Cardiology in the Young (2013), **23**, 568–581
doi:10.1017/S1047951112001412

Original Article

A systematic review of the pharmacological management of aortic root dilation in Marfan syndrome

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Abstract *Background:* Marfan syndrome causes aortic dilation leading to dissection and death. This systematic review examined the use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers in the management of aortic dilation in this disease. *Methods:* We searched four databases – Medline, EMBASE, Web of Science, and The Cochrane Central Register of Controlled Trials – two conference proceedings, references of retrieved articles, and a web-based trial registry. The primary outcome was mortality. The secondary outcomes were aortic dissection, need for elective surgical repair, change in aortic dilation, and adverse events. Two reviewers selected studies, abstracted data, and assessed study quality. Meta-analyses were not performed because of study heterogeneity. *Results:* A total of 18 studies were included – 12 completed and six in progress. Of the completed studies, three before-and-after treatment, one prospective cohort, three retrospective cohorts, and two randomised control trials examined beta-blockers; one randomised and one non-randomised trial examined angiotensin-converting enzyme inhibitors; and one retrospective cohort study examined angiotensin II receptor blockers. Studies in progress are all randomised trials. Mortality was not impacted by drug therapy, although studies were underpowered with respect to this outcome. All drug classes were associated with a decrease in the rate of aortic dilation (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers > beta-blockers); none had an impact on other secondary outcomes. *Conclusions:* On the basis of existing evidence, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers slow the progression of aortic dilation in Marfan syndrome. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may have more effect than beta-blockers; however, more methodologically rigorous studies currently in progress are needed to evaluate the impact of drug therapy on clinical outcomes.

Keywords: Beta-blockers; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers

Received: 22 April 2012; Accepted: 31 August 2012; First published online: 19 October 2012

MARFAN SYNDROME IS AN AUTOSOMAL DOMINANT connective tissue[1] disorder. Aortic root dilation affects up to 80% of Marfan patients[2,3] and predisposes to aortic dissection and death.[1,4] Medications such as beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers are used to minimise dilation.[5,6] There is one systematic review on this topic that has been published to date. Gersony et al[7] found no conclusive evidence to support the use of beta-blockers; however, this review examined only the use of beta-blockers and not angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, warranting a more comprehensive review on the topic. Therefore, the purpose of this systematic review was to examine the evidence for beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers to treat aortic disease in Marfan Syndrome.

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Methods

Study identification and selection

A literature search was conducted independently by two reviewers (V.T. and K.R.) in May, 2010 in four

databases – Medline, EMBASE, Web of Science, and The Cochrane Central Register of Controlled Trials – to identify relevant titles and abstracts. Databases were searched with the following terms: "Marfan*" or "Marfan syndrome"; "aortic root dilatation" or "aorta" or "aortic disease" or "aortic dissection" or "aortic aneurysm"; and "adrenergic beta antagonists" or "beta-blockers" or "angiotensin-converting enzyme inhibitors" or "ACE inhibitors" or "angiotensin II receptor blockers" or "ARBs". No restrictions were placed on patient age, language, or year of study; however, only human studies were included. All comparative study designs were eligible. Trials in progress were searched for on www.clinicaltrials.gov. The search strategy was repeated in April, 2012.

If a title and abstract appeared relevant, full text was retrieved and screened for inclusion using eligibility criteria (Table 1). References of eligible studies and the previous systematic review[7] were hand-searched. We examined conference proceedings of the American Heart Association and the American College of Cardiology from 1990 to 2010.

Risk of bias assessment

Risk of bias of selected studies was rated independently by two reviewers (V.T. and K.R.) using standardised forms. Separate forms were created for observational studies and clinical trials. Clinical trials were assessed for bias as recommended in the Cochrane Handbook.[8] Observational studies were evaluated using guidelines suggested by the MOOSE statement.[9] Corresponding authors of eligible studies were contacted to clarify any questions about study methodology. Disagreements between reviewers were resolved through discussion. Risk of bias of each study was discussed and summarised in a table as suggested by the Cochrane Collaboration.[8] Risk of bias was assessed only for completed studies.

Data abstraction

Characteristics of the study population, details of the medical treatment, and relevant outcomes were retrieved. Data were abstracted on the following outcomes: mortality, aortic dissection/rupture, need for elective surgical repair of the aortic root, change in aortic dilatation, and adverse events. Corresponding authors were contacted to clarify abstracted data to ensure accuracy. Study demographics, such as country in which the study was performed and year of completion, were recorded.

Analysis

The comparison of interest was the use of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers alone or in combination versus placebo or each other in the treatment of aortic root dilatation. The primary outcome was mortality, whereas the other outcomes (Table 1) were secondary. Meta-analysis of observational studies and clinical trials were planned and a priori hypotheses of heterogeneity, such as type of intervention, study design, and patient population, were determined; however, clinical and methodological heterogeneity across studies precluded the use of meta-analyses.[8]

Table 1. Eligibility criteria for identification and selection of studies.

