

Do β -Blockers Really Work for Prevention of Aortic Aneurysms?

Time for Reassessment

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Abstract

Since 1994, when a small 70-patient study seemed to demonstrate that β -blocker treatment could help prevent aortic aneurysms in patients with Marfan syndrome, β -adrenergic-blocking drugs have been increasingly believed to reduce the progression of aortic aneurysms in the general population with aortic disease. This literature review examines the scientific evidence of this treatment and questions whether β -blocker treatment for aortic aneurysms should continue to be uniformly recommended. Five separate clinical trials studying the effects of β -blockade therapy in patients with Marfan syndrome are analyzed, in addition to four other clinical trials studying the effects of β -blockade therapy in patients without Marfan syndrome. The analysis suggests that the scientific evidence for β -blocker treatment is unconvincing, because β -blockade therapy fails to consistently reduce aortic aneurysm growth in patients with or without Marfan syndrome. It is alarmingly clear that prospective, multicenter clinical trials are greatly needed to test the efficacy of this now conventional therapy in a more robust scientific fashion.

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Key Words

Aortic aneurysm • β -blocker • Marfan syndrome

Introduction

In 1991, an ad hoc committee appointed by the Society for Vascular Surgery and the International

Society for Cardiovascular Surgery defined an aneurysm as a localized dilation of an artery that increases the diameter of the blood vessel by $\geq 50\%$ [1]. Ruptured aortic aneurysms are the 13th-leading cause of death in the United States, estimated to cause $\approx 15,000$ American deaths per year [2]. Furthermore, because ruptures carry a 90% mortality rate [3], treatments to reduce the occurrence of aortic aneurysms are highly valued in the medical community.

People with Marfan syndrome, a genetic disorder caused by mutations in the gene that encodes fibrillin-1, are particularly susceptible to aortic aneurysms. The disorder is estimated to affect 1 in 5,000 people and is clinically recognized by tall stature and long appendages, which are the results of bone overgrowth [4]. Because Marfan syndrome may also stretch and weaken the aorta, 70% of Marfan syndrome deaths arise as a result of cardiovascular complications [5]. Furthermore, people with Marfan syndrome have an annual death risk between 1% and 2% [5]. In an effort to improve the lifespan of those with this genetic disorder, studies on aortic aneurysms have often centered on Marfan syndrome.

Fortunately, the mortality rates from aortic aneurysms have declined steadily since 1990 because of the introduction of various therapies [6,7]. β -Blockers in particular have frequently been used to treat aortic aneurysms since a small 70-patient study published in 1994 investigated their effects on pa-



tients with Marfan syndrome [8]. The results of that study and several others, all of which were performed on patients with Marfan syndrome, suggested that β -blockers could lower rates of aortic dilation and mortality [5,8,9]. Intuitively, the theoretical reasoning behind β -blocker usage seems logical: The drugs slow the heart rate and reduce arterial pressure, thereby decreasing stress on the aorta that could rupture an aneurysm [10].

Soon after the 1994 study by Shores et al. [8], β -blockers began to be prescribed to treat aortic aneurysms in the general populace, not just patients with Marfan syndrome. Today, β -blockers have become the standard treatment for small aortic aneurysms, despite an inadequate number of published studies to support β -blocker use for aortic aneurysms in patients without Marfan syndrome. These drugs, now considered the “gold standard” for aortic aneurysm treatment [11], carry the heavy responsibility of preventing approximately 15,000 annual deaths in the United States, yet they remain unproven in clinical trials—and, as we shall see, the supporting evidence is unconvincing at best.

This review analyzes the scientific basis for the use of β -blockers to prevent aortic aneurysms and questions whether this treatment is truly acceptable without conclusive evidence to substantiate its use. Just as other medical therapies closely vetted by the U.S. Food and Drug Administration require rigorous laboratory studies and clinical trials to ensure the safety and efficacy of medicinal products [12], β -blocker treatment and its role in aortic expansion need to be further delineated by prospective, randomized trials. This review seeks to draw attention to the limited evidence for β -blocker use for aortic aneurysms and encourages more critical investigations to prove that the therapy truly benefits this cohort of patients.

