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STATE OF THE ART REVIEW
Vascular biology and medicine

Pathogenesis and management of abdominal aortic aneurysm

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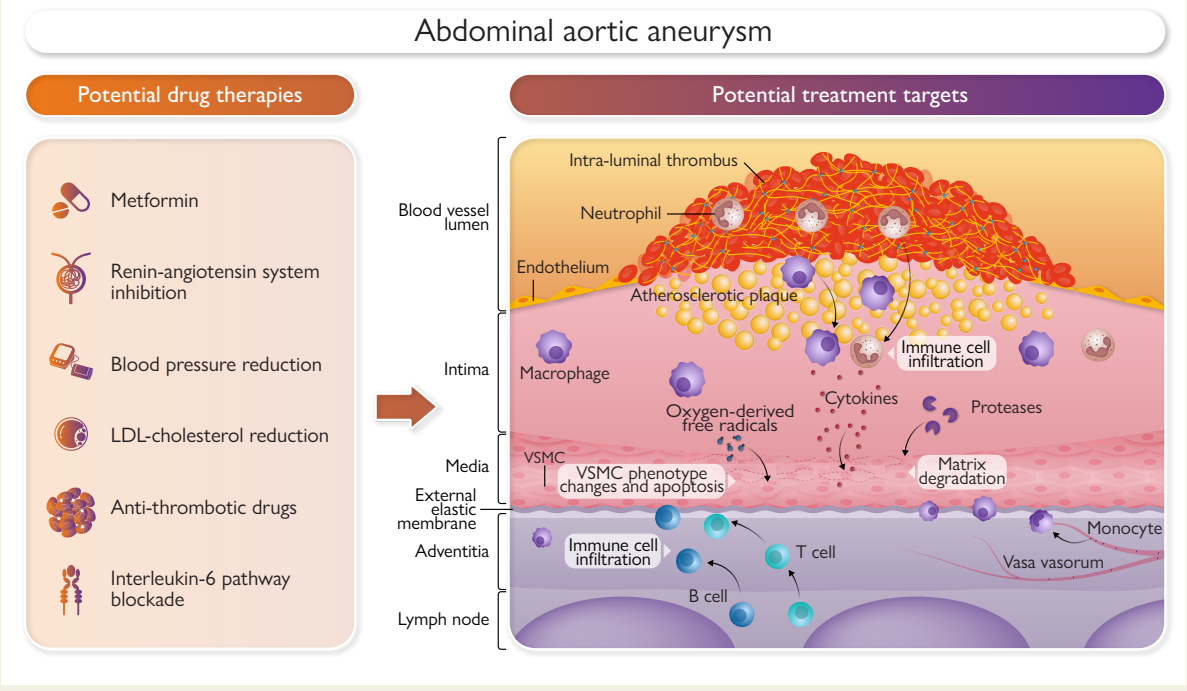
Graphical Abstract



Potential medical therapies to limit abdominal aortic aneurysm growth or rupture. VSMC, vascular smooth muscle cell; LDL, low density lipoprotein.

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Abstract

Abdominal aortic aneurysm (AAA) causes ~170 000 deaths annually worldwide. Most guidelines recommend asymptomatic small AAAs (30 to <50 mm in women; 30 to <55 mm in men) are monitored by imaging and large asymptomatic, symptomatic, and ruptured AAAs are considered for surgical repair. Advances in AAA repair techniques have occurred, but a remaining priority is therapies to limit AAA growth and rupture. This review outlines research on AAA pathogenesis and therapies to limit AAA growth. Genome-wide association studies have identified novel drug targets, e.g. interleukin-6 blockade. Mendelian randomization analyses suggest that treatments to reduce low-density lipoprotein cholesterol such as proprotein convertase subtilisin/kexin type 9 inhibitors and smoking reduction or cessation are also treatment targets. Thirteen placebo-controlled randomized trials have tested whether a range of antibiotics, blood pressure–lowering drugs, a mast cell stabilizer, an anti-platelet drug, or fenofibrate slow AAA growth. None of these trials have shown convincing evidence of drug efficacy and have been limited by small sample sizes, limited drug adherence, poor participant retention, and over-optimistic AAA growth reduction targets. Data from some large observational cohorts suggest that blood pressure reduction, particularly by angiotensin-converting enzyme inhibitors, could limit aneurysm rupture, but this has not been evaluated in randomized trials. Some observational studies suggest metformin may limit AAA growth, and this is currently being tested in randomized trials. In conclusion, no drug therapy has been shown to convincingly limit AAA growth in randomized controlled trials. Further large prospective studies on other targets are needed.

Keywords Abdominal aortic aneurysm • AAA rupture • IL-6 • Metformin • RAS • Single-nucleotide polymorphism

Introduction

Abdominal aortic aneurysm (AAA) is a focal expansion of the abdominal aorta usually diagnosed by maximum aortic diameter of ≥30 mm on imaging.[1] Abdominal aortic aneurysm is usually asymptomatic unless it ruptures which is fatal without successful surgical repair. It was reported that in 2017 there were 167 200 deaths and 3 million disability-adjusted life years worldwide attributable to AAA, although due to the low rates of post-mortems, it is likely these estimates are inaccurate.[2] Efforts to reduce AAA-related burden have focused on early identification and improved surgical treatment. Randomized trials found that ultrasound screening in men aged ≥65 years to identify cases for elective repair reduced aneurysm-related mortality, but the effect on all-cause mortality is controversial with one analysis showing a small significant reduction and a more recent one not confirming this.[3,4] Ultrasound screening of high-risk groups has been introduced in a number of countries, including Sweden, the UK, and the USA.[3,5] With declining smoking rates, the age-adjusted prevalence of AAA has fallen in some countries, leading to questions about how screening can be delivered in the most cost-effective and ethical way.[6] The widespread use of abdominal imaging has led to many asymptomatic AAA being identified incidentally, and advances in artificial intelligence are facilitating automatic referral to vascular surgeons and surveillance programs.[7,8] There have been tremendous advances in minimally invasive devices for endovascular aneurysm repair (EVAR), but durability of this treatment remains a problem, and rupture can still occur.[9]

A key remaining priority is the development of therapies to limit AAA growth and rupture.[10] A survey of 191 participants with an AAA from Oxford UK found that their top three aneurysm research questions were 'discovering why an AAA develops' (selected by 83%), 'discovering new medications that can make AAA shrink back to normal size' (selected by 71%), and 'discovering new medications that can stop an AAA from growing further' (selected by 64%).[11] A survey of 277 vascular surgeons working in Africa, Asia, Australasia, Europe, Middle East, North America, and South America found that their top three AAA research priorities were 'new tests that can predict if an AAA will be fast growing' (selected by 23%), 'new medications that can stop an AAA from growing further' (selected by 23%), and 'new medications that can make an AAA shrink back to normal size' (selected by 20%).[12] Effective new AAA drugs or intra-arterial therapies could treat early-stage aneurysms, act as adjuvant treatment after EVAR, and be used in people unfit for surgical repair. This article outlines the evidence supporting current management of AAA and research being undertaken to address these top priorities of better understanding of AAA pathogenesis and developing drug therapies (*Graphical Abstract*).

