INNOVATIONS IN HEART TRANSPLANT PATIENT SELECTION AND MANAGEMENT: WHO, WHEN AND HOW, DENNIS M. McNAMARA, MD

I am honored to as the Medical Director of the Transplant Program to be the second speaker, and my charge this morning is to talk about how things have changed in the last decade in terms of innovation from the medical perspective both in terms of patient selection, management and who – and I’ve titled it Who, When and How.

Now this slide reminds me of a couple of things. One is that this a celebration this year of the 30th anniversary, as Bart says, of cardiac transplantation here at UPMC. And there is no better place to be a heart failure physician certainly or a heart failure transplant physician than here in Pittsburgh. Not only due to the wonderful collaborative spirit that exists and the teamwork between our medical docs, our nurses and our surgeons, but also how wonderful the city is. And this slide was part of our first celebration of the 30th year and also tells me what a wonderful city Pittsburgh is and how your kids get you into things that you never really intended.

My daughter is a dancer, a sophomore at Princeton, and danced for a contemporary dance group, and I told them, her director last year, oh, after some function, oh that’s wonderful, you really should think about doing something about transplantation. And that’s all I had to say. And there became a innovative contemporary ballet Heart, which was totally about the emotions of transplant actually from the patient’s perspective, and this is the company and this is actually several of our transplant patients as well as one, two patients that were not transplanted, they were pre-transplant. But it really was a wonderful experience, a wonderful celebration for Pittsburgh and there was a special star who I think just looked away to the OR, who I’ll, who I’ll talk about in a little bit. But it’s a wonderful
celebration for the 30th year. And now – cardiac transplant at UPMC 2010, it’s been a very
wonderful decade, and how have things changed. And I want to talk about who we transplant, how
has that evolved over the last decade. When we do it, and how do we optimize our outcomes.

And this next slide is from the National, the ISHLT database which shows you that transplantation
really hasn’t grown very much. And the U.S. numbers are here in green, and it’s been roughly oh
about 2200 really for the last almost 20 years. There was a surge worldwide but now it dips down of
all the transplants done worldwide, and most of them are done in the U.S. And this really hasn’t
changed very much. Now one thing which has changed – oh actually this is Pittsburgh’s numbers.
Now Pittsburgh has had a rapid period of growth over the last decade in our cardiac transplantation
where we have moved from roughly oh a top 10 program to a top, top 3 program. We have done
very well over the last year, few years with the collaborative effort of our surgeons and our docs and
nurses and really if you look at Pittsburgh transplant of the 30 years, of the top 10 years, 5 have been
the last 5 years. The other 5 being in the early years where Bartley Griffith and as you said was
building the program 1984 to 1988. So that’s gone extremely well.

Outcomes have also done extremely well. Now this is the national numbers where you see that over
the last – by era. So if we look at in blue before 1991, in green the decade of the ‘90s essentially,
and in red here the early part of this decade. And you see that, if you just look at 6 year survivals
have gone from 60 almost to the low 70s, 72%, while 1 year survivals have really gone, gone up
dramatically as well.
And with growth we have seen the same thing in Pittsburgh. This is a snapshot of our, of our 1 year survivals where you’re seeing that it’s gone markedly up and as something I’ll get back to later, a lot of the improvement is in the early outcomes, and I think that’s a tribute to our surgeons and to some changes in strategies that I’ll talk about in a bit. But we’ve – this is kind of – this is actually raw data as it is coming up, this is our last year’s fiscal year of 56 hearts and if you look at one year survivals of 91% comparing very well nationally with I would argue as sick a population as you will transplant anywhere, we had 91% versus 87% nationally. So outcomes are very good, numbers are very good, it’s really a wonderful time for cardiac transplantation here in Pittsburgh.

Now when things are going well, the question is why and what does that allow you to do? Well, one thing it allows us to do is push back a little bit of the boundaries of who can we reach with transplantation? And the first aspect of I want to talk about is recipient age.

And I’ll start with a case, a case from earlier this year, 77 year old gentleman, class 3B heart failure, but minimal comorbidities, really an active gentleman, no renal dysfunction, really he was a one problem gent. Had been hospitalized multiple times required inotropic therapy, was borderline inotrope dependent, hadn’t been gone home on inotrope but was just about to. Now despite his heart failure he was very active in his community and actually involved in the care of his middle aged child who had, who had medical issues. So he was a very active, very, very I’d say physiologically young and robust gentleman despite his age, at 77. You know 10 years ago would we ever consider this?
Now one thing which has changed a little bit, gradually, and this is the same nationally is that our transplant age has gone up slightly. This is the median, this is a look at from earlier in the decade versus the latter part of the decade, a mean age of 53 versus 55, a gradual increase in the age. And why is that? Well, a number of factors. One is and this part I think we, we take pride in is we’ve gotten better about deferring cardiac replacement, beta blockers, Bi-V pacers, we’ve gotten better at trying to help someone to keep their own heart, cardiac repair. So that has pushed back a little bit the age at which people need.

