Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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

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### Webtable 1: Search Strategy

| Embase | Medline | CENTRAL |
|--------|---------|---------|
| 1. Randomized controlled trial/ | 1. Randomized Controlled Trial/ | 1. Marfan Syndrome/ or marfan.mp. |
| 2. Controlled clinical trial/ | 2. Controlled Clinical Trial/ | 2. 1 or 2 or 3 or 4 or 5 or 6 or 7 |
| 3. random$.ti,ab. | 3. Randomized.ab. | 3. exp animals/ not humans.sh. |
| 4. randomization/ | 4. placebo.ab. | 4. 8 not 9 |
| 5. intermethod comparison/ | 5. clinical trials as topic.sh. | 5. 10 Marfan Syndrome/ or marfan.mp. |
| 6. placebo.ti,ab. | 6. randomly.ab. | 6. 10 and 11 |
| 7. (compare or compared or comparison).ti. | 7. trial.ti. | 7. 8 or 11 |
| 8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 8. 10 and 11 | 8. 10 and 11 |
| 9. (open adj label).ti,ab. | 9. (evaluate or evaluated or evaluating or assessed or assessed).ti. | 9. 10 and 11 |
| 10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. | 10. 10 and 11 | 10. 10 and 11 |
| 11. double blind procedure/ | 11. double blind procedure/ | 11. 10 and 11 |
| 12. parallel group$1.ti,ab. | 12. parallel group$1.ti,ab. | 12. 10 and 11 |
| 13. (crossover or cross over).ti,ab. | 13. 10 and 11 | 13. 10 and 11 |
| 14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. | 14. 10 and 11 | 14. 10 and 11 |
| 15. (assigned or allocated).ti,ab. | 15. 10 and 11 | 15. 10 and 11 |
| 16. (controlled adj7 (study or design or trial)).ti,ab. | 16. 10 and 11 | 16. 10 and 11 |
| 17. (volunteer or volunteers).ti,ab. | 17. 10 and 11 | 17. 10 and 11 |
| 18. human experiment/ | 18. 10 and 11 | 18. 10 and 11 |
| 19. trial.ti. | 19. 10 and 11 | 19. 10 and 11 |
| 20. or/1-19 | 20. or/1-19 | 20. or/1-19 |
| 21. (random$ adj samp$ adj7 (cross section$ or questionnaire$ or survey$ or database$)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) | 21. (random$ adj samp$ adj7 (cross section$ or questionnaire$ or survey$ or database$)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) | 21. (random$ adj samp$ adj7 (cross section$ or questionnaire$ or survey$ or database$)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) |
| 22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) | 22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) | 22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) |
| 23. ((case adj control$) and random$) not randomi?ed controlled).ti,ab. | 23. ((case adj control$) and random$) not randomi?ed controlled).ti,ab. | 23. ((case adj control$) and random$) not randomi?ed controlled).ti,ab. |
| 24. (Systematic review not (trial or study)).ti. | 24. (Systematic review not (trial or study)).ti. | 24. (Systematic review not (trial or study)).ti. |
| 25. (nonrandom$ not random$).ti,ab. | 25. (nonrandom$ not random$).ti,ab. | 25. (nonrandom$ not random$).ti,ab. |
| 26. Random field$.ti,ab. | 26. Random field$.ti,ab. | 26. Random field$.ti,ab. |
| 27. (random cluster adj3 samp$).ti,ab. | 27. (random cluster adj3 samp$).ti,ab. | 27. (random cluster adj3 samp$).ti,ab. |
| 28. (review.ab. and review.pt.) not trial.ti. | 28. (review.ab. and review.pt.) not trial.ti. | 28. (review.ab. and review.pt.) not trial.ti. |
| 29. we searched.ab. and (review.ti. or review.pt.) | 29. we searched.ab. and (review.ti. or review.pt.) | 29. we searched.ab. and (review.ti. or review.pt.) |
| 30. update review.ab. | 30. update review.ab. | 30. update review.ab. |
| 31. (databases adj4 searched).ab. | 31. (databases adj4 searched).ab. | 31. (databases adj4 searched).ab. |
| 32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ | 32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ | 32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ |
| 33. Animal experiment/ not (human experiment/ or human/) | 33. Animal experiment/ not (human experiment/ or human/) | 33. Animal experiment/ not (human experiment/ or human/) |
| 34. or/21-33 | 34. or/21-33 | 34. or/21-33 |
| 35. 20 not 34 | 35. 20 not 34 | 35. 20 not 34 |
| 36. Marfan syndrome/ or Marfan.mp. | 36. Marfan syndrome/ or Marfan.mp. | 36. Marfan syndrome/ or Marfan.mp. |
| 37. 35 and 36 | 37. 35 and 36 | 37. 35 and 36 |

