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REVIEW

Pharmacological Interventions to Attenuate the Expansion of Abdominal Aortic Aneurysm (AAA) – A Systematic Review CME

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Abstract *Introduction:* Is it possible by pharmacological methods to attenuate the expansion rate of abdominal aortic aneurysms?
Method: An Internet-based systematic literature search was performed to identify published reports on pharmacological methods to influence aneurysmal expansion rate.
Results: Of an original 450 articles, 21 remained to review: they included 15 cohort studies with 12,321 patients and seven randomised clinical trials (RCTs) with 1069 patients. Most studies are performed without a pre-study sample size calculation. There is no consistent pattern of pharmacological influence on expansion rate, but statins, non-steroidal anti-inflammatory drugs (NSAIDs) and macrolides should be further evaluated.
Conclusion: Properly designed RCTs are needed before conclusions can be drawn on the possibility to pharmacologically attenuate aneurysmal expansion and prevent rupture.

Screening and early detection with elective surgical intervention is an effective way to decrease mortality in abdominal aortic aneurysmal disease, where rupture is the great threat to a patient's life.[1] Whether open or endovascular treatment is chosen, the interventional procedure is not without complications, also serious ones including mortality. Knowing the pathophysiology of expansion, at least theoretically, it should be possible by pharmacological means to inhibit expansion or decrease the rate (Cooper et al., 2009, Baxter et al., 2008),[2,3] and in several animal models this has been possible. The aim of this article is to systematically review the literature on pharmacological interventions to attenuate abdominal aortic aneurysm (AAA) expansion in humans.

Pathophysiological Background

In Fig. 1 are summarised the various aetiological and pathophysiological factors, which have been discussed in

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the development of AAA. Although all details are not known, it is important to separate two processes, which could be and most probably are different, and therefore also need different methods to influence them: the primary development of an AAA and the expansion when it has once been established. Although interesting and important, this article will not further deal with the development of an AAA, which will include primary prevention. When there is an AAA, the question is if anything can be done to inhibit or slow down its expansion rate and risk of rupture. The problem has become increasingly important today, when an increasing number of small AAAs are identified through various screening programmes and where the diameter of less than 5 cm will not indicate invasive treatment. Expansion rate is important to help in deciding when to intervene. The rate is significantly reduced in non-smokers compared with smokers.[4–8] Diabetes mellitus may have a protective role.[9] The remaining part of this article will analyse different pharmacologic methods. One initial caveat is the complexity of aneurysmal expansion with a number of genetic as well as environmental factors of importance, thereby making studies methodologically difficult.

Results from Animal Models

There are several animal models for development of aneurysm. Potentially, they can be used to test substances of interest in the clinical setting, and in fact there are several, which have shown to be effective in attenuating experimental aneurysmal expansion. The problem, however, is that the animal models used do not necessarily reflect the complex situation of aneurysmal development in humans, and therefore every substance of interest has to be evaluated in the clinical setting of patients with a small AAA. There are at least three important characteristics in clinical AAA, which are different from the animal models and which probably are of importance when studying the disease: it is a disease of the ageing individual, it coincides with atherosclerotic alterations in the aneurysmal wall and the aneurysmal sac usually contains thrombotic material. Moreover, most animal models use rather artificial means to induce aneurysmal development.

