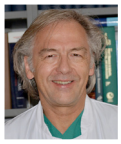


Christoph Nienaber

Improving long-term outcomes in patients with type B aortic dissection

Recent evidence from the INSTEAD-XL trial and a number of registries has shed new light on how best to manage type B aortic dissection. To discuss how pre-emptive stenting of the diseased vessel can improve long-term outcomes, *Confluence* caught up with Professor Christoph Nienaber, Medical Director of the Cardiology Department in the Department of Medicine, Divisions of Cardiology, University of Rostock, Germany.

How does aortic dissection present, in which patients does it present, and why is it important?

Aortic dissection is an acute condition of the aorta, which usually presents as a very acute and strong sensation of pain, described by some as the worst pain they have ever experienced in their lifetime. The pain, associated with a splitting of various components of the aortic wall, usually under the stress of hypertension, is usually felt in the patient's chest or back. Approximately 80% of patients that suffer from any kind of dissection are hypertensive patients so the hypertension, usually untreated, is the typical risk condition that leads to dissection.

However, patients are often incorrectly diagnosed when they first present, because of strange, sometimes neurological symptoms. The pain symptoms frequently lead the emergency doctor to suspect coronary disease or acute myocardial infarction, which is usually in fact not the case. This means we lose time by working up all of the differential diagnoses, rather than focussing on dissection as the primary cause of that tremendous pain symptom. This can be a bit frustrating.

Effective identification of patients with aortic dissection is vital. I still believe that we are seeing fewer patients than we should. We know the incidence of aortic dissection, and we should see more patients in tertiary care centres but we don't; we are missing almost 50% of the statistically expected number of patients! I presume that the reason for this is that some patients do not get the proper diagnosis, while others are retained in smaller hospitals and are not referred to tertiary care centres that can offer this treatment.
We are currently trying to explore why this problem occurs.

Is it true to say that time is of the essence when we are treating these patients?

Yes, time is particularly of the essence if you are dealing with proximal (type A) dissection, meaning that the dissection originates from the ascending aorta next to the coronary or the aortic wall. That's a more dangerous condition than the distal dissection, known as type B, in which only the descending aorta is involved.

Type A dissection is usually associated with stronger symptoms and more complications, and needs to be taken care of surgically; it is an emergency and there can be no delay. As soon as you diagnose type A dissection, the cardiac surgeon needs to be called and we have to basically decide whether the patient needs further diagnosis or further confirmatory imaging before they go into the operating theatre. In these patients, a typical operation would involve replacement of the dissected ascending aorta, sometimes with preservation or replacement of the native aortic valve, as necessary.

In type B dissection, the descending aorta, defined as being the area from the nadir of the aorta to the distal regions, is dissected. Therefore, the symptoms, and also some complications, can be different compared with those seen in type A. The symptoms are usually a little bit less severe and the pain tends to 'wander' downwards from chest to abdomen because of the dissection crawling down along the aorta. Sometimes the condition also involves some side branches that can become occluded or obstructed, causing malperfusion syndrome to the renals or to the legs. Indeed, this is usually a good way of identifying the problem before you resort to confirmatory imaging, a CT scan for example, or any kind of other imaging.

How is aortic dissection managed? What are the aims of treatment?

The aim of the treatment is usually to close the entry tear. The dissection originates from an entry tear, a laceration of the intima and media, which is simply a kind of a physical tear that separates the two layers and allows the blood to enter the space between the media and the adventitia.

Therefore, if you close this tear, or if you excise it and replace it with Dacron like in the typical type A scenario in the proximal aorta, then you stop the propagation of the dissection and you can realign the various components of the wall. This is usually done surgically in type A dissection and with stents in type B dissection. The stent option, known as thoracic endovascular aortic repair (TEVAR), is an endovascular, catheter-based treatment. The stent used is basically a covered stent that is placed across this tear in order to close it and seal it up. The aorta needs to self-heal and the stent is just a scaffold to help the aorta to re-orient around the stent, and eventually seal and heal. To date, TEVAR has been used widely to treat type B dissection in patients with complications such as malperfusion, early expansion of the false lumen or ongoing pain or imminent rupture.

