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The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: A meta-analysis

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Abstract

Objective: To assess the effect of beta-blockade therapy on clinical outcome in patients with Marfan's syndrome.
Background: Despite the lack of definitive evidence to support its efficacy, beta-blocker therapy is widely used prophylactically in patients with Marfan's syndrome.
Methods: A meta-analysis was instituted, which included studies identified by a systematic review of MEDLINE of peer-reviewed publications and by abstracts from annual scientific meeting. Outcome measures of mortality and major morbidity were compared between patients treated and untreated with beta-blockade therapy. Data was combined according to both a fixed-effects and random-effects model. The endpoints included aortic dissection or rupture, cardiovascular surgery, or death.
Results: Six studies were included, 5 were non-randomized follow-up studies and 1 was a prospective randomized trial (802 patients). Ninety-six of 433 patients treated with beta-blocker therapy and 74 of 369 untreated patients reached designated endpoints. Utilizing a fixed-effects model, patients treated with beta-blocker therapy were more likely to reach an endpoint (odds ratio = 1.50 with 95% CI 1.05–2.16). However, by a random-effects model, the treatment effect failed to reach significance (1.54 with 95% CI 0.99–2.40).
Conclusions: On the basis of this meta-analysis, there is no evidence that beta-blockade therapy has clinical benefit in patients with Marfan's syndrome.

Keywords: Marfan's syndrome; Beta-blockade; Aortic dissection

1. Background

The major causes of mortality and morbidity in Marfan's patients are the cardiovascular complications of aortic dissection and rupture [1]. In the late 1960s it was reported that blood pressure lowering medication improves survival in patients in the general population with acute dissection of aortic aneurysms [2–6]. This therapy then began to be utilized for the prophylactic treatment of patients with aortic root dilatation related to Marfan's syndrome. It has been reported by relatively small studies that beta-blocker therapy in Marfan's patients retards aortic root dilatation as measured by echocardiography [7–11], although this has not been a consistent finding [12]. If this treatment effect is confirmed, it would imply a benefit in overall morbidity and mortality. However, no studies have shown convincing evidence that long-term outcome is affected by beta-blocker therapy. Nevertheless, beta-blocker therapy is used routinely in patients with Marfan's syndrome. Given the discrepancy between clinical practice and the current evidence, we have carried out a meta-analysis of reported clinical outcome of Marfan's patients.

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2. Methods

2.1. Search

We searched Medline database from 1965, with the latest electronic search on July 10, 2005 for publications of long-term follow-up of patients with Marfan's syndrome. Keywords included Marfan's syndrome and outcome or beta-blockade or beta-adrenergic blockade or cardiovascular surgery. Language of publication did not influence article selection. Titles and abstracts were screened to exclude ineligible studies. References from these studies and from related review articles or editorials were reviewed for additional studies. Abstracts from the annual scientific meeting of the American Heart Association and the American College of Cardiology and the European Society of Cardiology were overviewed from 1990 to 2001. Authors of papers were contacted when specific data were unreported or ambiguous. Particular attention was paid to the identification of duplicate reports.

2.2. Inclusion and exclusion criteria

Eligible studies reported on long-term follow-up of patients with Marfan's syndrome, and data regarding the clinical endpoints of death, cardiovascular surgery, and aortic dissection or rupture were documented or could be inferred. Studies that did not have a control arm (patients not treated with beta-blocker therapy) were excluded.

The primary endpoints were death, cardiovascular surgery, and aortic dissection or rupture.

2.3. Data extraction

Studies selected for review were screened for information about patient characteristics, details of administration, treatment crossover and adverse drug reactions. All data were extracted by one author (DRG) and checked by at least one other author (MM) independently. Authors agreed on extracted data by discussion.