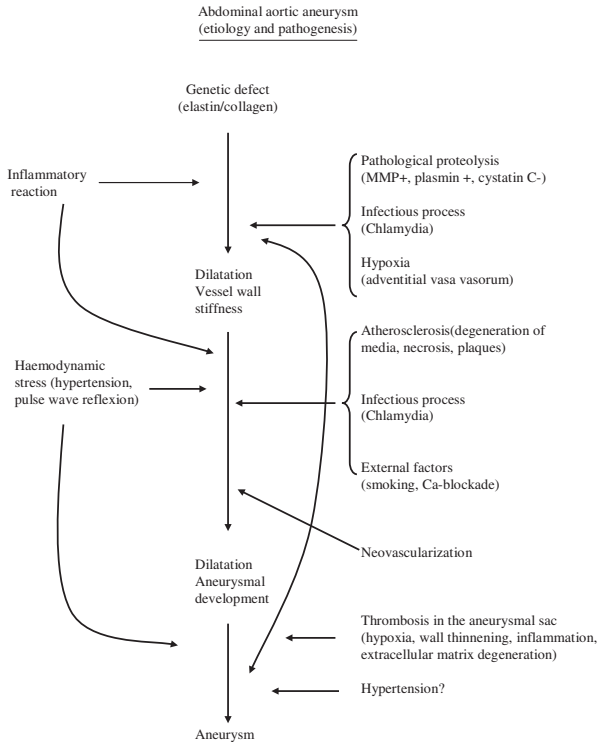

Figure 1 Etiological and pathogenetic factors in the development of AAA.

Method

A systematic literature search has been made in EMBASE, Cochrane and PubMed. Both randomised controlled trials (RCTs) and cohort studies have been accepted in dealing with human AAA, aneurysmal expansion (growth) and pharmacotherapy. In the identified studies, the reference lists were scrutinised for further studies of potential interest.

Results

A total of 460 articles on AAA and expansion were identified, 62 dealing with various aspects of pharmacotherapy. Twenty-one studies remained for review: 15 cohort studies with 12,321 patients (Table 1) and six RCTs with 1069 patients (Table 2). In Table 3, the results are summarised, the remaining substances of interest being statins and macrolides and possibly non-steroidal anti-inflammatory drugs (NSAIDs).

In one study, primarily focussed on compliance and safety with prolonged doxycycline and secondarily on matrix metalloproteinase (MMP) levels, there was no change in aneurysmal diameter over a 6 months' period.[10]

There is one large non-randomised population-based case-control study, which is of interest.[11] This is a study from a Canadian administrative database of 15,326 patients with the aim to analyse the influence of angiotensin-converting enzyme (ACE) inhibitors on the risk of AAA rupture, which can be seen as the final outcome of aneurysmal expansion. A total of 3379 patients were on ACE inhibitors with an odds ratio for rupture being 0.82 (95% confidence interval (CI) 0.74–0.90; $p < 0.0001$). In another observational study, also from Canada, renin-angiotensin blockade was, however, associated with an increased mortality after AAA repair.[12] In a recent publication from the UK Small Aneurysm Trial, patients taking ACE inhibitors had a faster growth rate than those without.[13]

Discussion

Today, an increasing number of individuals with small aneurysms will be identified through various screening programmes. As high as 90% of detected AAAs are small without indications for surgery, and the obvious and clinically relevant question is if those small aneurysms can be prevented from expansion.

Several pathophysiologically reasonable substances have been tested in cohort as well as randomised studies.

Table 1 Cohort studies on pharmacological interventions.

Author		No	Substances studied	Expansion rate, mm/y	*P*-value
Biancari[19]	2002	41	ß-block vs control	1.5 vs 2.2	NS
Brady[6]	2004	1743	Antihypertensives vs no	2.6 vs 2.7	NS
Ferguson[20]	2010	652	Statin vs no statin	OR 1.04	NS
Gadowski[21]	1994	121	ß-block vs control	3.0 vs 4.4	0.07
Leach[22]	1988	27	ß-block vs control	1.7 vs 4.4	NS
Lindholt[23]	2001	137	ß-block vs control	1.6 vs 2.5	0.01
Lindholt[24]	2008	148	ASA vs no ASA	2.5 vs 2.2	NS
Mosorin[25]	2008	121	Statin vs no statin	1.9 vs 2.6	NS
Schlösser[26]	2008	230	Lipid lowering vs no	Diff. 1.21	<0.02
Schouten[27]	2006	150	Statin vs no statin	2.0 vs 3.6	<0.001
Sukhija[28]	2006	130	Statin vs control	0 vs 0.4	<0.001
Sweeting[13]	2010	1701	ACEi vs no	3.33 vs 2.77	0.009
Thompson[29]	2010	1231	ACE vs no	Diff 0.28	NS
			Statin vs no	Diff 0.29	NS
Walton[30]	1999	78	NSAID vs control	1.5 vs 3.2	<0.01
Wilminck[31]	2002	5811	Antihypertensives vs no	0.5 vs 0.8	NS