Additionally, as these patients are usually hypertensive, in post-operative patients it is important to lower blood pressure to the lowest tolerated level. Thus antihypertensive treatment involving anti-impulse treatment is key; every patient needs to be placed on beta-blockers and controlled for blood pressure. However, the drawback of these therapies is that sometimes they are not tolerated or the patient is not compliant. Some patients forget or throw their pills away and don't care about medication any longer – that's a common observation.

Complications calling for the use of TEVAR are not apparent early on in approximately 50% of type B dissections. Such cases can be treated with beta-blockers and can be sent home, at least for the time being, on medication. However, medication does not repair the aorta. Recent data have shown that after a few years, patients treated with medication often experience aneurysm formation. This can only be avoided by early placement of a stent graft or early use of TEVAR because with TEVAR you realize that there is a chance of healing and thereby stabilizing the aorta.

Can you tell us about the INSTEAD-XL trial?

The INSTEAD-XL is a follow-up of the INvestigation of STEnt grafts in Aortic Dissection (INSTEAD) trial. The INSTEAD trial was the first ever randomized trial in aortic dissection. We selected patients that were considered to be suitable for medical management alone, so-called uncomplicated type B dissection (fig. 1); patients that you would

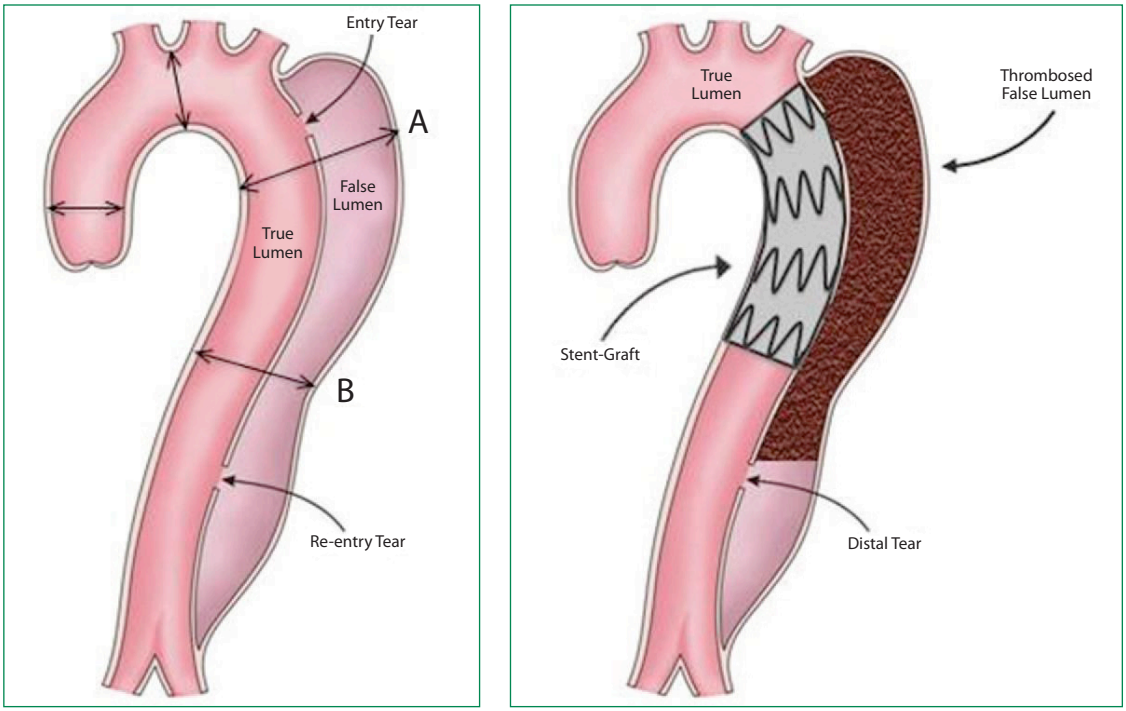


fig. 1

Illustration demonstrating typical features of type B dissection with flow in both the true and the expanded false lumen resulting from a major proximal entry tear (left). An endoprosthesis is placed to scaffold the dissected aorta and to seal the entry to the false lumen resulting in reconstruction of the true lumen with subsequent false lumen thrombosis (right). Aortic dimensions were defined at the level of the maximum aortic diameter (A), and at the hiatus (B), and followed over time.

usually just place on beta-blockers or a polypharmacotherapy in order to control blood pressure. We wanted to assess whether early, pre-emptive treatment with TEVAR could improve long-term survival and aorta-specific mortality.[1]