Literature Review

The study most frequently cited to demonstrate that β -blockers reduce the risk of aortic aneurysms was published in 1994 [8]. In that landmark study, Shores et al. divided 70 patients with Marfan syndrome into a control group of 38 patients who received no treatment and a treatment group of 32 patients who received propranolol. The authors de-

Table 1. Comparison of the Effects of β -Blockers on Patients with Marfan Syndrome in the 1994 Experiment by Shores et al. [8]

	Control group	Treatment group
Patients	38	32
Aortic ratio	0.084	0.023
Clinical end points	9	5

n=70 patients.

finied an *aortic ratio*: the slope of the regression line for the increase in aortic dimensions over time. The aortic ratio of the control group was 0.084 per year, whereas the aortic ratio of the treatment group was only 0.023 per year. Five patients in the treatment group, two of whom did not follow the propranolol regimen, and nine patients in the control group reached a composite clinical end point, which was defined as heart failure, aortic dissection, cardiovascular surgery, or death [8]. The authors contended that their results, summarized in Table 1, supported the use of β -blockers, propranolol specifically, in patients with Marfan syndrome to treat aortic aneurysms on two grounds: first, aortic dilation was faster for patients in the control group than for the treatment group, and second, more patients in the control group reached the composite clinical end point than in the treatment group [8].

The construction of a composite end point was necessary because no single clinical end point reached statistical significance on its own merit. Although the results were certainly promising, the authors concede that the study was neither placebo-controlled nor blind, with every patient and investigator aware of the patient’s group. Thus, although the results did show potential for β -blockers in aneurysm treatment, it is highly possible that the study’s results were subject to bias and a placebo effect. Furthermore, although heart failure, dissection, and death are hard end points, the decision for surgery is a softer call and might have been influenced. The study also did not have a definitive means of ensuring patient compliance; the patients in the treatment group may not have followed the correct propranolol dosage, and patients in the control group may have taken other medications.

The largest limitation of the study, however, was the small sample size. By the end of the trial, the already minimal population decreased by 20% be-

cause of clinical end points. Although the authors appropriately believed the presence of more end points in the control group supported their conclusions, a mere four-person difference between the control group and treatment group seems unconvincing, even more so when one takes into account that two of the deaths in the control group were unrelated to nonaortic complications (mitral valve prolapse and Wolff-Parkinson-White syndrome). Additionally, the control group was larger than the treatment group by more than 15%, so more clinical end points in the control group should have been expected. Lastly, because patient compliance could not be monitored effectively, the interpretation of the results would need to be tempered.

Expanded Clinical Trials on Patients with Marfan Syndrome

Further studies examining the clinical benefit of β -blockers on aortic aneurysms in patients with Marfan syndrome have done little to clarify the picture. Although supporting data certainly exist in the literature, the lack of definitive evidence has been demonstrated through a meta-analysis of six studies conducted by Gersony et al. [13], which concluded that no significant improvement in β -blocker treatment groups could be found compared with control groups.

One study in 1995, however, did concur with the findings of Shores et al. Over the course of 25 years, Silverman et al. [5] compared the health of 191 patients taking β -blockers with 142 patients who had never taken β -blockers and 84 patients whose β -blocker usage was unknown. The treatment group took various types of β -blockers, with atenolol being the most commonly used, followed by nadolol, propranolol, and metoprolol. By the end of the study, there were 8 deaths and 58 operations in the treatment group, whereas there were 39 deaths and 54 operations among the rest of the observed patients. Although the number of operations was comparable between the groups, the low number of deaths in the β -blocker treatment group was significant. Furthermore, the study noted that the life expectancy of those taking β -blockers was 72 years, whereas the life expectancy of those who had never taken β -blockers was 70 years ($P = 0.01$) [5].