**Sources**

Ovid SP was used to search Embase and Medline for relevant trial publications. The latest filter is found in the Cochrane Handbook for Systematic Reviews of Interventions: 4.51 Technical Supplement to Chapter 4: Searching for and selecting studies | Cochrane Training Medline filter is found in Box 3.d. Embase filter is found in Box 3.e. Cochrane CENTRAL registry https://www.cochranelibrary.com/central. There were no language restrictions.

**Search period**

Embase 1974 to 2nd November 2021, Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to 2nd November 2021, All CENTRAL records to 2nd November 2021

**Citation processing**

LH and HH completed the search. Results were downloaded into EndNote X7 where duplicates were removed. Reasons for exclusion were recorded in custom fields. The review of search results was done independently by two authors (two of HH, KW, KD and LH) and any adjudication was carried out by AP.
|               | ARB vs Control |               | ARB vs β-blocker |
|---------------|----------------|---------------|------------------|
|               | (n=353)        | (n=323)       | (n=384)          | (n=382)         |
| Aortic dissection | 0 (0%)         | 2 (2%)        | 2 (1%)           | 3 (1%)          |
| Aortic surgery   | 30 (8%)        | 23 (7%)       | 19 (5%)          | 12 (3%)         |
| Death           | 0 (0%)         | 3 (1%)        | 2 (1%)           | 1 (<0.5%)       |
| Any of the above | 30 (8%)        | 27 (8%)       | 21 (5%)          | 14 (4%)         |

Results are count (%).
**Webtable 3: Effects of ARB vs control and ARB vs β-blocker on the annual rate of change in other pre-specified outcomes**