Type of patients	Adult and/or children with Marfan syndrome diagnosed clinically, with McKusick criteria,[37] Berlin criteria,[38] or Ghent criteria[39,40]
Types of interventions	Studies evaluating treatment of aortic disease with: ● BBs ● ACE inhibitors or ARBs ● Combination of BBs with ACE inhibitors or ARBs Compared with: ● Placebo or no treatment ● Each other
Types of outcome measures	Studies including one or more of the following outcomes: Mortality Aortic dissection/rupture Need for elective surgical repair of the aorta Change in aortic dilatation Adverse events BBs: low blood pressure/impaired circulation, bradycardia, bronchospasm, headache/dizziness, nausea, sexual dysfunction, depression, insomnia, other ACE inhibitors: hypotension, cough, hyperkalaemia, headaches/dizziness, fatigue, nausea, renal impairment, angioedema, other ARBs: hypotension, headaches/dizziness, cough, hyperkalaemia, renal impairment, hepatotoxicity, angioedema, nausea, other
Types of studies	Prospective and retrospective cohort studies, cross-sectional, case–control studies, and clinical trials. Trials may be randomised controlled trials, quasi-randomised trials, or non-randomised. Case reports and case series are not eligible for inclusion

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; BB = beta-blocker

Results

Study identification and selection

The flow of studies through the screening and selection process is illustrated in Figure 1. A total of 18 articles[10–27] were included. Only one non-English

https://doi.org/10.1017/S1047951112001412 Published online by Cambridge University Press

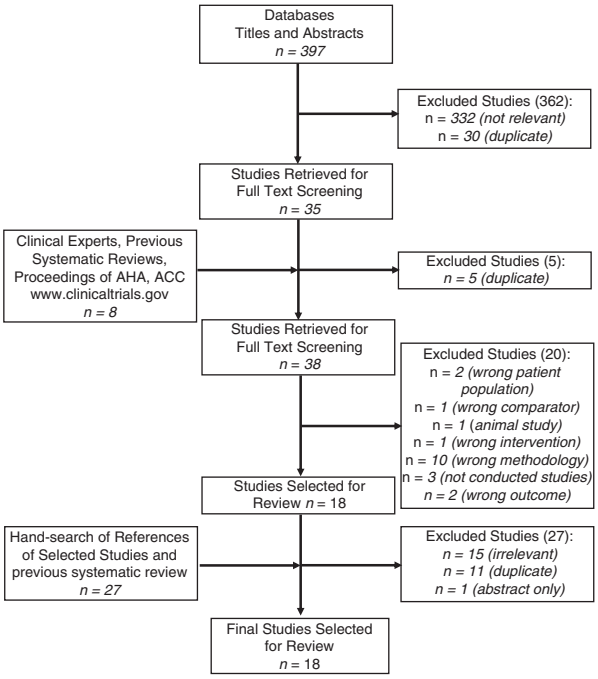

Figure 1.
Summary of study identification and selection. AHA = The American Heart Association; ACC = The American College of Cardiology.

study was retrieved[28]; this study was published in French and was a duplicate of an English publication.[16] Reviewers had good agreement with study selection ($\kappa = 0.79$). Our secondary search did not reveal any additional new studies published between May, 2010 and April, 2012.

Risk of bias assessment

Of the 18 studies,[10–27] there were nine observational studies[11,16,18–23,27] and nine randomised controlled trials.[10,12–15,17,24–26] Of the nine randomised controlled trials, six are in progress.[12–15,17,26] The authors for 13[10–16,18,19,21–24] of the included studies responded to our team and clarified the study methodology and abstracted data. High risk of bias was demonstrated in two of the trials,[24,25] whereas the third showed low risk of bias.[10] All observational studies[11,16,18–23,27] had at least one important methodological flaw, the most common being lack of blinding. Risk of bias assessment is summarised in Figures 2 and 3.

Characteristics of completed studies

Completed studies[10,11,16,18–25,27] were published between 1992 and 2008. Most studies were conducted in North America,[10,11,18–25,27] and there was one from Australia[10] and another from France.[16] The sample size for the nine observational studies

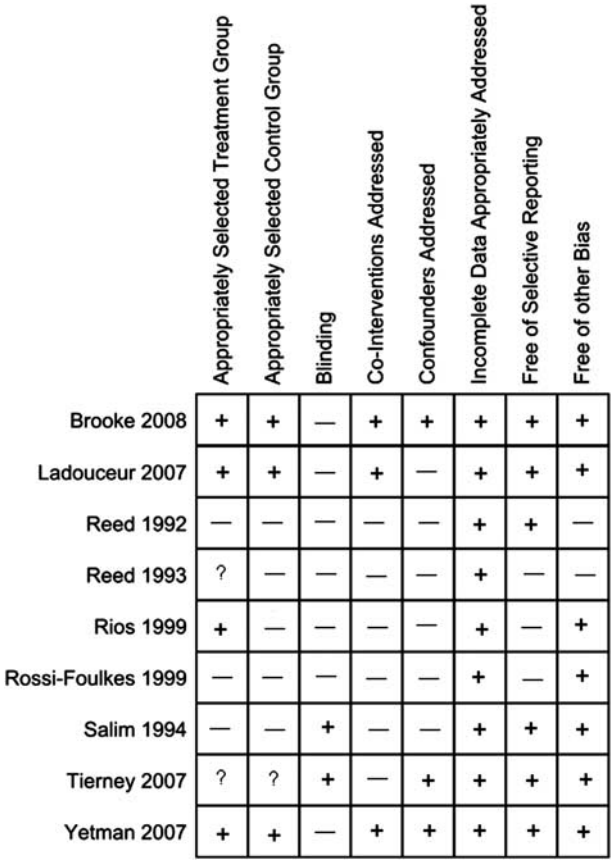

Figure 2.
Methodological quality summary for included observational studies. "+" indicates low risk of bias, "−" indicates a high risk of bias, and "?" indicates an unclear risk of bias.

