SPEAKER: Morning, everybody. Today our speaker is Dr. Wharton. He received his MD from Vanderbilt School of Medicine in Nashville. Completed an internship and residency at University of California, San Francisco where he was also Chief Resident. He then completed his cardiology fellowship at Duke in Durham, and subsequently served as Assistant Professor of Medicine and Director of Clinical Cardiac Electrophysiology and Associate Professor of Medicine with tenure at Duke. He is currently the Frank P. Tourville Professor of Medicine with tenure and the Director of Cardiac EP here at MUSC.

He's been awarded numerous honors and awards and has been named to the list of America's Top Cardiologists in multiple years as well as the Leading Physicians of the World. Dr. Wharton has published many articles and abstracts in many journals including the Journal of American College of Cardiology, Pacing and Clinical Electrophysiology, and Circulation. He currently serves on multiple advisory committees, editorial boards, and educational committees. His primary research interests are aimed at catheter ablation of AFib as well as other arrhythmias. And he's actively involved in several clinical research trials. Please join me in welcoming Dr. Wharton.

[APPLAUSE]

DR. J. MARCUS WHARTON: It's a pleasure to be here and talk about atrial fibrillation. It's obviously something near and dear to my heart. And I obviously spend a fair amount of time trying to fix it. And so that raises the issue of can we really fix atrial fibrillation. And that raises the deeper issue-- what actually causes atrial fibrillation. Can everybody hear me OK?

And so I'm going to spend a little bit of time talking about this. So this is a burning issue. And I hate to use metaphors and particularly extended metaphors for a distinguished group. But it's worthwhile maybe, and it adds a little bit of fun. But why is this a burning issue? Well, it's a burning public health issue, as we'll talk about. It's burning up our health care resources, as we'll talk about. Burning, which is what I do-- ablation is certainly a short term answer. But the longer term answer is a much more complicated piece. And that's burning calories and exercise, at least in part, as we'll get to.

So to put this into some perspective, we all know atrial fibrillation is a common problem, the most common sustained arrhythmia in the United States or a developed country. In the United States, probably three million new cases per year-- 5% of the population greater than 65. Or if we just look across this audience here, one in four of you in your lifetime will develop atrial fibrillation. And that number is changing rapidly.

Increased risk of stroke, increased risk of dementia, doubles the risk of mortality-- so there's lots of downstream adverse problems with atrial fibrillation. And so the question is can we do anything to change this. And it's interesting, and this is just recently published data in the worldwide age-adjusted prevalence rates. Look at this map and see what stands out to you. And what you see is that red is the highest prevalence, or also incidence if you look at different presentations.

And you see that in the United States, we have vastly more atrial fibrillation than anywhere else in the world including Western Europe. And the question is, why do we have so much AFib? And of course at first-- sort of blush-- you say, well, that's just because we're so good at being doctors, and we pick up so much more atrial fibrillation than the rest of the world does. But Western Europe does just as good, or better a job, actually, in detecting atrial fibrillation. And they don't have this incidence. So what are we doing wrong in the United States that's making atrial fibrillation such a specific health care problem in this continent?

And so you've seen these slides before. These are the predicted increases of atrial fibrillation in the United States from various, different health care databases. And I think it's interesting to look. There's two sets. There's a set in blue down below and a set in red up above. The set in blue down below is based primarily in California, primarily in Kaiser Permanente. I used to live in California. If you know California, Californians are pretty good about staying healthy.

The red are from Olmsted County. That's in Wisconsin. Wisconsin is probably more like South Carolina in terms of health care maintenance of patients. And you can see that a much higher predicted rate in places where people probably take care of themselves less well than they do in California. And in fact, the increase in the atrial fibrillation, although certainly due to the maturation of the baby boomers, about 40% of it, at least in the-- in the Olmsted County database is predicted to be due to the onslaught of the problem of obesity. And so I'll spend a fair amount of time talking about the issue of obesity and how that's related to atrial fibrillation.

So again, factors affecting the atrial fibrillation epidemic; increasing age of population, the maturation of the baby boomer population, increasing longevity of patients with heart disease and the increased longevity of exposure to risk factors for atrial fibrillation, the epidemic of obesity and its associated problems, the problem of inactivity, lack of exercise, and then also greater awareness and detection, environmental factors, smog for instance, increased carbon dioxide in the environment causes increased risk of atrial fibrillation, and certainly a number of unknown factors.

So the burning of our health care resources is illustrated here. This is fairly old data, now from mid-2000s. But you can see that in terms of health care expenditures in the United States alone, we're spending about $25 billion a year in AFib or AFib-related health care costs. About $6 billion of that is related to atrial fibrillation solely. So a huge chunk of our health care expenditures is going to the problem of atrial fibrillation. And so then the issue becomes-- is can we decrease this? Can we not just treat atrial fibrillation more cost effectively, but can we actually prevent atrial fibrillation so that we can spend these dollars perhaps in better-- better ways.

