[MUSIC PLAYING]

MARK ESTES: Hello, I am Dr. Mark Estes. I'm a professor of medicine at the University of Pittsburgh School of Medicine and director of the Clinical Cardiac Electrophysiology Program here at the Heart and Vascular Institute. I am going to be speaking today about prediction and prevention of sudden death with particular emphasis on sudden cardiac death in the setting of coronary heart disease, which as you'll see, is the most common substrate for cardiac death.

It's appropriate to start with a case presentation of a typical cardiac arrest that happened to be caught on a video camera. This is a gentleman at a ticket counter, interacting with the ticket agent. And as you can see what happens in this 73-year-old moderately obese male with hypertension and diabetes, he'd had an anterior wall MI an LAD stent, he collapses at the airport. CPR is initiated immediately by bystanders and a 911 call is made, and in 54 seconds there's a response.

The AED arrives at the scene and CPR is done for 2 minutes and 10 seconds. And the outcome was good, in that the AED shock delivered a 3 minutes and 43 seconds, by the video, by the timing, resulted in resumption of normal sinus rhythm after VF. This is a prototypical example of a sudden cardiac death after a myocardial infarction.

Now sudden death is common. It's the most common cause of death in this and virtually every industrialized country. In this particular case, the patient was transported to the hospital, stabilized. He underwent hypothermia protocol. His LAD was intact. He was neurologically intact.

He was treated with appropriate medical therapy and went home nine days later, having survived a sudden cardiac arrest, a good outcome. Unfortunately, the outcomes across the board in the United States, even with contemporary emergency response systems and contemporary advanced care, are not as good.

Now by definition, sudden cardiac death is a death that is not preceded by any symptoms or unwitnessed death. And in this case report, the treat of survival worked perfectly. There was immediate access to emergency call with 911, early CPR, early defibrillation, and excellent post-resuscitation care. What is missing from this equation is prevention. And indeed, primary prevention of coronary disease, which is where one of the opportunities for improving outcomes last.

And in the course of the next 45 minutes or so, we'll be talking about not only prevention, but risk stratification and intervention, focusing on identifying high-risk patients, treating them appropriately with medical therapy interventions and ICDs. We'll also be talking about response and resuscitation. In particular, optimizing resuscitation services and improving the delay in recognition and treatment definitively of cardiac arrest, most likely due to VF with AEDs.

And then finally, focusing on post-resuscitation care, in which there has been a considerable amount of improvement in outcomes based on improved neurologic outcomes from therapeutic hypothermia. And in particular, with specialized post-resuscitation care.

So with that background, we'll move along here and to talk about primordial prevention of coronary disease. Now within the chain of survival there is what I call the missing link. And this chain of survival, which is promoted by the American Heart Association, includes 911, CPR, defibrillation, and advanced care. What is missing is prevention. And indeed, this is where a huge opportunity exists to improve outcomes from sudden cardiac death.

Now when we look at the natural history of coronary disease in this country, from the time of birth until the time of sudden cardiac death, what we see is a progression, in part due to childhood and early adulthood obesity, smoking, hypertension, diabetes, ultimately progressing to premature coronary disease, which has been recognized really since the 1960s, when tragically, many of our young vets died and coronary disease was found, even in the 20 and 30-year-olds.

Now this is where the opportunity exists in prevention of coronary disease, as you'll see. By the time that people get these risk factors and develop lifestyles that have promoted coronary disease, in some respects the horse is out of the barn.

We deal very commonly with risk stratification and intervention at this end of the spectrum, once these people have established risk factors for coronary disease. And then we also look at the response, which is the chain of survival and the post-arrest care. And in this respect, there is a huge opportunity in prevention. And the evidence base is really quite robust that supports this.

If we look at the overall survival, shown in the upper right-hand corner of your slide from out-of-hospital cardiac arrest in the United States, it's about 10% across the board. Coronary disease is the underlying substrate in about 80% of these patients. This has been shown by a number of studies going back now to decades, that the underlying substrate for sudden cardiac death is underlying coronary disease developing over decades.

