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Abdominal Aortic Aneurysms: Pathophysiological Mechanisms and Clinical Implications

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- Pasterkamp G, Galis ZS, de Kleijn DPV. Expansive arterial remodeling: location, location, location. 2004;24:650–657.
- Shimizu K, Mitchell RN, Libby P. Inflammation and cellular immune responses in abdominal aortic aneurysms. 2006;26:987–994.

Abdominal Aortic Aneurysm Pathogenesis and Implications for Management

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Abstract—Abdominal aortic aneurysm (AAA) affects approximately 5% of elderly men and is responsible for a significant number of deaths in Western Countries. At present surgery by open or endovascular means is the only widely used therapy for this condition. In this review we examine the risk factors, serum, and genetic associations of AAA. Epidemiology studies suggest that smoking cessation and control of cholesterol and blood pressure should reduce the number of patients developing AAA. Natural history studies suggest that smoking cessation should reduce the rate of progression of AAA. Clear level 1 evidence for drug treatments of AAA are presently lacking; however, animal and human in vitro studies suggest that medication targeted at reducing inflammation and proteolysis are most likely to be beneficial, with limited data to support the use of statins, Angiotensin II inhibitors, and macrolides. Work has commenced in understanding which patients, identified by clinical, serum, and genotype, are more at risk of AAA progression and thus should be selected out for aggressive treatment. Well designed large multicenter randomized controlled trials are required to examine the medical treatment of AAA. (*Arterioscler Thromb Vasc Biol.* 2006;26:2605–2613.)

Key Words: abdominal aortic aneurysm ■ pathogenesis ■ medication

Abdominal aortic aneurysms (AAAs) usually occur in the infrarenal part of the aorta. An AAA is generally defined as a maximal aortic diameter of ≥ 3 cm, although definitions such as ≥ 4 cm and an infrarenal to suprarenal diameter ratio of 1.2 to 1.5 have also been used.^{1,2} Irrespective of the definition, the underlying problem in aneurysmal disease is weakening of the aortic wall, resulting in progressive dilatation and, left untreated, eventual aortic rupture. Less common complications include distal embolization, aortoenteric or aortocaval fistulae, and iliac

vein compression resultant in deep vein thrombosis. As a result, AAA is estimated to be the tenth commonest cause of mortality and is responsible for $\approx 2\%$ of all deaths. Estimates of mortality are hampered by low rates of postmortems and it is likely that some sudden deaths attributable to ruptured AAA are certified as cardiac deaths unless a preexisting AAA was documented. Unlike coronary heart disease, the incidence of AAA is reported to be increasing in Western Countries.^{3,4} In Scotland, for example, the mortality rates from AAA increased 2.6-fold

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TABLE 1. Risks Factors Associated With Aortic Aneurysm in Population Screening Studies

Study	AAA detected/ screened (%)	Age	Smoking	FH	Age	CHD	Cholesterol	Hypertension	Female	Black Race	Diabetes	
ADAM ¹	1031/73 451	(1.4)	50–79	5.57	1.95	1.65	1.62	1.54	1.16	0.22	0.49	0.54
Rotterdam ^{11,12}	112/5283	(2.1)	≥55	3.10	NA	2.70	1.70	1.80	1.80	0.15	NA	0.71
Tromso ¹³	337/6386	(5.3)	≥25	7.37	NA	3.31	NA	1.19	1.61	0.22	NA	NA
Genoa ¹⁴	70/1601	(4.4)	65–75	3.70	NA	NA	3.48	1.12	1.50	0.06	NA	1.02
Pittsburgh ²	451/4741	(9.5)	≥65	1.68	NA	1.31	1.85	NA	1.22	0.40	0.81	1.06
WA ¹⁵	875/11650	(7.5)	65–83	2.80	2.40	2.40	2.20	1.50	1.63	NA	NA	NA
Birmingham ¹⁶	219/2597	(8.4)	65–75	2.07	NA	NA	2.13	NA	1.24	NA	NA	0.83
Chichester ¹⁷	218/5392	(4.0)	65–80	1.56	NA	1.05	1.66	NA	NA	0.16	NA	0.80
Weighted mean	3313/111101	(4.0)	≥50	2.77	1.99	1.13	1.84	1.37	1.35	0.27	0.67	0.67
[CI]*		[3.9–4.2]		[2.48–3.10]	[1.61–2.46]	[1.10–1.16]	[1.68–2.02]	[1.26–1.49]	[1.24–1.46]	[0.23–0.31]	[0.54–0.82]	[0.58–0.77]

