ROBERT BONOW: I have no relationships to disclose. None other than the fact that I am humbled by learning more about Michael Beardslee and the opportunity to share his memory with you. If don't know if you've read these remarks from Alan Braverman, but they're very touching as to the family that you have here. And I hope that Northwestern we've got a very similar family, and our fellows say the same nice things about us that your fellows say about you, Doug. So we shall see.

AUDIENCE: There haven't been.

[LAUGHTER]

ROBERT BONOW: So I want to tell you a little bit about my story. This is kind of a story for the fellows and maybe for the mentors. This is me in 1992, and I'm leaving the NIH. That's my mentor, Steve Epstein. Now, it's remarkable how I look a lot different right now than I did back then. Steve hasn't changed a bit. He still looks like that. He was my mentor.

Here's the reason I'm telling this story. I went to the NIH in 1976 out of my residency. I was going to do two years and then move on. I wound up spending 16.

As I was going to the NIH, there was a very young guy coming out of the NIH to Penn, where I was, having been there a couple of years. And I thought I would ask him what I should do when I went to the NIH. He's now a very established echocardiographer. I'm not going to mention his name, but offline I can talk to the echo people about who this is. He's a very established senior echocardiographer.

And at that time he says, well, there's lots of things going on at the NHLBI, lots of interesting stuff. But here's my advice. Don't get involved in those aortic valve protocols. They're not going anywhere. I was stuck in the mud with them for a couple of years, and they're just not going to happen.

And so I went to the NIH. I bonded with Walter Henry and Dr. Epstein. And about six months into my tenure there, they said, well, we have these data on aortic valve disease that we just need to have a young person like you put some energy into it, see if we can turn these around. And at that point, I had to make a decision, because I was given this strong advice to go in this direction.

But it's the connections you make with people. It's the camaraderie and the chemistry of mentorship that kind of sometimes steers you in a different direction. So your careers are built upon those kinds of indescribable unexpected things that occur, where there's a fork in the road and you've got to make a decision. And then, so knowing your options and recognizing those options, becomes very, very important. And a lot of it's just total serendipity. I could have done something else entirely.

But it worked out pretty well, and I got involved in aortic valve disease. And along that time, there were some very seminal papers about aortic stenosis. This was kind of a must read for my generation. It's Paul Wood, seminal preeminent cardiologist in London, the 1950s. He died prematurely from coronary disease around 1962.

But this was his paper on aortic stenosis, where it was his clinical observations, where he makes a point that aortic stenosis is a simple mechanical fault which if severe enough imposes a heavy burden on the left ventricle. And sooner or later, overcomes it. That's pretty well put. That's probably true.

What's not true anymore is this whole idea that it's a simple disease. It's no longer simple. It's very complicated. It's changing in front of our eyes, and our knowledge about it and all of our new treatment options suddenly make this a very exciting subject. This talk may have been much less interesting 10 or 15 years ago.

Well, we know that aortic stenosis comes in three varieties, but we're not talking about rheumatic disease, because you and I see very little of that. So for you and me, it's mostly two varieties, of the bicuspid valve on the left, which occurs in somewhere between 1 and 1/2% and 2% of the population, depending upon our statistics. And then the disease on the right, which is what had been a normal aortic valve, which through time, and wear and tear, and risk factors that we'll talk about, leads to calcification and stenosis.

So we think of the valve on the left as being a disease of younger people. Which, of course, it is. The 20 or 30-year-old who shows up with aortic stenosis most likely has bicuspid disease. But it's not a disease only of young people.

Bill Roberts, another one of my mentors at the NIH when I was there in his pathology lab, has a study from his group in Dallas. These are data from explanted valves at surgery, patients with symptomatic aortic stenosis. And he determined that over the age of 60, 50% or more of men have bicuspid valves. And over the age of 81, one third of the men still have bicuspid valve.

We replaced a valve recently in a 92-year old woman who had a bicuspid valve. So it's not a disease only of young age. So this has some implications, of course. So if you're talking about TAVR, which we'll talk about, and that threshold starts getting reduced at the younger ages, well, we're going to see a lot of bicuspid valves.

And although there have been series of bicuspid valve patients getting expandable percutaneous delivered valves, the technology yet is not totally designed for that. And there's been no trial of patients with bicuspid valves. And of course, the other reason to know if a patient has a bicuspid valve are the things the Dr. Braverman is so good at educating the fellows about, and that's the associated aortopathy, which I'm sure is well-known to all the fellows here, but less well-known in many other corners of the world.

So what's going on bicuspid valves are related to aortopathy? So back in my training, we were taught that the reason the ascending aorta enlarges is because of the jet effect of the bicuspid valve. It's termed post-stenotic dilatation.