The second thing which has happened is we’ve gotten a little smarter about immune suppression. If you have an older patient, a 65 year old patient does not need to be immunosuppressed in the same way a 30 year old patient does. And if you can decrease the immune suppression you’ll improve outcomes.

We’ve looked at expanded donor strategies, which allow us access to more organs. We’ll see a great organ from a donor, perfect heart, cath is perfect but the donor may be 58. Now for probably some, some just emotional reasons we won’t put that 58 heart in a 30 year old. Can we use that in a 70 year old? Can we use that with good outcomes? And there is data, emerging data which supports that in well selected individuals transplanting can be a successful strategy even in older recipients.
Now this is again back to national data. This is from the ISHLT and it looks at 3 eras, essentially the ‘80s, the ‘90s and the last decade and what the recipient age was. And I just want to focus on these columns here. If you look at 6 of the 69 it is in the, in the ‘90s or ‘80s it was only a minor part of people transplant, more in the last decade and even more in the most recent decade, such that it’s roughly 25% of recipients in this national list were over the age of 60, and here over age 70. Now, none before 1990, small percentage and a couple of percentage, but this is 20,000 patients, so this is getting up to 700 patients, a fair cohort over the age of 70.

And what do the outcomes look like? Well, a couple of things I’d ask you to focus on this slide. One is that this is so by age, so over age 70 is in the deep blue here. Before age 70 there is not a whole lot of difference. Actually because our younger patients include congenitals which are all higher risk and perhaps we take a little higher risk with the younger patients, when we look at transplant outcomes as a whole it’s kind of a U shaped curve. The outcomes are actually poorer sometimes in our younger patients. But there’s not a whole lot of difference under the age of 70, even with patients here that are 60 to 69, identical. You are talking about long term 6 year outcomes at 70%. Now with patients age 70, the outcomes are not that, as good, but still look, you are getting 5 year outcomes in a 70 year old patient of 60%, compares favorably with a lot of our end stage therapies. And is a reasonable therapy I think for selected patients.

This is back to Pittsburgh data, what does our data look like in older recipients? And what have we done – how has this changed over the last decade? Now this looks at our survival by recipient age
over roughly a 10 year period, 1998 to 2008. And under age 45 is indeed blue again like the national slides, essentially not necessarily better than the young recipients. Middle age, I’ll call it, in green and in red, 45 to 55, 55 to 65, probably in this section had the best outcome. But here is age over 65, now granted as a single center we haven’t done that many patients over 70 although we’ve done, done a number. So we’ll lump them there, but that’s 60 patients. And I would argue that over 60, those outcomes really look virtually identical, over 65, excuse me.

Realizing that and being selective, I mean we don’t want to do things that are, that are not in the best interests of the patient, but in selected patients we can transplant people very successfully over the age of 65. And as a result and recognizing this the percentage of our patients over the age 65 over a decade has gone from 10%, 17% to 21%. And we have—although obviously there are limits, we are trying to look more at not a chronologic age necessarily but physiologic age as really the best metric for when transplantation makes sense.

Now I want to touch on another area where we are starting to kind of push back the boundaries. Now as our people are nationally and think about what it really means to be a transplant candidate, but first before I do that, I didn’t realize my slide. This is what happened with that ______. We did transplant this gentleman. He was benefitted by having a rare blood type so we only waited two months, his course was complicated by a minor DVT in an upper extremity, which was just a nuisance for him because he had to be on Coumadin for a while; but he’s doing wonderfully. And as
we see with older recipients, rejection is very uncommon. He has not been rehospitalized, and doing remarkably well.

Now I want to touch on another area where we are starting to push back the boundaries a little bit, BMI. As we all know, we all struggle as healthcare providers in the country with obesity. It’s an epidemic, and we see patients every day that struggle with this, young patients. And the question is for young patients with obesity and heart disease sometimes we think that handcuffs us, limits our options. But at what level does it have to limit our options? And can we help people who struggle with both heart disease and obesity?

