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Reviewing the updated European Society of Cardiology (ESC) guidelines on type B aortic dissection

Aortic disease is often associated with very poor outcomes and, therefore, rapid diagnosis and decision-making is critical. In order to ensure that physicians are equipped with the right tools to effectively manage their patients, the ESC has recently updated its guidance on the diagnosis and treatment of aortic diseases (Erbel et al. *European Heart Journal* (2014) 35, 2873–2926). Following the release of several important studies in type B aortic dissection, such as INSTEAD-XL, *Confluence* spoke to Professor Christoph Nienaber, University Hospital Rostock Heart Centre, Rostock, Germany, to see what has changed in the guidance around this condition.

Why are guidelines important in clinical care?

Christoph Nienaber (CN): In general, guidelines help younger or less experienced doctors to understand better what they are doing. Guidelines are not law or are not something you have to do, but give a lot of orientation. They provide advice on what to do, what to avoid, where to be cautious and when to consult more experienced or specialized doctors in their field. Guidelines help physicians to make structured and justified decisions about whether they should follow or not follow a given treatment strategy for a particular patient.

I think medicine, particularly cardiovascular medicine (and especially cardiology), is now specializing to such a degree that people don't know what the next doctor, with different areas or different specialities, thinks and does. I think guidelines help you to identify and realize your limitations and find the way through the jungle of various diagnostic and therapeutic options.

Guidelines also help doctors to be aware of the abundance of these options currently available and to properly select the appropriate option for a given patient. A patient has to rely on his doctor 100%, as not many patients really understand the subject themselves, so it is a matter of improving quality to have guidelines at hand and using them properly. It doesn't mean that you need to follow every guideline but it is an excellent orientation.

Why has it been necessary to update the guidance for type B aortic dissection?

CN: Over the last couple of years, registries, as well as some small trials, have provided new data on the imaging, diagnosis and treatment of type B dissection, in particular with regards to the, so-called, uncomplicated type B dissection. There is still some controversy and debate, however, regarding what particular type B dissection should be considered uncomplicated or complicated. The boundaries are blurring these days as there are more elements of complication that are now better identified and understood. Over the last 4 years, the community has better understood those patients who might be at risk and what might be a potential future complication, even if it is not present at the time.

Who is involved in the development of these guidelines?

CN: It is a mixed group, from active surgeons that treat type A dissections openly using classic surgical techniques, through to diagnostic specialists from radiology and cardiology, and vascular surgeons and interventional cardiologists, who treat dissection in Europe. We were one of the front-runners in this regard, because I, as an interventional cardiologist, became interested in this area some 20–25 years ago and basically followed this through the decades. We all participated in this really wonderful group of Guideline Committee members that met two or three times in various places and had lots of

telephone interviews and telephone calls in the last couple of years. The whole group worked together for almost 3 years to create these using standardized trial analysis methods guidelines.¹

Angina is another case, again managed with many of the same drugs. If people have definite chest pain symptoms and breathlessness, they will have a higher likelihood of taking the drugs. As you say correctly, in both of these scenarios one of the main reasons for increased compliance is that patients feel the benefit from the drugs, whereas they cannot see an immediate advantage in blood pressure reduction. It really takes quite an in-depth analysis to understand the long-term risk and potential risk reduction effects for any cardio- and neurovascular adverse events that a fall in blood pressure has. These may only affect you in 10 or 15 years' time, reducing the chance of a stroke, but actually taking that on board when you are younger, it is often quite difficult.

What information do the guidelines provide on the diagnosis of these conditions?

CN: They offer, basically, a diagnostic decision-tree for patients with acute chest pain or suspicious symptoms that are considered to at least have a 'rule-out' or are actually checked for aortic disease. We are dealing with patients that have, of course, a medical history, a clinical presentation in the emergency room (ER) or clinic (if the patient is elective) and, if they are, haemodynamically speaking, in a stable situation, you basically go by probability of aortic disease or pathology. There are patients with a high probability of aortic disease and patients with a low probability of aortic disease, and thus an imaging session is very important in the diagnostic work-up.

