MARTIN S. MARON: So I'm going to spend some time here over the next 20, 25 minutes giving you an update on really the emergence of cardiovascular magnetic resonance, or CMR in HCM, and its impact specifically on sudden death assessment. And as Mary [INAUDIBLE] really nicely outlined for you, what I'm showing you here represents the current risk stratification strategy in place for us to identify high risk patients, utilizing the five noninvasive risk markers that you see up here.

I think the principal points for this slide include that of course with each additional risk factor that an individual patient has, that patient's risk for sudden death increases. That's true. But on the flip side of the coin, so to speak, in this disease, one of the risk markers themselves may be enough to place a patient in a high risk category and to offer them ICD for primary prevention, particularly when that risk factor is extreme hypertrophy of 30 millimeters or more, family history of a close relative with sudden death due to HCM, or unexplained syncope, particularly when it occurs in the young.

And the strategy that I'm showing you here for risk stratification, and of course the ICD, has really served the HCM patient population very well. It's certainly helped the clinical cardiology community manage risk assessment for these patients. And for that reason, it's done very well. You saw some data from Dr. Bach demonstrating that it's pretty much this contemporary risk stratification strategy, which itself, over the last 15 years, has really made an impact in the natural history of this disease by lowering disease mortality to a low of 0.5% per year. So it's very effective strategy.

That said, there certainly remain challenges of risk stratification in this disease, and I wanted to highlight those. And it's important to understand where those gaps currently lie to understand where CMR may fit in to help us more reliably risk stratify patients.

And of course, as I'm showing you here, for patients that are clinically identified-- so this is a pyramid representing HCM patients that are identified clinically in the US and around the world. And about half of those patients will have one or more of the risk factors. Of course, if you've got two or three risk factors, I think there's very little question or doubt that that's a patient, of course, that undoubtedly deserves ICD for primary prevention.

That still leaves about a third of the patients with one risk factor. And that's still a substantial number of patients in which there may be, in that individual patient with one risk factor, some gray area, some uncertainty about risk based on the one risk factor. And so that's one area that I've termed the gray area of risk stratification. So that's an area of unmet need that we would like to sort of lower that-- shrink that gap to more reliably identify those patients who are at great risk there with the one risk factor.

On the other side of the coin are the zero risk factor patients, the bottom of the pyramid. These are patients who have none of the five markers that I showed you. And those patients have not-- their risk has been recently defined. And it's not zero. It's low. 0.5% per year. But still, not low enough. So it's these two areas, the gray area risk stratification and the zero risk factor group which are, in a sense, unmet needs for the disease, and are areas where CMR may improve risk stratification. So we're looking for new novel markers to help in those areas.

And this is what I'm talking about. This is cardiovascular magnetic resonance imaging with Late Gadolinium Enhancement or LGE. It's a technique in which there's an intravenous infusion of gadolinium. Gadolinium is taken up into areas of expanded extracellular space in the myocardium. Shows up as bright. These bright areas that you can see are areas of late gadolinium enhancement. Areas where there's no uptake of contrast or gadolinium are dark.

You can see six different HCM patients. And there's a very heterogeneous pattern to the late gadolinium enhancement in this disease. Almost any pattern is possible. About half the patients, when you scan them with this technique, will have LGE, and about half will not. So it's prevalent in about half the population.

Now this LGE that you're looking at can obviously be seen very reliably with the eye. But in addition to that, it can be using offline software quantified and expressed as a total amount in grams, or as a percent of the total LV mass. And for the purposes of this talk, we're going to equate these areas of LGE as imaging markers that represent predominantly myocardial fibrosis. LGE equals fibrosis in HCM. Does it always? Probably not always, but I'm not going to get too much more into that other than to tell you a little bit more at the end that not all LGEs [INAUDIBLE] fibrosis. But for the vast majority of cases and situations, think of it as scar.

And therefore, it doesn't take much of a leap of faith to look at images like this, particularly when the patient seeing you after they've come out of the CMR magnet, seeing you in clinic, and you're looking at images in which there can often be extensive LGE. In this case, transmural involving the anterior septum in this short axis image extending into the anterior lateral free wall and also, to some degree, into the posterior septum. That's a lot of LGE.

And of course, knowing what we know coronary disease were areas of scar from myocardial infarction, and of course the around the area, so-called gray area, are niduses for the generation of ventricular arrhythmias. It didn't take much of a leap of faith to look at these images and wonder if we were also looking at the nidus for ventricular arrhythmias with this technique as well in HCM.

And so the story about whether or not that was true really begin first with cross-sectional data demonstrating a very strong relationship between the presence of LGE and ambulatory nonsustained ventricular arrhythmias. So these are two different studies. Almost over 400-some HCM patient scanned with this technique. And you can see both of these studies demonstrating pretty much the same result. A very strong relationship between those HCM patients with LGE and NSVT, which again, as you remember, is itself a risk factor. Much greater than those patients who had no LGE. In fact, if you had LGE, you are about a seven-fold greater risk of experiencing ambulatory ventricular arrhythmias than if you didn't have LGE.