And in more than half of the cases, the initial manifestation of the coronary disease is indeed sudden cardiac death. Sudden cardiac death defined as abrupt loss of consciousness from a life-threatening ventricular arrhythmia or unwitnessed death.

Now this is not an acute myocardial infarction. There's roughly 800,000 to million acute myocardial infarction each year, patients presenting with chest discomfort, EKG changes, enzymatic evidence of ischemia. These are people in whom the initial manifestation of their coronary disease is an arrhythmic death, which if not treated within minutes, uniformly is fatal.

Now the mechanisms underlying this are complex, but they include what is known as the triple hit model for the perfect storm. Now we're focusing on coronary disease, but this also is the case with dilated or hypertrophic cardiomyopathies, arrhythmiagenic cardiomyopathies, valvular heart disease, congenital heart disease, and inherited arrhythmia syndromes as well.

But the focus today is on coronary disease because this is where most of the opportunity exists. Transient initiating events that might be ischemic, they might be neurologic, they might be related to sympathetic tone. Sometimes there are external stressors, alcohol indeed.

And, of course, the arrhythmia mechanisms most commonly re-entrant triggered, automatically arrhythmias, all of which result in EMD, asystole, VT, or VF. Most likely, VF is the early rhythm, progressing ultimately to asystole, which after attempt at resuscitation there's no mechanical coupling with the electrical activity, resulting in electromechanical dissociation.

Now mechanisms here include not only this triple hit model, but indeed multiple different types of monomorphic VT, particularly in coronary disease, polymorphic VT, ventricular fibrillation, and also very rarely Brady arrhythmias as well. And has different outcomes depending upon the initial documented rhythm. But we're going to be focusing mainly on early resuscitation from ventricular fibrillation, which remains the most common cause of cardiac arrhythmia resulting in sudden death.

Again, with the types of structural heart disease in these niche populations of primary electrophysiological conditions, such as congenital long-QT syndromes and so on, which typically affect the younger generation. That is, when sudden death occurs earlier than age 40, it is most commonly some type of inherited condition, not uncommonly primary electrophysiological conditions listed on this slide. And over 40, the vast majority of cases, over 80%, have underlying coronary disease.

So in this setting, what we need to do is to recognize the fact that's been recognized for over two decades, that there's a relationship between BMI and age for both males and females for onset of the first non STEMI, non transfer myocardial infarction. And indeed, the BMI is a metric of lifestyle. Diabetes, hypertension not uncommon, sedentary lifestyles, that begins many times in childhood.

Now it's been shown through a number of studies that if you look at the conventional risk factors for coronary heart disease, hyperlipidemia, hypertension, cigarette smoking, and diabetes are indeed the major risk factors. Obviously, family history as well. But these four are once in which we can intervene.

At least 80% of patients with coronary disease have at least one of the four conventional risk factors. And this is indeed where the opportunity exists to improve outcomes. And this comes from a number of studies, most important of which is predictors of lifetime risk of cardiovascular disease by age 50.

And the important conclusion of this very, very, very robust epidemiologic study is that the absence of established risk factors at age 50 is associated with a very low lifetime risk for cardiovascular disease and prolonged survival. And this is shown graphically here.

If you look at the adjusted cumulative incidence in males, on the left of your screen, and in females, on the right, what you can see is that if you are in that group of people who get to age 50 with none of these major risk factors for coronary disease-- this is the purple dotted line, that's the lowest one-- that your future probability of major cardiovascular events, myocardial infarction, heart failure, stroke, plateaus. In males it's about 5%. In females it's about 8%.

And there's an incremental risk as one goes up in the number of risk factors, all the way up to in males 69%, and females over 50%, if at age 50 they have risk factors. So prevention of risk factors by age 50, so-called primordial prevention-- not primary prevention, but primordial prevention-- is a worthy goal that would undoubtedly result in improved outcomes.

Now what we need to keep in mind is that the mortality reduction of potential drug versus lifestyle intervention in patients with coronary disease is strongly, strongly weighted towards lifestyle. Smoking cessation, physical activity, moderate alcohol, exercise, keeping BMI down, and the impact of this is much more profound than the medical therapy, which is represented on the left of your slide.

