Pharmaceutical stabilization of abdominal aortic aneurysms : changing its natural history

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Chapter 2

PHARMACEUTICAL MANAGEMENT OF SMALL ABDOMINAL AORTIC ANEURYSMS, A SYSTEMATIC REVIEW OF THE CLINICAL EVIDENCE

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ABSTRACT

Background

Management of abdominal aortic aneurysms (AAAs) fully relies on surgical repair of larger AAAs. Consequently, it has been pointed out that 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 long-standing interest in pharmaceutical AAA stabilization we considered a systematic review of the available literature relevant.

Objectives

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 clinically studied the 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 quenches AAA growth.

INTRODUCTION

The risk of rupture of an abdominal aortic aneurysm (AAA) progressively increases in larger AAAs, i.e. aneurysms larger than 55mm. Four large clinical trials do not show a benefit of earlier repair[1] (i.e. for aneurysms smaller than 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 outcome, 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, it has been pointed out that pharmaceutical means slowing down or stabilizing progression of small AAAs, and thus postponing or obviating the need for surgery could have major advances[3]. In fact, pharmaceutical stabilization of AAA is now considered an unmet medical need.

A large body of preclinical evidence shows 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 conclusion often inconsistent[6-8]. There are currently 78 reviews (this literature search) on pharmaceutical AAA stabilization, yet a comprehensive systematic review is missing. Given the renewed interest in pharmaceutical AAA stabilization we considered a systematic review of the available evidence on pharmaceutical interventions for stabilizing or impeding AAA growth in humans relevant.

METHODS

Search strategy

The studies included in this review were identified by searching 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.

We created two search themes, 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 aneurysms. 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 on the search strategy are available in the appendix I.

Inclusion criteria

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

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

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 3557 articles. Selecting on title and abstract narrowed the amount of articles to 30 original studies. Two of the 30 original studies were excluded because of missing data on 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, a total of twenty-seven original articles were available for this review (Figure 1). Identified studies are summarized in Table 1 and their quality assessed (STROBE scoring system[9], supplemental Table).

Anti-hypertensive drugs

Beta-blockers and other anti-hypertensive drugs were the first agents to be evaluated for their potential to reduce AAA expansion rate. Beta-blockers are 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) suggest a borderline-significant effect of beta-blockers on the aneurysm expansion rate[17;18]. Later, cohort studies, however, find no effect of beta-blockers on the growth rate of AAAs[16,18,21]. Similar to this, the two RCTs do not show an effect of propranolol treatment on the AAA expansion[14;15].

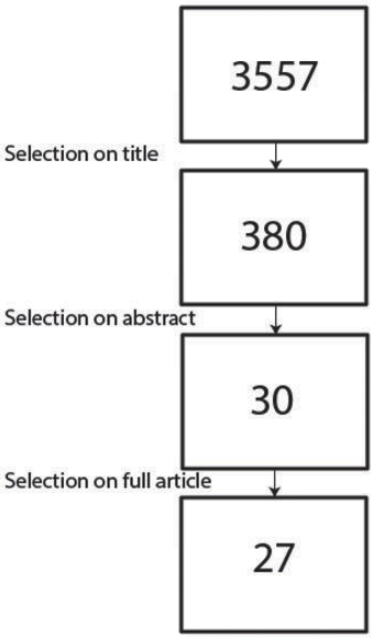

Figure 1. Systematic search strategy. First selection on title, second on abstract and last selection was made by reading the full article.

There are several reports on other classes of hypertensives. A retrospective study suggesting an effect of 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 analysis within a prospective case-control study[16;21] and two larger retrospective studies (n=1231 and n=242 cases) find no effect of ACE inhibitors on the 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, implying that ACE inhibitors may adversely affect AAA growth[23]. Other anti-hypertensive drugs (i.e. diuretics and calcium channel blockers) are evaluated in two retrospective analyses by respectively Wilmink et al. and Bhak et al. Both studies did not find an association between these antihypertensive agents and AAA growth rate[16,19].

