Cardioband: A New Era of Mitral Valve Repair

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Transcript

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PRESENTATION

Prof. Eberhard Grube:

I would like to announce a little change in the program. I think that Professor Kuck will demonstrate the results and Professor Nickenig will be talking, or demonstrating a case, so that's a little switch. Both are very competent, as you all know.

So, the background is, for this session, the treatment for functional mitral regurgitation is all about risk benefit. Low-risk treatment of this disease will allow to treat earlier and potentially affect the course of the disease. Effective treatment that avoids surgical risk will allow to treat more patients and reduce symptoms and improve quality of life, and lower the cost for the healthcare system, while reducing hospitalizations.

The goal of this session today is to get first-hand impressions from the leading users of this technology, evaluate the potential to perform this new procedure in your own practice, get the most updated results and see the benefit to your patients, and, finally, imagine and brainstorm together where this new treatment can lead us.

That sets the stage for the upcoming speakers, and I think, Mike, you are the first speaker. Dr. Michael Mack doesn't need any introductions, ladies and gentlemen. He's one of the leading cardiovascular surgeons in this world, not only in the US. It's a particular pleasure to welcome him here in Berlin. I know you had a long journey, a tough evening, and a tough night, depending. Percutaneous Annuloplasty: Another Step Towards Surgical Standards. Mike, welcome.

Dr. Michael Mack:

Thank you, Eberhard, for that kind introduction, I think. So, what I would like to do is to set the stage for the remainder of the session here and talk about Percutaneous Annuloplasty: Another Step Towards Surgical Standards. My conflict of interest is I am the co-principal investigator of the COAPT trial of

MitraClip. So, in order to do this, let's talk about what are the surgical standards that we are aspiring to, and I think you have to break it down into primary and secondary MR, because the treatment is very different and the outcomes are very different. So, let's talk about primary or degenerative mitral regurgitation.

It's a very heterogeneous disease from fibroelastic deficiency, on the left, to Barlow's, on the right, and the way we approach this spectrum of diseases is totally different. For Barlow's, on the right, we tend to resect tissue. For disease on the left, fibroelastic deficiency, we tend to what's called respect tissue and use artificial chords rather than resective techniques.

So, here's a patient that's more on the Barlow's end of the spectrum. You can see that the P2 portion of the posterior leaflet, there's a flail chord there and a triangular resection of the leaflet is being performed. It's been sewn together, and it's a very simple straightforward technique. However, with degenerative disease, almost all the time there is annular dilatation that occurs as a result of the disease. Now, this is artificial chords; this is the Leipzig loop technique in which we make a series of loops that we sew to the head of the papillary muscle, that you see on the bottom here, and then we can adjust the chordal length to whatever we need in order to restore coaptation.

Now, as a part of this procedure—we never do one thing in surgery, we do multiple things, and as well as addressing the leaflet, we have to address the annulus. There is annular dilatation that occurs in both primary and secondary mitral regurgitation. It is dilation of annulus, but mainly in the septal-lateral diameter, and so the whole idea behind an undersized annuloplasty is we restore coaptation after the mechanical problem with the leaflet is fixed by putting an annuloplasty ring in place. It can be either a complete ring or a partial ring, and partial rings we refer to as bands, and oftentimes in degenerative disease we will only use a partial band. The most common one is called a Cosgrove Band, after Dr. Cosgrove with the Cleveland Clinic.

Now, for the transcatheter approach to degenerative disease, we have two devices that are available to address the leaflet, per se, the MitraClip device and artificial chords by the NeoChord device. The MitraClip device is approved in the United States for degenerative disease only. In the guidelines, it's a IIB recommendation, level of evidence B, based upon the EVEREST trial. The artificial chord technique at the current time goes through the apex, the edge of the leaflet is grabbed and artificial chords are placed and then sutured on the outside of the apex.

Where I potentially could see this going is, MitraClip works quite well for degenerative disease, but it doesn't correct the annular dilatation, and I could see very easily combining a technique of MitraClip or artificial chords with a catheter-based delivery of a posterior band and have a fully percutaneous repair, exactly the same thing we are with surgery. Now, the results are very good with MitraClip, why would you think of doing this? I think that those patients with leaflet disease that have significant annular dilatation, we could improve the MitraClip results even more by adding an annuloplasty to it.

So, let's talk about secondary functional mitral regurgitation, and I think, as everybody in the room knows, it's not a disease of the valve, per se, it's a disease of the left ventricle, and the mitral regurgitation is caused by apical lateral distraction of the papillary muscles and tethering of the leaflets. The idea behind a surgical annuloplasty is using an undersized ring to correct the annular dilatation that occurs secondary, and again occurs greatest in the septal-lateral diameter, and restore coaptation, but it doesn't do anything to change the primary disease of the ventricle. This is an example of a typical patient that we do surgically with functional mitral regurgitation and we can acutely and completely correct it.

So there have been multiple different surgical annuloplasty rings. The first one was actually by Professor Carpentier in 1968, and it was a partial posterior band. The second one was a Carpentier-Edwards Classic ring. The one we use most commonly now is called the Physio ring. This is an Etiologix, which was designed actually by Dr. Adams and McCarthy, specifically for ischemic mitral regurgitation because

of the increased annular dilatation in the P3 area. Then, lastly, we have the Cardinal device, which is an adjustable ring placed surgically, that you can dial in the degree of coaptation that you want.

So, there's a lot of debate in surgery regarding complete versus incomplete rings or posterior bands. This is an article in 2010, from Israel that looked and showed that the recurrence of mitral regurgitation is less with a complete ring as compared to a partial ring.

Now, what we look at the role of surgery in this, and we see that for chronic severe secondary mitral regurgitation the recommendation from the guidelines is a IIB recommendation, level of evidence B. However, the problem is that this is very seldom utilized. So, in the United States, in 2014, there were a total of 450 isolated mitral annuloplasties performed. So, even though it's a IIB recommendation, the problem is we don't utilize it much in the United States, because it's very invasive treatment and it's uncertain that it has any benefit.

Now, we did undertake a trial in the United States, under what's called the CTSN, Cardiothoracic Surgery Network, which is a National Institutes of Health funded trial, and we found that replacement provided a more durable correction of mitral regurgitation than repair in severe ischemic mitral regurgitation. This was the result at 12 months. There was a 32% recurrence rate with repair and a 2.3% recurrence rate with replacement. However, in a sub-group analysis of this, if we look at the patients that were repaired that had recurrent MR, left ventricular remodeling did not occur. So, the main left ventricular end systolic volume index stayed the same. However, if a repair was successful, you can see that there's positive ventricular remodeling, even better than replacement, if you couldn't reliably do a repair that doesn't reoccur, and there's been a lot of work done of sorting out who those patients are, and I'll talk about that in just a minute.

Now, there was work done prior to this by Prof. Dion that actually says you can cure ischemic mitral regurgitation by restrictive mitral annuloplasty, and if you have a left ventricular end diastolic diameter of less than 65 millimeters, the results are actually great with a mitral valve repair. This shows the survival of patients that had smaller ventricles compared to larger ventricles in both left ventricular end diastolic and systolic volume. So, in other words, if the patients are treated before the ventricle is too dilated and the leaflets too tethered, the results of repair are great.

Now, the COAPT trial in the United States, I think is going to inform this field significantly. There's never been a randomized trial of surgery versus medical therapy, and that's part of the reason we don't know whether surgery works or not. So, this is the COAPT trial, which is 420 patients randomized between medical therapy and the MitraClip. As of this month, there have now been 278 patients randomized at 84 sites in the United States. As you can imagine, it's a very difficult trial to enroll, but hopefully by early next year this trial will be completely enrolled and we will be able to inform the field whether correcting mitral regurgitation, this disease, makes a difference compared to medical therapy.

Now, we do have a lot of transcatheter options. There's been two devices that are CE mark, one in 2011, a coronary sinus device, and then the Cardioband direct annuloplasty device has recently received CE mark. The Cardioband device is a surgical band delivered by a transfemoral access route. It's implanted in a supra-annular position, the exact same way we do it with surgery, and then there's controlled adjustment at the end under echo guidance to correct the mitral regurgitation and cause coaptation of the leaflets again. You can see on the top the baseline mitral regurgitation and then, again, the total correction of it afterwards.