Screening studies with ≥1000 patients were included, except for Oslo,¹⁸ Edinburgh,¹⁹ and Viborg²⁰ studies, which were excluded because only a small proportion of the control population had risk factors assessed or reported. ADAM indicates Aneurysm, Detection and Management study; WA, Western Australia; FH, family history; CHD, coronary heart disease, defined as history of myocardial infarction and/or angina.

*Weighted means for % aneurysm and for odds ratio are combined overall effect assuming fixed effects.

between 1981 and 2000.⁴ Larger increases in admissions and operations have been reported.³ Although improved detection and reduction in mortality from other types of cardiovascular disease may have contributed to these increases, the rising age-standardized mortality appears to indicate a genuine increase in the incidence of AAA.⁴

Two large randomized controlled trials have indicated that survival is not improved by elective surgery for AAAs <5.5 cm in diameter.^{5,6} Small abdominal aortic aneurysms are followed by periodic ultrasound surveillance until the aortic diameter approaches 5.5 cm when repair by open or endoluminal surgery is indicated for those patients deemed suitable. Trials comparing conservative treatment, open or endoluminal repair have identified shortcomings in both forms of intervention: a case fatality of 2.7 to 5.5% for open repair and a cumulative reintervention rate at 5 years of 20% for endoluminal repair.^{5–8} Trials comparing surveillance with endoluminal treatment of small (4 to 5.4 cm) AAAs have now commenced.⁹

The increased incidence of AAA suggests that the public health measures that have helped reduce the burden of occlusive cardiovascular disease are not effective for this condition. Surgery is currently the only therapy for individuals with AAA, but intervention is costly and associated with morbidity and mortality. This highlights the need for further research into the cause of AAAs to facilitate the development of medical therapies. With the possible introduction of screening for AAAs, large numbers of small aneurysms will be diagnosed over the next decade.¹⁰ The growing interest in treating small AAAs by endovascular repair may eliminate the opportunity to scientifically investigate drug therapies for the condition. This review outlines recent developments in the understanding of AAA pathogenesis and its relevance to the medical treatment of the condition.

Risk Factors for Abdominal Aortic Aneurysm

Our best understanding of the risk factors for AAAs comes from epidemiological screening studies (Table 1).^{1,2,11–20} Male gender and increasing age are consistently identified as non-modifiable risk factors for AAA. A positive family history of AAA is reported in 1% to 5% of patients (see below).^{1,15} Ethnicity may also be important with some evi-

dence that AAAs are more common in Northern Europeans than Asians or Africans.^{1,15}

All case control studies report that smoking is a significant risk factor for AAA (Table 1). The relative risk for current smokers is at least 2 and the association of ever smoking with AAA is 2.5 times greater than the association of ever smoking with CHD.²¹ Continued smoking also results in increased AAA expansion, a greater risk of rupture and a worse prognosis.²² There is some evidence of a slow decline of risk after cessation of smoking.²³ These studies indicate that smoking cessation is a priority in any patient with an AAA.

A history of, or being treated for, high plasma cholesterol concentrations has been associated with an increased risk of identifying an AAA in large screening studies.^{1,15} Most, but not all, case-control studies in which fasting lipids have been measured indicate modest elevations of total cholesterol and LDL-cholesterol concentrations in individuals with AAAs.^{2,11} Reducing cholesterol concentrations in patients is therefore desirable, although there is no evidence that this either prevents or slows the expansion of AAAs.