Statins

A potential effect of statins on AAA progression is evaluated in twelve studies. Six studies report a beneficial effect of statin use on the AAA growth[24-29]. In contrast, six other reports fail to show an effect of statins on AAA growth[22;23;30-32]. Eight out of the twelve studies had a prospective design, but none of them were randomized clinical trials[19;22;24;26;27;29-31]. Most studies do not specify the type of statin that is investigated. Simvastatin and Atorvastatin are the dominant statins in the four studies that specify 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 failing to confirm a relationship[24;25;30]. Moreover, none of the larger studies (viz. 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 marcolide treatment on the growth rate of small AAAs. Two RCTs evaluate the effect of roxithromycin on the expansion rate. The first, conducted in 2001, reports a significant lower expansion rate in the roxithromycin treated patients (p=0.02)[13]. The second study, also a small RCT, reports a borderline effect of a four-week treatment with roxithromycin on AAA progression (p=0.055)[33]. The effect of azithromycin, another member of the macrolide class, is investigated in a larger RCT conducted by Karlsson et al in 2009[34] (n= 247). This study does 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 doxycycline treatment on AAA expansion for the 6 – 12 and 12-18 months follow-up periods[35]. Next, a phase II study by Baxter et al. open safety and feasibility study revealed significant a significant reduction in MMP9 levels after 6 months of doxycycline treatment. Nevertheless, no significant change was seen for the overall AAA expansion rate[36]. Results from an adequately powered multicenter RCT fail to show a beneficial

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

	Year	Intervention	Study Design	Participants (Cases/Controls)	Outcomes
PATI (13)	2002	Propranolol	RCT	Total: 548 (276/272)	AAA diameter growth (mm/y): Cases: 2.02 Controls: 2.60
Lindholt (14)	1999	Propranolol	RCT	Total: 54 (30/24)	Relative Risk of expansion: Cases: 2.44 (0.88-6.77) Controls: 1.17 (0.74-1.85)
Wilmink (15)	2002	Anti-hypertensive drugs: Calcium channel blockers ACE inhibitors Diuretics Beta blockers	Prospective case-control study	Total: 5811 (48/284) (24/308) (54/278) (77/255)	AAA diameter growth (mm/y): Cases: 0.5 Controls: 0.8 Cases: 0.02 Controls: 0.8 Cases: 0.8 Controls: 0.7 Cases: 0.8 Controls: 0.7
Gadowski (16)	1994	Beta-blockers	Prospective case-control study	Total:111 (38/83)	AAA diameter growth (mm/y) Cases: 3.0 Controls: 4.4
Leach (17)	1988	Beta-blockers	Retrospective case-control study	Total: 27 (12/15)	AAA diameter growth (mm/y) Cases: 1.7 Controls: 4.4
Bhak (18)	2015	 Beta-blockers Cholesterol lowering Anti-hypertensive Aspirin	Prospective cohort study	Total: 534 unclear unclear unclear unclear	Adjusted difference in AAA diameter growth (mm/y) 0.009 -0.02 -0.001 -0.01
Kortekaas (20)	2014	ACE inhibitors	Prospective case-control study	Total: 286	Difference in growth rate: -0.24 mm/year

Significance	Strobe score	Study qualities	Study limitations
NS		1. Study medication was randomly and double blinded assigned 2. Valid power calculation	1. Slow growing AAAs and patients already using beta blokkers excluded 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 3. Mislabeling of a batch of study medication 4. No correction for non random drop out
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 2. Power calculation missing
	13.5/22	1. Large study size	1. Observational study, data derived from two separate screening populations with different baseline characteristics
NS			2. Limited number of cases 3. Power calculation missing
NS			4. No correction for non random drop out
NS			
NS			
NS	11.5/22	1. Longterm follow up	1. Observational study 2. Hetrerogenous with respect to type and dose of beta blocker
NS	11.5/22		1. Observational study 2. Retrospective study 3. Limited number of cases
p=0.004	14.5/22	1. Large number of overall participants	1. Number of patients per group unclear
0.51 0.18 0.78 0.48			2. Observational study 3. Both CT and ultrasound measurements
p>0.05	16.5/22	1. One-observer measurements only	1. Observational study

Table 1. (continued).

