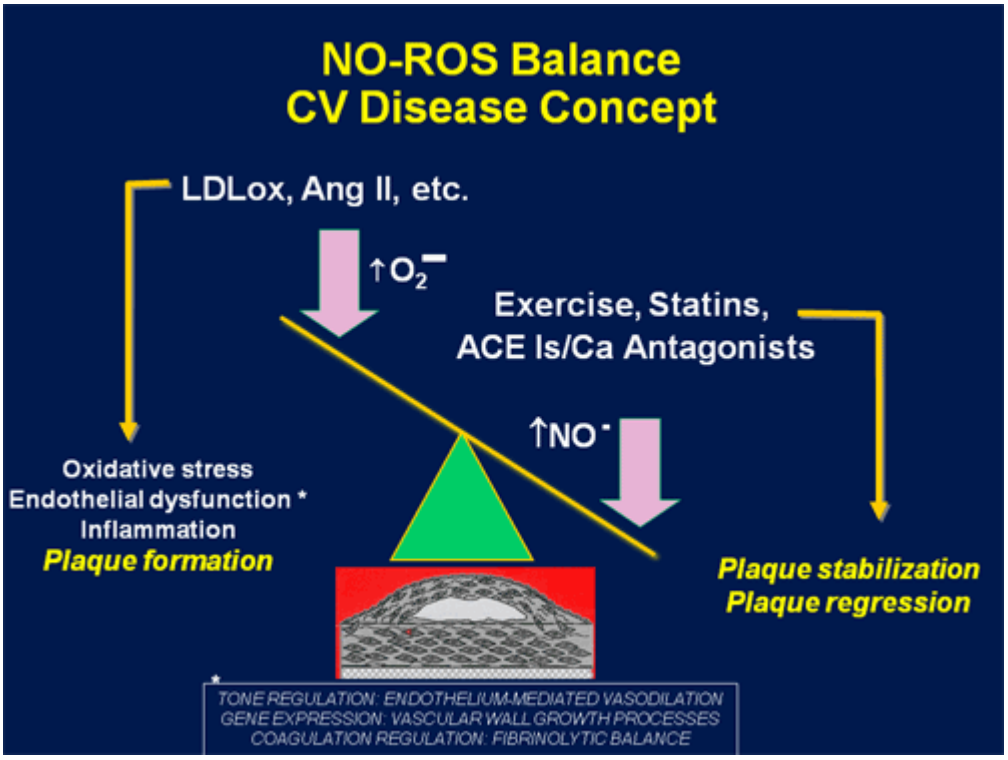
Slide 63.

The decrease in these circulating endothelial progenitor cells and also a decrease in their disease activity has been shown to correlate with inflammatory states. In this report, you can see that in a group of patients with rheumatoid arthritis, the patients who had active rheumatoid arthritis had about half the number of circulating endothelial progenitor cells compared with control reference patients without rheumatoid arthritis or compared with their counterparts who had their rheumatoid arthritis controlled by disease-modifying agents.



Slide 64.

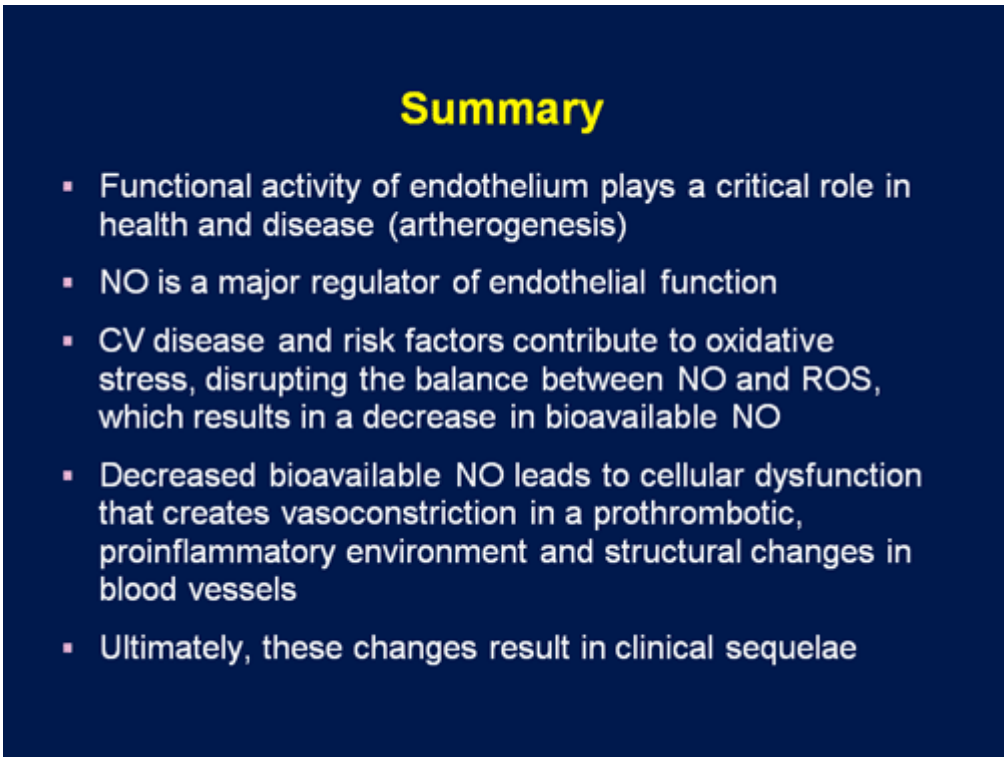
Indeed anti-TNF therapy in patients with rheumatoid arthritis to control inflammation has been shown to also improve endothelial function. Here patient sedimentation rates as well as their CRP are suppressed markedly after treatment with an anti-TNF molecule. In fact, the endothelial function in these individuals improves in parallel fashion.



Slide 65.

So what I have summarized for you in the preceding 15 minutes is a concept where NO and reactive oxygen species are

in balance. When they are balanced with appropriate amounts of bio-available NO, we have a healthy state where blood vessels are stabilized, plaques do not grow or progress, where tone is maintained in blood vessels, gene expression in the vascular wall is adjusted to an anticoagulant surface, fibrinolytic state at the surface of the endothelium. In disease states where there is an excess of reactive oxygen species, this balance is tipped to one where there is oxidative stress, endothelial dysfunction, inflammation, and the potential to drive plaque formation and disrupt other functions of the blood vessel wall.

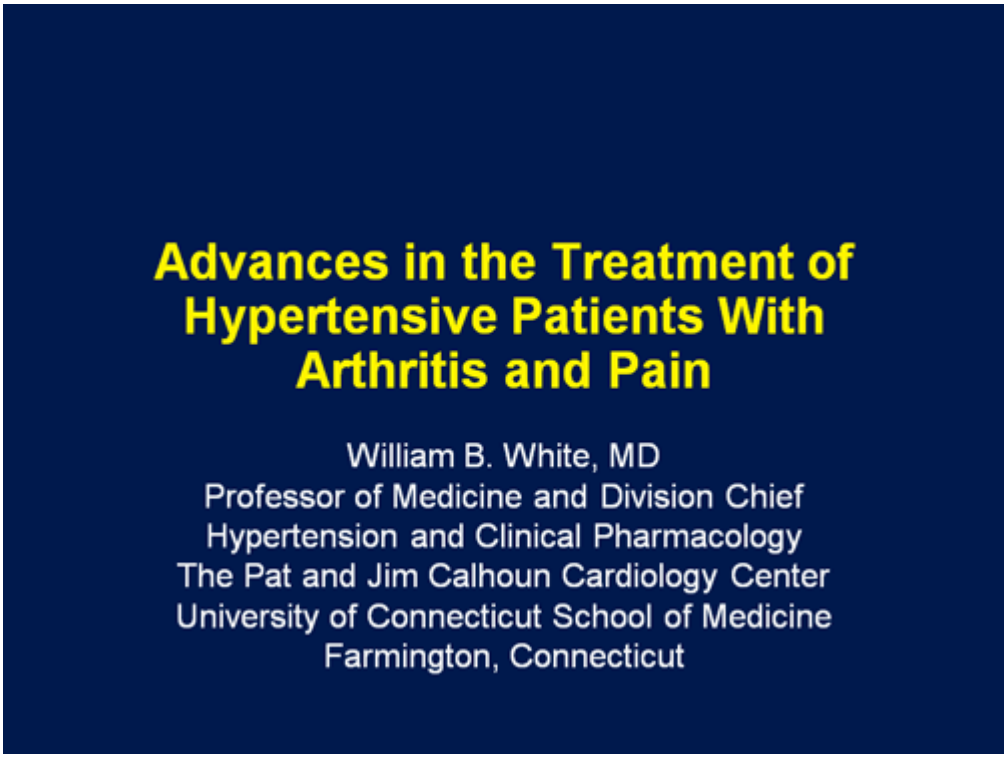


Slide 66.

