[MUSIC PLAYING]

SAMIR SABA: All right, so a little bit of a provocative title that I chose. Do Implantable Defibrillators for Primary Prevention of Sudden Cardiac Death Still Save Lives? And it's meant to be provocative. I want to reassure everybody, and mainly my EP colleagues, that it's not because I know the answer is no.

So it's just a question that is very timely because of a lot of the changes that have happened over the past two decades, and mainly over the past five years, in the world of managing patients with heart failure who are the typical recipients of defibrillators. So we'll talk. We'll go over all of these things and some of the bifurcation points in our field at this point in time that we need to address.

These are my disclosures. So I have relationships with many of the device companies equal. And as you will tell by the end of this presentation, this is not going to be buying me any brownie points with any of the device companies. But my main disclosure to you is the fact that this presentation will probably raise more questions than provide answers. So bear with me on that front.

As always, good to start with a case presentation. This is a patient that I saw in August, a typical patient that comes to the EP Clinic, 83-year-old Mr. M, who presented, has a history of hypertension, has a history of hyperlipidemia, chronic kidney disease. Unfortunately, he suffered an acute ST-elevation MI in March, so several months earlier, and basically underwent a primary PCI of the LAD.

That was complicated on the table. They jailed with a stent, a first diagonal. He arrested, VF arrest, was shocked a couple of times, was brought back. And thereafter, thankfully, his hospital course was a little bit uneventful. So he recovered.

His ejection fraction was, unfortunately, low. He was placed on medications. He was placed on amiodarone. And before discharge, he was given a LifeVest.

As far as guideline-directed medical therapy-- and that's going to be an important theme in what I'm going to be presenting today-- he was put, appropriately, on beta blockers and on spironolactone. He was not put on any of the ACE, ARB or ARNI medications because of a low blood pressure and because of his chronic kidney disease. Creatinine, I believe, was somewhere in the vicinity of 1.6, 1.8.

And a few months later, in July-- and this is something that we forged. In the minds of all the referring physicians, we need at least a few months of guideline-directed medical therapy before the patient qualifies for a defibrillator. So appropriately, patients get referred after they've had the repeat echocardiogram.

And unfortunately, this person, his repeat echocardiogram showed an ejection fraction that did not budge-- 28% in mid-July, still wearing the LifeVest, which blows my mind how some of the patients, anecdotally, it seems to me in my clinic, coming from Johnstown, end up wearing and bearing the LifeVest for long periods of time. But he was ready to get rid of it, and he wanted his defibrillator as soon as possible.

This is his EKG. And it shows normal sinus rhythm, QRS width of 118, so not a candidate for CRT. And basically, we had a discussion with him. I'm going to leave this patient for a little bit now-- we'll come back, we'll circle back, to what happened with him-- but take you through a little bit of what happened over the past two decades, or actually, now, probably closer to three decades, in the world of indications for defibrillators.

So as we all know-- and I know I'm preaching to the choir here-- sudden cardiac death is the number one killer. If anyone has ever written a grant on sudden cardiac death, invariably, the first sentence is, this is the number one killer in the United States-- about 300,000 to 400,000 deaths in the United States, 1,000 fatalities every day. And a lot of those patients are not known, at the time of their cardiac arrest, to have any cardiac disease-- no coronary artery disease or cardiomyopathy. So that would be the first manifestation.

And I put this graph, which many of you have seen previously in previous presentations, just to show you that it really dwarfs other conditions that potentially, in our minds, may be more prevalent. Because they get a little bit more publicity or a bit more advocacy in different circles. So more than strokes, more than cancers put together, more than auto accidents, AIDS, et cetera. It's really the number one killer.

We've done a couple of studies over the years. This pie graph on the left is from a couple of studies from our UPMC data set. It's a little bit of a biased data set because we only included the patients who had a cardiac arrest but who survived to discharge, about 1,100 patients. The majority, about half of them, had ventricular fibrillation, one-quarter, ventricular tachycardia. Between those two, 2/3 of the patients, roughly--

FEMALE SPEAKER: Sorry, I'm looking for Dr. Saba.

SAMIR SABA: Somebody had a question?

MALE SPEAKER: I think that was an accident, Samir. Sorry.

SAMIR SABA: OK, no problem. So about 2/3 of the patients have what we call the shockable rhythms, the rhythms that we can shock and hopefully restore a normal sinus rhythm. But about one third of the patients have either PEA or asystole, which are the non-shockable rhythms.

And I want to stress the fact through this Holter monitor that, again, you've seen probably in previous sudden cardiac death talks the fact that what rhythm we document first may be an artifact of the time of documenting this rhythm. This is an unfortunate patient who had a Holter monitor at the time of their cardiac arrest.