Another study by Salim et al. [9] also agreed with the results of the study by Shores et al. [8] and con-

cluded that β -blockers should be used at young ages to slow aortic root dilation. Between 1979 and 1992, 113 patients < 21 years of age were divided into a treatment group of 100 and a control group of 13. The study found that patients in the treatment group had an aortic root growth rate of 1.0 mm per year, whereas patients in the control group had an aortic root growth rate of 2.1 mm per year [9]. The limited number of patients in the control group compared with the treatment group, however, makes it difficult to lend credence to the comparison.

The results of the studies by Silverman et al. [5] and Salim et al. [9] are promising; however, these studies do not provide enough data to promote the use of β -blockers for aortic aneurysm treatment, particularly in light of other studies that provide conflicting findings. For example, in a study of 113 patients, Roman et al. [14] found that patients taking β -blockers and patients not taking β -blockers had similar aortic complication rates, with 33% of the treatment group and 30% of the control group having complications [14]. This study is difficult to analyze, however, because it was not specifically designed to address β -blocker treatment in patients with Marfan syndrome.

A paper published by Legget et al. [15] in 1996 concluded that no significant difference existed between the β -blocker treatment group of 28 patients and a control group of 55 patients. In fact, with clinical end points defined as death or surgery for ascending aortic aneurysms, the treatment group reached 9 negative end points, whereas the control group achieved only 8 negative end points over 5 years [15]. Unfortunately, this study also had a small sample size and did not focus solely on the effects of β -blocker treatment on aortic aneurysms.

For the reasons indicated above, these extended clinical studies, detailed in Table 2, have limitations and are simply not conclusive or convincing in their support of β -blocker treatment for aneurysm disease. A call for a large, multicenter, prospective placebo-controlled trial is needed.

Randomized Clinical Trials of Patients without Marfan Syndrome

Interestingly, despite the fact that the mixed literature on whether β -blockers actually help prevent aortic aneurysms in Marfan syndrome remains decidedly inconclusive [16,17], β -blockers appear more

Table 2. Comparison of the Effects of β -Blockers on Patients with Marfan Syndrome in Five Separate Clinical Trials

	Control group		Treatment group	
	Patients	End points	Patients	End points
Shores et al. [8]	32	5	38	9
Silverman et al. [5]	226	93	191	64
Salim et al. [9]	13	0	100	5
Roman et al. [14]	—	—	—	—
Legget et al. [15]	55	5	28	9
Total	326	103	357	87

commonly used to treat both thoracic aortic aneurysms and abdominal aortic aneurysms in the general aneurysm population as well. When these trials have been performed on patients without Marfan syndrome and with abdominal aortic aneurysms, β -blockers have failed to consistently decrease the growth rate of the aneurysms [18,19].

In a 2002 study published in *The Journal of Vascular Surgery*, the effects of propranolol on the growth rate of abdominal aortic aneurysms were studied [18]. In a double-blind, randomized fashion, 272 patients were treated with a placebo, whereas 276 patients were treated with propranolol, which means that this study, unlike the landmark 1994 study, was placebo-controlled and had precautions against bias [18]. During the observation period, which averaged 2.5 years, 73 patients in the placebo group stopped taking the medication, whereas an outstanding 117 patients dropped out in the propranolol group because of the drug's side effects, which caused patients taking propranolol to have drastically poorer quality-of-life scores in three dimensions of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). The groups were comparable in their number of deaths, with 26 in the control group and 33 in the propranolol group. Most importantly, the growth rates of the aneurysms were similar, with the placebo group having a mean annual growth rate of 0.26 cm per year and the propranolol group having a mean annual growth rate of 0.22 cm per year ($P = 0.11$). Interestingly, the β -blockers did appear to have some benefits, because only 35 patients in the propranolol group required aortic resection compared with 55 patients in the control group. Because surgery is typically only performed on relatively large aneu-

rysms, the drugs may help slow the growth rate of aneurysms past a certain size. However, the decision to operate is a subjective decision that reflects the state of mind of the surgeons, as well as physical processes in the patient. Regardless, the authors concluded that they could find no clinically significant effect of propranolol on the growth rate of the studied abdominal aortic aneurysms [18].

