Epidemiology of Atrial Fibrillation: Modifiable Risk Factors and Concept of Atrial Fibrillation as a Systemic Illness

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DR.USHA B. TEDROW: Hello everyone. Today, we are going to be talking about, "Epidemiology of Atrial Fibrillation: Modifiable Risk Factors and the Concept of Atrial Fibrillation as a Systemic Illness." My name is Usha Tedrow, and I am Associate Professor of Medicine at Harvard Medical School. I also work at Brigham and Women's Hospital where I am the Fellowship Director for the Clinical Cardiac Electrophysiology Program. Atrial fibrillation is very important to the cardiometabolic health community because it is the most common arrhythmia that we encounter in the United States, and it is the source of major morbidity and stroke in the United States, and I think it will be very important for such a clinician to understand this illness better.

So as I mentioned, atrial fibrillation is the most prevalent arrhythmia in the world really, and here you can see sort of a global map which is now a little bit out of date from 2010 but still it sort of makes the point that atrial fibrillation is present in many, many different countries, but it is certainly concentrated in North America and in Europe, and the reasons for that are not clear and whether this is a difference in screening between different communities, even a difference in mean age between these different communities, whether there are genetic predispositions or different lifestyle habits that contribute but certainly atrial fibrillation is present everywhere.

An estimated three to seven million people are diagnosed with atrial fibrillation, and in projection studies that have been done over the years, this number is expected to rise to 5.6 to 12.1 million by 2050 even in the most conservative estimates, so definitely, a very, very prevalent arrhythmia. Additionally, one observation that is very consistent across epidemiologic studies is that atrial fibrillation incidence increases by age with every decade of life and you can see here multiple studies showing the same thing, some of us in the atrial fibrillation epidemiology community joke that, "If we could all live to a 130, we would all be in atrial fibrillation." So certainly every decade of life increases incidence of atrial fibrillation, and it is not clear exactly what makes that happen but probably this is mediated to some degree by fibrosis that occurs slowly throughout life in the atrium.

So let us talk briefly about age and sex differences in atrial fibrillation. This is some data from the Framingham Heart Study, some very basic older data from the mid '90s. Just looking at men and woman, and the differences in incidence, and atrial fibrillation, as we mentioned, doubles with every decade of life, so certainly that contributes to increasing incidence for women because women have greater projected life expectancy; however, men have an adjusted 1.5 times risk of atrial fibrillation greater than women and you can see that demonstrated in the plot.

So what causes atrial fibrillation? It is a very interesting disease that we tend to think of in a two-compartment model. Shown on this slide, in the upper right, is a biopsy of the left atrium, and you can see the cardiomyocytes are the little pink cells that you can see with these interwoven blue fibrotic areas and if you imagine that what happens in the atrium is that conduction occurs from one cell to the other, than these fibrotic areas interrupt the conduction and cause slow conduction and erratic conduction and that certainly leads to irregular signals in the upper chambers of the heart that can contribute to atrial fibrillation and that is what we call the substrate for atrial fibrillation. It allows for it to propagate and continue beyond an initial episode. Down at the bottom, in the right lower chamber, you can see a cardiac MRI of the left atrium and you see four pulmonary veins, one, two, three, and four

coming into the left atrium. And one of the very interesting things is what triggers atrial fibrillation? The patient will so often ask, "Why is this happening at this given moment?" And from an electrical standpoint, what folks have noticed is that there are these tiny slips of myocardium or the heart muscle tissue that goes up into the pulmonary veins and those areas, for reasons that we do not totally understand, have the capacity to develop pacemaker activity. So patients with atrial fibrillation often have pacemaker activity up in the pulmonary veins that propagate into the main body of the left atrium and these little pacemaker cells are the trigger and then the atrial fibrillation is able to continue longer and longer depending on how much fibrosis or substrate areas.

So what causes this whole process to happen? So one of the biggest common reason that people develop atrial fibrillation is increased left atrial size and pressure, and that can be a result of high blood pressure, hypertension which can slowly lead to left ventricular hypertrophy and when the left ventricle is thickened then the left atrium sees a higher pressure and often becomes enlarged over time with more fibrosis. Similar process occurs when there is valvular heart disease. For example, if the mitral valve leaks the left atrium sees more pressure and becomes enlarged and additionally patients with heart failure either with low pumping function of the left ventricle or preserved function of the left ventricle, heart failure patients often have high pressures in the left atrium that contribute to fibrosis and enlargement over time. Now for patients that do not have structural heart disease, those can be a genetic predisposition to atrial fibrillation, and we will talk about that a little bit later in the talk that many patients who have a family member with atrial fibrillation are at increased risk of developing atrial fibrillation. Then lastly, there can be inflammation and neurohormonal influences that govern the initiation of atrial fibrillation. Patients who develop a pericardial effusion for example, can have elevated inflammatory markers that can cause more ectopic beats in the atrium and more initiation of atrial fibrillation.