Now, if we look at the preliminary results—and I'm not going to spend any time with this because our other speakers are, but you can see on the left the Cardioband results in 17 patients and the degree of residual mitral regurgitation at one year afterwards compared to multiple surgical series at one year, and I think that the results are actually quite comparable. I must admit there's a couple things that I never thought would work. MitraClip was one of them. Two is I didn't think Cardioband was going to work as

well as it is, because in surgery we just believe that you have to do complete rings, but these results are much better than I would have predicted.

So, we now have had a lot of movement in this field over the last eight weeks. There have been three transcatheter valve replacement devices that have recently been bought, as well as one mitral repair device. So, over these four companies, there's been $2 billion spent in the last eight weeks for these four companies. So, there's a lot of movement in this field happening right now and it'll be interesting to see how this is sorted out. So, there's a lot of money that says, yes, correcting mitral regurgitation is going to make a difference in this disease.

So, how are we going to sort out repair versus replacement? Well, I think we know from the randomized trial in the US, as well as multiple other series, that repair is better than replacement under certain circumstances, and if there's a coaptation depth of less than one centimeter, a tenting area of less than 2.5 centimeters, a smaller left ventricle, less tethering, defined by anterior and posterior tethering angles being less, all of which I think will respond quite well to a repair technique. Anybody that's more severe with that, I think we've learned from the surgical series that they do tend to recur; the recurrence rate is always about a third at one year, and I think those patients may be better off treated by replacement.

So, why is the benefit of mitral regurgitation so hard to find? Well, there's multiple hypotheses. One is that the recurrence rate is at least 20% with surgery and there's a significant operative mortality in these patients, so it may be that we're obscuring any benefit from this. Secondly, maybe there is no benefit, maybe mitral regurgitation is just a surrogate marker and not causally related to the outcome of the disease. Thirdly, maybe the benefit is limited to specific patient sub-groups that have not been well predefined in the current data sets, so maybe it's the etiology of disease. I think it may well be that ischemic and non-ischemic cardiomyopathies are different diseases that are going to respond differently. It may be the duration and the severity of MR, how bad the ventricle is, the functional class.

The way I see the state-of-the-art right now, it's like taking a group of patients with anemia and treating them all with B12, and it's hard to pick up a signal of benefit. Indeed, it's only the patients with pernicious anemia that are going to respond. So, I think that because we haven't got a signal there, it's like Vitamin B12, we can't say that it doesn't work because we haven't defined the pernicious anemia here. Lastly, there's no randomized trials with appropriate controls and core lab assessment of mitral regurgitation; COAPT will be the first, and I think that will not only be specific to the MitraClip device, but will significantly inform the whole field.

Thank you very much.

Prof. Karl-Heinz Kuck:

Mike, I just may have one short question for you. The advantage and potential disadvantage of surgery is that at the time of surgery you have to fix as much as you can fix. So, you mentioned that you have to do the annuloplasty plus, if necessary, any intervention on the leaflets, the chords, or whatever. Now, the potential advantage, or again disadvantage, of an intervention procedure could be, particularly in patients with secondary disease, that you could implant the annuloplasty ring first, see how things develop over time, and then in a secondary step, if things are not moving in the right direction, then do an additional either clipping procedure, or whatever will come in the future. So, that could potentially lead, because you are doing it sequentially, to a reduction of this mortality that you were addressing in surgery, and if the result from an efficacy point of view would be similar to surgery, then the benefit that you are questioning as a potential mechanism, because of the initial high mortality, could be shown in such a patient population, was that something that you would follow?

Dr. Michael Mack:

So, I think absolutely, yes. So, I'd say there's two disadvantages of surgery. One is we do the repair techniques in a non-hemodynamic situation. So, we're fixing it and then we're checking it afterwards, and if it's not right we have to go back and redo it. The transcatheter technique, you're fixing it under real-time monitoring, which is a difference.

The second is—as you're saying, we kind of have one shot to get it right and we can't do staged procedures, like you're suggesting, and I think that that is a good approach, and I think we will sort out who best is treated which way. I must say, I don't pretend to know which way this is going to sort out, but you could, as you say, do an annuloplasty first and then come with a leaflet technology, like MitraClip, afterwards, or do a MitraClip first and then, if it tends to recur, then do an annuloplasty afterwards…

Male Speaker:

Or at the same time.

Dr. Michael Mack:

Or at the same time. Or, thirdly, you could do an annular repair first and then, if it tends to recur, then on down the line come with a transcatheter mitral valve replacement. So, I think the whole choreography of how these procedures possibly could be staged is a wide open field.

Prof. Karl-Heinz Kuck:

Thank you. Thank you so much. So, we're going to proceed and I think now Georg Nickenig is ready to show a case of a Cardioband procedure, but before he does I just would like to mention that, again, I think the fascinating issue of this Cardioband procedure is that it's the first technology, that at least I'm working with, that really shows in a consecutive series of patients that you really can achieve what the goal of an annuloplasty procedure is; that is, to reduce the septal-lateral diameter. I think that Georg has a nice case to share with us where he can prove the concept. So, Georg, please.

Prof. Georg Nickenig:

Thank you, Karl-Heinz. I hope I can. The Company uploaded the file. Oh, okay. So, I think we have done like 14 cases, and I think the first three cases together with you, Francesco, or something, and the last 10/11 cases, and this is one of the cases. I have a very easy job, I just have to listen to the movie.

(Video presentation –transcribed)

Prof. Georg Nickenig:

Hello, everybody. This is the cath lab from the University of Bonn. On the right side is Prof. Vanna (ph), there is Dr. Hammerstingl in the back on the echo machine, and my name is Georg Nickenig, and we would like to show you today a Cardioband procedure.

It's a female patient, as you can see, with a very extensive past medical history, suffering from arterial hypertension and ischemic cardiomyopathy. She suffered from myocardial infarctions between 2010 and 2012, and finally she underwent a CABG procedure in 2013, with a single LIMA graft to the LAD.

The imaging studies showed in the echocardiography a severely impaired left ventricular function, with an ejection fraction of 25%, and what's most importantly for this case, today, a severe mitral regurgitation, as you can see on the numbers, PISA 0.7, ERO 0.5, and the regurgitation volume 55 ml per beat, which is quite a lot for a functional mitral regurgitation.

Christoph, I can hand over to you.

Dr. Christoph Hammerstingl:

You can see a long axis here of the left ventricle and the mitral valve, and what you can see is that the left ventricular function is poor. She has this acuteness of the anterior wall and what you can see is the patient suffers from severe functional mitral valve regurgitation. If you switch over to the intracommissural view, we see that it's brought a central jet of the mitral regurgitation located between P1 and P2. We have two accesses at the moment, one arterial access. This is important for later on, to see how the first and second screws may affect the circumflex artery. We have another venous access for the transseptal puncture, which you can see now in progress.

Prof. Georg Nickenig:

We are supposed to be very inferior and very posterior. We can show the echo procedure, where you can see that we are kind of on the posterior side. Maybe you can also measure the distance to the mitral valve. So, 3 centimeters—3.2 centimeters was the distance we should have.

Dr. Christoph Hammerstingl:

3.2.

Prof. Georg Nickenig:

We can place the coronary catheter once we have heparin on board. So, this is the guide catheter, it's called TSS, and it is 24 French, comparable to the systems which we use, for example, for the Evalve procedure, get it through the septum, so we have to aspirate at the same time in order to avoid any emboli. Now we connect the system to the stent. This is also readily done. Middle of the valve is fine. And like this, okay. Now, we have to flush the system and then advance it into the TSS.

Dr. Christoph Hammerstingl:

Yes, it's good, yes. So, you have anterior of the commissure.

Prof. Georg Nickenig:

On the fluoro, up front, first, we placed the TSS, which is the guide catheter. That's the blue one here, in 24 French. Now, we have a second catheter, the GC, the guiding catheter for the Cardioband, which has been placed in the guide catheter, and obviously now we have to aim to the first positioning, which is at the P1 side of the valve, and as far as we can, we would like to place the first screws anterior of the commissure, and we are aiming to place two to three screws in this area, in order to get really a tight and stable adherence of the Cardioband to the annulus. I think we are nicely in place already for the first screw.

We do have an (inaudible) catheter sitting in the left ventricle, which helps us to orientate the system. You can see that on the fluoro. You can see that also on the 3D echo.

Dr. Christoph Hammerstingl:

Yes, this is a surgeon's view of the mitral valve. The aortic route is here, the anterior valve leaflet opening here, and the posterior mitral valve leaflet here. This is the commissure. In relation to the aortic route, the catheter is between the commissure and the aortic route, so we are anterior of the commissure, and we do not touch the leaflets of the valve.