The imaging session should be either ultrasound, usually transoesophageal echocardiograms (TEE), or simple computerized tomography (CT). That differentiation should be done early in the workout, you should not leave the patient there alone, sitting in the ER for hours, before you come to a conclusion whether to image them or not. Imaging is moving to the front row of management and especially with a suspected dissection or suspected aortic disease, so don't waste time waiting for lab data and so forth, get the imaging properly done as soon as possible

because that gives you the opportunity to also look for evidence of even subtle changes in the aortic wall, which, if you pick it up early, can help to avoid later catastrophes. Communication is key, and the use of swift imaging needs to be implanted into the brains of ER doctors.

How is our understanding of complicated and uncomplicated type B dissection changing?

CN: The difference between uncomplicated and complicated type B dissections, as I said, is changing. It is a moving target because we are identifying more and more elements of complication that had not been seen and had not been understood some years ago. For example, it is not only malperfusion, pain and imminent rupture that identifies the classic set of outcomes, and we are now starting to understand it is more than those.

Silent malperfusion and silent evidence of inflammation are interesting areas of ongoing research; we are now identifying patients that are at risk, although they are, clinically speaking, uncomplicated with no obvious symptoms.

In addition, the ongoing difficulty in treating hypertension in type B dissection means that such patients represent a cohort that are also prone to later complications, as demonstrated by registry data published in 2010.² Furthermore, ongoing inflammation or partial false lumen thrombosis in subacute type B dissection also identifies a subset of patients that are likely to develop further and future complications in the weeks and months to come.

Continuing to the 2014 guidelines, a very important new aspect is that even in so-called uncomplicated type B dissection, or in the patients that are now showing these newly understood complications, you now have an option to treat these patients with thoracic endovascular aortic repair (TEVAR). This is given a IIA rating with a grade B level of evidence, which means that TEVAR should be considered in patients that are still considered to be uncomplicated. That is a new treatment choice that we have now at hand.

Moreover, in complicated type B dissection, we have also given an IC recommendation for TEVAR. We now have good evidence to treat these patients endovascularly with new TEVAR

technology in order to reconstruct the aorta, rather than managing them with drugs alone.³

Treatment of type B dissection has been enriched with the option of TEVAR. The target of this intervention is to not only relieve or reconstruct the true lumen but also to avoid distal malperfusion, and to start the process of remodelling by stent induced realignment of the lamella and eventually thrombosis of the false lumen, followed by remodelling over time – that is the target. We want to achieve this anatomic remodelling process in all patients, because that, obviously, guarantees stability of the aorta in the years to come.

Follow-up is also very important. Patients, even with the proper treatment, either surgically, endovascularly or medically, need follow-up. They should be followed by a specialized, knowledgeable team focused on aortic diseases, and, of course, should be subjected to a clinical visit every year and an imaging session every year, as recommended in a recent consensus statement.⁴

For young patients, I would recommend magnetic resonance imaging (MRI) as it is free of any ionizing radiation. Since these patients still need long-term follow-up, they shouldn't be exposed to unnecessary radiation. However, CT should be used in the initial diagnostic assessment.

You mentioned that these changes to the guidelines have been made on the basis of new evidence. Could you give us an overview of some of these key trials?

CN: With regards to complicated type B dissection there are a couple of single-arm studies looking at complicated type B dissection with malperfusion. These studies included the VIRTUE registry that comprised 100 and the STABLE trial,⁵ which included 86 patients. In complicated type B dissection, recently released data from the VIRTUE registry demonstrate that TEVAR is able to provide good protection from aortic-related death in the mid-term, albeit with a high rate of aortic reintervention.⁴ The STABLE trial also suggested benefits from TEVAR, even complex TEVAR with distal extension by bare metal components.⁵ There is, of course, no Level 1 evidence with a randomized group comparison, but there is observational evidence in very well

conducted single-arm trials which, basically, highlighted the better prognosis over a year and over 3 years.⁶ That has been published recently, and basically confirms what has been seen in the IRAD Registry, which is that complicated type B dissection really benefits from long-term scaffolding or TEVAR.⁷ However, they are only registry data and not Level 1 data.