So this started to sort of, for the first time, sort of paint this picture that in fact, we may be looking at the abnormal substrate for ventricular arrhythmias in HCM with LGE. But of course, this is cross-sectional data, and it's using ambulatory NSVT as a surrogate marker for sudden death. And so the next-- let me back up. The other-- so the point of that before I go on and miss the slide here is that this is the relationship between the presence of LGE and NSVT.

And the reality is that the presence of LGE itself, not going to really make a really robust and practical risk marker for sudden death prediction in this disease. Why is that? Because it's just way too common. I mean, about 60% of the patients that you scan will have LGE. And if you use that itself as a risk marker, kind of viewing LGE as a binary yes or no, and you use the other traditional risk markers, you're going to basically be implanting almost all patients with a device. That's not a practical strategy.

So it's this data that really started to raise the other issue, which was it may not be just about the presence of LGE, but actually the extent that was more of a practical and robust marker for future risk. In fact, it was going to have to be about that for those reasons.

And it was that which really set the rationale, I should say, for the study that I'm showing you here, which was recently published. This is an international study. US, Canadian, and European centers with HCM and CMR, demonstrating here that over 13-- almost 1,300 HCM patients with CMR with LGE done at the initial evaluation. Those patients followed for about three a half years for primary endpoint of sudden death events. So those are patients that after their CMR, a sudden death event. Could be sudden death. An appropriate ICD discharge through VT or VF. Of course, that device went in after the MRI or out of hospital cardiac arrest. Again, looking at the relationship between the extent of LGE and the primary endpoint.

And this is what we found. A strong relationship between the amount of LGE or fibrosis and increasing risk of sudden death events. So that you can see for every 10% increase in LGE, there was about a relative increase of 40% for that combined endpoint of sudden death event.

And this was all the patients, all 1,300 almost. This is patients with and without risk factors together. You can see that we even took into account with this model other risk markers that are important for sudden death prediction, like the other traditional risk factors. Age, wall thickness, mass, et cetera, demonstrating that LGE was an important independent predictor of sudden death events.

And the other thing I just want to highlight here with this slide too is that if you are an HCM patient and you have no LGE, LGE negative, no fibrosis detected with this technique, that's good. Associated with lower risk for sudden death events. And a point really of, I think, reassurance for patients too to know that they have no scar detected with MRI.

Now what I showed you here was all the patients, but perhaps most importantly was the data relative to those patients in this study who had none of the five traditional risk markers. So these are the patients that you and I would be seeing in clinic. We would consider those HCM patients to be low risk patients, of course, based on the current consensus guidelines because they have none of the five markers. And this is, again, showing you the relationship between LGE and sudden death events in these 700 no risk factor patients. Where again, with increasing LGE, increasing risk highlighted 15% here in red. It's an arbitrary cut point, but it's a two-fold greater risk for 15% or more compared to the no risk factor patient who has no LGE here.

And this is essentially data which helps to support the idea that we may be identifying with this data a subgroup, a small subgroup but an important subgroup, of patients who are in fact at increased risk for sudden death events, who may not be recognized as such without the results of the CMR. So in a sense, it's a paradigm shift in improving the risk stratification strategy by identifying new patients at risk that are currently not identified.

And in addition, it's a continuous relationship here. So it allows, again, for-- you heard this term, which is really the right term-- shared decision making between you and the patients regarding risk in the device, allowing that patient to interact with you in a shared decision making role to decide what level of risk may be acceptable or not for that individual patient.

And in addition, the patients-- so then, that was the no risk factor patients. But again, in patients with risk factors, does the CMR help? And of course, it's not good enough in today's world to have a biomarker or in this case an imaging marker that just is shown in a multivariate model to be an independent predictor. You've got to be able to demonstrate that that biomarker, or in this case, again, imaging marker, actually adds or improves the current risk model. Not just an independent predictor.

And of course, to do that you'd use a number of novel statistical methods, IDI, net reclassification index, et cetera, which we did. And all of those demonstrate that, in fact, the LGE does actually improve upon or make more robust the current risk model using the five risk markers. But to demonstrate that without showing you too complex statistical modeling is just to show you this. That if you've got one or more of the traditional risk markers, this is your annual risk of sudden death rate. Now you add into the equation, so to speak, the results of the CMR with LGE. And if that patient has one or more risk factors but no LGE, risk decreases, again, showing you that no LGE is a good thing.

With less than 15% LGE, risk jumps up. And at more than 15% LGE, risk increases even more. And this is extensive LGE, 15% or more. And again, I think that demonstrates reasonably well the concept or principle that LGE is a powerful marker for risk. That, in fact, does take the current model one step up.

Just to demonstrate, a patient from that multi-center study who had a CMR with LGE and unfortunately died suddenly about a year and a half after the scan. 32-year-old, asymptomatic, preserved systolic function. None of the traditional five risk markers, but extensive scarring as you can see here, quantified and occupying almost a quarter of the total LV mass. So maybe a patient that now, with data like this and hopefully others that will come along, support the idea that this may be a patient we would look at differently or have a different conversation with, and potentially consider for primary preventive therapy with a device for sudden death prevention.