Wilmink et al. [19] reached the same conclusions in a randomized, blinded study of 477 patients. The aneurysms in the placebo group (221 patients) experienced a mean growth of 0.25 mm during the observation period, whereas aneurysms in the propranolol group grew a mean of 0.24 mm. The investigators also found that compliance with propranolol treatment was exceedingly low, with 31% of the propranolol group dropping out of the study compared with 15% of the control group. One benefit that propranolol manifested in the study, however, was that aneurysms larger than 3.9 cm grew a mean of 0.44 mm in the placebo group and only 0.13 mm in the propranolol group, which demonstrates that β -blockers may potentially slow the growth rate in aneurysms larger than 3.9 cm. Nevertheless, as in the aforementioned study, the authors concluded that β -blocker therapy for aneurysms should not be recommended, because no statistically significant reduction in aneurysm growth could be demonstrated [19].

Still, other smaller studies provide data that suggest that β -blocker treatment is beneficial in the management of abdominal aortic aneurysms [20,21]. In 1988, Leach et al. [20] placed 12 patients in a β -blockade treatment group and 15 patients in a control group. The researchers found that over the course of 3 years, the control group had an annual aneurysm growth rate of 0.44 cm per year, whereas the treatment group had an annual aneurysm growth rate of just 0.17 cm per year. With the end points defined as death, rupture, or surgery, the control group had 6 end points, whereas the treatment group had 5 end points [20]. In 1994, Gadowski et al. [21] also found β -blocker treatment beneficial in slowing aortic growth rate. The 38 patients receiving β -blockers had a reduced aortic aneurysm growth rate of 0.36 cm per year compared with 0.68 cm per year for the 83 patients in the control group. Both of these studies concluded that β -blocker treatment significantly reduced abdominal aortic aneurysm growth rates.

Table 3. Comparison of the Effects of β -Blockers on Patients without Marfan Syndrome in Four Separate Clinical Trials

	Control group		Treatment group	
	Patients	Growth	Patients	Growth
Propranolol Aneurysm Trial Investigators [18]	272	0.26 cm/y	276	0.22 cm/y
Wilmink et al. [19]	221	0.25 mm	256	0.24 mm
Leach et al. [20]	15	0.44 cm/y	12	0.17 cm/y
Gadowski et al. [21]	83	0.68 cm/y	38	0.36 cm/y

We offer the additional observation that aneurysm growth is usually indolent, and very long follow-up is required for conclusive evidence regarding differential rates of aneurysm growth or patient death. Trials involving a mean follow-up of 5–10 years would be much more convincing. Although the studies of patients with small abdominal aortic aneurysms have not conclusively demonstrated an effect on growth rate, the follow-up has been short, and there is evidence to suggest that there may be a beneficial effect with longer follow-up and with larger aneurysms.

Thus, the medical community has been left without clear-cut evidence for or against the treatment of abdominal aortic aneurysms with β -blockers. As shown in Table 3, in the two largest studies, the investigators could not find a definitive correlation between β -blocker treatment and reduced aneurysm growth rate. Nevertheless, in two smaller studies, researchers found that aneurysm growth was significantly slowed by β -blockers. So, medical professionals are left with the following question: Are the potential benefits of β -blocker treatment worth the severe side effects and toll on the patient's quality of life?

Although the study by Shores et al. [8] and similar studies have suggested β -blockers could possibly be used to treat aortic aneurysms in patients with Marfan syndrome, it would be inappropriate to presume that such findings can be extrapolated directly to patients without Marfan syndrome. Furthermore, the few encouraging results of the abdominal aortic aneurysm treatment studies should not be extrapolated to thoracic aortic aneurysms because of the inherent differences between abdominal aortic aneurysms and thoracic aortic aneurysms [22].