So that brings us to this schematic. And that is-- let's see, how does this play-- so this schematic is showing how we're spending things. If you look at the number of patients who, in the United States-- or people in the United States-- adults in the United States who are at risk for atrial fibrillation because of one or more risk factors-- it's over half the population. That's why one in four of you will in your lifetime develop atrial fibrillation.

We spend that $25 billion taking care of this portion. That's about 1% of the US adult population. And so that's a lot of money for 1% of population. Certainly, I think it's well-spent. But again, the issue is is can we do something to impact on this group of patients so that we prevent atrial fibrillation. And we've all gotten used to using the so-called three p's of atrial fibrillation, the natural progression from paroxysmal to persistent to permanent, or now what we call longstanding persistent atrial fibrillation.

But I actually want you to start thinking in terms of the four p's. And that is, besides once you develop atrial fibrillation, this pre-AFib state where we have the potential of potentially doing things to prevent atrial fibrillation in the first place. So in terms of being able to do anything about atrial fibrillation, we first have to understand the pathophysiology behind atrial fibrillation. And we've learned a lot in the past couple decades.

We've learned for instance that the events that initiate atrial fibrillation are these very rapid atrial tachycardias that typically start in the pulmonary vein muscular sleeve. This is some work of hours from Duke from a long time ago. And you can see that for the most part in this is sort of Kermit the Frog display-- and the circles being here the pulmonary veins. Most of these sites, when you actually went to the detail of mapping each one of these points, occurred within the pulmonary veins. But you can also see that there is a relevance, or a relatively large smattering of sites occurring elsewhere besides the pulmonary veins.

So although it is true, at least early on in the disease, it is related to tachycardias in terms of initiators inside the pulmonary veins. As the disease progresses, it tends to be much more than just a pulmonary vein tachycardia problem. And that's relevant to what I do in terms of ablation.

And that is perhaps illustrated here. This is some work from Jonathan Coleman's group in Australia. We're doing some similar work here. But anyway, they're doing what's called voltage mapping. This is a posterior view of the left atrium. And they took control patients, young healthy patients with WPW, where they were over in the left atrium, and compared that to paroxysmal and persistent atrial fibrillations. This graphic-- blue is normal. Yellow is heavily scarred. Red is densely scarred.

And you can see that for the most part, the control patients had normal atria. But as you had paroxysmal atrial fibrillation, there's increasing amount of scar. And diseased atrial tissue is illustrated again by the red and the yellow, respectively. And then in persistent, even more disease within the atria. And we've known since the 50s in autopsy studies that the more atrial fibrillation you have, the more fibrosis that occurs. The question is can we prevent that scarring and fibrosis from occurring? Can we actually alter the natural history, that three p's that we've learned to talk about in terms of progression of atrial fibrillation.

The other thing that's superimposed in that-- and again, this is one of the discoveries-- key discoveries in the past two decades-- has been that atrial fibrillation begets atrial fibrillation. And what that means is that when you go into atrial fibrillation, as you start having increasingly frequent episodes of atrial fibrillation, the atrial fibrillation per se causes electrical, and mechanical, and structural changes in the muscle, eventually causes scar itself. So the AFib itself, a rhythm problem that is generated by the scar, actually generates more scar. So superimposed on whatever the underlying disease process is that's causing the atrial fibrillation, when you start having atrial fibrillation, that accelerates potentially the process. So that's what we call atrial remodeling.

Up until last week actually, there was no randomized perspective data to suggest that if we intervened early in atrial fibrillation, we could perhaps have some impact on decreasing the frequency of atrial fibrillation by stopping the remodeling process early. There are lots of retrospective analyzes that suggested that earlier treatment of atrial fibrillations could potentially slow down the process or decrease the frequency of recurrent atrial fibrillation.

Just last week, there was a randomized study shown here where they took patients with persistent atrial fibrillation undergoing cardioversion-- randomized them to TEE-guided therapy, or three weeks of [INAUDIBLE] in this situation and then cardioversion. So that's a early approach of TEE-guided cardiovert to end the episode quickly, versus anti-coagulate for three weeks and then cardiovert without TEE.

And what you can see is-- and this slide's a little bit hard, I think, to see. But you can see here that the patients who had early intervention compared to conventional intervention had less AFib in the short term follow up, again suggesting that earlier intervention in the course of atrial fibrillation can prevent remodeling and therefore decrease the frequency of atrial fibrillation.

They also looked at the analysis in terms of how long the patient was in AFib before they were randomized. And you can see that after about a couple of months of atrial fibrillation, it didn't make any difference which approach you had taken because the remodeling process had already occurred. So clearly this data, and hopefully we'll have more data in the near future, is showing that we need to intervene earlier if our goal is to decrease atrial fibrillation and to prevent the process that's causing the atrial fibrillation, or decrease the acceleration of the process that's occurring the atrial fibrillation in the background.

