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REVIEW

Editor's Choice – Pharmaceutical Management of Small Abdominal Aortic Aneurysms: A Systematic Review of the Clinical Evidence

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WHAT THIS PAPER ADDS

Pharmaceutical abdominal aortic aneurysm stabilization is an unmet medical need. To date, over numerous clinical and hundreds, of pre-clinical papers show the potential of numerous interventions. Yet conclusions from clinical reports are not fully consistent. As such, a systematic review of the available clinical data is relevant.

Background: Management of abdominal aortic aneurysms (AAAs) relies on surgical repair of larger AAAs. Consequently medical interventions inhibiting AAA progression could greatly reduce the need for surgical repair. A spectrum of pharmaceutical strategies has been reported, albeit conclusions often appear contradictory. Given the longstanding interest in pharmaceutical AAA stabilization, a systematic review of the available literature is relevant.

Objectives: The aim is to provide an up to date systematic review of the available data on pharmaceutical therapies for stabilizing or impeding AAA growth.

Methods: A search using Pubmed, Embase, Web of science, Cochrane, CINAHL, Academic Search Premier, and Science Direct identified 27 eligible papers that studied the clinical effect of the pharmaceutical therapy on AAA diameter growth.

Results: This review shows that there is currently no pharmaceutical strategy that reduces AAA growth. Most studies are of poor methodological quality. Initial promising reports are often not confirmed in subsequent larger studies, raising the possibility of selective reporting.

Conclusion: There is currently no pharmaceutical means that halts AAA growth.

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INTRODUCTION

The risk of rupture of an abdominal aortic aneurysm (AAA) progressively increases in larger AAAs > 55 mm. Four large clinical trials have not shown a benefit of earlier repair[1] (i.e. for aneurysms <55 mm). Therefore, the therapeutic approach to AAAs is surveillance of small aneurysms and prophylactic surgical open or endovascular aneurysm repair (EVAR) in AAAs over 55 mm.[2] Yet while open repair has excellent long-term outcomes, it has a significant peri-operative morbidity and mortality. Although EVAR comes with a significantly lower peri-operative morbidity and mortality, its cost effectiveness is being questioned. Consequently, a pharmaceutical means of slowing down or stabilizing the progression of small AAAs, and thus post-poning or obviating the need for surgery could provide a major advance.[3] In fact, pharmaceutical stabilization of AAA is now considered an unmet medical need.

A large body of preclinical evidence has shown that interference with aspects of vascular inflammation and/or proteolytic activity alleviates AAA formation in rodent models of the disease.[4,5] Clinical studies, on the other hand, are limited and their conclusions often inconsis-tent.[6–8] The clinical evidence has been reviewed in 78 papers (from a systematic literature search), yet a comprehensive systematic review is missing. Given the renewed interest in pharmaceutical AAA stabilization, a

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systematic review of the available evidence on pharmaceutical interventions for stabilizing or impeding AAA growth in humans is relevant.

METHODS

Search strategy

The studies included in this review were identified from PubMed, Embase, Web of science, Cochrane, CINAHL, Academic Search Premier, and Science Direct. The search was not limited, and thus all languages and publication types (e.g. reviews or conference abstracts) were included. The search was most recently updated on April 17, 2015.

Two search themes were created, which were combined in the search by AND. The first theme was created for AAAs by using all terms for abdominal aortic aneurysm, such as abdominal aneurysm or abdominal aorta aneurysm. The second term consisted of all terms for pharmacology, including specific drug group names, such as medical treatment or drugs or hydroxymethylglutaryl-coA reductase inhibitors. Details of the search strategy are available in the supplementary data.

Inclusion criteria

Only studies providing original clinical data on an effect of pharmaceutical therapy on AAA growth were included. Hence, all animal studies and studies that exclusively described an effect of pharmaceutical intervention on molecular processes in the aneurysm wall; all reviews ($n = 79$) and commentaries were excluded.

Two authors (V.K. and J.L.) independently reviewed the results of the search strategy. A first selection was made on title; all articles potentially reporting an effect of a pharmaceutical intervention on AAA disease were included. A second selection was made by reading the abstract of articles that were selected on the basis of the title. The final selection was made on basis of the full text.

