Drug combination may delay need for surgery in patients with Marfan syndrome

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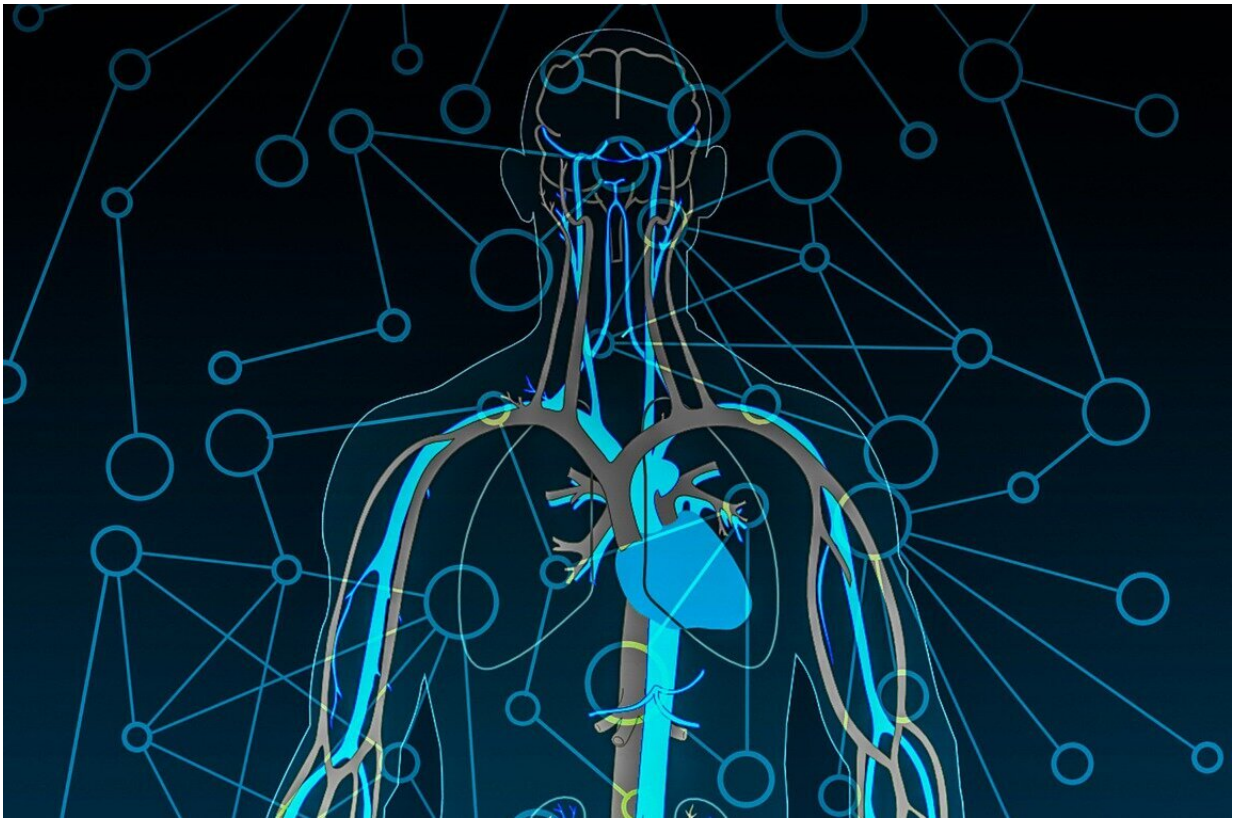

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Angiotensin receptor blockers (ARBs) and beta-blockers have similar and independent effects on reducing aortic root size in patients with Marfan syndrome, suggesting that several years of combined treatment

could delay the need for surgery. That's the finding of late breaking research presented in a Hot Line session on 29 August at ESC Congress 2022.

Marfan syndrome affects approximately one in 5,000 people worldwide and is often caused by a mutation in the FBN1 gene. Nearly all patients experience aortic root enlargement, which increases the risk of potentially life-threatening aortic dissection and rupture, sometimes in early adulthood. To prevent these consequences, elective surgery to replace the aortic root may be performed when dilatation reaches 4.5–5 cm. Beta-blockers are recommended to slow aortic growth based on a single, small, randomized trial. It has also been suggested that ARBs might slow aortic root growth in Marfan syndrome.

Researchers from Oxford Population Health conducted a meta-analysis on behalf of the Marfan Treatment Trialists' (MTT) Collaboration to assess the effects of 1) ARB versus control, 2) ARB versus beta-blocker, and 3) indirectly, beta-blocker versus control, on the rate of change in aortic root size adjusted for age, sex and body surface area.2 Effects were also examined in subgroups of patients, including those with or without a confirmed FBN1 pathogenic variant. The analysis included individual data on 1,442 patients with no prior aortic surgery from seven randomized trials.

The researchers first analyzed four trials involving 676 patients and comparing an ARB with placebo or open control. The average age was 29 years, 54% were women, 75% were receiving a beta-blocker at baseline, and 83% of genotyped patients carried an FBN1 pathogenic variant. During a median follow up of three years, ARBs approximately halved the annual rate of change in the aortic root Z score, a widely used measure of aortic root size. The annual increase was +0.07 with ARBs versus +0.13 with control, for an absolute difference of -0.07 (95% confidence interval [CI] -0.12 to -0.01; p=0.012). Similar effects were

observed when absolute aortic dimensions were analyzed.

Lead study author Dr. Alex Pitcher, Consultant Cardiologist at Oxford University Hospitals, U.K. said, "The benefit of ARB therapy was particularly large in patients with an FBN1 mutation at baseline, making it more plausible that the effect is real. There were no other detectable differences in treatment effect depending on other patient characteristics, including age, sex, and blood pressure. The benefit of ARB treatment was similar regardless of whether patients were taking a beta-blocker."

The researchers then analyzed the remaining three trials, which involved 766 patients and compared an ARB with a beta-blocker. The average age was 14 years, 44% were female, none of the patients were receiving a beta-blocker prior to randomization, and 86% of genotyped patients had an FBN1 pathogenic variant. During a median follow up of three years, the annual change in the aortic root Z score was similar in the two groups (absolute difference ARB minus beta-blocker 0.03; 95% CI -0.05 to 0.10).

Results from the two analyses were used to indirectly evaluate the effect of a beta-blocker compared with control. Allocation to a beta-blocker was also estimated to approximately halve the annual change in the aortic root Z score (absolute difference compared with placebo: -0.09; 95% CI -0.18 to -0.0033; p=0.04).

Dr. Pitcher said, "Our results suggest that ARBs and beta-blockers have similar, substantial and independent effects on reducing the aortic root Z score which, if maintained over a period of several years, would be expected to delay the need for elective aortic root surgery. The findings indicate that combination therapy, where tolerable, may benefit patients with Marfan syndrome."

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