Abdominal aortic aneurysm pathogenesis

While research on AAA pathogenesis has been ongoing for decades using animal models, *in vitro*, and human observational studies, the recent findings from genetic studies have led to major advances in our understanding of AAA. This review focuses mainly on recent clinical genetic, observational studies, and trials. Readers are referred to previous reviews on AAA animal models and laboratory studies.[13,14] Animal studies testing the effects of drugs on established aneurysms have been included since this experimental design simulates the clinical need for drug therapies to limit growth and rupture of small AAA.[15]

Traditional risk factors including sex disparity

Past studies suggest higher AAA prevalence in Caucasians compared with black and Asian races.[16] Racial inequality in access to AAA screening and treatment may account for the differences in prevalence reported.[17,18] Older age, male sex, hypertension, smoking, coronary heart disease, peripheral artery disease, and family history of aneurysm increase the risk of AAA (*Table 1*).[19–23] Diabetes is negatively associated with AAA.[28] Men have a 3- to 16-fold increased AAA risk when using a ≥ 30 mm definition.[21] Given that women have a smaller body size than men, this criterion underdiagnoses AAA in women.[29] Most animal research on sex disparity in AAA pathogenesis has focused on sex hormones or sex chromosomes.[30–33] Multiple clinical studies have associated low serum testosterone with increased risk of AAA in older men.[34,35] Both low and high

Table 1 Risk factors for abdominal aortic aneurysm diagnosis

Risk factor	Relative risk	95% CIs
Male sex[a]	5.93	4.26, 8.25
Hypertension	1.66	1.49, 1.85
Per 20 mmHg higher systolic blood pressure	1.14	1.06, 1.23
Per 20 mmHg higher diastolic blood pressure	1.28	1.12, 1.46
Current smoking	4.87	3.93, 6.02
Former smoking	2.10	1.76, 2.50
Per 10 pack years	1.78	1.54, 2.06
Family history of aortic aneurysm[a]	3.80	3.66, 3.95
Coronary heart disease[a]	2.29	1.75, 3.01
Peripheral artery disease[a]	2.50	2.12, 2.95
Diabetes	0.58	0.51, 0.66

[a]Odds ratios or relative risk and 95% CIs based on data from previous systematic reviews and large population screening or case-control studies.[19–27]

estradiol have been associated with AAA.[35,36] Women with both a history of smoking (≥20 pack year) and premature menopause have an increased risk of AAA.[37] Sex differences in extracellular matrix remodeling, the renin–angiotensin system (RAS), inflammatory pathways, and oxidative stress control have been reported in studies within animal models, cells *in vitro*, and human populations (see previous review).[38] One small study reported that the AAA wall strength was lower in samples from women compared with men; although the difference was not significant, this finding could contribute to the reported higher rate of small AAA rupture in females compared with males.[39,40]

Inherited risk

Population screening and case-control studies show that a family history of AAA increases the risk of AAA by between two- and four-fold.[24–27] Twin studies suggest that the heritability of AAA is very high at between 70% and 77%.[41,42] This strongly implicates genetic and epigenetic mechanisms in AAA pathogenesis, which is of importance since genetic determinants of disease are being successfully used to identify drug targets and determine which drugs are most effectively applied through personalized management.[43]

Genome-wide association studies (GWAS) have identified multiple common single-nucleotide polymorphisms (SNP) determining the risk of AAA (*Table 2*).[44–49] Case-control studies have implicated multiple non-coding RNAs in AAA.[64] A systematic review of 15 studies identified miR-15a, miR-15b, miR-21, and miR-15 to be the most consistently differentially expressed micro-RNA in the aorta and blood of people with AAA and controls.[64] One study identified 20 micro-RNAs associated with fast-growing AAA, but this could not be replicated in another population.[65,66] A number of long non-coding RNAs, such as H19, have also been implicated in AAA pathogenesis.[67]

The Million Veteran Program (MVP) analyzed 18 million DNA sequence variants in 12 614 AAA cases and 272 030 controls and identified multiple genetic loci determining AAA risk, such as a SNP within the intron of the interleukin (IL)-6 receptor (IL-6R) gene (*Table 2*).[45] An independent analysis of 5 other studies (4524 cases and 15 710 controls) found that a coding SNP in the IL-6R (rs2228145) gene was associated with AAA and requirement for aneurysm repair or rupture.[54] Administration of IL-6 to lymphoblast cells with varying IL-6R genotypes *in vitro* had significantly different effects on IL-6 target genes of signal transducer and activator of transcription 3 (STAT3) and intercellular adhesion molecule (ICAM)-1, suggesting the functional importance of the SNPs (*Figure 1*).[54] A meta-analysis of four mouse studies ($n = 69$) found that a variety of different ways of blocking the IL-6 pathway (e.g. a decoy protein blocking IL-6 trans-signaling called sgp130; see *Figure 1*) significantly limited aortic expansion.[55,56,68–70] Furthermore, a systematic review identified 7 studies ($n = 300$) which all found significantly higher levels of IL-6 in human AAA compared with control aortic tissue samples,[68] while a meta-analysis of 15 studies (1001 AAA cases and 1129 controls) found significantly higher circulating IL-6 concentrations in AAA participants compared with controls.[68] A transcriptomic analysis suggested activation of IL-6 signaling via the JAK-STAT pathway in human AAA (*Figure 1*).[55] Overall, these findings suggest that the IL-6 pathway plays an important role in AAA pathogenesis and represents a potential drug target. This is particularly relevant as monoclonal antibodies targeting the IL-6 pathway (e.g. tocilizumab) are in clinical use for treating rheumatoid arthritis and appear to be safe to use.[71]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) controls the degradation of the low-density lipoprotein (LDL) receptor, with monoclonal antibodies neutralizing PCSK9 in widespread use to reduce circulating LDL cholesterol (LDL-C). Single-nucleotide polymorphisms in the gene encoding PCSK9 have been associated with AAA (*Table 2*).[45] Gain-of-function mutations in PCSK9 promote angiotensin II–induced aneurysm formation in mice associated with increase in circulating cholesterol.[72] PCSK9 also inhibits vascular smooth muscle cell proliferation and promotes apoptosis.[50] In keeping with a key role of dyslipidemia in AAA, SNPs in the genes encoding the LDL receptor, apolipoprotein E (Apo E), and lipoprotein(a) have also been associated with AAA (*Table 2*).[44,45,47,51] Mendelian randomization uses the genetic determination of risk factors to examine their causal impact and is thought to avoid much of the bias of traditional observational studies.[43] Multiple Mendelian randomization analyses suggest causative roles for raised LDL-C and lipoprotein(a) and reduced high-density lipoprotein cholesterol (HDL-C) in AAA pathogenesis.[45,73,74] Mendelian randomization analyses also suggest causal roles for high pulse pressure[75] and diastolic blood pressure,[45] smoking initiation and heaviness,[45] and the CD40 inflammatory pathway,[76] but not raised systolic blood pressure[45] or C-reactive protein[77] in AAA. Counterintuitively, increased IL-1 signaling has been suggested to increase the risk of AAA, possibly by stimulating an increase in LDL-C which may in part explain the lack of benefit of IL-1 blocking antibody in a small trial in AAA participants (ClinicalTrials.gov Identifier: NCT02007252).[68,78]

Other SNPs identified in GWAS studies have supported roles for matrix metalloproteinase (MMP)-9,[44,46,60] lipid transport and uptake,[44,45,47,48,63] epigenetic mechanisms such as non-coding RNAs and histone methylation,[44,45,52,59,62] inflammation,[44,52,61] and cell senescence, proliferation, and apoptosis,[44,45,49,52,57,58] in AAA

Table 2 Single-nucleotide polymorphisms associated with the risk of abdominal aortic aneurysm validated in genome-wide association studies

