

Angiotensin receptor blockers and β blockers in Marfan syndrome : an individual patient data meta-analysis of randomised trials.

BACKGROUND: Angiotensin receptor blockers (ARBs) and β blockers are widely used in the treatment of Marfan syndrome to try to reduce the rate of progressive aortic root enlargement characteristic of this condition, but their separate and joint effects are uncertain. We aimed to determine these effects in a collaborative individual patient data meta-analysis of randomised trials of these treatments.

METHODS: In this meta-analysis, we identified relevant trials of patients with Marfan syndrome by systematically searching MEDLINE, Embase, and CENTRAL from database inception to Nov 2, 2021. Trials were eligible if they involved a randomised comparison of an ARB versus control or an ARB versus β blocker. We used individual patient data from patients with no prior aortic surgery to estimate the effects of: ARB versus control (placebo or open control); ARB versus β blocker; and indirectly, β blocker versus control. The primary endpoint was the annual rate of change of body surface area-adjusted aortic root dimension Z score, measured at the sinuses of Valsalva.

FINDINGS: We identified ten potentially eligible trials including 1836 patients from our search, from which seven trials and 1442 patients were eligible for inclusion in our main analyses. Four trials involving 676 eligible participants compared ARB with control. During a median follow-up of 3 years, allocation to ARB approximately halved the annual rate of change in the aortic root Z score (mean annual increase 0.07 [SE 0.02] ARB vs 0.13 [SE 0.02] control; absolute difference -0.07 [95% CI -0.12 to -0.01]; $p=0.012$). Prespecified secondary subgroup analyses showed that the effects of ARB were particularly large in those with pathogenic variants in fibrillin-1, compared with those without such variants (heterogeneity $p=0.0050$), and there was no evidence to suggest that the effect of ARB varied with β -blocker use (heterogeneity $p=0.54$). Three trials involving 766 eligible participants compared ARBs with β blockers. During a median follow-up of 3 years, the annual change in the aortic root Z score was similar in the two groups (annual increase -0.08 [SE 0.03] in ARB groups vs -0.11 [SE 0.02] in β -blocker groups; absolute difference 0.03 [95% CI -0.05 to 0.10]; $p=0.48$). Thus, indirectly, the difference in the annual change in the aortic root Z score between β blockers and control was -0.09 (95% CI -0.18 to 0.00; $p=0.042$).

INTERPRETATION: In people with Marfan syndrome and no previous aortic surgery, ARBs reduced the rate of increase of the aortic root Z score by about one half, including among those taking a β blocker. The effects of β blockers were similar to those of ARBs. Assuming additivity, combination therapy with both ARBs and β blockers from the time of diagnosis would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery.