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SYSTEMATIC REVIEW ARTICLE

Beta-Blockers and Abdominal Aortic Aneurysm Growth: A Systematic Review and Meta-Analysis

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ARTICLE HISTORY

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Abstract: ***Background*:** Aortic aneurysms are worrisome because of their predisposition to dissection and rupture. Beta-blockers are considered first-line therapy for aortic aneurysms. The following meta-analysis assesses if beta-blockers diminish aortic aneurysm growth.

***Methods*:** A literature search was performed to collect information on clinical trials that have assessed aortic aneurysm growth between beta-blockers and placebo. The primary endpoint was aortic aneurysm growth rate per year. A forest plot with a random-effects model was used for analysis.

***Results*:** Eight clinical trials were included in the analysis. Beta-blockers showed a statistically non-significant effect on aortic aneurysm growth (standard mean difference -0.44; 95% CI [-0.44, 0.00]).

***Conclusion*:** Beta-blockers do not significantly influence aortic aneurysm growth. Further studies are required to find a suitable medical therapy to reduce growth rates.

Keywords: Beta-Blocker, aortic aneurysm, aorta, medical therapy, blood pressure, meta-analysis.

1. INTRODUCTION

Aortic dissection and rupture are the feared complications of aortic aneurysms [1]. Ultrasound screening protocols exist to monitor aortic aneurysms smaller than those meeting criteria for intervention [2]. However, pharmacologic intervention to prevent these complications remains controversial [3-5].

Beta-blockers are believed to hinder aortic aneurysm growth. The current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend beta-blocker use for reducing aortic aneurysm growth rates [1, 6]. This is derived from non-randomized studies showing a reduction in aortic aneurysm growth with propranolol [1, 7, 8]. However, more recent randomized controlled trials show no difference in growth with beta-blockers [9-12]. This led the Society of Vascular Surgery (SVS) to advise against beta-blocker use for preventing aortic aneurysm enlargement [13]. The following meta-analysis aims to compile all the current evidence regarding the effect of beta-blockers on aortic aneurysm growth.

2. METHODS

2.1. Data Collection

An electronic search complied studies mentioning the change in aortic aneurysm growth with beta-blockers compared to a control group. Data search was performed on March 2020. Inclusion criteria included containing the comparison of beta-blockers with a control group with any type of aortic aneurysm. Duplicated studies, those focused on a disease associated with aortic aneurysms (*i.e.*, Marfan syndrome), and studies not reporting standard deviations, were excluded from the study. The primary endpoint was aortic aneurysm growth rate *via* centimeter per year.

Databases included Google Scholar and Pubmed. Keywords included: *beta-blocker, aortic aneurysm, thoracic aortic aneurysm, abdominal aortic aneurysm,* and *thoracoabdominal aortic aneurysm*. Abstracts and titles were reviewed for relevancy. Baseline characteristics and the primary endpoint were recorded for further statistical analysis.

2.2. Statistical Analysis

The meta-analysis used the Review Manager Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) software program. A forest plot was created using the program with the DerSimonian and Laird random-effects model to reduce heterogeneity. The mean difference with a confidence interval (CI) of 95% was reported with the inverse variance method. Due to using a scale, the value marking no significance *via* confidence interval was zero. An I^2 greater than 50% suggests significant heterogeneity.

3. RESULTS

The electronic search presented 2820 studies (Fig. **1**). Incorporation of the inclusion criteria reduced the selection to 16 studies. Exclusion criteria limited the number to eight

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studies (Table **1**). A total of 1032 beta-blocker subjects and 1667 control patients were included. Baseline characteristics regarding age, gender, follow-up period, initial abdominal aortic size, and blood pressure were similar between the study group and controls (Table **2**).

The nine studies combined showed a statistically non-significant effect of beta-blockers on aortic aneurysm growth (standard mean difference = -0.22 [95% CI -0.44-0.00]) (Fig. **2**). There was significant heterogeneity with I^2=80%, but the study was performed using a random-effects model to help counter the potential influencing biases.