	Year	Intervention	Study Design	Participants (Cases/Controls)	Outcomes
				(82/286)	
Thompson (21)	2010		Prospective cohort study	Total: 1231	Difference in AAA diameter growth between cases and controls (mm/y):
		ACE-inhibitors		294	ACE-inhibitors: -0.28
		Statins		383	Statins: -0.29
Sweeting (22)	2010		Prospective cohort study	Total: 1701	AAA diameter growth (mm/y)
		ACE-inhibitors		169	Cases: 3.33 Controls:2.77
		Calcium Channel Blockers		440	Cases:2.76 Controls:2.5
		Beta Blockers		255	Cases:2.70 Controls:2.85
		Statins		21	Cases:2.07 Controls:2.84
		Anti Platelet Therapy		501	Cases:2.89 Controls: 2.80
Periard (23)	2012	Statins	Retrospective case-control study	Total: 94 (50/44)	AAA diameter growth (mm/y) Cases: 2.93 Controls: 4.39
Karrowni (24)	2011	Statins	Retrospective case-control study	Total: 211 (136/75)	AAA diameter growth (mm/y) Cases: 0.9 Controls: 3.2
Karrlson (25)	2009	Statins	Retrospective case-control study	Total: 213 (85/128)	AAA diameter growth (mm/y): Cases: 1.6

Significance	Strobe score	Study qualities	Study limitations
			2. Significant difference in baseline characteristics 3. Power calculation missing
		1. Large study size	1. Patients lost to follow (n=158) up had a significantly lower AAA growth rate
NS			2. Time effect, patients identified between 1984 and 2007
NS			3. No correction for non random drop out 4. Secondary analysis, study not powered for an evaluation of a ACE inhibitor or statin effect
		1. Large study size	1. Observational study
p=0.009		2. Longterm follow-up 3. Data partially-adjusted and fully-adjusted available	2. Patients included between 1991-1995
NS			
NS			
NS			
NS			
p=0.01	17.5/22		1. Observational study
			2. Retrospective study 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
p<0.001	15.5/22	1. AAA patients who at follow-up were found to have a change in statin therapy were excluded	1. Observational study
			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
p=0.008	9.5/22	1. Consistent aortic diameter measurements via ultrasound	1. Observational study
			2. Retrospective study

Table 1. (continued).

	Year	Intervention	Study Design	Participants (Cases/Controls)	Outcomes
					Controls: 2.5
Schlosser (26)	2008	Statins	Prospective case-control study	Total: 147 (63/84)	Adjusted estimated difference in growth rate for statin use: -1.2 mm/year
Schouten (27)	2006	Statins	Retrospective case-control study	Total: 150 (59/91)	Adjusted estimated difference in growth rate for statin use: -1.6 mm/year
Sukhija (28)	2006	Statins	Prospective case-control study	Total: 130 (75/55)	AAA size changes from baseline(mm) until endpoint: Cases: 4.6 to 4.5 Controls: 4.5 to 5.3
Meij, van der (29)	2013	Statins	Retrospective case-control study	Total: 142 (103/39)	No growth data availabe
Ferguson (30)	2010		Prospective cohort study	Total:652	
		Statins		(349/303)	Statins: OR 1.23 (95% CI 0.86-1.76)
		Aspirin		(363/289)	Aspirin: OR 1.10 (95% CI 0.78-1.56)
		Beta-blockers		(182/470)	Beta-blockers: OR 1.13 (95% CI 0.76-1.67)
		ACE inhibitors		(242/410)	ACE inhibitors: OR 0.91 (95% CI 0.64-1.31)