Prof. Georg Nickenig:

Now, we have to check the depth of our system. This is an echo-driven procedure.

Dr. Christoph Hammerstingl:

So, we have a bi-plan view of the annulus. On the left side, you can't see the mitral valve opening, but on the right-hand side you see a modified intracommissural view, and what you can see on this view, you see the catheter and the spool which is moving. The catheter is stable. Here are the mitral valve leaflets and here is the hinge point between the annulus and the mitral valve leaflet, and we are 4 to 5 millimeters away from the hinge point, and the angle of the catheter to the annulus is approximately 90 degrees, so we wanted to place the first hinge point.

Prof. Georg Nickenig:

So, this looks like a perfect positioning. What you also could judge here is that there is a separation between the spool, I will move it intentionally, and our guiding catheter, which is the most distal part of the catheter system, where you have this marker, this opaque marker, and you have the separation showing you that the spool is sitting on the annulus, and we are right, with our GC, right on the spot. So, I'm going to stick to this system. Now, we're going to place the first screw.

Dr. Christoph Hammerstingl:

You see this screw here?

Prof. Georg Nickenig:

It looks good, right?

Dr. Christoph Hammerstingl:

It looks good, yes.

Prof. Georg Nickenig:

Okay. So, we are all agreed with the positioning of the screw, and then we're going to release it. Yes, release.

Dr. Christoph Hammerstingl:

I have to release the fabric.

Prof. Georg Nickenig:

You can see that this marker is to the proximal part of the catheter, which shows us that we released some of the Cardioband. So, what we check also is the vicinity of the circumflex artery. Sometimes we can be very close to it. We can visualize it on the TOE. Maybe you can also give us a clue where the circumflex artery is, Christoph? But we always do a fluoro at the same time. We have at least one centimeter of room to the circumflex artery right now. Even if you would screw through the circumflex artery, usually you can just unscrew the artery and everything is okay and reposition the system. So, we are confident that this is the right position.

In order to show that the system is really nicely attached to it, you can see on the fluoro, but you can also visualize it on the echo screen.

Dr. Christoph Hammerstingl:

The movement of the annulus here…

Prof. Georg Nickenig:

Oh, yes, wonderful. Now, we're going to place the third screw. I think, from the fluoro, the positioning looks already nice. As I said, we…

Dr. Christoph Hammerstingl:

The positioning looks good here on the commissural side of the mitral valve. All three screws are close to each other and the trajectory, if you look in 3D, the trajectory looks still perfect.

Prof. George Nickenig:

Now, we have placed all the screws, you can see it nicely on the fluoro. Maybe you can show both screens, one after the after, the 3D echo image. So, now we have to get rid of the GC, which provided us with the Cardioband, and then we have to start with the cinching process.

If you look at the fluoro, now we have placed already the SAT. This is now before cinching. You can see nicely the MR with a regurgitation volume of 55 millimeters and a PISA of 7 millimeters. So, we're going to start the cinching process and we're going to go to step one. So, now we have cinching step number two. We have cinching of 4.4 and, as you can see on the echocardiography, we have a very severe reduction of the annular dilation, and, secondly, we have only a trivial MR left. So, judging from here, that seems to be a very successful procedure. This is, I would say, the final cinching. This is the first one before we started to cinch and these are the various cinching steps, and this is the last one, and there you can easily appreciate the narrowing of the annulus. The screws are really tied together now.

(End of video presentation)

Prof. George Nickenig:

That's it. I think it's a wonderful procedure to attack the mitral annulus, especially in functional mitral regurgitation, and in most of our patients we have very nice results so far. I think we needed right now about two hours. So, thank you very much for your attention. Thank you.

Prof. Eberhard Grube:

Georg, very well done, and very nicely demonstrated. Just two questions before—Mike, maybe you can address the question that's raised there.

Number one, you see when you start the screws, there is a collection of three screws at the very beginning, versus the rest of the screws, the distance of the rest of the screws. Could you comment on that?

Prof. Georg Nickenig:

I think in one of the first cases, there was a detachment, detachment of the system, because at that time we had only one—we had a strategy, strategy number one, before we changed it, and only one screw at

that positioning, and I think the force there after cinching is very high in this number one positioning, and therefore the Company, together with Francesco, decided to change the procedure. I think, after we modified the procedure, we didn't have a detachment at this positioning. Correct me if I'm wrong, Francesco.

Prof. Francesco Maisano:

Yes, I think you answered perfectly. The most of the load of this annuloplasty happens at the anterolateral commissure for many reasons. Number one, you start there and then you start working on that (inaudible) where you make (inaudible) other implant. Second, also, when you start cinching, that is where you have the maximum tension. So, the first 2 centimeters, this way we implant four to five anchors, so that it is more stable. After we have done this modification, we have seen no more detachments at all, so I think it's been an important evolution.

Prof. Eberhard Grube:

Great. The second question, maybe to you, Georg and Mike, how far do you cinch down? If you have a patient with three or four, is this—we should just go down all the way to zero, or would you give the ventricle a chance to adapt and maybe go to one?

Prof. Georg Nickenig:

I mean, I don't know. I can only answer this from the perspective of the device right now. As far as the ventricle and recovery of the ventricle is concerned, I think we have to wait for more data. Maybe the surgeon is a better one to answer this. But, for the system, I think you should not overdo it. Better is the enemy of good. So, you should cinch as much as you can, until you have a nice reduction of the MR, and maybe then you should add 0.5 more and then you should stop, otherwise you are risking detachment of the system. So, usually, we go to 3.5, 4, 4.5.

Prof. Eberhard Grube:

Great. Mike, would you (inaudible)?

Dr. Michael Mack:

So, I think, ultimately, what we try to do in surgery and what you want to do here is not necessarily focus on eliminating the mitral regurgitation, which of course you want to do, but re-establishing the coaptation length of the leaflets, and so we try to get a coaptation length of 8 to 10 millimeters. I think that we will get more sophisticated in this field and figure out that you can have less recurrence if you get the proper coaptation length between the leaflets. So, I think that it's going to get to the stage that we not only will correct the MR completely, but look at what the coaptation length is, and that be the final arbiter of where we end up. I am, personally, not a strong believer in the pop-off effect of decompensating ventricles afterwards. I think the better you can do, the better off the patient's going to be from that standpoint.

Prof. Eberhard Grube:

That might actually be an interesting target for the echocardiographer, to look how much coaptation you have, instead of just looking at the PISA and at the reflux. Quite interesting, great insight.

Prof. Karl-Heinz Kuck:

I think one of the major advantages, and we've discussed it before, is that of course the cinching or the adjustment is done on the beating heart, so you really have the advantage in a kind of a stepwise

approach to go from one adjustment to the next adjustment, and even you can go back. So, even if you have the feeling that it's too much, for whatever reason, too much force, a negative effect on the ventricle, then you can easily go back. I think this is what I like so much during the procedure, I mean, that's what you showed, you know, you can do it stepwise, and you can discuss it even within the group. I think that we all would agree that we need more experience to call it at the end of the day the acute effect versus the chronic effect, but, I mean, there might be differences.

Francesco, you remember, we have discussed it. I mean, you are doing both, surgery and intervention, but the major difference here might be that you have these long screws, 6 millimeters, that are going into the left ventricle, and you always mention that the suturing is more superficial than the anchoring with these long anchors, which may lead to some kind of a ventriculoplasty effect in addition to the annuloplasty. Do you want to comment on this?

Prof. Francesco Maisano:

Yes, I think some of the—in my experience, the instance of surgical rings happen more often than declared. We learned that once we were trying to do valve in rings and we found out many patients would not be eligible for valve in ring because of detachment of ring. So, this is something that happens quite often, and it is because the sutures are—I see he doesn't agree, he also don't agree. Let's say it happens more in the past, so then we are happy.

Anyhow, there is an intrinsic difference here between a surgical implantation, and this implant, as you say, the anchors are fixated in the base of the ventricle, so there is an active base ventriculoplasty here. What is the effect long term? We don't know, but, as you have seen, I think Mike showed us that the outcomes at one year are somehow in the highest bar of surgical outcomes. Even including learning curve, including all the limitations of an interventional procedure, a partial annuloplasty behaves at least as good as surgery, so maybe there is something more than just annuloplasty.

Prof. Eberhard Grube:

Can we just address the questions for you both?

Prof. Karl-Heinz Kuck:

We can first—what about antithrombotic therapy after the procedure, anticoagulations?

