Meta-analysis Examining the Usefulness of Angiotensin Receptor blockers for the Prevention of Aortic Root Dilation in Patients With the Marfan Syndrome

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The Marfan syndrome (MFS) patients are highly predisposed to thoracic aortic aneurysm and/or dissection, with virtually every patient having evidence of aortic disease at some point during their lifetime. We conducted a meta-analysis to investigate the efficacy of angiotensin receptor blockers (ARBs) in slowing down the progression of aortic dilatation in MFS patients. PUBMED, EMBASE, and COCHRANE databases were searched for relevant articles published from inception to February 1, 2020. We included randomized clinical trials evaluating the effect of ARBs on aortic root size in patients with MFS with a follow-up period of at least 2.5 years. Seven studies were included with a total of 1,510 patients. Our analysis demonstrated a significantly smaller change in aortic root and ascending aorta dilation in the ARBs treated group when compared with placebo (mean difference 0.68; 95% confidence interval [CI] −1.31 to −0.04; p = 0.04, I^2 = 94%, and mean difference −0.13, 95% CI −0.17 to −0.09; p < 0.00001, I^2 = 0%, respectively). ARBs as an add-on therapy to beta-blockers resulted in a significantly smaller change in aortic root dilation when compared with the arm without ARBs (mean difference −2.06, 95% CI −2.54 to −1.58; p < 0.00001, I^2 = 91%). However, there was no statistically significant difference in the number of clinical events (aortic complications/surgery) observed in the ARBs arm when compared with placebo (Risk ratio of 1.01, 95% CI 0.74 to 1.38; p = 0.94, I^2 = 0%). In conclusion, ARBs therapy is associated with a slower progression of aortic root dilation when compared with placebo and as an addition to beta-blocker therapy.
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Marfan syndrome (MFS) is an autosomal dominant connective tissue disease and is estimated to affect ≈2 to 3 of 10,000 individuals.[1] It results from mutations that involve the FBN1 gene, which controls the production of Fibrillin 1.[2] Fibrillin 1 is an essential component of all connective tissue in the human body and mutated versions of this glycoprotein result in abnormalities that involve elastic tissues (i.e., lens, skin, heart, and aorta).[3] Aortic involvement in MFS includes aneurysm of the ascending, and to a lesser extent descending, and thoracic aorta and often subsequent aortic dissection,[4] which is the most common cause of mortality in patients with this condition.[5] Current management strategies of aortic involvement include periodic surveillance with imaging and surgically repairing the aorta when its dilation reaches a certain threshold (≥5 cm; growth >0.5 cm/year; ≥4 cm if family history of dissection or contemplated pregnancy).[6,7] Beta-blockers (BBs) have been used to decrease the rate of aortic root dilation.[8] Angiotensin Receptor Blockers (ARBs) have been shown to reduce the progression of aortic root dilation in mice models.[9] Subsequently, multiple clinical trials studied the effect of ARBs in MFS patients with variable results.[10−18] Hence, we performed this meta-analysis to evaluate the role of ARBs in MFS patients.

Methods

We conducted a comprehensive review of previous publications of all relevant studies through February 2020. We searched PUBMED, EMBASE, and COCHRANE databases. We included studies that met our criteria of: (1) the study was a randomized clinical trial published in a peer-reviewed journal, (2) the study evaluated the effect of ARBs on patients with MFS, (3) the study reported the mean difference of aortic root size with time, (4) the study followed the patients for at least 2.5 years. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[19] The search included the following keywords: ARBs or losartan or irbesartan; MFS; Aortic dilation or Aortic dissection. Two authors (AA and YS) independently reviewed the search results, extracted potential articles, and assessed their eligibility. The Cochrane Collaboration risk-of-bias tool was used by two different authors (AA and YS) to assess the quality of randomized clinical trials (RCTs). The primary endpoint of this meta-analysis was mean change in aortic root size. We collected

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the following characteristics of each study: first author's name, year of publication, single vs multicenter, number of participants in each arm, type of control arm, follow up duration, imaging modality, mean age, and mean aortic root size at baseline. Secondary outcomes included clinical events and change in ascending aorta diameter. Clinical events included aortic dissection, aortic surgery, cardiac mortality, cardiovascular-related mortality, and all-cause mortality. Statistical analysis was conducted using Review Manager (RevMan), version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). The Mantel-Haenszel random-effects models were used to estimate the mean difference and the corresponding 95% confidence intervals (CIs). Two-sided p values of <0.05 were considered as statistical significance. I^2 statistics were used to assess statistical heterogeneity. Sensitivity analysis was done with the exclusion of one to two trials to evaluate heterogeneity. A funnel plot was used to assess publication bias.