Hypertension has only a weak association with AAA (Table 1). Assessment of the correlation between blood pressure and AAA is complicated because the definition of hypertension is often based on whether the patient is receiving treatment for this condition.^{2,11–13,15} Interestingly, in subgroup analysis of data from the Chichester and Huntington population screening study, Wilmsink and colleagues reported an association between aortic aneurysm and treatment of hypertension only in patients receiving calcium channel blockers (adjusted odds ratio 2.6, 1.5 to 4.3).²⁴ The authors related the worse prognosis in these patients to increased aortic stiffness and reduced collagen turn-over.²⁴ Because medications prescribed for hypercholesterolemia or hypertension may themselves affect the development of AAA, the relationship between these risk factors and aneurysm presence is difficult to assess. Interestingly diabetes mellitus has a negative association with AAA, although the reasons for this are not known (Table 1).

Studies on Human Tissue and Serum

To identify critical mechanisms underlying aortic weakening and subsequent aneurysm formation, a large number of studies

TABLE 2. Examples of Gene Products Altered in Human AAA Formation or Expansion

	Proteolysis	Inflammation	Lipids	Extra Cellular Matrix
Tissue	↑ MMP-1, -2 & -9 ^{27,28‡} ↑ Cathepsin H & L ^{27,30‡} ↓ Cystatin C ^{32‡}	↑ Adhesion molecules ^{27*} ↑ Cytokines ^{27,29,33,34‡} ↑ Chlamydia antigens ^{35-37‡}	↑ Apo E ^{27*}	↓ Collagen VI α 1 ^{26*} ↓ Glycoprotein IIIA ^{26*}
Circulating markers for AAA presence	↑ PAI-1 ⁴¹ ↑ MMP-9 ⁴³	↑ Chlamydia antibodies ⁴⁰ ↑ Homocysteine ⁶¹	↑ HDL ^{13,38} ↑ LDL ^{38,39} ↑ Lp (a) ⁴¹	↑ Tenascin-X ⁴²
Circulating markers for AAA expansion	↑ MMP-9 ⁷⁹ ↑ tPA ⁷³ ↓ Cystatin C ⁷⁶	↑ Chlamydia antibodies ^{74,75} ↑ Osteoprotegerin ³¹		↑ PAP ⁷⁷ ↑ SEPs ^{78,79} ↑ PIINP ⁸⁰

MMP indicates Matrix Metalloproteinase; Apo E, apolipoprotein E; PAI-1, plasminogen activator inhibitor type 1; HDL, high density lipoprotein; LDL, low density lipoprotein; Lp(a), Lipoprotein a; tPA, tissue plasminogen activator; PAP, P-plasmin-antiplasmin complexes; SEPs, serum-elastin-peptides; NIINP, procollagen-III terminal propeptide. Data with respect to mRNA (*), protein (†) or both (‡).

have assessed aortic histology, protein abundance and gene expression, and circulating markers in patients and controls.²⁵⁻³⁷ The findings of these studies have been recently reviewed in detail.²⁵ Gene array studies have highlighted loss of extracellular matrix, accumulation of proteolytic enzymes, and cytokines as reproducible findings in human AAA biopsies (Table 2).

The assessment of circulating markers has identified a number of lipids, cytokines, extracellular matrix, and thrombogenic proteins altered in the presence of AAAs, including high-density lipoprotein, lipoprotein (a), antibodies to Chlamydia, the proteolytic enzyme metalloproteinase 9, plasminogen activator inhibitor (PAI)-1, Tenascin-X, and homocysteine (Table 2).³⁸⁻⁴³ The findings from different studies are not always in agreement. Sangiorgi et al reported higher serum levels of matrix metalloproteinase (MMP)-9 in patients with aortic aneurysm; however, a much larger study by Eugster and colleagues did not confirm these findings.^{43,44} Although these aortic biopsy and blood assessments give clues as to the mechanisms taking place in end-stage AAA they cannot clarify the initiating pathways since many of the abnormalities demonstrated will be a consequence of the underlying pathological processes.