And we talked about that for a couple decades, until molecular biology came along and started telling us that the embryology of aortic, of bicuspid aortic valve disease, is associated with inherent abnormalities in cell signaling.

You've got abnormalities of the aortic matrix that you can see here. Several studies, quite well done, pointing out increased degeneration of elastin and collagen-rich extracellular matrix, increased expression of MMPs and decreased expressions of tissue inhibitors of MMPs. Increased vascular smooth muscle cell apoptosis, and excessive TGF-beta signaling, which sends some signal to us that that could be perhaps a target for therapy.

And so it shifted to this concept that this is more of a cellular and self-signalling process, why the aorta will enlarge. But we need to stay tuned, because now we've got some other data coming down the pipe. This is a 4D MRI study by Michael Markl in our group in a series of patients with bicuspid valves.

And a normal valve will produce laminar flow in the aorta. When you have a bicuspid valve, you get these high-velocity vortices that you can see and measure and quantify. You can also identify the wall stress on the aorta itself. And when one does that, one sees interesting findings. That if you have a right-left fusion, the wall stress occurs in the lateral wall of the ascending aorta. And when you've got a non-coronary cusp fuse, then the wall stress and the hot spots occur in other areas.

Paper by Guzzardi and coworkers with Paul Fedak working with our group, has a paper in [INAUDIBLE] about a month ago where we did biopsies in patients having replacements of the aorta. And those hotspots, those heat maps developed by MRI, are the areas in which one sees the increased [INAUDIBLE] and the increased TGF-beta signaling, and also the decrease in elastin fibers. And so we may have some noninvasive ways of identifying where some of these biochemical abnormalities occur.

So what's going on here is probably a combination, where both camps are probably correct. There are indeed some cellular signaling abnormalities, but there's also probably some physics involved. And maybe there's crosstalk there, where the scientific community can come together and keep moving the science forward. This is now the subject of a R01 application that one of our young faculty is putting in.

Well, moving forward, whether it's a bicuspid valve or whether it's a tri leaflet valve initially, the process occurs that these cells become thickened and calcified. Probably the bicuspid valve does that at a younger age, because of the increasing stresses related to the higher velocity through that valve.

Let's just talk now about the valve itself. It's also an aging phenomenon. And so what one sees, as I'm sure you've seen before, with an aging population, one sees an increased prevalence of significant aortic valve disease, which is usually aortic stenosis, as shown in these population data from Olmstead county and three large US cohorts published by Nikomo and co-workers. So over the age of 75, somewhere in the ballpark of 5% to 6% of individuals have significant aortic stenosis. And of course, now with TAVR, we're seeing a lot of those elderly patients coming to us.

So what's driving this? Is it just wear and tear on the valve? That's, again, the concept I was given. A rusty gate left out in the rain long enough will get tight, and a valve which opens a couple of billion times during a lifetime can develop wear and tear. Well, it's not a passive process, as I was once taught. It's actually an active proliferative inflammatory lesion.

Here's some data to support that. It's a paper from the Framingham offspring study. Patients enrolled 30 years ago, 40 years ago now. Mean age in enrollment was 34 years. They didn't have CT imaging on enrollment, but they did CT imaging on follow up, between 2002 and 2005. So 30 years later, these individuals get a CT scan, and they go back and look at their baseline Framingham risk factors, with a median follow up of about 27 years, as you can see.

And what's plotted here across the x-axis is the Framingham risk score. Low risk, intermediate risk, high risk. And on the left, we see the prevalence of aortic valve calcification, higher in individuals who have a higher Framingham risk score. And on the right, the actual calcium burden being higher in those individuals as well.

This is followed by some other seminal papers looking at the impact of other inflammatory markers, like metabolic syndrome and diabetes. At the bottom, we have a paper by Katz and co-workers working with Matt Budoff, showing that both men and women, if they are having metabolic syndrome in red, or diabetes in green, higher likelihood of aortic valve calcification.

And these studies from Philippe Pibarot's group as well, showing individuals who have either a low Framingham risk score on the left, or a higher Framingham risk score on the right, with or without metabolic syndrome. Showing metabolic syndrome is in red, that the rate of aortic valve stenosis progression is greater. So patients are progressing at a more rapid rate when they've got metabolic syndrome, compared to no metabolic syndrome.

And so there's a story here. We know from valves explanted at the time of surgery, shown here by O'Brien and Catherine Otto and co-workers, that the valves that are thickened and getting calcified also show evidence early on of macrophage infiltration, and infiltration also of atherogenic lipoproteins.

Fast-forward now to the current era, where we can go through lots of other papers that kind of led to some of these observations. But now in 2012, Dweck and coworkers used positron emission tomography to look at calcification and also inflammation, using that F-18 sodium fluoride as a marker of calcification and FDG as a marker of inflammation. And showing that the areas that are calcifying through the recognition of sodium fluoride activity are the same areas that are showing areas of inflammation.