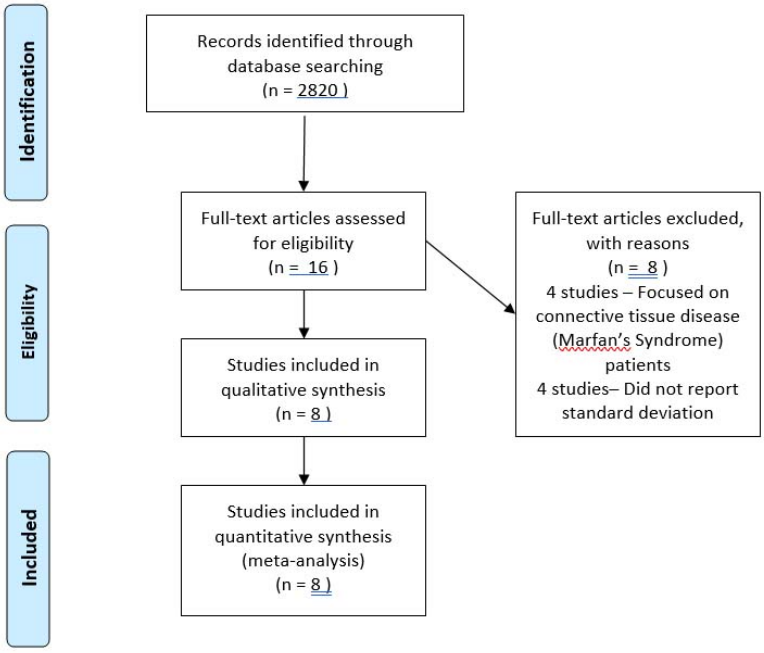

Fig. (1). Selection Flowchart.

Table 1. Details of selected studies.

Study	Type of Study	No. Patients	Aneurysm Location	Beta-Blocker Type
Leach 1988 [3]	Prospective	27 (BB=12; C=15)	Abdominal	Propranolol, Atenolol, Metoprolol Tartrate
Gadowski 1994 [8]	Prospective	121 (BB=38; C=83)	Abdominal	Propranolol, Atenolol, Metoprolol
Lindholt 1999 [10]	Prospective, Randomized	54 (BB=30; C=24)	Abdominal	Propranolol
Wilmink 2000 [11]	Prospective, Randomized	477 (BB=256; C=221)	Abdominal	Propranolol
Propranolol Aneurysm Trial 2002 [12]	Prospective, Randomized	548 (BB=276; C=272)	Abdominal	Propranolol
Biancari 2002 [14]	Retrospective	41 (BB=17; C=24)	Abdominal	Not specified
Wilmink 2002 [15]	Prospective	332 (BB=77; C=255)	Abdominal	Not specified
Thompson 2010 [4]	Prospective	1099 (BB=326; C=773)	Abdominal	Not specified

Abbreviations: BB- Beta-Blocker Group; C-Control Group.

Table 2. Baseline characteristics.

Characteristic	Beta-Blocker	Control	Studies Contributed
Age	69	70	Leach 1988; Gadowski 1994; Propanol Aneurysm Trial 2002; Wilmink 2002
Male	83	71	Leach 1988; Gadowski 1994; Propanolol Aneurysm Trial 2002; Wilmink 2002
Follow-up (months)	35	41	Leach 1988; Gadowski 1994
Initial Abdominal Size (cm)	4.02	3.92	Leach 1988; Gadowski 1994; Propanolol Aneurysm Trial 2002
Blood pressure	151/83	152/80	Leach 1988; Gadowski 1994; Propanolol Aneurysm Trial 2002; Wilmink 2002

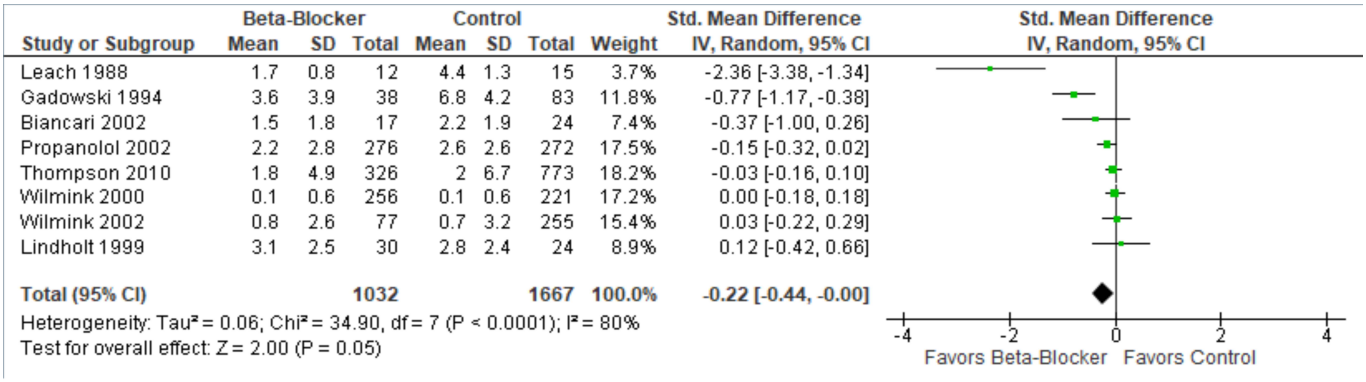

Fig. (2). Aortic aneurysm growth rate between beta-blockers and control. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. DISCUSSION