2.4. Statistical analysis

For each study, log odds ratio was estimated along with its standard error, and corresponding odds ratio and its 95% confidence interval were constructed. The 0 values in the studies conducted by Salim and Tahernia were added a value of 0.5 in the calculations. The heterogeneity of the six studies was examined by Cochran Chi-square tests. We used both fixed-effects model and random-effects model in the pooling of the log odds ratios. The treatment effect of beta-blocker compared to the control was assessed by the combined odds ratio by testing if it is different from 1 (no treatment effect). The publication bias was assessed by the plot of log odds ratio estimates of each study against their estimated standard errors, along with a formal test for publication bias based on linear regression (Ref. [13], pp. 205–208).

3. Results

3.1. Study selection and characteristics

Seventeen studies, which included relevant long-term follow-up data, were considered for inclusion in the study. Ten were excluded because of incomplete or redundant information. One study had no control group.

A total of 6 studies were thus included. All studies based the diagnosis on internationally established clinical criteria for Marfan's syndrome. The study by Salim et al. [10] used genetic information to confirm the diagnosis in one subgroup of patients. Clinical data from the six studies are shown in Table 1. Only one study [7] was a randomized clinical trial. Three were long-term follow-up studies which evaluated the effect of beta-blockade on aortic dilatation [7,10,11]. These studies (Table 1, #1, #3 and #4) clearly separated treated from untreated Marfan's patients and included data on cardiovascular surgery, aortic dissection or rupture and death. The remaining three studies (Table 1, #2, #5 and #6) were not designed specifically to observe the effect of beta-blocker therapy on either aortic root size or on clinical outcome, but the information was included in the reported data. Silverman et al. [14] evaluated survival curves, comparing life expectancy in patients with Marfan's syndrome in 1972 and in 1993. This study had the largest number of patients (226 controls, 191 treated); however the etiology of death in the two groups was not clearly delineated. Therefore, cardiovascular surgery was the only endpoint used for the purpose of this meta-analysis. A report by Roman et al. [15] was a prospective study examining the incidence of aortic complications in relation to clinical features and aortic root morphology. In this paper, medically treated patients were primarily treated with beta-blocker therapy; in some cases other blood pressure reducing medication was used. It was not clear if patients from this paper were also included in the Silverman study, therefore the statistical analysis was performed both including and excluding the Roman data. Legget et al. [16] reported long-term evaluation of clinical and echocardiographic predictors of outcome in Marfan's patients. The endpoints in this study included death, aortic root surgery, ascending aortic aneurysm and significant increase in aortic regurgitation.

3.2. Beta-blockade confirmation

Two of the six studies dosed the beta-blockade therapy as per heart rate response to exercise. In the study by Salim et al. [10] the patients were asked to run up and down 2 flights of stairs with a goal heart rate less than 110 beats per minute. In the Shores et al. study [7] the goal heart rate was 100 beats per minute after exercise. No confirmation of effect was documented in the remaining four studies.

Table 1
Marfan's syndrome study characteristics

Study	Year	Beta-blocker	Inclusion criteria	Exclusion criteria	Age (mean)	Treated (no. of patients)	Untreated (no. of patients)
Silverman	1995	Atenolol Nadolol Propanolol Metoprolol	CC	Death prior to	37±17	191	226
Shores	1994	Propanolol	CC	>50 years <12 years Significant valve disease EF<50% Contraindication to beta-blockers	C: 13 T: 14	32	38
Roman	1993	Not clarified[a]	CC	None	28±15	79	34
Salim	1994	Propanolol Atenolol	CC	Severe LV dysfxn 1st visit at >21 years	C: 10.2±4.6 T: 14.1±3.4	100	13
Legget	1996	None	CC	None	Median 21 years	28	55
Tahernia	1993	Propanolol	CC	None	C: 10 T: 9	3	3

Clinical data from the six included studies is shown in the above table. Three studies were long-term follow-up studies which evaluated effect of beta-blockade on aortic dilatation. These studies (#2, #4, and #6) clearly separated treated from untreated Marfan's patients and included data on cardiovascular surgery, death and aortic dissection or rupture. The three remaining studies (#1, #3, and #5) were not designed to observe the effect of beta-blocker therapy on either aortic root size or on clinical outcome, however, the information was included in the reported data.

