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So my task this evening is to talk about preventing sudden death. And when we talk to patients about preventing sudden death, it can be a bit of a sobering discussion, and can take some time because you're talking to people about something they really don't want to hear about. And you can't blame them.

So we're going to talk about some of the background. This kind of helps me, when I think about the discussions that I have to have with individual patients. These are my disclosures.

So I'm going to talk about the definition, the prevalence, the role of the substrate. We'll talk about treatment, prevention, and some controversies in the new risk prediction tools, in predicting whether or not someone has a significant risk of sudden death and hypertrophic cardiomyopathy. Then I'll have a brief summary.

So what is sudden death? Well, we all probably know that sudden death is an unexpected collapse occurring less than an hour from the onset of symptoms. And these patients usually had been previously well or stable. So documented of VF occurs in these people, and occasionally now in some of the clinical trials we'll use an appropriate ICD shock for ventricular arrhythmia as a surrogate. And it's reasonable to do that for a sudden arrhythmic death, but it's controversial to use ICD shock as something for total mortality.

And as someone that does a lot of time adjudicating clinical events, it can be really challenging to sort out what is the actual mechanism of how someone dies suddenly. But it's clinically a spectrum, and in hypertrophic cardiomyopathy we find that sudden death is intertwined with the disease process, and it's clearly been described as one of the most devastating complications. And if you have someone who has survived a sudden death come to your clinic with their parents, you see the agony on the faces of their parents. So preventing this in the patient who's at risk is really crucial.

So what are the modes of death in hypertrophic cardiomyopathy? Well, Dr. Maron and colleagues looked at this back in the year 2000. And they looked at it based on age, mechanism and age. So the dark bar is sudden death. There's also a bar for heart failure death. And to the far right of the screen, there is a bar in the older population for stroke related death. And this is from embolic events in atrial arrhythmias.

And so you can kind of see a distribution of modes of death. And sudden death tends to cluster in the younger patients. And as we've seen in other population, modes of death can change as time goes on.

OK, so the annualized rate of death in hypertrophic cardiomyopathy is around 1.5%. Sudden death is the bigger proportion of that, and then the heart failure and stroke death. So this speaks to why a center that has expertise in the full spectrum of hypertrophic cardiomyopathy is important, because changing in the substrate relates to changing clinical spectrum, and what patients' needs are.

So of the patients that experience sudden death, where does it happen, and in whom does it happen? We always counsel the young high school students, and maybe college students about sports participation. Well, it's interesting, because if you look at the where sudden death occurs, it occurs in people who tend to be less symptomatic.

They may not be right away that 29-year-old patient who presents to Dr. Bach's clinic with severe symptoms who's not treated. It tends to cluster in the lower New York Heart Association classes, or in the asymptomatic patients. And it can occur, like we talked about, at any age, but clearly in the young. And if you look at the other pie graph on the right hand side of the screen, you see that the sedentary exertion or no exertion tends to be the majority of when sudden death occurs in hypertrophic cardiomyopathy.

Well, why does it occur? Why do people have these arrhythmias? Well, their sarcomeres are abnormal, and so it leads to hypertrophy, disarray, fibrosis, and small vessel changes. And we see this, again, from a lovely paper done by Dr. Maron from *Circulation*, where they show the histology of a normal myocardium, which is on the left, and then the change is seen in hypertrophic cardiomyopathy, the fiber disarray, and then the vessel changes.

And I always think of this. Yes, it's a sarcomere, but then this paper really they brought to mind that there are vascular changes that go along with this substrate.

And in the electrophysiology world, if you have abnormal myocardium, you can have dispersion of refractoryness. And in the words of Dr. Josephson, we get ventricular arrhythmias.

So what about the defibrillator? We all hear about the defibrillators in hypertrophic cardiomyopathy. Where did it come from?

Well, it came from a series from 19 centers in the United States and Italy, 128 patients, and just a retrospective review of what these patients experienced when they had a defibrillator implanted. And these KM curves show you the shock rates. And so patients who were implanted as a preventative strategy had a rate of appropriate shocks around 5% per year. And if they had survived sudden death, then the shock rate was double that, 11% per year. So this was the beginning of the collective experience of different leaders in preventing death in patients with hypertrophic cardiomyopathy.

So other groups have also looked at this. And remarkably, a Polish series that was published more recently found similar rates. Now, the patients, again primarily were those who were implanted for primary prevention. And the number of factors that were looked at for what's the risk of having an ICD shock, and it turned out in this population, a little over 100 patients, that non-sustained ventricular tachycardia had the greatest hazard ratio for an appropriate shock. And we can see the curves for that.

And also, we see on the bottom the inappropriate shock rate. So you're starting to get a flavor of although we have a therapy that prevents rhythm related death, the therapy is also associated with some morbidity.