rs number	Nearest gene	OR (95% CI)	Proposed mechanisms
rs11591147	PCSK9	1.58 (1.38, 1.82)	Degradation of the LDL receptor, thereby controlling circulating levels of LDL-C and inhibit VSMC proliferation and apoptosis[45,50]
rs118039278	LPA	1.28 (1.21, 1.35)	Lipoprotein(a) concentrations[45,51]
rs73149487	ABHD16B	1.26 (1.16, 1.36)	Endocannabinoid homeostasis[45]
rs4007642	CDKN2BAS1	1.21 (1.17, 1.25)	Long non-coding RNA controlling apoptosis and inflammation[43,44,52]
rs964184	ZNF259/APOA5	1.18 (1.14, 1.23)	Triglyceride, cholesterol, and glucose concentrations[45,53]
rs429358	APOE	1.17 (1.12, 1.21)	Cholesterol transport[45]
rs646776	PSRC1-CELSR2-SORT1	1.15 (1.11, 1.20)	Cholesterol homeostasis[45,48]
rs73015016	LDLR	1.15 (1.09, 1.21)	Cholesterol homeostasis[44,45,47]
rs8124182	MMP9	1.15 (1.10, 1.20)	Matrix remodeling[44,45]
rs12730935	IL-6R	1.14 (1.10, 1.18)	Inflammation[45,54–56]
rs7994761	LINC00540	1.14 (1.09, 1.19)	Unknown[44,45]
rs4936098	ADAMTS8	1.13 (1.10, 1.16)	VSMC proliferation and AMPK activity[45,57]
rs7025486	DAB2IP	1.12 (1.08, 1.16)	Cell apoptosis[49,58]
rs55958997	CHRNA3	1.12 (1.09, 1.16)	Nicotine dependance[45]
rs4401144	CTAGE1	1.11 (1.08, 1.14)	T cell function[45]
rs12125521	SMYD2	1.10 (1.06, 1.14)	Histone methylation[44,45,59]
rs11172113	LRP1	1.10 (1.06, 1.14)	VSMC MMP-9 clearance[45,46,60]
rs2836411	ERG	1.10 (1.06, 1.14)	Inflammation[44,45,61]
rs7255	AC012065.7	1.10 (1.07, 1.13)	Long non-coding RNA expression[45,62]
rs3176336	CDKN1A	1.10 (1.07, 1.13)	Cell cycle progression[45]
rs10808546	RP11-136O12.2/TRIB1	1.10 (1.07, 1.13)	Long non-coding RNA[45]
rs1412445	LIPA	1.10 (1.07, 1.13)	Lipid homeostasis[45,63]
rs10023907	MEPE	1.09 (1.06, 1.12)	Calcium-binding phosphoprotein involved in bone mineralisation[45]
rs35254673	CRISPLD2	1.09 (1.06, 1.13)	Unknown[45]

Single-nucleotide polymorphisms were selected based on genome-wide significance ($P < 5 \times 10^{8}$) during discovery in one of nine previously published AAA genome-wide association studies and validation to be significantly associated with AAA in at least one other cohort including the largest and most recent study from the Million Veteran Program.[44–46,48,49] The ORs and 95% CIs shown are all taken from the Million Veterans Program study to allow comparison of effect sizes.[45] CDKN2BAS1, CDKN2B antisense RNA-1; IL-6R, interleukin-6 receptor; LDLR, low-density lipoprotein receptor; PSRC1-CELSR2-SORT1, proline/serine-rich coiled coil 1—cadherin, EGF LAG seven-pass G-type receptor 2-sortilin; MMP9, matrix metallopeptidase 9; SMYD2, SET And MYND domain containing 2; ERG, erythroblast transformation-specific related gene; LINC00540, long intergenic non–protein coding RNA-540; DAB2IP, disabled homolog 2 interacting protein; AC012065.7, clone-based Vega gene; CDKN1A, cyclin-dependent kinase inhibitor 1A; RP11-136O12.2/TRIB1, RP11-136O12.2 tribbles pseudokinase 1; LIPA, lysosomal acid lipase; ZNF259/APOA5, zinc finger protein/apolipoprotein A5; ADAMTS8, ADAM metallopeptidase with thrombospondin type 1 motif 8; CTAGE1, cutaneous T cell lymphoma-associated antigen 1; APOE, apolipoprotein E; PCSK9, proprotein convertase subtilisin/kexin type 9; LPA, lipoprotein(a); CHRNA3: cholinergic receptor nicotinic alpha 3 subunit; ABHD16B, abhydrolase domain containing 16B; VSMC, vascular smooth muscle cells; AMPK, AMP-activated protein kinase; LDL-C, low-density lipoprotein cholesterol; MEPE, matrix extracellular phosphoglycoprotein; CRISPLD2, cysteine-rich secretory protein LCCL domain containing 2.

pathogenesis.[45,53] The genetic risk alleles have been used to develop polygenic risk scores (PRS) in order to identify high-risk people needing screening for AAA.[45] The MVP combined 29 genetic risk alleles to develop an AAA PRS for which a one standard deviation score increase independently predicted AAA risk [odds ratio (OR) 1.27, 95% confidence interval (CI) 1.22, 1.32, $P < 0.001$].[45] The PRS identified people with a risk of AAA between 1.7% and 9.4% depending on ancestry with a lower effect size in African compared with European populations, possibly due to over-representation of European participants (59% of the sample).[45]

Current abdominal aortic aneurysm management and need for medical management to limit growth and rupture

Current management

Randomized controlled trials suggest that early elective open surgical repair (OSR) or EVAR of asymptomatic 40–55 mm AAA does not reduce mortality.[79] One trial suggested that EVAR did not significantly reduce

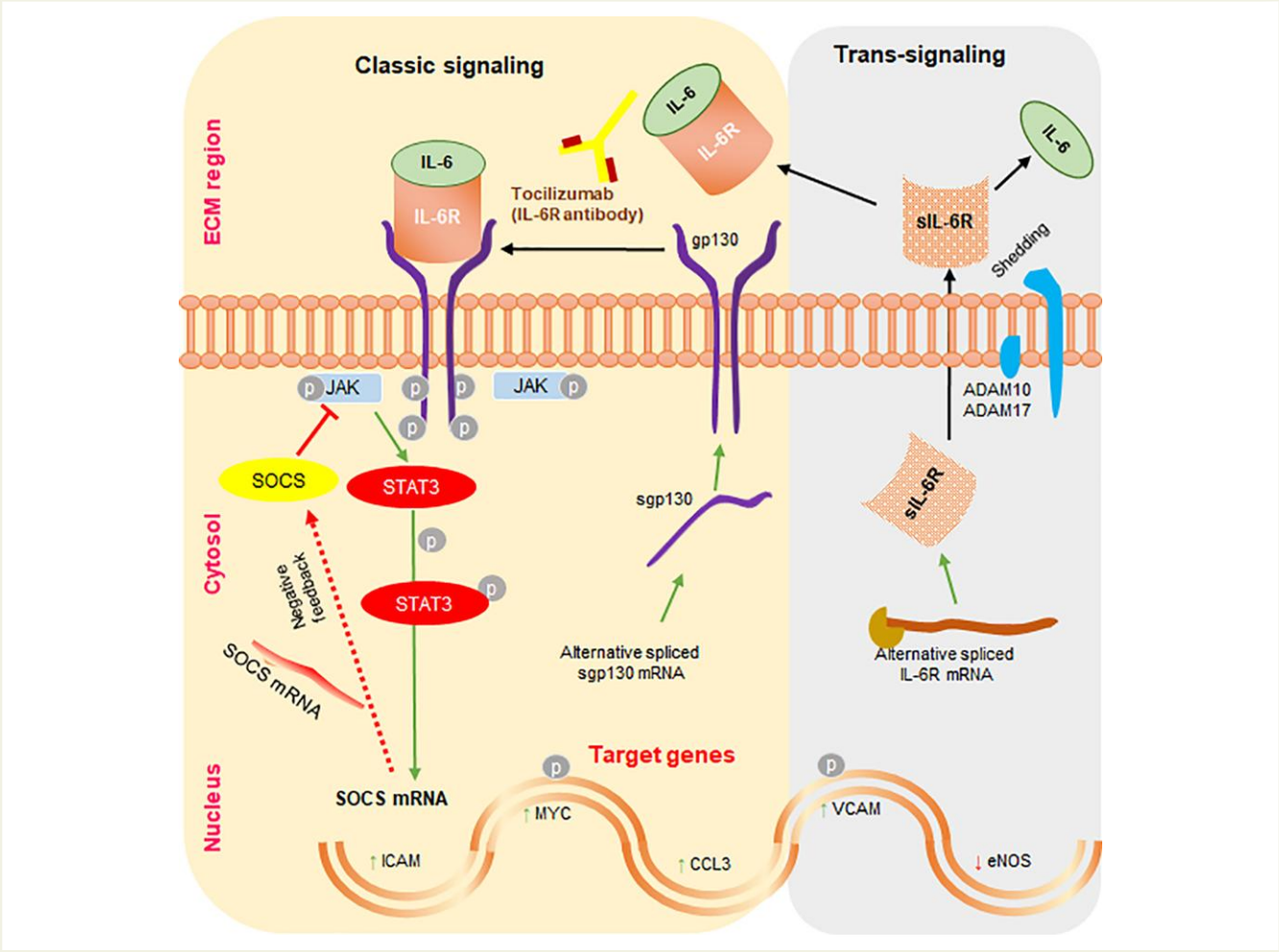

Figure 1 Illustration of the interleukin-6 pathway. Shown are both the classical and trans-signalling interleukin-6 pathways. ADAM, a disintegrin and metalloprotease; CCL3, chemokine (C-C motif) ligand 3; eNOS, endothelial nitric oxide synthase; sgp130, soluble glycoprotein 130; ICAM, intracellular adhesion molecule; sIL-6R, soluble interleukin-6 receptor; JAK, Janus kinase; MYC, myelocytomatosis oncogene; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription 3; VCAM, vascular cellular adhesion molecule; ECM, extracellular matrix; P, phosphorylation.

