Announcer: Hello, welcome to Interview with the Experts podcast. I'm Dr. Patty Pellikka at Mayo Clinic, and it's my pleasure to interview an expert today on the subject of advances in Understanding bicuspid Aortic Valve. Our expert is Dr. Hector Michelena, who is professor of Medicine at Mayo Clinic and an authority in echocardiography and valvular heart disease. Welcome, Hector.

Dr. Hector Michelena: Thank you so much. Patty,

Dr. Patricia Pellikka: You've written extensively on the subject of bicuspid aortic valve. What's the latest on the epidemiology and genetic basis for this disorder?

Dr. Hector Michelena: Yes, so, so still congenital bicuspid aortic valve is the most common heart defect. And what we have come about now is, is that even though before we thought based more on tertiary referral populations, that the prevalence was 2% more population based studies have clarified that, and it's really about 1% of the population, and that is probably divided into 2% in men and 0.5% in women approximately to give a ratio of men to women of about two to one, to three to one. In terms of the genetics and heritability of it, well, we know that it's highly heritable in an autosomal dominant way with reduced penetrance and variable expressivity, and therefore it is very heterogeneous in the way that it expresses physically. The most important thing for the viewer to know perhaps, is that most cases, approximately 90% of bicuspid aortic valve are actually sporadic. They are not familial, they are not syndromic, they are just sporadic. And about 8% are familial non syndromic, and about one to 2% are actually syndromic. And the most common syndromes that, that are associated with bicuspid aortic valve are uh turner syndrome, obviously, and the loeys-dietz syndrome. But there's a another group of syndromes that are, that are associated. The important thing of all of this is that there's about a 10 to 15% chance of a case or a proband transmitting the bicuspid condition to their offspring, and therefore first degree re relatives of, of bicuspid patients should be screened.

Dr. Patricia Pellikka: You mentioned that the disorder is heterogeneous and has variable expression, and I'm sure advances in imaging have improved our understanding of that. How would you summarize that?

Dr. Hector Michelena: So it is, it is highly heterogeneous and not only in the way that it expresses phenotypically, but it's highly heterogeneous in the way that it behaves from patient to patient, and therefore, outcomes and prognosis can also be highly heterogeneous because you can have a newborn with aortic stenosis based on bicuspid aortic valve, and you can have somebody who never presents clinically with bicuspid aortic valve and remains undiagnosed. The important thing to take into account is that this is a lifetime condition. You are born with this condition, number one, and you can express the consequences or morbidity of this condition throughout a lifetime. And the second critical thing that is, is that we should consider this a valvular aortopathy. This is a condition that has a pervasive aortic proximal, a, a thoracic aorta involvement, which manifests itself as dilatation of the aorta, basically root and ascending aorta and sometimes the arch, however, to try to reconcile these phenotypic differences

and these prognostic differences, what we have done is the international consensus classification and the nomenclature for the congenital bicuspid valve, which was published in 2021 in several journals, and it was based on imaging pathology and it was evidence-based. And what we came up with is that there are three types of SPI valve diffuse type, which has three sinuses of valsalva, and it's the most common that we see, and it's the one that expresses as right left fusion, right non fusion and left non fusion. Then we have the two sinus type, which is basically what, how it, how it sounds. It has, it's a two sinus containing two cusps, which are almost the same in in appearance, and then the partial fusion or form Proust, which is where there is a fusion of less than 50% of, of two cusps. Similarly, the consensus recognized three types of bicuspid associated aortopathy, and these are the root phenotype, which is dilatation preferentially at the root of the sinuses of Salva, the ascending aorta phenotype, which is by the way the most common affecting 70% and extended phenotypes as well. Now, in terms of prognosis, we have categorized and proven clinically that there are two categories, how you can see the neology of bicuspid aortic valve, which is the typical valvular aortopathy, which is the most common, and it consists of progressive bicuspid dysfunction with aorta dilatation without major concominant disorders and the long-term survival of both pediatric populations and adult populations with the typical valvular. Aortopathy is normal, at least up to 35, 40 years of follow up, which we have. The other one is the complex valvular aortopathy, which is more associated with clinical significant concomitant disorders like other congenital heart disease, severe, severe tion of the aorta syndromes and accelerated valvular aortopathy, meaning that it presents less than 30 years old. And we have shown that this group has a survival penalty compared to the general population in the long run.

Dr. Patricia Pellikka: Tell us about the aortopathy. Is this a, a consequence of the hemodynamics that are perturbed by the valve or is it just another part of a congenital defect in the aorta?