| Outcome                                           | ARB vs control (direct comparison) | ARB vs β-blocker (direct comparison) | β-blocker vs control (indirect comparison) |
|---------------------------------------------------|------------------------------------|--------------------------------------|--------------------------------------------|
|                                                   | Mean difference (95% CI)           | Mean difference (95% CI)             | Mean difference (95% CI)                  |
| Absolute aortic dimensions at the ascending aorta (mm) | 0.00 (-0.12 to 0.13)               | -0.01 (-0.15 to 0.13)               | 0.01 (-0.18 to 0.20)                      |
| Absolute aortic dimensions at the aortic annulus (mm) | 0.04 (-0.26 to 0.35)               | 0.16 (0.00 to 0.32)                 | -0.11 (-0.46 to 0.23)                     |
| Absolute aortic dimensions at the sino-tubular junction (mm) | 0.10 (-0.13 to 0.33)               | 0.27 (0.02 to 0.52)                 | -0.17 (-0.51 to 0.17)                     |
| Absolute aortic dimensions at the aortic arch (mm)* | -0.03 (-0.17 to 0.10)              | 0.95 (-1.74 to 3.63)                | -0.98 (-3.67 to 1.71)                     |
| Absolute aortic dimensions at the descending aorta (mm)† | -0.03 (-0.16 to 0.10)              | 0.16 (-0.35 to 0.02)                | 0.13 (-0.10 to 0.36)                      |
| Absolute dimension of pulmonary artery (mm)‡ | -0.36 (-2.11 to 1.39)              | 0.02 (-0.27 to 0.31)                | -0.38 (-2.16 to 1.40)                     |
| Systolic blood pressure (mm Hg)                    | -1.54 (-2.43 to -0.65)             | -0.44 (-1.18 to 0.30)               | -1.10 (-2.26 to 0.05)                     |
| Diastolic blood pressure (mm Hg)                   | -1.08 (-1.73 to -0.42)             | 0.43 (-0.25 to 1.10)                | -1.50 (-2.44 to -0.56)                    |
| Heart rate (beats/minute)                          | 0.21 (-0.85 to 1.27)               | 2.20 (1.21 to 3.19)                 | -1.99 (-3.44 to -0.53)                    |
| Pulse pressure (mm Hg)                             | -0.33 (-1.06 to 0.39)              | -0.73 (-1.22 to -0.25)              | 0.40 (-0.48 to 1.27)                      |
| Mean arterial pressure (mm Hg)                     | -1.26 (-1.92 to -0.60)             | 0.10 (-0.56 to 0.75)                | -1.36 (-2.28 to -0.43)                    |
| Height (cm)                                        | 0.03 (-0.36 to 0.43)               | 0.10 (-0.40 to 0.59)                | -0.06 (-0.69 to 0.57)                     |
| Weight (kg)                                       | 0.20 (-0.31 to 0.71)               | 0.00 (-0.39 to 0.39)                | 0.20 (-0.44 to 0.84)                      |
| Body Surface Area, m²                              | 0.00 (-0.01 to 0.01)               | 0.00 (-0.01 to 0.01)                | 0.00 (-0.01 to 0.01)                      |
| BMI, kg/m²                                         | 0.04 (-0.09 to 0.17)               | 0.00 (-0.11 to 0.11)                | 0.04 (-0.13 to 0.20)                      |
| Arm span (cm)                                      | -0.21 (-1.57 to 1.16)              | 0.07 (-0.55 to 0.70)                | -0.28 (-1.78 to 1.22)                     |
| Upper segment measurement (cm)†‡                   | -1.35 (-3.13 to 0.43)              | -0.19 (-0.55 to 0.18)               | -1.16 (-2.98 to 0.66)                     |
| Lower segment measurement (cm)†‡                   | 1.29 (-0.19 to 2.78)               | 0.17 (-0.29 to 0.62)                | 1.13 (-0.43 to 2.68)                      |

For each comparison positive values of the difference reflect a higher mean value in the ‘active’ arm than in the ‘comparator’ arm.
Data were not available to permit meaningful analysis of other outcome measures.

* Canada only, for ARB vs β-blocker.
† PHN only, for ARB vs β-blocker.
‡ Marfan-Sartan only, for ARB vs control.
¶ AIMS only, for ARB vs control.
**Webtable 4: Sensitivity analysis: Annual rate of change of the absolute aortic dimension at the sinuses of Valsalva by different imaging methods**

| Trial | Imaging method                  | Active | Control | Mean difference (95% CI) |
|-------|---------------------------------|--------|---------|-------------------------|
|       |                                 | n      | Mean (95% CI) | n | Mean (95% CI) |                        |
| AIMS  | Echo systole (primary method)    | 95     | 0.57 (0.38 to 0.75) | 85 | 0.83 (0.65 to 1.01) | -0.26 (-0.52 to -0.01) |
|       | Echo diastole (alternative method) | 95     | 0.65 (0.46 to 0.84) | 85 | 0.89 (0.73 to 1.05) | -0.24 (-0.49 to 0.01) |
| PHN   | Echo systole (primary method)    | 299    | 0.93 (0.70 to 1.15) | 294 | 0.75 (0.63 to 0.86) | 0.18 (-0.07 to 0.43) |
|       | Echo diastole (alternative method) | 296    | 0.85 (0.63 to 1.08) | 290 | 0.63 (0.52 to 0.73) | 0.23 (-0.02 to 0.48) |
| LOAT* | MRI diastole (primary method)    | 57     | 0.37 (0.19 to 0.55) | 55 | 0.47 (0.31 to 0.64) | -0.10 (-0.34 to 0.14) |
|       | Echo diastole (alternative method) | 64     | 0.68 (0.47 to 0.89) | 64 | 0.47 (0.32 to 0.62) | 0.21 (-0.05 to 0.47) |

