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REVIEW ARTICLE

Current Status and Perspectives on Pharmacologic Therapy for Abdominal Aortic Aneurysm

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Abstract: ***Background*:** Abdominal aortic aneurysm (AAA), a common disease involving the segmental expansion and rupture of the aorta, has a high mortality rate. Therapeutic options for AAA are currently limited to surgical repair to prevent catastrophic rupture. Non-surgical approaches, particularly pharmacotherapy, are lacking for the treatment of AAA.

***Objective*:** We review both basic and clinical studies and discuss the current challenges to developing medical therapy that reduces AAA progression.

***Results*:** Studies using animal models of AAA progression and human AAA explant cultures have identified several potential targets for preventing AAA growth. However, no clinical studies have convincingly confirmed the efficacy of any pharmacologic treatment against the growth of AAA. Thus, there is as yet no strong recommendation regarding pharmacotherapy to reduce the risk of AAA progression and rupture.

***Conclusion*:** This review identifies concerns that need to be addressed for the field to progress and discusses the challenges that must be overcome in order to develop effective pharmacotherapy to reduce AAA progression in the future.

Keywords: Abdominal aortic aneurysm, pharmacologic therapy, medical management, progression, animal study, clinical study, practice guideline, future perspective.

1. INTRODUCTION

Abdominal aortic aneurysm (AAA) is a common disease that causes segmental dilatation and rupture of the aorta. AAA has a high mortality rate, especially in older men [1, 2]. Patients with large AAAs that are at high risk of rupture are treated by surgical repair. However, when surgical treatment is not an option, an AAA inevitably progresses, increasing in diameter and consequently increasing the rupture risk. Notably, close observation alone is recommended for patients with small AAAs; there are no alternatives to surgical repair that are available for these patients. There have been considerable efforts focused on developing medical treatments, especially pharmacotherapy, for AAA [3-7]. AAA is characterized by chronic inflammation and by the degradation of the extracellular matrix (ECM) by proteolytic enzymes, such as matrix metalloproteinases (MMPs); together, these lead to segmental dilatation of the aortic wall and eventually to rupture [7-10]. Although the real cause of AAA onset remains unknown, AAA progression is thought to be driven by factors that include hemodynamic stress and smoking. These multifactorial causes accelerate the immune and inflammatory responses in AAA tissue. Various inflammatory mediators, such as cytokines, chemokines, and prostaglandins, as well as the renin-angiotensin system, are involved in maintaining and augmenting the inflammatory responses, including inflammatory cell infiltration. Intracellular signaling molecules, such as c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB), are activated by most inflammatory mediators, while activated signaling pathways enhance the expression of inflammatory mediators, thus propagating a vicious cycle of chronic inflammation. In turn, inflammatory signaling pathways activate ECM degradation enzymes, such as MMP-9, and lead to vascular smooth muscle cell (VSMC) dysfunction, thereby causing an overall loss of elastic fibers and AAA progression (Fig. **1**). These mechanisms are supported by accumulating evidence that the progression of AAA in animal models can be suppressed by

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pharmacologic intervention that target various aspects of these pathophysiological processes.