6:02 AM, they go into what seems to be a monomorphic ventricular tachycardia. A couple of minutes later, it starts changing pattern and becoming a little bit more polymorphic. Five minutes later, six or seven VF and then asystole.

So you can imagine if the EMTs showed up two minutes later or five minutes later or 10 minutes later, the rhythm, the presenting rhythm, would be different. So just put that in the back of your minds.

And that's where the defibrillators came from, correct? Defibrillators, because the EMS folks cannot show up on time and many patients don't make it to survive, what if we had a device implanted and automatically detecting the abnormal rhythm and shocking it?

And as you see, the fellows are definitely very used to seeing these things. A ventricular tachycardia, more Vs on the second channel compared to the As on the top channel on the left. Ventricular tachycardia, a 31 joule shock restores sinus rhythm. And this is how this patient is saved.

And how do we know that those patients get saved? Multiple trials in Canada, the CIDS trial in Hamburg in Germany, the CASH trial. A couple of them missed the statistical significance with the p-value but definitely showing the separation between medical therapy in patients who've have had a cardiac arrest versus ICD.

And the one trial that, basically, we quote, which is the American trial, the AVID trial, which took patients who had a cardiac arrest from a non-reversible cause-- I'm not going to delve into what's reversible and what's not reversible because that's a full topic on its own-- but if a patient had a cardiac arrest from a non-reversible cause, if they got a defibrillator, they survived. Their all-cause mortality is improved. And that is basically how we got to the secondary indications, which, again, are not the topic of this presentation.

This is a very important slide that maybe, also, you've seen before, from Myerburg, in circulation in 1992. At the bottom of this graph, you see that if we were to focus only on the patients who had a cardiac arrest, we have a good marker. They had a cardiac arrest, so they're going to be at risk of having further cardiac arrest.

But the number of patients on the right panel that would be saved is minimal. The bulk of the cardiac arrest, the bulk of the deaths from cardiac arrest in the United States-- about 300,000, almost the full volume-- is in patients who do not have any history. It's in the general population. But again, how do you screen the general population for the risk of sudden cardiac death? Very difficult.

So we ended up settling for somewhere in the intermediate range. What if we took patients who have heart failure, who have a reduced ejection fraction, we have some form of marker. And the number of cardiac arrests in that subgroup is a little bit larger. So by putting a therapy that can save lives, we may save more lives and have more of an impact.

And this is where the primary prevention trials of sudden cardiac death started. And we had a ton of those trials. I'm going to just highlight the two that have made the most impact. MADIT-II trial, published in *The New England Journal* in 2002, took patients with ischemic cardiomyopathy, a low ejection fraction below 30%, and randomized them to conventional therapy beta blockers, primarily, versus defibrillators. And all-cause mortality-- again, this is not sudden cardiac death, this is all-cause mortality-- is positively impacted by the defibrillator.

And then we struggled a lot with the nonischemic cardiomyopathy. The nonischemic cardiomyopathy patients, by virtue of having lower event rates, we could not get to this trial that would cross the p-value of 0.05. So there were a number of them, CAT and DEFINITE, et cetera. And finally, there was SCD-HeFT.

And SCD-HeFT is actually a mixed ischemic/nonischemic cardiomyopathy, the largest of the defibrillator trials, that had three arms-- placebo, which is basically beta blockers, amiodarone versus ICDs. And for those patients who have a lower than 35% ejection fraction-- it doesn't matter whether ischemic or nonischemic-- those that had the defibrillator ended up living longer. Again, all-cause mortality on that was basically define the current guidelines that we practice.

Needless to say, whenever we have any indications, there is always a push. Can we expand the indications? And I'm going to just mention the DINAMIT trial, which was, can we implant the defibrillator very early after the acute MI, within 40 days, in order to be able to save more lives and protect the patients as early as possible?

And as you can see from the curves, if you implant a defibrillator very early, within 40 days, it doesn't save lives. Why? Because very early after an acute MI, there are a lot of competing reasons why people die beyond just the arrhythmic death.

So patients can have a VSD-- another MI, they can have a VSD. They can have a rupture of the free wall. They can die from multiple other things. So just covering one aspect of the possibilities or mechanisms of death would not protect the patient.

There was another trial because we didn't believe DINAMIT when it happened. We did go with another trial called IRIS, which showed the same exact results. By the way, none of these trials I'm presenting them in a chronological order. I'm just painting a picture of how we evolved over time in the primary prevention.

There was a trial called CABG Patch in the mid '90s that basically looked at whether the defibrillator after revascularization, after CABG-- so those are patients who have CABG-- at the time of the CABG, they had patches placed on their epicardium, and those were connected to a defibrillator turned on or not turned on. And as you can see, after revascularization, in this population, if you put in a defibrillator, it doesn't make a difference.