With regards to stable type B dissection, there are two randomized studies that collected data since late 2005/06, and have now provided mid-to-long-term follow-up data – INSTEAD-XL⁸ and the follow-up to the ADSORB trial.⁹ Both trials were prospective trials assessing patients randomized to either conservative management or medical management, in addition to TEVAR scaffolding. In particular, INSTEAD XL looked at 5-year follow-up and showed an edge, in terms of all cause and aorta-specific mortality and progression of disease, in those patients that underwent early intervention with TEVAR and scaffolding. The benefits showed not sooner than 2 years after implantation and were, basically, hidden by the early hazard with the intervention in the early months after treatment. Then, with longer follow-up between 2 and 5 years, there was a clear, significantly better outcome in those patients that underwent the early intervention, as shown in the landmark analysis in INSTEAD-XL.⁸

What this tells us – and the same has been seen in ADSORB,⁹ a smaller study containing only 60 patients – is that, obviously, with TEVAR we invest in the future of the patient, allowing the patient to remodel and the aorta to reconstruct, leading, eventually, to a long-term stable course, a plateauing Kaplan–Meier curve with no evidence of late cardiovascular mortality or enhanced/increased mortality. Whereas in the control group – the group that did not get the early intervention but rather was followed on medical management – we see an ongoing crossover or even late rupture complications that occur later on and lead to an attrition rate which is ongoing, rather than plateauing, as in the control group.

Both groups, of course, get medical management and a lot of attention, follow-up and repeat imaging, but those that had the early investment of scaffolding obviously do better, because they stabilize, while the others have an ongoing attrition rate and, of course, an ongoing crossover

rate, because they have these late complications that need to be treated at the time.

We spoke about remodelling being that key goal of the intervention. Looking at these data, how thorough was that remodelling? Is it as complete as you would like or could more be done?

CN: Of course, the ideal patient would be the patient who has only one entry site that could be sealed and no re-entries and that is it, but that is not the nature of this disease. It is more complex and we see patients with numerous re-entry sites, smaller or larger. The small ones are not a problem, but the large re-entry sites obviously are and feed blood retrogradely into the false lumen from down below, at the level of the abdominal aorta.

Unfortunately, we are not always able to address these problems initially with the first intervention, but rather with later follow-up interventions. If we treat a patient and treat them appropriately by sealing the proximal thoracic aspects of the aorta, we still have to follow the patient and look for later silent reperfusion of the false lumen or silent problems more distally, which can be addressed later on with a side-branch stent, local occluder or anything that is good to seal any re-entries, to make sure that the false lumen is completely isolated from pressure and from flow. That is the ideal goal. We don't always reach that goal, but we are happy if there is no expansion in the distal part of the aorta. This is another reason to follow these patients and look carefully for expansion once a year by imaging – as long as there is no expansion, there is no risk of future rupture.

What are the characteristics of an ideal device for type B aortic dissection?

CN: I think we have understood in the last couple of years that we should not use those stents that have been built and constructed for aneurysmatic disease; dissection is a different animal and needs a different treatment. To tame a dissection I think the best device would be a very flexible stent with low radial force that is not over expanded or not greater or bigger than the natural dimension of the aorta before it dissected.

What we really want to do is mimic the previous aorta, before dissection, and put in a scaffold that the dissected layers of the aorta can re-orient around, basically nothing but a healing scaffold. That is my idea and my concept of a treatment of

a dissection. We don't need all these stents in the way – they were built and initially considered for aneurysmatic disease, we need scaffolds for the aorta to reorient and realign around it.

That means the ideal device should not be oversized, but should be, maybe, a little bit tapered from the top to bottom. It should not have excessive radial force, but rather a low radial force, and it should not overexpand the true lumen, it should just reach the original dimension and no more than that.