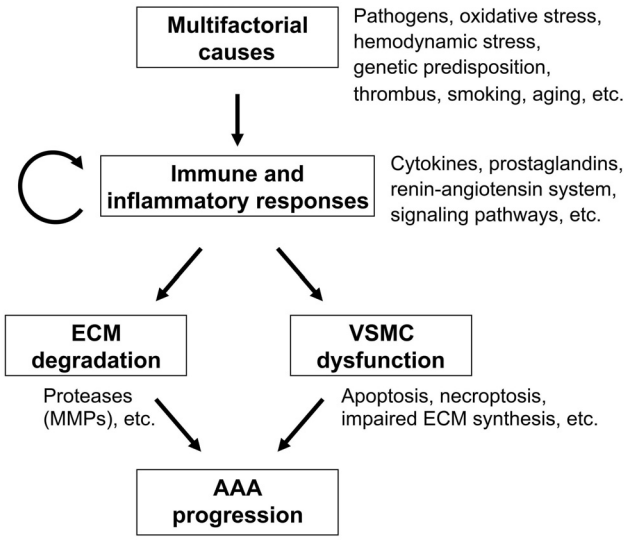

Fig. (1). The pathophysiological processes underlying the progression of AAA. Immune and inflammatory responses may be driven by the indicated causes in aortic tissues, leading to ECM degradation and VSMC dysfunction, thereby resulting in AAA progression. The pharmacologic agents discussed in this review target one or more of these processes. AAA, abdominal aortic aneurysm; ECM, extracellular matrix; MMPs, matrix metalloproteinases; VSMC, vascular smooth muscle cell.

2. CURRENT STATUS

2.1. Basic Studies of Pharmacologic Therapy for AAA

2.1.1. Studies Using Animal Models of AAA Progression

Although researchers have identified a large number of potential targets for the treatment of AAA, a limited number of them have been investigated using *in vivo* animal models of AAA progression. Golledge *et al.* noted that many rodent studies assess the effect of interventions in limiting AAA development rather than the effect of the agent on pre-established AAA [5]. Importantly, current animal models of AAA, including the elastase model, calcium chloride model, xenograft model, and angiotensin II model, have two disease phases: first, the initial development phase, which is model-specific; second, the progression phase, which mostly recapitulates human disease [11, 12]. An intervention that is used throughout the entire experimental period cannot distinguish between effects on the progression phase *versus* effects on the initial development phase. This review focuses on studies that have demonstrated that the pharmacologic intervention inhibits the progression phase of preexisting AAA in animal models (Table **1**). In these studies, interventions were started after the initial development of AAA, and the primary outcome was a change in AAA growth that was assessed by measuring the maximal aortic diameter.

Most of the interventions shown in Table **1** target immune/inflammatory responses among several aspects during AAA progression. Specifically, these interventions demonstrated that regulating proinflammatory mediators, including cytokines [13-15], the renin-angiotensin system [16, 17], and prostaglandin metabolism [18, 19], was effective in slowing the progression of preexisting AAA. Treatment with immunosuppressive agents [20, 21] and interventions that inhibit inflammatory signaling pathways [22-24] were also shown to be effective in stopping AAA progression. Indeed, our group reported previously that treatment with the JNK-specific inhibitor SP600125 after AAA formation reduced the diameter of the aneurysm and restored the once-disrupted elastic lamellae [22]. Our recent study also demonstrated that phase-limited inhibition of focal adhesion kinase (FAK) could block further progression of pre-existing AAA in a mouse model [25]. In addition, interventions that abrogate ECM degradation using MMP inhibitors [26, 27] or pentagalloyl glucose (PGG) [28, 29] are effective in preventing AAA progression. Recently, the pharmacological inhibition of necroptosis was reported to stabilize preexisting AAA [30].

2.1.2. Studies Using Human AAA Explant Cultures

Although animal studies have been important for demonstrating proof-of-concept and for assessing the efficacy and safety of new pharmacologic therapies, there are considerable differences in the pathophysiology of humans *versus* animal models. Accordingly, experiments that use *ex vivo* cultures of human AAA tissue are conducted in addition to animal studies [22, 36, 37]. The major advantage of *ex vivo* cultures is that one can apply therapeutic agents directly to human tissue, bypassing concerns about systemic effects or safety. However, there is always the question of whether an agent will have a similar effect *in vivo*. Thus, *in vivo* animal models and *ex vivo* cultures of human tissue are complementary approaches. Although the widespread use of endovascular aneurysm repair (EVAR) is making it more difficult to utilize human AAA tissues, both types of studies are valuable and contribute to our understanding of AAA. Table **2** summarizes the studies that have investigated pharmacologic therapy in human AAA explant cultures. These studies mainly assessed the secretion or the production levels of marker proteins, such as MMPs, interleukins, and monocyte chemotactic proteins (MCPs), rather than using the AAA growth rate as in *in vivo* studies.