mortality in people with large AAA unfit for OSR although this evidence maybe outdated due to advances in EVAR.[80] One trial found that EVAR and OSR had similar 30-day mortality for ruptured AAA.[81] Quality of life was better in the EVAR group, and 3-year mortality was lower after EVAR in participants with proven rupture.[81] The risk of small aneurysm rupture is higher, and outcome of surgery is worse in women compared with men.[40,82] Based on this evidence, current European Society for Vascular Surgery guidelines recommend monitoring of small AAA (<55 mm in men; < 50 mm in women) through imaging surveillance, elective surgical repair of large aneurysms in fit patients, and EVAR of ruptured AAA, if morphologically suitable.[1] The intervention threshold for women is not evidence-based and remains a research priority.[1]

Small abdominal aortic aneurysm and large abdominal aortic aneurysm that do not undergo surgical repair

The risk of rupture of small AAA in men is <1%/year.[79] The 3-year rupture rate of unrepaired 50–54 mm AAA in women was 3.4% in a recent study.[83] Most small AAA grow in size over time, with the UK small aneurysm trial finding that 70% of 40–55 mm AAA grew to 55 mm within 5 years.[79] Large aneurysms have a higher risk of rupture (estimated as 2.2%, 6.0%, and 18.4% over 3 years for 55–60 mm, 61–70 mm, and >70 mm AAA, respectively).[83] Rupture rate of large AAA is significantly greater in women than men, with a recent study reporting women with unrepaired 61–70 mm AAA had a 3-year incidence of rupture of 12.8% compared with 4.5% in men.[83] There is no evidence that the growth rate of small AAA has changed over time.[40] Thus, medical treatments that can slow AAA growth and reduce the risk of small aneurysm rupture are needed. The remainder of this review summarizes previous research performed to test and develop medical therapy to limit AAA growth and rupture.

Previous clinical trials and observational studies testing drugs to limit abdominal aortic aneurysm growth

Table 3 summarizes the results of the 13 completed placebo-controlled trials testing drug therapies to limit AAA growth, and the findings of both observational and randomized trials are described in this section.[84–96]

Table 3 Previous randomized placebo-controlled trials testing drugs to limit abdominal aortic aneurysm growth

Trial	Drug tested (daily dose)	Sample size	AAA growth (mm)		AAA events	
			Active	Placebo	Active	Placebo
Blood pressure lowering						
TEDY[84]	Telmisartan (40 mg)	210	1.7 (1.8)	1.8 (1.8)	11 (10.3%)	8 (7.8%)
AARDVARK[85]	Perindopril (10 mg)	227[e].	1.8 (1.7)	1.7 (1.8)	10 (13.3%)	9 (11.4%)
AARDVARK[85]	Amlodipine (5 mg)	227[e]	1.8 (1.7)	1.7 (1.8)	7 (9.6%)	9 (11.4%)
PAT[86]	Propranolol (240 mg)	552	2.2 (2.8)	2.6 (3.1)	57 (20.6%)	73 (26.5%)
Propranolol[87]	Propranolol (80 mg)	54	3.1 (2.5)	2.8 (2.4)	7 (23.3%)	5 (20.8%)
Antibiotics						
Azithromycin[88]	Azithromycin (variable[a])	247	2.3 (1.8)	2.2 (1.9)	16 (13.1%)	13 (10.4%)
Roxithromycin 1[89]	Roxithromycin (300 mg for 28 days)	92	1.6 (1.5)[b]	2.8 (2.5)	5 (11.6%)	7 (14.3%)
Roxithromycin 2[90]	Roxithromycin (300 mg for 28 days annually)	84	1.6 (1.5)	2.5 (2.5)	12 (28.6%)	14 (40.5%)
Doxycycline 1[91]	Doxycycline (150 mg for 3 months)	32	1.5 (2.4)	3.1 (4.7)	2 (11.8%)	3 (20.0%)
PHAST[92]	Doxycycline (100 mg)	286	2.8 (2.1)[c]	2.1 (2.1)	21 (14.6%)	24 (16.9%)
N-TA^{3}CT[93]	Doxycycline (200 mg)	261	3.6 (2.1)[d]	3.6 (2.8)[d]	13 (9.8%)	9 (7.0%)
Anti-platelet						
TicAAA[94]	Ticagrelor (180 mg)	136	2.3 (1.7, 2.9)	2.2 (1.6, 2.7)	4 (5.8%)	0
Mast cell inhibitor						
AORTA[95]	Pemirolast (20 mg)	326[f]	2.6 (2.1, 3.1)	2.0 (1.6, 2.5)	5 (6.3%)	2 (2.4%)
	Pemirolast (50 mg)	326[f]	2.3 (1.9, 2.8)	2.0 (1.6, 2.5)	2 (2.6%)	2 (2.4%)
	Pemirolast (80 mg)	326[f]	2.7 (2.3, 3.2)	2.0 (1.6, 2.5)	6 (7.1%)	2 (2.4%)
Fibrate						
FAME-2[96]	Fenofibrate (145 mg)	140	1.0 (3.7)	1.4 (3.7)	0	0

Shown are mean standard deviation or 95% CIs of AAA growth from ultrasound or numbers (%) of AAA events (repair or rupture). PAT, propranolol aneurysm trial; AAA, abdominal aortic aneurysm; N-TA^{3}CT, Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial; PHAST, Pharmaceutical Aneurysm Stabilization Trial; TEDY, TElmisartan in abDominal aortic aneurYsm trial; AARDVARK, Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK; AORTA, Anti-inflammatory ORal Treatment of AAA; FAME-2, Fenofibrate in the Management of Abdominal Aortic Aneurysm 2; TicAAA, The Efficacy of Ticagrelor on Abdominal Aortic Aneurysm Expansion.
[a]600 mg/d for 3 days then 600 mg/week.
[b]AAA growth significantly slower in the roxithromycin group, $P = 0.02$.
[c]AAA growth significantly faster in the doxycycline group, $P = 0.007$.
[d]Growth rate over 2 years rather than annual.
[e]Sample size for all three groups including placebo, amlodipine, and perindopril.
[f]Sample size for all four groups including pemirolast (20 mg), pemirolast (50 mg), pemirolast (80 mg), and placebo.