Significance	Strobe score	Study qualities	Study limitations
			3. Sub-analysis of a studying evaluating an effect of azithromycin 4. Details regarding statin therapy missing
p=0.021	16.5/22	1. AAA expansion rates were adjusted for age, initial AAA diameter, and hyperlipidemia in the multivariate linear regression model	1. Obervational study 2. Retrospective study 3. Time effect, inclusion window 1996-2007
p=0.006	16.5/22	1. Patients with an inflammatory (n=12) and mycotic (n=1) AAA were excluded 2. Different types of statins were recorded	1. Observational study 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 5. Statins were not randomly assigned 6. Power calculation missing
p<0.001		1. Measurements were consistently made with CT-scan	1. Observational study 2. Power calculation missing
NS		1. One-observer measurements only	1. Significant differences in baseline characteritics and cardiovascular risk management between cases and controls 2. Growth data missing 3. Non-randomized 4. Power calculation missing
		1. Sample size calculations were made	1. Obervational study
NS		2. Different types of statins were recorded	2. Growth data missing
NS			3. Significant differences in baseline characteristics
NS			
NS			

Table 1. (continued).

	Year	Intervention	Study Design	Participants (Cases/Controls)	Outcomes
Morosin (31)	2008	Statins	Retrospective case-control study	Total: 121 (34/87)	AAA diameter growth (mm/y) Cases: 1.9 Controls: 2.6
Vammen (11)	2001	Roxithromycin	RCT	Total: 58 (27/31)	AAA diameter growth (mm/y) Cases: 1.56 Controls: 2.75
Hogh (32)	2009	Roxithromycin	RCT	Total: 84 (42/42)	AAA diameter growth (mm/y) Cases: 1.61 Controls: 2.52
Karrlson (33)	2009	Azithromycin	RCT	Total: 213 (106/105)	AAA diameter growth (mm/y) Cases: 2.2 Controls: 2.2
		Aspirin	Retrospective case-control	(101 /100)	Cases: 1.8 Controls: 2.6
Morosin (34)	2001	Doxycycline	RCT	Total: 32 (17/15)	AAA diameter growth (mm/y) Cases: 1.5 Controls: 3.0
Baxter (35)	2002	Doxycycline	Prospective cohort study	Total: 36	AAA diameter (mm) At baseline: 41.0 mm ± 0.9 mm At 6 months: 42 .7 mm ± 1.3 mm
Meijer (36)	2014	Doxycycline	RCT	Total: 286 (144/142)	AAA diameter growth (in 18 months) Cases: 4.1 mm [95% CI, 3.6 to 4.5 mm] Controls: 3.3 mm [CI, 2.8 to 3.7 mm]
Aorta Trial (37)	2014	Mast Cell Inhibitor (CD007)	RCT	Total: 326 10mg (80/84)	AAA diameter growth (mm/y) Cases (10mg): 2.58

Significance	Strobe score	Study qualities	Study limitations
NS			1. No randomization 2. Power calculation missing
p=0.02		1. Roxithromycin was randomly assigned 2. Well defined exclusion criteria	1. Power calculation missing
NS		1. Roxithromycin was randomly assigned 2. Single-observer measurements only	1. Power calculation missing 2. Possible selection bias as only one third of the eligible AAAs was included
NS		1. Azithromycin was randomly assigned 2. In addition to ultrasound, for each patient a volume calculation by CT scan was made	1. Power calculation missing 2. Differences in baseline characteritics
p=0.004			1. Observational study 2. Retrospective study
NS		1. One-observer measurements only 2. Doxycycline was randomly assigned	1. Power calculation missing 2. 3-month intervention 3. Major differences in baseline AAA size between the groups
NS			1. Missing control group 2. Treatment period 6 months 3. Power calculation missing
p=0.016		1. One-observer measurements only 2. Doxycycline or placebo were randomly assigned 3. Long-term treatment with doxycycline 4. Valid power calculation	1. High number of elective repairs 2. Doxycycline dose of 100 mg was possibly too low or too high 3. Drop-outs where not followed
NS		1. Mast Cell Inhibitor was randomly as signed 2. AAA diameter was measured via 2D Ultrasound	1. No proof for an effect on the aneurysm wall 2. Power calculation missing

Table 1. (continued).