* MRI measurements recorded at baseline and month 36 only. Echo measurements recorded at baseline and months 12, 24 and 36.
Webtable 5: Sensitivity analysis: Effect on annual rate of change in BSA−adjusted aortic root dimension Z score at the sinuses of Valsalva when analysed using standard random effects meta-analysis

| Comparison                      | Mean difference in annual rate of change in BSA−adjusted aortic root dimension Z score (95% CI) | p-value |
|---------------------------------|-------------------------------------------------------------------------------------------------|---------|
| ARB vs control (direct comparison) | -0.06 (-0.15 to 0.03)                                                                          | 0.17    |
| ARB vs β-blocker (direct comparison) | 0.02 (-0.14 to 0.19)                                                                           | 0.80    |
| β-blocker vs control (indirect comparison) | -0.08 (-0.27 to 0.10)                                                                         | 0.39    |

For each comparison positive values of the difference reflect a higher mean value in the ‘active’ arm than in the ‘comparator’ arm. The random-effects analysis (which assumes that the trials are ‘representative’ of an underlying population of trials) estimates both the average and variability of effects across studies and incorporates both into the effect estimates shown. The pre-specified primary analysis shown in the main results was the assumption-free inverse-variance-weighted average of the trial results, which makes no assumptions about the true heterogeneity of effects between studies (in particular it does not assume that such heterogeneity is zero) and should be used to guide clinical interpretation of the results.
623 records identified through Medline and Embase

Additional 121 records identified through other sources

744 records screened

164 duplicate records removed

580 full-text articles assessed for eligibility

509 articles excluded:
- 492 not relevant
- 14 review articles
- 3 trial incomplete

71 articles involving 10 trials (1836 randomised patients)

Data for 2 trials (296 patients) sought but not received (Table 1)

Individual-level-data provided for 8 trials (1540 patients, 1470 without prior aortic root surgery*)

- 1442 patients without prior aortic surgery from 7 trials included in main meta-analyses.
- 28 patients without prior aortic surgery from one trial included only in sensitivity analyses

*70 patients with prior aortic root surgery at enrolment are excluded: 2 (ARB) vs 5 (placebo) from Ghent Marfan and 27 (ARB) vs 36 (control) patients from COMPARE.
### Webfigure 2: Annual rate of change of BSA–adjusted aortic root dimension z–score at the sinuses of Valsalva in patients with confirmed FBN1 pathogenic variant

| Trial                | ARB n mean (SE) | Comparator arm n mean (SE) | Difference mean (95% or 99% CI) |
|----------------------|-----------------|-----------------------------|---------------------------------|
| **ARB vs Control** (<span style='text-decoration: underline;'>χ²</span><sub>2</sub> = 5.0; p=0.17) |                 |                             |                                 |
| Marfan–Sartan        | 114 −0.03 (0.04) | 112 −0.03 (0.05)            | 0.00 (−0.17, 0.17)              |
| COMPARE              | 59 0.09 (0.02)   | 59 0.18 (0.03)              | −0.09 (−0.18, 0.00)             |
| AIMS                 | 69 0.02 (0.06)   | 62 0.18 (0.04)              | −0.15 (−0.32, 0.02)             |
| Ghent Marfan         | 10 0.32 (0.24)   | 5 0.02 (0.08)               | 0.30 (−0.35, 0.94)              |
| **Overall**          | 252 0.06 (0.02)  | 238 0.14 (0.02)             | −0.08 (−0.13, −0.03) p=0.0041   |
| **ARB vs Beta–blocker** (<span style='text-decoration: underline;'>χ²</span><sub>2</sub> = 3.6; p=0.06) |                 |                             |                                 |
| PHN                  | 87 0.02 (0.12)   | 89 −0.17 (0.03)             | 0.19 (−0.13, 0.50)              |
| LOAT                 | 41 −0.20 (0.06)  | 42 −0.10 (0.06)             | −0.10 (−0.31, 0.12)             |
| **Overall**          | 128 −0.16 (0.05) | 136 −0.16 (0.03)            | 0.00 (−0.14, 0.13) p=0.95       |

