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receptors. The type 1 receptor (AT1) increases TGF-beta signaling and contributes to the formation of aortic aneurysms. The type 2 receptor (AT2) is less well understood, and there has been debate about its effect on TGF-beta signaling.

Losartan and other angiotensin receptor blockers are specific inhibitors of AT1 and have no effect on AT2.

In the recent reports, Marfan mice lacking the AT2 receptor had greater TGF-beta signaling and more aortic root dilation than did Marfan mice with intact AT2 receptors. Furthermore, losartan was much less effective in reducing TGF-beta signaling or protecting the aortas among Marfan mice lacking the AT2 receptor.

The implication of these results is that the AT2 receptor actually downregulates TGF-beta signaling and can be protective with respect to aortic root aneurysm formation.

It then follows that ACE inhibitors, which act upstream of angiotensin II, and therefore decrease activity of both the AT1 and AT2 receptors, may not be as effective as angiotensin receptor blockers are in reducing TGF-beta signaling or protecting the aorta in Marfan syndrome.

Indeed, in the reports by Dr. Dietz and his coinvestigators, enalapril was able to

slow the progression of aortic root diameter in the mouse model but was not able to match the reversal of aneurysm size achieved by losartan.

The other important finding in these latest studies is further identification of the specific pathways downstream from TGF-beta that are involved in aneurysm formation.

The critical players appear to be extracellular signal-regulated kinases (ERKs) and c-Jun amino-terminal kinases (JNKs). This knowledge brings us one step closer to a complete understanding of exactly how aneurysms develop in Marfan syndrome and serves as an excellent example of how basic science and clinical research can overlap and synergize.

In the mouse studies, losartan shut down the excess ERK signaling, while enalapril had no effect on this pathway. This lends further support to the idea that angiotensin receptor blockers may be superior to ACE inhibitors as a clinical treatment.

Even more significantly, the inhibitors of ERK and JNK used by Dr. Dietz's group in their research are under evaluation for clinical application, and they – or drugs modeled after them – might ultimately prove extremely valuable in the treatment of patients with Marfan syndrome.

So what should we do with this information clinically?

There are strong mouse data and preliminary human clinical data that losartan can slow or even reverse aortic aneurysm in Marfan syndrome. A number of well-designed randomized clinical trials are now underway to evaluate the clinical utility of angiotensin receptor blockers in this situation, and results are expected in the next 3 years.

Until we have detailed clinical safety and efficacy data, we should stick with the standard of care. Beta-blockers are still indicated as first-line therapy in Marfan syndrome patients with a dilated aortic root.

Those who cannot tolerate beta-block-

ade, or whose aortic diameter continues to enlarge despite maximal beta-blockade, should be considered for referral to a clinical trial (searchable at www.clinicaltrials.gov).

However, if participation in clinical research is not an option for patients, it seems reasonable at this point to use losartan clinically as a second-line medication. ■

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National Marfan Foundation Launches Mobile Web Site

The National Marfan Foundation is launching a new mobile Web site, www.MarfanDX.org.

The site is compatible with Droid and iPhone smartphones.

The mobile site, which is also viewable on a desktop computer, is compatible with the Safari and Firefox browsers.

The site content is based on the new criteria for Marfan syndrome, and it also provides differential diag-

nosis and management for related conditions.

The site includes:

- ▶ Seven simple formulae for diagnosing Marfan syndrome.
- ▶ An interactive z-score calculator, which can be used to determine the size of the aorta compared with body surface area.
- ▶ Key points about the role of genetic testing and family history.

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