Limitations

As with all reviews, the present review is limited by the publications it analyzes, which vary widely in their

design. For instance, the studies varied in the type of β -blockers used, with some using propranolol, others using atenolol, and still others using a mix of different β -blockers. The studies also varied greatly in the age of the patients observed; therefore, it is possible that the age of the patients influenced how well the patients responded to β -blocker treatment. Most importantly, the studies varied in the standards used to compare treatment and control groups. Some trials emphasized an annual aneurysm growth rate, whereas others focused on end points such as death and rupture.

Conclusions

Our review discusses the evidence (or lack thereof) to support the routine administration of β -adrenergic blockade in patients with aortic aneurysms. The review seeks to underscore why a conventional treatment for aortic aneurysms requires more robust scientific evidence for its use. Although the theoretical reasoning behind β -adrenergic blockade therapy is logical, that is simply not enough. β -Blockers have not been proven to consistently reduce the aortic aneurysm growth rate in Marfan syndrome or the general population.

The current American College of Cardiology Foundation/American Heart Association guidelines include a class I recommendation for the use of β -adrenergic-blocking drugs for all patients with Marfan syndrome and aortic aneurysm to reduce the rate of aortic dilation, but acknowledge a level B evidence for their recommendation [23]. In addition, there is a class IIa recommendation for patients with thoracic aortic aneurysm for the use of β -blockers (as well as angiotensin-converting enzyme inhibitors or angiotensin-receptor blocker blockers) to lower blood pressure to

the lowest point patients can tolerate without adverse effects.

Our findings do not dispute these recommendations but reinforce a strong call for larger, multicenter, randomized clinical trials to test the efficacy of β -blockers to reduce the rate of dilation and clinical outcomes in individuals with aortic aneurysm. Finally,

our results also do not address or impugn the use of β -adrenergic blockade in individuals with aortic dissection or its variants or in individuals with fixed atherosclerotic disease, for whom evidence remains for their use.