So to summarize, the functional activity of endothelium plays a critical role in health and disease. NO is recognized as perhaps the master regulator of endothelial function. Cardiovascular disease states and its risk factor conditions contribute to oxidative stress, disrupting the balance between NO production and reactive oxygen species production and this can result in bioavailable NO. Decreased bioavailable NO leads to cellular dysfunction that creates an environment that promotes vasoconstriction as well as a pro-thrombotic, pro-inflammatory environment that results in functional and structural changes in blood vessels. Ultimately, these changes will lead to clinical sequela.

The next speaker in this symposium is Dr. Bill White from the University of Connecticut. Bill is professor of medicine and director of the clinical pharmacology division and hypertension division. His topic is Advances in the Treatment of Hypertensive Patients With Arthritis and Pain.

Advances in the Treatment of Hypertensive Patients With Arthritis and Pain



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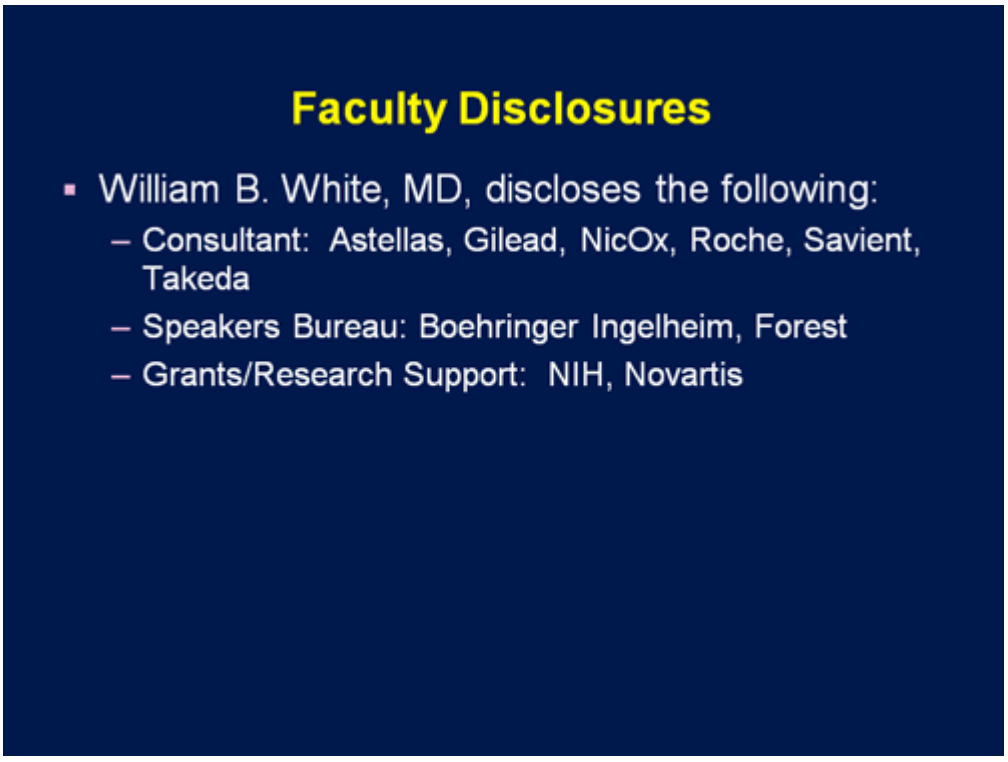
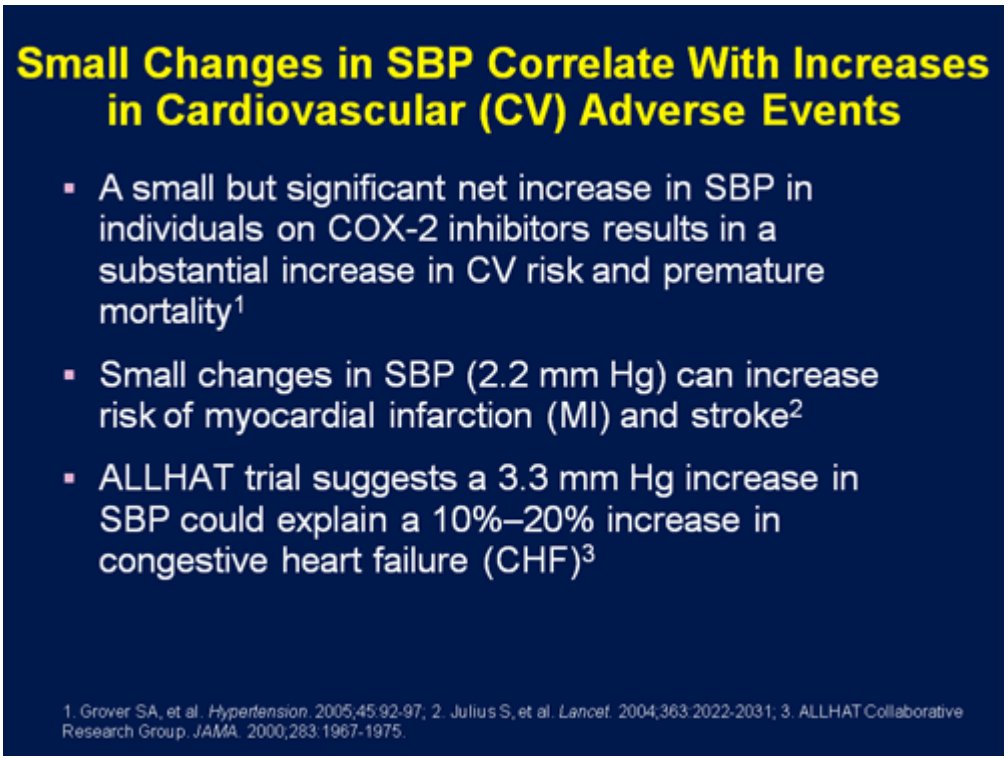


Slide 68.

Slide 69.