Genetics and AAA

Screening studies suggest that having a first-degree relative with an AAA is associated with an odds ratio of 1.9 to 2.4 of developing a similar problem (Table 1). AAAs develop in ~20% of brothers of patients with the condition.⁴⁵ These and other findings including the presence of multiple aneurysms and systemic abnormalities in aneurysm patients eg, increased connective tissue laxity, all highlight a role for genetic factors in AAAs.⁴⁶

A variety of strategies have been used to identify possible genes important in AAA development. A small number of studies have concentrated on multiplex AAA families (with at least 2 affected members).^{47,48} Genome-wide scans of these patients have suggested a role for genes located on chromosome 19q13 and 4q31.⁴⁷ Candidate genes in these regions include interleukin (IL)-15, endothelin receptor A, programmed cell death 5, and LDL receptor-related protein 3.⁴⁷ More commonly, a candidate gene approach has been used with testing of the association between genetic variants and the presence of an AAA.^{41,49-61} Because it is likely that any

single polymorphism will only impart a modest increased risk (odds ratio 1.2 to 2), association studies require very large numbers (up to 12 000 for alleles present in 5% of the population), appropriate controls, clear categorisation of phenotype, and careful analysis, as has been highlighted in a number of reviews and editorials.⁶²

As with other complex diseases, replication of gene association studies has been inconsistent. Strauss and colleagues reported an association between the C677T variant of the methylenetetrahydrofolate reductase gene and AAA in a small study (63 cases & 75 controls), a finding confirmed by Sofi and colleagues.^{41,63} Jones et al in a larger study (428 cases & 270 controls) were unable to replicate this result.⁵² Table 3 summarizes some of the larger genetic association studies of AAA carried out to date.^{41,49-61} The type of controls used in these studies are important to consider. They must have aortic imaging to exclude AAA and be sourced from the same population with matching for ethnicity, age, and gender, and this is often not the case (Table 3). The identification of genes of importance in AAA requires multicenter collaborative establishment of large numbers of patients and controls with accurate aortic imaging, recording of clinical risk factors, and DNA. Such collaborative data sets are presently being generated and will allow the assessment of a large number of candidate genes using rapidly developing technology able to screen for enormous numbers (>1500) of single nucleotide polymorphisms in a sample using high through-put assays. The use of the HapMap will aid in the selection of appropriate polymorphisms.⁶⁴

Natural History of AAA

Our understanding of the rates of expansion of AAA and risk factors for expansion comes from longitudinal studies of cohorts with small (3 to 5.5 cm) AAAs.^{22,65,66} Data about larger AAAs and risk factors for rupture come from studies of patients deemed unsuitable for surgery.⁶⁷

The study of the expansion of AAAs presents a number of methodological challenges. Firstly, the change in aortic diameter over time is small and characterized by periods of rapid growth and quiescence. Simple estimates of growth usually overestimate the rate of progression, and, given that losses to follow-up are inevitable, estimation techniques such

TABLE 3. Genetic Polymorphisms Associated With AAA

SNP	Population	AAA			Control			OR
ACE I/D		II	ID	DD	II	ID	DD	
	Florence ^{49*}	38	108	104	70	113	67	
	Italy ^{50*}	17	46	61	36	48	28	
	Japan ^{51*}	51	48	26	54	70	29	
	Total	106	202	191	160	231	124	2.33 [1.67–3.25] for DD
MTHFR C677T		CC	CT	TT	CC	CT	TT	
	Dunedin ^{52†}	210	169	49	137	104	30	
	Florence ^{41*}	141	217	80	166	211	61	
	Total	351	386	129	303	315	91	1.22 [0.90–1.67] for TT
MMP-9 C1562T		CC	CT	TT	CC	CT	TT	
	Dunedin ^{53‡}	257	145	12	129	43	0	2.94 [1.57–5.45] for T allele
PAI-1 4G/5G		4G4G	4G5G	5G5G	4G4G	4G5G	5G5G	
	Dunedin ^{54§}	65	93	32	57	83	21	1.34 [0.69–2.57] for 5G5G
eNOS G894T		TT	GT	GG	TT	GT	GG	
	Florence ^{55*}	69	109	72	29	110	111	0.27 [0.16–0.46] for GG
Oestrogen receptor β		AA	Aa	aa	AA	Aa	aa	
	Pisa ^{56*}	22	57	20	77	112	36	1.94 [0.94–4.01] for aa
Chemokine receptor CCR5 Δ 32 deletion		WT/WT	WT/ Δ 32	Δ 32/ Δ 32	WT/WT	WT/ Δ 32	Δ 32/ Δ 32	
	Milano ^{57§}	51	18	1	152	20	0	2.70 [1.41–5.15] for Δ 32 allele
IL-10 1082		GG	GA	AA	GG	GA	AA	
	Leicester ⁵⁸	17	49	34	29	48	23	2.52 [1.13–5.61] for AA
Haeme oxygenase-1 short repeats		SS	SL	LL	SS	SL	LL	
	Vienna ^{59‡}	2	27	41	8	36	26	0.16 [0.03–0.81] for SS
TIMP1 nt+434		T allele	C allele		T allele	C allele		
	Detroit ^{60§}	176	135		103	109		0.72 [0.51–1.03] for C allele
HLA-DR B1 *02		Allele present	Allele absent		Allele present	Allele absent		
	Rochester ^{61¶}	40	62		30	88		1.89 [1.07–3.36] For allele
HLA-DR B1 *04	Rochester ^{61¶}	36	66		29	89		1.67 [0.93–3.00] for allele