- 99% or 95% CI

**χ²** values and p-values indicate statistical significance.
Webfigure 3: Annual rate of change of the absolute aortic dimension at the sinuses of Valsalva

| Trial                      | ARB n | ARB mean (SE) | Comparator arm n | Comparator arm mean (SE) | Difference, mm mean (95% or 99% CI) |
|----------------------------|-------|---------------|------------------|--------------------------|------------------------------------|
| Marfan–Sartan              | 145   | 0.42 (0.07)   | 145              | 0.42 (0.09)              | 0.00 (−0.29, 0.29)                 |
| COMPARE                    | 77    | 0.28 (0.06)   | 67               | 0.45 (0.07)              | −0.18 (−0.40, 0.05)                |
| AIMS                       | 95    | 0.57 (0.09)   | 85               | 0.83 (0.09)              | −0.26 (−0.60, 0.07)                |
| Ghent Marfan               | 10    | 0.89 (0.57)   | 5                | 0.18 (0.20)              | 0.71 (−0.85, 2.27)                 |
| Overall                    | 327   | 0.38 (0.04)   | 302              | 0.52 (0.04)              | −0.14 (−0.26, −0.02) p=0.03        |
| ARB vs Control (χ² = 4.5; p=0.21) |       |               |                  |                          |                                    |
| PHN                        | 299   | 0.93 (0.11)   | 294              | 0.75 (0.06)              | 0.18 (−0.15, 0.51)                 |
| LOAT                       | 57    | 0.37 (0.09)   | 55               | 0.47 (0.08)              | −0.10 (−0.42, 0.22)                |
| Canada                     | 8     | 1.61 (0.64)   | 9                | 0.26 (0.54)              | 1.36 (−0.78, 3.50)                 |
| Overall                    | 364   | 0.60 (0.07)   | 358              | 0.66 (0.05)              | 0.05 (−0.12, 0.22) p=0.57          |
| ARB vs Beta-blocker (χ² = 5.1; p=0.08) |       |               |                  |                          |                                    |

99% or 95% CI
Webfigure 4: Sensitivity analysis: annual rate of change of BSA–adjusted aortic root dimension z–score at the sinuses of Valsalva after including Taiwan trial

| Trial                  | ARB n | ARB mean (SE) | Control n | Control mean (SE) | Difference mean (95% or 99% CI) |
|------------------------|-------|---------------|-----------|-------------------|--------------------------------|
| ARB vs Control (χ² = 12.5; p=0.01) |
| Marfan–Sartan          | 145   | −0.03 (0.04)  | 143       | −0.03 (0.04)      | 0.00 (−0.14, 0.15)              |
| COMPARE                | 77    | 0.11 (0.02)   | 67        | 0.17 (0.03)       | −0.07 (−0.15, 0.02)             |
| AIMS                   | 94    | 0.03 (0.05)   | 85        | 0.19 (0.04)       | −0.16 (−0.32, 0.00)             |
| Ghent Marfan           | 10    | 0.32 (0.24)   | 5         | 0.02 (0.08)       | 0.30 (−0.35, 0.94)              |
| Taiwan                 | 15    | −0.02 (0.05)  | 13        | 0.28 (0.07)       | −0.31 (−0.54, −0.07)            |
| Overall                | 341   | 0.06 (0.02)   | 313       | 0.14 (0.02)       | −0.08 (−0.13, −0.03)            |

ARBr better than Control: p=0.0009
## Sensitivity analysis: Annual rate of change of BSA-adjusted aortic root dimension z-score at the sinuses of Valsalva estimated using the Campens method

