DENNIS MCNAMARA: Heart failure in African-Americans, it's a very important clinical problem, very common, unfortunately. Has a unique epidemiology. It's a bit distinct from the heart failure we see in the white counterparts. There's a lower incidence, despite risk factors, of coronary disease. And there's a higher incidence, much higher incidence, of hypertension.

Unfortunately, and the reason it's so important, is there's a worse prognosis. Higher rates of hospitalization, higher rates for the same ejection fraction of sudden death. And increased mortality, even on multi-variate analysis, both for African-American men and women. And how can we use medical therapy and genetics to really improve this unfortunate distinction? There is clearly a distinct response to medical therapy, to the point where we now have heart failure medications that are actually approved separately for self-designated African-Americans.

Now, I would argue and will show, that our investigations show that the heart failure phenotype, the distinctions in the heart failure phenotype particularly when it comes to hypertension, are genetically-based. That some of those same differences affect clinical outcomes and potentially are targets for therapeutic intervention.

Now this next slide shows data from a number of multi-center trials about the incidence of patients with systolic heart failure in our trials, VF1, VF2 are some of the oldest VA trials. SOLVD was a good ACE inhibitor trial. Carvedilol, BEST and MERIT are the trials that really made beta blocker standard therapy.

And then if you look in the subjects in those trials, if you look at the white subjects which are primarily in purple, they had primarily coronary disease as the etiology of their heart failure. While if you look at the black subjects in red at the bottom part of the slide, they probably had hypertension. It somewhat mirrors what we see in the clinic. It's a little bit of a different phenotype.

That has led to studies of genomics going back two decades now to try to understand that difference. The other thing we know in terms of heart failure is left ventricle hypertrophy seems to be more pronounced in our black subjects with heart failure than in white counterparts. This is from a group in the Dallas Heart Study of self-designated African Americans not treated, so at time of presentation, that looked at the correlation LV mass with blood pressure presentation. Of course it goes up. But looked at the distinction by the presence or absence of a genotype of corin, which is really only seen in black cohorts, and not seen in whites. Corin is the converting enzyme for BNP, so it's felt natriuretic peptides, which are cardio-protective. So a deficiency in production, more common in African-Americans, leads to greater LV hypertrophy for any given blood pressure.

Now we have been interested, in the Heart Failure Center at University of Pittsburgh, on genomics, and particularly on myocardio recovery in nonischemic cardiomyopathy for about the last 20 years. And we've done a number of multi-center trials. I'm going to show some data from IMAC 2-- Intervention in Myocarditis and Acute Cardiomyopathy-- which is a study of all recent onset nonischemic myopathy, both men, women, and women's with peripartum disease, at 16 centers, completed about five years ago. And I'll also show some data from IPAC. That's a more recent study at 30 centers, specifically in women with peripartum cardiomyopathy.

Now this is from IMAC 2. So this is the ejection fraction at baseline, when they enter-- all patients with new onset nonischemic myopathy-- and six months, by race. The 80 black subjects, 293 white subjects, roughly similar ejection fractions at presentation-- to both, about 23%, 24%. But at follow-up, there was less recovery in the African-American subset. And this is despite similar therapy.

If you look at outcomes, again, this is survival free from heart failure hospitalization. There is also a distinct difference based on race, with much poorer event-free survival in black patients compared to whites.

And again, I don't think that this is a treatment difference. Treatment of both groups was similar in terms of ACE inhibitors and beta blockers. This is an entry, but it's actually even closer at six months. And this timeline is their time to ICD implantation, so just to give you a sense of how people were managed. And it looks virtually identical in black and white subjects across the 16 IMAC centers. So therapy looked quite similar, but outcomes were distinct based on race.

This is from our peripartum study, so a hundred women cross 30 centers. And peripartum cardiomyopathy is an unfortunately common complication-- rare, but a complication of pregnancy-- unfortunately a common cause of maternal mortality. The women presented. When the black subjects on the right side of the screen-- about 30% of the cohort was black-- and then non-black, mostly white patients on the left side, the black patients came in with a lower mean ejection fraction and just never caught up. Again, similar treatments. The best we can say, just came in a little bit more severe LV dysfunction, and just don't catch up.

This list, which is which is growing every decade, is the therapies. And this is part of the problem we have. These are the therapies which improve survival in heart failure with reduced ejection fraction. We have seven different combinations of nine different therapies, growing every day, but no patient in the world is going to take all of these. Which ones work for which patients?

The oldest therapy, and the one I'm going to talk more in detail about, is Hydralazine in combination with Isosorbide dinitrite-- the oldest and first therapy to improve survival in patients with systolic heart failure. Now, this has a relatively unique mechanism compared to most of the other drugs, which are working more directly [INAUDIBLE] system. And we believe it acts primarily through NO. So Isosorbide dinitrate is a organic nitrate that stimulates NO production. There is a physiologic pathway which is cardio protective through cyclic GMP, as well as through post-translational modification, that is certainly beneficial in heart failure. There is also a pathologic pathway where it can combine with a superoxide ion to form peroxynitrites, which has a detrimental effect.