Prof. Georg Nickenig:

Yes, nobody, nobody really knows. Unfortunately, most of the patients do suffer from atrial fibrillation, so they go back on oral anticoagulation, and if they don't have atrial fibrillation, we treat them for four weeks to 12 weeks with dual antiplatelets. Nobody really knows whether oral anticoagulation would be superior to that, we have to test this, but 70% of the cases we have to go for oral anticoagulation, if I recall the baseline criteria right.

Prof. Francesco Maisano:

I have no idea. The point is we know what we implant. We implant a Dacron band, and a Dacron band probably doesn't need anticoagulation, per se. The reasons to anticoagulate patients after surgery in the past was double: number one, you plant something with Dacron that is enabling thrombus formation; number, you manipulate—there are sutures, there are other things, you've touched the endocardial, so that is the background for anticoagulating after surgery. But, I have to say there are many surgeons today who don't do anticoagulation any more after mitral valve (inaudible).

Prof. Georg Nickenig:

Yes, just to clarify, I wouldn't go for oral anticoagulation just for the Cardioband; it's just for the co-morbidities of the patients.

Prof. Eberhard Grube:

Mike, could you comment on that one?

Dr. Michael Mack:

Sure. I think it's a matter of there's not one size that fits all, and I think we'll be able to discriminate and figure out how these procedures are complementary to one another.

Replacement's always had a bad name in surgery and there's been a bias in surgery against replacement and toward repair. The reason for that, in the early days of valve replacement, we used to excise the valve and the subvalvular apparatus. Oftentimes, because it was rheumatic disease and you had to do that, but that translated to non-rheumatic disease also. Those ventricles decompensated afterwards, and it was said that, well, you took away the pop-off effect. I'm not a strong believer in that. I think what really happened is you were causing atrial ventricular disconnection; that the tethering effect of the chords and the papillary muscles was actually keeping the football shape to the ventricle and converting it to a basketball when you excised it all.

The way we do replacement nowadays is a valve-sparing replacement. So, we put a valve inside the previous valve, and there's a lot of modifications of a technique how you do that and not cause left ventricular outflow tract obstruction, but be that as it may, we're not disconnecting the ventricle from the annulus. So, that's exactly the way that the transcatheter mitral valve replacements are happening right now.

So, what I think is that there is not one size fits all. We know from surgery now, multiple surgical trials, that if you have an inferobasal aneurysm, that's better off replacing rather than repairing. If your ventricle is severely dilated, left ventricular end diastolic diameter over 65, replace; under that, repair. Posterolateral angle greater than 45, replace; less than that, repair. If there's no annular dilatation, like in atrial fibrillation, Type 1 disease, you're not going to fix that with an annuloplasty, because there's no sense correcting it if there's not annular dilatation present. Those are better off replaced.

So, I think we'll get smarter and smarter—the surgical field will help inform this, but we'll get a lot smarter as we get more experience in the transcatheter field.

Prof. Eberhard Grube:

Great insight, Mike. Thank you very much.

Prof. Francesco Maisano:

I have one comment and one question. Number one comment is, you know, I've done more than 200 implants, including animals and humans, so I had my learning curve. Now, I'm interested to ask Georg—he has shown us a two-hour procedure was done. I was not there. How many cases you have done to now?

Prof. Georg Nickenig:

Fourteen, I think, yes.

Prof. Francesco Maisano:

What has been your learning curve? When did you start to get kind of okay with this procedure? How many cases, in your experience, were needed to understand the procedure?

Prof. Georg Nickenig:

I'm still learning, but I think we did three or four cases together and then you abandoned us and we had to keep going, and it somehow worked out. No, I think you have to have a proctor for three or four cases, as you always have to have for such a procedure, and then I think you can start doing the procedure yourself, if you're familiar with the mitral space, if that is your question, but of course you have an additional learning curve over time, as we have seen it also for TAVI. I mean, in TAVI, we are still progressing right now, even after thousands of implants.

But, to make a long story short, I think if you are an interventional cardiologist and if you have assistance in the first four or five cases, you can go for it.

Prof. Eberhard Grube:

For both of you, and Karl-Heinz, too, the prerequisite is excellent patient workup by computer technology and then good imaging, excellent imaging, doing the procedure; is that correct?

Prof. Karl-Heinz Kuck:

Yes, I would like to make an additional comment. I think that the Company really developed very nicely over the last couple of years. I mean, Francesco has done so many cases. He can probably even try to make his eyes not looking at the monitor or the echo and the fluoro. He is very intuitive with the procedure. But, the Company has moved from this intuitive approach and a very standardized approach, which I really like. So, based on his experience and based on the limited experience of other operators, everybody came up with a very systematic, very standardized approach, so, you know at least 90% of all the time during the procedure what you have to do, and then you need, in addition, 10% intuitive movements that really help you to guide through the procedure, and what Eberhard is mentioning now, with all the CT work that is done before, and they're shown during the procedure, so you really know precisely what projections you should use, how to look at that site in this projection and in the yellow projection. So, there's a lot of guidance now that helps the operator really to move during the procedure in a correct fashion. Otherwise, it wouldn't be possible. I mean, to understand the anatomy, to understand and control the device, it's still not an easy procedure; it's very much like in MitraClip, but I have to say what is very similar is that it's a safe procedure.

I mean, until now, very much like MitraClip, it's an extremely safe procedure. Even if it takes time at the very beginning to do it, it still is safe, which I believe is extremely important, if you start something new, that you have safety instead of only efficacy. I think that safety is the most important part, and I think that we would all agree how the safe the procedure is.

Prof. Georg Nickenig:

Absolutely. I mean, we haven't lost one patient in the whole study group during the procedure.

Dr. Karl-Heinz Kuck:

They are very sick patients.

Prof. Georg Nickenig:

Yes.

Prof. Eberhard Grube:

Great, thank you. So, we move on, and now we come to the most charming, most intelligent, most eloquent speaker of the course, Alec Vahanian, who's giving us The Ideal Cardioband Patient, Based on A Successful Case Presentation

Prof. Alec Vahanian:

Thank you. So, with such friends, you don't need enemies, first statement, and I thought that Eberhard was, you know, interested in women, but now you should notice that…

Prof. Eberhard Grube:

I know you're not.

Prof. Alec Vahanian:

He moved beyond that. Okay, good. Now, to be serious, I'm going to give you an intermezzo between the fantastic demonstration by Georg and the outstanding presentation of the results by Karl-Heinz. Why do I accept this very modest role? Because I love Francesco, he's a great person…

Prof. Eberhard Grube:

Whoa.

Prof. Alec Vahanian:

No, wait a minute. You said that you love me; I can say I love Francesco. No, he did really outstanding work in this field and we have to pay homage to him, and also the people working with us, the engineers and all the people behind did an outstanding work, and that's why we are there. So, my conflicts. Now, let's see a very brief case before the results.

So, it's a French patient, 62-year-old female, a bit of coronary disease, STEMI, CABG, and I should say, I should say it was not done in my hospital, only venous graft. If there's any surgeon in the audience, it's a shame. And this poor patient had ischemic mitral regurg. On top of that, she had chronic A-fib. She received CRT-D. But, despite the good medication, despite all we did, she had a pulmonary edema in June and presented it to us in severe functional disability, NYHA Class 3, and she was high risk. So, she had also diabetes, dyslipidemia, hypertension, overweight. We looked at the echo and grossly the LV function is not good, below 40%. In MR, it means it's very bad. LV is dilated; we did not reach at 65, only 64, you notice that, and systolic diameter is 46, and EROA is 25, millimeter, I'm sorry, and is quite a severe regurg and regurgitation volume is 38, and she has severe pulmonary hypertension. The coronary-angio, left main is occluded, distal right is occluded, and the graft at (inaudible), and there is no viability in the territory where there was MR. In France, she received some medical therapy and we tried to do our best to optimize this medical therapy, and that's key. So, medical therapy, CRT in place, plus all the bypass and no need for vascularization.

So, we read the guidelines, because we have to, and in the guidelines, if we consider indication for surgery, of doing something with the valve, this patient fits here because ejection fraction is over 30%, remained definitely very symptomatic despite what we can consider as good medical management.

Unfortunately, our patient doesn't fit into the group of low co-morbidity, but in the group of high co-morbidity. If we look at the guideline from our friend from the US, well, it is also somewhere as a IIB recommendation—you should explain to me, Michael, where is the B coming from. Well, according to the guidelines, we have to do something, but it's a very high risk for surgery.