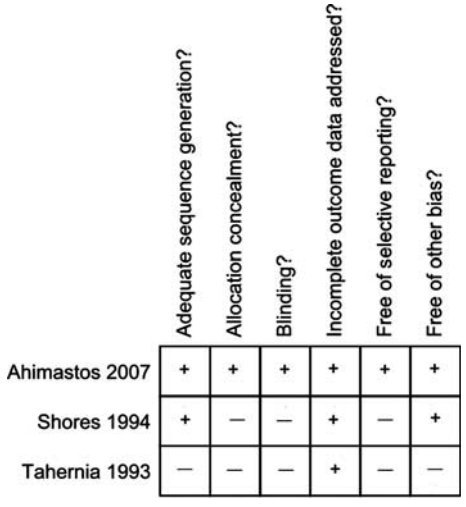

Figure 3.
Methodological quality summary for included randomised controlled trials. "+" indicates low risk of bias and "−" indicates a high risk of bias.

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ranged from 22 to 155 patients (median 55), with a total of 579 patients. There was one observational study[20] conducted exclusively in adult patients, six studies[16,18–22] were conducted exclusively in children, and two studies[11,27] included both adults and children.

The sample size for the three completed randomised controlled trials[10,24,25] ranged from 6 to 70 patients (median 17), with a total of 93 patients overall.[10,24,25] All completed randomised controlled trials[10,24,25] were single-centre studies; one was conducted exclusively in children, [25]one was conducted exclusively in adults,[25] and one included both adults and children.[24]

In all, three before-and-after treatment,[18–20] one prospective cohort,[22] three retrospective cohorts,[16,21,23] and two randomised controlled trials[24,25] examined beta-blockers. Of these studies, four examined atenolol,[18–20,23] two studies examined propranolol,[24,25] and one study examined both atenolol and propranolol.[22] The remaining two studies[16,21] examined different types of beta-blockers; however, it is unclear which beta-blocker was used predominantly. Dose ranges for atenolol or propranolol were similar across studies (see Table 2). One non-randomised trial[27] and one randomised controlled trial[10] examined angiotensin-converting enzyme inhibitors versus beta-blockers; the non-randomised trial evaluated enalapril, whereas the randomised trial examined perindopril. There was one retrospective cohort[11] that examined angiotensin II receptor blockers, specifically losartan in 17 patients and irbesartan in one patient. The details of inclusion and exclusion criteria, study interventions, and baseline characteristics of the included patients are provided in Tables 2 and 3.

Characteristics of studies in progress

Protocols for studies in progress[12–15,17,26] were published between 2007 and 2010. In Europe, four studies in progress are being conducted.[12–15,17] A large multi-centre study is being conducted in North America[15] and one study is being conducted in Asia.[26] All studies are randomised controlled trials using a conventional parallel group design, and all include losartan.

Analysis of outcomes

Mortality (Fig 4). A total of five observational studies[16,20–23] and one randomised controlled trial[24] evaluated mortality in patients treated with beta-blockers. There were two studies that examined atenolol,[20,23] two studies that examined propranolol,[22,24] and the remaining two studies examined all types of beta-blockers.[16,21] There were two studies examining angiotensin-converting enzyme inhibitors that evaluated mortality. Enalapril[27] was examined in one observational study, one randomised controlled trial evaluated perindopril,[10] and one observational study[11] examined losartan. None of the studies demonstrated an impact on mortality.

Aortic dissection or rupture (Fig 5). In all, five observational studies[16,20–23] and one randomised controlled trial[24] evaluated aortic dissection or rupture in patients treated with beta-blockers. There were two studies that examined atenolol,[20,23] two studies that examined propranolol,[22,24] and the remaining two studies examined all types of beta-blockers[16,21] There were two studies examining angiotensin-converting enzyme inhibitors that evaluated dissection or rupture. There was one observational study that evaluated dissection in patients treated with enalapril,[27] one randomised controlled trial that evaluated the effect of perindopril.[10] One observational study evaluated ARBs, specifically losartan, that reported aortic dissection. In six studies,[10,11,16,20,22,27] aortic dissection and/or rupture did not occur in any patient. Rossi-Foulkes et al[21] evaluated the use of all types of beta-blockers versus no treatment and reported three patients in the control group with aortic dissection and/or rupture. Selamet Tierney et al[23] examined the use of atenolol versus no treatment; one patient in the treatment group had a dissection. In the trial by Shores et al,[24] which examined the use of propranolol versus no treatment, four patients in the control group and two patients in the treatment group had a dissection. The occurrence of aortic dissection was not statistically significant in any of these studies.

Need for elective surgical repair of the aorta and/or aortic valve because of severe aortic dilatation (Fig 6). In all, five observational studies[16,20–23] and one randomised controlled trial[24] evaluated the need for elective surgery in patients treated with beta-blockers. There were two studies that examined atenolol,[20,23] two studies that examined propranolol,[22,24] and the remaining two studies examined all types of beta-blockers.[16,21] There was one observational study that evaluated the need for surgery in patients treated with enalapril,[27] one randomised controlled trial that evaluated perindopril,[10] and one observational study examining losartan[11] that evaluated the need for elective surgery. In four studies,[11,16,22,27] patients required elective surgical repair of the aorta and/or aortic valve. Salim et al[22] examined propranolol versus no treatment and reported that five patients in the treatment group required elective surgery compared with no patients in the control group. In the study by Ladouceur et al[16] examining the use of all types of beta-blockers versus no treatment, five patients in the control group required elective surgery versus two patients in the treatment group. Yetman et al[27] evaluated enalapril versus propranolol and reported

Table 2. Characteristics of the included studies.