The challenge becomes in our health care system, certainly in the United States, undertaking these lifestyle measures doesn't have an economic incentive. They're very difficult to achieve. And many times they're achieved outside of the domain of organized medicine, certainly outside of the domain of what we do in our office with patient counseling about healthy lifestyles.

So the American Heart Association has an impact goal, which they have met through 2020, which was published now two decades ago, looking at national standards for reduction in cardiovascular health promotion and disease reduction. And indeed, what they've stressed is that primordial prevention is minimally influenced by medical interventions.

Lifestyle modifications is in the domain of behavioral sciences. It's largely culturally influenced. And the cultural influence is different by race, by demographics, even by religion. And to a large extent, it's out of the domain of organized medicine.

Institutional policies are influential. In particular, employers who incent healthy lifestyles have been shown to work. Economic incentives work. Insurance companies' incentives work. Policies that promote healthy lifestyles within schools work. And government policies work as well.

It requires a lot fiscal resources and political will. And it is, I think, abundantly clear that the economic incentive for industry to intervene early and prevent development of coronary disease just isn't there in the way that it is in a sense for bypass surgery, for implantable defibrillators.

And these economic incentives are key to understanding not only the individual, but the corporate response to this lifestyle intervention. One has to think long term, and one has to think about decades of lifestyle modification to impact favorably, really move the needle on prevention of coronary disease by getting people to age 50 without any major risk factors.

Now part of the challenge with the issue of sudden cardiac death, which occurs in anywhere between 250 and 400,000 people in the United States, depending upon your data source and your definitions, is the following. If we look at patients shown on the lower left-hand corner with prior myocardial infarction low ejection fraction, they have a very high incidence of sudden cardiac death.

But when studied, as they were in the MADIT I and the MUSTT trial, if you look at the proportion of all of the sudden cardiac deaths in this country it represents a distinct minority. And, in fact, more sudden cardiac deaths come in the general population where the incidence of sudden death is low, about 1 in 1,000 a year. But because the number of patients, as shown in the upper right, is so substantial, many, many more sudden cardiac deaths occur in patients without known coronary disease, without prior cardiac arrest, without prior ejection fractions less than 35% or prior coronary disease.

And shown on the right are the trials that have been looked at to try to intervene favorably on these patient populations, including MADIT I and MUSTT in the lower right-hand corner, trials in which we have taken high risk patients, put defibrillators in, and shown benefit. Secondary prevention trials, with AVID, CASH, and CIDS, with defibrillators. High-risk primary prevention patients shown in SCD-HeFT and MADIT. Home defibrillator trials, public access to fibrillation trials, and more recently, the LifeVest trial. And we'll have more to say about that.

So moving on to the next slide, we're going to talk now about risk stratification and intervention in these high-risk patients. They have a high risk of sudden cardiac death, but overall they represent a distinct minority of the patients having sudden cardiac death because the vast majority occur in patients without prior MI, without heart failure. But it's the first manifestation of their underlying coronary disease.

So if we take a look at the known epidemiology, very robust evidence shows that about 50% of the total mortality in the first year, post-MI, occurs in the immediate post-MI period, with a considerable drop. So if you're going to die, most likely you're going to die early. This time dependence is critical. Because in the high-risk post-MI patients, you need to intervene early to impact on this very high-risk period, particularly the first six months.

And prediction of sudden death is dependent upon risk stratification that are practical, sensitive, and have a high predictive accuracy, a very high true positive, a very high true negative for the overall predictive accuracy. And we do know that prevention of death is dependent. Once you have identified high-risk patients on intervening in a cost effective fashion, that unequivocally improves survival.

Now we've looked at a number of risk stratifiers in post-MI patients to try to increase the risk of sudden death total mortality. And frankly, the left ventricular ejection fraction remains the gold standard. None of these other techniques, either non-invasive or invasive, have identified patients who have an increased risk of sudden death over total mortality, despite many, many trials trying to identify these risk stratification techniques or a combination of non-invasive and even non-invasive and invasive ones that identify high-risk patients.