And so that's graphically illustrated here. And I think this is an important slide in terms of trying to get a grasp of what actually we're talking about in terms of the substrate issues for atrial fibrillation. Again we know that as shown here, atrial fibrillation starts occurring. At first we don't know the episodes are occurring, or they're not occurring-- that quiet pre-AF period. Start having episodes of paroxysmal AFib-- eventually have persistent AFib, potentially permanent atrial fibrillation.

So as you have those episodes, they cause in this sort of pink hash or red hash area a remodeling after each acute episode. You go back in normal rhythm, that can reverse to some extent. But over time, presumptively, that has a cumulative effect. And so it certainly makes sense that if we intervene as shown by that cardioversion-- or suggested at least by that small cardioversion study-- that if we intervene earlier, we can potentially prevent some of that from happening.

But the bigger issue is this underlying issue of the substrate that's evolving to cause the atrial fibrillation in the first place. And can we stop that? And does prevention or slowing of that process have some role in our overall management of patients with atrial fibrillation. There's also this issue of just aging-- natural aging changes that occur in the atrium that also would facilitate atrial fibrillation. And can we stop that? And they're actually working on drugs to slow down the aging changes within the atria. Whether they'll have any impact on atrial fibrillation management remains to be seen.

So in terms of our approaches for treatment of atrial fibrillation, we've had several different approaches. The approaches that we've always used and we all have the most exposure to is the use of anti-arrhythmic drugs. And because of our exposure, we also know that anti-arrhythmic drugs don't work. They maybe palliate to some extent. Despite how much we use anti-arrhythmic drugs, there's still no data showing that it actually changes the natural history of atrial fibrillation.

In terms of other [INAUDIBLE] therapies that people have looked at trying to alter the disease substrate that underlines the incurrence of atrial fibrillation in the first place is what we call upstream therapy because it's upstream from the actual development of the arrhythmia. People have looked at the angiotensin converting enzyme inhibitors, the ARBs, the statins, other antifibrotic drugs, the antioxidants, and a number of other drugs. And there's a lot of enthusiasm here. But it's all show, at least at the present time-- not much to be enthusiastic about. Certainly catheter ablation can cure some but not all patients with atrial fibrillation. But we still get into this problem, as we'll see, about what the long term picture is with catheter ablation, unless we treat the underlying disease.

So in terms of just a quick review of trying to prevent or upstream therapy for atrial fibrillation, there are the issues of the use of ACEs and the ARBs and aldosterone antagonist. And there's a lot of reasons why these drugs were thought to be potentially useful for prevention of atrial fibrillation. They have pretty intense, antifibrotic anti-hypertensive effect in the atrium, and have a number of electrical effects. They decrease inflammation. So it sounded like a reasonable agent to use. And since the most common associated co-morbid illness of atrial fibrillation is hypertension, you can use it to treat the hypertension and potentially decrease the risk of atrial fibrillation. Or potentially, if you have atrial fibrillation already, [INAUDIBLE] other pharmacologic approaches.

And in addition, these agents block what we call triggered activity. You can see over here, and I'm not going to dwell too much on electrophysiology, but after these little spikes, those are action potential membranes. You can see a little blip there. That little blip is what we call a delayed after depolarization. And from the bulk of the work that we have from animal studies, that is probably the mechanism underlying the little pulmonary vein initiator. So it was thought that, well, besides the antifibrotic, anti-inflammatory properties of the ACEs and the ARBs, that they would also maybe directly decrease the triggered activity that's causing the pulmonary vein triggers in the first place.

Unfortunately, numbers of trials have been done. But really, none of those have been shown to be-- have suggested much effect. These are reviews of various different metaanalyzes looking at primary prevention of atrial fibrillation using ACEs and the ARBs. You can see that in the primary prevention in the heart failure group, there is indeed data to suggest that the uses of ACEs and ARBs primarily by controlling the heart failure, decrease the risk of developing atrial fibrillation in a person who doesn't already have it.

But in the hypertensive patient, at modest effect or mild effect [AUDIO OUT] at best, other populations really [AUDIO OUT] no effect. So the ACEs and ARBs, although good for treating hypertension and good for treating heart failure, really have not proven to be an adjunct to our management of patients with atrial fibrillation, or prevention in this case. Or if I show you data in terms of people who already have atrial fibrillation, GISSI-AF and ACTIVE-I, both looked at patients who had preexisting atrial fibrillation. Not all of them had hypertension. You can see again that the ACEs and the ARBs have really no adjunctive effect for decreasing AFib episodes compared to more conventional anti-hypertensive agents. So that did not pan out as initial early studies, which were always optimistic, suggested.

So the other strategy that was looked at was the use of statins. We know statins also, besides lowering cholesterol, have a number of other potentially beneficial effects such as the their antioxidant properties and from inhibition from inflammation and the like, as shown here. And so the question was, well, could statins be used as an upstream therapy that would potentially decrease the risk of developing atrial fibrillation in terms of primary prevention or decrease it in terms of secondary prevention in patients already who have atrial fibrillation.