Most of the interventions shown in Table **2** targeted the immune/inflammatory responses during AAA progression, except for one study that showed the effectiveness of an MMP inhibitor [36]. Interventions that regulate proinflammatory mediators, including cytokines [38], the renin-angiotensin system [39, 40], and prostaglandin metabolism [41-44], reduced the levels of AAA-related markers. Interventions that inhibit inflammatory signaling pathways were also effective in human AAA tissues [22, 25, 45]. In addition, our group demonstrated that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) inhibit the Rac1/NF-κB pathway, thereby suppressing MMP-9 and chemokine secretion in human AAA walls [46].

2.2. Clinical Studies of Pharmacologic Therapy for AAA

2.2.1. Previous and Ongoing Clinical Trials

Clinical trials are critical for developing new ways to treat diseases. A single randomized clinical trial or multiple

Table 1. Pharmacologic therapy that prevents AAA progression in animal models.

Authors	Year	Animal Model	AAA Inducer	Intervention (Period)	Target	Effect on Progression of Preexisting AAA
Huffman *et al.* [26]	2000	Rats	Elastase	Doxycycline (daily on days 7–21)	MMP	Stopped progression (on day 21)
Yoshimura *et al.* [22]	2005	Mice	$CaCl_2$	SP600125 (daily on days 43–84)	JNK	Stopped progression (on day 84)
		Apoe-/- mice	Ang II (for 28 days)	SP600125 (daily on days 29–84)		Stopped progression (on day 84)
Isenburg *et al.* [28]	2007	Rats	$CaCl_2$	PGG (local injection on days 28)	Elastolytic degradation	Decreased progression (on day 56)
Inoue *et al.* [16]	2009	Apoe-/- mice	Ang II (for 28 days)	Candesartan (daily on days 28–168)	Ang II receptor	Decreased progression (on day 168)
				Lisinopril (daily on days 28–168)	ACE	Decreased progression (on day 168)
Dai *et al.* [20]	2011	Rats	Xenograft	Cyclosporine A (daily on days 14–21)	Immune response	Decreased progression (on day 70)
Ghoshal *et al.* [18]	2012	Apoe-/- mice	Ang II (for 56 days)	Celecoxib (daily on days 21–56)	COX-2	Stopped progression (on day 56)
Morimoto *et al.* [31]	2012	Rats	Elastase and $CaCl_2$	Edaravone (daily on days 7–28)	ROS	Stopped progression (on day 28)
Mukherjee *et al.* [19]	2012	Mice	Ang II (for 28 days)	Celecoxib (daily on days 5–28)	COX-2	Decreased progression (on day 28)
Johnston *et al.* [13]	2013	Mice	Elastase	Anakinra (continuously on days 7–21)	IL-1β	Decreased progression (on day 21)
Iida *et al.* [14]	2013	Mice	Elastase	MKEY peptide (daily on days 5–14)	CXCL4–CCL5	Stopped progression (on day 14)
Rouer *et al.* [21]	2014	Mice	Elastase	Rapamycin (daily on days 4–10)	Immune response	Decreased progression (on day 10)
Seto *et al.* [17]	2014	Apoe-/- mice	Ang II (for 28 days)	Aliskiren (daily on days 29–56)	Renin	Decreased progression (on day 56)
Michineau *et al.* [15]	2014	Mice	$CaCl_2$	AMD3100 (continuously on days 4–14)	SDF-1/CXCR4	Decreased progression (on day 14)
		Rats	Xenograft	AMD3100 (continuously on days 14–42)		Decreased progression (on day 42)
Cheng *et al.* [23]	2014	Apoe-/- mice	Ang II (for 28 days)	DAPT (3 times a week on days 8–28)	Notch	Decreased progression (on day 28)
Yan *et al.* [24]	2015	Mice	$CaCl_2$	TLR2-neutralizing antibody (weekly on days 42–84)	TLR2	Decreased progression (on day 84)
Nosoudi *et al.* [27]	2015	Rats	$CaCl_2$	Nanoparticles loaded with batimastat (weekly on days 10–38)	MMP	Stopped progression (on day 38)
Ren *et al.* [32]	2016	Mice	Elastase	Andrographolide (daily on days 7–14)	Inflammation	Decreased progression (on day 14)
Moran *et al.* [33]	2016	Apoe-/- mice	Ang II (for 28 days)	B9330 (every other day on days 29–56)	B2R	Stopped progression (on day 56)
		Rats	$CaPO_4$	B9330 (single injection on days 7)		Decreased progression (on day 28)

(Table 1) contd….