Antibiotics

Six trials tested the efficacy of tetracycline (doxycycline, $n = 3$) or macrolide (azithromycin, $n = 1$; roxithromycin, $n = 2$) antibiotics in limiting AAA growth.[88–93] One reason for testing antibiotics was due to their ability to inhibit MMP activity. Doxycycline, for example, was found to reduce plasma concentrations of MMP-9 in patients with AAA.[97] There was also interest in antibiotics because of a postulated role of the bacterium *Chlamydophila pneumoniae* in AAA in some[98,99] but not other studies.[100] Furthermore, a 2-week course of doxycycline was reported to reduced AAA wall neutrophils and cytotoxic T cells and down-regulated inflammatory pathways implicated in AAA pathology, including IL-6 expression within a 60-participants randomized controlled trial.[101] This preliminary evidence appeared to be supported by a 92-participants trial showing that roxithromycin significantly reduced AAA growth compared with placebo (*Table 3*).[89] These findings were not confirmed in subsequent larger trials (*Table 3*). The largest antibiotic trial ($n = 286$) found significantly faster aneurysm growth in the doxycycline compared with placebo group.[92] The other four trials found no significant effect of the antibiotics tested (*Table 3*). A meta-analysis of these trials found no significant effect of antibiotics on AAA growth [standardized mean difference (SMD) −0.11, 95% CI −0.38, 0.16, $P = 0.42$] and AAA repair or rupture [risk ratio (RR) 0.93, 95% CI 0.69, 1.25; $P = 0.61$].[102]

Renin–angiotensin system inhibition

The RAS has been strongly implicated in AAA pathogenesis through studies in animal models and human aortic samples.[13,103] A meta-analysis of three mice studies ($n = 45$ intervention; 36 controls)

found that administration of RAS inhibitors (aliskiren, telmisartan, or ramipril) significantly reduced the diameter of established AAA.[15] This evidence was supported by the findings of a Canadian population case-control study of patients with ruptured ($n = 3379$) and intact ($n = 11\,947$) AAA.[104] Angiotensin-converting enzyme (ACE) inhibitor prescription was associated with a reduced risk of AAA rupture (OR 0.83, 95% CI 0.73, 0.95).[104] Only 1% of the population were prescribed angiotensin receptor blockers (ARB), and this was not associated with reduced risk of AAA rupture (OR 1.24, 95% CI 0.71, 2.18). A Danish registry study of 9441 patients also found a reduced risk of aneurysm-related mortality for those prescribed ACE inhibitors (HR 0.64, 95% CI 0.51, 0.80) or ARBs (HR 0.65, 95% CI 0.48, 0.88).[105] Angiotensin-converting enzyme inhibitor (HR 0.86, 95% CI 0.74, 0.99) but not ARB (HR 1.02, 95% CI 0.84, 1.23) prescription was associated with reduced risk of aneurysm repair.[105] Another study of 3586 patients with rupture AAA and 17 271 patients with intact AAA reported an association of ACE inhibitor prescription with reduced aneurysm rupture in an unadjusted analysis (OR 0.89, 95% CI 0.84, 0.94), but in a propensity matched case-control sub-analysis, neither ACE inhibitor (OR 1.02, 95% CI 0.88, 1.19) nor ARB (OR 1.02, 95% CI 0.83, 1.26) prescription was associated with aneurysm rupture.[106] Analysis of two cohorts with small AAA from Western Australia and the UK found no association between ACE inhibitor prescription and aneurysm rupture (HR 1.25, 95% CI 0.13, 12.14 for $n = 685$ in Western Australia; 1.17, 95% CI 0.50, 2.72 for $n = 2227$ in the UK).[40] Our meta-analysis of these studies ($n = 48\,536$) suggested ACE inhibitor prescription was associated with reduced risk of AAA rupture (OR 0.82, 95% CI 0.70, 0.95, $P = 0.007$), but the potential for confounding of these unadjusted observational data needs to be acknowledged (*Figure 2*).

In contrast, among cohorts with small AAA, there is no evidence that ACE inhibitors or ARBs limit AAA growth. A meta-analysis of seven cohorts ($n = 4826$) found no association between ACE inhibitor prescription and AAA growth.[40] These observational findings were supported by the result of the Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK (AARDVARK) placebo-controlled trial that randomized 227 patients with 30–54 mm AAA to perindopril (10 mg), amlodipine (5 mg), or placebo.[85] Neither perindopril nor amlodipine significantly reduced AAA growth (*Table 3*).[85] Similarly, the TElmisartan in abDominal aortic aneurYsm (TEDY) trial ($n = 210$) found that 40 mg of the ARB telmisartan did not significantly reduce AAA growth (*Table 3*).[84] Combined, these two trials only included a total of 182 participants allocated to perindopril or telmisartan, and both trials excluded all patients currently eligible or ineligible for ACE inhibitors or ARBs due to co-morbidities such as hypertension, renal disease, or diabetes. The small sample size means they were underpowered to identify a moderate or small treatment effect. Two placebo-controlled trials found that propranolol did not slow AAA growth, but 42% of participants allocated to propranolol in the largest trial had to discontinue drug due to side effects (*Table 3*).[86,87] A meta-analysis of all four blood pressure–lowering placebo-controlled trials found no effect of blood pressure lowering on AAA growth.[102]

The main aim of interventional treatment is to limit the risk of aneurysm rupture. The risk factors (and likely mechanisms) for AAA growth and rupture are not identical, and thus, it cannot be assumed that the effect of a drug on aneurysm growth and rupture is the same (*Tables 1* and *4*).[40] Of note, higher blood pressure had been associated with increased risk of small aneurysm rupture in some studies but not AAA growth (*Table 4*).[40,102,107] Since the risk of small AAA rupturing is very low and most large aneurysms undergo repair, it is very difficult to design trials adequately powered to test the effect of a treatment on aneurysm rupture.[10,83] In all previous placebo-controlled trials, increase in aneurysm size (mainly diameter) was the primary outcome.[10] While the trials did record AAA-related events, these were dominated by elective aneurysm repairs (*Table 3*). Aneurysm diameter is not always an accurate reflection of the risk of rupture since some small AAA do rupture and many large aneurysm remain intact for many years.[83] Methods have been developed for reproducible estimation of the biomechanical risk of AAA rupture using aortic peak wall stress (PWS) and peak wall rupture index (PWRI) (*Figure 3*).[108] Previous meta-analyses have reported higher PWS and PWRI in ruptured than intact AAA.[110,111] Although the association between PWS/PWRI and aneurysm rupture is attenuated by adjustment for aneurysm diameter, it is possible these alternative surrogate measures may better reflect the risk of AAA rupture and be valuable outcomes in trials of drug therapies. We used data from the TEDY trial to assess the impact of telmisartan and blood pressure reduction on the change in PWS and PWRI over 24 months of follow-up.[109] In this sub-analysis of 124 participants from TEDY ($n = 65$ telmisartan; 59 placebo), telmisartan significantly reduced the increase in PWS and PWRI (*Figure 4*).[109] As expected, allocation to telmisartan was associated with a reduction in blood pressure.[109] After adjusted for systolic blood pressure at 1 year, the annual changes in PWS and PWRI were no longer significantly different between groups although in the same direction.[109] The exploratory and selective nature of this analysis is acknowledged given the primary analysis for TEDY was negative. It should also be noted that the role of high PWS in aneurysm rupture remains controversial since low wall shear

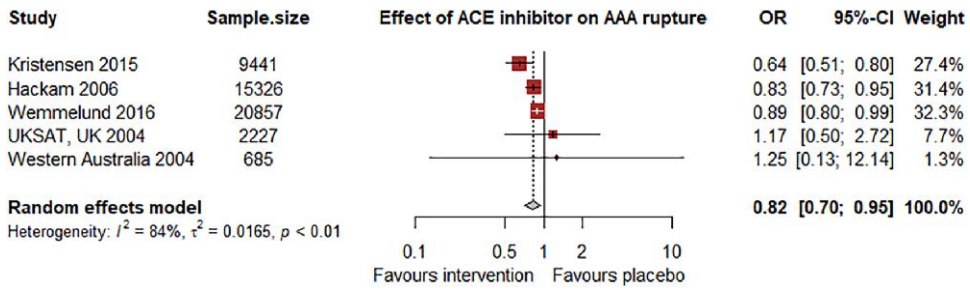

Figure 2 Meta-analysis of observational studies assessing the association between angiotensin-converting enzyme inhibitors and abdominal aortic aneurysm rupture. Included were the unadjusted ORs and 95% CIs from previously reported observational studies.[40,104–106]

Table 4 Risk factors for growth and rupture of small abdominal aortic aneurysm based on a previous individual patient data meta-analysis