But again, as you can see in the upper portion of this meta-analysis, and it's pretty small-- but you can see that there was no impact in terms of statins for primary prevention. There is a trend towards an impact in secondary prevention, but that's mostly in patients who are post-bypass surgery. But if you look at patients who are not in immediate bypass surgery point of view, there was little impact of statins for secondary prevention of atrial fibrillation either.

So again we kind of drew a short straw there. We don't have a pill that readily prevents or decreases the frequency of atrial fibrillation in this population. We've talked about, or have not talked about, but there is a concern about underlying inflammation as a cause of atrial fibrillation, for causing that scarring and fibrosis that I've showed you on some of those pretty slides showing scar within the left atrium.

The thought would be, well, maybe we could use anti-inflammatory agents, NSAIDs, to prevent that inflammation. And perhaps that would decrease the scarring process and decrease the risk of developing atrial fibrillation. But again, if you look at those meta-analyzes, if anything, the use of NSAIDs-- and this is relevant through recent news about NSAIDs-- but NSAIDs of atrial fibrillation actually increased the probability of developing atrial fibrillation, primarily due to salt retention and the increased risk of hypertension of patients taking NSAIDs, presumptively, and also a decrease of renal function. So NSAIDs, likewise, have not panned out.

There are a number of different enthusiasts for different dietary modifications trying to improve or decrease the risk of atrial fibrillation; the use of polyunsaturated fats, decreasing alcohol, vitamin C as an anti-oxidant, the concern about caffeine which we all have being something that promotes various different rhythms including atrial fibrillation. And so these have then looked at to various degrees of strictness with some effect. So the biggest enthusiasm was the use of polyunsaturated fatty acids, [INAUDIBLE].

Again, they have a number of different potentially beneficial effects, but not really for decreasing inflammation and decreasing fibrosis. But they also have some direct channel effects, which theoretically could decrease the risk of atrial fibrillation. But trial after trial that has looked at these in a randomized perspective fashion, again, has not shown any benefit for these in either preventing atrial fibrillation or decreasing the recurrence of atrial fibrillation in patients who already have episodes of fibrillation.

We do know however that alcohol is bad for you. Hate to tell it you all, because we all like our glass of wine at night with dinner. But if you look at pooled analyzes-- and this is an instructive analysis done here by Kodama et al-- but for every 10 grams of alcohol that you drink, that increases your risk of atrial fibrillation by 8%. To put 10 grams-- since most of us don't think of alcohol in terms of how many grams we're consuming, a standard US drink, which is the same-- it means one beer, 12 ounce beer is the same as five ounces of wine, which is the same as 1 and 1/2 ounces of hard liquor. So they're all standardized to have the same amount of alcohol content.

But one US drink is 14 grams. So that means that for every drink of alcohol you drink per day, you're increasing your risk of atrial fibrillation about 10% per se. So if you have two glasses of wine at dinner per night, that's a 20% increase in atrial fibrillation over your lifetime. So clearly, in our patients with atrial fibrillation, or patients who are at risk for having atrial fibrillation, trying to instruct them to decrease the frequency and quantity of alcohol that they consume becomes a very important part of their daily management.

Contrariwise I see patients all the time. And they've stopped drinking alcohol, because their doctor said, oh, you can't drink alcohol if you have atrial fibrillation, because that makes it-- OK, so you can't drink caffeine, because that makes it worse. Drinking coffee-- think about for you all, if you all had to stop drinking coffee what a disaster that would be. That's a really bad thing to-- to wish on your patient.

Interestingly enough, if you look at the various different studies that have looked at this-- caffeine in this analysis has in summary of these source-- studies has no impact one way or another. In fact, in the Kaiser Permanente said that it was recently published, some 36,000 patients drinking four cups a day or more of caffeinated coffee decreased your risk of atrial fibrillation by 25%. That was sponsored by Starbucks I was told, but there was no-- no conflict of interest in that study at all.

But the old doctor's tale, as I call it, of telling your patient to stop drinking coffee when they have atrial fibrillation of other rhythms is actually not held up by the data that is available. So the one benefit-- they have to stop drinking alcohol, but at least they can continue to drink coffee. So it's not all bad.

But the biggest issue is the problem of obesity. As I've already mentioned, projections of how much atrial fibrillation we're going to see in the future is heavily predicated on this massive epidemic of obesity that we're seeing in the United States. And one speculation for why the US has so much more atrial fibrillation than other developed countries such as Western Europe, is the fact that we do a really poor job in managing our weight in general in the United States.

You can see a number of different studies-- that the greater your weight, the higher your probability of having atrial fibrillation. So if you're obese, a body mass index of greater than 30 kilograms per meters squared, then your AFib risk is at least doubled. And some studies quadrupled compared to baseline.