Authors	Year	Animal Model	AAA Inducer	Intervention (Period)	Target	Effect on Progression of Preexisting AAA
Nosoudi *et al.* [29]	2016	Rats	$CaCl_2$	PGG-loaded nanoparticles (every other week on days 10–38)	Elastolytic degradation	Decreased progression (on day 38)
Pope *et al.* [34]	2016	Mice	Elastase	Resolvin D2 (every third day on days 3–14)	Inflammation	Decreased progression (on day 14)
Harada *et al.* [25]	2017	Mice	$CaCl_2$	PF573228 (daily on days 22–42)	FAK	Stopped progression (on day 42)
Di Gregoli *et al.* [35]	2017	Apoe-/- or Ldlr-/- mice	Ang II (for 28 days)	miR-181b LNA inhibitor (weekly on days 29–42)	TIMP-3	Decreased progression (on day 42)
Wang *et al.* [30]	2017	Mice	Elastase	Necrostatin-1s (daily on days 7–14)	Necroptosis	Stopped progression (on day 14)

AAA = abdominal aortic aneurysm; ACE = angiotensin converting enzyme; Ang II = angiotensin II; Apoe-/- = apolipoprotein E deficient; B2R = kinin B2 receptor; COX-2 = cyclooxygenase-2; FAK = focal adhesion kinase; 1L-1β = interleukin-1β; JNK = c-Jun N-terminal kinase; Ldlr-/- = low density lipoprotein receptor deficient; LNA = locked nucleic acid; MMP = matrix metalloproteinase; mTOR = mammalian target of rapamycin; PGG = pentagalloyl glucose; ROS = reactive oxygen species; SDF-1 = stromal cell-derived factor 1; TIMP-3 = tissue inhibitor of metalloproteinase-3; TLR2 = toll-like receptor2.

Table 2. Pharmacologic therapy that reduces levels of AAA-related markers in human AAA explants.

Authors	Year	Intervention	Target	Effect on Human AAA in *Ex Vivo* Culture
Franklin *et al.* [36]	1999	Tetracycline	MMP	Reduced secretion of MMP-9 and MCP-1
Franklin *et al.* [41]	1999	Indomethacin	COX-2	Reduced secretion of PGE2, IL-1β, and IL-6
Walton *et al.* [42]	1999	Indomethacin	COX-2	Reduced secretion of PGE2, IL-1β, and IL-6
		Mefenamic acid	COX-2	Reduced secretion of PGE2, IL-1β, and IL-6
Nagashima *et al.* [47]	2002	Cerivastatin	Mevalonate pathway	Reduced secretion of MMP-9
Bayston *et al.* [43]	2003	Indomethacin	COX-2	Reduced secretion of IL-6
		Dexamethasone	COX-2	Reduced secretion of IL-6
Nagashima *et al.* [48]	2004	Trapidil	CD40-CD40L interaction	Reduced production of MMP-2
		Anti-CD154 antibody	CD40-CD40L interaction	Reduced production of MMP-2
Moran *et al.* [39]	2005	Irbesartan	Angiotensin II receptor	Reduced secretion of OPG
Dai *et al.* [38]	2005	Recombinant human active TGF-β1	TGF-β1	Reduced secretion of MMP-9 and MMP-2
Yoshimura *et al.* [22]	2005	SP600125	JNK	Reduced secretion of MMP-9 under basal and TNF-α-stimulated conditions
Moran *et al.* [49]	2009	Rosiglitazone (PPARγ agonist)	PPARγ	Reduced secretion and production of OPG, production of MMP-9, and secretion of IL-6
		Pioglitazone (PPARγ agonist)	PPARγ	Reduced secretion and production of OPG, production of MMP-9 and secretion of IL-6
Shintani *et al.* [40]	2011	Recombinant human HGF		Reduced secretion of MCP-1 under TNF-α-stimulated conditions
		Imidaprilat	ACE	Reduced secretion of MCP-1 under TNF-α-stimulated conditions
		Perindoprilat	ACE	Reduced secretion of MCP-1 under TNF-α-stimulated conditions

(Table 2) contd….