Now while Isosorbide dinitrite stimulates production of NO, we believe, Hydralazine is an inhibitor of the oxidase production and, we feel, drives it through a more cardio-protective pathway. As I said, this was the first therapy shown to improve survival in systolic heart failure. The classic VHEF 1 is a VA study. And when that study demonstrated improvement in survival, in the top of the screen, what we didn't know at the time was there was a much different response by race.

So in VHEF 1, the nitrites and Hydralazine combination, in orange, improved survival-- so a lower curve. Overall, it was a positive trial. But when you break down the subsets analysis, it was only effective in the black subset, and there was very little benefit in whites. Subsequently, that was followed by VHEF 2, which was one of the first studies to say, aha! ACE inhibitors are the real savior in this circumstance and general standard of care, and have been that way ever since. But when you look back in Vhef 2 and did the same breakdown, the treatment group of Enalapril was superior only in whites. And the only randomized study ever done-- Vhef 2-- of nitrites and Hydralazine versus ACE inhibitors in black subsets showed no difference.

This led to the rationale for the A-HeFT trial, which is now over 10 years old, which looked specifically in a cohort with systolic heart failure which were self-designated as African-Americans. And it used it on top of all other therapy. And it was stopped early. It's a small trial by heart failure standard. It's only a thousand people, 500 in each treatment group, 160 centers-- so very difficult to do. But was stopped early because of a huge survival benefit, a 43% reduction in mortality of patients on therapy. Now, this is over 10 years.

Now, what percentage of African-Americans are currently on this combination therapy shown to reduce mortality by 40%? Nationwide? About 20%. 80% of African-Americans with systolic heart failure are not on this therapy. Think about if we had the same thing with ACE inhibitors or beta blockers. We'd be, like, all up in arms. Why? I don't think it's just doctors not being aware. Right now, this is additive therapy, and it's hard to get your patients to take their sixth and seventh medication.

Now we were the genetic core lab for A-HeFt. And as part of the theme, you know, all therapies do not work for all people, we tried to look at what the genetic differences were and if we could tease out why this therapy was more effective in African-Americans and if we could tease out a genomic signature rather than a racial construct for determining therapy. Now this is just a schematic of the renin-angiotensin pathway where we begin with adrenalin and drive forward through A2, as well as aldosterone production. This is where most of our therapies-- and I would argue that Hydralazine and nitrates, also [INAUDIBLE] works on several of these points, as well. All are therapies-- older therapies-- which improve survival. Act on this point. And there are significant polymorphisms-- genetic variants-- which affect the functionality of each of these points, and I would argue also affect the impact of our medical therapies.

In graph, the genetic sub-study, we looked at a panel of SNPs, which have either been shown to affect heart failure and other cohorts, and the majority of these are differentially prevalent in black versus white cohorts. Been studied extensively in hypertension. We're just trying to apply that to heart failure, and I want to focus for probably the rest of the talk on GNB3.

GNB3 three is a gene. It's a G protein subset, which is an important subunit which is important in alpha adrenergic signaling. There is a common polymorphism studied mostly in hypertension, where the T allele is associated with increased signaling and low renin hypertension, and it's much higher in prevalence in black cohorts than in whites. How does it work from the schematic? It's actually just a marker. It's in 100%. It's the silent mutation, but it's in 100% disequilibrium with a splicing variant. It's really the T haplotype, and the splicing variant in exon 9 results in increased signaling.

It's very different in black and white cohorts. In black, the cohort from A-HeFT and from graph, about 50% of the subjects are homozygous for the T haplotype, where it's only present in about 15% of whites. We have seen in other cohorts that this same T allele-- and this is in a predominately white cohort. This is from Grace, presented at the AHA, currently being submitted for publication-- submitted last year-- from our clinic, where, in a predominately white cohort, the TT genotype in blacks-- excuse me, in the black line here in a mixed cohort, was associated with poor survival.

We'd see the same thing previously. This is the TT genotype now in red in the IMAC2 cohort. Less significant, less events, but the same prevalence. What did we see in A-HeFT? Did it affect the effectiveness of therapy? Well it did, to a great degree. The primary endpoint for A-HeFT was a composite score that involved both survival, hospitalization, and improved quality of life, and that led to your composite score. If your composite score was high, that's a good thing. If it's low, that means it's bad. If you look at the improvement on therapy in red, in the group with the TT genotype, it was very strongly positive. Very effective, and if you look at the other half of the cohort without the TT genotype, we saw very little effective therapy.