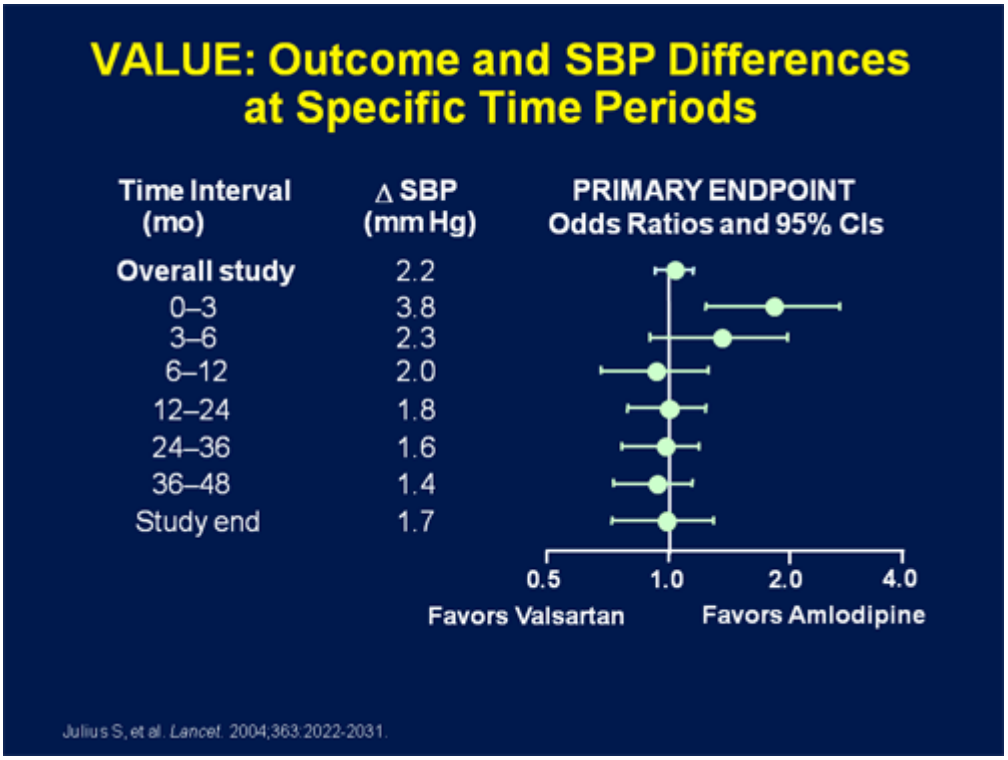
You have heard about the importance of the comorbidities of arthritis, vascular disease, hypertension, and so forth. You have also now heard about the importance of nitric oxide (NO) biologically and clinically in patients with cardiovascular disease and inflammation. I am going to try to do a little tying together of these 2 areas as I talk about some novel concepts in the treatment of arthritis in patients who actually have hypertension and cardiovascular disease.



Slide 70.

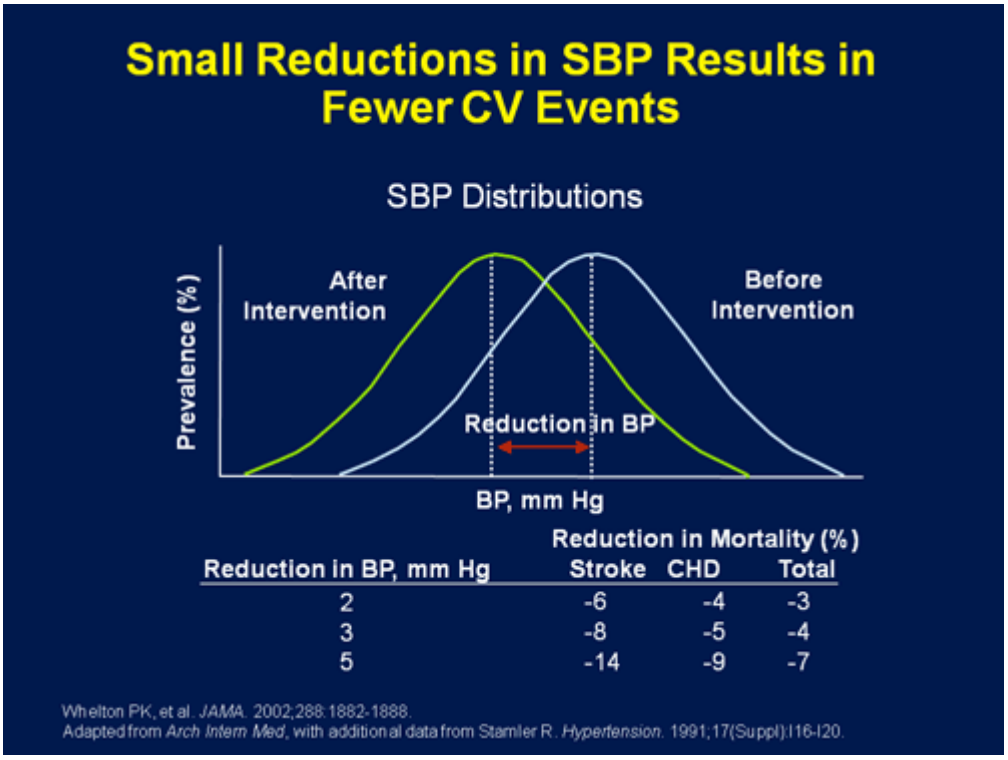
We know that, as you have heard, that small changes in blood pressure correlate with cardiovascular adverse events. In fact, one can argue about this to some extent at what threshold we see changes epidemiologically or in clinical trials,but it is about 2 mm Hg for systolic blood pressure and probably around the same number, 1.5 to 2 mm Hg for diastolic blood pressure. We have learned this both from prospective cohorts such as Framingham and other big analyses and from the differences in outcomes that occurred in clinical trials such as ALLHAT, in which a 3 mm Hg difference between treatment groups led to a very significant difference in congestive heart failure rates especially when you look at the rates on

doxazasin or lisinopril compared with other treatments, including chlorthalidone and amlodipine treatment populations.



Slide 71.

In the VALUE study, I think we learned something about timing and how long it took for these events to, in fact, develop, because in the VALUE trial half the group with cardiovascular disease and hypertension got valsartan and the other got amlodipine. Unexpectedly, the blood pressure was lower in the patients who received amlodipine for the first half of the year because of differences in doses and the inability to add second and third drugs up to that point in time. In that same period of just 6 months, a 2 to 3 mm Hg difference in systolic blood pressure translated into a very substantial difference in the rate of myocardial infarction and the development of stroke. So I think we learned that it does not take years and years in a population, especially if they have background vascular disease, to develop events when their blood pressure is not as well controlled.

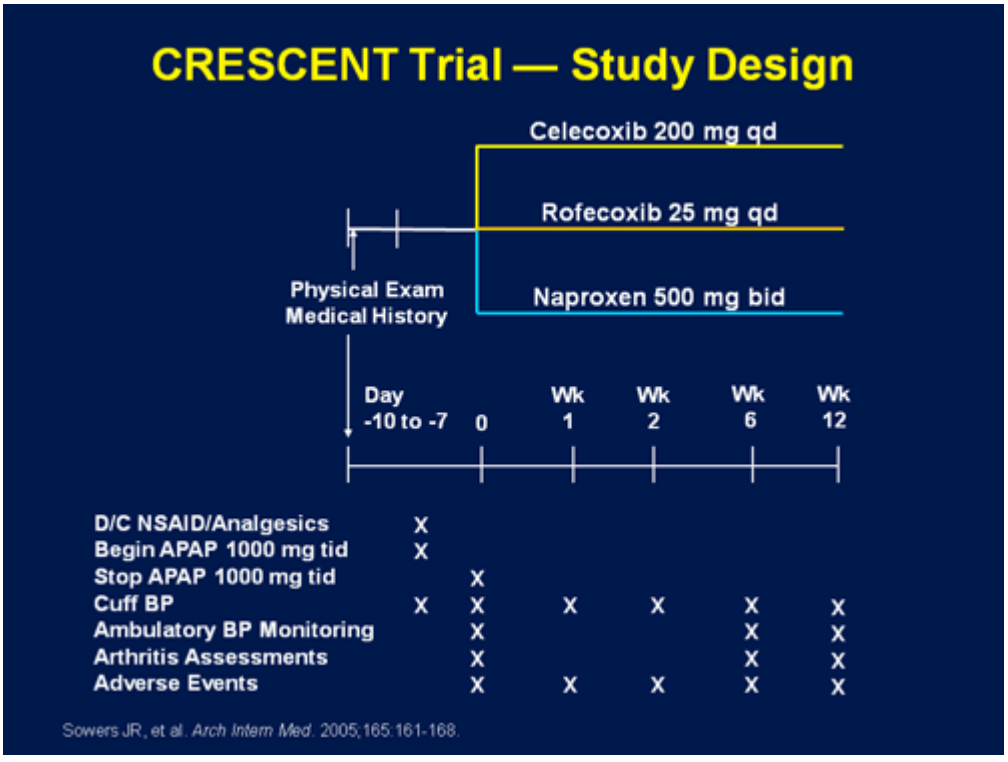


Slide 72.