[a] Primarily beta-blocker therapy, some patients on other blood pressure lowering medication.

3.3. Adverse effects

Only one of the six studies [7] clearly documented adverse reactions in beta-blocker treated patients. These adverse reactions included third degree heart block, first degree heart block, lethargy, depression, insomnia, dream disturbance, mild bronchospasm and exaggerated effects of alcohol (22 episodes out of 30 compliant patients).

3.4. Mortality and cardiovascular events

The individual study results as shown in Table 2 are expressed as death, cardiovascular surgery, or aortic dissection or rupture in the treated and untreated groups. The treatment effect is given as an odds ratio. The Chi-square statistic for testing heterogeneity of the 6 studies is 5.53 with 5 degrees of freedom, with p-value=0.354. The pooling is done by fixed-effects model and random-effects model with log odds ratios. In random-effects model, the estimate of standard deviation of random effects is 0.193. The pooled odds ratio of the 6 studies with fixed effects model is 1.50 with 95% CI of 1.05–2.16; with random-effects model it is 1.54 with 95% CI of 0.99–2.40. This is shown in Fig. 1.

Table 2
Mortality or cardiovascular events in patients with Marfan's syndrome

Study	Data from studies		Statistical calculations	
	Deaths or CV events/no. of patients		Odds ratio	95% CI
	Beta-blocker (%)	Control (%)		
Silverman[a]	58/191 (30)	54/226 (24)	1.39	0.90, 2.14
Shores	5/32 (15)	9/38 (24)	0.60	0.18, 2.01
Roman	18/79 (23)	3/34 (9)	3.05	0.83, 11.15
Legget	10/28 (36)	8/55 (15)	3.26	1.11, 9.58
Salim	5/100 (5)	0/13 (0)	1.37	0.07, 26.52
Tahernia	0/3 (0%)	0/3 (0%)	1.00	0.01, 69.00

[a] Only cardiovascular surgery was included as endpoint in this group.

After excluding the Roman data, the Chi-square statistic for testing heterogeneity of the 5 studies is 4.30 with 4 degrees of freedom, with p-value=0.367 (Fig. 2). The pooling is done by fixed-effects model and random-effects model with log odds ratios. In random-effects model, the estimate of standard deviation of random effects is 0.165. The pooled odds ratio of the 5 studies with fixed-effects model is 1.417 with 95% CI of 0.97–2.07; with random-effects model it is 1.422 with 95% CI of 0.91–2.22.

The publication bias was assessed by the plot of log odds ratio estimates of each study against their estimated standard errors, along with a formal test for publication bias based on linear regression (Fig. 3). In the plot, a pattern that studies with larger odds ratio also have larger standard errors would indicate possible publication bias. The visual inspection of Fig. 3 shows that there is no such trend and indicates there is no strong evidence of publication selection bias. This is also confirmed with a formal test for publication bias based on linear regression analysis (Ref. [13], pp. 205–208) with standardized log odds ratio as response and the inverse of its standard error as covariate, the estimate of the intercept was 0.170 with 95% CI (−1.16, 1.50) which includes zero and indicates the smaller and larger studies are similar.

4. Discussion

Clinical use of beta-blocker therapy and other anti-hypertensive agents for dissecting aortic aneurysms began in the late 1960s. This treatment was instituted after the