	Year	Intervention	Study Design	Participants (Cases/Controls)	Outcomes
				25mg (78/84)	Cases (25mg): 2.33
				40mg (84/84)	Cases (40mg): 2.70 Controls: 2.04
Lindholt (37)	2008		Prospective case-control study	Total: 148	AAA diameter growth (mm/y)
		Aspirin			AAA baseline <40 mm:
					Cases: 2.52
					Controls: 2.23
		Aspirin			AAA baseline >40-50 mm:
					Cases: 2.92 Controls: 5.18
Franklin (39)	1999	NSAIDs	Unclear case-control study	Total: 78	AAA diameter growth (mm/y)
				(19/59)	Cases: 1.8 Controls: 3.2

NS = not significant

effect of 18 months doxycycline therapy on AAA progression. On the contrary, an acceleration in AAA growth rate is reported during 18 months follow up period[37].

Anti-Mast Cell therapy

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

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 reports 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 similar expansion rate with or without using aspirin[39]. Significant reduced AAA progression in patients using aspirin was reported in a sub-analysis of a case-control data of a small RCT investigating the effect of azithromycin. Average growth rate of the 101 patients using aspirin was 1.8 mm/year compared to 2.6 mm/year in those not on antiplatelet therapy ($p<0.01$)[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.

Significance	Strobe score	Study qualities	Study limitations
		3. Long-term treatment with the mast cell inhibitor	
			1. Overall growth data not available
AAA baseline <40 mm: NS			2. Observational study
			3. Contradictory conclusions for small and intermediate AAA
			4. Power calculation missing
AAA baseline >40-50 mm: p=0.017			5. Self-reported aspirine use
p=0.004		1. Matched cases and controls	1. Conference abstract only
			2. Unclear study design

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<0.01.

DISCUSSION

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

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

The majority of studies was of moderate quality as illustrated by a low to moderate score in the STROBE scoring system[9]. Most studies have a retrospective design, and have a 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. On the same

Table 2. Overview of ongoing clinical trials.

Name	Intervention	Estimated completion date	Clinical trial number
PISA	Anti-hypertensives	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	Cyclosporin A	September 2018	NCT02225756

token patients with larger aneurysms, 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 is 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 is available for cardiovascular risk management (beta-blockers, ACE-inhibitors and statins). Trials with the beta-blocker propranolol experienced a high dropout rates because of poor tolerability[14,15]. Statins and ACE inhibitors are well tolerated, yet a recent meta-analysis on the available data concludes that these drug classes do not influence AAA progression[45].

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

In conclusion, interpretation of the available data is hampered by the moderate quality of the available data. A role for beta blockers, doxycycline and the mast cell inhibitor pemirolast is 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 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 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].

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SUPPLEMENTAL DATA

Supplemental table 1. Full STROBE score of all articles selected in this review.