*Age and sex matched healthy controls.

†Matched for age, sex, and coronary artery disease, but controls have greater frequency of hypercholesterolemia and diabetes with less history of smoking.

‡Age and sex matched patients with peripheral vascular disease.

§Controls not matched for age or sex.

||Age and sex matched vascular patients, some controls without aortic imaging.

¶ Matched for ethnicity only, with lower age range in controls and no other factors such as gender presented.

as a Bayesian multilevel random effect model have been recommended.²² Secondly, the measurement of aortic diameter using ultrasound (and to a lesser extent CT) has an error margin of 2 to 3 mm,^{22,65,68} which is larger than the annual expansion of many small AAAs. Finally, larger AAAs are regularly lost to surveillance when clinicians recommend surgical intervention on the basis of risk of rupture. This is a particular problem in studies of 4 to 5 cm AAA (the group most likely to require medical treatment) where the intervention rate is around 10, 25, and 40% at 1, 2, and 3 years, respectively, even in centers with conservative surgical protocols.^{1,6}

Determinants of AAA Expansion

Understanding the cause of AAA progression can help identify secondary prevention strategies aimed at slowing expansion. The importance of diameter in predicting subsequent aneurysm growth has been clearly identified in studies

of small AAAs.^{5,6,22,65,66} Maximum aortic diameter is also the best determinant of the risk of rupture. In a study of 198 patients unsuitable for surgery, in which postmortems were carried out in 46%, rupture rate was estimated as \approx 8%, 10%, and 20% per year for aneurysms measuring 5.5 to 5.9, 6.0 to 6.9, and \geq 7.0 cm, respectively.⁶⁷

Current cigarette smoking is associated with AAA growth resulting in an estimated increase in expansion rate of 15% to 20%.^{22,69} Other atherosclerotic risk factors such as hypertension and dyslipidemia are of uncertain importance with many studies finding no association.^{22,65} Conversely, diabetes and peripheral vascular disease have been negatively associated with expansion.^{22,70} Of the risk factors known to be associated with AAA presence, only smoking and diabetes mellitus have been consistently shown to predict AAA progression. Thus different factors may promote progression as opposed to initiation of AAA.

A number of investigators have assessed circulating and genetic predictors of AAA growth. Weak associations between polymorphisms in Apo E and Cystatin C with AAA growth rate have been identified.^{71,72} The adjusted mean expansion rate for men with E2E4 and E3E4 Apo E genotypes were 4.2 (2.7 to 5.6) and 1.3 (0.7 to 1.9) mm/year, respectively, $P=0.001$.⁷¹ Because of the variety of Apo E genotypes, however, only 3 and 17 patients, respectively, had these genotypes. The growth rate of patients with GG (n=263) and AA (n=20) genotypes for the +148 G to A polymorphism of Cystatin C were reported as 0.37 and 0.30 cm/year ($P=0.03$ adjusted for smoking, gender, and age).⁷²

As outlined above, genotype is likely to play a role in AAA development and would also be expected to influence expansion; however, because the effect of most single polymorphisms is small, large studies are required.⁶² Identification of phenotypically distinct groups of AAAs probably requires a minimum follow-up of five years. As many patients will require intervention during follow-up, the generation of adequately-sized cohorts is extremely difficult.