What impact do you see this guidance having on clinical practice? Is there going to be resistance to it or is it going to be widely accepted and taken up?

CN: The real problem we have is that aortic disease has a relatively low incidence as compared with, for instance, hypertension or coronary disease. Therefore, the chance to be exposed to this difficult pathology for a fellow or for any doctor working in this field is much, much lower. So learning by experience will take much longer, of course, or only in specialized centres that see these patients more frequently.

That is why guidelines are of particular importance in this particular field. People who have read them before they see the patient are likely to better understand the dynamics, the clinical presentation, the various symptoms and science of dissection. It is not that difficult, but you just have to be aware of the complexity, and the current guidelines really open your eyes to the various subgroups of dissection – all of this is thoroughly discussed.

Since we don't have any Level 1 data on these pathologies, the authors should be praised in having provided really careful wording around their recommendations, particularly in those areas of intramural haematoma (IMH) as well as penetrating ulcers, focusing on follow-up, imaging and repeat imaging, because these pathologies may show changes within a few days. We all need to be aware of the changes that can happen and then, of course, to find reasons to treat actively.

Can you tell us about ongoing studies in this area?

CN: We will certainly see more data. For instance, IRAD, the large International Registry of Aortic Dissection founded some 19 years ago by Drs Isselbacher, Nienaber and Eagle, is not only

collecting type B dissection but all sorts of dissection.¹⁰ Moreover, they have branched out to include an interventional subset in their registry, looking at treatment of type B dissection with endografts. This subgroup in IRAD was founded about 3 years ago and they are looking, particularly, for more detailed information on patients that undergo endovascular treatment, open surgery or just are left alone on medication. This will be an important source of information as we are talking about hundreds, if not thousands, of patients.

Finally, there are plans to launch a large follow-up to the INSTEAD trial, which is called the INTACT trial, INTACT/AD, and stands for Trans-Atlantic International Controlled Trial on Aortic Dissection. It is planned that the first patient will be enrolled in Q3 2015, and the study will look at 1,800 patients randomized in both EU and US on the basis of entries into the IRAD Registry and The Vascular Quality Initiative (VQI) Registry in the US. They are basically collecting patients within that framework of the Registry and allowing them to participate in

a randomized trial within that Registry. Following 1,800 patients over 5 years will help to answer the key question whether mortality is going to be lower once you are subjected to TEVAR with a type B dissection, irrespective of any kind of complications.

When do you foresee another update coming?

CN: The next update needs to be written as soon as elementary new or critical new data will be available. As I said, there is a long international trial on the horizon and there will be more registry data coming in as well as from some smaller observational trials. However, I think the bulk of new information will not be available sooner than 5 years from now. I think the next update will need to take place in 2019, though of course this is just a guess. I see this moving slowly in the clinical field, but rapidly in the technology area, because technology is improving every year and we can, basically today, use technology that we did not even dream of some 15 years ago, when all this started.

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REFERENCES:

1. Erbel R, et al. *Eur Heart J* 2014;35(41):2873-926.
2. Trimarchi S, et al. *J Thorac Cardiovasc Surg* 2010;140(4):784-9.
3. Nienaber CA, et al. *J Vasc Surg* 2011;54(5):1529-33.
4. VIRTUE Registry Investigators. *Eur J Vasc Endovasc Surg* 2014;48(4):363-71.
5. Lombardi JV, et al. *J Vasc Surg* 2014;59(6):1544-54.
6. Fattori R, et al. *J Am Coll Cardiol* 2013;61(16):1661-78.
7. Fattori R, et al. *JACC Cardiovasc Interv* 2013;6(8):876-82.
8. Nienaber CA, et al. *Circ Cardiovasc Interv* 2013;6(4):407-16.
9. Brunkwall J and Lubke T. *Eur J Vasc Endovasc Surg* 2013;46(3):274-7.
10. Hagan PG, et al. *Jama* 2000;283(7):897-903.

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