Author (year), location	Study design	Inclusion criteria	Exclusion criteria	Intervention (sample size)	Control (sample size)
			BBs		
Reed and Alpert (1992), USA[18]	Before and after treatment	Marfan syndrome diagnosed by a clinical geneticist	Unclear	Atenolol (9); 2 mg/kg/day	Self-control (9)
Reed et al (1993), USA[19]	Before and after treatment	Marfan syndrome diagnosed by a clinical geneticist	Unclear	Atenolol (22); 2 mg/kg/day	Self-control (22)
Tahernia (1993), USA[25]	Randomised controlled trial single-centre parallel	Criteria for Marfan syndrome by Pyeritz and McKusick[37]	Unclear	Propranolol (3); <1 mg/kg/day	No treatment (3)
Salim et al (1994), USA[22]	Prospective cohort	1. Berlin criteria[38] 2. Evaluated between 1978 and 1990	1. History of bronchospasm 2. 1st visit age >21 year 3. Requiring treatment >1 year 4. Treatment for diabetes mellitus 5. Severe ventricular dysfunction 6. Resting bradycardia (<50 bpm) 7. Patient or parent refusal	Propranolol or atenolol (80); propranolol maximum 40 mg/day; atenolol 12.5–25 mg/day	No treatment (13)
Shores et al (1994)[24]	Randomised controlled trial single-centre parallel	1. Marfan syndrome patients meeting Berlin Criteria[38] 2. Seen within one year of start of study	1. Age >12 and <50 years 2. Current treatment with propranolol 3. Previous aortic dissection or cardiovascular surgery 4. Aortic regurgitation on auscultation 5. Moderate–severe mitral regurgitation 6. Signs and symptoms of congestive heart failure 7. LV ejection fraction <50% 8. AV conduction delay 9. Contraindication to BBs	Propranolol (32); initial dose 10 mg q.i.d, increased until heart rate remained <100 beats/min with exercise.	No treatment (38)
Rios et al (1999), USA[20]	Before and after treatment	1. Patients in Marfan syndrome clinic	1. Age <18 year or >45 year 2. Ongoing treatment with BBs 3. Aortic dissection or previous cardiac surgery 4. Significant decrease in left ventricle systolic performance 5. Moderate or severe mitral regurgitaiton, aortic insufficiency by 2D echo 6. Resting bradycardia <50 bpm or any degree of heart block 7. History of diabetes or bronchospasm	Atenolol (23); starting dose 25 mg/day; maximum dose variable to target heart rate of 50–60 beats/min, systolic BP no <90 mmHg or side effects	Self-control (23)
Rossi-Foulkes et al (1999), USA[21]	Retrospective cohort	1. Berlin criteria[38] 2. Female patients age <17 and male patients age <19	Unclear	BBs; type and dose not specified (15)	No treatment (27)

Table 2. *Continued*

Author (year), location	Study design	Inclusion criteria	Exclusion criteria	Intervention (sample size)	Control (sample size)
Ladouceur et al (2007), France[16]	Retrospective cohort	1. Berlin criteria[38] 2. <12 years at diagnosis	1. Neonatal Marfan syndrome 2. >12 years taking BBs for 1st time 3. Children receiving ACE inhibitors	BBs (atenolol, nadolol, propranolol) (77); doses not specified	No treatment (78)
Selamet Tierney et al (2007), USA[23]	Retrospective cohort	1. Ghent criteria[39] 2. Age ≥18 years	Unclear	Atenolol (29); 25 mg/day children; 50 mg/day adolescents	No treatment (34)
			ACE inhibitors		
Yetman et al (2007), USA and Canada[27]	Prospective cohort	1. Ghent criteria[39] 2. Evidence of cardiac involvement	1. Undergone previous surgery 2. Pregnant 3. >mild aortic or mitral insufficiency	Enalapril (32); starting dose 5 mg/day to maximum of 20 mg/day	Propranolol (if <1 2.5 kg) or atenolol (if >12.5 kg) (25); propranolol 2 mg/kg/day; atenolol starting 1 mg/kg/day to maximum of 2 mg/kg/day
Ahimastos et al (2007)[10]	Randomised controlled trial single-centre parallel	1. Ghent criteria[39] 2. Ages 18–40 years 3. Serum Cr <1.2 mg/dl 4. Systolic BP <140/90 5. No history of previous aortic surgery or BB therapy	1. Homocysteinuria	Perindopril + BBs (10); perindopril starting at 2 mg/day to maximum of 8 mg/day BB type and dose not specified	Placebo + BB (7); BB type and dose not specified
			ARBs		
Lacro et al (2007)[15]	Randomised controlled trial multi-centre (14 centres) parallel	1. Diagnosis of Marfan syndrome by Ghent[39] criteria 2. Age 6 months to 25 years 3. BSA-adjusted aortic root score >3.0 4. Informed consent and assent	1. Prior aortic surgery 2. Aortic root dimension >5 cm 3. Planned aortic surgery within 6 months of enrolment 4. Aortic dissection 5. Clinical or molecular diagnosis of other connective tissue disorders (Loeys–Dietz, Shpritzen–Goldberg) 6. Therapeutic use of ACE inhibitors, BBs, or ARBs (hypertension, arrhythmia, ventricular dysfunction, valve regurgitation) 7. History of angioedema with ACE inhibitor 8. Previous intolerance of ARB 9. Previous intolerance of BBs 10. Renal dysfunction 11. Asthma 12. Diabetes mellitus 13. Planned pregnancy within 36 months of enrolment 14. Inability to complete study procedures – for example, poor acoustic windows	Losartan (302); starting dose 0.4 mg/kg/day to a maximum daily dose of 1.0–1.4 mg/kg/day, not to exceed 100 mg/day	Atenolol (302), starting dose 0.5 mg/kg/day to maximum of 4 mg/kg/day not to exceed 250 mg/day