So LVEF with a cutoff traditionally at 35% or less remains the marker of risk in post-MI and in dilated cardiomyopathy patients as well. And unfortunately, it does not increase this ratio of sudden death to total mortality. Because, of course, intervention with defibrillator only impacts on sudden death.

Now LVEF is an independent predictor of total mortality. Then the risk of sudden death increases progressively as the decrease in EF occurs. And typically, 40%-- but in particular, in these trials 35% to select at a higher risk group has been shown, but it does lack specificity for predicting sudden cardiac death. Nonetheless, it remains the gold standard.

Now if we look at patients post-MI who are at high risk based on low ejection fraction, what you can see is the freedom from sudden cardiac death is a function of time shown in yellow. And in these patients, in the initial 12 months, there's over 20% risk of sudden cardiac death if you've got a high ejection-- a low ejection fraction. And it continues to go out-- down to about a 40% risk of sudden cardiac death at four years based on older data.

Now the data's improved. That curve has shifted north with contemporary opening of arteries and contemporary medical therapies. Nonetheless, the time dependence is still the same. But if we look at the low-risk subgroups free of cardiovascular events, you can see that the risk is small and remain small out to four years.

So with this background, I want to show you a patient and give you something to ponder. So this is a 58-year-old male with an acute anterior wall in line with cardiogenic shock, high risk, requiring balloon pump pressures. He does have a PTCA of the LAD, and he has subsequent VF. So he's got a lot of markers of high risk. He's got non-critical disease in the circ in the right.

His CF is 20%. He's got anterior wall hypokinesis. He is really struggling with hypertension, class II to III heart failure. He's on all the medical therapy. So the question is, which of the following are evidence-based strategies that are going to prolong the survival of this unfortunate 58-year-old male?

I'm going to put an ICD in and train the family with CPR and AEDs. Gave him a LifeVest. None of the above. So I want you to think about this. Really, what's the evidence-based strategy that prolongs survival. Well, the correct answer, unfortunately, is D, none of the above.

And this is something that I think is important to understand, is that intervening in the acute post-MI patient, who's a particularly high risk, like this patient, has not been shown with any evidence base to improve survival. Nonetheless, it's very common to put a LifeVest on a patient like this. But I want to review really the reason that I put this particular case in with the evidence.

So risk stratification needs to be evaluated based on actual clinical utility. Clinical utility is defined as a modification of practices or intervention in a way that unequivocally and significantly prolongs life. You need a prospective randomized trial that's ethically acceptable, obviously, with clinical equipoise.

So we've learned through antiarrhythmic drug trials that there's harm. Very few that have benefit and they've all been related to beta blockers. When the drugs failed, we started to look at devices. Now, this is the post-MI high-risk patient of the type we just showed you, who's randomized to receive a defibrillator versus no defibrillator, the so-called DINAMIT trial. One would think that if you reduce the risk of sudden cardiac death, there would be an improvement in total mortality. It didn't work.

Acute intervention with an ICD in the immediate post infarct patient population does not decrease total mortality. And the reason is, although you can decrease arrhythmic mortality, which it's been shown to do, these patients are at high risk for total mortality. Such that eliminating sudden cardiac death just leaves them at risk for dying of heart failure complications from their myocardial infarction, recurrent infarction. So early intervention with a prophylactic ICD immediately after the ICD, regrettably, doesn't work.

And if this wasn't enough, this was substantiated that prophylactic ICDs don't reduce overall mortality in a subsequent similar study, the so-called IRIS study, again published five years later in *The New England Journal of Medicine,* looking very hard to try to improve these outcomes. Immediate implantation of defibrillator in patients with acute myocardial infarction and reduced ejection fraction does not prolong survival. It does reduce arrhythmic death, but total mortality remains unchanged.

So what about other strategies? What about using home defibrillators? Well, we know that if we look at patients who have an acute myocardial infarction and have out-of-hospital VF, if they get resuscitated early, they do better. But the home defibrillator trial, randomizing patients to family CPR and home AEDs showed no benefit in total mortality. And the reason is most of these people die at night. They go to sleep, they don't wake up.

So if it's unwitnessed, you can't intervene with 911, CPR, AED use, and advanced care. So home defibrillators do not work. Defibrillators do work in public locations.