Results

Seven RCTs were included with a total of 1,510 patients (Figure 1). Characteristics of included studies and patients are described in Tables 1 and 2. A pooled analysis of the data had a significantly smaller change in aortic root dilation in the ARBs group when compared with placebo (mean difference −0.68; 95% confidence interval [CI], −1.31 to −0.04; p = 0.04, I^2 = 94%; Figure 2). Sensitivity analysis showed that heterogeneity was the lowest (I^2 = 0%) when Chiu et al[13] and Groenink et al[12] were excluded. Subgroup analysis of the clinical trials that compared ARBs as an add-on therapy to BBs demonstrated that the addition of ARBs to BBs results in a significantly smaller change in aortic root dilation when compared with BBs-alone (mean difference −2.06, 95% CI −2.54 to −1.58; p < 0.00001, I^2 = 91%; Figure 3). When ARBs were compared head to head with BBs, we found a smaller change in aortic root dilation in the BBs-alone arm (mean difference 0.06, 95% CI 0.05 to 0.07; p < 0.00001, I^2 = 0%) (Figure 4).

There was no statistically significant difference in the number of clinical events observed in the ARBs arm when compared with placebo (Risk ratio of 1.01, 95% CI 0.74 to 1.38; p = 0.94, I^2 = 0%; Figure 5), or BBs (Risk ratio of 1.20, 95% CI 0.48 to 2.98; p = 0.69, I^2 = 64%; Figure 6). There was a statistically significant smaller change in the diameter of the ascending aorta in the ARBs arm when compared with placebo (mean difference −0.13, 95% CI −0.17 to −0.09; p < 0.00001, I^2 = 0%; Figure 7). However, BBs-alone had a significantly lower rate of change in ascending aorta diameter when compared with ARBs-alone (mean difference 0.05, 95% CI 0.04 to 0.06; p < 0.00001, I^2 = 0%; Figure 8). Funnel plot was used to assess for publication bias (Figure 9).

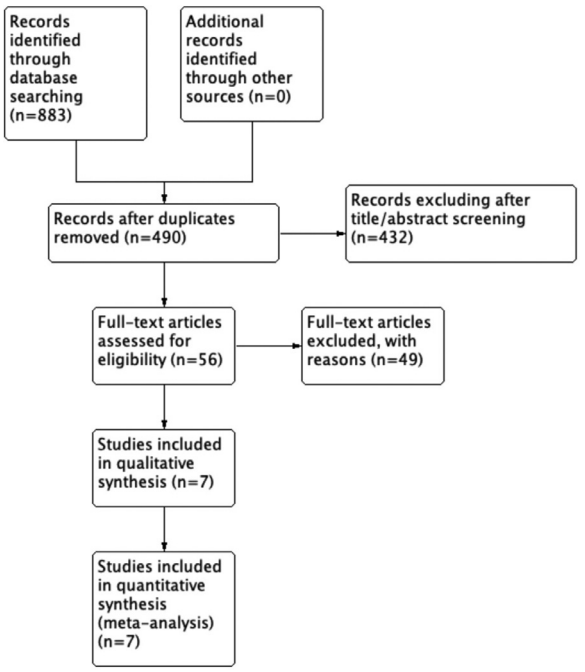

Figure 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

Discussion

Since the 1970s, BBs had shown efficacy in slowing down the progression of thoracic aortic disease in animal models.[20] Subsequently in 1994, Shores et al, randomized 70 patients diagnosed with MFS to propranolol versus placebo. After 10 years of follow-up, the propranolol arm demonstrated a significant reduction in aortic root growth and the development of aortic complications.[21] Subsequent observational reports demonstrated contradicting evidence of BBs in slowing down the progression of aortic dilatation.[22–24] Although the currently available evidence does not provide a strong rationale for the β-adrenergic