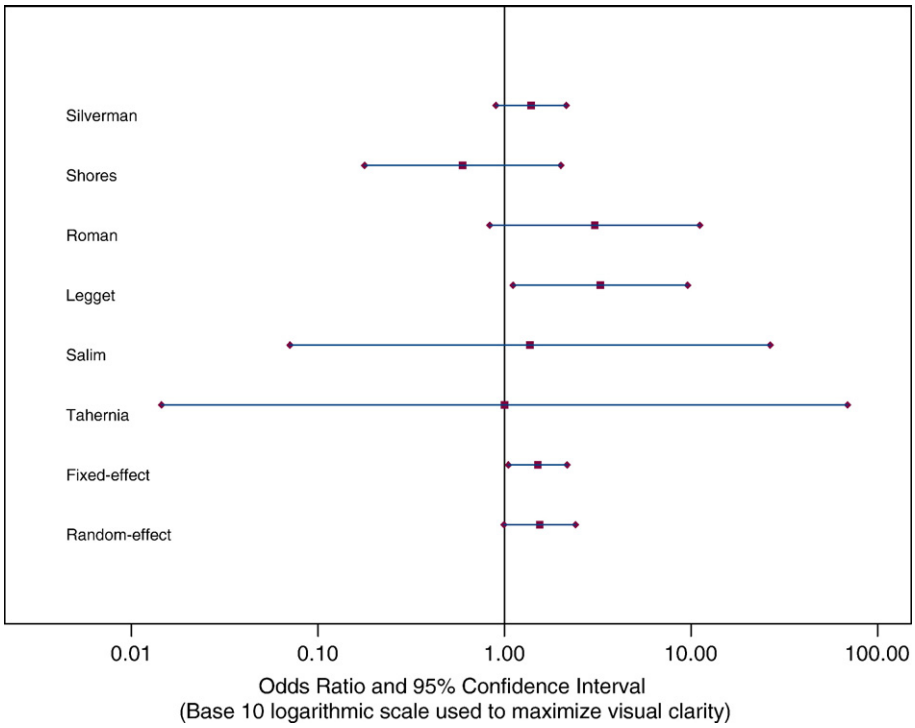

Fig. 1. Mortality or cardiovascular events in patients with Marfan's syndrome, all 6 studies.

observation that patients with aortic dissection or rupture had a high incidence of hypertension (75%) [4]. Studies with turkeys demonstrated that propanolol appeared to prevent aortic rupture at a dose which did not significantly alter mean arterial pressure but did decrease cardiac impulse [17 18]. This finding suggested that beta-blockade therapy might not only be beneficial in the prevention of aortic dissection or rupture in patients with hypertension but also could be used effectively in patients with other forms of aortic disease. However, in 1977, Ose et al. treated 25 patients with