Now, in this particular patient, despite the lack of evidence, this high-risk 58-year-old gentleman, a LifeVest was put on. And six days post discharge, VF in the middle of the night. Shocked, survived. ICD was placed. He had progressive heart failure and got a heart transplant.

Now we all know of cases like this in which the LifeVest anecdotally has saved a life. And they tend to influence our decision making. But when we do look at prospective trials of the LifeVest, and I'll show you the data, they don't make a difference.

So risk stratification has a lot of limitations, looking at populations versus the individual patient. And in this respect, optimal therapy needs to be done with all of the appropriate medical therapies we have available today, revascularization. And then primary prevention ICD use, after the patient's been revascularized at least six weeks, and at least 90 days-- I'm sorry, six weeks after myocardial infarction, 90 days after revascularization, this is where the primary prevention ICDs come in.

Most of the sudden deaths occur in low-risk categories without ICDs, as I've emphasized before. So we have a great dilemma, is that we can identify a high-risk group immediately post-MI, but we don't have an intervention that's going to unequivocally prolong survival because the total mortality is so high.

So there are many, many limits. It's a consistent finding that most individuals who experience sudden death fall outside of the current guidelines for consideration of an ICD. In a sizable percentage of individuals, sudden death is the first manifestation of coronary disease.

Now what's shown here is some work that has been done previously by Bob Myerberg, looking at the distribution of clinical status of individuals suffering sudden cardiac death. So take a look at the right hand. In 30% of people, it's the first clinical event. And in a third of patients, also they may have known positive stress tests. They may have angina, be on appropriate medical therapy, but they don't have any of the high-risk markers.

So two thirds of these events are occurring in low-risk populations. Notice that at the other end of the spectrum, on your left, 5% to 10% of arrhythmia markers occur in individuals who are at high risk. So you can see the dilemma that has been created by the epidemiology of sudden cardiac death.

Now, once you get out 30 days after revascularization and once you get out six weeks post myocardial infarction with revascularization, we do have data that primary prevention ICDs and appropriately selected patients prolong survival. Now, I don't have time to go into all the data here. But if we look at primary prevention trials and we look at the outcomes in these trials, there's been benefit in many of these trials, and for the secondary prevention there's been a benefit as well.

There have, indeed, been some neutral trials-- IRIS, the DINAMIT trial, as well as CABG-PATCH. CABG-PATCH was a very early trial looking at prophylactic defibrillators immediately after revascularization. But we should all know that after revascularization and after appropriate medical therapy 90 days of the remains less than 35% in patients with coronary disease there's clear unequivocal survival benefit with primary prevention. And if somebody has had a cardiac arrest and survives, a distinct minority, but a larger group of people, who with contemporary therapy, no question, secondary prevention based on the CASH, AVID and CIDS trial.

So let's go on to opportunities for improvement with optimizing resuscitation services to improve response times and effectiveness of interventions. And this is really where I think we have made a lot of progress. Faster EMS responses, AED use, and advances in CPR, and ACLS have all contributed to improved outcomes. But the largest improvement, is actually in neuro preservation, as you'll see.

So most of this data is known to you. If you look at survival and function at 10 minutes of time in ischemic cardiac arrest, survival goes down by about 10% per minute. So early recognition, early initiation of CPR, calling 911, early use of AEDs in these individuals with ischemic arrest. And it's very similar for most other causes of cardiac arrest.

So the time dependence of response is really critical. And in this respect too, if we look at AEDs in preventing sudden cardiac death, there are a number of trials that show benefit, including the public access to defibrillation, the second from the bottom. But the HAT trial, immediately post-MI did not show it.

Now the public access defibrillation trial showed an improvement in survival in public locations where they're typically witnessed. But in homes, they don't work. Most of the cardiac arrests occur in the home setting. So you can see the dilemma that the AED is useful in public, but not in home locations, which isn't to say that there's not an occasional patient who might benefit from it.

So the evidence base demonstrates decrease time to defibrillative therapy with AED use improves survival in public settings. And there have been a number of organizational, institutional, and federal policies. But regrettably, for survivors of anterior wall MIs who were not candidates for a defibrillator, access to AEDs did not improve outcomes.