Authors	Year	Intervention	Target	Effect on Human AAA in *Ex Vivo* Culture
Yokoyama *et al.* [44]	2012	ONO-AE3-208 (EP4 antagonist)	EP4	Reduced secretion of MMP-2 and production of IL-6
Vucevic *et al.* [50]	2012	Recombinant human IL-10	Immune response	Reduced secretion of IL-6 under PMA-stimulated conditions
Yamashita *et al.* [45]	2013	PF573228	FAK	Reduced activation levels of ERK and JNK, and reduced secretion of MCP-1 and MMP-9
Yoshimura *et al.* [46]	2015	Simvastatin	Mevalonate pathway	Reduced activation levels of JNK and NF-κB under TNF-α-stimulated conditions Reduced secretion of MMP-9, MCP-2, and CXCL-5 under basal and TNF-α-stimulated conditions
		Pitavastatin	Mevalonate pathway	Reduced secretion of MMP-9, MCP-2, and CXCL-5 under basal and TNF-α-stimulated conditions
		NSC23766	Rac1	Reduced secretion of MMP-9, MCP-2, and CXCL-5 under basal and TNF-α-stimulated conditions
Moran *et al.* [33]	2016	B9330	B2R	Reduced secretion of MMP-9, OPG, and osteopontin
Harada *et al.* [25]	2017	PF573228	FAK	Reduced secretion of MCP-1 and MMP-9 under TNF-α-stimulated conditions

AAA = abdominal aortic aneurysm; ACE = angiotensin converting enzyme; B2R = kinin B2 receptor; COX-2 = cyclooxygenase-2; EP4 = prostanoid receptor EP4; ERK = extracellular signal-regulated kinase; FAK = focal adhesion kinase; HGF = hepatocyte growth factor; 1L-1β = interleukin-1β; IL-6 = interleukin-6; IL-10 = interleukin-10; JNK = c-Jun N-terminal kinase; MCP = monocyte chemotactic protein; MMP = matrix metalloproteinase; NF-κB = nuclear factor-κB; OPG = osteoprotegerin; PGE2 = prostaglandin E2; PMA = phorbol myristate acetate; PPARγ = peroxisome proliferator-activated receptor-γ; TGF-β1 = transforming growth factor-β1; TNF-α = tumor necrosis factor-α.

large non-randomized studies are needed to provide unambiguous evidence to support the safety and efficacy of pharmacologic therapy for AAA. A large cohort study and a systematic review of clinical trials for AAA treatment were conducted previously [51, 52]. In this article, we focus on randomized clinical trials of pharmacologic interventions for AAA (Tables **3** and **4**). All of these randomized clinical trials aimed to evaluate the efficacy of a pharmacologic therapy in limiting the progression of small AAA. Therefore, growth rate was commonly used as the primary outcome, and the maximal AAA diameter was measured using ultrasonography (US). Computed tomography (CT) and magnetic resonance imaging (MRI) is currently being used to assess the AAA diameter in ongoing trials. Indeed, AAA diameter remains the most widely used and the most important marker of disease progression, because large diameter and a rapid increase in the AAA diameter are thought to be risk factors for rupture and are generally accepted as an indication for surgical repair [53]. Notably, there is large individual variability in growth patterns. The sample sizes in previous trials varied, but current (ongoing) trials are larger, with more than 100 patients, and they have follow-up periods greater than one year.