If you put this in a picture of the relationship as a continuum of blood pressure as it relates to cardiovascular events, and we look at before an intervention this normally distributed curve of blood pressure and then after an intervention and then we examine the relationship between the reduction in blood pressure particularly in this case systolic blood pressure, a 2 mm Hg reduction in clinical trials leads to a 6% reduction in stroke and a 4% reduction in coronary heart disease mortality. If we go up to a 5 mm Hg reduction in blood pressure between treatment groups, this is even more impressive in that we now have a 14% reduction in stroke, 9% in coronary heart disease, and a total difference of 7% improvement in mortality. So I do not think we should discount small differences in clinical trials. As you saw from Dr. Whelton's presentation in the VIGOR trial, most people were thinking along the lines of prothrombosis, but we cannot extricate blood pressure from the equation because the blood pressure differences in those particular treatment arms were substantially different from each other for up to 10 months of median therapy.

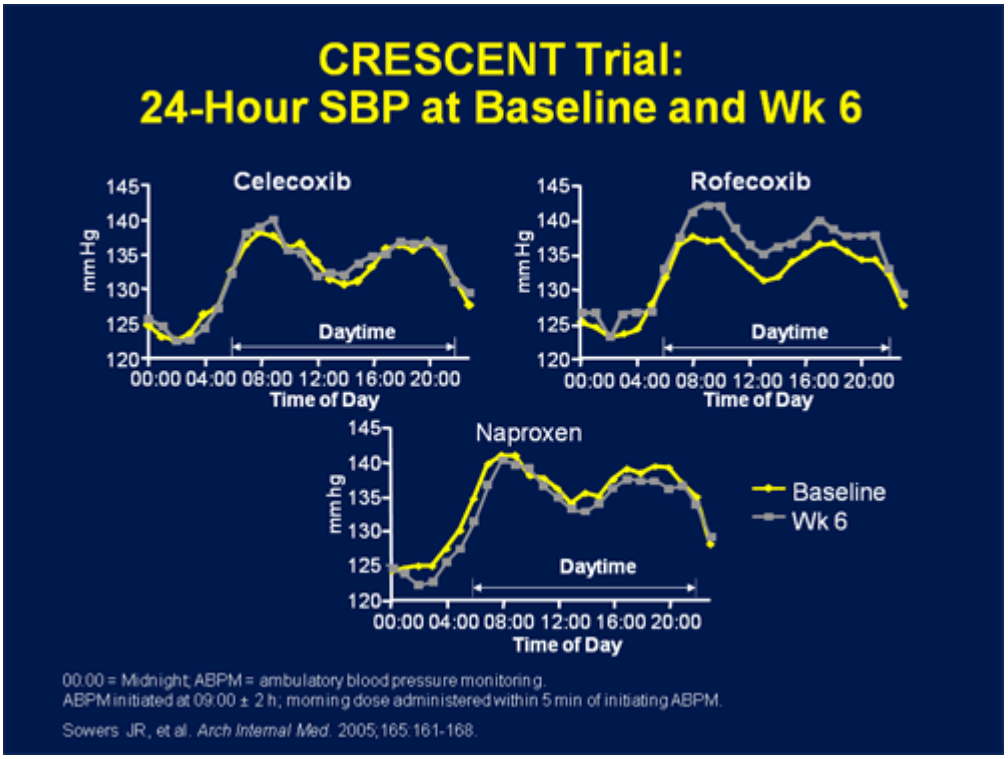
Slide 73.

What are the effects of the NSAIDs, just to reiterate a little bit?



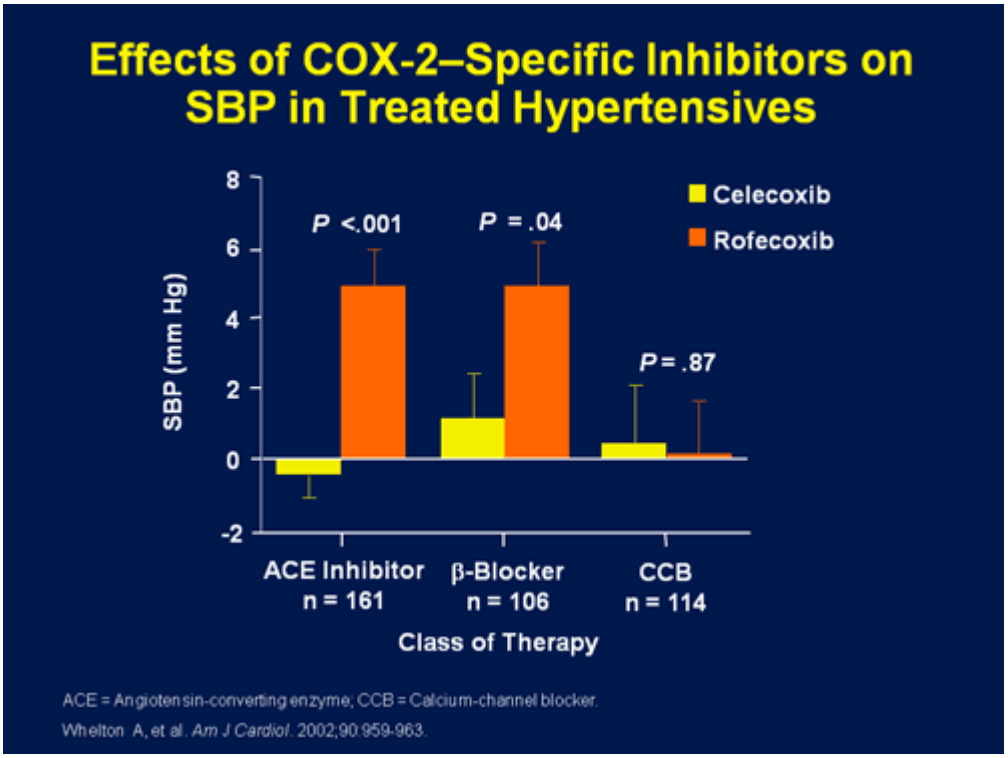
Slide 74.

So if we examine one study that Dr. Whelton and I participated in a number of years ago called the CRESCENT trial. We were trying to evaluate the potential to destabilize systolic blood pressure in a high-risk population, those with hypertension, diabetes, and osteoarthritis. You had to have all 3 comorbidities. We randomized about 500 such patients to celecoxib, rofecoxib, and naproxen. Naproxen was the control arm. We did not have placebo in this study because we did not think patients would stay in this study for 3 months because of the pain associated with their inflammatory condition. We did an intensive analysis in this study of the efficacy as well as the destabilization using 24-hour blood pressure monitoring.



Slide 75.