Risk factor	*n*	Growth			Rupture	
		n	Mean difference	*P*	HR	*P*
Age (per year)	13 966	13 966	−0.001 (0.006)	0.82	1.04 (1.01, 1.07)	0.004
Female sex	8472	8472	0.142 (0.150)	0.34	3.76 (2.58, 5.47)	<0.001
Body mass index (per kg/m^2)	3439	3439	−0.008 (0.009)	0.35	0.93 (0.88, 0.99)	0.029
Current smoking	7486	7486	0.354 (0.065)	<0.001	2.02 (1.33, 3.06)	0.001
Diabetes	5697	5697	−0.505 (0.097)	<0.001	1.27 (0.45, 3.54)	0.65
Mean blood pressure (per 10 mmHg)	5957	5957	0.013 (0.021)	0.53	1.32 (1.11, 1.56)	0.001
Pulse pressure (per 10 mmHg)	5957	5957	−0.027 (0.014)	0.06	1.11 (1.02, 1.22)	0.019
Cardiovascular disease	6302	6302	−0.105	0.23	1.32 (0.77, 2.27)	0.32

The data presented are from an individual patient meta-analysis including 15 475 patients with small AAA attending surveillance programs in the UK, Australia, Norway, the USA, Sweden, and Denmark as previously reported.[40] Data available varied for different risk factors; thus, the sample size for each risk factor has been shown (*n*). Shown are estimated mean difference (standard error of the mean) in AAA growth (mm/year) for each risk factor or hazard ratio (HR; 95% CI) for risk of aneurysm rupture as previously reported.[40] Abdominal aortic aneurysm growth estimates were adjusted for the other risk factors shown in the table and initial AAA diameter, while HRs were adjusted for current AAA diameter only.

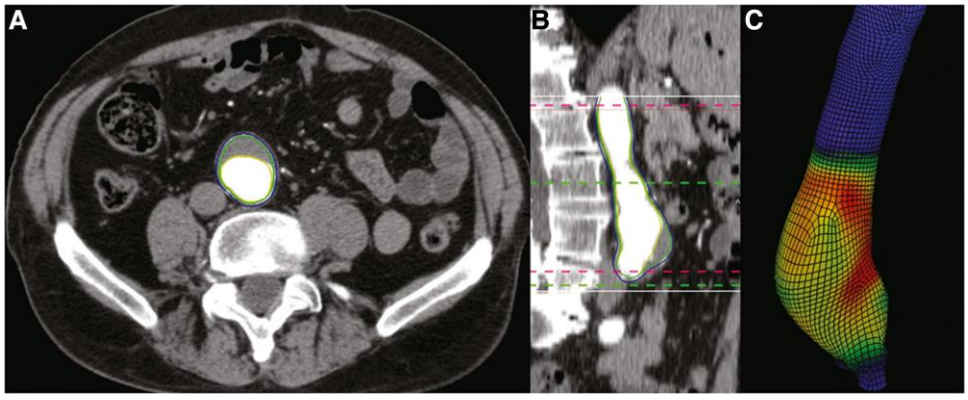

Figure 3 Measuring peak wall stress in an abdominal aortic aneurysm. Finite element analysis using the A4 Clinics software estimated peak wall stress using computed tomograms of an abdominal aortic aneurysm. (*A*) Axial and (*B*) sagittal views of an AAA. (*C*) Three-dimensional segmentation of the aneurysm generated using finite element analysis. The red pixels indicate areas of high aortic wall stress. Reproduced with permission.[109]

stress has also been associated with AAA growth and rupture.[112,113] Collectively, however, these data provide evidence that blocking the RAS does not inhibit small aneurysm growth but may limit the risk of aneurysm rupture.

Anti-thrombotic drugs

Most aneurysm have large volumes of intra-luminal thrombus that contains large number of inflammatory cells and high concentrations of proteolytic enzymes and cytokines.[13] The volume of intra-luminal thrombus is correlated with the rate of aneurysm growth after adjusting for aortic diameter.[114] A meta-analysis found that the volume of intra-luminal thrombus was significantly greater in rupture than intact AAA.[115] This association was no longer present in a sub-analysis restricted to participants matched for aortic diameter although this was under-powered ($n = 181$).[115] A meta-analysis of 6 animal studies ($n = 138$ intervention; 133 control mice) found that administration of anti-platelet drugs (e.g. aspirin or clopidogrel) or anti-coagulants (e.g. fondaparinux or rivaroxaban) significantly reduced the diameter of established AAA, although the effect on aneurysm rupture was non-significant.[15] A small human observational study associated aspirin prescription with slower aneurysm growth in 31 patients with 40–49 mm AAA.[116] The prescription of therapeutic anti-coagulant drugs was also associated with reduced requirement for aneurysm repair or rupture-related mortality (HR 0.61, 95% CI 0.42, 0.90) in a large 1161 patient study of participants with unrepaired AAA.[116,117] Another observational study ($n = 3926$) found that aspirin prescription was associated with reduced AAA rupture in unadjusted (OR 0.72, 95% CI 0.66, 0.79) but not adjusted (OR 0.97, 95% CI 0.86, 1.08) analyses.[118] An analysis of more than 245 million hospital admissions recorded in the US

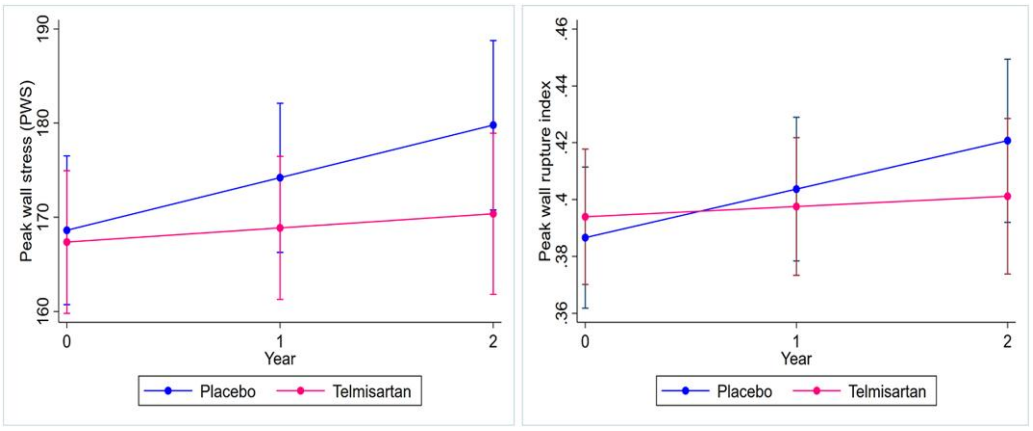

Figure 4 Telmisartan limits increase in peak wall stress (left) and peak wall rupture index (right) within data from the telmisartan in the management of the abdominal aortic aneurysm trial. Reproduced with permission.[109]

National Inpatient Sample database found an association between anti-platelet prescription and reduced risk of AAA admission (OR 0.70, 95% CI 0.68, 0.72) and rupture (OR 0.67, 95% CI 0.54, 0.82).[119] In the only placebo-controlled trial testing an anti-thrombotic drug, the anti-platelet drug ticagrelor did not significantly reduce AAA growth.[94] Larger randomized controlled trials are needed to thoroughly test the efficacy of anti-thrombotic drugs in limiting AAA growth and rupture.