Table 2. *Continued*

Author (year), location	Study design	Inclusion criteria	Exclusion criteria	Intervention (sample size)	Control (sample size)
Brooke et al (2008), USA[11]	Retrospective cohort	1. Ghent criteria[39] 2. F/u between October 1996 and November 2007	1. No prior aortic surgery 2. Intolerance or contraindication to BBs or ARB	Losartan or irbesartan; starting losartan dose 0.6 mg/day to maximum of 1.4 mg/day; starting dose irbesartan 1.4 mg/kg to maximum of 2 mg/kg + BBs type and dose of BB unclear (18)	BBs (65); type and dose of BB unclear
Jondeau, 2008[14]	Randomised controlled trial multi-centre parallel	1. 10 years or older 2. Marfan syndrome according to international criteria 3. Signed informed consent	1. Previous surgery of the ascending aorta, or surgery planned 2. Poor acoustic windows 3. Contraindication to ARB 4. Pregnancy or planned pregnancy within 3 years 5. Breastfeeding 6. Non-member of the social security 7. Participation in another clinical study	Losartan 50 mg/day if <50 kg, 100 mg/day if >50 kg (150)	Placebo (150)
Wu, 2008[26]	Randomised controlled trial single-centre parallel	1. Marfan syndrome with recognised aortic root dilation 2. Patients must be older than 1 year of age 3. BB treatment for at least 3 months 4. Must sign an informed consent form	1. Prior aortic root surgery 2. Aortic root dimension >5.5 cm 3. Aortic surgery within 6 months 4. Diabetes mellitus or liver and renal dysfunction or asthma 5. Pregnancy 6. Intolerance to losartan therapy	Losartan + atenolol or propranolol (22); losartan adult 100 mg/day; paediatric 50 mg/day; atenolol 50 mg/day; propranolol adult 40 mg/day; paediatric 1 mg/kg/day to maximum of 2 mg/kg/day	Atenolol or propranolol (22); atenolol 50 mg/day; propranolol adult 40 mg/day; paediatric 1 mg/kg/day to maximum of 2 mg/kg/day
Gambarin et al (2009)[13]	Randomised controlled trial single-centre parallel	1. Diagnosis of Marfan syndrome: Ghent[39] criteria and genetically proven defect of the FBN1 gene 2. Age: 12 months to 55 years 3. BSA-adjusted aortic z-score 2 measured at the level of the sinuses of Valsalva at baseline or absolute aortic root diameter >38 mm for females and >40 mm for males	1. Prior aortic surgery and/or dissection 2. Aortic root diameter at the level of the sinuses of Valsalva 5 cm 3. Planned aortic surgery within 6 months of enrolment 4. Clinical or molecular diagnosis of non-MFS connective tissue diseases sharing some features with Marfan syndrome (Shprintzen–Goldberg syndrome or Loeys–Dietz syndrome 5. Progression >5 mm/year even in patients with aortic root disease <5 cm 6. Known side effects while taking an ARB or a BBs 7. Intolerance to ARB 8. Intolerance to BB 9. Renal dysfunction (creatinine level more than upper limit of age-related normal values) 10. Diabetes mellitus 11. Pregnancy or planned pregnancy within 48 months of enrolment 12. Technical limitations for the imaging studies including poor acoustic windows 13. Asthma	Losartan and nebivolol or losartan alone (97 both or 97 losartan alone); losartan dosing adult dose starting 12.5 mg daily to maximum of 100 mg daily; paediatric dose starting 0.2 mg/kg to maximum of 1.4 mg/kg; nebivolol dosing adult dose starting 1.25 mg daily to maximum of 10 mg daily; paediatric dose starting 0.02 mg/kg to maximum of 0.16 mg/kg	Nebivolol (97); adult dose starting 1.25 mg daily to maximum of 10 mg daily; paediatric dose starting 0.02 mg/kg to maximum of 0.16 mg/kg

Table 2. *Continued*

Author (year), location	Study design	Inclusion criteria	Exclusion criteria	Intervention (sample size)	Control (sample size)
De Backer, 2009[12]	Randomised controlled trial single-centre parallel	1. Age >10 years 2. Ghent[39] criteria or genetically proven FBN1 mutation or linkage 3. Consent obtained 4. Z-score of aorta at the level of the sinus of Valsalva ≥2 5. ARB naive patients	1. Poor echocardiographic window 2. Contraindication to ARB 3. Intolerance to ARB 4. Pregnancy or breastfeeding 5. Absence of effective contraception 6. Liver dysfunction 7. Heart failure 8. Patients included in other clinical trials	Losartan + BBs (unclear); losartan 50 mg/day if <50 kg or 100 mg/day if >50 kg; type and dose of BB unclear	BBs (unclear); type and dose of BB unclear
Radonic et al (2010)[17]	Randomised controlled trial single-centre parallel	1. Diagnosis of Marfan syndrome by Ghent[39] criteria 2. Age ≥18 years	1. >1 vascular prosthesis 2. Aortic root diameter >50 mm 3. Renal dysfunction (Cr >130 μg/ml or K >5 mmol/ml), 4. Treatment with ACE inhibitors or ARBs 5. History of angioedema or intolerance to ACE inhibitors or ARBs 6. Intolerance of intravenous contrast for magnetic resonance angiography or computed tomography 7. Aortic surgery within the last 6 months	Losartan ± BBs (unclear); losartan starting 50 mg/day to maximum of 100 mg/day; type and dose of BBs unclear	No treatment ± BBs (unclear)

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; AV = atrioventricular; BB = beta-blocker; BP = blood pressure; BSA = body surface area; FBN1 = fibrillin-1; LV = left ventricular; MFS = Marfan syndrome

Studies are listed according to primary treatment under evaluation

Table 3. Age and gender of subjects in completed studies and adverse events.