This is a case, a gentleman of mine I’m taking care of now, 36 year old gentleman, former firefighter, long history of non-ischemic myopathy, EF 20%. Earlier this year, roughly about 10 months ago I guess, or a little bit longer, really progressed, Class 4 heart failure, Bi-V pacer no help, beta blockers no help, really becoming inotrope dependent; but he was a blood type 0, 6’ 2”, 300 pounds, BMI of 38, 39. Now he underwent an LVAD II as a bridge to what? Shall we try bariatric surgery? Get his weight down? What can we do for this gentleman? But he was a young man, we are certainly not going to let him go. He’s actually done very well with the VAD and he is not yet transplanted, but this is what we looked at in terms of what our options are. Can we transplant him?
Well, why do we still worry about obesity in transplantation? I mean obviously there are issues with surgical risk in markedly obese patients, but there’s also the risk and the concern in transplantation that immunosuppression itself has side effects which complicate, or are complicated by obesity.

So hypertension, this is from again the national data, if you look at the incidence of hypertension in transplanted patients, it’s extremely high to in this data set almost universal by 10 years, renal dysfunction as well goes up, but here metabolic syndrome, diabetes goes up 5 and 10 years posttransplant. Hyperlipidemia goes up again almost universal after 10 years on immunosuppression, and brings with it the risk of allograft vascular disease. So if you have a patient who has metabolic syndrome, who obesity, you know can you transplant him and suffer through all these side effects, is that really going to – is the patient really going to suffer for that?

Well, once again the national data, this is from the last year from the Journal of Heart/Lung Transplantation, and this looks at the impact of BMI including a BMI greater than 35 on outcomes posttransplant. And before a BMI of 35 you really don’t see very much actually, but you do begin to see a decrease in outcomes in patients at high weights, but it’s not dramatic. This is if you looked at, this is a fair amount of patients, although it gets a little smaller here, a couple hundred patients, but patients are having poor outcomes at 5 years, but it’s 5 or 10 points. So if you are talking about a 36 year old, is it worth it? And can you do better than that?
Well, we have been working on innovative immune suppression in Pittsburgh to see if actually we can push that further and can actually do better. And this is where again, looking at our Pittsburgh statistics, this is a, a BMI, thinner patients in blue, 20 – BMI 20 to 30, and 30 to 35 in green and red, and greater than 35 in purple. Now mind you, this is single center data so this is only 30 patients. But clearly, and I’m not going to argue that they do better if they are obese, but clearly at least in this look at the data, 30 patients, BMI’s done the last decade, BMI over 35, they are certainly not doing worse. So perhaps it’s really only a relative contraindication and then the patient is obese but doesn’t have other contraindications. Now mind you, most of these patients I should say they are all essentially 35 to 40, there is a limit to what we can accomplish surgically. But it should not be necessarily a limit.

So metabolic syndrome, diabetes, very prevalent posttransplant, immune suppression is really largely responsible and steroids are a major factor. The question we asked in Pittsburgh a number of years ago and actually led by Bob Cormose and Mike Shula, our transplant pharmacist who has really been instrumental in initiating this protocol and it’s a vital part of our program. Can they be diminished or eliminated? Now, steroids still fortunately or unfortunately are a mainstay for transplant care you now worldwide, this is from recent data, again from the ISHLT, so if you look at in blue that’s 2007 to 2008 and this is at one year follow-up you are looking at still mostly 65% of the country still has people on steroids, down a little bit but not dramatically. All patients or 90% of patients are on a calcineurin inhibitor, either Tacrolimus or Cyclosporin, most patients are on CellCept, but a fair amount are still on steroids. This is from again recent data, 2000 to 2008
nationally. What’s the 5 year? Still 5 years you have 50% of the patients on steroids, long term sequela. No wonder there is concern about doing patients with obesity.

So in Pittsburgh, again, I have to give Mike Shula a lot of credit for really initiating and being the bug and helping pushing the other docs along. The steroid protocol was initiated, the goal is to be off Prednisone by 6 months, 6 to 12 months. That was largely achieved by 2004. And later on the protocol I’m not going to talk about much because I think, I think other speakers will, induction change in Pittsburgh led by Ken McCrory and now by Yushi Toyota, and with the use of Ellen Tusamab steroids essentially have been eliminated completely for the majority of patients done recently.

