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Remote Heart Failure Management of Patients

Reducing hospitalisations and mortality: myth or reality?

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JOHN MORGAN: WELCOME & INTRODUCTION

Good evening and welcome to this live webinar on Boston Scientific's hf- channel.com. We are going to talk tonight about the remote heart failure, management of patients. And I am very privileged to be joined by my very good friend and colleague Professor Martin Cowie, from Imperial College. My name is John Morgan, I am Boston Scientific´s Chief Medical Officer for rhythm management in Europe and also joining us from Arden Hills in Minneapolis is another good friend and colleague Yi Zhang who is Boston Scientific's Research and Development Manager for HeartLogic™ the United States.

So we are going to start off first of all with Martin telling us about the background to the use diagnostics and the management of heart failure patients. This is an area of great interest to Boston Scientific and it's fair to say it´s been an area of general disappointment in recent years because the evidence base, that supports the use of diagnostics in heart failure management has been rather thin in terms of the efficacy, in terms of preventing hospitalisation and reducing patient mortality. And the question before us is, are there things that are in our near future, that might change that? So first of all, Martin over to you: the use of diagnostics and the management of heart failure patients.

MARTIN COWIE: THE USE OF DIAGNOSTICS IN THE MANAGEMENT OF HF PATIENTS

Thanks very much John. So this has been a very interesting journey, trying to develop technologies that help us monitor patients better with heart failure. And this cartoon shows us what we all know in clinical practice that patient has variable level of symptoms and after a period of stability, often there are episodes of decompensation that require hospitalisation. So it is in everybody's interest to try and improve the situation and to use technology to remotely collect data, to make better

decisions and make sure patients live better lives and spend less time in hospital. And of course the concept of remote monitoring could be just as simple as telephoning patients, which can be very effective on its own. But also we usually think about this in terms of using equipment more complex than a telephone, to transmit data from the patient's home back to the physician/nurse team. It could be standalone equipment like weighing scales, blood pressure cuff etc or probably and more interestingly and more effectively using information from implanted devices with multiple streams of data, that should be relevant to physiology and the idea is you get the data to the physician, rather than the patient to the physician. It should be more effective, much more convenient for the patient but the challenge is, that you've said John, is trying to demonstrate how to do this and for which patients. This is the short list but it could be a very very much longer list for all of the things that we can in theory monitor. So there is no difficulty in measuring lots of different things and telemetry-ing that data back to the hospital for decisions to be made. That's not the problem, I think the issue is that we want to integrate that information into decision making and of course the ideal is to try and pick up episodes of decompensation much earlier so we can then give patients tips about maintenance of their lifestyle changes, about their diet, also using perhaps extra diuretics or getting them to come for an early clinical review. And all of this of course builds on the patient's self monitoring as many patients now with heart failure adjust the diuretics themselves depending on how they are feeling and their weight and this would be on top of this. But it has been a challenge to demonstrate how we can do this and what technology and at what stage in the disease condition.

So let´s very briefly look at some of the evidence that has accumulated to date. This shows just telephone monitoring and some very early studies and where usual care was not very good, very small studies, there was a hint that you could change mortality. Presumable by intervening earlier and also a strong suggestion that hospitalisation and re-hospitalisation rate could be reduced. So this was encouraging even with such simple technology as the telephone.

Moving then, to the standalone equipment- weighing scale, oxygen saturation meters, blood pressure symptom levels for example. A lot of the early small studies that were published in the journals at least, were very strongly positive in reduction of mortality and also hospitalisation. So we see this was published back in 2011 or so, there was huge enthusiasm at this time and the case had been proven but as we found out where we moved to larger studies, it's actually more difficult to demonstrate it. So I think there was a lot of publication bias, enthusiasts, editors that like small studies that are positive. So, just very quickly to fill in the landscape. Big study in United States Tele-HF published in the new England Journals 1600 patients plus, absolutely no difference to outcome with this first large randomised trial. Moving to Germany the TIM-HF trial which was published just a few years ago also, we were very tightly controlled with central tele-monitoring centre, once again no difference in any of the hard endpoints. But we noticed at that point, the patients had very mild symptoms that had heart failure for years, who weren´t on very good background therapy, making the point that you need to choose the patient population better, where you can make a difference. And in a more recent study, (randomised) which was published just last year in JAMA and this was in California academic medical centres, with coaching as well as telemonitoring and 6 months follow up

and for this standalone equipment, once again that has been no difference in hospitalisation and mortality. So pretty disappointing in terms of just the simple systems. Maybe it's not enough data, maybe it's not the correct data, maybe we can't interpret it. But at the present time, we can't translate it into better outcome.