The efficacy was similar among the 3 treatment groups by week 2, so I think we can discount that as being a confounder of what happened to blood pressure. I will point out that these are the 24-hour profiles of systolic blood pressure after 6 weeks. The results were a bit different at 12 weeks and I will mention that in just a second. Here is the nighttime when people are sleeping, the early morning surge, and then the rest of the day. You notice each one of these curves has a little bit of a dip in the middle of the day after patients ate and were relaxing and having more blood go to their splenic circulation than their peripheral circulation. Plus there is the peak effect of anti-hypertensive therapies, but celecoxib and naproxen did not cause major destabilization of systolic blood pressure in contrast to rofecoxib, which in fact did throughout the entire daytime. At 12 weeks, there was little difference in the findings in the sense that the naproxen arm started to show a little bit of an increase in clinical blood pressure, which was significant for the systolic pressure, about 1.5 to 2 mm Hg. The other 2 groups stayed about the same. So if you want to look at it as outliers, about 30% of patients who were treated with rofecoxib became hypertensive, about 19% on naproxen, and 16% on celecoxib, keeping in mind that we did not have a placebo arm. So one of the things that we were very interested in at that time was what about the types of medications for the treatment of hypertension is going to create a difference in the effect.

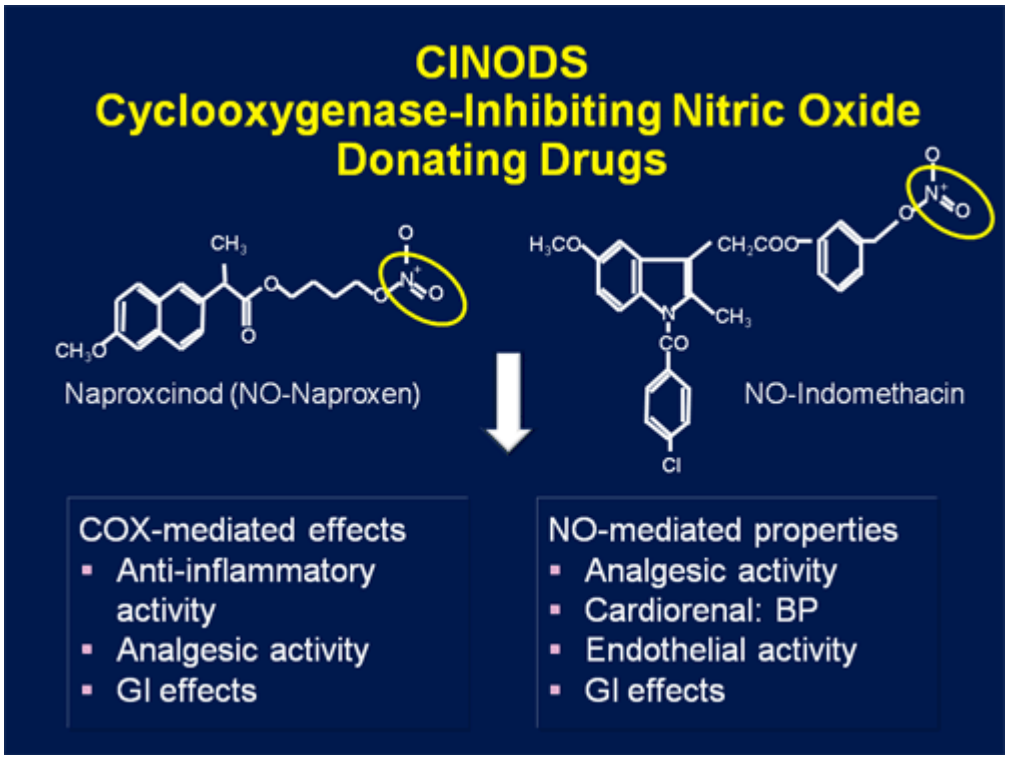


Slide 76.

We had the ability to do this in that 1100 patient study that was referred to earlier by Dr. Whelton in which we had about 300 or 400 patients who were on monotherapy of either a renin-angiotensin blocker, a beta blocker, or a calcium channel blocker. I just want to point out in the rofecoxib group, which had the destabilization by about an average of 3 to 4 mm Hg in the overall arm, that if you were taking an ACE inhibitor at baseline or a beta blocker, there is where you saw the most impressive increases in blood pressure. In contrast, those patients taking a calcium channel antagonist alone, this is monotherapy now, did not seem to show this result. So we began to recognize a couple of things, one is that if the patients had salt and water retention from their NSAID, they clearly caused an impact on blood pressure control on the RAS blockers and the beta blockers. As has been shown in many other studies, the calcium antagonists were somewhat insensitive to this phenomenon, just as if you were increasing salt intake. Secondarily, patients taking the renin angiotensin blockers, in particular, do need some substrate of prostacyclin for the full benefit of their pharmacological effect, That, of course, is being removed in part by the use of an NSAID or a COX-2 inhibitor, in this case rofecoxib.

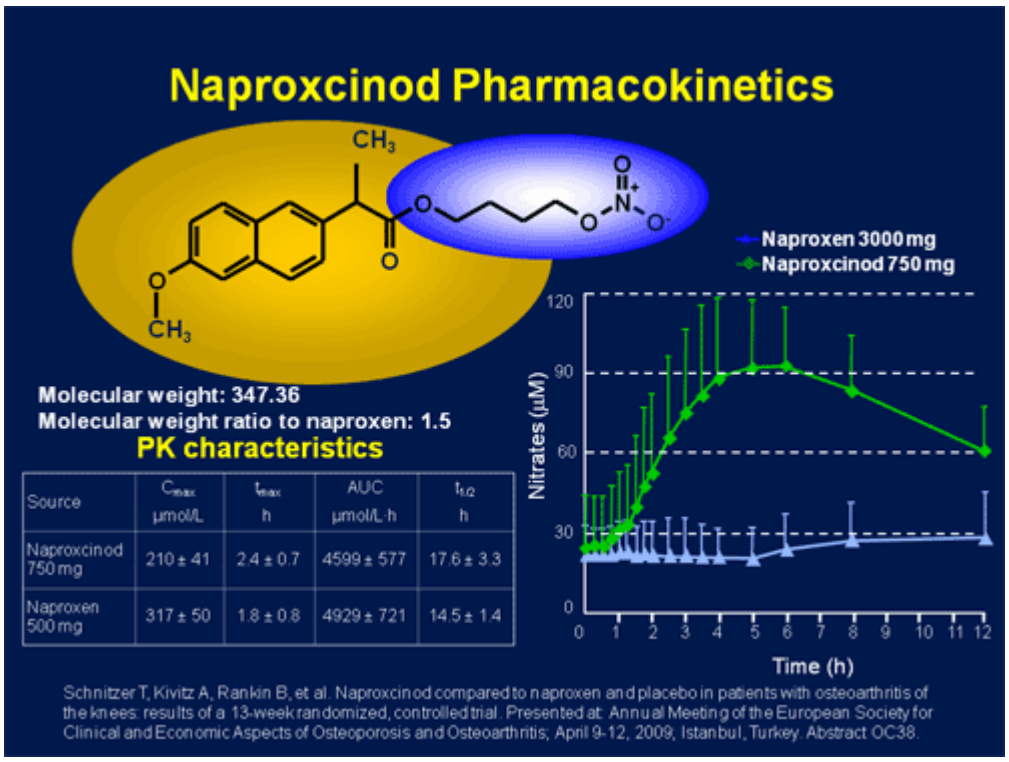
Slide 77.

This leads me to the discussion of what are the possible benefits of NO donation in the management of osteoarthritis patients who also happen to have hypertension.