Chlamydia pneumoniae is suspected to play a pathogenic role in AAA development, although this has not been proven. Accordingly, several randomized clinical trials have been conducted to test the efficacy of antibiotic treatment. Mosorin *et al.* first published a randomized trial of doxycycline, a tetracycline antibiotic, in patients with small AAAs. They showed that the expansion rate of AAAs treated with doxycycline was slower than with placebo, but the difference did not reach statistical significance [54]. Treatment with roxithromycin, a macrolide antibiotic, significantly reduced the AAA expansion rate [55, 56]. However, it is not clear whether the effect was due to its anti-microbial or anti-inflammatory activities. Later, a randomized clinical trial of azithromycin, another macrolide antibiotic, was conducted in a larger population, but found no effect on the AAA growth rate [57]. More recently, the effect of doxycycline, which was tested as an MMP inhibitor, was examined in a randomized clinical trial in a larger number of patients. That trial found that doxycycline treatment did not reduce AAA growth [58]. Propranolol, a β-blocker, was one of the first drugs to successfully inhibit the development of experimental AAAs in animal models [59, 60], and this prompted researchers to conduct clinical studies to test its effect on the growth of small AAAs. However, in a randomized trial, patients with AAAs did not tolerate propranolol well, and the drug did not significantly affect the growth rate of small AAAs [61]. Also recently, two randomized trials of pemirolast [62], a mast cell inhibitor, and perindopril [63], an angiotensin-converting enzyme (ACE) inhibitor, were conducted, but the results were disappointing (Table **3**).

There are currently several ongoing randomized clinical trials that aim to assess the effects of the following on the growth rate of small AAAs: doxycycline (NCT01756833), an MMP inhibitor; ticagrelor (NCT02070653), a platelet aggregation inhibitor; telmisartan (NCT01683084)/valsartan (NCT01904981), an angiotensin II receptor blocker (ARB); cyclosporine A (NCT02225756), an immunosuppressive agent; and eplerenone (NCT02345590), an aldosterone antagonist (Table **4**). Interestingly, several clinical studies have demonstrated an association between statin administration and decreased AAA growth [64-67]. However, the beneficial

Table 3. Completed randomized clinical trials of pharmacologic therapy to prevent AAA progression.

Authors	Year	Intervention	Sample Size	Follow-up, Months	Growth Rate, mm/year		p-value
					Intervention	Placebo	
Mosorin *et al.* [54]	2001	Doxycycline (3 months)	32	18	1.5	3.0	NS
Vammen *et al.* [55]	2001	Roxithromycin (28 days)	92	18	1.56	2.75	0.02
PATI [61]	2002	Propranolol	548	30	2.2 (High dropout rate and low QOL score)	2.6	NS
Hogh *et al.* [56]	2009	Roxithromycin (28 days)	84	60	1.61	2.52	0.055
Karlsson *et al.* [57]	2009	Azithromycin (15 weeks)	247	18	2.2	2.2	NS
Meijer *et al.* [58]	2013	Doxycycline	286	18	4.1 (higher than placebo)	3.3	0.016
Sillesen *et al.* [62]	2015	Pemirolast	326	12	2.58 (10 mg) 2.34 (25 mg) 2.71 (40 mg)	2.04	NS
Bicknell *et al.* [63]	2016	Perindopril Amlodipine	227	24	1.77 (perindo-pril) 1.81 (amlodip-ine)	1.68	NS NS

AAA = abdominal aortic aneurysm; NS = not significant; PATI = propranolol aneurysm trial investigators; QOL = quality of life.

Table 4. Ongoing randomized clinical trials of pharmacologic therapy to prevent AAA progression.