So, now we looked at what could be the criteria for success—and Mike already showed you the success criteria, ventricle was not too large, tenting was not too important, coaptation, we're almost there, posterior angle, we're almost there. Well, you should not be completely anaesthetized by, you know, non-magic numbers. Anterior angle was not perfect, and the sphericity index wasn't the right site. So, clinical indication was correct and anatomical criteria for success of surgical annuloplasty was there. Here I show only one CT, but really the CT is analyzed in depth to give you the size, but to show you also what should be the end size view. Unfortunately, I do not have this scan here, but it shows you also, if you are planning to put your screws, if you are going to go into the fat tissue, or if you are going to go into the muscles; it also shows you some relationship with a coronary. So, in this case it was not.

So, the advice was to put an implant Size E, it means it's good for this patient, and the number of anchors planned and done were 14. The procedure time was a 90-minute procedure. The procedure, I won't insist, you know, you've already seen it from Georg. You have to do that and then you cinch, cinching was there. We went up to four in this procedure, you see, and here you can see what happens, but it's always very conventional, I won't insist. You see the MR before, which is really severe, and the MR after is really trivial. So, and here the reduction in the septal-lateral dimension was 20%.

So, let's say it was an immediately successful procedure. But, what is the interest of this very short presentation is to see what happened to the patient during the year. In point of fact, this poor lady was hospitalized very often before, was not hospitalized any more for heart failure during the following year. That's a very important result. This lady was really functionally improved. That's very important. And she improved the six-minute walk test. Unfortunately, we do not take care of the legs, and now she had some leg pain and was not able to exercise at one year follow-up, but you see that the scores are also improving. So, clearly, there's a dramatic functional improvement, and in term of cost, it is a change, having no more heart failure hospitalization.

If you look at the MR, the MR was severe to a definitely mild (inaudible) at discharge, one month, six months, and nothing was seen. After one year, you see the decrease in the septal-lateral. The cinching was still there. Of course, the PISA decreased dramatically and there are proofs that MR disappeared in this patient. What about the ventricle? Well, there is a slight decrease, a very slight decrease in end-diastolic dimension. If you look at the volume ejection fraction, it happens very often, these poor—they are very poor ventricles, they don't like closing the mitral, but then they recover, and now you see the ejection fraction went down and now is going slightly up, but very important finding, is also consistent with the clinical improvement. The pulmonary systolic pressure was decreased by 100%—no 50%, so there is a dramatic improvement in pulmonary pressure.

So, it's a very brief presentation, but showing clearly that with this procedure—and you're going to see during the result presentation, which is safe, which takes some time, but okay, can be done—that after the procedure, if you are able to target the good candidate—not too sick. Like, this one was not too sick, but deserves an additional treatment to medical therapy and CRT—the patient will derive a real and consistent clinical benefit, we know, up to one year.

So, thank you for attention.

Prof. Eberhard Grube:

Thank you, Alec. That was wonderful. Thank you so much.

Prof. Alec Vahanian:

Only thank you. No more? Oh, okay.

Prof. Eberhard Grube:

Otherwise, I'm going to get—you know, people get suspicious about me.

Male Speaker:

They already are.

Prof. Eberhard Grube:

They already are. Good. So, can we add a few more comments on the questions? The question is, is there an increase in the mean gradient, Georg?

Prof. Georg Nickenig:

No, we haven't seen any increase in the mean gradient whatsoever. It's not like in the MitraClip cases, in my experience. I don't know about the other centers, whether you have encountered any increase, and I have to look at the whole data set and I haven't seen that.

Prof. Alec Vahanian:

No, I don't think so. Probably, Karl-Heinz, you can answer, but I don't think so.

Prof. Karl-Heinz Kuck:

No, there is no gradient.

Prof. Alec Vahanian:

Maybe we never—probably, I'm not aware of any testing during stress echo, but I don't think so.

Prof. Francesco Maisano:

I think what we reach at the end of the procedure, in average, is a ring Size 30. Ring Size 30 is equivalent to a mean gradient about 3 in most patients after surgery.

Prof. Eberhard Grube:

Okay, the next question, does deep anchoring in the ventricle cause arrhythmias?

Prof. Francesco Maisano:

We need an EP guy here. Karl-Heinz.

Prof. Karl-Heinz Kuck:

No, I think it's a good sign. If you don't see ventricle arrhythmias at the time when you screw in, then you're probably not in the ventricle. So, every time that you put your anchor into the tissue, you cause arrhythmias, short runs of ventricular tachycardia, ventricular premature beats, which of course doesn't

need to be treated, but it's a good sign; it's a good physiological sign that you're really touching the left ventricle, instead of just going somewhere within the annulus. The day after, we have never ever seen any severe arrhythmias. It's just an acute effect when you screw in.

Prof. Eberhard Grube:

Okay, the next question is a tricky one. It's a nice one, a tricky one, but we need to stay in time, so whoever takes it, please, can you explain the indication versus the MitraClip? Who wants to take that?

Prof. Francesco Maisano:

I think it's a very nice question. I think I would be very biased in this answer. But, first of all, there are different things. Number one, this (is treating the annulus, the clip is treating the leaflets. That means that an operator who can see the position of the annulus in echo would be eligible to do the procedure. You don't need to understand much more from mitral valve disease. So, this makes this procedure probably learnable from the majority of the operators in the cath lab. Number two, this procedure doesn't close the door for further treatment, either with a clip or with valve replacement. With clip, we still don't know whether we can do any valve replacement; I doubt it.

The other important point is about efficacy, which one would be more efficacious, and I think, to some extent, this annuloplasty is ideal for patients in the earlier stage with less tethering. MitraClip would work better in patients with tethering, but I think in these patients, probably, MitraClip will go in antagonism with a replacement. So, really, I see complementary; I see antagonism, but it's too early to give a definite answer to this question.

Prof. Eberhard Grube:

Georg, anything to—or, Alec, yes, Georg.

Prof. Georg Nickenig:

Maybe just one word of caution. We have implanted right now, I think 48 Cardiobands versus more than 20,000 MitraClips, so we have to live up to this over time, but I couldn't agree more. I think if annular dilation is the most important and prevalent pathology, then taking the annular dilation with the direct annuloplasty device is, I think, the way to go, and not doing a MitraClip which gives you not a chance to do another procedure, the door is still open. On the other hand, if you have a lot of tethering, you won't be able to resolve the MR issue with a Cardioband, we have seen that also in patients, and if you have a severe degenerative issue on the valve itself, then it doesn't make sense to use a Cardioband.

Prof. Eberhard Grube:

Alec?

Prof. Alec Vahanian:

No, I fully agree with what was said, but really we have to move forward and step into the future and think combination. I'd like to ask Mike and Francesco…

Prof. Eberhard Grube:

Not yet.

Prof. Alec Vahanian:

If you think combination, what will be your strategy?

Prof. Eberhard Grube:

Guys, can we…

Prof. Alec Vahanian:

Maybe you can use both, are you willing to…

Prof. Eberhard Grube:

Can we just defer that to the end, because otherwise we…

Prof. Georg Nickenig:

Only Eberhard asks the questions, right?

Prof. Eberhard Grube:

No, we're getting a little bit tight on the schedule. Alec, can we defer that to the end?

Prof. Alec Vahanian:

Yes, we can.

Prof. Georg Nickenig:

Yes, you can have a combination.

Prof. Eberhard Grube:

Yes, you can do the combination, that's perfect.

Prof. Alec Vahanian:

Okay, we can go…

Prof. Eberhard Grube:

So, now it's my please and honor to introduce well, he doesn't need an introduction, Karl-Heinz Kuck, a good friend in good and not so good times, and sometimes tough times, 12 months results for multi-center CE mark clinical study.

Prof. Karl-Heinz Kuck:

Yes, Eberhard, ladies and gentlemen, it is my real pleasure, on behalf of the Cardioband investigators, to give you a short summary of where we stand with respect to the overall results. So, these are my disclosures.

I think this is an experienced audience. I just would like to remind everybody that patients that suffer from severe mitral regurgitation have a poor prognosis. This is a summary of a rather recent publication that

shows to you that the one-year mortality in patients suffering from severe mitral regurgitation is 20% and the five-year mortality is 50%, as shown in dark blue, and if you add, in light blue, the rate of hospitalizations, then you can see that after five years 90% of these people have to be hospitalized that don't die. So, it's a severe condition that requires treatment. If we look to what treatment options are available, and this has been discussed very nicely by Michael Mack, then we can easily appreciate the sicker the patient is, if the ejection fraction is below 20% to 30%, the percentage of patients undergoing surgery is rather low at 6%; it improves up to 18% in those that have a better ejection fraction, but the overall number in this rather large series is only 11%. So, there is urgent need for other treatment options, as we have discussed.