And this is where the guidelines came from. So this is what we practice today. Patients for primary prevention who have a low ejection fraction-- less than 35%, class I, II, or III class of heart failure on guideline-directed medical therapy, so far, still defined by CMS, by what we put in the NCDR as primarily ACE inhibitors, ARBs, as well as beta blockers-- and those patients, if they've had their cardiomyopathy and they're outside of the context of an acute MI, 40 days, and outside of the context of revascularization, 90 days-- it doesn't matter whether it's open heart or revascularization with PCI-- and if they have an expected longevity greater than one year, they have an indication for a defibrillator.

And the numbers skyrocketed over time with all these trials. And this is worldwide. And in the US, it was no different. This is a study that is from 2008 looking at up to 2004. And as you can see, the ICD curves are moving upwards.

Roughly, you can estimate that the number of devices implanted in the US represents about one third of what's represented worldwide. And early in the 2000s, in the new millennium, we started having CRT devices. And that was, as I show in the lower curves, in the orange and yellow curves, more CRT-Ds, overwhelmingly more CRT-Ds than CRT-Ps. And I'll come back to that point a little bit later in the presentation.

So that was basically the status. And then there was a study. The first one that pumped the brakes a little bit came in *JAMA* from Sana Al-Khatib, who is a friend and a classmate of mine from medical school but who visited and interviewed with us a couple of years ago. She's at Duke.

And she presented out of the NCDR data about how often do we implant defibrillators outside of what's considered evidence-based defibrillator implantation, meaning within 40 days of an acute MI, without having the full three months of guideline-directed medical therapy or within revascularization, et cetera. And about one fifth-- 22.5% of the patients-- get implanted outside of what we call evidence-based indications.

And she looked beyond that at, how often do those patients die? And they have a higher mortality, and they have higher procedural complications. And she looked at who's implanting them. And we're all guilty. The electrophysiologists, as you can imagine, are the overwhelming majority of the implanters. So they were very close to the median.

But city surgeons were guilty, and maybe guiltier, if you want to look at the exact numbers and non-EP cardiologists who implant defibrillators were also guilty of this. And that was the first time where we pumped the brakes on, should we just keep putting defibrillators in patients without too much attention to the details of what's the evidence in the trials?

Around the same time-- and the two things were linked-- there was, as you probably remember, or most of you remember-- I know Bill Barrington and Sandeep remember it very well because the three of us reviewed a ton of cases from UPMC about what was flagged by the DOJ. That was nationwide. Every single institution-- Cleveland Clinic, Mayo-- everybody was part of that investigation.

But there was an investigation from the DOJ based on a whistleblower that said, well, we're putting too many defibrillators. And the two had nothing to do with each other, this manuscript and the DOJ thing. And around that time, I did a study with one of our fellows back then, Nasir Shariff.

We looked at the patients that were part of the audit, part of the DOJ audit, and a control from the same period of time of patients. And we confirmed, basically, what the *JAMA* article showed, which is that when we look at those patients who were audited, presumably because they were outside of the absolute clear or clean indications, they had a worse prognosis in terms of their survival free from defibrillator shocks. Actually, this was all-cause mortality in this population.

So one may ask, well, defibrillators are good. They save lives. What are the concerns with defibrillators? And I know a lot of these things are very known to most of you.

First of all, there are the usual short- and long-term complications of having a device, the short-term complications at the table-- perforations, tamponade, et cetera; long-term complications-- mechanical complications of the device, as well as infections and endocarditis, which are definitely things that happen. Thankfully, they don't happen in very high numbers, but they do happen.

The second one is that only a minority of those patients that we implant defibrillators in ever get a shock from their defibrillator, which means that we're not very specific in choosing those patients. In the primary prevention world, somewhere between 25% and 30%, on the upper end, would receive a defibrillator.

Equally, if not more important, not every shock delivered by a defibrillator is equal to one saved life. How do we know that? When you look at the randomized trials, you look at the number of shocks in the ICD arm, much higher than the number of deaths in the control arm.

And this is how you can equate. About three to four shocks equate one saved life. Because a lot of shocks get delivered a little bit prematurely for things that would have terminated on their own, et cetera.

Needless to say, there are inappropriate shocks that happen. Needless to say, a lot of patients that we implant defibrillators in get committed forever for having a defibrillator, regardless of whether they recover their ejection fraction or not. There have been plenty of recalls of defibrillators and leads. The Riata lead and the Fidelis lead is well-known to most people.

And lastly, something that we have always talked about, which is the association between receiving shocks and basically having a higher all-cause mortality, meaning that the shocks potentially increase the risk of mortality. And we've always said, well, you know what? It's a little bit of a circular argument. Patients that get shocked are sicker. Therefore, they die.