The quality of the identified studies was scored using the STROBE scoring system.[9]

Statistical analysis was not performed because of the marked heterogeneity of the included studies.

RESULTS

The search strategies identified 3,557 articles. Selecting title and abstract narrowed the number of articles to 30 original studies. Two of the 30 original studies were excluded because of missing data on the AAA growth rate.[10,11] Another article, written in Danish,[12] was excluded since it was also published separately in English.[13] As a result, 27 original articles were available for this review (Fig. 1). Identified studies are summarized in Table 1 and their quality assessed (STROBE scoring system,[9] Supplementary Table).

Antihypertensive drugs

Beta blockers and other antihypertensive drugs were the first agents to be evaluated for their potential to reduce the

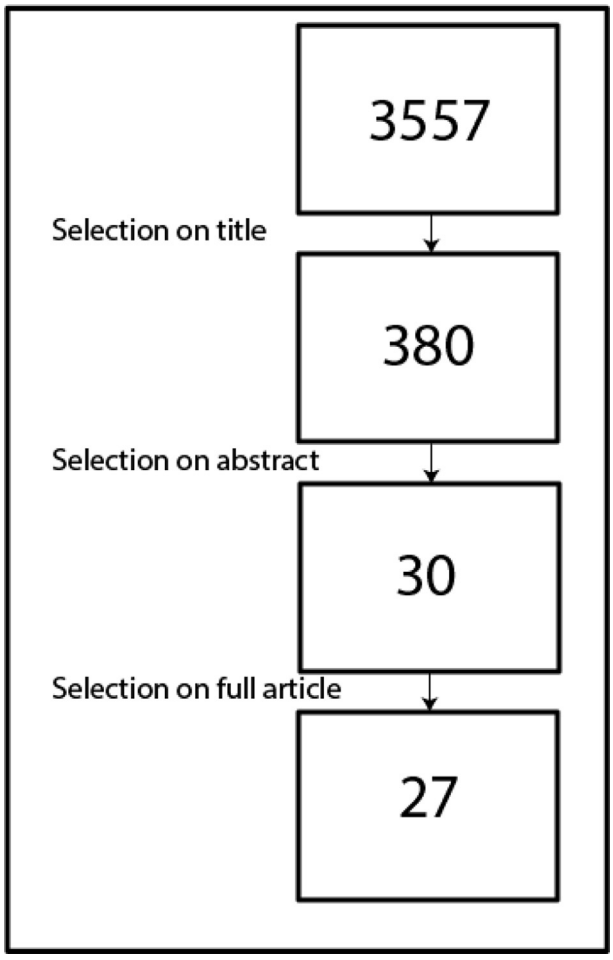

Figure 1. Systematic search strategy. First selection on title, second on abstract, and last selection was made by reading the full article.

AAA expansion rate. Beta blockers were evaluated in two randomized controlled trials (RCTs),[14,15] three case control studies,[16–18] and two cohort studies.[19,21] The two earliest, very small studies ($n = 38$ and $n = 12$ cases) suggested a borderline significant effect of beta blockers on aneurysm expansion rate.[17,18] Later cohort studies, however, found no effect of beta blockers on the growth rate of AAAs.[16,18,21] Similar to this, the two RCTs did not show an effect of propranolol treatment on AAA expansion.[14,15] Importantly, both RCTs concluded that the drug propranolol is poorly tolerated, with a 42% drop out rate in the propranolol group.[14]

There are several reports on other classes of hypertensives. A retrospective study suggesting an effect of angiotensin converting enzyme (ACE) inhibition on AAA stability[20] was followed by five studies investigating an effect of ACE inhibitors on AAA growth. Four of these studies, two small retrospective analyses within a prospective case control study[16,21] and two larger retrospective studies ($n = 1231$ and $n = 242$ cases) found no effect of ACE inhibitors on aneurysm expansion.[21,22] In contrast, a recent prospective cohort study of 1701 patients participating in the UK small aneurysm trial, unexpectedly indicated a significant increase in aneurysm growth rate in patients taking ACE inhibitors,

Table 1. Full survey of all articles included in this systematic review.