The investigation of the association between circulating proteins and AAA progression may identify factors which are influenced by both environmental and genotypic factors. Circulating markers associated with AAA growth or rapid progression include osteoprotegerin,³¹ tissue-type plasminogen activator (t-PA),⁷³ anti-chlamydia pneumoniae antibodies,^{74,75} macrophage migration inhibitory factor (MIF),³³ Cystatin C (negative correlation),⁷⁶ P-plasmin-antiplasmin-complexes,⁷⁷ serum-elastin-peptides,^{78,79} procollagen-III-N-terminal propeptide (PIIINP),⁸⁰ and MMP-9⁸¹ (Table 2). Circulating biomarkers such as these could be used to monitor the progress and response to treatment of AAA. Sufficiently powered multicenter studies with long follow-up of aortic diameter are required so that the relative merits of a number of these potential biomarkers can be compared. Such studies may identify characteristics associated with different growth patterns such as AAA regression, stasis, or rapid progression.

Role of Medication for AAA: Animal Studies

A number of animal models of aortic aneurysm have been developed in rabbits, rats, and mice.^{82–84} The rabbit and rat models have principally relied on a chemically induced aortic degeneration stimulated by painting or infusion of elastolytic solution onto the infrarenal aorta.^{82,83} The availability of a range of genetically modified mice has allowed for a greater variety of models in this species (see review by Daugherty and Cassis⁸⁴). These studies have highlighted the importance of inflammation, proteolysis, and antioxidant mechanisms in aortic degeneration. A number of investigators have assessed the role of medication in suppressing aneurysm development in these models (Table 4).^{83,85–106} These studies demonstrate the potential of a wide range of medications including those inhibiting MMPs, Angiotensin II synthesis and receptors, and oxidative stress. A recent study using 2 mice models reported the regression of aortic aneurysm using a c-Jun N-terminal kinase inhibitor.¹⁰⁶ Most studies indicate an independent effect of the medication on aneurysm and atherosclerosis in these models (Table 4).

Role of Medication for AAA: Human Studies

Three types of human studies have been carried out to investigate the efficacies of putative medical therapies for AAA, namely explant studies, medication association studies, and randomized controlled trials. In explant studies biopsies retrieved from AAA at the time of open surgery are incubated with drugs to assess their ability to modulate biological factors associated with AAA progression. In this type of study allowance needs to be made for patient heterogeneity and the concurrent use of drugs by subjects from which the biopsies are removed. The viability of cultured samples is also limited (usually around one week). These studies have highlighted the potential of statins, Angiotensin II inhibitors (Angiotensin Converting Enzyme inhibitors and Angiotensin II blockers), macrolides, and cyclooxygenase inhibitors in reducing the production of proteinases and cytokines from human AAA biopsies.^{31,107–109} Indomethacin for example has been demonstrated to reduce IL-1 β , IL-6, and PGE₂ secretion from explants but had no effect on MMP production.¹⁰⁹ Similarly, Angiotensin II blockers have been shown to reduce the production of the cytokine osteoprotegerin from aortic aneurysm explants.³¹ Tetracyclines have been shown to reduce MMP production,¹⁰⁸ while the MMP-3 and MMP-9 concentrations are reduced in the AAA biopsies of patients receiving statins.¹⁰⁷ The findings of human in vitro and animal studies (Table 4) suggest potential benefit from statins, Angiotensin II inhibitors, beta adrenoceptor blockers, nonsteroidal antiinflammatory medications, and macrolides in the treatment of AAA.