Now we've done a lot for many years to really flip the legal arguments that used to be stacked towards home use of defibrillators or public use of defibrillators had some liability. It's actually the other way around, in which as a matter of public protection, if you don't have a defibrillator, you've got liability. So there's a number of legal initiatives now that have strongly influenced public locations, hotels, certainly health clubs, airports, to have AEDs. And it's clearly result of improved outcomes, including some prospective randomized trials.

So what about the wearable cardioverter defibrillators? Now one would think that with a LifeVest on, based on a number of studies that are summarized here, that the VEST trial-- V-E-S trial, which randomized patients post-infarct to wearing a LifeVest, versus no LifeVest, would have improved outcomes. Unfortunately, there was no improvement in sudden death in a randomized trial published in *The New England Journal of Medicine.* There was no improvement in non-arrhythmic death, although a trend towards a lower mortality. It didn't reach statistical significance.

And as you can see here, death from any cause in the device group was lower. It reached statistical significance. But without a decrease in arrhythmic death, importantly, what happened is many of these patients would have arrhythmias detected by their LifeVest, which resulted in early intervention. Sometimes it was AFib with early intervention with anticoagulants, with stroke rates actually being lower in the device group.

So we cannot say that the LifeVest improves survival post-infarct, which isn't to say that there may not be individual patients, such as the patients that I showed you. Now the risk of a LifeVest are not high. They are not perfect in terms of patient utilization. Unless the patient's compliant with it, they're not likely to be used. But can we really say there's an evidence base that improves survival? Well, unfortunately not in these post-MI patients.

So the American Heart Association and other groups, the ACC and Heart Rhythm, have come up. And notice that the only two-way indication is in patients with defibrillator, in whom you have an infection. And you're treating the infection. You can wear the implantable defibrillator-- I'm sorry-- the wearable defibrillator for a short period of time.

And in patients with an increased risk of sudden death, not eligible for an ICD. Awaiting cardiac transplant is a IIb indication. Also, a IIb if they're 40 days post-MI, newly diagnosed, non-ischemic, revascularized within the last 90 days, and other substrates. So a very, very limited role based on the evidence for this wearable cardioverter defibrillator.

This comes up very, very commonly for the clinical electrophysiologist or the general cardiologist in patients after MI going home. And I think you have to take a shared decision making, individualized approach with each patient. But you also have to imprise unless they're compliant with it, it's not likely to be beneficial.

OK, so what about post-resuscitation care, to move on to the final area, that really is quite striking in terms of the improvement. So I showed you this earlier. The cumulative meta analysis of the effectiveness of defibrillator capable emergency services. And take a look. At best, we're doing a 20% in the 1990s and so on.

Now most of the mortality in patients with sudden cardiac death, who get to the hospital, are from anoxic brain damage of varying degrees. And we all see this, tragically, in our own practices, where we have a recovery of the myocardium with stable electrical activity. Some stunting of myocardial function, but neurologic recovery that is poor. And until recently there wasn't any therapy that documented, despite multiple attempts with pharmacologic therapy and other interventions.

Well, we all now know that if we look at anoxic brain injury, it is the most common cause of death among patients who get to the hospital. And more and more patients are getting to the hospital with public access to defibrillatior and a wider awareness that when somebody collapses, don't check a pulse. Don't hesitate. Call 911, start CPR, put the AED on. And then follow the commands of the defibrillator. And the outcomes are good.

This is one of the major lessons of the trials, for example, with American Airlines, and in public access to defibrillation in airports. Both trials published in *The New England Journal of Medicine* that showed improved outcomes with AED use by laypeople.

These are minimally trained airline personnel. Or in the case of Chicago O'Hare Airport, bystanders who are not medically trained. And in casinos, where you've got security forces that are trained, outcomes were spectacularly good, with all of the monitoring that goes on and recognition immediately of when somebody collapses.

Now when they get to the hospital, neuroprotective therapy is an important intervention. And indeed, what we can do now is to do therapeutic hypothermia. And it's beyond the scope of really what we can cover here, but there is a lot of good basic translational science that goes into therapeutic hypothermia, with minimizing the cytotoxicity and brain death that goes on for hours and hours after an ischemic event.