First author/trial	Year	Intervention	Study design	Participants (Cases/Controls)	Outcomes	Significance	Strobe score	Study qualities	Study limitations
PATI[14]	2002	Propranolol	RCT	Total: 548	AAA diameter growth (mm/y):	NS		1. Study medication was randomly and double blinded assigned	1. Slow growing AAAs and patients already using beta blockers excluded
				(276/272)	Cases: 2.02			2. Valid power calculation	2. Low compliance, high drop out rate: 26.8% and 42.4% of the patients in the placebo arm and the propanolol arm stopped their medication
					Controls: 2.60				3. Mislabeling of a batch of study medication
									4. No correction for non-random drop out
Lindholt[15]	1999	Propranolol	RCT	Total: 54	Relative risk of expansion:	NS		1. Study medication was randomly and double blinded assigned	1. High drop out rate: 60% and 25% of the patients in the propranolol and placebo arm stopped their medication
				(30/24)	Cases: 2.44 (0.88—6.77)				2. Power calculation missing
					Controls: 1.17 (0.74 —1.85)				
Wilmink[16]	2002	Antihypertensive drugs:	Prospective case control study	Total: 5811	AAA diameter growth (mm/y):		13.5/22	1. Large study size	1. Observational study, data derived from two separate screening populations with different baseline characteristics
		Calcium channel blockers		(48/284)	Cases: 0.5	NS			2. Limited number of cases
					Controls: 0.8				3. Power calculation missing
		ACE inhibitors		(24/308)	Cases: 0.02	NS			4. No correction for non random drop out
					Controls: 0.8				
		Diuretics		(54/278)	Cases: 0.8	NS			
					Controls: 0.7				

		Beta blockers		(77/255)	Cases: 0.8	NS			
					Controls: 0.7				
Gadowski[17]	1994	Beta blockers	Prospective case control study	Total: 111	AAA diameter growth (mm/y)	NS	11.5/22	1. Long-term follow up	1. Observational study
				(38/83)	Cases: 3.0				2. Heterogeneous with respect to type and dose of beta blocker
					Controls: 4.4				
Leach[18]	1988	Beta blockers	Retrospective case control study	Total: 27	AAA diameter growth (mm/y)	NS	11.5/22		1. Observational study
				(12/15)	Cases: 1.7				2. Retrospective study
					Controls: 4.4				3. Limited number of cases
Bhak[19]	2015		Prospective cohort study	Total: 534	Adjusted difference in AAA diameter growth (mm/y)	$p = .004$	14.5/22	1. Large number of overall participants	1. Number of patients per group unclear
		Beta blockers		unclear	0.009	.51			2. Observational study
		Cholesterol lowering		unclear	−0.02	.18			3. Both CT and ultrasound measurements
		Antihypertensive		unclear	−0.001	.78			
		Aspirin		unclear	−0.01	.48			
Kortekaas[21]	2014	ACE inhibitors	Prospective case control study	Total: 286	Difference in growth rate: −0.24 mm/year	$p > .05$	16.5/22	1. Single observer measurements only	1. Observational study
				(82/286)					2. Significant difference in baseline characteristics
									3. Power calculation missing
Thompson[22]	2010		Prospective cohort study	Total: 1231	Difference in AAA diameter growth between cases and controls (mm/y):			1. Large study size	1. Patients lost to follow ($n = 158$) up had a significantly lower AAA growth rate
		ACE inhibitors		294	ACE inhibitors: −0.28	NS			2. Time effect, patients identified between 1984 and 2007
		Statins		383	Statins: −0.29	NS			3. No correction for non-random drop out