So clearly, managing atrial fibrillation becomes important. Trying to understand why obesity causes atrial fibrillation becomes much more complex. Because as we also know, obesity is heavily related to a number of other risk factors to atrial fibrillation. If you're obese, it increases your risk of hypertension. It increases your risk of sleep apnea. It increases your risk of diabetes and metabolic syndrome-- increases the probability that you're inactive. It increases the risk of cardiovascular disease. All of which can cause or increase the probability of developing atrial fibrillation.

And so the question then becomes-- is if we manage obesity better, not just the risk factors associated with atrial-- with atrial fibrillation-- other risk factors-- [INAUDIBLE] obesity, excuse me-- can we decrease the risk of developing atrial fibrillation. And we're actually finally getting some data on this. This is a really important issue. And you think it would have been addressed much earlier than now. But we're just beginning to see some very early data.

And some really pretty studies have looked at obesity, or even more importantly perhaps, the amount of pericardial fat. Shown on the left here is a MRI showing in the blue coloration the amount of pericardial fat. And the amount of pericardial fat has actually been associated much more strongly with your risk of atrial fibrillation. But also, all other types of cardiovascular diseases correlates less well to, actually, body obesity. And there are lots of complex reasons, which perhaps we can discuss in the discussion section about this.

But you can see on the right hand side of this slide that the more pericardial fat or epicardial fat that you have have, the increased probability that you're going to have permanent atrial fibrillation. So little-- you have no AFib. Then you start having paroxysmal persistent, permanent AFib increasing the amount of pericardial or epicardial fat. Likewise though, you could show a similar display for just overall [INAUDIBLE] body obesity.

Again, yeah, the issues of complex interplay of obesity with other sorts of co-morbid illnesses-- shown here is just a slide looking at obesity and also severity of sleep apnea. And you can see that either one of these is associated with an increased risk of atrial fibrillation. Both of them together increase your risk of atrial fibrillation-- developing atrial fibrillation-- even higher. So there certainly is an interplay between the obesity itself and the co-morbid factors that go along with it.

We're beginning to see some interesting animal studies. This was just published about a month ago or so. They're now taking sheep-- there's a sheep model-- and force feeding it, basically, Twinkies, but junk food. And they like junk food just like we like junk food. And this is an important model, because sheep, the way they sleep and the way their chest structure is, don't develop sleep apnea no matter how much obesity or weight they gain.

So these sheep are force-fed for a couple of months this high fat American type of diet to the point they are twice the average weight of a normal sheep. And you can see on the left hand side here that they develop a fair amount of fat on the epicardium. But perhaps more importantly if you look here, that fat marbles the atrial tissue.

So you know how we like a good steak because it's marbled with fat? It makes it really good, and it makes it juicy and succulent for us to eat. Well, that fat in the muscle may be good to eat, but it's not good in terms of what it does in terms of the risk of atrial fibrillation. That's making the muscle heterogeneous-- causes a number of different electrical, and mechanical, and structural problems. It increases left atrial pressure for instance. It decreases conduction, homogeneity through the tissue. All of those things are profibrillatory. So obesity can have a direct effect on the atrial tissues to promote atrial fibrillation, at least in the animal models that by inference-- also in the human body.

So what can we do to try to prevent that. Certainly dieting would be a big issue, and we'll back to that. But also, we know that exercise at least in portion is protective. Shown here are studies from humans-- relatively small study as all these studies are. And they're showing that-- and I like this to explain why they don't exercise too much.

But you can see that it's using couch potatoes as a reference. They're incidence of atrial fibrillation here is 1. If you do low to moderate levels of exertion, then you decrease your risk of atrial fibrillation. But if you do high levels of exercise-- so marathon runners-- extensive exercise. You actually increase your risk of atrial fibrillation. And there have been interesting, again, animal studies looking at this with a-- when they exercise dogs excessively. And what you start doing is you actually start causing remodeling with extensive exercise of the atria in a adverse fashion. [INAUDIBLE]

You also start increasing vagal tone, which in terms of atrial fibrillation is profibrillatory. So extensive exercise is actually bad for you. But moderate exercise, like in everything in cardiovascular health, is good for you. So again, part of the prescription for patients should be to increase their exercise. But that's easy to prescribe, harder for patients to follow.

There is an interaction between exercise and obesity that's not quite linear, shown here both for men and women in two different separate studies-- population based studies shows that your risk of atrial fibrillation goes up markedly higher if you're obese and if you don't exercise. But if you are obese and do exercise, it has a pretty dramatic impact in terms of decreasing your probability of developing atrial fibrillation in the long term follow up. So exercise is important not just for the thin patients, but also for the obese patients in terms of decreasing their risk of developing atrial fibrillation.