Anti-inflammatory drugs

Studies of human and animal model AAA samples show marked infiltrations by a wide range of immune cells.[13] A meta-analysis of 10 mice studies ($n = 154$ intervention; 141 controls) found that administration of a broad range of drugs proposed to have anti-inflammatory effects (e.g. receptor interacting protein 1 inhibitor, celecoxib, c-Jun *N*-terminal kinase inhibitor, and bradykinin 2 receptor antagonist) significantly reduced the diameter of established AAA and lowered the risk of aneurysm rupture.[15] Genomic studies of human aneurysm samples show up-regulation of multiple inflammatory pathways.[120,121] A Mendelian randomization analysis found genetic predicted CD40 levels were inversely associated with AAA (OR 0.91, 95% CI 0.84, 0.98).[76] Thus, blocking inflammation has been proposed as a treatment to limit AAA growth. There are however multiple challenges to targeting inflammation as a treatment for AAA. Firstly, given the widespread activation of inflammatory cascades, it is likely down-regulating one component will lead to compensatory changes. Secondly, there are potential safety concerns with immune suppression of promoting cancer and serious infections. Thirdly, whether the inflammatory response is a cause or effect of the aneurysm is not resolved. While there is strong evidence from animal studies that both the adaptive and innate immunity promotes aneurysm development and rupture, there is less evidence from clinical studies.[13,14] A small study of 20 patients with AAA that had received organ transplantation and were prescribed intensive immune suppression reported they had rapid AAA growth of ~10 mm/year.[122] A retrospective observational study ($n = 176$) found that prescription of oral steroids was associated with AAA growth greater than median.[123] These studies suggest that immune suppression may promote rather than inhibit AAA growth. In contrast, an observational study of 621 patients with AAA measuring between 30 and 50 mm found no significant difference in AAA growth in participants that were and were not prescribed immunosuppressant drugs.[124] Concurrent malignancy and AAA is common, and a recent study of 217 patients with small AAA receiving radiotherapy and/or chemotherapy reported that radiotherapy was associated with significantly slower AAA growth.[125] Topoisomerase inhibitors and anti-androgens were also associated with non-significant reductions in AAA growth.[125] The only placebo-controlled trial to test an anti-inflammatory drug reported no effect of the mast cell degranulation inhibitor pemirolast on growth of small AAA (*Table 3*).[95] Overall, there is no consistent evidence that blocking inflammation inhibits AAA growth, but more targeted approaches may be effective although this remains to be tested.

Lipid-modifying medication

Some observational studies suggest that statin prescription is associated with reduced AAA growth and rupture with one meta-analysis finding a mean reduction in AAA growth of 0.82 mm/year and an OR for rupture risk of 0.63 among statin users.[126] This finding appears to be driven by smaller studies since the larger prospective studies have found no significant association between statin prescription and AAA growth or rupture.[40,127] The only placebo-controlled trial which has tested the effect of a lipid-modifying medication on AAA growth was the Fenofibrate in the Management of Abdominal Aortic Aneurysm 2 (FAME-2) trial.[96] FAME-2 tested the triglyceride-lowering drug fenofibrate. The rationale for this trial was based on animal evidence that suggested fenofibrate down-regulated the bone proteins osteopontin and osteoprotegerin to limit AAA development.[128,129] However, in the human clinical trial, fenofibrate did not significantly limit AAA growth or reduce serum osteopontin or osteoprotegerin (*Table 3*).[96] Furthermore, a related placebo-controlled trial of 40 patients undergoing OSR (FAME) found that a short course of fenofibrate did not down-regulate AAA wall concentrations of osteopontin or reduce aortic inflammation.[130]

Genomic data suggest a key role for LDL-C in AAA pathogenesis and it is possible that intensive LDL-C reduction might limit AAA growth. The counterintuitive association of peripheral artery disease with reduced AAA growth reported in previous observational studies and an analysis of the TEDY trial may have been driven by better control of modifiable risk factors such as LDL-C in these patients.[131,132]

Trials testing the value of intensive control of LDL-C on AAA growth are needed and could incorporate the impact of this intervention on the incidence of cardiovascular events given myocardial infarction, stroke, and cardiovascular death are very common in these patients. The 5-year incidence of major vascular events was 38% in a recent study of patients with small AAA.[133]

Challenges and lessons from previous drug trials

All past trials have tested the effects of medications in limiting AAA growth, which is usually slow and subject to measurement error and incomplete data and competing risks, as patients are lost to events such as AAA repair or death.[84,85,92,93,95,96] Also patients with AAA are usually elderly, often with multiple co-morbidities, meaning they frequently cannot tolerate drugs with side effects which can lower drug adherence.[84,85,92,93,95,96] Only two previous trials included sample sizes over 300 patients, and one of these trials tested three different doses of drugs, and so group sizes were still under 90 participants, and the other has very poor drug adherence.[86,95] All these trials likely overestimated the treatment effect of the intervention they tested. Much larger sample sizes of at least 300 patients per group with longer follow-up of ~5 years are needed to identify a realistic treatment effect on AAA growth. Also, the effects of drugs on very small AAA could be different from those of AAA approaching the threshold for surgical repair but previous trials have not been designed to test this. The primary outcome in one current trial is the clinically relevant end-point of AAA repair or rupture rather than AAA growth, but this design requires a sample size of ~2000 participants to reliably test a realistic treatment effect.[134]

Ongoing trials testing metformin

Diabetes is a negative risk factor for AAA diagnosis (*Table 1*) and growth (*Table 4*).[135] Multiple theories have been proposed to explain these findings, such as hyperglycemia causing aortic wall cross-linking and blocking proteolytic degradation and inhibiting vascular inflammation.[136,137] Metformin has also been reported to inhibit AAA development in animal models.[138,139] A meta-analysis of 8 observational studies involving 35 240 patients who were and 118 313 who were not prescribed metformin to treat diabetes found metformin was associated with significantly slower aneurysm growth (*Figure 5*).[140] Metformin prescription was associated with a 40% reduced risk of AAA repair or rupture (RR 0.60, 95% CI 0.40, 0.90). An example of the findings from one observational study is shown in *Figure 6*.[141] It should be noted, however, due to the observational nature of these findings, the moderate or high risk of bias of five of the eight studies, and the heterogeneity of studies, the GRADE summary suggested that the certainty of evidence that metformin limited AAA growth was very low.[140] The results of four ongoing randomized trials testing the ability of metformin to limit AAA growth and events are therefore needed to clarify whether this drug is an effective treatment for AAA (*Table 5*).[134,142–144]

Other targets for therapies to limit abdominal aortic aneurysm growth and future directions

Other risk factor targets for abdominal aortic aneurysm growth

In an analysis of 18 cohorts including 15 475 people with small aneurysms, the prevalence of current smokers varied between 18% and 60%.[40] Current smoking was associated with faster AAA growth and increased risk of aneurysm rupture (*Table 4*).[40] Measurement of AAA diameter in routine practice has considerable measurement error which can be improved by use of core laboratories, standardized measure protocols, and single observer readings as used in some of the randomized trials.[84,93,94] In unadjusted analyses, the Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^{3}CT) reported that current smoking was associated with faster AAA growth, while diabetes, larger body mass index, ARB, and statin prescription were associated with slower AAA growth.[145]

Developing and testing novel targets to limit abdominal aortic aneurysm growth

Taking advantage of the enormous and growing tissue and blood biobanks, novel drug targets are expected to be identified from ongoing technical advances in genomics, phenomics, and proteomics.[45] The availability of appropriate laboratory models to test potential AAA drugs remains challenging with drugs such as fenofibrate initially shown to be promising in animal studies later found to be ineffective in human clinical trials.[96,128–130] Detailed ultrasound investigation suggests that

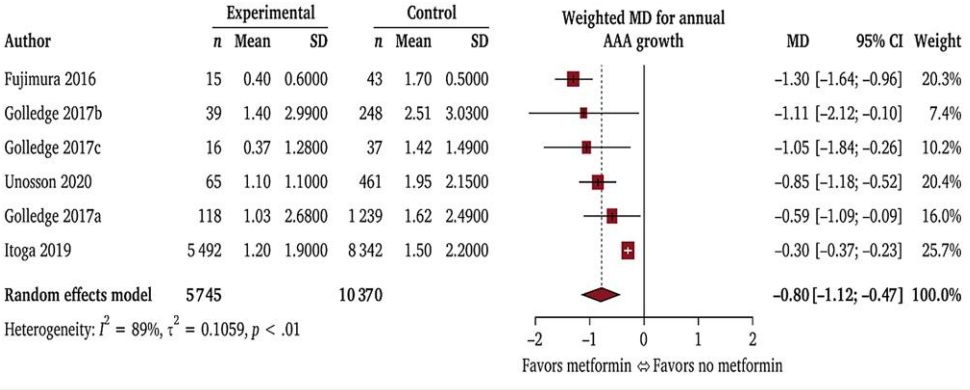

Figure 5 Metformin prescription is associated with slower annual abdominal aortic aneurysm growth: results of a meta-analysis of observational studies. Mean difference (MD) in annual abdominal aortic aneurysm growth shown in millimetres. Reproduced with permission.[140]

