Marfan症候群に対する新たな治療戦略（Abstract 61361）

Marfan症候群の小児においてロサルタンの大動脈拡大速度低下効果はアテノロールと同等である

Losartan equally as effective as atenolol for slowing rate of aortic enlargement in children with Marfan Syndrome

Marfan症候群の小児の大動脈拡大速度を低下させる治療の選択肢が広がったと、American Heart Association年次集会で発表された。Marfan症候群患者におけるアテノロール治療とロサルタン治療とを比較したスタディの結果、大動脈拡大速度は2つの治療群間で有意差がなかった。研究者らは、Marfan症候群患者608人（生後6か月から25歳）においてアテノロール（Marfan症候群患者で最も一般的に用いられる薬剤）とロサルタン（一部の研究においてアテノロールよりも有効である可能性が示唆されている薬剤）を比較した。両薬剤ともに体格で指標化した大動脈根部の経時的な低下をもたらした。3年間の大動脈拡大速度は2群間で有意差がなく、特に若年者において両群ともに大動脈拡大重症度は時間とともに低下した。この結果の原因は不明である。研究者らは薬物の用量設定が重要であると強調している。アテノロールの用量は患者の心拍数で調整され、日常診療においてMarfan症候群患者に使用されているよりも高用量であった。このスタディ結果は同時に*New England Journal of Medicine*に掲載された。

Full Text

Between 70 and 80 percent of patients with the connective tissue condition Marfan syndrome have aortic-root dilation. This condition can result in serious illness and sometimes death. A National Institutes of Health-funded study comparing treatment with widely used blood pressure medications atenolol or losartan in patients with Marfan syndrome who had an enlarged aortic root found no significant difference in the rate of aortic-root dilation between the two treatment groups over three years.

The results of the Atenolol versus Losartan in Children and Young Adults with Marfan Syndrome study, supported by NIH's National Heart, Lung, and Blood Institute (NHLBI), were presented at the American Heart Association (AHA) Scientific Sessions in Chicago. The study was published simultaneously in the *New England Journal of Medicine*.

Marfan syndrome is a genetic disorder that affects connective tissue. Standard care includes frequent cardiac imaging, exercise restriction, administration of a beta-blocker such as atenolol or other medications that may decrease the rate of aortic enlargement, and elective aortic-root replacement when the aortic root becomes too large. Although early diagnosis and refined medical and surgical management have improved survival, patients with Marfan syndrome continue to have high rates of complications and death from heart problems, even at a young age.

This randomized trial, which was conducted by the NHLBI's Pediatric Heart Network, ran from 2007-2011 at 21 clinical centers in the United States, Canada and Belgium and included 608 patients aged 6 months to 25 years. The two drugs work in different ways. Atenolol works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure. Losartan blocks the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently.

Researchers compared atenolol (the drug most commonly used in patients with Marfan syndrome) to losartan (a drug that some research studies suggested might work better than atenolol) in 608 patients (aged 6 months to 25 years) with Marfan syndrome. They found no significant difference in the rate of aortic enlargement between the two groups who were studied over three years.

They noted that drug dosing is important. The dose of atenolol was adjusted to the patient's heart rate and was higher than the dose used in other studies and in routine clinical care of patients with Marfan syndrome. The dose of losartan was the highest FDA-approved dose at the start of the study. However, a higher dose of losartan might have shown a different effect on aortic growth rate. The beneficial effects of each drug seemed to be greater when given to younger children.

Few bothersome symptoms or major side effects occurred with either drug. Researchers conclude that both drugs are well tolerated and safe, therefore therapy can be chosen based on individual patient and health provider preference.

Previous small studies had suggested that losartan might be more effective in slowing aortic-root enlargement than atenolol, which is the most common current therapy. The NIH-funded study, the largest study to date, showed that there is no important difference between the two drugs when used for this purpose.

"These study results are very valuable for clinical practice," said Dr. Gary H. Gibbons, director, NHLBI. "Both drugs were well-tolerated by study participants, and losartan may be another treatment option for patients with Marfan syndrome. Furthermore, evaluating the effect of therapies in children is essential to ensuring evidence-based pediatric care."

Although the rate of change in the aortic root did not differ between treatment groups, the severity of aortic-root enlargement decreased over time in both groups, particularly in young subjects. The cause of this outcome is unknown. Further research is necessary to evaluate the magnitude of this benefit.

"This finding suggests that there is merit in starting therapy at a younger age and at an earlier stage of the disease," said the study's principal investigator, Dr. Ronald V. Lacro, director of the Cardiovascular Genetics Clinic and Marfan Syndrome Program, Boston Children's Hospital. "We have to remember that although this study did not show one drug to be more effective than the other, it still helped us greatly expand our knowledge of Marfan syndrome and the effects of atenolol and losartan."

The Marfan Foundation helped recruit participants and raised funds to support some trial costs. "The Marfan Foundation greatly appreciated the opportunity to partner with the NHLBI and Pediatric Heart Network on this trial, which was critically important to our Marfan community," said Josephine Grima, Ph.D., senior vice president of research and legislative affairs, The Marfan Foundation. "Their commitment to this large pediatric study opened the door to additional research on therapeutics for Marfan syndrome around the world, with scientists in nine other countries conducting trials."

"Public-private partnerships were a hallmark of this trial," said Gail Pearson, M.D., Sc.D., associate director, Division of Cardiovascular Sciences, and director, Office of Clinical Research at NHLBI. "Through the Pediatric Heart Network, we were able to bring together government, industry and patient communities to answer important questions in a population with a rare condition. This is a model that we hope will become more common."

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