But then there was a trial another, MADIT trial, MADIT-RIT. MADIT-RIT, RIT stands for Reduction of Inappropriate Therapy. And this one randomized patients who had primary indications for defibrillators to different kinds of programming of the device in order to reduce inappropriate shocks.

And based on the programming and the reduction in all kinds of shocks-- inappropriate and appropriate-- those patients that were randomized to the arms with less shocks ended up having less mortality. So this is in a randomized setting now, a proof that, actually, the shocks, maybe through creation of inflammation or whatever in the heart, increased the risk of all-cause mortality. So those are the concerns with defibrillators.

I'm going to switch gears for a second and talk a little bit about CRT. This panel on the left comes from the VEST trial. This is not the VEST trial with the LifeVest. This is the original VEST trial that the heart failure folks know where many years ago, Vesnarinone, a inotropic agent, was used to see if it helps with better survival in patients who have heart failure.

And we all know the story about these inotropic agents. They end up killing more patients than not. But the main point is that Venk Gottipaty, who was in our group many years ago-- about two decades ago-- did this study looking at, in the VEST trial, the width of the QRS with respect to mortality in patients who have, basically, heart failure.

And anecdotally-- this is an abstract that never made it to becoming a manuscript because circulation sent some request for modifications to Venk. And Venk felt very offended. And he never resubmitted the manuscript. So it stayed as one of the most publicized abstracts. But it surely shows us that the width of the QRS corresponds to more mortality in those patients.

And we've always thought that, you know what? This is part of heart failure. Patients have left bundle branch block, et cetera. We never linked the dots until two decades ago where we started saying, well, maybe this is adding insult to injury. And this is where the CRT world started from.

So you see on the echo-- I hope it's playing for you-- you see this patient with a left bundle branch block where the heart is dilated, the ventricle is contracting asynchronously. You see this wobble between the septum and the lateral wall. And down there, down in the lower panel, you see that it's still dilated, but now you have more of a synchronous contraction. And this is basically what CRT achieves.

I just put this video from a recent VT ablation that I did on a patient with a CRT. Let me see if it's going to play-- that shows, basically-- this is using CARTO-- how CRT basically depolarizes the left ventricle from close to the apex and from the base in the lateral wall and how that creates a little bit more synchrony in the contraction of the ventricles.

So what do we know about CRT? There were multiple trials. I'm going to highlight COMPANION, which you were a part of, randomizing patients to optimal medical therapy, CRT with a pacemaker versus CRT with a defibrillator.

And this is basically a major trial that showed us that patients that have CRT, regardless of CRT pacemaker or defibrillator, have a significant improvement in their primary endpoint of reduction in death or cardiovascular hospitalizations. When you look at all-cause mortality alone, you see that, between the CRT-P and CRT-D, there is a little bit of a separation in the curves. But this never reached statistical significance.

Another trial around that time-- there were probably a half-dozen trials before that that looked at endpoints of quality of life and echocardiographic findings. I'm just highlighting the ones that have looked at hard endpoints of death. And this is the CARE-HF. It was done in Europe.

Because it was done in Europe, it was overwhelmingly more CRT pacemakers, not defibrillators. And this is comparing CRT, primarily pacemakers versus medical therapy. And for the endpoint of all-cause mortality, CARE-HF also showed that there was a significant reduction in mortality with CRT.

Around that time, we were trying to figure out, how can we improve the response rate of patients? So we did this study called STARTER. This is a randomized trial that we did at UPMC, all at UPMC when John Gordon was still here, looking at speckle tracking echocardiography and looking at the echocardiogram and trying to look at the latest site of activation.

So you see here the base, and you see here the mid-ventricle. And when we look at those strain curves, which our echo colleagues are very versed with, and you can identify that, in this patient, the base posterior lateral part of the left ventricle is the latest activation.

And that trial, the STARTER trial, randomized 187 patients at UPMC who had the clinical indications for regular CRT to echo-guided, meaning that the operator would look at this and try to target the latest site with the positioning of the LV lead versus being blinded to the echo report and putting the lead wherever it goes.

And basically, that showed significant improvement with echo-guided approach in terms of the reduction in the left ventricular and systolic volume at one year. More importantly, the primary endpoint was death or hospitalizations. And the echo-guided group compared to the routine LV lead placement, there was a significant improvement.

Around the same time, maybe a couple of months before that was published, completely independently, in the UK, there was the TARGET trial-- similar design, similar everything, similar results. So independently tested and confirmed with another trial. Anyway, this never took off in terms of becoming the practice because not every site and location can do these speckle tracking determination of the site of latest activation.

But regardless, the indications based on care and companion for CRT were low ejection fraction, less than 35%, class III or IV heart failure indications, and the width of the QRS has to be more than 120 milliseconds. And as always, driven by industry funds, we try to expand the indications.