So we will move then to the implanted devices and increasing our patients with a CRT or ICD platforms. And of course we monitor these devices for safety and battery levels routinely at the moment and that's great. But the question here for this evening is, can we use multiple streams of physiological data to manage the heart failure better, remotely? The idea's quite simple, as you can see in this example - the blue line shows you when the patient was admitted to hospital and you can see that actually up to 3 weeks before, things were going in the wrong direction. There was quite a lot of noise but you can see the trends were going in the wrong direction. And, in theory, you should be able to pick this up, intervene and stabilise the patient again and potentially avoid the hospitalisation. But we've also learnt - and this was DOT-HF study that I was involved with - where we had an alert to just transthoracic impedence we did change healthcare but it was an increase of hospitalisation by 79%. So the way we set up the system is hugely important and I don't like the term 'alert' and I don't think you like it either John because it means that people feel like they have to take action and sometimes that is not necessary. We can move to other systems where clever algorithms can actually identify signal from noise; and this is the publication in the European Heart Journal 3 or 4 years ago, where you can actually construct an algorithm post hoc that clearly separates high-risk from low-risk patients. The issue is integrating the information into the decision making.

One of the most recent studies that you and I did John, in the UK was REM-HF, just published in European heart journals so really hot off the press, 1650 patient followed up for an average of 3 years so much larger and much longer study. And this is using multiple streams of data from all of the major manufactures. And I'm afraid that once again, this showed that there was no evidence that changed this combined endpoint of all-cause mortality or cardiovascular hospitalisation. So certainly you can remotely monitor, the big issue is - how can we interpret the data or how can we have it interpreted for us, so clearly actionable items are identified and can make a difference. And, just to depress us even more, you can see all of the secondary endpoints in REM-HF were completely neutral, so no positive signal. And we are also monitoring and moving towards an era where we might implant the devices just for monitoring. This is a CardioMEMS system in pulmonary artery, you can see pulmonary artery pressure, a new therapeutic target, use medication differently, drive down the pressure and that translated at least in this one small study in the US to reduction of hospitalisation. So it's just at our finger tips but we just haven't quite got there, as of yet. Now what does the future look like? Well we will discuss this in the webinar but I'm sure technology will be there to support our decision making and help patients be more empowered and activated. But we haven't got there quite yet.

JOHN MORGAN BRIDGE

Martin, thank you very much for that fantastic expert overview of the background to the monitoring of heart failure. What I would like to do now, is just change gear a little bit and consider what it is about the HeartLogic™ concept that maybe importantly different and could perhaps give us different insights, different tools, for the remote monitoring of heart failure. And to do that, I'm going to speak with Yi about the management of the patients using the HeartLogic™ concept. So, Yi over to you.

YI ZHANG: HEART LOGIC™ Concept

Thank you Professor Morgan, this is Yi Zhang from Boston Scientific. Thank you Professor Cowie for the introduction for the background. It is my honour to introduce you to HeartLogic™ heart failure diagnostic service.

As Professor Cowie mentioned it is important to monitor the right parameters and also monitor multiple parameters. In the HeartLogic™ concept, it is looking at multiple sensors that's measuring the underlying physiology, associated with the common signs and symptoms of worsening of heart failure. Starting with heart sounds, S1 heart sound is monitoring the ventricular contract function of the heart and S3 evaluating the early the diastolic filing pressure. The elevated filing pressure appears to be the main driver of the worsening of heart failure. And pulmonary edema or congestion is also a major sign of worsening heart failure and that is what thoracic impedance is monitoring, fluid accumulation in the thorax associated with congestion. And also, often patients complain of shortness of breath and they often present with rapid shallow breathing pattern. That is what the respiration sensor is monitoring and then of course heart rate and activity is a general cardiac condition and patient status indicator. Among those sensors heart sounds and respiration are unique to Boston Scientific.