Continued

Table 1-*continued*

First author/trial	Year	Intervention	Study design	Participants (Cases/Controls)	Outcomes	Significance	Strobe score	Study qualities	Study limitations
									4. Secondary analysis, study not powered for an evaluation of an ACE inhibitor or statin effect
Sweeting[23]	2010		Prospective cohort study	Total: 1701	AAA diameter growth (mm/y)			1. Large study size	1. Observational study
		ACE inhibitors		169	Cases: 3.33	$p = .009$		2. Long-term follow up	2. Patients included between 1991 and 1995
					Controls: 2.77			3. Data partially adjusted and fully adjusted available	
		Calcium Channel Blockers		440	Cases: 2.76	NS			
					Controls: 2.5				
		Beta Blockers		255	Cases: 2.70	NS			
					Controls: 2.85				
		Statins		21	Cases: 2.07	NS			
					Controls: 2.84				
		Anti Platelet Therapy		501	Cases: 2.89	NS			
					Controls: 2.80				
Periard[24]	2012	Statins	Retrospective case control study	Total: 94	AAA diameter growth (mm/y)	$p = .01$	17.5/22		1. Observational study
				(50/44)	Cases: 2.93				2. Retrospective study
					Controls: 4.39				3. Uncommon definition of AAA (>25 mm)
									4. Limited number of size measures
									5. A higher number of CT estimates (over estimates AAA size) in the non-statin group
Karrowni[25]	2011	Statins	Retrospective case control study	Total: 211	AAA diameter growth (mm/y)	$p < .001$	15.5/22	1. AAA patients who at follow up were found to have a change in statin therapy were excluded	1. Observational study

				(136/75)	Cases: 0.9 Controls: 3.2				2. Retrospective study 3. Mixed imaging modalities and absent definition of max. diameter 4. Only 10% of the patients was imaged at 3 or more occasions
Karrlson[26]	2009	Statins	Retrospective case control study	Total: 213	AAA diameter growth (mm/y):	$p = .008$	9.5/22	1. Consistent aortic diameter measurements via ultrasound	1. Observational study
				(85/128)	Cases: 1.6 Controls: 2.5				2. Retrospective study 3. Sub-analysis of a studying evaluating an effect of azithromycin 4. Details regarding statin therapy missing
Schlosser[27]	2008	Statins	Prospective case control study	Total: 147	Adjusted estimated difference in growth rate for statin use: −1.2 mm/year	$p = .021$	16.5/22	1. AAA expansion rates were adjusted for age, initial AAA diameter, and hyperlipidemia in the multivariate linear regression model	1. Observational study
				(63/84)					2. Retrospective study 3. Time effect, inclusion window 1996−2007
Schouten[28]	2006	Statins	Retrospective case control study	Total: 150	Adjusted estimated difference in growth rate for statin use: −1.6 mm/year	$p = .006$	16.5/22	1. Patients with an inflammatory ($n = 12$) and mycotic ($n = 1$) AAA were excluded	1. Observational study
				(59/91)				2. Different types of statins were recorded	2. Retrospective study 3. Statin users also used more warfarin derivates and angiotensin II antagonists 4. Amongst cases a wide range of different statin types was used

Continued

Table 1-*continued*

First author/trial	Year	Intervention	Study design	Participants (Cases/Controls)	Outcomes	Significance	Strobe score	Study qualities	Study limitations
									5. Statins were not randomly assigned
									6. Power calculation missing
Sukhija[29]	2006	Statins	Prospective case control study	Total: 130	AAA size changes from baseline(mm) until endpoint:	$p < .001$		1. Measurements were consistently made with CT scan	1. Observational study
				(75/55)	Cases: 4.6 to 4.5				2. Power calculation missing
					Controls: 4.5 to 5.3				
Meij, van der[30]	2013	Statins	Retrospective case control study	Total: 142	No growth data available	NS		1. Single observer measurements only	1. Significant differences in baseline characteristics and cardiovascular risk management between cases and controls
				(103/39)					2. Growth data missing
									3. Non-randomized
									4. Power calculation missing
Ferguson[31]	2010		Prospective cohort study	Total: 652				1. Sample size calculations were made	1. Observational study
		Statins		(349/303)	Statins: OR 1.23 (95% CI 0.86—1.76)	NS		2. Different types of statins were recorded	2. Growth data missing
		Aspirin		(363/289)	Aspirin: OR 1.10 (95% CI 0.78—1.56)	NS			3. Significant differences in baseline characteristics
		Beta blockers		(182/470)	Beta blockers: OR 1.13 (95% CI 0.76—1.67)	NS			
		ACE inhibitors		(242/410)	ACE inhibitors: OR 0.91 (95% CI 0.64—1.31)	NS			
Morosin[32]	2008	Statins	Retrospective case control study	Total: 121	AAA diameter growth (mm/y)	NS			1. No randomization
				(34/87)	Cases: 1.9				2. Power calculation missing
					Controls: 2.6				
Vammen[13]	2001	Roxithromycin	RCT	Total: 58	AAA diameter growth (mm/y)	$p = .02$		1. Roxithromycin was randomly assigned	1. Power calculation missing
				(27/31)	Cases: 1.56			2. Well defined exclusion criteria	
					Controls: 2.75				