Table 1
Baseline characteristics of studies included in the meta-analysis

Study (year)	Number of centers	Arbs group (N)	Control group (N)	Arbs arm	Control arm	Follow-up duration (years)	Imaging modality used for follow-up
Mullen (2020)	Multi	104	88	Irbesartan	Placebo	5	TTE
Teixido-Tura (2018)	Multi	64	64	Losartan	Atenolol	6	CMR
Muino-Mosquera (2017)	Single	12	10	Losartan	Placebo	3	TTE
Milleron (2015)	Multi	151	148	Losartan	Placebo	3.5	TTE
Lacro (2014)	Multi	305	303	Losartan	Atenolol	3	TTE
Chiu (2013)	Single	15	13	Losartan	Atenolol, Propranolol	3	TTE
Groenink (2013)	Multi	116	117	Losartan	Usual care	3	CMR

Abbreviations: ARBs = angiotensin receptor blockers; CMR = cardiac magnetic resonance imaging; TTE = transthoracic echocardiography.

Table 2
Baseline characteristics and outcomes of studies included in the meta-analysis

Study (year)	Age, years (mean)	Male (%)	Presence of causal fbn1 mutation (%)	Baseline z-score	Baseline aortic root diameter, mm (mean)	Change in absolute root diameter, mm (mean)	P-value of the change in root diameter	Prior beta-blockers (%)
Mullen (2020)							0.035	
A, N = 104	18	45	NA	3.2	34.4	0.15		54
C, N = 88	18	52	NA	32.3	34.4	0.05		59
Teixido-Tura (2018)							0.754	
A, N = 64	25.6	35.9	83.3	3.2	35.7	0.4		0
C, N = 64	23.8	46.9	80	3.2	30.9	0.4		0
Muino-Mosquera (2017)							0.768	
A, N = 12	36.83	33.3	NA	3.57	25	1		NA
C, N = 10	35.4	60.1	NA	3.48	25.8	1		NA
Milleron (2015)							0.36	
A, N = 151	30.9	44	78.1	3.74	39.1	0.44		86
C, N = 148	28.9	41	77.7	3.69	39.2	0.51		80
Lacro (2014)							0.20	
A, N = 305	11.0	61	31	1.8	34	0.75		57
C, N = 303	11.5	59	29	1.7	34	0.69		56
Chiu (2013)							0.03	
A, N = 15	12.5	33.3	NA	3.79	21.8	0.3		100
C, N = 13	13.7	46.1	NA	3.26	20	2.7		100
Groenink (2013)							0.014	
A, N = 116	36.8	59.5	74.8	3.9	44.8	0.77		75
C, N = 117	38.3	47	88.2	3.8	43.7	1.35		70.10
Total							NA	
A, N = 767	24.5	44.6	66.8	NA	33.5	0.54		62
C, N = 743	24.2	50.3	68.7	NA	32	0.96		60.8

Abbreviations: A = angiotensin receptor blockers arm; C = control arm; NA = not available.

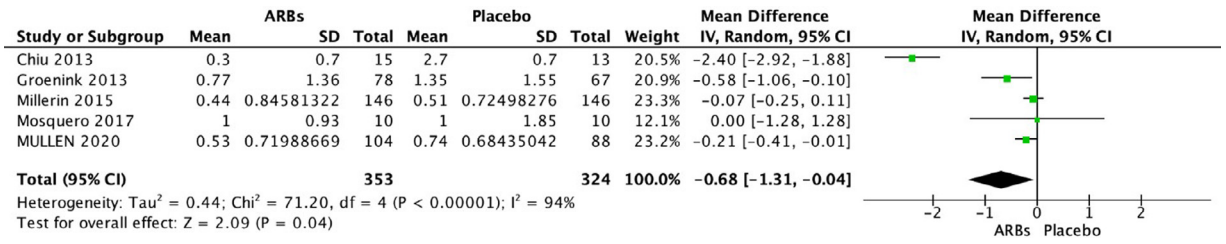

Figure 2. Forest plot of change in aortic diameter in ARBs versus placebo groups.