Would patients with lesser degrees of heart failure benefit? The answer is yes. MADIT-CRT and reverse showed that class II and Class I heart failure with wider QRS complex and left bundle do benefit.

We tried to go along the other axis, which is to say, do patients with less severely depressed ejection fraction benefit? And this is where BLOCK-HF showed that patients may benefit from CRT in terms of hard endpoints, even up to an ejection fraction of 50%.

And lastly, we tried to basically throw away this whole QRS duration as the poor man's way of assessing the synchrony. And the two trials were done. RethinQ was a smaller trial, and nobody believed the result. And it did not show any difference, or any advantage, of taking patients with the synchrony but with a narrow QRS complex towards CRT. They did not benefit from it. And echo CRT put the last nail in the coffin, whereby patients that had CRT and had a narrow QRS complex, although they had the synchrony by echo or what have you, actually ended up having a higher mortality rate. So that completely stopped any attempts at putting CRT in patients with a narrow QRS complex.

So those are the indications. I'm not going to dwell in them. But the most important thing that I want to point out is that we have CRT indications, and we've had them for a while, but there is really nothing that tells us whether we put in a CRT pacemaker or defibrillator. We have CRT indications. We don't have CRT pacemaker or defibrillator.

And it's ludicrous in my mind. Because the two devices couldn't be any different. The pacemaker is much smaller, has a battery longevity that is better, has been subject to less recalls than defibrillators-- by defibrillator, I mean defibrillator systems, meaning leads and everything-- costs a fraction-- literally one fourth to one fifth of the cost of the defibrillator-- has less resource utilization.

You can imagine patients with defibrillators may get shocks appropriately, inappropriately. They come to the emergency room. They come to the clinic. They get admitted. So a lot of source utilization. The shocks and the source utilization may affect their quality of life.

And the only difference in terms of the functionality that may be positive for the CRT defibrillator is that it can terminate ventricular arrhythmias, although in the primary prevention context, it's never been shown to make a difference. So this is where we are. Those are the CRT indications. And I'm not going to belabor the point.

Needless to say, as you can see from this slide, there have been studies looking at how often do we use CRT defibrillators or pacemakers absent guidelines that push us in one direction versus the other? And as you can see, in the United States, 86% of all CRT devices are defibrillators.

And if you look stratified by age, less than age of 75 years, 91% are CRT defibrillators, and only a fraction-- 9%-- are CRT pacemakers. Still, in the older than 75, it's still almost 80%.

I always thought that in other countries, it was much, much better-- I shouldn't say better, I should say more balanced-- between CRT pacemakers and defibrillators. But still, in all countries of the world-- you're looking at European, Asian, and African countries-- still, overwhelmingly, CRT defibrillators over pacemakers.

Annie Canterbury and I did a review not too long ago looking at all the CRT trials. And as you can tell, minimal comparisons between CRT pacemakers and defibrillators. When you look at all-cause mortality or at the primary endpoint, COMPANION compared them, and there were similar results. And BLOCK-HF have compared them, and they had similar results. And no study has shown a superiority of the CRT defibrillator over pacemakers.

Now, if you put in perspective a spectrum of risk, needless to say, if a patient needs a CRT and had a cardiac arrest, they need to have a CRT defibrillator. Needless to say, if they need a CRT and they have a normal or more preserved ejection fraction above 35%, they should get a CRT-P.

But there is a large gray zone where we, the physicians, are making those choices, many times not even the EP. The referring physician is making that choice. And that, basically, is where there is a lot of work to potentially be done.

So two major questions that I want to ask and try to answer with some of the data that we've developed and others have developed. One, in the presence of other life-limiting conditions, does the defibrillator save lives? And second one is, in the presence of other lifesaving therapies, does the defibrillator still have additive lifesaving functions?

For the first question, we have minimal guidance from the guidelines, meaning that it says, well, part of the indications for a defibrillator is that the patient should have a expected longevity of more than one year. And you know how good we are at expecting or making that assessment-- not that good. But again, there is some guidance that the patient should basically have a better longevity.

And the analogy here that I'm using is that of the firing squad. This is actually an analogy that I used in a editorial that I wrote in 2011 in the aftermath of the publication of the DINAMIT trial, whereby the thought was, why do defibrillators not save lives if you implant them very early after an acute MI?

It's because the patient is facing a firing squad. It matters little that they dodged one bullet, meaning that you can save them because they had a cardiac arrest. If there are so many other reasons that they're going to be dying-- because of a VSD or a second MI or what have you-- they're still going to die, and the defibrillator is not going to save their lives.

You can take that same analogy of the firing squad and expand it to other conditions. Similarly, if the patient is going to die of cancer or COVID or what have you, it doesn't matter that you're saving them with a defibrillator that's going to only terminate sudden cardiac death. I'm sure-- and I say it half jokingly-- none of us is believing that the defibrillator is saving any of these other conditions, which is why it is important.