And then we have other data. Here's some data of valves removed again, at the time of surgery, showing [INAUDIBLE] regulation of phospholipase A2, which is a protein that will degrade phospholipids into fatty acids and phosphatidylcholine, which then is a modulator of inflammation. And down on the right, we see that that same activity, where you've got the higher activity of PLA2 is where you've got oxidized LDL going on as well.

And so nice, interesting new concepts, but Paul Wood was pretty good at this as well, back in the 1950s. He was saying, you know, it's unclear whether aortic stenosis in elderly and middle-aged subjects is atherosclerotic or rheumatic. So we've got new tools and good ways of testing things, but a lot of our ideas are kind of old ideas.

If you look hard enough, you might find this vectors of pathology paper from Germany in 1902, where an astute pathologists was beginning to wonder whether these valves he was seeing were really rheumatic, or whether they just kind of looked like atherosclerosis.

And then finally, in the genomic era, there's this [INAUDIBLE] study. Thousands of patients who were studied looking for the associations of valvular calcification and aortic stenosis against a genome, identifying a hot spot here in chromosome 7, which is where LP little a resides. And if you're actually interested in following this literature, you would have seen a paper last month from Philippe Pibarot's group, [INAUDIBLE] and coworkers, finding that individuals who have higher LP little a are patients who have more aortic stenosis and more rapid progression of aortic stenosis.

So this is kind of an interesting subject now. There's actually lots of areas for investigation. On the clinical side, clearly, which we're going to talk about in a minute. But also as to what's going on here. What are the targets for therapy? Why can't we slow down this process?

The trials with statins have been ineffective, maybe because statins won't work, or because maybe by the time we identify the patients to enroll in those statin trials, the horse is already out of the barn. They've got a murmur. They've got calcification. Maybe we should have treated them at an earlier age.

So here's a schematic from Catherine Otto. And you can see many of these from other investigators as well, but this was the prettiest one to show you. And so you start out with some initiating factors on the left, a bicuspid valve perhaps, those genetic factors that we talked about. Shear stress, perhaps, bicuspid valve or otherwise, leading to damage to the endothelium and then infiltration lipids and monocytes and so forth, leading to the same kind of oxidative pathways one sees with atherosclerosis. Turning on some signals, then, which take myofibroblasts and make them start behaving more like osteoblasts and start creating calcification.

So yeah, this phenotypic transformation. This is at least a concept we have now. Maybe instead, perhaps, there are circulating stem cells that wind up in those valves too, and maybe it's the stem cells being turned on.

So there's areas of investigation that might identify in the future some targets for therapy to slow down what is otherwise this inexorable process, where patients develop more and more tight aortic stenosis.

I mean, a terrific trial-- which you conceptualize but will never happen-- is taking young people with bicuspid valves-- because you know that they're going to develop something like calcification over the course of decades. Let's give them drug x, y, or z, and randomize them and see how they do.

And of course, it will never happen, because no one's going to do a trial that's going to last a couple decades. And we don't know what the right drug target is yet. But I think there's an opportunity here, at least, for further research. And until we have that, we have to get back down to the basics here, of how do we deal with our patients who have diseases like this.

OK. Well, we have guidelines. Guidelines first came out in 1998, actually, updated in 2006 and 2008. And if you think about what happened between 2008 and 1998, there was nothing. And so the guidelines in 2008 were almost a carbon copy of what had been published 10 years earlier.

A lot's happened in the last six years, and so the guidelines in 2014 tried to stake out some new turf based upon new findings about the pathophysiology, new findings regarding issues of low flow, low gradient aortic stenosis. And then, of course, how do we deal with the new kid on the block in terms of therapy, transcatheter valve replacement.

Well, the first thing that was done-- and this is a tip of the hat to Catherine Otto, she and Rick Nishimura were the chairs of the updated guidelines-- and the thought was, let's start looking about thinking about valve disease as being similar to how we deal with heart failure. Let's talk about the early stages here, where we have people at risk, stage A, as well as the people who have more advanced clinically obvious disease with or without symptoms.

So we have a stratification here, very similar when you deal with day in and day out with heart failure. B is mild, moderate asymptomatic disease. C, severe disease, but asymptomatic, with or without normal LV function. And D is severe symptomatic valve disease. So how does that play out for us? It's a way of thinking about the continuum here, with the patient first and foremost, but also the valve. What's the etiology and the anatomy and the pathology? What's the flow through the valve? What's its impact on the left ventricle?