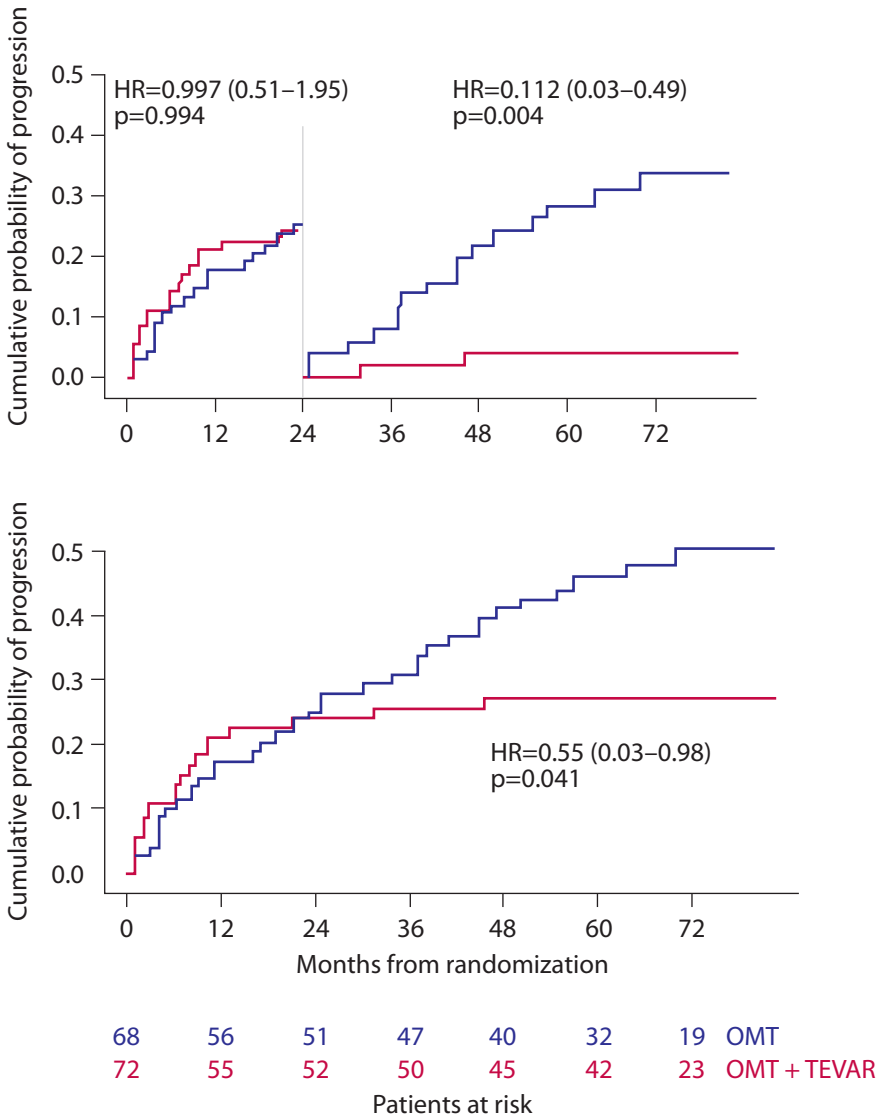
A total of 140 patients were enrolled and randomized to medical treatment alone (n=68), or randomized to medical treatment plus TEVAR (n=72). We followed patients for two years and after this time, in this particular setting of stable dissection or uncomplicated type B dissection, we were unable show any kind of difference between the two groups in terms of survival, aorta-related mortality or progression of disease.

As complications often occur after this time, we amended the protocol to include follow-up for five years; this became the so-called INSTEAD-XL trial. The patients who were already enrolled in INSTEAD had to agree to be included in this extension of INSTEAD, the so-called XL which means extended length of follow-up, and they got another three years of follow-up.

Fortunately, we could collect 100% follow-up of all survivors and we found that with longer follow-up, those two Kaplan–Meier curves separated slowly and gradually, showing a significant survival advantage, particularly from aorta-related or vascular survival, in those patients that got an early stent (fig. 2). Furthermore, we had a larger fraction of crossovers and additional interventions in the medication-only cohort, probably due to the progressive nature of the disease.

fig. 2

Kaplan–Meier estimates of a combined endpoint of progression and adverse events (aorta-related death, conversion, and ancillary interventions, including the second stent graft procedure, access revision, peripheral interventions) with a breakpoint at 24 months are shown for optimal medical treatment (OMT) and OMT+TEVAR. With TEVAR, less progression of disease was observed in the late phase of follow-up compared with OMT.