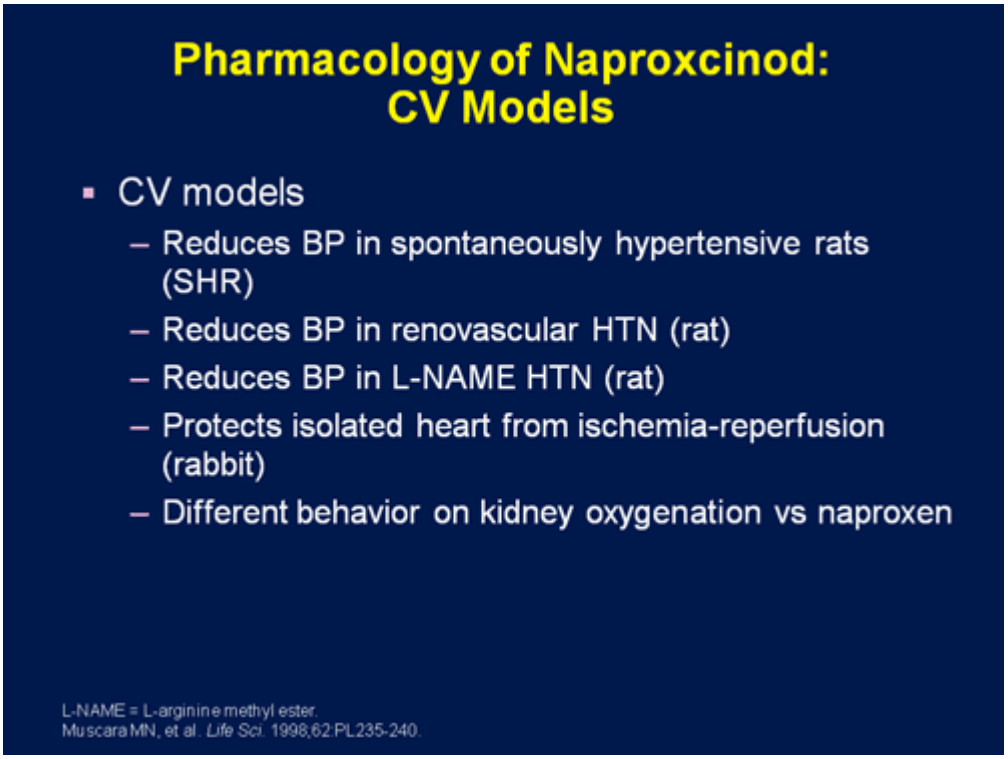
Slide 78.

There has been the development of a very interesting set of compounds, which we are referring to today as CINODs, cyclooxygenase-inhibiting nitric oxide donating drugs. The technology allows for a NO molecule to be linked by an ester to a standard NSAID molecule, such as naproxen or in this case indomethacin. This lends itself to having a dual effect. On the COX side, we have the anti-inflammatory activity, the analgesic activity, and, of course, in part the negative effect, which is GI toxicity from the removal of COX-1. On the NO-related properties, there has been some theoretical analgesic benefits, but primarily we are talking here about the effects on blood pressure, on endothelial activity, and also a potential benefit on the GI side. These are some of the things that were generated hypothetically when the molecules were manufactured.



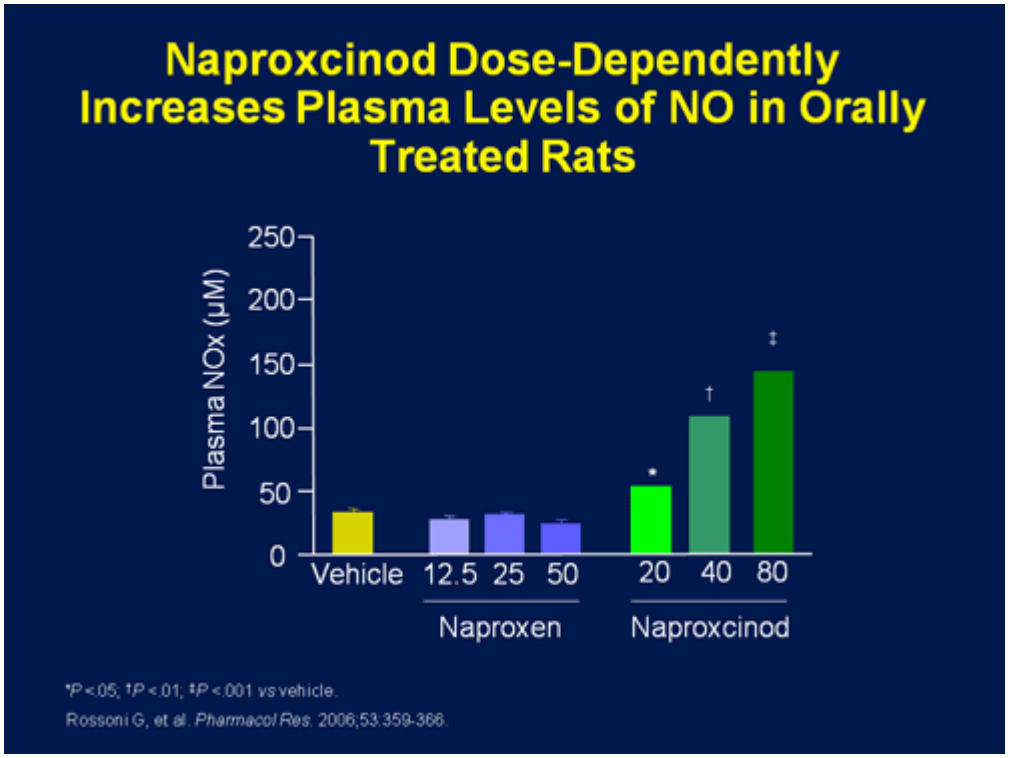
Slide 79.

In the case of naproxcinod, which has been under development for some time now, it has an interesting pharmacology. Of course, the immediate thing that happens when one would take naproxcinod is that the NO would be dissociated from the naproxen. So you can have the naproxen having its COX-1 and 2 blockade and you would have the NO benefits intracellularly. That occurs over a period of time and the NO diffuses intracellularly to have its major benefit. Pharmacokinetically, the naproxcinod concentration peaks in about 2 hours and has a half life that lasts for about 17 hours. It has been developed for dosing twice daily. It has a difference in molar effect, so it has 1.5 times the effect. So 750 mg of naproxcinod would be equivalent to 500 mg of naproxen, which is the standard twice-daily dose.



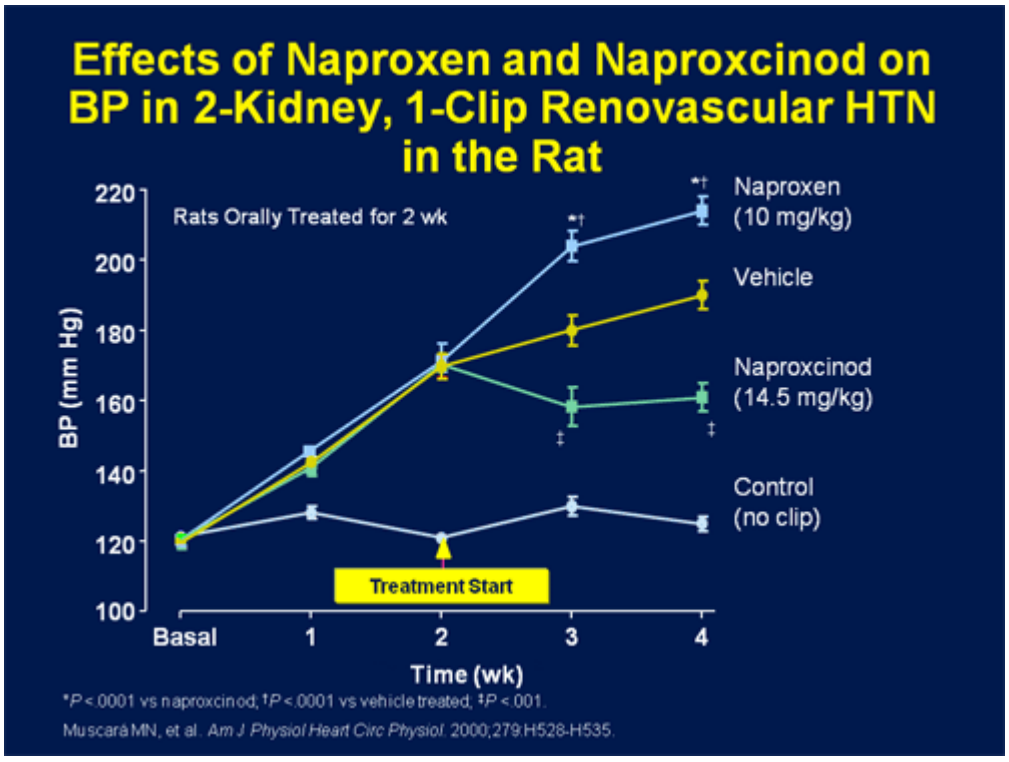
Slide 80.