So just to follow up a little bit on that information commentary we are all seeing all these patients these days with COVID-19 and I thought I would throw in one slide about atrial fibrillation and COVID-19 that were done by some of my colleagues at Mount Sinai in New York and so these are some data from the height of the pandemic in New York almost four to five thousand patients were analyzed in this study. And they looked at patients that wound up in the ICU with severe disease and then they looked at a similar cohort of patients who developed hospitalization related to influenza to try to determine whether atrial fibrillation in patients with COVID-19 was particularly bad compared to other viral illnesses where patients get hospitalized and one of the interesting take-home points from this study, if you look at the bottom right figure, you can see that the relative risk of mortality in patients with COVID-19 versus patients with influenza was 1.7, so just about the same although you noticed that overall the COVID-19 patients especially at this point early in the pandemic have significantly more mortality than the influenza patients.

From this data, the investigators concluded that, "While there is increased mortality associated with atrial fibrillation in both of these viral illnesses, the atrial fibrillation itself was probably not the bad actor but just a marker for more severe illness." This whole observation of increased mortality in patients with atrial fibrillation was probably mediated by increased inflammatory markers, myocardial injury, as well as

critical illness and presence in the ICU. So the conclusion from this study, in terms of management, is, "Certainly we should encourage our atrial fibrillation patients to be vaccinated for both COVID-19 and influenza and avoid these illnesses if possible."

So what are the different types of atrial fibrillation? We sort of alluded to this when I was speaking earlier in the section. There is paroxysmal atrial fibrillation where you have an episode and it usually starts and stops by itself within a few hours, and the patient may have palpitations and irregular heartbeat that often does not have to come to the hospital unless they are severely affected by their symptoms. Then we have persistent atrial fibrillation where the episodes are longer, lasting days to weeks, and sometimes have to be terminated by an external shock called cardioversion. And then there are patients that eventually develop permanent atrial fibrillation where fibrosis of the atrium has progressed to the point where atrial fibrillation is continually present. So early in the disease, when we are paroxysmal, the triggering is very, very important. So those little pacemaker cells in the pulmonary veins are the most important part and then as we move from persistent to permanent atrial fibrillation, the fibrosis, those little blue meandering pathways that we saw earlier in the talk become the main component of what is driving the atrial fibrillation.

So here is some great work from the late '90s from Michel Haissaguirre in Bordeaux. Their group was really the pioneers of figuring out the triggering for atrial fibrillation, and here we see a little circumferential gross pathology specimen of a cross section of a pulmonary vein and here you can see those myocardial sleeves that I was alluding to previously that can contain pacemaker activity that can trigger atrial fibrillation. And then what you see below here is a little bit of a tracing that we might see in the electrophysiology lab when we are doing a catheter ablation for atrial fibrillation. What we are seeing upon top here, these first four lines, are an EKG and the EKG is just one, two, three, four leads but we see here is a P-wave and then a QRS and then initiation of atrial fibrillation with irregularly irregular QRSs that follow. What we see below is a catheter that has been placed in the right inferior pulmonary vein. So what kind of electrical signals do we see there?

We see stuff from the atrium and we see stuff from the pulmonary veins and what you noticed is there is a signal here that lines up with the P wave so that is atrial activity but then before the atrial fibrillation really gets going, you see these triggering beats, very rapid electrical activity, and then this irregular beating within the pulmonary vein, and those are actually those accessory pacemakers in that myocardial sleeve that are triggering the atrial fibrillation. When we do a catheter ablation for atrial fibrillation that is what we target. We usually try to do something called pulmonary vein isolation and this is just a picture from one of my patients where you see an MRI of the left upper chamber of the heart. We are now looking from the front instead of from the back like we were in some of the other slides. So these are the right sided pulmonary veins. These are the left sided pulmonary veins, and sticking out towards us here is the left atrial appendage which is where a lot of the thrombi come from in patients that develop strokes from atrial fibrillation. What we do in terms of ablation is we zap the areas around the veins. Here we see it again from a posterior aspect and the idea is to block these electrical signals from the veins from reaching the left atrium and thereby prevent atrial fibrillation.