Now, the development to what's this percutaneous device was a very physiological one, I would say. As you can see on the left side, this is more or less the same device—it's called the Cardinal device. The only difference is that this is a complete device; it's a complete band or complete ring that has been implanted surgically, but it's the same Dacron band as we are using now with the Cardioband, the only difference being that we are just covering from the anterolateral commissure towards the postreceptor commissure, as shown here in this slide, and the other difference that we also addressed, that this is a ring that is sutured to the annulus, and these anchors, meanwhile we are using, instead of 4 millimeter anchors, 6 millimeter anchors, and with these anchors, with the length of the anchors, the problem—the only problem of detachment has been solved. In addition, as you can see, there are the two distal anchors that are implanted today.

Now, it has been shown that, of course, a transseptal approach, in contrast to an open heart surgical approach, is better for safety reasons. Very much like in surgery, this is a supra-annular fixation of the device, and it has also been shown in the initial series that there is a significant reduction of annular dimensions that can be achieved with this device, very similar as to a surgical ring, to a Size 28, and as we discussed just recently, preserves you of doing further interventions over time, like clipping, and maybe also other interventions, whatever would come up there in the future, because you leave the leaflets alone, and you're not touching the chords.

Now, this is what Eberhard Grube did address, how does imaging help to do the procedure today? As you can see, there is careful measurement of the annular size, based on CT imaging, which really helps to understand what size of device should be used in the individual case; so sizing is extremely important. It gives you the projections, as you can see here in the yellow view, but also in the ERO view, we do have these projections, they are doing the intervention, so that we'll precisely know where to position and how the position should be. It helps us to locate the transseptal puncture. That puncture should be posterior, but it should be significantly lower, as in patients that undergo clipping, at the range of 1.5 centimeters to 2 centimeters above the annulus, and it really helps you with a 3D preview to position the entire system.

Now, it's a four-step procedure. The transseptal puncture, as has been addressed, then you insert the system, you implant via the delivery system, and then at the end of the day we have the adjustment tool to really come, during the beating heart process, to the optimal reduction of the mitral regurgitation.

I'm not sure, for time reasons, I probably should skip—I have a short video that I wanted to show, but I think for time reasons, we go over it. Georg showed very nicely this case, so I can skip my video. But, the learning that we have is—and I think you have seen a couple of examples. This is just one example in our laboratory, where you can immediately appreciate, just by looking at the change of the dimension, of the annular dimension, the significant reduction. In this particular case, there was a reduction based on the adjustment of 40% of the annular dimension in this particular patient.

Now, this is the example. There is a significant reduction of the dimensions, as shown, but this is really associated with a significant reduction in mitral regurgitation, and that's exactly what we would like to see. So, you have this stepwise approach, and once you see that the mitral regurgitation is almost completely eliminated, you can stop at this point in time and leave the annulus alone. So, this, for me, it was a great

learning, to see how this stepwise approach really helps to completely eliminate the MR, if the patient is correctly selected for the procedure.

Now, the European first-in-man trial now consists of 48 patients. I'm showing the result of the early 45 patients. It's a single arm multicenter prospective trial to evaluate the performance and safety of the Cardioband procedure for repair of functional mitral regurgitation. Now, these are the hospitals that were included. We have started with three hospitals. At this point in time, there are six hospitals involved in the procedure and more are ready to go.

The major inclusion criteria are shown here. We are looking to patients with moderate to severe functional mitral regurgitation, with an ejection fraction equal or above 25% and end-diastolic diameters of less than 70 millimeters.

Now, the primary endpoint of the procedure is the safety endpoint, with the overall rate of major serious adverse events at hospital discharge time at 30 days. In addition, what are the definitions of major serious adverse events? It's a combination of death, myocard-infarc, cardiac tamponade, device-related cardiac surgery, and stroke. Furthermore, we have performance endpoints, such as the technical success rate, the technical feasibility of the device, and of course the ability to reduce mitral regurgitation once a reduction in annulus size has been demonstrated.

The same is done for safety reasons as secondary endpoints up to 20 months following the procedure, and we're also looking to performance endpoints with assessment of mitral regurgitation severity at six months, 12 months and 24 months, functional parameters such as a six-minute walk at 6, 12 and 24 months, and quality of life parameters at 6, 12 and 24 months.

Now, the patient demographics as shown in this slide, the mean age is 71 years. They were 34 male patients and 11 female patients. The baseline New York Heart classification shows an advanced heart failure patient population, with 87% of these patients being in New York Heart Failure Class 3 and 4. Twenty-four patients had ischemic underlying heart disease, 70 non-ischemic underlying heart disease. The end-diastolic diameter, on average, was 61. The ejection fraction actually was rather low, at 32%. It's also important to mention that these patients were suffering from significant co-morbidities, as shown on this list.

Now, the device really achieved what we wanted to achieve, which is a significant reduction in the dimensions of the annular, as measured with the septo-lateral dimension, as shown here. Yes, the answer really is, yes. As you can see for almost all of these patients, this primary endpoint could be achieved if you looked to the performance of the device. On average, there was a 20% reduction in the septo-lateral diameter, moving from 36 millimeters down to 29 millimeters, so, on average, 30 millimeters of this diameter at the end of the procedure.

This was, ladies and gentlemen, associated with a significant reduction in mitral regurgitation, not only as measured at discharge of the patient, but this effect could be maintained at one month, six months and one year, at least for those patients that are still in follow-up. Now, if you look to the one-year results, as you can see, 94% of the patients had mitral regurgitation either equal or less to 2+ at 12 months, which I believe is really a very impressive series of results over time in a consecutive series of patients.

This was associated with functional improvement of these patients at six months for the six-minute walk test, quality of life parameters, and also for New York Heart classification. As you can see, there was a significant improvement in the six-minute walk, from 250 to 330 meters; a significant improvement also in the Minnesota Living Heart Failure qualification, from 38 to 18; and there was also a significant improvement in the New York Heart classification, and that improvement was not only shown at 6 months, but could be maintained at 12 months, as indicated in this slide.

Now, if you look to the safety of the device, and the procedure, we had two deaths in this series. One patient was dying from a hemorrhagic stroke who was under treatment therapy. The second patient had to undergo mitral valve surgery because of detachment of the device in the early series, when the anchor lengths were only 4 millimeters instead of 6 millimeters, the lengths that we are working at now. There were some bleeding complications, as we see in this type of interventions, two patients had renal failure, but there was no infarc, no respiratory failure, and no cardiac tamponade in any of these patients.

So, if you look to the overall results in this early 45 patient population with respect to the effectiveness of the procedure, as you can see, at 6 months and 12 months there was a significant reduction of mitral regurgitation in 86% and 94% of the patients. The procedure was successful in all of these patients. There was a significant reduction of mitral regurgitation which was associated with the reduction of the septol-lateral diameter in the range of 20% in 43 out of the 45 patients. Again, there was no procedural mortality and there were two patients that died before discharge. There were no device-related major adverse events, as we mentioned, very much like for the MitraClip procedure.

So, before I would like to finish, I would like to share this one case with you. As you can see, a 69-year-old male with underlying ischemic heart disease, ejection fraction 36%, end-diastolic diameter 60 millimeters. The patient has significant co-morbidities. After 12 months, there was a significant reduction of the septo-lateral diameter, from 4.56 to 2.77, which was associated with a significant reduction of mitral regurgitation, improvement in the New York Heart classification, improvement in quality of life, improvement of six-minute walk, and, most importantly, also associated with reverse remodeling of the left ventricle, with a decrease of the end-diastolic volume by 23% and of the end-systolic volume by 43%, as shown in this slide.

This is the evidence for the significant reduction of the septal-lateral diameter, this is baseline value, and this is at the end of the procedure there was a reduction from 41 to 25 millimeters, which is a 37% reduction in diameter, and these are the TTE data one year after the procedure, with a reduction of moderate MR to mild MR after one year.