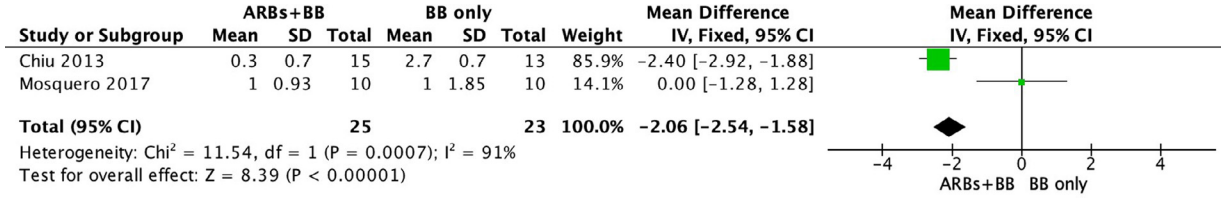

Figure 3. Forest plot of change in aortic diameter in ARBs as an add-on to beta-blockers vs beta-blockers alone.

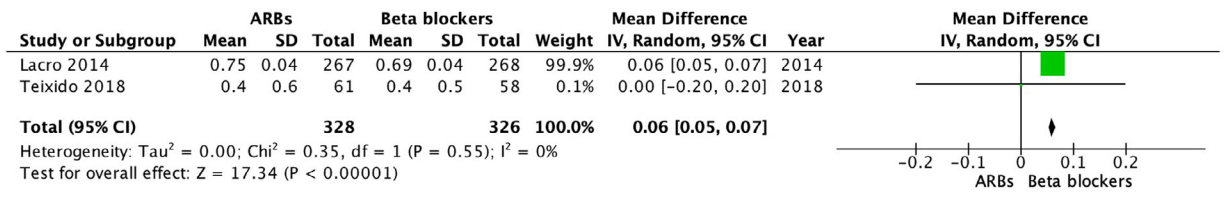

Figure 4. Forest plot of change in aortic diameter in ARBs alone vs B-blocker alone.

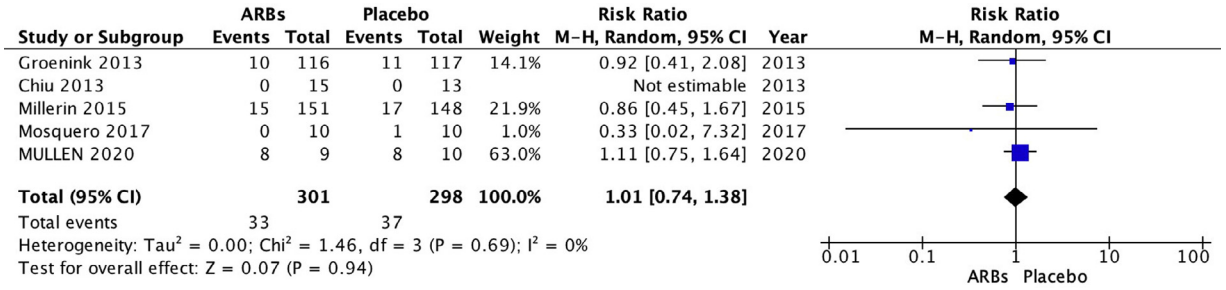

Figure 5. Forest plot of clinical events in ARBs vs placebo.

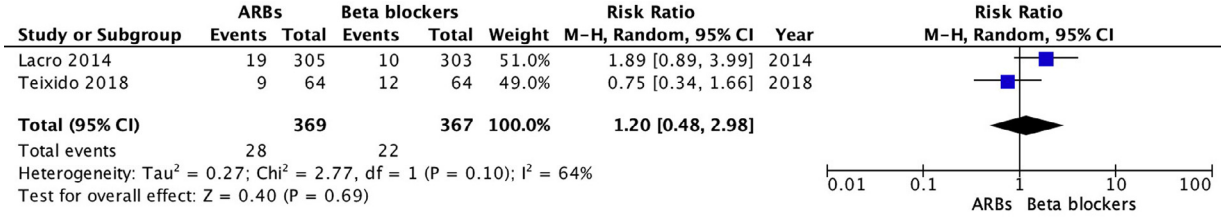

Figure 6. Forest plot of clinical events in ARBs alone vs B-blockers alone.