And there's a number of references here that are shown to you, that you can refer to. But we now have good evidence base based on randomized controlled trials that there are dramatically improved neurologic outcomes in patients who get to the hospital with spontaneous return of consciousness, or even comatose with stable cardiac rhythms.

Now, with this in mind there had been a number of non-randomized trials that suggest this versus historical controls, looking at favorable outcomes. But the randomized trials, many of them now, that have looked at more recently nuances of hypothermia. And it turns out these nuances are not so important. The temperature, the target temperature, the duration are not so important. It's just implementing therapeutic hypothermia.

And indeed, the American Heart Association has taken a look at this in a very evidence-based thoughtful way. And the number needed to treat is only six. It's a very small number. More likely alive with stable neurologic outcomes at six months, again number needed to treat. No difference in complications, with a little bit a trend towards bleeding in patients who get therapeutic hypothermia, but not requiring transfusion. So it's considered to be minor bleeding.

And there's a non-significant trend towards an increase in sepsis as well, which we always mitigate in these patients anyway because many of them do have aspiration. And when treated the outcomes of the infection are typically very good.

So with this in mind, the American Heart Association has actually taken a position statement that in unconscious adult patients with spontaneous return of consciousness after a possible cardiac arrest, they should be cooled. It's a Class I indication.

It's also true for non VF, the evidence base is not as robust. And as you can see here, it's a Class I and Class II indication. There's now a policy statement-- much like we have trauma centers, much like we have stroke centers, much like we have STEMI centers, that there be centers that are regionalized to improve the outcomes of patients with out-of-hospital cardiac arrest.

And indeed, when you get these patients to these centers, triaged by ambulance or transferred after stabilization, the outcomes are-- the neurologic outcomes are better. And there's evidence base to this. So the American Heart Association actually does have a system of regionalized care for improved implementation of cardiac arrest.

So the opportunities, I think, are shown here. The major opportunity, the primary prevention of coronary disease, It is a huge challenge. It's one that certainly in the American health care system we've not been able to meet.

It takes long-term thinking. It takes policies that are outside of the domain of what we do in our office day to day with counseling patients by the time they've got established disease, many times with angina, heart failure, not just at risk for sudden cardiac death, but many of the patients certainly the physiologists see have already survived cardiac arrest. We need to change the paradigm of thinking, thinking about early intervention, thinking long term to prevent this.

Risk stratification improved response and advanced care does hold great promise, but there's also what I'll call a zone of futility, in which there's not much that we can do. So let me summarize and conclude here by saying that this is, I think, a single figure that really captures what we're up against.

If we look at the general population, where most of the sudden cardiac death occurs, and coronary disease with no MI, or post-MI low-risk patients, public access to defibrillation, as well as lifestyle modification, and optimal medical therapy does hold improved outcomes as a potential result of early access, to public access to defibrillation. But it's got to be coupled with centers that have the expertise to not only to do therapeutic hypothermia, but to appropriately evaluate the patients, most typically delaying coronary angiography in those patients as well.

So if we look at the heart failure trials, including SCD-HeFT, MADIT, and CRT trials, the ones in which the defibrillator works, prior cardiac arrest for secondary prevention or post-MI high-risk patients with MADIT trials, certainly intervening in those patients with the optimal medical therapy and the ICD works. But most of the cardiac arrests are actually going to come in this lower-risk population, in which primary prevention of coronary disease and automatic external defibrillators in public locations are going to work.

So the opportunities, I think, really are along the lines of prevention of coronary disease, defining the mechanism of sudden cardiac death, improving risk stratification, optimizing medical therapy, looking at community-based public access to defibrillation programs, which are evidence based. Using very selectively the implantable cardioverter defibrillators in patients who fit the profile of the trials. And then regionalized systems of post-resuscitative care.

So with that, I will conclude, thanking you very much for your attention. And if any questions come up, if any comments come up, please feel free to contact me here at the Heart and Vascular Institute at UPMC. Thank you and I will sign off and leave at this juncture.