Dr. Hector Michelena: Yeah, so, so it's very interesting because there is significant amount of evidence to make both hypothesis be valid. One hypothesis being the genetic hypothesis which is consistent of a genetic disorder that, eh, eh, acts generating abnormal tissue signaling during embryogenesis, okay, with epigenetic modifications. And this affects how the cells and the tissues organize such that it has been demonstrated that in neonates, the, the, the histology in neonates with bicuspid valve, the histology of the ascending aorta is already altered and therefore, you know, there is a considerable amount of genetic suggestion here. Also, patients who tend to have the root phenotype dilatation of the aortic root have been proven genetically to have enrichment of a certain genetic abnormalities. And, and it is associated, for example, with more genetic conditions such as Loeys-dietz for example. Now there's the other hypothesis which is the flow hypothesis because the bicuspid valve by itself is abnormal, even if it's not stenotic or if it doesn't leak significantly, it is an anatomically abnormal, and when it opens, it interferes with the flow that's coming out of the heart and it changes the flow and it creates turbulence and it creates sheer stress, which has been measured very interestingly and, and and magnificently by groups here in the US and, and, and Europe and has been shown to predict what areas of the aortic valve are going to di- I'm sorry, what areas of the aorta are going to dilate according to the phenotype of the bicuspid aortic valve, given the abnormality that it causes in flow. Therefore, I believe that yes, both genetic and flow theories are playing a role, perhaps the genetic more in towards the root phenotypes and the flow hypothesis, perhaps more into the ascending arch phenotypes. There are other obviously

things that can, that can influence this. I mean, uncontrolled hypertension is a risk factor for further dilatation of the aorta smoke continued smoking is another risk factor for further dilatation of the aorta. And, and, and, and therefore it's a, it's a, it's a multifactorial process where both genetics and flow abnormalities are clearly involved.

Dr. Patricia Pellikka: So we, we know that the bicuspid aortic valve disease presents tends to present at an earlier age compared to degenerative aortic valve disease, but what other differences are there in the natural history of bicuspid versus tricuspid aortic valve disease?

Dr. Hector Michelena: Yeah, so, so, so lemme tell you just, just a couple of things that I, that I, that I think are important for physicians and patients to know and for physicians to let patients know is that again, the, the, the bicuspid condition is a lifetime clinical valvular neuropathy with a high morbidity that in a lifetime we have calculated likely exceeds 80%. So you're gonna have at some point some problem and the complications or morbidity associated with the typical value aortopathy of bicuspid aortic valve, which is the more common one, a a in order of frequency, our progression to severe as and ar, that's number one. Okay? And there AS is more common than AR obviously the result of that is having more aortic valve surgery, and that is the number one morbidity aortic valve surgery led by aortic stenosis. Immediately following that is aortic aneurysm. And after that is obviously surgery for a aortic aneurysm. But we must not forget that there is quotation of the aorta which incurs surgery earlier in life, and there are two bad players there, which are effective endocarditis and aortic dissection, which thankfully are in absolute terms, still not very common yet. They are, both of them are several times more common than the general population in a bicuspid patient. Now, if we talk for example about bicuspid aortic valve stenosis as compared to tricuspid aortic valve stenosis, the first thing we have to recognize is that the bicuspid patient is going to be younger at least 10 years. So if we're talking tricuspid aortic valve, seventies, eighties, we're talking sixties in bicuspid aortic valve. And it's very interesting. We, we have, we have studied the progression of disease, which we have found to be the same between tricuspid and bicuspid. And we have studied the, the, the survival. And we have found that the survival of bicuspid aortic valve patients is much better than tricuspid aortic valve patients. And this is independent of age, okay? It's not because they're younger, it's because bicuspid aortic valve is a, is a, is an, is an independent protector. Why do we think that this happens? Well, what we have shown is that of the secondary effects or the cascade of cardiac damage that is associated with aortic stenosis, those components of cardiac damage are much, much, much more prevalent in tricuspid aortic valve than bicuspid aortic valve regardless of age. And therefore bicuspid aortic valve, eh, eh, carries more with a valvular burden, which needs to be corrected, don't get me wrong, but the tricuspid patient with as carries with a double burden and it's a burden, it's a valvular burden and a burden of much higher cardiac damage. Now, in terms of aortic, and this is a very important thing also for patients and physicians to know the difference in age as we have shown it, eh, eh, aortic regurgitation is a disease that's predominantly in males an impact. And in bicuspid aortic valve is even more so, okay, the typical, eh, severe aortic regurgitation in bicuspid aortic valve occurs in younger males with a mean age of 46. I'm talking patients being referred because they have clinical significant AR at a very young age, and that means that we must have a lifetime plan for them. And that lifetime plan begins by trying to avoid giving a 30, 40-year-old a a prosthetic valve. And the way we do that is by considering the possibility of bicuspid

aortic valve repair and or Ross procedure. And obviously this cannot be performed everywhere and this will improve much more over time. But we need to be cognizant of this. Obviously we need to know also that a young patient that whose valve is not repairable or is not a candidate for a Ross operation, then should likely be offered a mechanical valve because there's no evidence out there that bioprosthesis are superior to mechanical inpatients less than 50 years old. But the evidence of the contrary does exist big time.