Now this is just event free survival. Similar, if you looked at event free survival by treatment, within the TT subset, you saw significant impact of therapy on the left side of the screen, but not in subjects without the genotype. Now this is a small cohort, which kind of just begs some type of validation study, and we are currently involved in that validation. We are coordinating that, which is graph two, which is collecting another cohort of up to 500 subjects of self-designated African-Americans with systolic heart failure, who we will treat with a fixed dose combination of hydralazine and nitrates, and try to generate the same A-HeFT composite score to try to see if we can validate that previous study. We do it at the 20 centers throughout our A-HeFT-- excuse me, our graph network, but that's being coordinated through our heart failure center at University of Pittsburgh, through a grant from the NIH.

We hope to also look for other loci, which may explain the differences in drug effect. This looks at admixture analysis and just points out the fact that most-- that race is kind of a social construct, and that most self-designated African-Americans have a combination of African genomic ancestry and European genomic ancestry. From A-HeFT, 2/3 of the cohort were between 5% and 20% European. You can use that admixture to actually do genomic screening with a large enough cohort. And putting multiple loci together, even in A-HeFT one-- GNB3, NOS3, aldosterone synthase, CORIN-- is probably the way to go in the future, and this just shows an example of that, that you can really try to, be using more than one loci-- you can really try to tailor your therapy to an individual.

Now in the last couple of minutes, I just want to show the importance of the same genotype in myocardial recovery, and use our peripartum cohort to do that. It's, as I said, a major cause of maternal mortality. Phenotype identical to other forms of non-ischemic myopathy, but specifically occurring in young women of childbearing age around the time of delivery. It's increasing in occurrence, I think, because of recognition. It involves several thousand women each year in the US, and it's an important, unfortunately, problem.

Now there's a marked difference. Race is a risk factor. It's more common among black women than among whites. In our cohort in Pittsburgh and nationally, we have 10% of an African-American population in the city. About 30% of my patients are African-American with the disorder. It's also much more prevalent in Africa and in Haiti, and I do think that African genomic risk factor, as is with other non-ischemic myopathies, is a risk factor-- is a problem-- is a risk factor.

So for IPAC, we looked at these 30-- 100 women across 30 centers, and this is the same data I showed you before, but a different way, and again, black women in yellow came in with a lower ejection fraction and just don't recover as much at 6 and 12 months, with a mean that's almost 10 points lower than their white counterparts. I think the same genetics are likely at place here, and this from a recent publication in circulation. Heart failure from our group shows now the recovery baseline-- six and 12 months-- by genotype. So the GMB3 TT genotype in white. Other genotypes in purple, and you see that they begin with a little difference, but by 12 months, it's more than 10 EF units. This is by genotype, not by race.

It was statistically significant in both racial subsets, and was actually more prominent in the black cohort. As you see, there's a difference of almost 15 EF units by 12 months. Much more powerful in this subset. But in the white cohort, also significant. Also significant. There are other genetics obviously involved here, and we recently published this earlier this year in the New England Journal for the IMAC2 and IPAC investigators-- findings of the prevalence of mutations of titin or other genes, which cause cardiomyopathy in familial cardiomyopathy.

What is their prevalence in the sporadic disease? This was a collaboration with Cricket and John Simon out of Boston, who had previously reported that in sporadic dilated cardiomyopathy, not familial, that you could find type mutations in 12% to 13%. So we looked in not only in the IMAC and IPAC cohort, but in four other smaller cohorts. Two from Pennsylvania, one from Germany, one from Japan, and what we saw, particularly in the IMAC and IPAC cohorts is that of these sporadic cases, these PPCM cases, 12% or 13% had type mutations, and 18% had some mutations. These are truncations changing the protein, despite the fact that they didn't have a family history. Indeed, 10% of the women in our PPCM cohort had a family history of dilated cardiomyopathy, but it was a different 10%, it turned out to be. If you add that, you'd get almost 28% with some genetic etiology.

Now again, this is titin. It's a large protein, and the mutations both of DCM and peripartum were primarily in the A band, and were about the same prevalence. Both about 12% to 13% in both. What's its impact in recovery? Now this is adapted from that paper. The women with the titin mutations, and this is specifically IPAC in yellow, did seem to recover less. But this doesn't tell the whole story, and indeed, if you looked at the white cohort of the IPAC, the type mutation didn't seem affect it. Now six and 12 months. How about the black cohort? Well that's where you're seeing the impact. But as I said, I think race in this regard is just a marker for genetic background. So let's go and list-- all that data was in the paper, but that racial difference made us downplay, I think appropriately, that we didn't understand exactly how titin was affecting recovering.

But let's do it differently. Don't do it by race. Do it by GNB3, and this is very small. But if you look at without the TT genotype, this includes now some blacks and some whites-- no effective titin. Now co-inherit this genotype and you see a much more profound effect. Numbers are very small. We have in the planning stages, awaiting funding, a much larger cohort for hopefully we will tease this out. But should we be targeting differently?

So finally, genomics and heart failure in African-Americans. There's a distinct phenotype, more hypertension, more hypertrophy. I think all these differences are predominantly genetically based. The same genomic template can help us predict outcomes, and I would hope will be, particularly with GNB3 TT genotype, will be a target for future intervention.