Unfortunately, clinical studies to examine the role of these medications in slowing AAA progression have been limited to date.^{110–112} In a cohort of patients in the UK small aneurysm trial the concurrent use of nonsteroidal antiinflammatory medication was noted to be associated with reduced aortic expansion.¹¹³ Concerns regarding the cardiac effect of cyclooxygenase inhibitors might limit the use of this medication.¹¹⁴ The largest and best conducted study to date examined the effect of propranolol in a randomized controlled trial of 548 patients with small (3 to 5 cm) AAAs followed for a mean of 2.5 years.¹¹⁰ No effect on AAA growth, intervention rate, or mortality could be demonstrated for the treatment group. Furthermore, 42% of patients receiving propranolol had to discontinue the medication and the patients randomized to this group reported a worse health-related quality of life.¹¹⁰ The effect of antibiotics targeting Chlamydia pneumoniae in patients with AAAs have been studied in two small randomized trials.^{111,112} In addition, the antibiotics used, doxycycline and roxithromycin, have also been shown to reduce MMP production in animal models and/or human explants, and inhibit aneurysm development experimentally (Table 4). Mosorin and colleagues randomized 32 patients with small aneurysms to doxycycline or placebo and followed them for 18 months, reporting a nonsignificant reduction in expansion overall.¹¹¹ Vammen et al randomized 92 patients with small aneurysms between roxithromycin and placebo over a mean of 1.5 years and reported a significant reduction in aortic expansion from 2.75 to 1.56 mm/year, although growth rate appears to have been calculated by linear regression.¹¹² Neither of the medications were associated with significant side-effects and drop-outs were minimal.^{111,112}

TABLE 4. Medication Demonstrated To Inhibit AAA in Animal Models

Medication	Model	Diameter control	Diameter treated	Mechanisms
Propranolol ^{85,86}	WKHT elastase	6.9±3.5 (n=18)	2.9±1.24 (n=14)*	Blood pressure reduction.§
Propranolol ⁸⁷	Male BLO	1.70±0.10 (n=14)	1.13±0.09 (n=11)	Not investigated.
Simvastatin ⁸³	Rat elastase	4.3±0.19 (n=19)	3.4±0.08 (n=19)*	Antiinflammatory, proteolysis & oxidative stress.
Simvastatin ⁸⁸	Mice Apo E ^{-/-} elastase**	1.37±0.08 (n=25)	1.14±0.07 (n=28)†	MMP-9 suppression, elastin and VSMC preservation.
Doxycycline ⁸⁹	Mice Apo E ^{-/-} /All**	18/21 (86%)	7/20 (35%)‡#	Not clarified.
Doxycycline ^{90,91}	Rat elastase	4.26±0.64 (n=24)	2.73±0.18 (n=24)*	Elastin preservation and MMP suppression.
BB-94 ⁹²	Rat elastase	4.2±0.2 (n=11)	3.6±0.1 (n=12)*	Elastin preservation, decreased inflammation.
Rs132908 ⁹³	Rat elastase	5.98±1.02 (n=6)	3.59±0.34 (n=8)*	Preservation of elastin.
Captopril ⁹⁴	Rat elastase	5.17±0.44 (n=6)	2.96±0.21 (n=6)*	Elastin preservation.
Losartan ⁹⁴	Rat elastase	5.17±0.44 (n=6)	4.58±0.57 (n=6)	No effect.
1400W ⁹⁵	Rat elastase	5.6±0.9 (n=10)	3.8±1.1 (n=10)*	Aortic elastin preservation.
Aminoguanidine ⁹⁶	Rat elastase	8.7±1.2 (n=8)	4.8±0.6 (n=8)*	Suppression of iNOS.
Fasudil ⁹⁷	Mice Apo E ^{-/-} /All**	2.1±0.2 (n=24)	1.5±0.1 (n=29)*	Suppressed VSMC apoptosis and proteolysis.
Vitamin E ⁹⁸	Mice Apo E ^{-/-} /All**	2.25±0.2 (n=10)	1.7±0.25 (n=10)*	Antioxidant, decreased macrophage infiltration and OPN concentration.
PDTC ⁹⁹	Mice elastase	1.44±0.03 (n=34)	1.16±0.02 (n=49)†	NF- κ B, MMP-9 and IL-1 β & IL-6 suppression.
Rapamycin ¹⁰⁰	Rat elastase	4.5±0.5 (n=18)	3.3±0.8 (n=20)*	Suppression of NF- κ B and MMP-9.
Indomethacin ¹⁰¹	Rat elastase	5.27±2.37 (n=82)	3.45±1.11 (n=73)*	Elastin preservation, suppression of PGE ₂ and MMP-9.
Celecoxib ¹⁰²	Mice Apo E ^{-/-} /All**	22/30 (73%)	2/19 (11%)‡#	Selective inhibition of COX-2, reducing inflammatory prostanoid production.
17 β -estradiol ¹⁰³	Rat elastase	538±105% (n=13)Ⓢ	241±57% (n=13)*¶	Suppression of macrophages, MMP-9 and elastin preservation.
17 β -estradiol ¹⁰⁴	Mice Apo E ^{-/-} /All**	1.9±0.1 (n=20)	1.45±0.1 (n=19)*	Suppression of atherosclerosis, NF- κ B and adhesion molecules. Increased PPAR α and γ .
Tamoxifen ¹⁰⁵	Rat elastase	434±30% (n=6)	218±37% (n=6)*¶	Increased antioxidant capacity, decreased inflammation and MMP-9.
SP600125 ¹⁰⁶	Mice CaCl ₂	1.2±0.05 (n=9)	0.95±0.05 (n=9)‡	Inhibition of c-Jun N-terminal kinase led to regression of AAA.

