JAY WIDMER: Greetings. I'm Jay Widmer, cardiovascular fellow at Mayo Clinic. Today in theheart.org, we'll be discussing the recent late breaking trial published in the *New England Journal of Medicine* comparing losartan versus atenolol for reducing aortic dilatation rate. And with my colleague Dr. Juan Bowen who is the director of the Marfan and Thoracic Aorta Clinic at the Mayo Clinic here in Rochester. Welcome Dr. Bowen.

JUAN BOWEN: Good afternoon.

JAY WIDMER: Well, let's start with the basics. Take us through what is Marfan Syndrome.

JUAN BOWEN: Well, the Marfan Syndrome is a heritable disorder of connective tissue. It affects about 1 in 5,000 people. And at first it was described as a collection of physical characteristics but the cause wasn't known. But it was thought to probably be a structural protein. Eventually, a mutation in the fibrillin-1 gene was found in 1991. And this is a component of elastic microfibrals. But later on, it was found out that this particular protein is also a regulator of the TGF beta pathway. So it has important effects on the morphogenesis of tissues. The Marfan Syndrome affects the cardiovascular system. It affects the skeletal system. And it affects the eye. But the dangerous consequences have to do with the cardiovascular system, primarily with aortic aneurysms and the proximal aorta.

JAY WIDMER: Absolutely. Well, going to that and speaking to that, what's the natural history of a patient with Marfan Syndrome?

JUAN BOWEN: Well, before we had effective therapy, Marfan patients often died very young, often in their 30s or even younger. And the cause of death was usually aortic dissection, sometimes heart failure from progressive aortic regurgitation. But therapy eventually improved in the Marfan Syndrome. And today life expectancy in some patients can be normal or near normal.

JAY WIDMER: Excellent. Well, what is that standard therapy that allows patients to have a normal life expectancy? And why is better treatment needed?

JUAN BOWEN: Well, there are two components of therapy. And really, the surgical treatment that was developed in the late 1960s really gets the credit for the long survival that patients have today. At that time, surgeons had the insight that a composite aortic graft could be used to repair the aorta in a prophylactic way. And then survival jumped up because that turned out to be a very effective therapy.

Today, those operations continue to be done but there are refinements now, as particularly the valve sparing operation is a promising operation that's been used in recent years. But medical protection of the aorta with beta blockers has been around also since about the 1980s, 1990s with reasonably good evidence that it works. So patients today receive medical aortic protection with beta blockers. They undergo prophylactic repair of the aorta when their aorta roots reach certain dimensions, right around 5 centimeters. And they require lifelong monitoring with imaging. And then of course, they have non cardiovascular problems having to do with the eye and the skeletal system.

JAY WIDMER: Exactly. Well, that's interesting you mention beta blockers. And it's what most of us use in our practice. If those are so effective therapies, then why did we study an angiotensin receptor blocker in this trial?

JUAN BOWEN: Well, there's an important insight that once the structure and the function of the fibrillin molecule was understood and its relationship to the TGF beta pathway, it was found that in an animal model, Marfan mice, the TGF beta pathway was quite overactive. And it turns out that you can block TGF beta dysregulation by blocking the AT1 receptor. And ACE inhibitors block both AT1 and AT2. But angiotensin receptor blockers block AT1. In the animal model, it turned out that losartan was a very effective therapy. And Marfan mice given losartan at a young age really developed very well and did not have the serious aortic enlargement compared to wild type mice. And also when compared to propranolol treated mice, the effects on the aorta were much better with losartan. This, of course, led to human trials since this drug was already approved and already in wide use for hypertension.

JAY WIDMER: Exactly. You gave us a very promising animal data. Tell us, before this Lacro and colleagues trial, had we looked at angiotensin receptor blockers in humans?

JUAN BOWEN: Well, there are approximately 10 trials worldwide. Now, two trials were reported last year. One was a small trial in children with only 38 patients. And it was a positive trial showing the benefit of losartan when compared to the combination of losartan plus beta blocker. A larger trial was later reported with 233 patients, this is the compare trial, and also demonstrating the benefit of losartan. And about 75% of losartan treated patients were also treated with a beta blocker. And this was a trial in adults.

JAY WIDMER: So what did the Lacro trial investigators find when they compared losartan to a atenolol by itself over a three year period?

JUAN BOWEN: Well, this was a much anticipated trial because this is the largest trial to date with over 600 patients. Now this trial compared losartan to beta blocker without a placebo group. So it was a direct comparison. And most people expected that this trial would show a definite benefit of losartan in the rate of aortic dilatation. However, it did not. It did not show that losartan had any advantage compared to beta blocker.

JAY WIDMER: And why do you think this losartan was not shown to be superior to atenolol in this trial?

JUAN BOWEN: Well, we think there are several possible reasons. For one, compared to the other trials, in the other trials the combination of beta blocker and losartan was shown to be superior to beta blocker alone. It is really possible that in this trial, the beta blocker was more effective than had been anticipated. High doses of atenolol were used in this trial.

Now it's also possible that treating patients who are somewhat more mildly affected might be more effective. These patients were severely affected with aortic z scores over three. The age range was age six months to 25 years. So it's possible that treating patients who are less severely affected might prove more effective.

JAY WIDMER: Excellent. So how will these results change your practice and what you tell colleagues such as myself in treating patients with Marfan Syndrome?

JUAN BOWEN: In our clinic we consider beta blockade to be the primary therapy. We do think that losartan does show efficacy. For example, in the Lacro trial, both losartan and beta blocker did reduce the z score change. So they were both effective. It's just that losartan was not more effective. So we think there is evidence for effectiveness in both. There's just not effectiveness for superiority of losartan. So we will continue to use beta blockers as primary therapy. But particularly in patients who are intolerant of beta blockers, we will use losartan. And in selected patients, the combination.

JAY WIDMER: OK. Great. Tell us were surgical therapy comes in. Does the medical treatment alleviate the need for surgical treatment of these patients?

JUAN BOWEN: Well, what's really important to understand is that the medical treatment with beta blockers is really directed at hemodynamics and doesn't change the pathophysiology of the disease. And the great appeal of TGF beta dysregulation directed treatment is that it has the potential for actually changing the pathophysiology of the disease. And one would hope that if this therapy were found to be effective, not only the cardiovascular manifestations would be attenuated but these Marfan patients, as they live longer, they experience quality of life problems related to their problems with vision, to their problems with musculoskeletal pain and disability.

So right now, both beta blockade and angiotensin receptor blocker therapy really do not prevent aortic surgery but they probably delay aortic surgery. And when patients undergo aortic surgery, this doesn't really fix their cardiovascular problem for life. They will require lifelong monitoring. There remains a problem with the section involving particularly the descending aorta and then of course, all the non-cardiovascular issues. So these are patients who require medical therapy, at times well well-timed surgical therapy, lifelong monitoring. And that's why really the dream of translational medicine approach that would really change the natural history of the disease remains an important goal.

JAY WIDMER: Certainly an elusive goal. And I see the multi-modality treatment will be important for these patients for the duration.

JUAN BOWEN: Yes it will.

JAY WIDMER: Thanks, Juan, for these great comments on this exciting trial that's going to be coming out in the *New England Journal* soon. We're looking forward to reading you and Dr. Connelly's editorial on such. Thanks, Juan, for the commentary on this important trial. And thanks to our viewers. We hope you will continue to check out future content on Mayo Clinic's page at theheart.org on Medscape. Thank you.