Here is from a paper by the paper by Mike Shula and Jeff Tuteberg, our Associate Director of Transplant who will be speaking on other topics later in the symposium and this just shows that you really can get people, even in the old days, this is from our data in the last part of the last decade, we still would get patients off, but that would begin at about 2 years and, and still about 4 years we’d still have some patients on steroids. That was pushed back markedly with, with the protocol initiated by Dr. Shula and we started getting patients off very early and had the majority off by a year. And this is again from their paper, and you just look at 2004, the goal was largely accomplished 6, 9 and 12 months. By 12 months 82% of the patients were off steroids.
Now what does that do? Well one of the first looks Mike and Jeff looked at was what does to the metabolic syndrome. So this is hemoglobin A1C pre-protocol in the first 2 years of it you see trends towards reductions, not dramatic but trends. And you saw similar trends towards reduction in LDL in concern with statin therapy. So they said well you know that looks a little bit better but not quite what we would have expected, we were hoping for a little bit more. But look at our outcomes in diabetics. This is our outcomes pre the steroid minimization, we used 2004 because that’s really when people were really – it was fully realized. This is diabetics, because of the metabolic syndrome did have poor outcomes and this is the same nationally. But post-steroid minimization, look at the change in the diabetics, and this is just from a look with the first 134 patients, but with more data and more time this is holding true that steroid minimization I really believe does markedly help our diabetic outcomes. And it actually may allow us to transplant people like the patient I just presented, the young 36 year old who doesn’t have diabetes but is markedly obese.

Okay, now, unfortunately Bob is not here with my second heart slide, which reminds me to talk about when to transplant. And be careful what your kids get you into, be careful what your colleagues get you into. I, I said, I asked Bob to help me with this project and I was – I had appeared on stage, and I said I am not going to appear on stage with this thing, but I said – but Maria, who is the, the artistic director who is here said to Bob she wants to do a duet with you. And Bob said you are kidding. But for our patient, Dr. Cormose, now this is actually from a university, this is actually a hodgepodge of two. This is not actually what the duet was. Bob did, he said they are not going to make me put on a tutu are they? No, he appeared in surgical gown and it was actually –
very, the most moving part of the whole piece was Bob in full surgical gown did a wonderful artistic, now these surgeons really are artists you know, and we medical guys are very jealous of that. He did this pantomime of a, of a transplant with the director here, not in this garb but in – but in nursing surgical garb telling him when to do everything to the music because outside they had a dancer playing the failing heart which Bob at that point in the operation led the failing heart off stage, led a new dancer who was a new heart onstage and continued with this pantomime. So Maria was very careful telling Bob when to do the transplant for the dancer. Oh, there were tears, everyone in the audience, there was not a dry eye in the house. It really was moving. I think Bob has a new career if the VADs don’t work out. I think he’s going to take over Memen Oz’s position you know.

Okay, now when. I just want to – I’m going to finish off quickly, I just want to talk one thing about when. Okay, most of our patients who transplant these days are status 1, a lot of them are status 1A actually. By definition though, by the time they are transplanted they are fairly sick. They are Inotrope or LVAD dependent, the longer your waiting time, and that’s the more complicated, the more compromised the patient the higher your operative risk. I’m not a surgeon but that I understand, that my surgical colleagues have taught me. So when to transplant? One simple answer, as soon as possible.

So one of the changes which have gone over the last decade is the expansion of both the medical side, we have now 8 positions in the heart transplant side, on the cardiology; and the surgical side there are now 6 staff cardiac surgeons working in our transplant program. It’s wonderful to be in
Pittsburgh and to have that kind of support. And what we’ve seen, and this is actually a couple of years old but the _____ will be the same. What we’ve seen therefore, with this dedicated team, with innovative donor procurement strategies which I won’t speak of, I’ll let my surgical colleagues do that, but what we have seen is our wait time has gone from 2003, 200 days 2004, cut in half in 2005, cut in half again in 2006. So with a dedicated team, aggressive surgical strategy, very experienced in procurement this has been a huge boon to our patients, because I want to go back to the slide of outcomes and I have to say although we’ve made improvements as the medical side, you know, a lot of our improvement outcome it’s been this, the first 30 days. This is improvement in surgical mortality, and I think a lot of that is getting to patients sooner, as well as some technical advances which you may hear about. So this has been a huge boon to us.

Pittsburgh’s a great place to be a heart failure transplant physician and we have a wonderful team, and I’d be remiss in pointing out that besides the wonderful 6 colleagues I have and the surgical staff as well as their fellows and my 8, roughly 8 partners in heart failure cardiology we have 20 nurse coordinators that work with us, our transplant pharmacists like Mike Shulo, our social workers, support people, you know biomedical engineers, they really are the backbone of this program and I’ll say just like Bartley said, that’s why this program is what it is, and that’s why you know I’ve been here 17 years, it’s hard to leave, to leave a place like this.

So just finishing up, there’s been significant growth in our program over the last decade. It’s been maintained and with improved outcomes. We have seen transplantation of older recipients
accomplished with excellent survival, steroid sparing regiments have markedly improved outcomes in our diabetics and subjects with metabolic syndrome, and a coordinated multidisciplinary approach supports adaptation and innovation and makes Pittsburgh a great place to be a doc taking care of these patients. And with that I thank you and this is from the program for the dance, it’s UPMC’s for Innovation in Dance and in Medicine. Thank you all.