STROBE score Full article	PATI (14)	Lindholt (15)	Wilmink (16)	Gadowski (17)	Leach (18)	Bhak (19)	Kortekaas (21)	Thompson (22)	Sweeting (23)	Periard (24)	Karrowni (25)	Karrlson (26)	Schlosser (27)
Titel & Abstract (study design and balanced summary)	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Background & Rationale	1	1	1	1	1	1	1	1	1	1	1	1	1
Objectives & Hypothesis	0.5	0.5	1	1	1	1	1	1	1	1	1	x	1
Study Design (early in paper)	x	1	1	0.5	0.5	1	1	1	1	1	1	0.5	1
Setting (locations, dates, periods recruitement, exposure, follow-up & data collection)	1	0.5	0.5	0.5	0.5	1	1	1	1	1	1	0.5	1
Participants (criteria, selection methods, follow-up)	1	0.5	x	1	1	0.5	1	1	1	0.5	1	1	0.5
Variables (outcomes, exposure, confounders, predictors)	0.5	0.5	0.5	x	1	x	1	0.5	x	1	0.5	x	1
Measurements (source of data, methods)	1	1	1	1	1	1	1	0.5	1	1	1	1	1
Bias (incl efforts to avoid)	0.5	0.5	0.5	1	1	0.5	1	x	x	1	0.5	x	1
Study size (explain how arrived)	1	x	x	x	1	x	x	x	x	x	x	x	0.5
Quantitative variables	1	1	1	1	x	1	x	1	1	x	1	1	1
Statistics (incl missing data)	0.5	0.5	1	1	x	0.5	1	0.5	1	1	1	1	0.5
Participants (report numbers in each stage, flow diagram)	1	1	0.5	0.5	0.5	x	1	1	x	1	x	x	0.5
Descriptive data (characteristics of study participants)	1	1	x	0.5	x	0.5	1	1	1	1	1	1	1
Outcome data (numbers in each exposure catagory)	1	1	0.5	1	0.5	x	x	1	0.5	1	0.5	0.5	1
Main results (unadjusted estimates and confounder adjusted)	1	1	x	x	x	1	0.5	1	1	1	1	x	1
Other analysis	1	x	x	x	x	1	x	x	x	1	1	x	x
Key results (summary with reference to objectives)	1	0.5	0.5	0.5	x	1	1	1	1	1	1	x	0.5
Limitations (incl direction and magnitude of potential bias)	1	0.5	1	x	0.5	1	1	0.5	0.5	1	1	x	1
Interpretation (overall considering objectives, limitations & results similar studies)	0.5	1	1	0.5	0.5	0.5	1	x	0.5	1	0.5	0.5	0.5
Generalisability (external validity)	x	0.5	1	0.5	1	0.5	0.5	0.5	x	0.5	x	x	x
Funding (give source)	x	1	1	x	x	1	1	x	x	x	x	1	1
Total	16.5	15.5	13.5	11.5	11.5	14.5	16.5	14.0	13.0	17.5	9.5	16.5	16.5

Schouten (28)	Sukhija (29)	Meij, van der (30)	Ferguson (31)	Morosin (32)	Vammen (13)	Hogh (33)	Karrlson (34)	Morosin (35)	Baxter (36)	Meijer (37)	Sillesen (38)	Lindholt (39)	Franklin (40)	STROBE score Abstract
0.5	0.5	0.5	0.5	0.5	1	0.5	1	1	1	1	0.5	0.5	0.5	Titel (study design)
1	1	1	1	1	1	1	1	1	1	1	1	1	x	Authors (contact details)
1	x	1	1	1	0.5	0.5	1	1	1	x	0.5	1	1	Study Design
1	0.5	1	1	1	x	0.5	1	x	1	1	1	1	x	Objective & Hypothesis
1	0.5	0.5	1	1	1	1	1	1	0.5	1	1	1	x	Setting (methods incl follow-up dates)
1	0.5	1	0.5	1	1	0.5	1	x	0.5	1	1	1	x	Participants (eligibility criteria & sources)
1	x	x	x	x	x	x	x	0.5	x	1	1	x	1	Variables (primary outcome)
0.5	0.5	1	1	0.5	1	0.5	1	1	0.5	1	1	1	x	Statistical Methods (incl confounding control)
1	1	x	x	x	x	x	x	0.5	x	0.5	0.5	x	0.5	Participants (begin & end)
x	x	x	1	x	0.5	1	0.5	x	x	1	1	1	0.5	Main results (incl measures of variability and uncertainty)
1	x	1	1	1	1	x	1	1	x	1	1	1	1	Conclusions
1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	1	1	1	0.5		
x	x	x	x	1	1	1	1	1	1	1	x	1		
1	1	1	1	1	1	1	1	1	1	1	1	1		
1	0.5	1	0.5	1	1	1	1	1	1	1	1	1		
1	x	1	x	1	1	0.5	0.5	0.5	0.5	1	1	1		
x	x	x	x	1	x	x	1	x	x	1	x	x		
1	0.5	x	1	x	1	1	1	0.5	1	1	1	1		
1	x	1	1	1	1	1	1	x	1	1	0.5	1		
0.5	x	1	0.5	1	1	0.5	1	0.5	1	1	0.5	0.5		
x	0.5	0.5	0.5	x	x	x	0.5	x	0.5	0.5	x	x		
1	x	1	x	x	1	1	x	1	x	1	x	x		
16.5	8.0	14.5	13.0	13.0	15.5	13.0	17.0	14.5	13.5	20	15.5	15.5	4.5	