Those sensors, the way they are combined into HeartLogic™ algorithm, we are actually evaluating the absolute value of those sensors and assessing the patient risk for decompensating on a daily basis. In the meantime we are also looking at changes in those sensors, from the patient's baseline. And these two pieces of information are combined into a single index called HeartLogic™ Index which is displayed in the bottom chart. This feature will have a programmable threshold, that the user can tailor to their own preference and also to the patient. And when the patient is in alert status you will see this warning sign or this triangle sign on the display.

This illustrates the benefit of the multiple-sensor approach. Where you have only a single sensor, you could have some changes in the sensor signal irrelevant to worsening of heart failure, this indicated thoracic impedance in the 2 cases here - both are from the study MultiSENSE that we conducted.

If you go to the next slide, you will see multiple sensors evaluated in the MultiSENSE study that was developed into the HeartLogic™ index. Where you have concordant changes from multiple sensors,

as illustrated on the left side, which resulted in the HeartLogic™ Index. There you have confidence of the worsening heart failure happening is much higher as compared to the case on the right, which is impedance-only alert where no clinical events occurred. So by combining sensors that's relevant to worsening heart failure and looking at concordant changes we were able to improve the performance of detection, very much which Professor Cowie will demonstrate next.

On the LATITUDE, the remote monitoring system you actually see a comprehensive report. Which will demonstrate on the top, the HeartLogic™ Index. And then the current base value is displayed as bold number 54. In this particular case, this patient is in alert status and the contributing trend, that contributes to the alert will be displayed, in the bars underneath the HeartLogic™ Index. In the shaded area in each of the bar, indicates the contribution portion of each of the sensors into the alert. On the left side there's S3 heart sounds, S1 heart sounds and also on the top 3 trace on the right, impedance, respiratory rate and heart rate, those 5 trends are contributing trends into the HeartLogic™ alert. Besides that, we also incorporated other diagnostics available on the device for the user, to have a comprehensive view of the patient. The couple of trends that's not displaying data, was just missing data for this particular patient in the trial. With that I will get back to Professor Morgan and Professor Cowie.

JOHN MORGAN BRIDGE

Yi thank you very much for that great overview of the nuts and bolts of how HeartLogic™ actually works. So what we now want to do, is to discuss what potential this new technology has on improving on the relatively disappointing outcomes of the earlier heart failure management studies that Martin alluded to. So Martin is going to speak now about the evidence base that has currently been developed to support HeartLogic™'s claims to be potentially of value to hearth failure management. And then we will look to the longer term future, of how that potential could be realised in improving outcomes for heart failure patients. So, Martin.

MARTIN COWIE: MULTISENSE STUDY

Thank you very much, John and Yi. So its very exciting to watch the development of this new approach and as you've said it's about physiological variables that physicians can connect with in terms of patient activity, heart sounds, respiratory rate etc. so it kind of makes sense at a basic level and it's nice to know that it has been developed in a very robust way. So, people should look at JAAC HF and relatively recently and the design paper was published and this is where actually they prospectively set up to collect data and to develop the algorithm and then validate it, in another group of patients. So this is really state of the art development of this algorithm - we have learnt from the past. So you are collecting data from the Boston device using it collecting remotely and developing this algorithm and testing it, in another group of patients. And what they have found in this, which is very exciting, is this curve here - and if I can just explain it for a second or two. So there's always a compromise between sensitivity and the unexplained or false positive alert. Physicians don't like false positives, it worries the patient, the physician and action is unnecessary.

They don't need too many of those to switch them off entirely. So it's good to see that you can get a very low level of that, combined with very high sensitivity for a meaningful heart failure decompensation. And looking at the curve and alert level threshold of 16 seems to optimise this compromise between sensitivity and unexplained alert rate. And certainly it was much better than the designers of the studies set out to prove, you can see it there, in that box there. Very much higher than they pre-specified, they wanted at least 40% sensitivity. They got 70%. They wanted below 2 unexplained alert rates and they got 1.47. So, real success in the development of this algorithm so far.