So for aortic stenosis, a lot of people at risk for disease. Those with bicuspid valves, rheumatic heart disease, but anybody with cardiovascular risk factors, as we discussed, would also be at risk for developing aortic stenosis. And then the severe side, we need to be much more cognizant of the fact that severe symptomatic valve disease, as said before, is no longer simple. The high gradient aortic stenosis is something we can recognize quite easily. But how about these low patients with low gradient with or without LV dysfunction?

So let's just take a look at that. This is also wonderfully reviewed by Catherine Otto. She's actually a good friend of mine, and a good friend of many of you as well. And she has this review article in the *New England Journal of Medicine*. Came out last year, so it's a must read for all the fellows. Takes you through these various stages. Takes you through the diagnostic inquiry, as well as the treatment options.

The must read for me, independent of that Paul Wood paper, which was 1950s. I wasn't in medical school in the 1950s. But I was entering medical school when this paper came out. This is from my mentor's mentors, Gene Braunwald and John Ross Jr. This is their seminal paper on aortic stenosis, where they make the point that there's this grey prognosis that appears to accompany the onset of certain symptoms.

And this is where the very famous cartoon shows up, which you know I was going to show, because everybody who talks about aortic stenosis shows this figure. So I'm going to put Dr. Lindman on the spot here. Brian, how many patients were in this paper?

BRIAN LINDMAN: I actually don't know.

ROBERT BONOW: OK. Anybody know?

AUDIENCE: 15?

ROBERT BONOW: Close. 12. There's 12 patients in this paper. How long is the paper? It's about a page and a half. So another take-home message for everybody here is you don't have to have a 30,000 patient trial anymore to get a paper published which has lasting impact. It was a concept based upon a few patients studied by some very bright people who had a light bulb go off and said, wait a minute, these patients who died were doing fine until they got symptoms.

That's why there's no patients here. I mean, this is a cartoon. Where the patients? There are no patients. And yet, you know, it works. In the current era, this curve shifts to the right. So I've modified the figure to tell you what we see these days. It's somebody developing symptoms at age 90, or 85, or 75.

But the same phenomenon occurs. Once symptoms occur, there's a very rapid downhill slide toward a bad outcome. And now some thoughts that maybe there's maybe some asymptomatic patients with severe disease where the curve may begin to shift even before symptoms occur.

And so the remarkable things about this figure are, number one, I'm showing it, because you knew I would. Everybody shows this figures. It's based on very few patients, but bright ideas. And the third thing is it's accurate, because we actually have data supporting this over the next 40 years.

So here's a more recent one by David Bach at the University of Michigan following patients who have symptoms, not undergoing surgery, where just as Ross and Braunwald indicated, that over three years there would be a 50% percent mortality, they observed that 50% mortality.

So why are these patients with symptoms at the University of Michigan not having surgery? That's a good question. If you read it, these patients had lots of comorbidities. This was pre TAVR. And maybe these patients were dying of the comorbidities. It wasn't really the aortic stenosis or not.

That's unclear, but it does lead to some very simple statements and guidelines. Symptomatic patients, severe aortic stenosis, aortic valve replacement, class I. It's not level of evidence A, because we don't have clinical trials. We'll probably never do a clinical trial of symptomatic aortic stenosis, surgery or otherwise.

But that's an easy one from the guidelines committee. It's also very easy for you when you take your boards, OK? You've got the symptomatic patient with severe aortic stenosis. Should you recommend surgery? You deal with that question, and move onto the next more difficult question, because this one's pretty easy.

But that's where it stops being easy. It's easy for a guidelines committee, and it's easy for you taking the boards, where you're told the patient has symptoms. But in real life, how do you know that the patient who's got symptomatic aortic stenosis has symptoms because of the aortic stenosis? If your patients are like mine, as they're getting older and deconditioned and overweight, they're a little short of breath, maybe because of their lifestyle, and is it really the aortic stenosis?

Now, I would have no trouble if I have a patient with severe aortic stenosis who's now getting a little short of breath, saying, OK, that's-- I'm not going to play around with that. That may or may not be aortic stenosis, but we should still replace the valve.

But how do you deal with a patient who's a little short of breath now, who's got mild aortic stenosis? And as you're following the patient, the aortic stenosis is getting more and more severe and the patient's still a little short of breath. So these are clinical issues that really are not so easy at all. Very, very difficult to know what a symptom really is with aortic stenosis.

And that kind of leads to the next point. Let's talk about the management challenges beyond the simple aspect of symptomatic severe AS. How about the asymptomatic patient with severe AS? The flip side of the last discussion is how many of your asymptomatic patients are really asymptomatic?

Because my patients, and I suppose your patients, once they start developing symptoms, stop doing things. They start down-regulating their activity to match their symptom level. They're playing nine holes of golf or putt-putt golf instead of 18 holes of golf anymore. They're no longer so active. And you take a history and they tell you that they're feeling fine. And so it's not clear, really, how many of our asymptomatic patients with severe AS are truly asymptomatic.