So what are those other conditions? The one that comes to mind first is age. Age is the main and biggest determinant of longevity and mortality. And there have been a ton of debates. I participated on both ends of the debate, actually, over the years and multiple debates over, should there be an age cutoff beyond which we don't put in a defibrillator?

And although most people agree that, as we get older, there is a time when the defibrillator is no longer going to save lives, nobody can agree as to what is this age cutoff? And for obvious reasons. But what are the arguments against putting in a defibrillator in people that are older?

The first argument is Kaplan-Meier curves all eventually converge down to zero. And if somebody is converging very quickly to zero, like in this red curve, they're not going to have enough time to get the benefit of the defibrillator. So they may not benefit from the defibrillator.

The second argument is that of the firing squad. If they're going to die of other conditions, they're not going to benefit from the defibrillator. The third one, and probably an important one that not too many people know of, is that, as we get older, we're more likely to die, obviously. But the likelihood of receiving a shock from the defibrillator, an appropriate shock-- and I'll show you the data on this-- becomes lower and lower.

I'm not going to deal with the other two because they're a little bit off topic. One of them is, well, how about saving quality of life survival? True, but we're not talking about that. We're talking about pure longevity at this point.

And the other one is a philosophical reason. When people exceed their expected longevity, should we try to prolong their lives? It's a more of a philosophical or societal discussion that I'm going to steer away from.

So you look at the average age in the bottom part of this slide, the primary prevention trials-- mid-60s for the patients who are indicated for a defibrillator. When you look at the United States life tables, you get to see what is the likelihood of a patient dying in the coming year.

So if you're at 80, you have a 6% likelihood of dying in the year following your 80th birthday. At 85, you have a 10% likelihood of dying. At 90 years, you have a 16%. This is in one year.

So what is the life saved in one year by the defibrillator, according to the primary prevention trial? Somewhere between 1% and 3%. So as you can tell, these numbers get to be dwarfed significantly in terms of lifesaving from sudden cardiac death.

About 12% of patients above the age of 80 are the recipients of the total number of defibrillators that we implant. And there have been a couple of studies, one from Andy Epstein, looking at what's the likelihood of patients implanted with the defibrillator dying, and what are the causes of that. And again, sudden cardiac death-- 3% over two years, dwarfed by non-sudden cardiac death and by non-cardiac death.

I did the study with Ure Mezu, who was a fellow with us many years ago-- and she's an electrophysiologist in Youngstown at this point-- looked at patients who are octogenarians, low ejection fraction. This is not randomized. This is basically who got a defibrillator, who did not get a defibrillator.

And as you can imagine, there are differences between these groups. A lot of them died over the course of 2.3 years. But no matter what model you ran, what multivariable model you ran, the predictors of death are age and the glomerular filtration rate, the kidney function. Defibrillators, whichever model-- and we ran six of them-- there was no impact of the defibrillator on long-term survival.

This is more important. This is what I told you earlier. This is a study that I did with Evan Adelstein a few years ago out of the ALTITUDE database, which is the LATITUDE database from Boston Scientific.

So we took all the patients who received their first defibrillator, and we looked at the decade of implanting a defibrillator, whether they are less than 50 or by decade of age. As you can imagine, whether it's a CRT-D dual chamber or single chamber, patients die more frequently when they're older.

But as they get older, the likelihood of receiving a shock becomes less and less. So if patients get older and they're dying more and less likely to get a shock from their defibrillator, you can imagine that those curves are going to cross at some point. And you're going to have no benefit from the defibrillator at a certain age. What age remains to be defined.

And when we talk about old age, we talk about comorbidities, mental decline, physical decline. This is what we imagine. But the other side of this coin, which brings in the topic of frailty, is that this is another octogenarian.

Some of you will recognize that this is our own Joe Maroon, one of our neurosurgeons. He's 81. He's a patient of mine, and I have his OK to show these pictures. He's already won this year two Olympic-distance triathlons, this one on September 11 in Florida, in scorching heat and humidity.

And just to tell you that not all octogenarians or older people are the same, which prompted this study that I did with Roy, who used to be one of our heart failure fellows-- he's now at [INAUDIBLE]-- and with help from Dan Forman. We looked at 36 determinants of frailty in a older CRT population. 20% of them had a CRT-P. And I'm going to quickly go through the results.

As you can imagine, all-cause mortality increases whenever you go from the fit patients to the mildly, moderately, and severely frail patients. And when you look at the multivariable determinants of this, frailty is a big determinant, age is a determinant of mortality, the ejection fraction, the kidney function.