So, in conclusion, ladies and gentlemen, Mr. Chairman, the transcatheter surgical annuloplasty device, the Cardioband device, is a procedure which is feasible; it has a very nice safety profile which is similar to equivalent transcatheter procedures; it is associated with a significant and consistent reduction in septo-lateral dimensions and that is again associated with a significant and consistent reduction in the severity of mitral regurgitation. The reduction in mitral regurgitation is stable over time and is associated with clinical improvement of these patients at six months but also at 12 months, and I think that's something what we believe is important that it remains open with this procedure for future interventions.

Thank you very much for your time.

Prof. Eberhard Grube:

Thank you very much, Karl-Heinz, for this overview. Now we come to the next speaker, a wonderful speaker, a very eloquent speaker, Professor Frank Ruschitzka from Switzerland, talking about device and medical therapy intervention and functional MR. Welcome.

Prof. Frank Ruschitzka:

Thank you, Eberhard, for the kind words, thank you all for having me. I feel like being on a party and I'm being enthusiastic about it, but let's see these five, seven minutes I do have and some cautionary words from a friend. I love Michael's words when he said "This is a disease of the left ventricle: functional regurg," and that is something a little bit out of your comfort zone, you guys. You guys are valvular interventionalists; you love TAVI. I love TAVI too. Even TAVI is HFpEF, is heart failure and we have low-flow low-gradients. There's a lot of heart failure in it but it is stenosis, fix it, patient better. You go in functional regurg it's a different ball park; it's a different story. Does that mean I'm less enthusiastic about

it? Not at all. I just offer you help as a humble heart failure guy. That's what I would like to talk to you about because if you will see potential for Cardioband, and I see it, I'm flabbergasted. When I look at these pictures I see opportunities; I see potential and I see challenges, but let's do that together. Why? Because FMR is a huge problem. That is, for me, the new frontier in heart failure; it's not the coronaries anymore. I do come from the place where Andreas Gruentzig in '77 did the first angioplasty. We are actually, I'll tell you, and you all will be called and in two years invited are going to do the 40 years anniversary party there, another one party, but there's a lot of cautionary tales from the way he developed the procedure, how carefully he took step by step with support of friends. But coronary interventions go down while heart failure goes up, in prevalence; it moves center stage. I think it's fair to say that heart failure and valvular disease will dominate cardiology in the years to come.

Certainly. Why is it a bit different than the rest? Because heart failure when you ask yourself—and we had a symposium earlier today I said the same thing there, said "If you ask a patient you want to have cancer or heart failure many would go for the former but in heart failure the prognosis is grim; 50% of our patients are dead within three to four years. With the exception probably of small lung or pancreatic carcinoma, heart failure carries the worst prognosis." I see, I told you, the opportunities, because there is a tsunami coming of heart failure patients which is just massive. The companies see money; I see a need, a need to help them. If you just look at here of symptomatic patients, these are US data—we have the same in Europe—and just look at the New York Heart IV that means being symptomatic dyspnoeic at rest. This patient will trade a relief of symptoms for anything. He would even say "I will offer you a couple of months of my life if you just help me now." So, the New York Heart IV patients alone, patients would qualify potentially for a VAD, at 250,000 in the US. That potential, and in Europe the same and not talk about Asia and other places. So this is a million almost there. It's huge and it's growing.

The history of heart failure is like that; it's going to be stable, that's where you—in the beginning. Hopefully after decompensation you bring him back, stable, this is the time for meds, then he gets these bouts of decompensation and you have to help him through this in acute heart failure with certain drugs and devices but get that schizophrenic block out of your head that you'll say drugs or devices, they're one. We know that from stents. When we look at the drug-eluting stents we bring them together, we have very soon we will have CRT devices that deliver drugs. Don't think these are the meds guys and these are the device guys. We will move together and it's only that's how we advance the field. If you want to bring up a new drug or a new whatever device in heart failure you have to realize that the threshold is high; the bar is set very high. In stents, you get away with target legion revascularization endpoints which enriches the endpoint to win a trial.

In heart failure, we have seven lifesaving, mortality-reducing therapies; seven reducing mortality that started with ACE inhibitors and the beta-blockers, then the MRIs, then we have ICD/CRT—I count them as heart failure therapies, Karl-Heinz. We have the VADs and we have transplant. But at the drugs we have ACEs, beta-blockers and MRAs, and as we speak, because I have just to tell you where we are preparing, as we speak—and some of you don't probably realize that, there's a new drug coming as we speak now in my country, it just got Swissmedic approval on Friday, the FDA gave it a couple of weeks in approval, it's Entresto. This is a combined neutral and a peptidase valsartan inhibitor which reduces mortality. To give you an idea what we are talking about and what arena in heart failure we're working about is they reduced it with a P-value of seven zeros behind the comma. So this is huge. This were 150 deaths less in the active treatment arm. Hundred fifty—this is how many is here were less in the arm treated with this new drug. So, it's hard to sell; it will be a tough sell to just come for a 10 meter or 20 meter six-minute walk test improvement to convince regulatory authorities and the community at large to offer new therapy.

Think about that. But we have to work together because when you looked at the slides here mortality is still staggeringly high, and we need new options, so we have to work together on—it's very unlikely that we will have a new drug in chronic heart failure to come after Entresto has been introduced now so we will have to move and shift gears to valvular, to new frontiers. There is potential; this is where I see it, but to get there we have to work together. This is—and actually three quarters of our patients with heart

failure present with FMR and the big question is when? Timing. Timing is everything. When should we intervene? I don't know.

Back to Michael, and I saw Ted Feldman here and back to a comment of Georg and I bring that together, we have how many patients now treated with MitraClip here? Twenty-five thousand? Why is it that we have to ask a surgeon in Dallas to run a trial with Greg in the US to answer this question with 250 patient cohort and why have we not helped him with one of these 25,000 patients in Europe to come up with asking the question whether it helps? Whether we should intervene earlier? We should intervene better or interact or whatever? No we—this is no hindsight 20/20—this is a criticism and take that seriously. I'd said that before and that, Georg, don't take it seriously, Germany is part of the solution in devices but it's also part of the problem.

You have to really think about that. When we move forward, FMR—medical therapy improves FMR, beta-blockers, ACEs, whatever, so you have to work on the background of that. Karl-Heinz, you will agree with me, CRT, much of the benefit works by reducing MR, and unfortunately those whose MR you don't—could be a surrogate, could be closely related—you don't reduce MR with CRT. The so-called non-responders, they do worse. That's a problem. When you look at MitraClip we have some registries and blah, blah, blah, all good, nice to have, but no definite proof, but I'm waiting, bated breath for Michael's trial. This is—I'm—but honestly, doesn't it go to your pride that a surgeon has to run a cardiology outcome trial together with Greg in the US? We should have done it here instead of all these studies with MitraClip and that way for me MitraClip has an FMR no more data in evidence which would suffice for a guideline qualification than Cardioband—has little.

You have procedural safety's probably better proved now but improved benefit, you can tell me what you want, but I don't believe that. I'd rather believe in this. This is DMR, and this is FMR. I picked an American versus a European way. Is the evidence for functional MR there? Not really. Europe needs a bit of help. Why do we need help? Ted says—so I'm coming to an end—just give me two minutes, Eberhard; I'm finished in a second. But EVEREST I hear it all the time "Well we will have the data for MitraClip?" Do we really in FMR? In EVEREST we don't. DMR we do and FMR we don't have the data, but yet under the assumption we did have the FMR evidence, which we don't have, people adopted it and did it like crazy; more than 20,000, we missed it. Why I am saying that just because here's your opportunity. What I wish as a humble heart failure guy that now with the wonderful Cardioband procedure, do it better. Don't miss out on the opportunities which you've missed out with MitraClip. I want something now. Do it; get on. We embrace it. I guarantee you of my heart failure community the support. But I want you to do something which proves it in a clinical trial moving forward. So the MR reduction is there, Karl-Heinz have already shown that; you have seen efficacy, the functional improvement is hypothesis generating. It's not blinded; it's modest; it's fine; it's stimulating. I see potential. Let's do it. That's my last slide.

A friend who's cautionary in—a cautionary tale in here. Look at the CRT. I like what Michael said. I'm amazed, was flabbergasted hearing a surgeon talking about anemia. Well we know in heart failure, think CRT. CRT there's no such thing, Michael, as an unmitigated good; it's not. Not everything is good for everything; not one size fits all. Even CRT is not good for everything. The QRS sweet spot is above 140. I painfully proved that with my team when we published EchoCRT that below QRS you would actually kill patients. That does not mean that CRT is one of the most spectacular successes we've seen in heart failure therapy. Take that. Let's define the anemia, the CRT, all these lessons, define the move—the route moving forward, do it together and then we are there and let's walk the talk; not talk about the Heart Team, let's walk it together. That's what I am as a President of the Heart Failure Association love to see, that after all these years nobody was interested in heart failure and even the industries started buying companies because they see heart failure as a full circle. You have to go from meds to CRT to VADs to transplant to valvular intervention, and I want Cardioband to be a part of that, but do the trials; let's do it together and let's conquer it and then I think our patients will benefit. Thank you so much.