You're aware of the exercise test data that have been done showing that maybe a third to 40% of soon to be asymptomatic patients put on a treadmill will develop what appear to be cardiac symptoms on a treadmill. I'm a little bit concerned about those data, because what's a cardiac symptom on a treadmill? Everybody develops symptoms sooner or later on a treadmill. And is it really cardiac, or is it deconditioning?

But that does lead, at least, to the implication that the stress test could be helpful. It shows up in our guidelines that if the patient has symptoms on a treadmill, presumably asymptomatic before you put them on the treadmill, it's probably a symptom.

Again, teasing out what is cardiac symptoms is not so easy, but at least a symptom is a symptom that becomes a class I indication. A abnormal blood pressure response becomes also a consideration for surgery. It's a 2A only, because we don't have lots of patients and lots of data. Although conceptually, it makes sense.

OK. So let's now assume we've got a truly asymptomatic patient, really asymptomatic. What do we recommend? Here's a patient of mine. He's 82 or 84 years old. He's a retired economics professor from University of Michigan. Has a farm in downstate Illinois where he's very, very active. Not interested in surgery. Telling me he feels good.

He's [INAUDIBLE] got calcified aortic valve. He's got left ventricular hypertrophy. LV function looks OK. His Vmax is 4.6. That leads to a mean gradient of 52, and aortic valve area is 0.7. So I made this one easy. This patient's got severe aortic stenosis, normal LV function.

And so of course, it's not always so easy, and we'll get into when it's less easy in a second. But this patient at least fulfills all three criteria, echocardiographically, for severe AS, so we can at least start with a simple case.

But he's asymptomatic and he's 84 years old. So what do we recommend, now? This is where it stops being simple. Should we just do watchful waiting? Should we do more testing, stress test? BNP? One of Dr. Lindman's new biomarkers? What should we talk about? Or just replace the valve?

None of those are wrong answers. They all could be right answers, depending upon your interaction with the patient. And watchful waiting now has a whole new connotation. What's watchful waiting? Let's watch for the patient to develop symptoms in five years, and now he's a candidate for TAVR.

So watchful waiting actually sounds like it's not a bad idea anymore, because he'll be a TAVR candidate sooner or later. So transcatheter valves have actually kind of upset the apple cart now. We have lots of new conundrums to deal with.

But it is true that if we wait five or six years and then recommend TAVR, he probably will be symptomatic in five or six years. Because what I did with my patient who's an economics professor was to start talking to him about the outcome here. He's got severe aortic stenosis. Vmax of 4.6, mean gradient of 52. What's the likelihood of being asymptomatic in five years? It's not that high.

And being an economics professor who was very good with data, I actually discussed some of the data we have. Here is a paper from Catherine Otto in asymptomatic individuals who are followed over the course of five years who started out with a Vmax of greater than 4. And look at all the events. Over the course of five years, there's event free survival of zero.

Now, careful here, the events are not death. There were 56 events here, 8 deaths, and 48 patients developing symptoms. And most of the endpoints here are patients developing symptoms.

And again, that's got to be taken with a grain of salt. These patients are being followed very, very carefully by a very good group. They already know they've got a Vmax greater than 4. They're probably being followed very, very carefully. And any symptom at all, which could be cardiac or otherwise, would lead to aortic valve replacement.

The patients who died were patients who either were waiting for surgery or had refused surgery. So there were no deaths in asymptomatic people. But these data are not unique. You see very similar data from Rosenhek and co-workers in Vienna, Austria, [INAUDIBLE] and co-workers at the Mayo Clinic, Stewart and coworkers in the UK, and a colleague of mine, Stefano Nistri, in Florence, Italy. So you have five studies here all pointing in the same direction. Now every patient has one of these events over the course of five years, but the majority do.

The data from Rosenhek, shown on the previous slide, are also interesting, because they subdivided the patients according to the severity of calcification. And the valves that were more calcified also identified patients who were more likely to come to surgery. If you're following that literature, CT scanning to quantify aortic valve calcium scores has been shown to be a useful independent marker of who progresses more rapidly. That could be done with CT scans these days. Rosenhek did it with echo.

And then finally, Rosenhek's group came back with about twice as many patients, all with Vmax greater than 4, subdividing the patients into severe, more severe, most severe aortic stenosis. So these are all patients with a Vmax greater than four. But as you see when you get into the groups with a Vmax of 5 or 5.5, the likelihood of having symptoms in the course of three years is so high that you gain very little in waiting.

So these are discussions I have with my patients. The valve is progressing. It's getting more and more tight. It's so inevitable that you're going to come to surgery, maybe we should have surgery now.