Dr. Patricia Pellikka: So you've emphasized the lifetime situation with bicuspid aortic valve and the need for follow-up clearly must be there. How do you recommend follow up of your asymptomatic patients with bicuspid aortic valve?

Dr. Hector Michelena: Yeah, so, so the first thing that I do with a bicuspid patient is sit down with them and ask them several questions exploring the possibility of of more complex valvular aortopathy instead of a typical valvular aortopathy. Therefore, the first thing you should know, I believe, is ask them about family history of bicuspid valve, family history of thoracic aneurysms, family history of an of thoracic aneurysmal catastrophes, family history of sudden cardiac death at a younger age, unexplained family history of syndromic abnormalities. Number two is to do a very good clinical exam and if there are abnormalities or, or syndromic abnormalities, well then, you know, this is, this is more of a complex situation. If a patient presents very young with accelerated valvular aortopathy, particularly dilatation of the aortic root that we were mentioning was a little more genetic. And what I mean young and accelerated is, is you know, fast dilatation less than 30 years old probably in their twenties, that probably should light up your head and say, Hey, maybe this is not just a typical bicuspid valvular aortopathy, maybe there's something more and I need to talk to genetics or, and this and that, or have other people come in and take a look at this. Okay, now that being done, say we have the typical valvular aortopathy patient, okay, that is discovered or presents in their forties and fifties because somebody heard a murmur or somebody found an accident, an incidental dilated aorta. The follow up will depend for the valve on the valve guidelines because really what these patients are developing is AS and AR and we follow the guidelines of AS and AR for for determination of of of how often we see them and how often we follow them. Obviously a couple of things there patients with AS and bicuspid aortic valve because their LVOT is bigger, particularly men tend to have a higher valve area. So you will find occasionally somebody who falls into the severe hemodynamic as category in Gradient 45 a peak velocity 4.5, but the valve area is 1.05. Okay. Okay. Why? Because the LVOT is big and that those cases should be treated. We have evidence as severe it is, you know, even though the valve is not making the cut of less than than one. Now in terms of follow up of the aorta, it is critical that the aorta be examined in that first TTE and that obviously includes the thoracic aorta. Typical bicuspid valvular aortopathy does not affect the abdominal aorta or the pelvic aorta, just the thoracic aorta. So it is very important that we are able to evaluate the LVOT, the root measurement, both in long axis and short axis, the ascending aorta, the arch and rule out quotation. If we cannot do this in a patient because we can't see, okay, then that patient with bicuspid valve should definitely go to get a ECG guided cardiac CT angio angio of the heart or MRI, right? Obviously another reason to refer somebody to CT or MRI because of aortopathy is if any segment measures 45 or more millimeters, that should be confirmed. We know that CT and MRI are the gold standard above echo for measuring the aorta. So, so those should be confirmed. Now say that you have

a patient that you measure by echo a number of the ascending aorta and you send them for confirmation with CT or MRI and it turns out the echo was wrong, then the follow-up of the aortopathy of this patient needs to be done by the CT or the MRI that you did. Generally speaking, once we have established that the aorta is not progressing at a tremendously fast rate, we can then just image those aortas yearly and that's good enough. The usual progression of root ascending aorta in bicuspid patients is no more than 0.4 millimeters per year. So it's very small progression. When you see progressions that are getting to one millimeter and obviously more than two to three millimeters, well then that has to get your attention that there for some reason there's being accelerated dilatation. And that's of course is a red flag that that needs to be discussed further.

Dr. Patricia Pellikka: So indeed these patients need careful follow up. Yeah, but, but should have a good outcome if, if that is done.

Dr. Hector Michelena: Yes. And I will mention just one more thing, eh, and we have noted that, eh, of the life threatening complications, bicuspid aortic valve infective endocarditis is actually the lifetime risk of it is, is more common than aortic dissection. And we believe one of the reasons is some endocarditis are being missed and some patients are being referred late and therefore referred with more complications, abscess and et cetera. So, so education to the patient, eh, eh, as to prevention of aortopathy and education as to prevention of endocarditis, which basically is two things that we can do. One is very good dental hygiene and the other one is very good skin hygiene are therefore warranted as the education piece for these, for these patients.

Dr. Patricia Pellikka: This has been very educational, Hector, and your enthusiasm and commitment to our understanding of bicuspid aortic valve is it's clearly evident. Thanks for all your contributions to this area and thanks for visiting with me today.

Dr. Hector Michelena: My pleasure. Thank you Patty.