What's going to happen now, the FDA has just approved the protocol and I am part of the steering committee and very excited about this. Where the FDA has said they love the algorithm, we like what you are trying to prove but you need to prove this. So there will be a phase 1 of this MANAGE-HF study so please look out for discussion of this. Phase 1 is where we are going to optimise how physicians and nurses should act in response to the HeartLogic™. And then in phase 2 we are going to robustly demonstrate, we hope, that if you give this tool into hands of physicians and nurses, you can make a meaningful difference to the patient outcome. And that will be a study between 1500 and 2500 patients, so very respectable indeed. So, everything is to play for and this looks extremely exciting, we've learnt from the past, the algorithm looks really clever, lets hope it quickly translates into better outcome for patients and easier decision making by physicians and nurses. And on that point, I'm going to hand back to you John, thank you very much.

JOHN MORGAN: MODERATING Q&A

Martin, Yi, thank you very both the very robust introduction to HeartLogic™, the details of the technology, the outcomes of the development so far and the potential for the development of future evidence base. It seems that this technology does have very significant potential to help make us, enable us, to better manage heart failure patients. With that in mind, I would like to ask those of you who are listening to us and watching us, whether you have any particular questions that you would like to raise about HeartLogic™ and the remote management of heart failure more generally. I have available to me, the questions on the screen so whilst I'm waiting for an initial response. Let me start of by asking you Martin.

Q1: How do you see this being used practically in terms of heart failure management? How would you integrate this into your clinical practice?

Well, I use remote monitoring quite a lot with different systems over the years. I think it has to be part of a modern heart failure service. That actually if you have a device, then you do monitor them obviously for safety reasons but you can actually use the data, we hope, to make better decisions. So for example I have some patients with standalone equipment, many patients with implanted devices and a few patients CardioMEMS. And all of them on the different platforms, we look at the information, and we see if it's telling us that the patients are going off or action needs to be taken and the heart failure nurse team is very used to doing that. So I would see that as a modern digital

approach to heart failure management and it's just a sensible way forward. What we've lacked up until now though is a killer algorithm that says this is the best one to use. This one is really easy to use, it won't give you a false alert but when it does tell you there's something going wrong, you do need to act and you do need to drill down and find out what's happening and then act on them. So I think that is the way of the future but we need to demonstrate this really clearly.

Q2: So I have a question here, which I think might be best directed to you, Yi. The question is – How can I understand the impact of each sensor in the final index in HeartLogic™? What is the weight of each sensor in contributing to that number, which is the HeartLogic™ score?

As I've shown on the LATITUDE heart failure report, when the patient is in the HeartLogic™ alert state, you will see those contributing trends; you will not actually see them when they are not in the alert. And then in each of those boxes, if that particular trend contributed to the alert you will see a graded area that shows the level of contribution or the strength of changes in that particular signal, relative to the maximum level of signal that sensor can contribute to. So by looking at that shaded area, you can see what sensor triggered this particular alert and if you're interested you can go into individual trends. Underneath the HeartLogic™ index, you'll see what the signal change look like compared to the patient base line.

Q3: Very good, thank you very much, so I have another question here, probably should go to Martin. Can we state the body weight and blood pressure monitoring are now obsolete in daily practice?

It's a very good question, I think a systematic usage for every heart failure patient is obsolete. I think we've done 3 large randomised trials, that have demonstrated no difference. That's not to say of course, with carefully identified and tailored patients it might be useful. And I think you're probably like me, I've got some patients who struggle to identify fluid build up, which is quite obvious when you see them in clinic. And they can't get their shoes on and they still haven't noticed that the fluid is building up. There I think weight monitoring is probably sensible. But the routine approach to every heart failure patients is just a lot of data, a lot of effort and really doesn't deliver what the textbook says it does. So we really do need to change the textbooks and get with it.

Q4: So another question, I think here for you Martin. How should I react once I see an alert? This is picking up on the conversation that we had before and you mentioned about the issue to do with calling alerts "alerts" - this a panic button. Should I directly call the patient for consultation, should I review the patient myself and look at each of the sensor values or do I just follow the patient more closely? What does "alert" really mean do you think, for what you've seen so far of this technology?