Here's a echo in an asymptomatic patient of mine. We've got a very calcified aortic valve. And you can see how the Vmax increased over the course of time from 2006 to 2011. This led to the expected increase in gradient and expected decrease in aortic valve area. So we finally recommended valve surgery.

Now, many in the audience are saying, what am I waiting for? Why in 2009 and 2010 didn't this patient have surgery? Well, I was talking with the patient, and I was trying to get him ready to put this concept that he's asymptomatic, he's doing really good. We put him on treadmills and he burns up the treadmill, why are you waiting? Well, I was trying to get him to have surgery earlier, and I only convinced him when it was so inevitable this was his progressive that he was going to need surgery soon and he could get in trouble while he was waiting.

And so that becomes also a criterion in the guidelines. Severe aortic stenosis, choose the variable that fits your comfort level. And you have a committee where you have to have a community vote on the comfort level. We settled on greater than 5 meters per second. It's a 2A recommendation. Or rapid progression, low risk of surgery.

Now, low risk of surgery means low risk patient and also low risk surgeon. So you won't be talking about operating upon asymptomatic people, you want to make sure you have a good team, like you have and I have. But it's not universal across the country. Let's choose a good surgeon where you can deliver a 1% or less operative risk for an asymptomatic individual. So that's what we mean by low surgical risk, it's the patient and it's also the center.

And so the guidelines, as you can see, are kind of moving toward earlier indications for surgery based upon severity of AS, severity of calcification, left ventricular function, exercise responses. How about biomarkers? BNP is the biomarker du jour. Didn't quite make it into our guidelines, because there were no thresholds that were well defined. Lots of studies showing BNP may be a good marker. No one actually had identified thresholds.

What's happened since those guidelines got published is a really interesting paper by Clavel and co-workers working with Philippe Pibarot and the group in Quebec and Mayo Clinic looking at asymptomatic patients. And this is survival over the course of five years based upon BNP.

And what they did was the obvious point that BNP varies according to gender and also varies according to age. So let's identify what is the upper limit of normal for age and gender, and then what's the patient's BNP relative to that? So the ratio is the patient's BNP divided by the upper limit of normal for age and gender.

And so if you've got a ratio less than 1, your outcome's quite good. But if the ratio starts going up, then you're at higher risk. So this is something which I think could be easily bought into clinical practice. They also identified who would do well with or without-- after surgery, having had surgery in some of these patients.

Well, we have also novel biomarkers. A paper by Chin and coworkers looking at high sensitivity to component [INAUDIBLE]. Brian Lindman's paper this year in *Heart* looking at some very novel biomarkers. Growth differentiation factor of 15, which is a marker of fibrosis and inflammation. Soluble FCS2, marker of myocardial stress. Brian, did I get that right? OK, thank you. And terminal pro-BNP.

When you start combining these biomarkers, you're identifying higher-risk patients. Now, Brian studies patients looking at the outcome after surgery, and I hope that you're acquiring data in the asymptomatic patients to start determining whether these same biomarkers will be predictive of which patients have a more rapid attrition rate over the course of time as well.

And so having dealt with the asymptomatic patients, let's not lose sight of the fact that we have strong indication for surgery in symptomatic patients. And as you know, we've not done a very good job at getting that message out to our referring community.

And when you have a TAVR program like you and I have, suddenly you're seeing these patients referred in, many of whom are good candidates for surgery, but they've been held onto for a long period of time by their primary care physicians because of issues of age and other comorbidities, could have had surgery.

OK. Let's just quickly move on and wrap this up with a couple other short comments about other conditions. Have a low flow, low gradient severe stenosis. You know, we talked already about normal flow, high gradient, normal LV function. That was the discussion we just had.

Low flow, low gradient comes in two varieties. One is the one that we can conceptualize relatively easily as a patient where the AS is so severe that you now have left ventricular systolic dysfunction. And here we can give a low dose dobutamine in the echo lab or cath lab to increase the flow across the valve, get a better calculation of the hemodynamics, identify who has truly severe aortic stenosis. Also look at the contractile reserve as a marker of low and high risk.

So this one is something that I think that your lab and my lab does quite common in patients who've got low gradient, low flow LV dysfunction aortic stenosis. The new kid on the block, which has become a real problem for us, is the patients who've got low flow, low gradient, normal LV function.

And I think we were missing these patients for years. I can think of patients of mine who 10 years ago, I wouldn't have thought had aortic stenosis, and we didn't manage them as we might manage them now. Because we now know that a large subset of patients with AS have a normal ejection fraction, but may have a little stroke volume.

In this case, because of severe hypertrophy, where you've got a low end diastolic volume leading to the low stroke volume. Or how about if you have hypertension at the time you study the patient, where you've got a second impedance to ejection? And if you're this low the blood pressure, suddenly the gradient goes up.