Now what I would like you to be convinced of over the next couple of slides is that not all patients with atrial fibrillation are created equal. Here is an example of a patient who is 84 years old with atrial fibrillation and severe mitral regurgitation, and this is from the group at Utah who has pioneered using MRI to try to look at fibrosis in the atrium and so in their little 3D reconstructions, here you see it is a bit more pixelated than what we were looking at before, but the dark blue areas are normal tissue, and the light green areas are fibrosis. And what you can see is in this patient with severe mitral regurgitation, the left atrium has become enlarged and there is a lot of fibrosis that is present and when you look at a biopsy sample you also see a similar thing that from the endocardium, which is inside surface of the heart, to the epicardium, you see a lot of blue areas of fibrosis on the biopsy specimen, and these contribute to atrial fibrillation.

There is a range of atrial fibrosis that we find in patients, and here is a series from the same group where we see a patient with a normal left atrium. So this might be a patient with known atrial fibrillation that has a pretty structurally normal heart yet still has atrial fibrillation and you see very little evidence of fibrosis. Then you see a patient similar to the one we were just looking at where we see some moderate regions of fibrosis and perhaps this might be a person with more persistent atrial fibrillation, and then lastly, you see someone with very severe left atrial enlargement and a lot of fibrosis, and a lot of us in electrophysiology wonder if these very severe patients if it is at all even possible to get them back to normal rhythm sometimes.

So let us talk about some modifiable risk factors that influence atrial fibrillation risk. So there are a lot of things like your age. Some would say your sex maybe you cannot change so easily. You can try to change it but it might not be something that would modify your atrial fibrillation risk but certainly modifiable risk factors include blood pressure, weight, exercise level, alcohol, smoking, diabetes, and sleep apnea and 50 to 60 percent reductions in AF risk are associated with optimal AF risk factors in observational studies.

So let us look a little bit at blood pressure. These are some data from the Women's Health Study, and I am going to show a lot of data from the Women's Health Study because we have done a number of studies looking back at validated incident atrial fibrillation in this particular study where there were 40,000 women that were studied over a number of years. So this allows us to look at folks who did not have atrial fibrillation at the beginning of the study and how they behave with incident atrial fibrillation down the road, and here we looked at age-adjusted atrial fibrillation incidence by baseline systolic blood pressure and then this is the work by Dr. David Conen when he was working in our group with Christine Albert. And here we see that as our systolic blood pressure increases we see an extremely insignificant increase in the incident and hazard ratio for developing atrial fibrillation.

Then we also can look at obesity and so this is some work from the Framingham Heart Study and you can see that if you compare normal weight, overweight, and obese individuals, you see a statistically significant increase in the probability of developing atrial fibrillation, and the hazard ratio for obesity versus normal was observed at 1.5. So a 50% greater incidence among the patients who were obese and that this observed the fact was mediated mostly by left atrial enlargement. So similar to what I was talking about in another section of the talk, as the left atrium becomes enlarged, the thought is that

there is more fibrosis and more atrial fibrillation. We then looked at this in a more granular way again in the Women's Health Study, looking at dynamic body mass index changes, so changes in weight over time which unfortunately with the majority of these were increases in weight, and so we looked at people that went from normal to moderately-obese to obese and looked at the risk for developing atrial fibrillation, and we found that for each kilogram per meter squared of body mass index, there was an statistically significant increase in incident atrial fibrillation and that has subsequently been shown in meta-analysis where we took a whole bunch of other subsequent studies that had a similar observation and it is a way of sort of averaging that observation we found that each kilogram per meter squared of increased body mass index was associated with a 4% increased risk of incident atrial fibrillation. This is extremely important in the context of the obesity epidemic.

Subsequently, a group out of Australia has done some really nice work in atrial fibrillation risk factor modification focusing here on obesity where they took patients and randomized them to a medication program versus a directed weight loss program and exercise program and in the patients that were able to lose weight, you can see that they had a significantly important decrease and ablation-free, drug-free AF freedom, and the patient's weight loss greater than 10% resulted in a six-fold increased arrhythmia-free survival compared to the other two groups. Then a separate analyses of the same patients showed an arrhythmia-free survival was greatest in those who gained fitness. So a gain of greater than or equal to two metabolic equivalents on exercise testing compared to those with smaller gains and cardiorespiratory fitness. What we like to say when we look at these data is that the weight loss benefit was almost equivalent to an atrial fibrillation ablation. So I try to motivate my patients by saying that if you can move from an obese category to a moderately obese category even you can achieve very extreme benefits in your atrial fibrillation incidence.