In terms of prospective studies, do we have any studies that aggressive intervention in terms of weight reduction and hypertension control, sleep apnea control, and control of their diabetes has any sort of impact on their atrial fibrillation? And we do. This is a very interesting study where they randomized a fairly large number of patients to aggressive intervention versus just a control. And so even in the control group, just because they're part of a study, you can see on the top lines they're waist circumference, or BMIs, or AF symptom scores and severity. You can see they had some benefit just from being part of the trial and being educated.

But the patients who had aggressive intervention ended up obviously losing weight, decreasing their waist circumference size-- BMI. But also had-- these patients already had atrial fibrillation-- had a dramatic reduction in spontaneous atrial fibrillation just by controlling other factors. So not by treating them with drugs or anything else, but just by being good doctors, getting them to exercise, getting them to take care of themselves, getting them to lose weight, that had an impact in terms of decreasing atrial fibrillation.

And so this is something we don't like to hear as physicians, because this is really hard work, to get people to exercise and take care of themselves. But it's so important for all cardiovascular diseases. And now also it's important for atrial fibrillation. But unfortunately, if you look at this study, there's a 40% dropout. It's highly selective in terms of who these people are. They say this is predominantly a well-educated, middle class, Australian community. So this doesn't necessarily reflect the patients that we all take care of. So again, it reflects the difficulty of prescription of these types of behavior on our patient population for managing atrial fibrillation.

So that brings us up to what I do. And this is the burning for cure. So maybe we can't do a whole lot other than try to improve our health care provision of patients at risk for developing atrial fibrillation in terms of primary prevention of atrial fibrillation. But we certainly can do a lot in terms of curing patients once they develop that little 1% of that pie chart

And we've gone through an evolution in terms of ablation. We knew that the pulmonary veins had these initiators that cause atrial fibrillation. Early sorts of procedures back a decade and a half ago-- little small circles around the pulmonary veins. We started getting more aggressive in making these larger circles, what we call a wide area of circumferential ablation, taking out all the pulmonary veins en block.

And then we say, well, that's still not good enough. We're still having atrial fibrillation. So we started doing all sorts of additional lines in ablation, complex areas of conduction or other neurologic areas-- things that we thought were involved in the pathogenesis of atrial fibrillation. But we still haven't cured everybody of atrial fibrillation despite all these attempts and this progression of the ablation procedures.

But clearly, it's better than anti-arrhythmic drug therapy. There have been now about 20 randomized perspective-- about a half a dozen of them, FDA monitored trials looking at catheter ablation versus anti-arrhythmic drug therapy. And they all show, with one exception, that catheter ablation is superior to anti-arrhythmic drug therapy. You can see symptomatic AFib or protocol [INAUDIBLE] catheter ablation with one or more procedure, vastly better than anti-arrhythmic drug therapy. So we know that from our clinical practice.

But it's not perfect. And you can see that despite the claims that people will say that they have a 100% cure rates and stuff like that-- in these randomized perspective FDA monitored trial, which this is, you can see that with one more procedure, the cure rates are still about 70%. Part of that problem is that there's a huge problem with all the available technologies of what we call recurrence of conduction between the pulmonary veins and the rest of the atrium. So that's why there's a frequent need acutely for second procedures. But as you'll see, there's also a risk of developing what we call late atrial fibrillation beyond the acute reconnection phase.

If we look at ablation-- if we look at the positive sides of ablation-- if you look at our ability from pool studies here to ablate paroxysmal persistent atrial fibrillation, even though there's a worsening of substrate in the persistent atrial fibrillation as I've showed you, nonetheless the results are pretty good. Somewhere in the 70% range for a single procedure-- up into the 90% range with one or more procedure.

With chronic atrial fibrillation, or permanent atrial fibrillation-- longstanding, persistent, however you want to call it-- the results are somewhat worse, because by that time, you've allowed the patient to have so much remodeling of the atrium, that there's an extensive amount of atrial scar there. And it makes the ablation procedure much more difficult. So this is one of the pieces of information that suggests that if you're going to try to cure the patient, if that's an important issue-- and we can talk about the potential benefits of earlier intervention-- but we should intervene early, not late. Oh, let them stay in AFib in 10 years and then send them to the electrophysiologist. But intervene earlier before you allow the atrial fibrillation itself to invoke or cause so much remodeling that the procedure becomes less successful.

In terms of age group, pretty much all age groups have the same success rate. You can see here, people less than 50, 50 to 65, greater than 65-- we've actually done some data out to in the 80s-- but the cure rates are pretty much the same. So age per se is not a reason to not refer somebody. But certainly after people get into the 80s, the risk of complications from the procedure go up even if the success rate stays the same.

Quality of life is improved, in this study at least. It suggests that both in terms of physical function scores and mental function scores from an ff36 analysis normalized, in the blue here, at post-ablation to age and sex match controls. Whereas pharmacologic therapy resulted in a decrease in the order of a decrease that you'd see with patients with heart failure. So the impact on the quality of life of atrial fibrillation is quite dramatic. So trying to ablate that and cure that obviously becomes important to give better quality of life to our patients.