But whether they get a CRT-P or a CRT-D does not predict mortality in this population. I'm by no means an expert on neural networks. But I plugged all of this in a neural network, two layers, looking at mortality. Actually, the performance of the network is pretty good. Predicting mortality had an area under the curve of 0.84.

But when you look at the determinant by importance of what determined who lived and who died, whether they got a CRT-P or a CRT-D was on the same order of magnitude of whether they have urinary problems, as opposed to things like QRS width or age or what have you, which were much more important determinants.

Quickly, to the second question. Are patients still getting an advantage or a reduction in their all-cause mortality in the presence of other lifesaving treatments, meaning all of the things that are advances in the heart failure world, in SGLT2s and ARNIs and aldosterone antagonists and what have you. And there was zero guidance from the guidelines here.

I struggled with the analogy. And the only analogy I could come up with is that of the drowning person. If a person is drowning, does it make a difference if you threw at them two floaters or 10 floaters compared to one floater? The answer is, I don't know. Maybe they have a benefit but maybe not.

This is a slide that was sent to me by Jessie Houston. It kind of caught my attention when she and others were presenting on the MOC Clinic a couple of months ago.

And it shows that, in the presence of ARNIs, beta blockers, aldosterone antagonists, SGLT2 inhibitors, quadruple therapy, we have a significant reduction in the all-cause mortality-- 73% relative reduction, 26% absolute reduction. The number of people to treat over two years is less than four in order to save one life.

So in the presence of this, do we still save lives by having a defibrillator? And I worked with Mark Zandi, one of our EPI fellows, on this question using our UPMC data set. About 6,000 patients, secondary prevention are 1,400, primary prevention are about 5,000. And whether the patients are on zero, one, two, three or four guideline-directed medical therapy, their one-year mortality after device implantation is significantly affected by the presence of more guideline-directed medical therapy in this primary prevention defibrillator cohort, not in the secondary prevention cohort.

When we look at it in Kaplan-Meier curves, you can see, whether it's the ICD patients or the CRT-D recipients, similarly, survival is better with more guideline-directed medical therapy. And when you adjust for Elixhauser comorbidity score, ejection fraction, age, you have a 42% in the risk of death in one year after ICD implantation per one incremental guideline-directed medical therapy added in the ICD group and 29% reduction in the CRT-D group.

So what if we were to look at the trials that have happened over the years? This is not very scientific. If you go from MADIT-II in 2002 to DANISH in 2016, the implementation, in the bar graph, you see the increase in guideline-directed medical therapy. And concomitantly with this, you have a reduction in all-cause mortality and shocks.

So if we were to repeat some of those trials that were done before in the presence of current-day therapy from the heart failure perspective, would we have still the benefits of the defibrillator? The answer is I do not know. And it's hard to repeat those trials.

But we have kind of a repeat here between SCD-HeFT and DANISH. So not lost on me nor you that SCD-HeFT included ischemic and nonischemic cardiomyopathy and was positive. That was in 2005. The DANISH trial took only nonischemic cardiomyopathy patients. But it was, again, a primary prevention trial and looked at whether the defibrillator makes a difference.

And there was no difference here, whereas there was a difference here. What are the differences between the trials? At least some of the differences were in the guideline-directed medical therapy, the heart failure management.

69% beta blocker use in SCD-HeFT, 92% in DANISH. 0% CRT in SCD-HeFT, 58% in both the ICD and the control arm in DANISH, which may be a big part of why DANISH is negative, whereas SCD-HeFT is positive.

I've been interested in the whole CRT-P versus CRT-D survival in patients. This is nonischemic patients from the Medicare database, no difference in all-cause mortality between CRT-P versus CRT-D recipients. This is older population, above the age of 75.

What's different is definitely the cost, total medical cost, cardiac cost. At seven days, 12 months, and 24 months, the cost difference of that starts at about $18,000 less for CRT-P, grows up at two years to about $27,000, which tells you that it's not only the difference in the cost of the device, it's what's carried on over time in terms of resource utilization between the two devices.

I don't want to belabor the point. This is a meta analysis from Divyang Patel, who used to be a medical student working with me a number of years ago. And he did this, again, looking at all the nonischemic trials and studies, no difference between CRT-P and CRT-D.

Going back to the COMPANION trial, this is an analysis in 2016. This is what I showed you earlier, that there is really a separation between CRT-P and CRT-D in the COMPANION trial. But if you look at the cohort of patients that who were actually on guideline-directed medical therapy, ACE/ARB plus beta blockers, you see that the mortality in the CRT-P group ends up being reduced by about 5% absolute when you look at guideline-directed medical therapy.

And the separation between CRT-P and CRT-D is definitely reduced and significantly reduced, which tells me that maybe if we did a better job with these guideline-directed therapies, we shrink the differences between CRT-P and CRT-D, as well as potentially reduce the potential benefit of a defibrillator, which, as I showed you, could be problematic in terms of the complications that we can talk about.