In cardiovascular models — that are important for the understanding of what might happen in the future fin the human population — a number of observations have already been recognized. Naproxcinod was able to lower blood pressure by about 15% in a spontaneously hypertensive rat (SHR) model, which has a mean systolic blood pressure of about 210 mm Hg. These are very severely hypertensive animals that often have high stroke mortality. It also has, I will show you this in a moment, it has been able to reduce blood pressure in a renovascular hypertensive model as well as a model in which NO synthase is depleted by L-NAME and it also has been shown to have some protective effects in the ischemia reprofusion model in the rabbit as well as preservation of renal effects via reduction in oxidative stress.



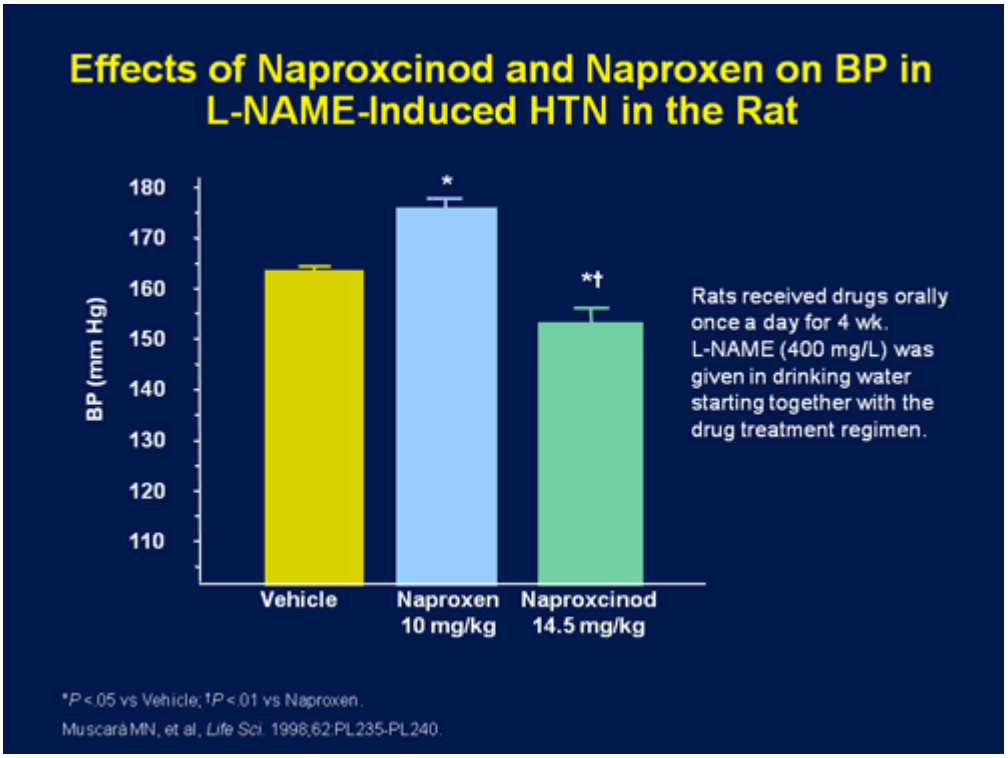
Slide 81.

Not surprisingly, when animals receive naproxen, there is no change in NO concentration in the plasma.With naproxcinod, it goes up in a dose-related incremental fashion.



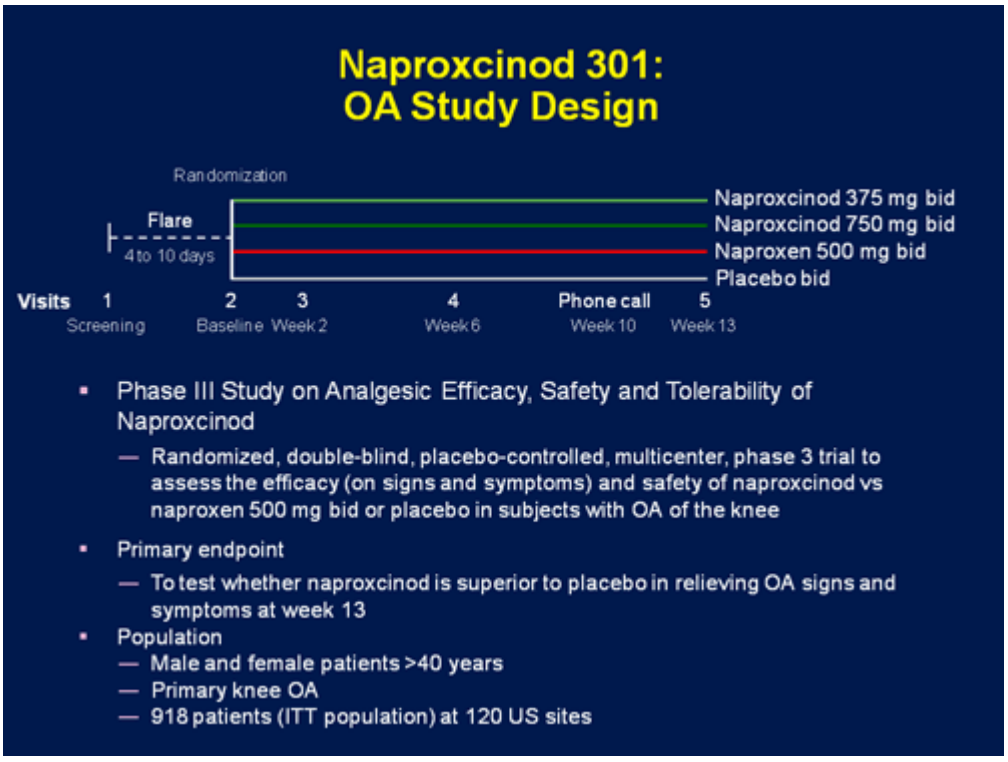
Slide 82.

This is the renovascular model I was mentioning. The way this was working was the animals received a clip on 1 renal artery at time 0 and had the other kidney remaining intake. This is the classic Goldblatt-2 kidney 1-clip model, which is angiotensin-dependant. As you can see, the blood pressure began to go up in the clipped animals right off the bat and the unclipped control animals stayed stable. At 2 weeks after that surgery occurred, the animals were treated randomly with naproxen, vehicle, and naproxcinod. Of interest, the animals treated with naproxen had even higher blood pressures than the slope for the untreated animals, whereas naproxcinod was demonstrated to reduce blood pressure in this model despite the fact that renin and angiotensin concentrations were virtually identical in all 3 treatment groups. So there was no confounding occurring with the level of renal artery-induced activity.



Slide 83.

In addition, in the L-NAME model, of course, which is a direct inhibitor of NO synthase so NO levels fall. In that model, you can also see that naproxen increased blood pressure significantly. Naproxcinod decreased significantly relative to vehicle and more significantly relative to naproxen, so there is evidence of a benefit in particular in that population as well.