Medical therapy for slowing aortic aneurysm growth remains elusive [4, 5]. The presented meta-analysis shows no significance with the use of beta-blockers. This is with a confidence interval barely crosses the line of insignificance.

The most worrisome complications of aortic aneurysms include dissections and ruptures [1]. Beta-blockers were presumed to decrease the rate of aneurysm growth and complications. This is reflected by the official guidelines by the AHA/ACC, giving a Class IIa and Class IIb recommendation for beta-blocker use to reduce the growth of thoracic and abdominal aortic aneurysms, respectively [1, 6]. This was first supported by multiple animal models [16-18]. This was followed by nonrandomized controlled trials [3, 7, 8]. The theory was based on decreasing heart rate and hemodynamic stress on aortic walls [3]. This decreases tension based on Laplace's Law [8, 19-21]. However, the beta-blockers benefit was not supported by randomized controlled trials [9-12, 22]. This meta-analysis supports the claims made by the randomized trials and the Society of Vascular Surgery (SVS) [13].

The recommendations made by the SVS are for abdominal aortic aneurysms [13]. This meta-analysis while not its intent- comprises only abdominal aortic aneurysm cases. Beta-blockers have not been studied significantly for thoracic aortic aneurysms. Current acting guidelines by the American Heart Association/American College of Cardiology (AHA/ACC) label the beta-blocker use a Class IIa recommendation for controlling hypertension in patients with thoracic aortic aneurysms [6]. However, the studies supporting this suggestion are based on patients with Marfan's syndrome [23-25]. There are no controlled studies showing the relationship of beta-blockers with thoracic aortic aneurysm growth in all thoracic aneurysm patients.

While beta-blockers may not affect aortic aneurysm growth significantly, they confer other benefits. This includes increased survival [14]. For patients that undergo aortic aneurysm repair, beta-blockers reduce perioperative mortality and complications [26].

Other medications show aortic aneurysm growth inhibition potential. These include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), tetracyclines, macrolides, statins, and medications for diabetics. The evidence regarding ACE inhibitors and ARBs remains equivocal [4, 15, 27, 28]. Antibiotics, including doxycycline and macrolides, decrease matrix metalloprotease activity in the aortic wall and therefore, may decrease aortic aneurysm growth [29, 30]. Statins also share an anti-inflammatory and cholesterol-reducing benefit to the aortic aneurysm wall in addition to decreasing matrix metalloprotease activity, but its effect on aneurysm growth also remains controversial [4, 31, 32]. Studies have suggested that hypoglycemic medications used with diabetics may decrease aortic aneurysm growth, but this may be confounded by the established fact that diabetes is associated with decreased aortic aneurysm growth [4].

4.1. Limitations

A limitation of this study was the exclusion of studies that did not report a standard deviation along with their growth rates. This could have influenced this meta-analysis since the confidence interval includes zero as one of the range extremes. However, most of the studies excluded were non-randomized trials. The conclusions made by randomized controlled trials bear more weight and therefore support the claims of this meta-analysis.

Another limitation is the significant lack of medication compliance within the trials used in the meta-analysis. Some trials report the self-discontinuation rate of beta-blockers being up to 39% [4, 12]. This factor may contribute to the large heterogeneity seen in this meta-analysis. The quality of life is diminished by beta-blocker side-effects, explaining the noncompliance rate [4, 12].

Heterogeneity was significant during this analysis. With an I^2 of 80%, there may be multiple biases and discrepancies among the studies selected. However, a random-effects model was used to decrease this limitation.

CONCLUSION

Beta-blockers do not reduce aortic aneurysm growth. This is evident with abdominal aortic aneurysms. Guidelines should reflect these findings. Further studies are required to find a suitable medical therapy that can be applied to decelerate aortic aneurysm growth.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines have been followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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