So this is how we use the data at Tufts. Now today if you've got a patient who you assess with the traditional risk markers and they've got none of those five, we use the CMR routinely in all patients initially that we can, and if that patient has extensive LGE. And that 15% or more that you're looking at, that's a lot of scar, OK? Don't be confused. That 15% or more is a lot of LGE. Even just looking at it visually, you can tell that's a lot of LGE. Although it's nice to be able to quantify it, I think you can come to a reasonable assessment of extensive LGE just through visually looking at the image as well. And if you've got that situation, then I think you can consider, based on these data, whether that patient should belong in a higher risk category and to, again, in shared decision making manner, potentially discuss the device for primary prevention.

On the other side of the coin again is the idea that if you assess a patient with the five markers and they are in a gray area, they've got maybe one marker or you're not sure if that one marker is enough to move forward with lifelong device therapy, getting the CMR and showing that there's extensive LGE can help sway that decision making. In this case, toward device therapy. But if there's no LGE or minimal LGE, it can help sway maybe that decision making for that patient in the gray area away from device into a lower risk category, potentially avoiding unnecessary device placement for that patient.

Now I'll just finish up a couple more slides. The risk of sudden death really is about the amount of LGE. I've made-- I've tried to make that case tonight. What it's not about really is the location or the pattern of the LGE. Why is that?

It's because that in this disease, as I showed you earlier, there just really is no clear patterns that have emerged of LGE and HCM. It's all over the map. You see basically everything. So we're never going to be able to fit patients into discrete patterns of scar that themselves would be associated or not associated with increased risk.

The only exception to that-- and there is an exception that has emerged-- is this. LGE that's confined to what we call the RV insertion areas. And this pattern has been associated with HCM, although it's not actually specific for HCM. You can see LGE at the RV insertion point in other diseases like pulmonary hypertension and some congenital heart disease as well. But certainly, reasonably common. It's the only pattern that systematically has emerged as a consistent pattern. You can see it in both RV junctions or one, either the anterior or the posterior.

And if you look at just that pattern, and of course if you quantify the amount of LGE when it's just confined in the RV insertion points, it's usually almost always less than 8%. And actually, in fact, for the vast majority, it's less than 5% of the total LV mass. But if you don't qualify it and you just looked at the pattern of patients with RV insertion, which is what we did as a sub-study, you can see that there's no difference in sudden death event rates compared to those patients with no LGE at all. And that's how we look at it. We look at it almost equivalent to no LGE when the contrast is just confined to the RV insertion point areas.

So you may ask, why is that, then? Why is that a lower risk pattern, so to speak? Oh. Oh. That's out of place. Sorry. For some reason, that's out of place. I'll come back to that slide. So why is that? It's because the RV insertion area is a unique location of the myocardium.

Bill Roberts, back in the early '90s, I think eloquently showed us that the RV insertion areas in HCM is an area in which there is almost a collision of fibers from the RV and LV that come together, and result in an expanded-- exaggerated, expanded extracellular space where that gadolinium can collect, and therefore does not represent, when it's located in those regions, to be replacement fibrosis like it represents when it's in the septum or other areas of the LV. So again, not all LGE is replacement fibrosis, particularly when it's here. And this may also histologically explain why this pattern is a low risk pattern.

Now I'll just finish up by emphasizing one other point about CMR and risk, and that's that with this technology has emerged important subgroups that were really, in some ways, under the radar screen prior to CMR. And one of those is the HCM patients with LV apical aneurysms.

So this is HCM. You're looking at HCM. These are the same diseases we've been talking about. They develop these patients thinning the aneurysm rim here, probably because of adverse remodeling that's due to high apical LV systolic pressure. It's a phenotype associated with mid-cavitary obstruction. This rim that you're looking at is fibrosis. It's LGE, usually transmurally here. And then that rim of fibrosis, as I'm sure Mary [INAUDIBLE] will tell you, interacting with the other myocardium is an area where you'll often see the nidus for the generation of ventricular arrhythmias. And the aneurysm itself is a nidus for thrombosis, clot formation. As you can see in panel C, clot in the aneurysm in a patient in normal sinus rhythm.

This is a high risk subgroup that's really emerged to be characterized very well using CMR. And when we identify these patients, this is a high risk group because their event rates are much higher than the general HCM population. Adverse event rates almost double that of a typical phenotype. Increased risk for sudden death for the reasons I talked about, stroke, progressive heart failure as well. So when we make the diagnosis of HCM with apical aneurysm, we don't take that lightly. We raise management considerations just based on that phenotype of ICD for primary prevention and anticoagulation for stroke prophylaxis.

So I'll finish by just summarizing that CMR is particularly well suited to characterize the diverse phenotype expression of this disease. This is incorrect. Sorry. Incorrect. But the last two points are correct that, just to summarize what I said about risk, it's about extensive LGE, identifying a novel subgroup of patients who are at increased risk for sudden death that would not be considered otherwise without the CMR, and who may now be candidates for device therapy. And on the other side of the coin, the absence of LGE associated with low risk may serve to help influence decision making, particularly in those patients who reside in the gray zone. Thank you very much for your attention.

[APPLAUSE]