Prof. Eberhard Grube:

Okay. I think time is almost over. Frank, thank you very much for not only a very educational but also a very entertaining presentation. I think that it's important to mention of course that more evidence is needed. Trials are underway not only the co-op trial, there are other trials underway. But I fully agree with you, I'm also always very much disappointed that with all the interventions that we do in Europe that we are doing so badly in setting up a big randomized trial. So let's see how things will develop. Francesco, how to learn the technique and future directions.

Male Speaker:

But he's right and...

Prof. Eberhard Grube:

What do you need? The title?

Prof. Francesco Maisano:

No, a title I have. No, there was a question from the audience I wanted to answer.
Yes, we can answer here.

Prof. Eberhard Grube:

Okay.

Prof. Francesco Maisano:

So there was a question about septo-lateral dimension reduction whether this is real or just a reduction of the device. No, it is real. It is obviously measured by Corplab, and it is about 23% in average, there are patients who are 30%, 35%, other patients had less, but in principle this is what you get in most patients.

So, okay, so I have to conclude the session with one thing I have to say. We never spoke about the team. The team has been a mix of friends, excellent operators, excellent people who have been supporting me. I don't have time to express the gratitude to everybody. But there is also a good engineering team, a good management team behind the success—behind having achieved CE Mark. I have to share with Frank Ruschitzka the same opinion that having CE Mark doesn't mean much. I think the sky's the limit. This device can really change the world with the three patients with heart failure, and we will try to go in this direction.

The first challenge we have now is to make everybody able to do this procedure. This challenge I suffered all myself the day that I became Director of Zurich, yes, because I had no time to proctor anymore, and this was a difficult time for the Company and for friends who were asking me to go and help them in doing the procedures. But it was also an important step because we were forced to build a training program which I think is going pretty well. So, the aim of this procedure is to make the operator able to implant the band on the annulus from commissure to commissure. This is what you have to do, nothing else. No decision-making; no problems; no fancy intuitions. You just have to put this band in position without having complications. After that, you have to cinch it, as you cinch it DMR will go away. So this is—after the implantation, this is a basic MR. You cinch, cinch, cinch, MR goes, goes, goes. Whether this will have a clinical impact we will see, but at the moment what we need to obtain is a minimal MR after the implantation.

So the procedure is divided in four steps. Transseptal puncture we have seen before. It's a little bit different than for a MitraClip for instance, it is a little bit lower on the annulus anyhow with this planned on CT scan; there is nothing special. You still have to puncture in the fosoval (phon); it's nothing special. Then there is the deployment in the anchoring of the device, commissure to commissure and finally we implant a size adjustment. The—what you need to know is first of all you need to learn the anatomical

implant. This is planned on CT. There is also possibility to train on it 3D print of the individual heart. On CT scan, it is planned each individual step of the procedure. It is predicted the ideal plane of fluoroscopy. It is also predicted the ideal angle of the device targeting the annulus. So really there is very little place for improvisation, and we can really provide a lot of support to learn this procedure and do it fast.

The imaging is based on fluoro and echocardiography just like for other such interventions and there are systematic standard maneuvers that I will show you in brief in just few minutes here. There's a huge difference between doing MitraClip and Cardioband MitraClip requires dynamic decision-making. As you do the procedure you need to take decisions and you have to take decisions that sometimes are difficult. Second clip? Where to put the first clip? What is the outcome? Is it enough? Well, in Cardioband the difference is you just have to put the Cardioband in position, then you have to cinch. That's it; no much decisions.

This is how it looks. The first anchor everybody says is it the most important one. I also have to say it is the most important one. The good news is that's probably the simplest to implant because there is a simplified method. You have seen in the live case there is a wire which supports the first anchor implantation and then from the first to the last you will be supported by the previous anchor. So there is not so many degrees of freedom. After one anchor is implanted, it is a sequence of multiple anchors, and at the end again the annual reduction. So, part of the training is to understand the anatomy of the device and how it looks at fluoro and on echo using different echo modalities which are again very standardized.

CT scan you have already seen. It is planned to size the annulus. We implant the Cardioband at the same size as the systolic measure of the annulus. You plan the position of the transseptal puncture to where the easy and safe conductance of the procedure and then you have all the simulation of all the anchor implants. This is how the device looks at fluoroscopy with all the markers, which are important to guide the procedure safely and effectively, and this is again I don't go too much into the details but you can easily recognize all these pieces of the device.

This is how you maneuver the device. Basically you maneuver the transseptal sheet which is tearable and it allows navigation around the annulus. The other piece is the implant delivery system that you can steer to move in and out compared to the leaflets and to the annulus. Again, it is very standardized. In P1 what we do we just use the steering of the guide catheter and the transseptal steerable system, to navigate the first third , this is what you do, then you go in P2 you just have to pull back the system to go from P1, P2, P3, and then once we are in P3 you start the maneuver which we call hooking; that basically means that you are steering the guide catheter of the implant delivery system. The last part will be a release of the curves to achieve the location of the last anchor which is in posterior medial commissure.

So how to learn? You can—we have developed a special simulator that you can see here. On the left is a human implant. On the right side is a simulator implant. It's a simulator that can be put in a cath lab and simulates both fluoro and echocardiography and it is good to train the Heart Team. This simulator you can see it here in this picture, it can come in a training center for one and a half day, you learn the technicalities of the procedure and then you will be able to run your cases supported by one product specialist.

So I think this is more or less the study, what has been done until now. I think this is an important way in front of us. Many other opportunities are coming. The first one I think which is very important and is a great value is this joint venture between a valve company and a heart failure company to underline once more the importance of continual care, future direction of Valtech Cardio is towards degenerative MR, developing solutions for 3D impressions with DMR and also importantly applying the same technology on a tricuspid level.

I would like to thank everybody. We are a bit late.

Prof. Eberhard Grube:

Thank you very much. Thank you very much, Francesco. We come to the last. Mike is kind enough to wrap up quickly. I know we are very late, so my apologies for that, but I think it was still entertaining. Mike, please?

Dr. Michael Mack:

So I'll finish up by just making a statement in response to Frank about why we do a randomized trial in United States and not Europe. There's one simple difference. It's called the Food and Drug Administration. We have an FDA that made us do it, and is making us do it. But I would argue that—it's always fun to bash the FDA and everybody does it, but I would argue they actually are accelerating the field rather than inhibiting the field. I think the whole field of TAVI is much better off because of the strong evidence-base that we have of randomized trials, and I think the same thing will happen here. Very painful trial to enroll but it's significantly going to inform the field. You always have to be careful what question you ask.

Male Speaker:

Right.

Dr. Michael Mack:

What we're asking is, does mechanically fixing the mitral regurgitation add anything to optimal guideline directed medical therapy plus appropriate resynchronization therapy? It may be that we get the same answers we have with renal denervation that it adds nothing to three drug resistant hypertension so we may end up obscuring a signal, but I do want to acknowledge and applaud the FDA for requiring us to do the trial. So thank you all for a great session. It's been absolutely superb and...

Prof. Eberhard Grube:

One moment. Alec wants to say something.

Dr. Michael Mack:

Alec.

Prof. Alec Vahanian:

If you'll allow me, I just want to make a short comment: there are two trials, two randomized trials ongoing in Europe and we don't have any FDA but we have investigator (inaudible) trail, the RESHAPE-2 heart failure, in France, the MITRA-FR. They are enrolling quite fast as regards the MITRA-FR and hopefully will be the first one to finish.

Prof. Francesco Maisano:

MATTERHORN.

Prof. Alec Vahanian:

Okay.

Prof. Francesco Maisano:

MATTERHORN.

Prof. Alec Vahanian:

MATTERHORN, also, There are three. (inaudible) is in primary, huh. But we are also doing some randomized trial.

Dr. Michael Mack:

All right. On that note, we are going to end. The next session in this room will be chaired by Susheel Kodali and Philip MacCarthy, Achieving the Best Outcomes After TAVI. Thank you all very much.