What this tells us is that with longer follow-up, the advantage of an early intervention eventually pays off, stabilizing more patients over time compared with medication alone.

Are there any drawbacks of early intervention?

You have to provide the service in a very safe manner. The safety profile of the intervention itself is much better nowadays than in 2005 when we started the study. The material and technology has improved significantly, with two or three further generations of stent grafts now on the market, so all of the equipment, all of our skills, are better than they were in the early days. So I expect that a second round of INSTEAD trials or similar trials would show an edge much sooner because we wouldn't run into that hazard period seen in the early days, in which the intervention itself caused some problems.

Is there any other evidence that supports your findings?

There are data from a meta-analysis published in January 2013 that assessed observational data from selected European and US prospective studies and registries: the Medtronic Outcomes of THoracic Endovascular Repair (MOTHER) trial. That is just a retrospective registry analysis. It came to the same conclusion, i.e., that you find a late benefit from patients that undergo early intervention, even in stable situations.[2]

A similar observational report from China was published in February in the *Journal of Vascular Surgery*. Based on data from various centres in China, the authors again came to the same conclusion; that in a retrospective analysis, you see a late advantage in patients who undergo early stenting, although they were stable and clinically speaking, they could have been left on medical management alone.[3]

And there is another interesting observation from the largest registry in the world, the International Registry of Aortic Dissection (IRAD), that published in August this year in *JACC Interventions*. This found that the late advantage of stenting can be shown beyond three years. The two mortality curves again separate very clearly, with an advantage for the early intervention.[4]

We can conclude that, in anatomically suitable patients with a considerable remaining life expectancy, pre-emptive stenting is the way to go in type B dissection, regardless of the clinical scenario, in order to prevent late complications. That would be my conclusion.

When will these data appear in guidelines?

As all of these publications appeared in 2013, they are not yet in the guidelines. However, I presume that in the next guideline session those data need to be analyzed, need to be critically reviewed and probably will change the guidelines. The next guideline committee session will take place in 2014.

Are you noticing this impact in clinical practice already? Are people taking notice of these data?

While the data have only been in the public domain for three weeks now, I see more patients asking for pre-emptive stenting and some patients have even read the papers. There is also considerable interest from colleagues who work in the field.

However, I must state that I do not stent everybody. Factors such as lifespan must be considered. For example, I would not stent an 85-year-old with no symptoms – that makes no sense to me. But in a 75-year-old with no symptoms and dissection, I would probably go ahead and try to realign all the various layers of the aorta in order to give them a chance to heal.

Again, we should encourage the medical community, based on these new data, to refer the patient to tertiary care and to ask for pre-emptive stenting. We are dealing with survivors that should get a second chance.

What benefit are patients going to see?

TEVAR treatment has a psychological impact on patients because they usually feel more secure, regardless of whether it was used to manage a complication or employed pre-emptively. They just feel more secure, they feel more confident and they don't feel that their dissection is a kind of lurking time bomb that can go off any time. In fact, we do not see much late rupture with the stents. We saw that only in the control group and not in the stented group, so this may actually represent a true effect of stenting.

Moreover, there is a lot of confidence gained from the CT scans. We do not see any late expansion of the aorta once the patient has been successfully treated with a stent graft. That again gives some security and some comfort to the patient because

they can see on the CT scan that their aorta is no longer growing. That helps a lot.

What is next for aortic dissection?

We don't think that there will be another randomized trial for those uncomplicated type B dissections. I guess what we will get and see in the near future is more data from registries following these patients. This will allow us to follow-up patients for even longer than the five years in INSTEAD- XL. Additional randomized trials are unlikely as they are difficult to carry out in this field. This is because, while the impact for the individual is high, the incidence of the disease is relatively low. Therefore, to find a sufficient number of suitable patients, you have to really screen them carefully. For example, we had to analyze 600 patients to randomize 140.

What will also be beneficial is the so-called dissection-specific design of a new generation of stents. The current generation of stents are still not perfect and the companies are now starting to understand that dissection is different from aneurysm. A stent that has design features that solely address the needs of a dissection would be better to encourage aortic healing.

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