	Intervention			Control		
Author (year)	**Age (years; mean ± SD)**	**% Female**	**Adverse events**	**Age (years; mean ± SD)**	**% Female**	**Adverse events**
			BB			
Reed and Alpert (1992)[18]	14.7	44	Not given	n/a	44	n/a
Reed et al (1993)[19]	14 ± 3	36	None	n/a	36	n/a
Tahernia (1993)[25]	10 (10, 9, 11)	67	Not given	8 (14, 5, 6)	0	None
Salim et al (1994)[22]	10.4 ± 3.4	30	Insomnia/dream disturbance 5, bronchospasm 1, depression 1, heart block 4, attenuated effects of alcohol 1, pt with >1 side effect 10	10.2 ± 4.6	30	Not given
Shores et al (1994)[24]	14.5	38	Lethargy 4, peripheral oedema 1	15.4	50	None
Rios et al (1999)[20]	31 ± 14.2	52	Bronchospasm 1, intolerance to BB 4	n/a	52	n/a
Rossi-Foulkes et al (1999)[21]	11.2 ± 5.3	Unclear	Not given	8.0 ± 5.2	Unclear	Not given
Ladouceur et al (2007)[16]	6.1 ± 3.2	48	Bronchospasm 1, depression 1, exercise intolerance 4, fatigue 4	7.4 ± 5.2	46	Not given
Selamet Tierney et al (2007)[23]	9.2 ± 4.0	52	None	8.8 ± 4.8	53	Bronchospasm 1, depression 1, headaches/dizziness 4, fatigue 1
			ACE inhibitors			
Yetman et al (2007)[27]	14.6 ± 7.7	52	None	12.0 ± 7.6	49	Depression 2, fatigue 2, memory loss 2
			ARBs			
Ahimastos et al (2007)[10]	34 (5)	20	None	31 (2)	29	None
Brooke et al (2008)[11]	Median 6.5 (range 1–16)	50	None	Median 12 (range 4 months–19 years)	19	None

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; BB = beta-blockers

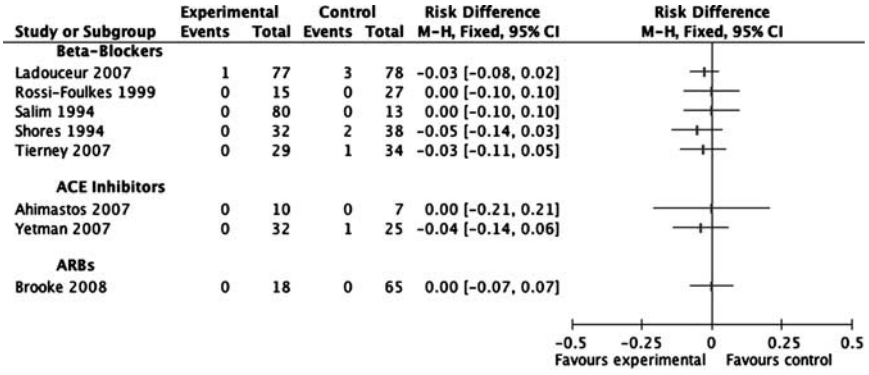

Figure 4.
Impact of pharmacological therapy on mortality. Experimental and control interventions varied across studies and are detailed in Table 2. ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; M–H = Mantel–Haenszel.

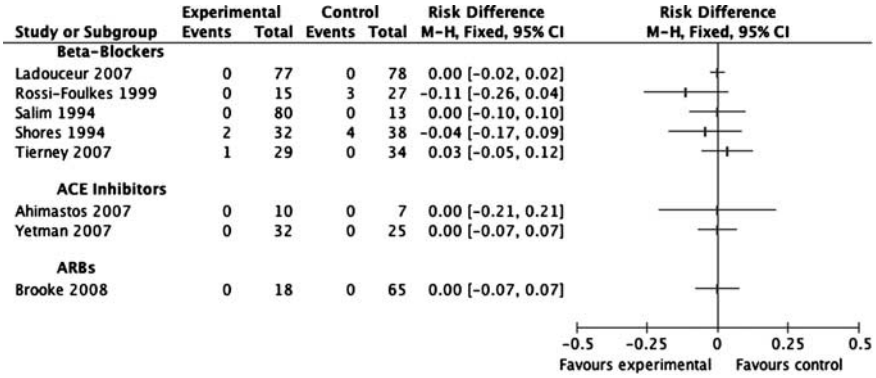

Figure 5.
Impact of pharmacological therapy on aortic dissection or rupture. Experimental and control interventions varied across studies and are detailed in Table 2. ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; M–H = Mantel–Haenszel.