### Table: Annual change

| Trial                  | ARB n | ARB mean (SE) | Comparator arm n | Comparator arm mean (SE) | Difference mean (95% or 99% CI) |
|------------------------|-------|---------------|------------------|--------------------------|---------------------------------|
| **ARB vs Control**     |       |               |                  |                          |                                 |
| Marfan–Sartan          | 145   | 0.00 (0.02)   | 143              | 0.01 (0.02)              | −0.01 (−0.08, 0.06)             |
| COMPARE                | 77    | 0.03 (0.01)   | 67               | 0.07 (0.02)              | −0.04 (−0.10, 0.01)             |
| AIMS                   | 94    | −0.02 (0.03)  | 85               | 0.06 (0.02)              | −0.08 (−0.17, 0.00)             |
| Ghent Marfan           | 10    | 0.21 (0.18)   | 5                | −0.02 (0.06)             | 0.23 (−0.25, 0.71)              |
| **Overall**            | 326   | 0.01 (0.01)   | 300              | 0.05 (0.01)              | −0.04 (−0.07, −0.01)            |
| **ARB vs Beta-blocker**|       |               |                  |                          |                                 |
| PHN                    | 299   | −0.05 (0.02)  | 294              | −0.10 (0.01)             | 0.05 (−0.02, 0.12)              |
| LOAT                   | 57    | −0.04 (0.02)  | 55               | 0.01 (0.02)              | −0.05 (−0.12, 0.02)             |
| Canada                 | 8     | 0.20 (0.17)   | 9                | −0.08 (0.16)             | 0.28 (−0.31, 0.87)              |
| **Overall**            | 364   | −0.04 (0.01)  | 358              | −0.06 (0.01)             | 0.00 (−0.04, 0.04)              |

**Arrows indicate: 99% or 95% CI**
### Webfigure 6: Sensitivity analysis: annual rate of change of BSA–adjusted aortic root dimension z–score at the sinuses of Valsalva estimated using the Pettersen method

| Trial             | Annual change | Difference | p-value |
|-------------------|---------------|------------|---------|
| **ARB vs Control** |               |            |         |
| Marfan–Sartan     | −0.02 (0.02)  | 143 −0.01 (0.03) | −0.01 (−0.09, 0.08) |
| COMPARE           | 0.06 (0.01)   | 67 0.10 (0.01) | −0.04 (−0.08, 0.01) |
| AIMS              | −0.08 (0.04)  | 85 0.02 (0.02) | −0.10 (−0.22, 0.02) |
| Ghent Marfan      | 0.22 (0.17)   | 5 −0.01 (0.08)  | 0.24 (−0.26, 0.73) |
| **Overall**       | 0.03 (0.01)   | 300 0.06 (0.01) | −0.04 (−0.07, −0.01) |
| **ARB vs Beta–blocker** |           |            |         |
| PHN               | −0.06 (0.02)  | 294 −0.11 (0.02) | 0.05 (−0.02, 0.12) |
| LOAT              | −0.03 (0.02)  | 55 0.01 (0.03)  | −0.04 (−0.14, 0.07) |
| Canada            | 0.03 (0.17)   | 9 −0.03 (0.14)  | 0.06 (−0.50, 0.62) |
| **Overall**       | −0.04 (0.01)  | 358 −0.09 (0.01) | 0.02 (−0.02, 0.07) |

- 99% or 95% CI

---

**Disclaimers:**

1. The values presented are annual changes in the BSA–adjusted aortic root dimension z–score at the sinuses of Valsalva.
2. The p-values indicate the statistical significance of the differences between the ARB and Comparator arms.
3. The confidence intervals provide a measure of the uncertainty around the estimated differences.
4. The annotations for PHN and LOAT suggest the use of 99% CI for a more conservative approach.

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**Note:** The diagrams illustrate the distribution of changes with 99% or 95% CI, highlighting whether ARB or Comparator arm better.