Hogh[33]	2009	Roxithromycin	RCT	Total: 84	AAA diameter growth (mm/y)	NS	1. Roxithromycin was randomly assigned	1. Power calculation missing
				(42/42)	Cases: 1.61		2. Single observer measurements only	2. Possible selection bias as only one third of the eligible AAAs was included
					Controls: 2.52			
Karrlson[34]	2009	Azithromycin	RCT	Total: 213	AAA diameter growth (mm/y)	NS	1. Azithromycin was randomly assigned	1. Power calculation missing
				(106/105)	Cases: 2.2		2. In addition to ultrasound, for each patient a volume calculation was made by CT scan	2. Differences in baseline characteristics
					Controls: 2.2			
		Aspirin	Retrospective case control	(101/100)	Cases: 1.8	$p = .004$		1. Observational study
					Controls: 2.6			2. Retrospective study
Morosin[35]	2001	Doxycycline	RCT	Total: 32	AAA diameter growth (mm/y)	NS	1. Single observer measurements only	1. Power calculation missing
				(17/15)	Cases: 1.5		2. Doxycycline was randomly assigned	2. 3 month intervention
					Controls: 3.0			3. Major differences in baseline AAA size between the groups
Baxter[36]	2002	Doxycycline	Prospective cohort study	Total: 36	AAA diameter (mm)	NS		1. Missing control group
					At baseline: 41.0 mm $\pm$ 0.9 mm			2. Treatment period 6 months
					At 6 months: 42 .7 mm $\pm$ 1.3 mm			3. Power calculation missing
Meijer[37]	2014	Doxycycline	RCT	Total: 286	AAA diameter growth (in 18 months)	$p = .016$	1. Single observer measurements only	1. High number of elective repairs
				(144/142)	Cases: 4.1 mm (95% CI, 3.6 to 4.5 mm)		2. Doxycycline or placebo were randomly assigned	2. Doxycycline dose of 100 mg was possibly too low or too high
					Controls: 3.3 mm (CI, 2.8 to 3.7 mm)		3. Long-term treatment with doxycycline	3. Drop outs where not followed
							4. Valid power calculation	

Continued

Table 1-*continued*

First author/trial	Year	Intervention	Study design	Participants (Cases/Controls)	Outcomes	Significance	Strobe score	Study qualities	Study limitations
Sillesen[38]	2014	Mast cell inhibitor (CD007)	RCT	Total: 326	AAA diameter growth (mm/y)	NS		1. Mast Cell Inhibitor was randomly assigned	1. No proof for an effect on the aneurysm wall
				10 mg (80/84)	Cases (10 mg): 2.58			2. AAA diameter was measured via 2D Ultrasound	2. Power calculation missing
				25 mg (78/84)	Cases (25 mg): 2.33			3. Long-term treatment with the mast cell inhibitor	
				40 mg (84/84)	Cases (40 mg): 2.70				
					Controls: 2.04				
Lindholt[39]	2008		Prospective case control study	Total: 148	AAA diameter growth (mm/y)				1. Overall growth data not available
		Aspirin			AAA baseline <40 mm:	AAA baseline <40 mm: NS			2. Observational study
					Cases: 2.52				3. Contradictory conclusions for small and intermediate AAA
					Controls: 2.23				4. Power calculation missing
		Aspirin			AAA baseline >40 −50 mm:	AAA baseline >40−50 mm: $p = .017$			5. Self reported aspirin use
					Cases: 2.92				
					Controls: 5.18				
Franklin[40]	1999	NSAIDs	Unclear case control study	Total: 78	AAA diameter growth (mm/y)	$p = .004$		1. Matched cases and controls	1. Conference abstract only
				(19/59)	Cases: 1.8				2. Unclear study design
					Controls: 3.2				

NS = not significant.

implying that ACE inhibitors may adversely affect AAA growth.[23]

Other anti hypertensive drugs (i.e. diuretics and calcium channel blockers) were evaluated in two retrospective analyses by Wilmink et al.[16] and Bhak et al.[19] Both studies found no association between these antihypertensive agents and AAA growth rate.