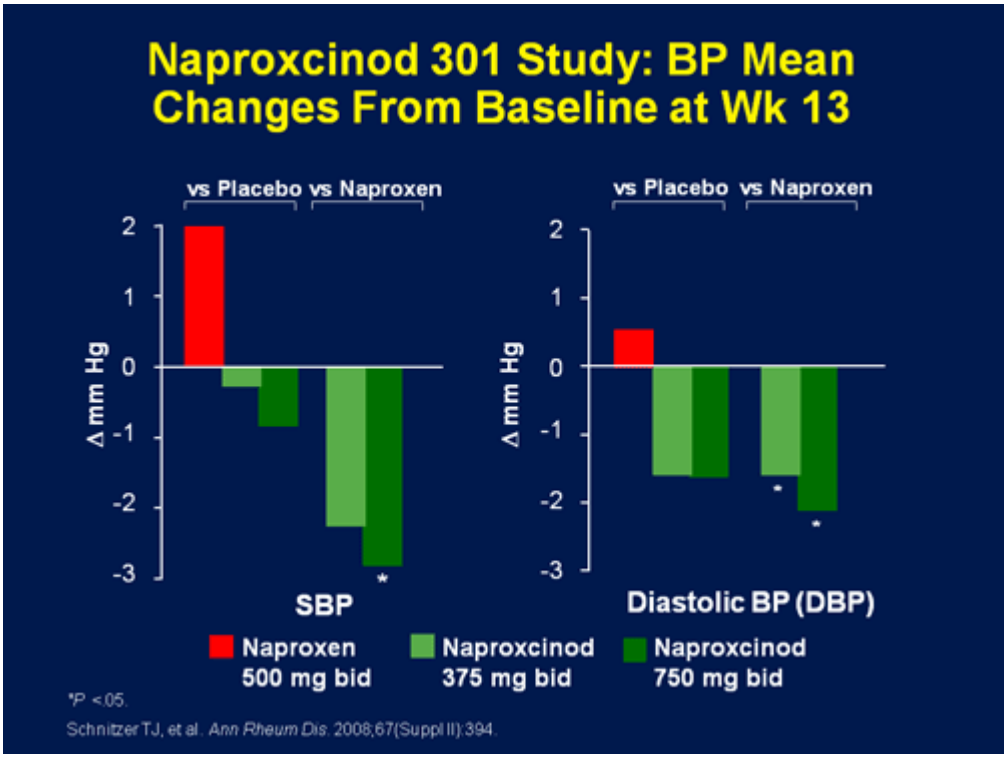


Slide 84.

I would like to now segue into a discussion of what is going on in the clinical arena with naproxinod in the treatment of osteoarthritis. Several studies are underway or have been performed in human patients with osteoarthritis, some of which have hypertension and some of which do not. I would like to mention that at the American College of Cardiology, we did present the Naproxcinod 301 study, which was the first pivotal trial for the evaluation of how this drug was working in the osteoarthritis patient with a focus on blood pressure.

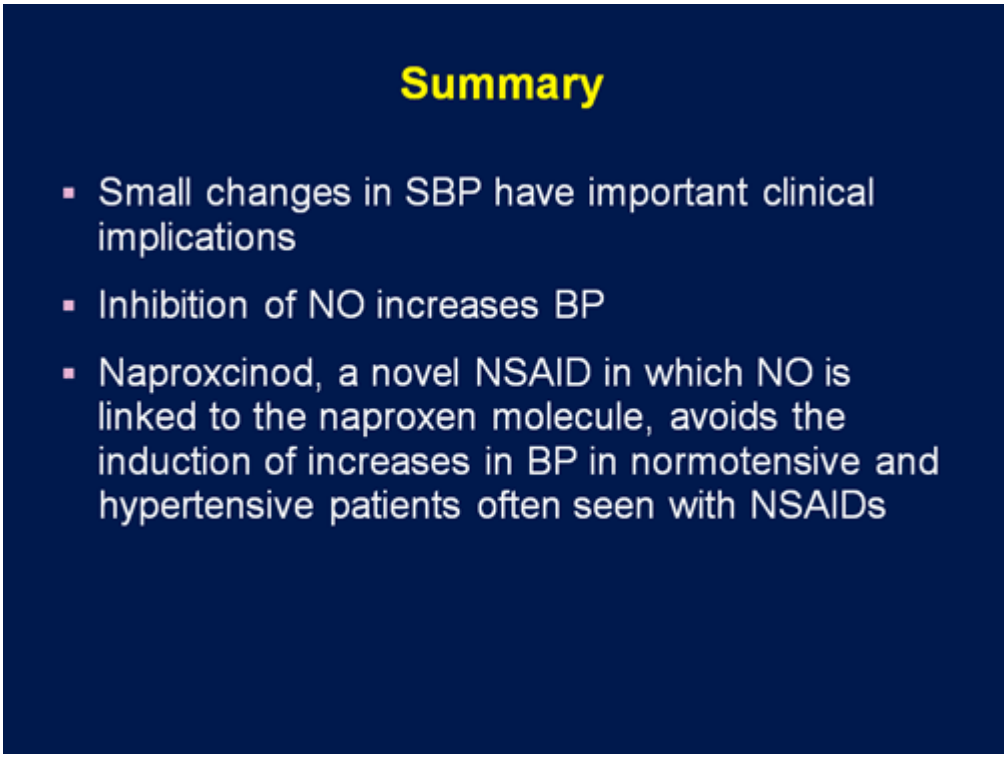
The study was designed to evaluate the efficacy, tolerability, and safety of naproxcinod at 2 doses — 375 mg twice daily,

which would be bio-equivalent to naproxen 250 mg twice day, and naproxcinod at 750 mg twice a day, which is equivalent to 500 mg of naproxen BID or twice a day. Then, of course, a control arm of naproxen and a placebo arm. Of importance, this is the only study I know of in which we had a standardized method of measuring blood pressure and had a placebo arm for an entire 3-month period, so that will give us some very interesting information. This was done in a 1-1-1-1 randomization scheme with 918 patients, about 220 to 230 patients per treatment group. It was randomized, double-blind, multi-center and was the first of 3 major trials in which the same question was being addressed, to have eventually a total of nearly 3000 patients studied with this particular problem. As expected, the population is mostly women, about two-thirds to 70% are women and the classical age of a population like this is typically in the 60s, the mid-60s.



Slide 85.

Now we will talk about the changes in blood pressure, because the efficacy was proven to be effective in all 3 active treatment groups. This figure actually characterizes naproxen in red and the 2 doses of naproxcinod versus placebo on the left-hand portion of this panel and then versus naproxen versus the 2 doses of naproxinod on the right-hand panel. The systolic pressure is on the left and diastolic pressure on the right. In contrast to placebo, naproxen raised the blood pressure by about 2 mm Hg systolic and by about 0.5 mm Hg diastolic. I should point out that in this population who is their 60s or 70s, who has primarily systolic hypertension, we typically do not see much change in diastolic pressure due to vascular stiffness, widened pulse pressure, and so forth. The naproxcinod population showed no difference with placebo, even somewhat of a numerical reduction in diastolic pressure, but this was not statistically significant. In comparison with naproxen, the systolic pressure on 375 mg fell by about 2 mm Hg and the 750 mg by 3 mm Hg, which was statistically different. The diastolic blood pressure, in fact, was significantly lower on naproxcinod relative to naproxen by about 2 mm Hg on the lower dose and 2.2 mm Hg or so on the higher dose.



Slide 86.

In summary, I think we do understand that small changes in blood pressure, primarily from clinical trial data, have led to important clinical implications and reductions in harm. Inhibition of NO is associated with an increase in blood pressure. Naproxcinod, which is the novel non-steroidal anti-inflammatory drug, in which NO is linked to naproxen, avoids this induction of increases in blood pressure in normotensive and hypertensive patients often seen with NSAIDs as a class. Thank you.