In the heart failure patients, perhaps there is the most to be benefited. And certainly we can by ablation and getting rid of atrial fibrillation improve left ventricular function. And as recent data has suggested, there may be an improvement in overall survival in patients who are treated with heart failure with atrial fibrillation ablation compared to treated with pharmacologic therapy. But again, more prospective randomized data is needed to confirm this retrospective data.

But we can alter the natural history. So there's a lot of good things with ablation-- made a huge amount of progress. And we can alter the history. This is just some, again, retrospective data-- fairly large study. If you were ablated, the probability of developing permanent atrial fibrillation out to five years of follow-up was small. And patients treated with anti-arrhythmic drug therapy, the probability of developing chronic atrial fibrillation and longstanding persistent atrial fibrillation is higher. That's not to say that the patients who were ablated weren't having atrial fibrillation, but they weren't permanent atrial fibrillation.

And there's data recently that's saying that the more AFib you have, all things else considered or maintain the same in terms of anti-coagulation-- but the more AFib you have, the lower your-- or the less AFib you have, the lower your risk of stroke. So if you have paroxysmal compared to permanent atrial fibrillation on a NOAC say, your risk of stroke is dramatically reduced. So AFib burden may have some clinical impact besides just quality of life, but may impact harder endpoints such as stroke and mortality.

And that's emphasized here. Again retrospective data-- hard to get prospective data, obviously, in these types of studies. But this is a huge trial done in Utah, where they looked at 4,000 consecutive patients treated for ablation, compared that to 6,000-- 16,000, excuse me-- patients with atrial fibrillation treated medically. And compared that to 16,000 patients who didn't have atrial fibrillation. All of these age and sex, but not necessarily diseased matched.

And what you can see is that in the ablation patients, their mortality decreased to that-- to patients who are age and sex matched, but who did not have atrial fibrillation. There's was substantially less than patients who had atrial fibrillation treated medically. Likewise the risk of stroke in various different types of dementia, however you want to define it, normalized to the age and sex matched group of patients without atrial fibrillation.

So there are data suggesting, but not proving, that ablation has impacts greater than just improving-- just improving the quality of life. And as several analyzes have shown, it is cost effective relative to medical therapy. So it's this litany of various different things suggesting that catheter ablation is vastly better than anti-arrhythmic drug therapy or rate control only approaches in terms of both quality of life and potentially harder endpoints such as mortality and stroke.

Given the wealth of data showing the advantages of catheter ablation over pharmacologic therapy and the most recent guidelines from the American Heart Association and the American College of Cardiology, catheter ablation has now been put as front-line therapy-- front tier therapy. Up until last year, catheter ablation was suggested only after you had failed one of more trials of an anti-arrhythmic drug. But as shown here, regardless of whether you have structural heart disease or not have structural heart disease, catheter ablation is listed as a reasonable option up front, particularly if the person is young and healthy and is going to be living with the atrial fibrillation for a while.

So this is tacit approval by the regulatory boards that catheter ablation is a very reasonable way of trying to cure or limit the frequency of atrial fibrillation. But there are lots of problems with this, and it's not by any means perfect. So if you start looking at realistic sorts of studies like registries of patients not just in teaching institutions but in private practice, those areas, the risk of complications are much higher. And so you have to factor this in as you start looking at or counseling a patient to undergo ablation.

There's also the concern that although a lot of times we think somebody is cured, that they may-- and they may in terms of symptomatic atrial fibrillation look much better. If you start doing detailed monitoring, there may be a lot of asymptomatic atrial fibrillation that's going on that poses risk in terms of stroke and other complications in the long-term follow-up.

But perhaps most important for this discussion today is the fact that even in patients who are cured up front, so who've done really well for a year with no recurrence of atrial fibrillation, that doesn't mean they're cured. We used to say a decade ago-- I'd tell patients, well, if we fix you, you're cured. You're done with your AFib. We don't say that anymore. Because if you look at long term recurrence rates, you can see that after single ablation or multiple ablations, there is a slow recurrence of atrial fibrillation in some patient populations. And so the question is who are those patients populations, and can we prevent that process from happening?

We know that scar is closely related to the success rate of the procedure. This is kind of an interesting analysis using delayed enhanced MRI images. This is, in this left hand side, showing lone AFib versus AFib in the setting of heart disease. And Dr. [INAUDIBLE], this gets back to your comment. You can see that actually the probability of scar is the same-- scar distribution is the same whether you have lone AFib or have AFib associated with heart disease. So lone AFib may be a misnomer. And a lot of lone AFib actually is AFib related to probably obesity.

But you would also see that the more scar you have in the left atrium, by this type of analysis, the less your success rates are, both in the short term, but also in the long term analysis. We also know-- and this is a problem that we got really aggressive, right, about extending these lesions and doing more aggressive sorts of procedures to try to improve our success rate. But when we do that, we also create scar. And then the question is are we creating substrate for further atrial fibrillation?