The proposed mechanism of weight loss and atrial fibrillation reduction is shown here in this slide where we look at a bunch of different risk factors that may interact with one another. So when you have weight loss, there is an improved cardiovascular risk factor burden, there is a more favorable metabolic and neurohormonal profile and that certainly can contribute to lower atrial fibrillation recurrence. There is also improved cardiorespiratory fitness, and there is reverse cardiac remodeling that happens both as a part of exercise training and as a component of weight loss. So we think that this is one of the most important modifiable risk factors for atrial fibrillation. This is particularly important because obesity and atrial fibrillation are so difficult. The patients have symptoms from atrial fibrillation that limit their ability to exercise sometimes yet they also have difficulty undergoing catheter ablation because many studies show that catheter ablation is less effective and more risky in the obese population and that is just because their groin access can be more challenging, some of the visualization by fluoroscopy can be more challenging, even the perioperative imaging can be more challenging in patients who are morbidly obese.

So let us talk for a moment about sleep apnea which definitely dovetails a little bit with the obesity discussion, so obstructive sleep apnea markedly increases the risk of both atrial fibrillation and stroke. OSA patients are five times more likely to develop atrial fibrillation than those without sleep apnea. The risk of atrial fibrillation is directly correlated with severity of sleep apnea. The mechanisms for this are

not totally clear, but there is thought to be an autonomic component where a sleep apnea stimulates excess vagal tone while triggering the activation of the sympathetic nervous system, and there can also be a worsening of underlying hypertension from the actual apnea episodes. There is also a structural and hemodynamic argument where upper airway obstruction during inhalation results in negative intrathoracic pressure, increasing atrial blood volume which may directly mediate left atrial enlargement and both of these feedback groups are thought to be modifiable, so we definitely recommend that our patients with atrial fibrillation are screened for sleep apnea and treated appropriately. Here is another meta-analysis looking at atrial fibrillation recurrence in users versus nonusers of continuous positive airway pressure to treat their sleep apnea in two groups of patients with sleep apnea, both of those undergoing ablation and nonablation and both groups of patients really are benefited by using CPAP to prevent atrial fibrillation essentially. So we would recommend that patients even after their AF is controlled that they continue to use their CPAP.

So let us talk for a moment about type 2 diabetes and atrial fibrillation. Patients with type 2 diabetes have a 35% increased incidence of atrial fibrillation compared with age and gender matched control subjects. SGLT2 inhibitors are a class of prescription medications that are relatively new and they are FDA approved for use with diet and exercise to lower blood sugar in patients with type 2 diabetes and here is just a very extensive meta-analysis of the different of SGLT2 inhibitors that are on the market showing that SGLT2 inhibitor use can reduce atrial fibrillation risk by 19%, and that is really important. I think we are just starting to understand how these medications influence arrhythmia risk. There is actually, incidentally, separate from this topic, an observed improvement in sudden cardiac death risk with these medications as well.

So let us shift gears and talk a little bit about exercise. So we looked at that study in obese patients showing that improving exercise capacity can decrease atrial fibrillation. Unfortunately, this is most likely a U shaped curve where there are patients with obesity and cardiometabolic risk factors on one side that benefit from exercise, but there is also a group with more extreme exercising that appear to have an increased risk of atrial fibrillation as well, and this is thought to be also mediated by increases in left atrial size. The thought is that with chronic cardiovascular exercise like jogging, bicycling, you can see slow dilations, slight dilation of the left ventricle cavity and you can also see enlargement of the left atrium. So there is definitely a statistically significant increase in incident atrial fibrillation in extreme exercisers and that has been seen consistently again across a group of studies looking at athletes with atrial fibrillation. This group can be very difficult to treat clinically because they often have very slow heart rates because they have high levels of vagal tone at rest when they are not in atrial fibrillation and then their atrial fibrillation is very rapid because they are often younger than the other group that we see with atrial fibrillation.