Statins

A potential effect of statins on AAA progression was evaluated in 12 studies. Six studies reported a beneficial effect of statin use on the AAA growth.[24–29] In contrast, six other reports failed to show an effect of statins on AAA growth.[22,23,30–32] Eight out of the 12 studies had a prospective design, but none of them were randomized clinical trials.[19,22,24,26,27,29–31] Most studies did not specify the type of statin investigated. Simvastatin and Atorvastatin were the dominant statins in the four studies that specified the statin type.[28–31]

There is an apparent paradox in conclusions for an effect of statins, with the earlier small studies reporting an association between the statin use and reduced AAA expansion,[27–29] but the more recent studies failed to confirm a relationship.[24,25,30] Moreover, none of the larger studies (including more than 250 patients) found a difference in AAA expansion rate between statin users and non-statin users.[22,23,31]

Macrolides

A presumed role for chlamydia in AAA growth led to studies testing an effect of macrolide treatment on the growth rate of small AAAs. Two RCTs evaluated the effect of roxithromycin on the expansion rate. The first, conducted in 2001, reported a significantly lower expansion rate in the roxithromycin treated patients ($p = .02$).[13] The second study, also a small RCT, reported a borderline effect of a 4 week treatment with roxithromycin on AAA progression ($p = .055$).[33] The effect of azithromycin, another member of the macrolide class, was investigated in a larger RCT conducted by Karlsson et al.[34] in 2009 ($n = 247$). This study did not observe a significant difference between the AAA expansion rate in the azithromycin treated patients and controls.

Tetracyclines

In 2001, a small RCT showed a pronounced effect of 3 months of doxycycline treatment on AAA expansion for the 6–12 and 12–18 month follow up periods.[35] Next, a phase II open safety and feasibility study by Baxter et al.[36] revealed significant reduction in MMP9 levels after 6 months of doxycycline treatment. Nevertheless, no significant change was seen for the overall AAA expansion rate. Results from an adequately powered multicenter RCT failed to show a beneficial effect of 18 months of doxycycline therapy on AAA progression. On the contrary, acceleration in AAA growth rate was reported during the 18 month follow up period.[37]

Anti-mast cell therapy

Sillesen et al.[38] investigated whether the mast cell inhibitor CRD007 (pemirolast) halted growth of small AAA. However, no difference in AAA growth rate was found between placebo and the mast cell inhibitor treated patients.

Anti-platelet therapy

Five studies investigated the potential of anti-platelet therapy in stabilizing human AAA growth.[19,23,31,34,39] A first case control study including 167 patients reported a decrease in AAA progression in those patients with a diameter between 40 and 49 mm. Patients with an AAA diameter smaller than 4.0 cm had a similar expansion rate with or without using aspirin.[39] Significantly reduced AAA progression in patients using aspirin was reported in a subanalysis of case control data of a small RCT investigating the effect of azithromycin. The average growth rate of the 101 patients using aspirin was 1.8 mm/year compared with 2.6 mm/year in those not on antiplatelet therapy ($p < .01$).[34] In contrast analyses performed on patients participating in the UK small aneurysm trial,[23] the ADAM study,[19] and a cohort study incorporating 363 patients[31] failed to identify an effect of platelet therapy on aneurysm progression.

One small study ($n = 19$) investigated the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on AAA growth.[40] The median growth rate of the AAA diameter of 1.8 mm/year compares favorably to the 3.2 mm/year in patients not taking NSAIDs, $p < .01$.