So there's a growing awareness of this low flow, low gradient, normal LV function, but also some question about how common it really is. Because you can under-diagnose this and also over-diagnose it. And so here we may need to do some other markers of whether this is truly aortic stenosis or not. Is the valve calcified? What's the myocardial strain look like? Maybe ejection fraction is the wrong measure to be using here. Myocardial fibrosis with MRI. What's most important is good clinical judgment. This is where you have to be a good doctor to kind of tease these patients out. Does the physical exam sound like aortic stenosis?

But it's not uncommon. This is a really great paper by Minners and coworkers in Germany, where they've got 300 patients who've got aortic stenosis, normal ejection fraction, studied both by cath and echo. And so they're plotting here the mean valve area versus the mean pressure gradient-- sorry, the valve area against the mean pressure gradient.

So on the lower right, where you've got patients who've got a valve area less than 1 and a pressure gradient greater than 40, we would feel comfortable saying those patients have severe aortic stenosis. And in the upper left, where you've got a valve area greater than 1 and a mean pressure gradient less than 40, those patients probably don't have severe aortic stenosis.

The problem is in the lower left, where we've got patients who've got a pressure gradient less than 40, aortic valve area less than 1. And so it's one third of the patients by echo, and one quarter of the patients in cath. So you can't argue that the echo itself is imprecise. It can be, because measuring that valve area is the weak spot by echo, but it happened also in the cath lab in the vast majority of those same patients.

Well, maybe the valve area of 1 is just set too high. That's an arbitrary marker. Let's lower the valve area to 0.8. [INAUDIBLE] has a great editorial indicating that's probably the better valve area to be using in this situation. That gives us a fewer number of patients in the lower left.

The problem is it gives us more patients in the upper right. And what do we do with those patients? They've got a mean gradient greater than 40. That's probably significant aortic stenosis. What this means to me is that there's no single marker. We need to use lots of good clinical judgment and all the other parameters that we can bring to bear to try to determine who these patients are. And if we index the valve area, say to 0.6, the same phenomenon occurs. So even when you index the valve area for body surface area.

So lots of discussion. There's a paper almost every month in our cardiology literature about this. People are looking at the valve calcification, myocardial strain, myocardial fibrosis. There will probably be other markers and biomarkers as well that could be helpful.

And whether or not these patients are at higher risk is also a question. You have one paper here from the Cleveland Clinic by Ozkan and co-workers, symptomatic patients, low flow, severe AS, normal EF, showing that if we recommend surgery, there's a better outcome and medical therapy. This is not a randomized trial. It's a propensity match series. It may or may not be matching all the patients adequately. But it does suggest that these patients are at higher risk without surgery.

And then you've got a paper just this year by Tribouilloy and co-workers, and he's a very good person when it comes to valve disease. And the patients who get better with valve surgery than medical therapy on the left are those who have a high gradient. The patients with low flow, low gradient AS had the same outcome whether treated with surgery or not.

So how could this be when you have one study showing the outcome is better with surgery, another study disputing that? I think it all depends on how we're identifying those patients. These are very complex patients to identify, is who has truly severe aortic stenosis when you've got a low flow state. And I think there's lots of room for more observations, and more data and bright minds to try to unravel this one. And it's very common.

But specialty guidelines, normal EF in patients with low flow, low gradient AS, if you've got hemodynamic anatomic data to support severe [INAUDIBLE], then the key here is the clinical gestalt is this may be severe aortic stenosis. And it's a 2A because we're lacking very good data.

Finally, indications for TAVR. This has been totally transformative, because I would have bet 15 years ago that this probably wouldn't work quite so well. It's got enormous potential. It's efficacy and safety need to be kept in mind to temper the consumer expectations, because all of your patients would rather have their valve replaced this way, as would mine. And the consumers are also our referring physicians.

Surgical AVR is still the standard, with a proven safety and durability for the majority of patients. And the broad application of TAVR starts representing some challenges of patient selection, cost effectiveness, the need to develop these heart valve teams that you have and I have.

Can we move that beyond an academic center into the community to deliver the same kind of results we see in clinical trials? Well, there's some positive markers here, because every patient in Medicare getting TAVR is in the TVT registry.

And when we look at the first 12,000 patients with one year follow-up reported by David Holmes, there's a relatively high mortality over the course of 12 months after TAVR. But the 24% one year mortality was identical to what was achieved in the partner trial. And so taking this from a clinical trial, moving the technology, the teamwork, and all that stuff, and selection of patients to the community actually seems to be working pretty well.

What I hope we get we is get more patients in this registry to start looking at the data and are there high volume centers and low volume centers? Are there high quality centers? Can we begin to identify what it takes to be a good center, so we can begin our patients to the right places? And so I think that would be another outcome of this very important registry.