Let us talk now about atrial fibrillation risk factors specific to women. There are some studies that have been done looking at estrogen. So shown on the left is a graph from the Women's Health Initiative looking at 10,000 women with prior hysterectomy who were randomized to estrogen and it has been noticed that there are hormonal changes in ectopic beats and that there are sometimes more ectopic beats at different stages of the menstrual cycle and in this study they showed that women who are

randomized to estrogen had 17% more atrial fibrillation than those that were not treated with estrogen and that was confirmed in another analysis of the Women's Health Study which were 30,000 women without TAH-BSO, and the hazard ratio for women on estrogen alone was 22% higher in the patients that were treated with estrogen. There was no increased risk associated with menopause beyond that associated with age; however, the number of pregnancies that a women had in the Women's Health Study was associated with incident atrial fibrillation risk as shown here.

Let us talk a little bit about dietary targets for atrial fibrillation. One of the strongest pieces of data for a dietary target is alcohol. So here is one of the early studies from the mid 2000s showing that heavy alcohol consumption in men in the Copenhagen City Heart Study showed higher adjusted atrial fibrillation risk, and this risk was not explained by other cardiovascular risk factors. In this study, the increased risk was not observed in women but interestingly in this group of patients, women did not drink heavily. Subsequently, we have done an analysis from the Women's Health Study that did confirm that two drinks a day in women increased risk of atrial fibrillation significantly, so this is probably an effect across the sexes.

Here is another meta-analysis now that has been again confirmed in multiple populations that alcohol intake and the risk of atrial fibrillation is a significant association, and I think this is really important because a lot of our patients have heard in the past that, "Oh, drinking red wine will be beneficial for the cardiovascular risk factors." It may be when they are thinking about their lipids and their hyperlipidemia; however, when it comes to atrial fibrillation it is very, very clear that there is a dose-response relationship between alcohol intake and risk of atrial fibrillation.

And here is some really nice mapping data from that same group in Australia that did some of those obesity analyses. This is from Jon Kalman's group, and they looked at some patients where they did catheter mapping of the left atrium during atrial fibrillation and ablation and compared nondrinkers, mild drinkers, and moderate drinkers and in this what we have done is during the ablation procedure, we have a little paintbrush like catheter that we move around the inside surface of the left atrium and sampled the voltage, and the voltage in different spots of the atrium is a proxy 4 whether there is fibrosis or not because the very low voltage measurements correlate with fibrosis.

So in this nondrinker we see that there is very little fibrosis that can be detected. This mild drinker we see that there is a little bit of fibrosis in the posterior aspect of the left superior pulmonary vein, and in the moderate drinker you see there is more left atrial enlargement and there is patchier fibrosis. So the thought is that actually alcohol is toxic to the atrium and promotes fibrosis. There was a big study recently published in the New England Journal of Medicine from the same group where they randomized patients to an abstinence protocol with no alcohol for six months versus a control group that continued to consume their usual amount of alcohol and the atrial fibrillation recurrence rate was significantly lower among the group that was doing the abstinence protocol, and the median percentage of time in atrial fibrillation in the six months of follow up was significantly lower as well. So I tell all my patients with atrial fibrillation that they are adults, they can make decisions about their alcohol intake, but the best thing is the least amount of alcohol that they are comfortable consuming.

Caffeine intake, however, is a very mixed bag. A lot of folks are told by their physicians sometimes, "Oh, you have atrial fibrillation, you should not have any caffeine." There are as many studies showing that caffeine causes increased incidence of atrial fibrillation as there are that seem to show that caffeine intake is protective. That said, there are certainly individual patients that are triggered by caffeine intake and if your patient, by history, is triggered by caffeine intake, I think it is reasonable to tell them to cut down or avoid caffeine but as a group atrial fibrillation patients is not really supported by the data to tell them to avoid caffeine intake. And there is good news with respect to chocolate intake as well, so these were some data from the Danish Diet, Cancer, and Health Study looking at different levels of chocolate intake, and it appeared that chocolate intake definitely was protective in the incidence of atrial fibrillation. So you can definitely tell your patients to continue to eat their chocolate.

Let us talk a bit about omega-3 fatty acids. It has got into the press a lot and that folks thought taking fish oils and different types of omega-3 fatty acids would be helpful in the secondary prevention of atrial fibrillation; however, similar to the caffeine story, there are several studies that are now conflicting in the sense that there are some that show that it is protective, some that show it was detrimental, and on balance the P value on the meta-analysis crosses 1 which means it is not clear whether omega-3 fatty acids were effective in the secondary prevention of atrial fibrillation. Then sort of the nail in the coffin sort of for omega-3 fatty acids for atrial fibrillation was in a recent study that was published by Christine Albert in JAMA just this past year looking at a large group of patients that were randomized, most of the studies that I showed in the meta-analysis on the previous slide were observational series but this is a large randomized cohort that shows there is really no benefit to treatment of patients with atrial fibrillation with omega-3 fatty acids, and so these findings do not support the use of omega-3 fatty acids or vitamin D3 in adults to prevent atrial fibrillation, and I think this is important because fish oil is a tricky medication to give our patients with atrial fibrillation. It is a slight blood thinner and it is not recommended to be given with patients that are on a blood thinner for stroke prevention in atrial fibrillation, so I think that we really should probably make sure our atrial fibrillation patients are not on these medications.