DISCUSSION

This systematic review shows that the number of studies evaluating a potential effect of pharmaceutical strategies to halt AAA growth in humans is limited. The majority of identified studies were of moderate quality, and initial promising reports were not confirmed by later larger studies. At this point, no pharmaceutical therapy can be recommended for the stabilization of AAA.

The search strategies identified 27 original papers that evaluated the potential of pharmaceutical intervention for AAA stabilization. Identified interventions can be subdivided into strategies that are part of general cardiovascular risk management (antihypertensive agents, statins, anti-platelet therapy), and into “anti-inflammatory” strategies: macrolides, tetracyclines, and mast cell inhibition.

The majority of studies were of moderate quality, as illustrated by a low to moderate score in the STROBE scoring system.[9] Most studies had a retrospective design, and small sample size.[41] Interpretation is hampered by poor matching, lack of standardized diameter measurements, and inappropriate statistical analyses. Studies on longitudinal data such as aneurysm progression are prone to non-random drop out.[42] For example, older patients are more likely to drop out because of death, but are less likely to undergo repair due to different risk estimates. By the same token, patients with larger or fast growing AAA are more likely to drop out prematurely because of repair. As such

follow up studies in AAA patients require specific statistical approaches,[43] a prerequisite that was not met in most studies. Moreover, it was observed that initial promising studies from small cohorts were not confirmed by later larger studies, an observation hinting at the phenomenon of selective reporting.[44]

Most data are available for cardiovascular risk management (beta blockers, ACE inhibitors and statins). Trials with the beta blocker propranolol experienced high drop out rates because of poor tolerance.[14,15] Statins and ACE inhibitors are well tolerated, yet a recent meta-analysis on the available data concluded that these drug classes did not influence AAA progression.[45]

The second of the tested interventions was the anti-inflammatory group, with anti-inflammatory referring to an anti-microbial action, in the case of AAA because of a suspected causative role for chlamydia infection in the disease, or alternatively anti-inflammatory in the context of chronic tissue inflammation that is thought to drive AAA progression (doxycycline, mast cell inhibition).[46] Although aspirin has anti-inflammatory properties, it is unclear whether the dose used for anti-platelet therapy is sufficient to exert an anti-inflammatory effect on the aneurysm wall. Again, there was no evidence for a beneficial effect of anti-inflammatory strategies on AAA progression. On the contrary, evidence was found for growth acceleration in patients taking doxycycline.[37]

The above conclusions contrast sharply with the available preclinical evidence that shows that pharmaceutical interference with aspects of the RAS system, cholesterol metabolism, vascular inflammation or protease activity alleviates aneurysm formation in rodent models of the disease[4,5]; an observation pointing to impaired translatability of the available preclinical models.[46]

In conclusion, there is currently no established medical therapy for the stabilization of growing AAA. Interpretation of the available data is hampered by its moderate quality. A role for beta blockers, doxycycline, and the mast cell inhibitor pemirolast has been ruled out in RCTs. Available observational data for ACE inhibitors and statins is not consistent with a beneficial effect on aneurysm progression. A number of interventions are currently being evaluated in clinical trials (Table 2). At this moment, no therapy can be recommended although it cannot be excluded that AAA growth and rupture are disparate processes. Consequently although some interventions do not influence AAA progression, they may influence the AAA rupture rate,[47] a notion that requires independent confirmation. Moreover, although cardiovascular risk management does not influence AAA progression, it is important to point out that risk management is indicated in AAA patients as this group is at an extremely high cardiovascular risk.[2]

Table 2. Overview of ongoing clinical trials.

Name	Intervention	Estimated completion date	Clinical trial number
PISA	Antihypertensives	December 2013	NCT01425242
AARDVARK	ACE inhibitors	October 2014	NCT01118520
ACZ885	Canakinumab (anti IL1-beta)	December 2015	NCT02007252
TicAAA	Ticagrelor	December 2015	NCT02070653
TEDY	Telmisartan	August 2016	NCT01683084
BASE	ACE vs. beta blockers	October 2016	NCT01904981
N-TA-3CT	Doxycycline	June 2017	NCT01756833
ACA4	Ciclosporin A	September 2018	NCT02225756

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2015.08.010.

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