A subsequent meta analysis took over 2000 hypertrophic cardiomyopathy patients from 27 series, follow up pretty good, nearly four years, and looked at who the patients were that got appropriate ICD interventions, 14% of them. The cardiac mortality was around 3%, 0.6% per year, and the non-cardiac mortality was 2%.

Now, this was meta analysis, so it wasn't a group of people sitting in there with all the data and the source documents and the death certificates, trying to adjudicate death. So with the issues that go along with meta analysis, we have to take a little bit with a grain of salt, but you can still see that cardiac mortality in these patients predominates.

As Dr. Bach talked about, alcohol septal ablation or surgical septal reduction therapy, there is still mortality and sudden death mortality in these patients. But look how similar they are. And so in this series, this kind of parallels the data that Dr. Bach showed us earlier, the KM curves about survival in patients who've had the myectomy, versus alcohol septal ablation. So the overall sudden death risk is diminished, but it's not 0.

What about antiarrhythmic drugs? We heard about Norpace, Disopyramide. What about other antiarrhythmic drugs? Well, I went back and looked at some of the series where the use of antiarrhythmic drugs was reported, and you can see that the percentage of patients in some of these series who are on an antiarrhythmic drug is low. But yet, they still had an event rate for ICD shocks that were deemed appropriate.

So you have to be careful in interpreting this, because ICD shocks is one kind of endpoint, but the other thing is that antiarrhythmic drugs can be proarrhythmic. These patients have abnormal substrate. And so one of the things we don't know is if you had less antiarrhythmic drug use, would your shock rate be the same? We don't know.

The other thing to keep in mind is these patients tend to be on the younger spectrum. And I use young to say 50 and less, so that I can be in this group. But nevertheless, some of them don't want to take an antiarrhythmic drug. If I were 35 years old with hypertrophic cardiomyopathy, I don't want to be on Amiodarone for 10 or 20 years. So we have to think about the impact of our therapies on our patients and their quality of life. So drugs, as well as defibrillators.

Now moving into the risk factors, this is something that we've all seen from Dr. Maron in circulation, and there we know that there are groups of patients with hypertrophic cardiomyopathy that carry the greatest risk. Those are patients who have had a prior cardiac arrest.

But there are other qualities or factors that put people at increased risk, a familial history of sudden death, unexplained syncope, marked thickness of the left ventricular septum, or any other wall. And then there's modifying risk factors that may play into that, and we're going to hear about those later on in the symposium with MRI imaging, as well as genetics.

So I think of this is one of the most telling visuals of the role that wall thickness has in the incidence of sudden death. And this came from Dr. Spirito's group and was published in the *New England Journal*. And the mass of hypertrophy patients that we see whose thickness is 3 centimeters, shown in the orange bar, it's just really impressive as to what their sudden death risk is.

Well, what are these other mitigating factors? We've heard about obstruction. Dr. Maron and colleagues have shown us that survival is different, whether or not you're obstructive in your hypertrophic cardiomyopathy or not. Delayed gadolinium enhancement. I will tell you that having studied for the MOC section that's going to be at this meeting in electrophysiology, there is a question on this actual topic. So Dr. Maron, you made the ABIM here. And so this is an MRI picture that shows actually some of the enhancement.

Well, based on this, we have our AHA, American College of Cardiology Foundation HCM guidelines that help us determine where an ICD is reasonable. The green means it's absolutely acceptable. The yellow means it's reasonable. The orange means you need to do some thinking, and the red means well, maybe we should reevaluate the implantation of a defibrillator. And so when I sit in clinic and talk with our Fellows and we see a patient who has risk factors, we use this algorithm. And I tell patients, these are the risk factors that you have, and this is what's influencing our medical decision making, for shared decision making in these patients.

Well there's also been interest lately in the European Society of a different risk assessment tool. And so they've looked at selection of patients for primary prevention defibrillators, and they agree that it's challenging, because the disease is heterogeneous. And we know this. There's a variable effect of each of the risk factors, and you may find a paper that says that family history is the biggest risk factor, or maybe not so much a risk factor. But a clinical prediction model that helps physicians and patients guide individualization is necessary or important. And I certainly think this is useful to think about.

And so they did this, the Europeans. They did a retrospective, multicenter longitudinal cohort study, Cox proportional hazards modeling bootstrapping, which is very intense computing, and an external validation in over 3,000 patients with a 24 3-1-3 patient year followup duration. And they came up with this equation.

So I tried to use this equation in clinic. I had a smart fellow, tried to punch in all the numbers and do all the exponents, and it didn't make sense. We didn't get a number that was reasonable. But ESC has since made an app for that, and that's shown in this slide.

And interestingly enough, their factors that you input are age, wall thickness-- left atrial size, curiously-- left ventricular outflow tract gradient, family history, non-sustained BT and unexplained syncope. So things that we have heard about this evening, but weighted maybe in a different fashion.