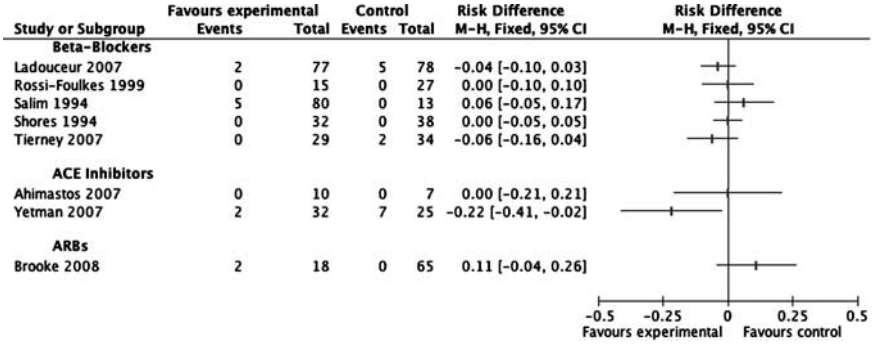

Figure 6.
Impact of pharmacological therapy on need for elective repair. Experimental and control interventions varied across studies and are detailed in Table 2. ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; M–H = Mantel–Haenszel.

that seven patients in the propranolol group versus two patients in the enalapril group required elective surgery. Brooke et al[11] evaluated losartan versus beta-blockers and reported that two patients in the losartan group required elective surgery and that no patients in the beta-blockers group required surgery. The need for elective surgery was not statistically significant in any of these studies.

Change in aortic dilatation (Fig 7). In all, seven observational studies[16,18–23] and one randomised controlled[24] trial evaluated aortic dilation in patients treated with beta-blockers. There were four

https://doi.org/10.1017/S1047951112001412 Published online by Cambridge University Press

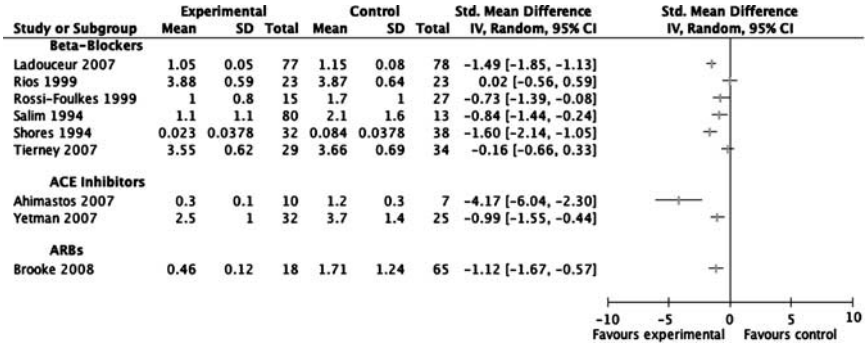

Figure 7.
Impact of pharmacological therapy on aortic dilatation. Note: *Studies varied in how they measured this outcome. Experimental and control interventions varied across studies and are detailed in Table 2. This figure is intended to provide a general graphical display of study findings. ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; IV = inverse variance; M–H = Mantel–Haenszel; SD = standard deviation.*

studies that examined atenolol,[18–20,23] two studies that examined propranolol,[22,24] and the remaining two studies examined all types of beta-blockers.[16,21] There was one observational study that examined aortic dilation in patients treated with enalapril versus beta-blockers,[27] one randomised controlled trial[10] that evaluated perindopril versus beta-blockers, and one observational study that examined aortic dilation in patients treated with losartan versus beta-blockers.[11] In the three before-and-after studies examining atenolol,[18–20] there was no significant difference in aortic root size. In the study by Selamet Tierney et al[23] examining atenolol versus no treatment, there was also no statistically significant difference between treatment and control groups in aortic root diameter ($p = 0.52$). In the remaining four studies examining beta-blockers, there was a difference in aortic dilation between the treatment and control groups. Salim et al[22] evaluated the use of propranolol or atenolol versus no treatment and reported a slower aortic growth rate in the beta-blockers group (1.1 mm/year $\pm$ 1.1) versus the control group (2.1 mm/year $\pm$ 1.60, $p < 0.006$). Rossi-Foulkes et al[21] evaluated the use of all types of beta-blockers versus no treatment and also found a statistically significant difference in aortic root growth rate (mm/year) between the beta-blockers group (1.0 ± 0.8) and the control group (1.7 ± 1.0, $p < 0.05$). Ladouceur et al[16] evaluated the use of all types of beta-blockers versus no treatment and found that the rate of aortic dilation (mm/year) was significantly different in the beta-blockers group, 1.05 ± 0.05 versus 1.15 ± 0.08 for the control group ($p = 0.001$). Shores et al[24] evaluated propranolol versus no treatment and found a significant difference in the rate of change in the aortic ratio, defined as the measured aortic diameter divided by the diameter predicted by the patient's height, weight, and age, between the beta-blockers (0.023 per year) and control (0.084 per year) groups ($p < 0.001$). Yetman et al[27] examined the rate of change in dilation (%/year) and found a significant difference between treatment with enalapril (-2.5 ± 1) and propranolol (1.7 ± 1.2, $p < 0.001$). Ahimastos et al[10] examined the aortic root diameter in systole indexed to body surface area (mm/m^2); the perindopril group had a significantly smaller indexed root diameter (0.3 ± 0.1 mm/m^2) compared with the propranolol group (1.2 ± 0.3 mm/m^2, $p = 0.01$). Brooke et al[11] also found a statistically significant difference in aortic root growth rate (mm/year) between losartan (0.46 ± 0.12) and beta-blockers (1.71 ± 1.24, $p < 0.001$).