I'm not preaching at all that we shouldn't put in a defibrillator. As you know, that's what I do for a living. I put in defibrillators, and appropriately so. But we need more data. And this is a study that was funded by the NIH that we led at four sites at Duke.

Obviously, UPMC, Duke, Ohio State, and the VA in Pittsburgh, where we took older patients who had an indication for a CRT device and randomly assigned them to CRT-P versus CRT-D. Those that refused the randomization ended up being put in a registry and were given their device of choice.

The accrual and recruitment was affected by COVID but, overall, was pretty good. And this is pilot, so don't take it as those are results. But it's important what we get out of these pilots. One is when we compare the patients who are in the registry versus the randomized controlled trial, those that were randomized did better overall as a group, regardless of CRT-P versus CRT-D.

They were a little bit less sick. But at least it shows you that if you did a large pivotal trial of CRT-P versus CRT-D, you're not going to be putting the patients that you randomize at a higher risk than the patients that you just give them their device of choice.

And when we look within the randomized controlled trial at CRT-P versus CRT-D, again, pilot data, we don't see any difference in survival. This is all-cause mortality. Very small numbers but definitely is a good starting point to make the argument for a pivotal trial of CRT-P versus CRT-D.

Going back to Mr. M. Quickly, what did we do? Well, obviously, we gave him a defibrillator because it's still indicated. But the other thing that we do always now because, number one, it's mandated, but it's the right thing and now more than ever because of everything that I presented to you is that we sit down with those patients and we talk to them about the pluses and minuses of the defibrillators in the context of shared medical decision-making.

And I've been referring a lot, and I'm sure a lot of my EP colleagues and all of us have been referring a lot, to the Medications Optimization Clinic that is led by Jen Kliner and Jessie Houston and everybody in heart failure, a huge resource. Because beta blockers and ACE inhibitors or one or the other because the patient has some kidney dysfunction is no longer the standard of care. Shooting for quadruple guideline-directed medical therapy is the way to go. So kudos to that clinic and everybody who's supporting it.

What is needed next? So I'm going to close very shortly. We need to understand better the role of the ICD in the current era of quadruple medications. We need to understand if there is an incremental benefit in primary prevention for CRT-D over CRT-P, either in the general population or in subsets-- the nonischemics, the older patients, et cetera.

And the other part that I didn't touch on, but I'm going to show you one or two slides on, is the fact that, once we put in the defibrillator, regardless of whether the patient never received a shock and whether they recovered their ejection fraction, they're always going to need a defibrillator down the line. And that's not necessarily true, either.

Sana Al-Khatib that I mentioned earlier published a couple of years ago this article that says, well, maybe there is a path towards if the patient, on their first device, never got a shock-- appropriate shock-- and they recovered their ejection fraction to above 35%, maybe we need to have a discussion with them about not having another defibrillator implanted. In the CRT-D world, maybe if they recover their ejection fraction to above 45% with CRT and never got a shock, maybe a CRT pacemaker is indicated.

We don't have much data on this. The only data comes from Sanjay Dixit in the VA system where they did a retrospective analysis of patients who, at the time of their device change-out, they were divided into three groups.

Either they did not get any therapies from their first device and their ejection fraction recovered to above 40%-- they were called not indicated for a defibrillator-- or they had a shock, or they remained low on the ejection fraction-- they were indicated-- and an unclear group, meaning that those patients never had a reassessment of their ejection fraction. So factor those out.

When you compare the ICD not indicated versus ICD indicated, survival-free from ICD therapy was significantly better-- 2.8% per person year versus 10.7%. Now, it's an argument whether 2.8% is low enough to not give those patients a defibrillator. But this is as much data as we have.

I'm going to close by saying that there is still a lot to be learned. There are a lot of other devices, not only pacemakers and defibrillators. There are cardiac contractility modulation devices. There are autonomic modulation devices. How do those impact the overall well-being of our heart failure patients? And what they benefit from and what they don't benefit from is a big question.

It's hard to secure industry funding when you're trying to limit product or market development, even when you are trying to shift market from CRT-D, which is much more expensive to CRT-P. So the onus is on us as a medical community to look for alternative sources of funding-- NIH, societies, foundations, et cetera. But I'm very pleased to say that, as a medical community and a cardiology community, it's very receptive to these concepts.

I floated this idea-- where better to float it than at the Heart Rhythm Society meeting this past July? I had two presentations, one at the periphery of that in the Stanford Biodesign symposium and one as part of the sessions of heart rhythm. And overall, very well-received by the electrophysiologists, who theoretically should be the most threatened by this. So I know I probably went a little bit over the time that I wanted to take for this, but I'm going to stop here. Thank you.