So I've looked at the data from MultiSENSE and seen examples from it but of course I have not used it in my own practice yet but will do very shortly. What is clear is, it does give you quite a lot of

advance notice so I don't think you have to throw your hands up in the air in horror and start phoning an ambulance for these patients. But you do need to drill down to the different components of this and find out what's happening. Is it the patient activity what is going down?, quite often it's the heart sounds, that their intensity is changing. And this is a level that you wouldn't pick up with your stethoscope but it suggests that cardiac function is changing, pressure is probably rising, so you need to pay more attention to the data for while and if things continue in the wrong direction, you probably do need to phone the patient. Are they taking their diuretic? If they are, then you need to drill down to the information about compliance, about their heart rhythm are they having episodes of atrial fibrillation etc, have they changed their diet. So at some point you will have to collect extra information. But I don't always think it has to be face to face. And the great thing about the HeartLogic™ is that for many patients you get quite a lot of time to do these things. Which is advance warning so it will be very interesting as this rolls out, how we make sense of this. Phase 1 of the new study is exactly that question. How can you drill down and make really intelligent responses to the algorithm and that will be fun to work out.

Q5: So it says here, here's a question, I think Yi. Which you may want to answer. When will HeartLogic™ be available in current devices? Yi can you just explain to everybody, where HeartLogic™ is, in the technology that Boston has available at the moment? Where do you find it, on what devices?

HeartLogic™ is available in the Resonate family of devices, including CRT-D and ICDs, also known as NG4. It is currently CE marked and has also received FDA approval. It will be available limited this year, pilot activities and also clinical studies. It will be fully launched in 2018.

Q6: Thank you very much. So here is another question, I think this should be answered by you Martin. If we assume the HeartLogic™ algorithm proves to be very effective at identifying well in advance, those patients likely to have a heart failure event. What do you think the impact will be on clinical work load?

It's a good question and in the past I was always told that, it will be a swamped with a tsunami of data but in actual fact, these systems are quite clever: they will only identify the patient where things are going in the wrong direction. Once you get used to looking at remote data, it doesn't take very long to drill down and see what's happening. So, for example I had 200 patients in the REM-HF study and by the time the nurse was experienced at looking at, it was only a few minutes each week to look at all of the data. So I think it's frightening in the concept but it terms of practicalities, as long as you set up the system correctly it doesn't swamp services. But it is a very good question, you can't just take a technology, drop it into your standard service and think it's going to work. You have to think about who is going to look at it. Do they have the competence to look at it, if so are they empowered to take action or are there other steps that slow them down. So you have to think about the pathway issues but actually once you've done that, and supported them, it's actually relatively straight forward and not as much data as you think. What I don't like of course is, is SMS coming

from systems to individual doctor's phone on every single patient, every single day - that is madness and I certainly would never introduce that into a service. But it is certainly possible if you think about it.

Q7: So and here's another question, I think maybe again for Martin. How do you think patients should be involved in the use of HeartLogic™ and heart failure management? Should there be some sort of patient interface?

It's a great question and I think the landing zone for all of this, will ultimately get rid of the expensive nasty doctor, and the nurse etc. and actually get the information to the patient. Why can't they in their smartphone have an indication "have you taken your meds?" "do you need to take more diuretic?" "do you feel as well etc?" and actually that kind of feedback loop is with patient. Only if that doesn't work or it becomes more severe, you actually involve the healthcare professionals. What we are talking about is someone living with heart failure, hopefully for many years, being increasingly expert and informed by technology to keep them out of hospital and managing their own condition and getting on with their life. So that is the ultimate goal. This is probably the halfway step until we gain more experience.

JOHN MORGAN CONCLUSION

Very good. So I think this has been a very, for me, interesting and useful discussion. I'm very grateful to Yi and to Martin for contributing to this, maybe it would be possible for us to wrap up at this stage. I think it is very difficult to come up with any very definitive conclusions about remote monitoring because it's fair to say that, the studies to date have been somewhat disappointing in terms of the outcomes and it may be that HeartLogic™, which clearly has enormous promise because of its sensitivity and specificity - a sensitivity of 70% for an only inappropriate rate of 1.47 events per patient-year; of up to 30 days advance notice of heart failure events it clearly has enormous potential as a tool for predicting heart failure deterioration. One of the things we now really need to do is to understand how best to integrate this into clinical practice and to deliver the evidence base through clinical studies that shows that this can deliver the goal of better heart failure management. And as Martin has said look out for the design studies for Manage-HF and ultimately the outcomes of Manage-HF and other supporting studies. So thank you to you all for listening to us and watching us on this webinar and thank you to the team that put it together and thank you most of all to Yi Zhang and Professor Martin Cowie for their time and eloquence this evening and goodnight.