Then let us look at the Mediterranean diet and olive oil and atrial fibrillation study which is very interesting. They had patients randomized to a control diet, Mediterranean diet with nuts and a Mediterranean diet with extra virgin olive oil, and there was a significant benefit. The metabolic diet with extra virgin olive oil, and I think that the hazard ratio here was 0.62 which is pretty impressive, and I think these data probably deserve a little bit more investigation, but if patients are looking for what they might add to their diet to improve their atrial fibrillation risk that is certainly something to think about.

Let us talk now about combinations of risk factors and atrial fibrillation risk scores. We want to see if we can identify patients at high risk. So here is some data from the AF Risk Prediction in Individuals without Cardiovascular Disease from the Women's Health Study. So these were the kind of patients that you might see in the office trying to predict who is at risk for developing atrial fibrillation in the future. Certainly, as we talked about many of these players that we talked about earlier in the talk including age, weight. One of the interesting factors is height, which is actually associated with increased risks of atrial fibrillation and that is conserved across - even birth height actually is associated with increased risk of

atrial fibrillation. That is probably correlated with increased left atrial size, systolic blood pressure, as we discussed earlier, drinking more than two drinks per day of alcohol and anyone who has ever been smoker and these are all factors together that are independent in terms of predicting risk of developing atrial fibrillation.

In CHARGE-AF they attempted to develop the risk score with a multivariable model for five year risk of AF combining data from a large number of studies and they have added a few different other risk factors to refine the model and you can see here that in addition to systolic blood pressure they have included diastolic blood pressure. They have also included antihypertensive medication use, diabetes, heart failure, myocardial infarction, left ventricular hypertrophy as well as some ECG findings and they were able to very tightly predict the development of atrial fibrillation in a model and then they were able to validate that an observational series was effective in both minority populations as well as in white patients. So the idea of developing a score like this is that we could evaluate putative novel clinical risk factors to reclassify an individual's risk of developing atrial fibrillation. We also could select high risk individuals for trials of primary prevention or intensive monitoring for AF detection.

Now going back to the Framingham Heart Study and some nice work by Dr. Fox, through their looking at AF genetics showing that patient's parental history of atrial fibrillation is a very strong risk factor for developing atrial fibrillation and atrial fibrillation in more than one parent has an odds ratio of almost twofold for developing atrial fibrillation and if that parent is less than 75 without a history of heart disease, it is a threefold risk. So this really speaks to genetics playing a strong, strong role in atrial fibrillation risk. And the lifetime risk of developing clinical atrial fibrillation is also stratified by genetic risk and you can see that if you take an average lifetime risk of developing atrial fibrillation and develop a polygenic score, you can stratify patients into high intermediate and low risks.

And here you can look at AF genetic risk scores that have been attempted to be developed with data in multiple populations and the idea is that the pooled five year relative hazard of incident atrial fibrillation can be increased if your genetic profile is high risk. So the real Holy Grail of this is atrial fibrillation genetics and it is clear that when we do genome-wide association analyses, we can see that there are certain genes that are represented in these patients with high incident risk of atrial fibrillation and beyond these classifications of paroxysmal, persistent, and permanent atrial fibrillation, we hope that knowing more about these genes and the gene products will help us with outcome prognostications and maybe even help us identify new targets for therapies for atrial fibrillation.

So just to conclude, the reasons for the atrial fibrillation epidemic are not entirely clear but are partly related to the aging of the population, improved longevity from cardiovascular disease, improved detection, and rising obesity rates. There are currently several potentially modifiable risk factors for AF that may provide strategies for AF prevention including blood pressure control, weight loss, moderate physical activity, smoking avoidance, and minimization of alcohol intake. There are also reproductive and hormonal AF risk factors unique to women suggesting a possible impact of multiple pregnancies and estrogen use on atrial fibrillation risk. And a combination of AF clinical and genetic risk factors can be utilized to identify high-risk patients for targeted AF screening and hopefully for future intervention trials in atrial fibrillation.