BB-94 indicates Batimastat, an MMP inhibitor; Rs132908, MMP antagonist; 1400W, selective iNOS inhibitor; PDTC, Pyrrolidine dithiocarbamate, an antioxidant that specifically suppresses NF- κ B; SP600125, specific inhibitor of c-Jun N-terminal kinase; WKHT, genetically hypertensive Wistar-Kyoto rats; BLO, the spontaneously aneurysm-prone blotch mouse; Apo E^{-/-}, Apolipoprotein e knock-out mice; Apo e^{-/-}/All, Apolipoprotein e knock-out mice infused with Angiotensin II; MMP, Matrix Metalloproteinase; VSMC, Vascular Smooth Muscle Cell; iNOS, Inducible Nitric Oxide Synthase; OPN, Osteopontin; IL, interleukin; PGE₂, Prostaglandin E₂; COX-2, cyclooxygenase-2; PPAR, peroxisome proliferator-activated receptor.

* $P < 0.05$.

† $P < 0.05$ using Mann-Whitney U test.

‡ $P < 0.05$ using Fischer exact test.

§No effect in normotensive rats.

||Using gene chips.

¶Percentage increase of diameter after elastase infusion only reported.

#Percentage of aneurysm formation only reported.

**Models in which atherosclerosis as well as aneurysm is promoted.

Larger studies with longer follow-up incorporating these and other medications are needed to clarify the role of these treatments on a range of end points, including expansion and intervention rates. In addition to considering the effect of variable growth rate, losses to follow-up, measurement error, and calculation of expansion, investigators should also pay attention to concurrent medication. A recent follow-up study of 150 patients with small AAAs reported an association between concurrent statin therapy and reduced AAA expansion.¹¹⁵ However, without a randomized controlled trial it is impossible to be clear that the medication rather than another associated factor, such as other risk factors in these patients or other concurrent medications, were responsible for this finding. Previous studies have highlighted that >40% of patients with AAA are routinely prescribed statins, beta adrenoceptor

blockers, and angiotensin II inhibitors. Use of these drugs will probably increase as evidence for their benefit accumulates. Although it is plausible that concurrent use of these drugs would inhibit AAA expansion, it may now be impossible to assess this in a large randomized controlled trial.

Future Directions

Data from epidemiological studies highlight the potential benefit of smoking cessation and control of blood pressure and lipids in reducing the development of AAA. In patients who already have an AAA, treatments which reduce aortic inflammation and proteolysis and support vascular smooth muscle cell (VSMC) recovery are required. In vitro and animal studies highlight the potential of statins, Angiotensin II inhibitors, macrolides, and medication blocking inflamma-

tory pathways. Work has commenced on understanding how traditional risk factors, circulating markers, and genotype can be used to define risk of AAA progression and therefore select out patients for aggressive treatment.

The further development of specific medical therapies for AAAs requires a number of carefully planned large randomized trials using such promising medications in at risk patients. When effective medications have been identified it may be possible to incorporate these with surgical treatments. Thus oral medications or drugs coated onto an endoluminal graft may improve the results of endovascular AAA repair.

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