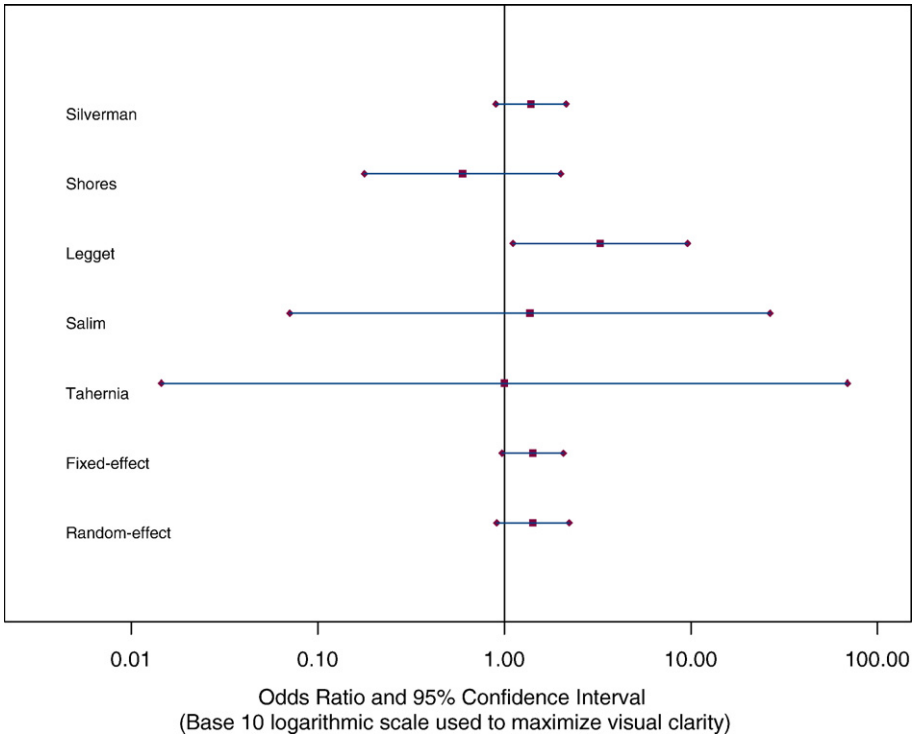

Fig. 2. Mortality or cardiovascular events in patients with Marfan's syndrome with 5 studies.

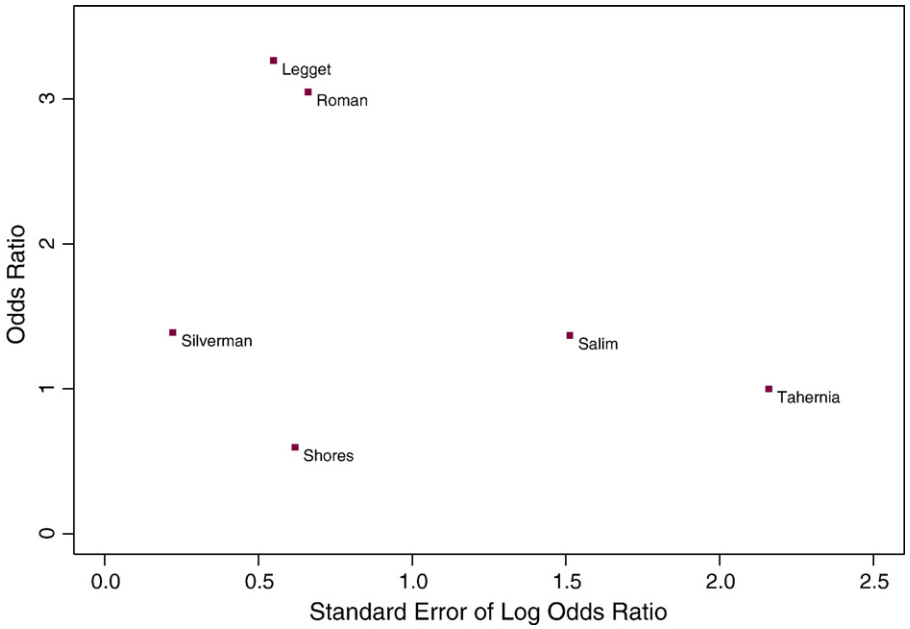

Fig. 3. Funnel plot.

Marfan's syndrome and aortic root dilatation or aortic insufficiency with beta-blocker therapy for a mean period of 2.5 ± 1.5 years, and found that a relatively high percentage (20%) of these patients nevertheless had a cardiovascular complication of either dissection or rupture over a 6-year follow-up [19]. Thus, while animal studies implied a benefit in terms of clinical outcome in patients at risk for aortic dissection, the initial clinical study in patients with Marfan's syndrome did not find such a benefit.

Several studies have evaluated the effect of beta-blockade on aortic root dimension in patients with Marfan's syndrome as measured by echocardiography, and have reported that beta-blocker therapy delays the progression of aortic root dilatation [7–11]. Recently, a blinded study from two medical centers [12] prospectively evaluated the rate of change in aortic root dimension in 34 patients on medical therapy and 34 patients treated with beta-blocker therapy. Rates of change in aortic root dimension and clinical outcome were not statistically different between the two groups (untreated 0.08 cm/year versus treated 0.09 cm/year, $p = 0.42$). Thus, there appears to be conflicting data in terms of the effect of beta-blocker therapy on delaying the progression of aortic root dilatation in young patients. A recent study utilizing ACE inhibitors has indicated beneficial effect on the rate of aortic dilatation, but no clinical outcome data is yet available [20].