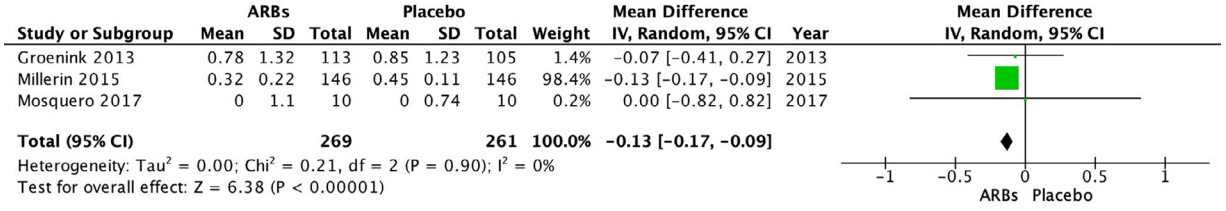

Figure 7. Forest plot of change in ascending aortic diameter in ARBs vs placebo.

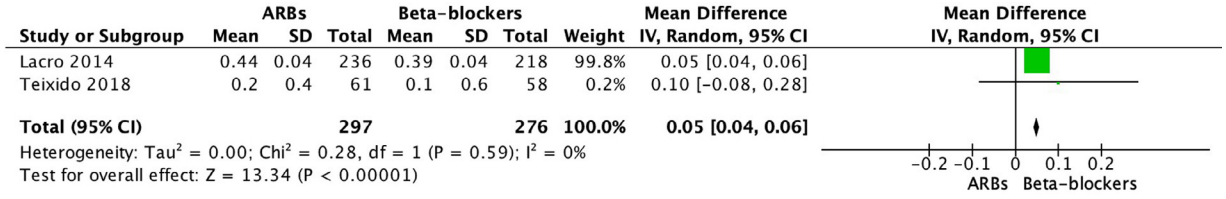

Figure 8. Forest plot of change in ascending aortic diameter in ARBs alone vs B-blockers alone.

blockade, it is still considered by many physicians to be the "gold standard." The 2010 American Heart Association/American College of Cardiology guidelines stated that "For patients with thoracic aortic aneurysm, it is reasonable to reduce blood pressure with BBs (Class IIA, level of evidence B)."[8] This recommendation concurs with the 2017 hypertension guidelines, which recommend BBs as the preferred antihypertensive drug class in patients with hypertension and thoracic aortic disease.[25]

The discovery of the Transforming Growth Factor pathway unraveled another avenue in the management of MFS. The Transforming Growth Factor pathway can be blocked by ARBs, precluding this finding of paramount significance as it provided the first new therapeutic option in over 2 decades.[9] In a small cohort study that included 18 pediatric patients, the addition of ARBs to BBs therapy in patients with MFS significantly slowed the rate of progressive aortic root dilation.[26] Afterward, off label losartan became widely used in MFS patients and several RCTs were conducted. In a multicenter RCT that included 233 participants comparing losartan with no additional treatment, aortic root dilatation rate after 3.1 years was significantly lower in the losartan group than with conventional treatment (0.77 vs 1.35 mm). However, no significant differences in aortic dissection, elective aortic surgery or cardiovascular death between the groups were demonstrated (10 vs 11 events).[12] Since irbesartan is a selective angiotensin type-1 receptor blocker with greater bioavailability, a longer half-life, and more powerful antihypertensive effects than losartan, Mullen et al randomized 192 participants to irbesartan or placebo. At 5 years follow up the mean rate of aortic root dilatation was 0.53 mm/year in the irbesartan group