Unfortunately, the study methodology has been suboptimal and, of the seven RCTs, only three had performed a pre-study power calculation. This is necessary to decide on a sufficient sample size. Of the substances tested so far, statins and macrolides should be in focus for further well-conducted trials. The seemingly positive effects of statins in the cohort studies should be verified in RCTs.

Studying statins in RCTs may, however, be difficult in the future as many patients already are on statin medication, and, moreover, statin treatment may decrease the risk for death, myocardial infarction and stroke, at least postoperatively.[14,15]

Regarding NSAIDs, the results are dubious but a subgroup analysis in one of the macrolide trials indicates an inhibitory effect on AAA expansion with acetylsalicylic acid.[16] Existing studies are usually of rather short duration with insufficient follow-up time in the perspective of aneurysmal development. An effect of ß-blockers seems to have been excluded (three RCTs) and is, moreover, poorly tolerated by patients.

There are a number of studies on several potential biomarkers for aneurysm expansion,[17] but using them as the sole end point in studies on pharmacological prophylaxis of expansion is not recommended, as their clinical relevance is not yet known. Until more knowledge is available, the biomarkers must be considered as surrogate end points and should be in focus for research.

There are a number of difficulties in studying an effect on expansion rate of AAA. The expansion is probably complex, influenced by several factors (Fig. 1), which could also vary between individuals. The mean expansion rate on a group basis is exponential,[18] meaning that there must be a correction for initial diameter but this should be of less importance in an RCT of sufficient size. Moreover, the expansion rate is individually unpredictable and does not follow a simple mathematical formula. Doses and duration of various potential pharmacotherapies are insufficiently known. Although risk of rupture increases with aneurysmal size, the true relationship between size, expansion rate and rupture is unclear, and several factors are probably of importance. Hence, for instance, the aneurysmal volume, the presence of 'blebs' and the amount of intraluminal thrombus material have been mentioned as important for expansion as well as rupture to occur. Expansion rate is, however, a reasonable surrogate for risk of rupture.

In conclusion, more properly designed RCTs are needed before we know how to pharmacologically attenuate aneurysmal expansion with the ultimate aim to prevent rupture. The increasing number of aneurysms detected by screening should, as far as possible, be used for such studies.

Table 2 RCTs on pharmacological interventions for attenuation of AAA expansion.

Author		No	Substances studied	Expansion rate mm/y	*p*-value
Høgh[32]	2009	84	roxithromycin vs placebo	1.6 vs 2.5	0.055
Karlsson[16]	2009	259[a]	azithromycin vs placebo	2.2 vs 2.2	NS
Lindholt[33]	1999	54	ß-block vs placebo	3.1 vs 2.8	NS
Mosorin[34]	2001	32	doxycyclin vs placebo	0 vs 2	NS
Propranolol[35]	2002	548[a]	ß-block vs placebo	2.2 vs 2.6	NS
Vammen[36]	2001	92[a]	roxithromycin vs placebo	1.6 vs 2.8	0.002

[a] Statistical power calculation.

Table 3 Summary of studies on pharmacological intervention for attenuation of AAA expansion.

Type of study	No of patients (no of studies)	No of studies with effect/without effect					
		Statins	NSAID	ACEi	ß-block	Macrolides	Antihyper-tensives
Cohort	12,321 (15)[a]	3/3	1/1	—/2	1/3	—	—/2
RCT	1069 (6)	—	—	—	—/2	2/2	—

[a] In one study[29] both statin and ACEi were studied.

Conflict of Interest/Funding

None.

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