This is a patient referred to us-- been ablated twice-- a very conservative procedure-- just basically a very narrow pulmonary vein isolation type procedure. But What you can see is you can see scarring in the pulmonary veins. But there's scarring in the posterior portion. Here's the septum-- extensive scar throughout the atria. And so we're doing some studies now looking to see if the ablation procedure we're doing is causing the scar. And this is raising the concern that perhaps we should be doing less aggressive, not more aggressive procedure. We should do less burning, less destruction of atrial tissue, which sets up an inflammatory response, which may kill more than just the anticipated targets.

Certainly the ability to better define targets will help limit how much burning we have to do to cure atrial fibrillation. And this interesting, novel technologies-- this case, a basket catheter that you expand out in the left atrium. And it allows you to see-- if you can see this, but these color maps are showing little rotors of activity around pivot points outside of the pulmonary veins-- allow for specific ablation rather than making perhaps lots of linear lesions which have more extensive atrial myocardial damaging effects.

But the biggest issue gets back to the issue we've been talking about today, and that is that you've got to prevent the underlying disease. Shown here is an analysis of late results from an ablation based on how much pericardial fat you have. And if you have extensive pericardial fat-- look at that-- your probability of staying cured, at least in this study, was 20%.

And so that brings us back to this slide here. We can go in and do an ablation procedure. And we can get rid of your atrial fibrillation. And that may prevent this portion here that's caused by acute remodelling from the atrial fibrillation. But that doesn't stop the disease progression. So if we're truly going to cure atrial fibrillation, not just for a five year period or a 10 year period but for the patients lifetime, we still have to go back to that active lifestyle intervention.

And so there are a number of studies now, and none of these are great studies, but they're at least-- are suggesting that indeed that's part of our task now. I'm no longer just an ablationist, but I have to be a good doc. And that is I got to sit down and talk to my patients about counseling, and losing weight, and controlling their hypertension. Shown here is a study looking at post ablation results after controlling either people's metabolic-- or whether they had metabolic syndrome or sleep apnea. And the more risk factors you have, the worse your results were.

Getting into intervention, a number of studies-- this is from the LEGACY AF study showing that in patients with atrial fibrillation, aggressive weight control decreased their need for subsequent therapy. So if they were able to lose 10% of their body mass, their risk of developing atrial fibrillation down the line was half that of patients who weren't able to do that. And results in terms of long-term results after ablation, either with or without the anti-arrhythmic drugs in this forecast, were much better if they were able to lose weight.

We would get back to that same issue that it's really hard to get people to lose weight. So there's other issues that may be impacting on these data analyzes. Because people who are motivated enough to lose 10% of their body mass, probably do a lot of other things besides just losing body mass. It may have impact in terms of decreasing the recurrence rates after ablation.

This is just another study. This is the Arrest Trial, again showing this is a more thing-- just more than just looking at weight reduction, but looking at aggressive risk factor modification across the board. People that would do that had much less AFib than patients who didn't. And again, there's a lot of confounding issues here.

So if we look at in summary the post-ablation care of patients, trying to make sure that patients aren't just acutely cured by their ablation, but have a long-term cure. If we look at the same things we've looked at for primary prevention-- if we look at ACE inhibitors, ARBs, statins, there's no impact of those for decreasing the long-term risk of atrial fibrillation that we know of or have been able to define. Steroids can decrease the acute occurrence of atrial fibrillation within the first three months by decreasing the inflammation related to the procedure. But actually over the long term, steroids increase your risk of atrial fibrillation, at least in part because of the increased risk of pericardial fat with steroids.

Colchicine may decrease acutely and possibly long term the risk of atrial fibrillation. But the big issues in terms of decreasing the risk of atrial fibrillation in the long term after ablation are going to be control of the various risk factors such as obesity, hypertension, sleep apnea, and metabolic syndrome. But it's hard things for us to do.

So in some way to get back to the original question, can we cure atrial fibrillation? Well, sure in patients who already have atrial fibrillation, we can ablate them. And we can cure them or fix them for the short term. But we still have this nagging problem that we have to manage the underlying disease processes that caused them to have atrial fibrillation in the first place. Otherwise we're back to where we started from.

In terms of the vigor health care policy issue, in terms of primary prevention of atrial fibrillation, can we care that? There's not any strong data suggesting we can. Certainly a lot of suggestive data that dieting, exercise, appropriate care of patients decreases the risk of developing atrial fibrillation long term.

But again, in terms of implementing that across large portions of the population becomes very difficult to do. So can we move the United States from the red zone, where we have this high density of AFib compared to the rest of the world, to a more normal distribution? It's going to take a huge push in terms of modifying patients' lifestyles-- very difficult thing for us to do. Thank you.

[APPLAUSE]