I will tell you that this is under discussion. I don't think that there is a definitive answer if we should be using this tool or not, but I think it's important to know that it's out there. Our distinguished colleague, Dr. Maron and Dr. Maron, actually took this tool in a recent publication and applied that risk model to a separate population. It's a little bit of a complicated slide, but if you look at the lower left hand portion where it breaks down the bars into what their ESC risk is, green, low, pink, medium, yellow, high, and then just look at the part that shows sudden death. You can see that even the ESC scores really didn't predict the patients who were going to go on and experience sudden death.

So we use this tool is still controversial. And when it boils down to it, in the clinic on our side of the Atlantic, I use the AHA guidelines to help guide the discussion with a family and patients.

So the other thing that I think is important to realize is that defibrillators have complications, and they have consequences. And they have consequences for young people who are going to have decades of life with these devices. So we know that they have complications, and we know that there are longer term complications. And battery longevity is an issue with multiple procedures.

Leads are an issue. Leads are a big issue. And we have our hypertrophic cardiomyopathy symposium where we invite patients and family members, many of the questions I get are about leads-- leads wear, lead extraction, lead failures. So this is significant for our patients. And it's a lifelong concern.

So we know from other series and registries, and this is from the replace registry, that complications occur. And they continue to occur. And lead complications are the most common.

OK, what about inappropriate shocks? Well, in younger people they tend to have more inappropriate shocks. That's a problem atrial arrhythmias and again, lead malfunctions, leading to inappropriate shocks.

So there have been series that looked at this. And we can look at the ICD appropriate shock rate and the inappropriate shock rate. And unfortunately, they're rather similar. And this is from the meta-analysis. So the appropriate shock rate was around 3.3%. The inappropriate shock rate was 4.8%.

Now, this was done prior to mated RIT. And mated RIT was a prospective trial that actually looked at programming strategies specifically designed to reduce inappropriate shocks. This is critical in the younger patients who have hypertrophic cardiomyopathy, because they can have very rapid atrial fibrillation that can get up into VF detection zones. And so reducing inappropriate shocks in this patient population is of paramount importance.

Well, complication rates. This is actually the complication rates in patients with hypertrophic cardiomyopathy. It's not trivial. [INAUDIBLE] rate for lead malfunction, 6.2, and annualized rate of 1.5, 1%, 1.5% per year. And overall, 3.4% lead dislodgement, infection.

And importantly, the psychological impact. And again, these young patients who have a series of shocks are traumatized by this. So when we sit down in clinic and talk to patients about how ICDs can be lifesaving, I also spend significant time telling them these are other things that can happen. And they need to be aware of it.

All right, what are some contemporary areas that we're looking at, and that the field is moving towards? Well, the subcutaneous ICD. If lead problems are such a problem, and lead fractures and taking up space in the vein and leading to venous occlusion, DVTs, well, if we can get leads out of the vein, maybe that will help.

So we have a subcutaneous ICD. You've probably all seen pictures and heard of it. The effortless registry, which was a recent publication looking at patients who have had this device, there were only 54 who had hypertrophic cardiomyopathy, so I can't tell you that we have long term follow up with this device for these patients, but it's coming.

Cardiac resynchronization therapy, to reduce outflow tract gradient. An area of exploration, only in 10 patients. They did not have a significantly widened QRS. They did have Heart Association Class 3 symptoms, and maybe had some benefit from this. But clearly not in this general guidelines for CRT at this time.

Risk stratification with age. If you've survived to be 60 years old, maybe your risk of sudden death is actually mitigated by this. And we're certainly going to hear about the role of delayed enhancement from our expert.

Genetic testing-- there's interest in genetic testing. And from a patient point of view again, patients say, well, if you know what gene it is, can you tell me what's going to happen to me based on that gene? Dr. Cresci is going to give us some detailed information about that. And I will just say that there is some evolving interest and preliminary data talking about that. And maybe patients who have more than one mutation may be at a higher risk for experiencing sudden death.

All right, so if we look at the guidelines they say that sudden death risk stratification at initial evaluation for all patients. And that is what we do at our center. We talk to patients about what their potential risk is. A Class 2 recommendation is if there's a blood pressure response to exercise, reevaluate periodically. And again, the role of MRI is evolving. But electrophysiologic studies for risk stratification in hypertrophic cardiomyopathy in the absence of WPW, or a documented wide complex tachycardia is really not done.

So in conclusion, we think, as the guidelines state, that all patients with HCM should undergo an evaluation of sudden death risk. It doesn't mean they all need to see an electrophysiologist, but we do need to think about it and then refer, if appropriate. And to date, the defibrillator is the only therapy that reduces arrhythmic death. There have been no trials versus ICD versus medications prospectively, nor ICD versus placebo, and I doubt that we will ever see a trial that addresses that.

Transvenous ICDs have adverse effects, and this impacts a consent discussion and in shared decision making. Despite that we believe that sudden death is prevented with defibrillators, what patients experience is tantamount in their mind, as well. And the genetic testing role is evolving. Thank you very much.