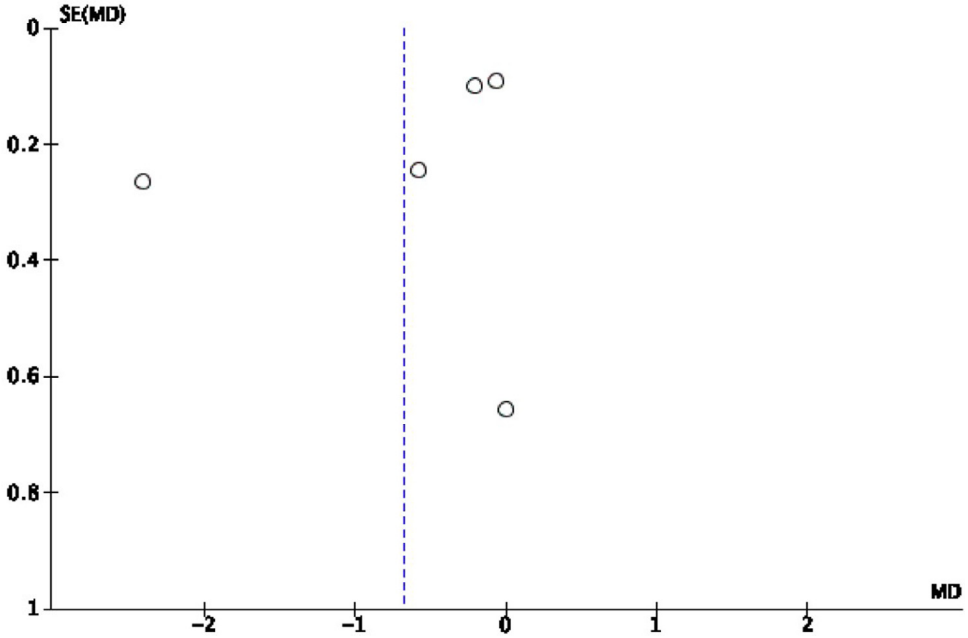

Figure 9. Funnel plot of the mean change in aortic root size.

compared with 0.74 mm/year in the placebo group ($p = 0.030$). There were 5 aortic surgical procedures in the irbesartan group and 4 in the placebo group.[18] Although the study provided valuable information, nonetheless there were several limitations. The study did not achieve the needed power due to low numbers and high drop-out rate. Furthermore, 56% of the patients were on BBs, the study was underpowered to perform meaningful subgroup analysis to investigate the role of ARBs in addition to BBs. In order to evaluate the effect of losartan in combination with BBs, Chiu et al randomized 28 patients with MFS on BBs to receive losartan as add on therapy. After a 35 month follow-up period, the losartan group had a significant reduction in the aortic root dilation.[13] In contrast, a similar design study by Mosquera et al that randomized 22 patients on BBs therapy to either losartan and placebo, did not have additional effect with losartan on inhibiting aortic growth at 3-year follow up.[16] In our meta-analysis, there was a significantly smaller change in aortic root and ascending aorta dilation in the ARBs group when compared with placebo (Figures 2 and 7). Subgroup analysis of the clinical trials that compared ARBs as an add-on therapy to BBs demonstrated that the addition of ARBs to BBs results in a significantly smaller change in aortic root dilation (Figure 3). Yet, there was no statistically significant difference in the number of clinical events observed in the ARBs arm when compared with the placebo. Given the rarity of the clinical events in MFS, we hypothesize that the trials conducted to date might not have been sufficiently powered to detect differences in clinical outcomes. However, although most trials aimed for the maximum tolerated dose of ARBs, it was still relatively a low dose in comparison to the doses used in animal trials.[9]

Two trials evaluated BBs and losartan head to head. The first was a multicenter randomized trial comparing losartan with atenolol in 608 patients with MFS. There was no significant difference in the rate of aortic root dilation between the 2 groups over 3 years. Moreover, although 10 patients in the BB arm vs 19 patients in the losartan arm had aortic complications/surgery, it did not reach statistical significance between the 2 groups ($p = 0.10$).[11] The second, a study that included 128 participants randomized to atenolol versus losartan followed for 6.7 years, found no significant difference between the groups. Additionally, 9 events (14.1%) occurred in the losartan group and 12 (18.8%) in the atenolol group, which was also statistically nonsignificant.[10] In our metanalysis, the subgroup analysis comparing ARBs to BBs demonstrated a statistically significant smaller change in aortic root and ascending aorta dilation in the BBs arm (Figures 4, and 8). However, there was no significant difference in the number of clinical events (Figure 6).

In conclusion, this meta-analysis demonstrated that the use of ARBs in MFS patients can significantly slow down the progression of aortic root dilatation. Subgroup analysis demonstrated that BBs-alone was associated with a significantly smaller change in aortic root diameter when compared with ARBs-alone therapy. However, ARBs as an add on therapy to BBs had significantly slower progression of aortic root dilation in comparison to placebo. There was no significant difference in aortic complications/surgery when using ARBs.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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