Comment on this Article or Ask a Question

References

1. Johnston KW, Rutherford RB, Tilson MD, et al. Suggested standards for reporting on arterial aneurysms. *J Vasc Surg.* 1991;13:445–450.
2. National Center for Health Statistics. Deaths, percent of total deaths, and death rates for the 15 leading causes of death: United States and each state, 2000. Hyattsville, MD: National Vital Statistics Systems, 2001.
3. Upchurch GR, Schaub TA. Abdominal aortic aneurysm. *Am Acad Fam Phys.* 2006;73:1198–1204.
4. Dietz HC, Pyeritz RE. Mutations in the human gene for fibrillin-1 (FBN1) in the Marfan syndrome and related disorders. *Hum Mol Genet.* 1995;4:1799–1809.
5. Silverman DI, Burton KJ, Gray J, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol.* 1995;75:157–160. 10.1016/S0002-9149(00)80066-1
6. Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed Mortality File 1979–1998 and Compressed Mortality File 1989–1998 on CDC WONDER Online Database, compiled from Compressed Mortality File 2000 Series 20 No. 2A and 2003 Series 20 No. 2E.
7. Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed Mortality File 1999–2006 on CDC WONDER Online Database, compiled from Compressed Mortality File 2009 Series 20 No. 2L.
8. Shores J, Berger KR, Murphy EA, et al. Progression of aortic dilation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med.* 1994;330:1335–1341. 10.1056/NEJM199405123301902
9. Salim MA, Alpert BS, Ward JC, et al. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. *Am J Cardiol.* 1994;74:629–633. 10.1016/0002-9149(94)90762-5
10. Danyi P, Elefteriades JA, Jovin IS. Medical therapy of thoracic aortic aneurysms: Are we there yet? *Circulation.* 2012;124:1469–1476.
11. Matt P, Habashi J, Carrel T, et al. Recent advances in understanding Marfan syndrome: Should we now treat surgical patients with losartan? *J Thorac Cardiovasc Surg.* 2008;135:389–394. 10.1016/j.jtcvs.2007.08.047
12. U.S. Food and Drug Administration. How drugs are developed and approved. U.S. Food and Drug Administration website. Available at: <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm>. Accessed April 1, 2013.
13. Gersony DR, McClaughlin MA, Jin Z, et al. The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: A meta-analysis. *Int J Cardiol.* 2007;114:303–308. 10.1016/j.ijcard.2005.11.116
14. Roman MJ, Rosen SE, Kramer-Fox R, et al. Prognostic significance of the pattern of aortic root dilation in the Marfan's syndrome. *J Am Coll Cardiol.* 1993;22:1470–1476. 10.1016/0735-1097(93)90559-J
15. Legget ME, Unger TA, O'Sullivan CK, et al. Aortic root complications in Marfan's syndrome: Identification of a lower risk group. *Heart.* 1994;75:389–395.
16. Ladouceur M, Fermanian C, Lupoglazoff JM, et al. Effect of beta-blockade on ascending aortic dilation in children with the Marfan syndrome. *Am J Cardiol.* 2007;99:406–409. 10.1016/j.amjcard.2006.08.048
17. Selamet Tierney ES, Feingold B, Printz BF, et al. Beta-blocker therapy does not alter the rate of aortic root dilation in pediatric patients with Marfan syndrome. *J Pediatr.* 2007;150:77–82. 10.1016/j.jpeds.2006.09.003
18. Propranolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: Results of a randomized trial. *J Vasc Surg.* 2002;35:72–79. 10.1067/mva.2002.121308
19. Wilmink ABM, Hubbard CSFF, Day NE, et al. Effect of propranolol on the expansion of abdominal aortic aneurysms: A randomized study. *Br J Surg.* 2000;87:499.
20. Leach SD, Toole AL, Stern H, et al. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. *Arch Surg.* 1988;123:606–609. 10.1001/archsurg.1988.01400290092015
21. Gadowski GR, Pilcher DB, Ricci MA. Abdominal aortic aneurysm expansion rate: Effect of size and beta-adrenergic blockade. *J Vasc Surg.* 1994;19:727–731. 10.1016/S0741-5214(94)70048-6
22. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm: Clinically pertinent controversies and uncertainties. *J Am Coll Cardiol.* 2010;55:841–857. 10.1016/j.jacc.2009.08.084
23. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol.* 2010;55:e27–e129.

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EDITOR'S COMMENTS AND QUESTIONS

Dr. Scott A. LeMaire, Professor, Baylor College of Medicine, TX, USA

In this well-written review, the authors present and discuss the evidence (or lack thereof) supporting routine administration of β -antagonist medications to patients with aortic aneurysms. The topic is compelling and provides convincing rationale for the need to conduct prospective multicenter trials to examine the issue in an appropriately robust scientific fashion. I believe this could be of substantial interest to readers.

Questions

1. Now that you have conducted this review of the literature, which shows that the data is at best inconclusive on the efficacy of β -blockade in thoracic aortic aneurysm, have you or your colleagues changed your practice patterns?

My clinical practice has unquestionably changed as result of this overview article. Whereas the role of

β -adrenergic receptor blockade remains strong for aortic dissection and any of its variants, or perhaps for patients with Marfan syndrome, I am disinclined to begin these agents simply for generalized thoracic aortic disease until further clinical data are available.

2. If an aneurysm patient were intolerant of β -blockers, say by virtue of tiredness or sexual dysfunction, would you hesitate to stop the drug?

If an aneurysm patient were intolerant of a β -blocker, I would have little reservation to discontinue this treatment.

3. How do you feel about the magnitude of the decision to start a 20- or 30-year-old patient on lifelong β -blockers for a small aneurysm?

The magnitude of starting a 20 or 30 year old on a β -blocker (assuming this is in the absence of Marfan syndrome) is overwhelming. Very little data prospective data exists for this indication. The outcome data is limited, with sample sizes being small. I have no reservation to defer treatment, if needed.