Adverse events (Table 3). In all, four studies[16,18,19,22] did not report adverse events, whereas eight studies[10,11,20,21,23–25,27] did. Of these eight studies, five studies[20,21,23–25] evaluated various side effects of beta-blockers, two studies evaluated side effects with angiotensin-converting enzyme inhibitors,[10,27] and one study evaluated side effects with angiotensin II receptor blockers.[11] The three observational studies evaluating beta-blockers[20,21,23] – two evaluating atenolol[20,23] and one evaluating all types of beta-blockers[21] – did not report any significant adverse effects. The randomised controlled trial by Tahernia[25] did not find any adverse events in the propranolol group. In the randomised controlled trial by Shores et al,[24] the authors reported heart block as a side effect of propranolol. There were three patients who had a first-degree block and one patient who had a third-degree heart block. Ahimastos et al[10] did not find any adverse events in the group treated with perindopril versus the control group treated with propranolol. In the study by Brooke et al,[11] examining losartan, there were no adverse events in the treatment or control group.

https://doi.org/10.1017/S1047951112001412 Published online by Cambridge University Press

Discussion

This systematic review examined the use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers to manage aortic root dilation in Marfan syndrome. These drugs did not reduce mortality, aortic dissection, or the need for elective aortic root or valve surgery; these events were rare, and studies to date have not been powered to detect statistically significant differences in these outcomes. However, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers were associated with a decrease in aortic root dilation. Adverse events among all three drug classes were rare and mild, with the exception of a single patient experiencing a third-degree heart block while on propranolol.

Most studies evaluating beta-blockers examined the use of atenolol.[16,18–20,23] Beta-blocker therapy is thought to be beneficial with respect to aortic root dimension by decreasing heart rate and blood pressure and by decreasing change in aortic pressure during left ventricular ejection.[29] These changes decrease aortic stretch and reduce aortic stiffness, which prevents or minimises dilatation[20]; however, the exact mechanism of action remains undefined.[20] Atenolol is more beta-1 selective than propranolol and may be of more benefit in the treatment of aortic root dilation.[24] Studies examining angiotensin-converting enzyme inhibitors used enalapril[27] and perindopril.[10] There is growing evidence that inappropriate activation of the renin–angiotensin system may be involved in aortic dilation.[30] Angiotensin-converting enzyme inhibitors may stop the abnormal activation of the renin–angiotensin system.[30] The single completed study examining angiotensin II receptor blockers evaluated losartan.[11] Aortic aneurysm has been found to occur with increased transforming growth factor beta signalling.[31] Angiotensin II receptor blockers inhibit transforming growth factor beta signalling and have reduced aortic dilatation in a mouse model.[31]

There were two studies[10,27] that found that angiotensin-converting enzyme inhibitors were associated with a slower rate of change of aortic size compared with beta-blockers, and one study[11] that showed that angiotensin II receptor blockers may be superior to beta-blockers as well. However, studies were small in sample size and firm conclusions about the benefits of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors over beta-blockers cannot be made from the existing literature. Studies in progress may provide better evidence for one drug class versus another once completed.

Limitations of the existing evidence

In the majority of completed studies[10,11,16,20–23,25,27] a measure of change in the size of the aorta was used as a primary outcome. Change in aortic root dimension is an appropriate surrogate outcome;[32–34] however, clinical events such as mortality, aortic disection, and need for surgical repair need to be evaluated as well. In Marfan syndrome, there is variability in dilatation within and between individuals.[35] Aortic dilatation may be "silent" for variable periods,[13] necessitating frequent follow-up. Increased survival of patients with Marfan syndrome is likely attributable to the ability to repair the aorta surgically.[36] Evaluating mortality may be challenging because of the length of follow-up required; a composite outcome including mortality, aortic dissection, and/or need for surgical repair may be more feasible.

Strengths and limitations of the review

Reviewers used multiple data sources to identify eligible studies; as such, the included studies thoroughly represent the existing literature. A protocol for conducting meta-analyses and exploring heterogeneity with a priori hypotheses was planned by reviewers before commencing the review in order to minimise any bias from the reviewers in assessing the data; however, as the data were abstracted, it was clear that there was significant heterogeneity across studies. For this reason, planned meta-analyses were not performed. Randomised controlled trials in progress[12–15,17,26] have defined their primary and secondary outcomes clearly and may be more amenable to pooling and performing meta-analyses.

Directions for future research

Currently, the evidence for using beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers in the treatment of aortic disease in children and adults with Marfan syndrome is based mostly on observational studies and few completed clinical trials. Clinicians require more rigorous evidence to guide the pharmacological management of Marfan patients. Future studies should examine mortality, need for surgery, aortic dissection, and adverse events. Conducting multicentre trials may result in sufficient sample size and power to evaluate these clinically meaningful outcomes. There are six randomised controlled trials in progress,[12–15,17,26] of which two are multi-centre.[14,15]

Conclusions

Beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers all reduce the rate of aortic dilation; however, studies

had small sample sizes and were not sufficiently powered to demonstrate an impact on mortality, aortic dissection, need for elective surgical intervention, or adverse events. There are six randomised controlled trials currently in progress.[12–15,17,26] Although each individual study may not be powered for these outcomes, a subsequent systematic review may provide greater insight into the effect of pharmacological therapy on clinical events.

Acknowledgement

Dr Varsha Thakur was awarded a trainee grant from the Department of Pediatrics, University of Alberta.

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