And so the class I indication is develop a heart team first and foremost. Surgical AVR for patients at low or intermediate risk. The surgical AVR is still what we recommend, even though we're seeing data now in lower risk patients coming out of Europe, and patients in this country are being randomized in clinical trials.

TAVR for patients who have prohibitive surgical risk. The patients in whom a surgeon and cardiologist believe this is too high a risk, life expectancy greater than 12 months. So these are the class I indications. A2A is that TAVR is an alternative for patients at very high surgical risk.

So these are what we have now. Now, since those guidelines got published, the partner A trial got published, subsequent core valve studies got published. So we have more and more data coming out with longer follow up. So is this still a 2A? Shouldn't that be a class I now, based upon what we see in the core valve that even high risk surgical patients, isn't this an alternative approach? It certainly is my center now, probably in yours.

And how about this one? Surgical AVR for patients at low or intermediate risk. If you're following the literature in the subject, we've seen lots of data in patients who've got lower surgical risk having very good outcomes with TAVR. Should that be an alternative? TAVR as an alternative, as opposed to seeing surgery is the class I indication.

So that what we need to do is have guidelines that become much more maneuverable. And so we're trying to update the guidelines, stay on top of the data, watch the trials, so that when the trials get published, the guidelines are ready to go with the push of a button, already proved, ready to go in the hopper. And see if we can't keep up with the field.

Because there are people arguing that TAVR really leads to better results than surgery. So here's data from the FCS database, 141,000 patients, looking at the predicted outcome from the STS score in grey, and the observed 30 day mortality in red for surgery. And so the STS score works very, very well, because the predicted 30 day mortality is almost identical to the observed.

And then the TAVR advocates say, well, look what we achieve with TAVR. Now here's high risk, intermediate risk, low risk, predicted versus observed with TAVR in red, coming in with much lower mortality than predicted, unlike what you see the surgery. And so there's people pushing the envelope here and saying, we should be doing TAVR because we're going to have much lower risks than expected.

The problem for me is this, that some of these patients were enrolled in clinical trials where we also have surgery results, and the surgery results are shown in green. And so in clinical trials, you find that the predicted versus observed is a lot different than what you see in the community, in the upper panel. So surgeons do quite well when you've got them involved in a heart team, part of a clinical trial, patients are being followed very carefully, and so forth.

So we really need clinical trial data that are ongoing and happening before we can start moving the threshold down to these lower risk individuals. Because surgeons are doing a good job. Just to wrap this up, here is data in surgery for patients in Medicare. So this is obviously all patients over the age of 65 having aortic valve replacements.

And what's the hospital mortality? In the 1990s, it used to be 8.8%. By 1999, it was 7.6%. Dropped to 4.2% in 2011. Is that because we're selecting patients differently, or is it we're operating on less patients? We're actually operating on more patients. And as you know, these are more complicated patients. And yet the mortality is coming down. Not only in everybody over the age of 65, but even over the age of 85.

The highest risk individuals, which is the most rapidly growing proportion of patients in Medicare, where the 30 day mortality with surgery has dropped from 12.3 to 5.8. This is before TAVR was a possibility, so operation was the only option for those patients. So our surgeons are doing very, very well. So there's good outcomes now for our patient, whether they're having surgery or candidacy for TAVR.

OK. So I've talked a little bit about the guidelines. They're indeed works in progress. Have they actually filled the gaps in our knowledge that allow us to then move to our patients? Only as a framework. I mean, what really allows us to manage our patients is what you and I do. So this is another discussion for our fellows.

So here's one of the issues about education. Here's two devices that capture sound waves. The one on the left is the one I was taught about. The one on the right is what all the fellows are taught about, it's the echo transducer. And my fellows are very good on the right here. They're better than I am, and they're constantly educating me about some of the new things one can do with echo.

I'm still kind of a novice when it comes to Doppler tissue imaging and strain. Fellows are very, very good. I'm better than they are on the left. And by that, I don't mean that I have better ears, because I think my fellow have younger years and they're better. But I have clinical gestalt. And so the left hand device is clinical judgment that's only built on years of seeing patients and talking with them.

And so we need to be talking with our fellows about how we develop clinical experience as well as technical expertise. Because there's now a third hand involved in this as well. And that's the hand that's holding the transcatheter valve. So cardiologists now come in different shapes and sizes, with different opportunities to both diagnose and treat our patients.

And so we have an evolving field. It's evolving actually quite rapidly now. And becoming very, very exciting at both the basic science clinical diagnostic level, and also treatment. So for me, it's been kind of a nice work in progress, having followed this field for decades. And hopefully the conversation we've had today is useful for all of you. May have turned on a few opportunities for research with young people. And I'll be happy to answer any questions. Thank you very much for this honor.

[APPLAUSE]