If beta-blocking medication does indeed retard aortic root growth, there is an implied benefit in terms of clinical outcome since the risk of an event increases markedly with severe aortic dilatation. One study reviewed for this meta-analysis has evaluated such outcome [7]. Shores et al. [7] reported 9 out of 38 untreated patients and 5 out of 32 treated patients reaching a clinical endpoint of aortic dissection or rupture, cardiovascular surgery or death. Although there was a trend towards benefit in the treated group, this finding was not statistically significant. The only 2 deaths in the study, which were both in the control group, occurred in patients with mitral valve prolapse and a history of paroxysmal tachyarrhythmia. Neither patient had aortic dissection or rupture, and at autopsy no cause of death could be identified. If these two deaths are excluded from the analysis, the difference in clinical outcome would be even less apparent. The other five studies in this meta-analysis showed no benefit in outcome for patients on beta-blockade therapy.

Long-term beta-blocker therapy in both children and adults can have adverse effects. Acute bronchospasm is a well-recognized side effect of beta-blockade treatment and is generally contraindicated in patients with reactive airway disease. Propanolol has been associated with a number of neurological symptoms including depression, agitation, nightmares, insomnia and confusion [21]. In children, the most commonly reported adverse effects are sleep disturbances and attention disorders [21,22]. Beta-blocker therapy affects glucose and lipid metabolism and may mask the warning signs of hypoglycemia in patients with diabetes mellitus such as palpitations, tremor and hunger. Changes in serum tipoproteins include reduction in high-density lipoproteins, elevation of triglycerides and an increase in the ratio of total cholesterol to high-density lipoprotein [23]. In addition, the accidental or intentional overdose of beta-blocking medication can cause severe complications [24].

4.1. Limitations

A significant limitation of this meta-analysis is the design of the primary studies. Only one study was designed to evaluate clinical outcome of beta-blocker therapy in patients with Marfan's syndrome in the form of a randomized clinical

trial [7]. The remaining studies were not randomized clinical trials. We are aware that there are debates regarding this aspect of combining randomized and non-randomized data. However, standard meta-analysis texts state "for the sake of completeness, it may be prudent to consider studies of all designs to be eligible for a meta-analysis of non-experimental studies" [25]. Our conservative conclusions carefully consider this issue. A second limitation is that the data from Silverman et al. [14], which is a large proportion of patients in this meta-analysis, did not delineate the etiology of death (cardiovascular or otherwise) in patients treated versus not treated with beta-blockade therapy. Therefore cardiovascular surgery was the only endpoint included in our analysis from this study. Another limitation is that three of the included studies did not document the length of time of beta-blocker therapy [14–16]. A short duration of treatment could account for the lack of beneficial effect documented in our analysis. The effect of beta-blockade therapy may vary depending upon the age of the patient population. In this meta-analysis both children and adult patients were included without clear separation by age of treated versus untreated patients. Therefore, important conclusions regarding patient age at beta-blocker initiation and treatment effect could not be addressed in this study. Finally, there are no data included as to whether patients placed on beta-blocker therapy had more advanced aortic disease. This would skew the complication rate toward treated patients. These limitations do not allow the conclusion to be made that patients with Marfan's syndrome treated with beta-blocker therapy have a worse clinical outcome than untreated patients as indicated by the statistical analysis. However, these results also do not indicate that such therapy decreases morbidity or mortality in Marfan's syndrome.

4.2. Conclusions

Although the limitations of meta-analysis are apparent, these negative results nevertheless serve as an admonition; a lifetime therapeutic regime has become accepted by many as conventional therapy without clear evidence of efficacy. Rationale for long-term treatment of Marfan's syndrome with beta-blockade therapy may appear to be reasonable, but is insufficient. Further studies are required to provide the needed evidence.

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