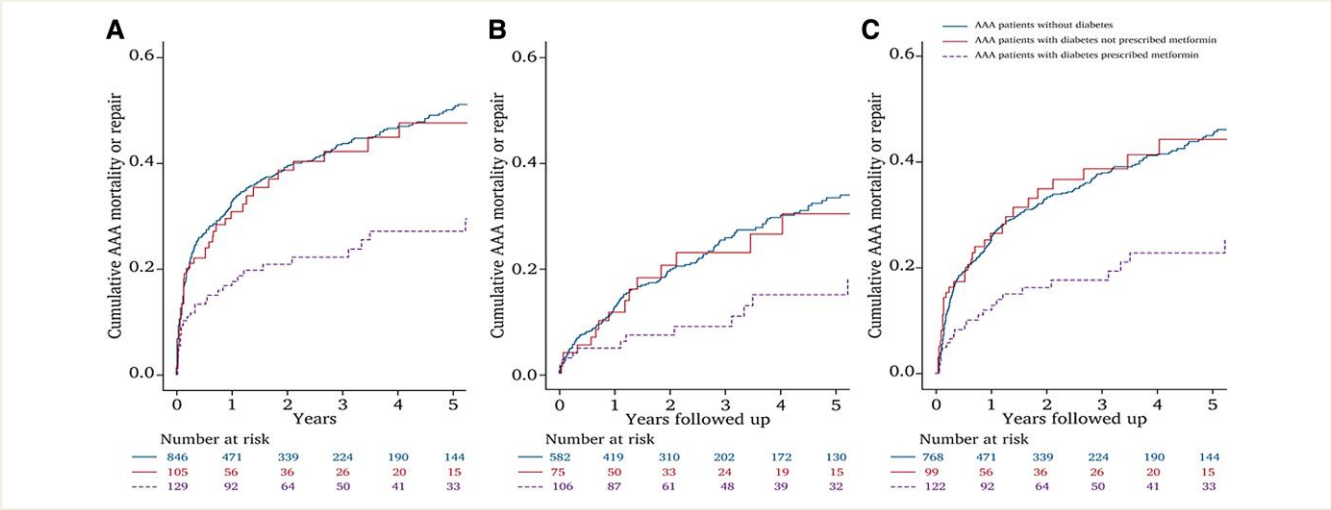

Figure 6 Combined incidence of abdominal aortic aneurysm (AAA) repair or mortality from AAA rupture (AAA events) in patients with diabetes prescribed metformin (purple dotted line), those with diabetes not prescribed metformin (red line), and those without diabetes (blue line). Graphs show cumulative proportion of events over 5 years for the whole cohort (*A*), patients with initial AAA diameter ≤ 50 mm (*B*), and patients with ≥6 month follow-up (*C*). In the whole cohort, the incidence of AAA events was less in patients with diabetes prescribed metformin than in patients who had diabetes but were not prescribed metformin ($P = 0.003$) or patients who did not have diabetes ($P < 0.001$). The incidence of AAA events was similar in people who had diabetes but were not prescribed metformin and patients who did not have diabetes ($P = 0.839$). Numbers at risk during different stages of follow-up are shown below the graphs. Reproduced with permission.[141]

Table 5 Design of randomized trials testing metformin as a treatment for abdominal aortic aneurysm

Trial	Registration number	Planned sample size	Design	Daily dose	Control	Primary outcome	Anticipated completion data
MAT[134]	ACTRN12618001707257	1954 to achieve 616 primary outcome events	PCRT; active 6 week run-in; event driven	1500 mg	Placebo	AAA repair or rupture	2028
MAGGI[142]	NCT04224051	500	Open label	2000 mg	No metformin	AAA growth measured by orthogonal diameter from CT over 5 years	2026
LIMIT[143]	NCT04500756	480	PCRT	2000 mg	Placebo	AAA growth measured by orthogonal diameter from CT over 24 months	2028
Met-AAA[144]	NCT03507413	170	PCRT	2000 mg	Placebo	AAA growth measured by orthogonal diameter from CT over 12 months	2023

MAT, Metformin Aneurysm Trial; MAGGI, Metformin for Abdominal Aortic Aneurysm Growth Inhibition; LIMIT, Limiting Abdominal Aortic Aneurysm With Metformin Trial; PCRT, placebo-controlled randomized trial; CT, computed tomography; Met-AAA, metformin therapy to inhibit progression in non-diabetic patients with abdominal aortic aneurysm.

the elastase, angiotensin II, and $CaCl_2$ models have limited severity of and variable abdominal aortic expansion, meaning there is limited ability to first establish a small aneurysm then examine the effect of a drug on AAA growth over an extended time.[13–15,146] Furthermore, the most commonly used angiotensin II model does not cause aortic dilatation in all mice and induces aortic dissection rather than true aneurysm formation.[147] In contrast, a new model that combines two methods of inducing AAA using application of elastase to the adventitia of the infra-renal aorta and oral administration of a lysyl oxidase inhibitor holds more promise for testing drugs.[148] In this model, expansion of

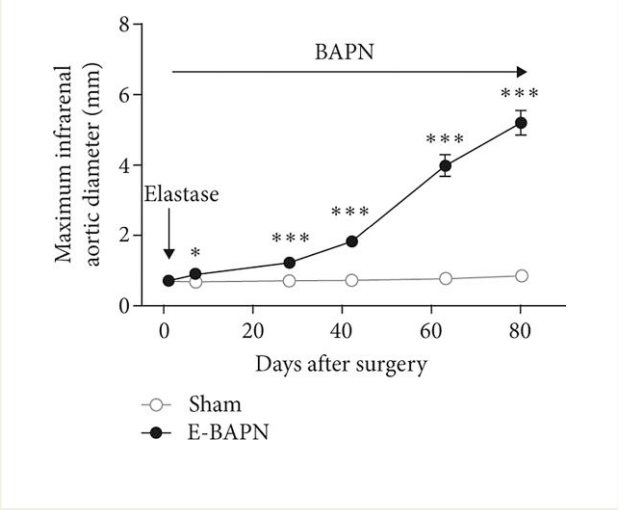

Figure 7 Illustration of maximum infra-renal abdominal aortic diameter in the adventitial elastase and β-aminopropionitrile mouse model. Previously reported by Phie and colleagues.[148]

aortic diameter occurs over 3 months (*Figure 7*). The model also illustrates typical human AAA characteristics of true aneurysm formation, intra-luminal thrombus, marked aortic wall inflammation, and a rupture rate of ~30%.[148]The use of this and other novel animal models along with rigorous study design similar to clinical trials may identify drugs more likely to translate to patients.

Personalizing drug therapy

When AAA drug therapies are established, ideally, these need to be targeted at patients most likely to benefit. Personalizing AAA drugs requires accurate ways to determine people most likely to benefit due to good drug responsiveness and excellent tolerance. The drugs also need to be targeted at people most at risk of aneurysm-related complications. The use of genomic data may in the future provide a means to personalize drugs by identifying people able to respond to the medications due to their ability to metabolize it and because the drivers of their AAA are sensitive to it. Risk models able to predict AAA growth using established traditional risk factors (*Table 4*) along with new PRS may also provide a way to better identify those patients most at risk of fast aneurysm growth and rupture. Future drug trials need to consider whether a more targeted approach using genomic and other biomarkers might be a better way of selecting participants for inclusion.

Under-represented groups

Given the worse outcome of AAA in women than men, there is a need for more focus on AAA in women.[83] There is also a need to address racial disparity in access to AAA treatment and to better understand the unique features of AAA in different ethnicities.[17,18]

Conclusion

Current management of AAA is by imaging surveillance of small aneurysm and surgical repair of large, symptomatic, or ruptured aneurysms. Patients and clinicians require effective drug therapies to limit AAA growth and the risks of both AAA repair and rupture. The diabetes drug metformin holds some promise and is being evaluated in ongoing trials. Other areas that could be targeted regarding development of drugs are dyslipidemia, IL-6 signalling, and stabilization of the extracellular matrix.

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Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

Data Availability

No new data were generated or analyzed for this manuscript.

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