NCT Number	Intervention	Phase	Primary Outcome	Status	Estimated Completion Date	Sample Size
NCT01756833	Doxycycline	2	Growth by CT at 48 months	Ongoing but not recruiting	September 2019	261
NCT02070653	Ticagrelor	2	Growth by MRI at 24 months	Ongoing but not Recruiting	July 2017	145
NCT01683084	Telmisartan	4	Growth by CT at 48 months	Ongoing but not recruiting	August 2017	300
NCT01904981	Valsartan *vs*. Atenolol	4	Growth by CT at 12 months	Unknown	October 2016	400
NCT02225756	Cyclosporine A	2	Growth by CT at 12 months	Recruiting	September 2018	360
NCT02345590	Eplerenone	4	Growth by MRI at 12 months	Recruiting	December 2019	172

AAA = abdominal aortic aneurysm; CT = computed tomography; MRI = magnetic resonance imaging; NCT = National Clinical Trial.

effect of statins has not been confirmed in larger non-randomized clinical trials [68, 69]; notably, a randomized clinical trial of statins may not be feasible, because statins are already prescribed to many patients with AAA [70].

2.2.2. Recommendation in Clinical Practice Guidelines

Several practice guidelines strongly recommend that patients with a fusiform AAA measuring 5.5 cm or larger undergo repair in the absence of significant co-morbidities and

that most patients with a fusiform AAA measuring 5.4 cm or smaller should be monitored. These guidelines include the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines [71], the Society for Vascular Surgery (SVS) Guidelines [72], the AAA Guidelines of the European Society for Vascular Surgery (ESVS) [2], and the European Society of Cardiology (ESC) Guidelines [73]. Notably, all strongly recommend smoking cessation to slow AAA growth. However, there is no strong recommendation regarding pharmacotherapy to reduce the risk of AAA progression and rupture. At the present time, there is only a very weak recommendation that the use of statins and ACE inhibitors be considered to reduce the risk of AAA growth [72, 73]. Table **5** summarizes recommendations for the medical management of AAA in the current practice guidelines.

3. FUTURE PERSPECTIVE

3.1. Pharmacologic Therapy for Primary Prevention

Because AAA is life-threatening, preventing AAA rupture is an important goal. We are hopeful that in the future, pharmacologic treatment will play a key role in the primary, secondary, and tertiary prevention of AAA (Table **6**). In primary prevention, the goal of pharmacotherapy is to reduce the incidence of AAA, but there is not yet a clear way to do this due to a lack of understanding of the mechanisms underlying AAA. Although it is widely accepted that multifactorial causes, including smoking and hypertension, drive the progression of AAA (Fig. **1**), the primary cause of AAA onset remains unclear. If the cause is identified, a drug or drugs can be identified or developed and utilized to prevent the onset of AAA. Therefore, researchers should continue to investigate the pathogenesis underlying AAA.

There are several known risk factors that contribute to AAA development, such as hypertension and hypercholesterolemia [72]. The incidence of AAA might be reduced by appropriate pharmacologic treatment of these risk factors. Avoiding the risk factors and increasing physical activity to reduce the risk factors might also reduce the incidence of AAA. Moreover, the pharmacologic management of cardiovascular risk factors is generally important in people at high risk of developing AAA [2].

3.2. Pharmacologic Therapy for Secondary Prevention

The goal of pharmacotherapy for the secondary prevention of AAA is to reduce disease progression and the risk of surgical referral. Many patients presenting with AAAs measuring less than 5.5 cm are simply monitored, while treatments such as surveillance or early repair remain controversial in the management of patients with AAAs between 4.0 cm and 5.4 cm in diameter [72, 73]. Therefore, pharmacologic therapy to prevent AAA progression, or ideally to reverse AAA formation, would have a huge impact on the management of patients with small AAA once it is established and becomes a first-line treatment, replacing surveillance and early repair.

Unfortunately, no pharmacotherapy for AAA has been realized despite great effort, and there are several challenges that need to be addressed (Table **7**). First, it is possible that appropriate drug targets in human AAA have not been identified. Indeed, many animal studies have assessed the effects of interventions in limiting AAA development rather than the effects on pre-established AAA. In addition, the experimental opportunities for analyzing human AAA specimens

Table 5. Medical management recommendations for preventing AAA progression in current practice guidelines.

Guidelines	Year	Recommendation	Class of Recommendation	Level of Evidence
ESC [73]	2014	Encourage smoking cessation to slow the growth of the AAA.	I (Evidence and/or general agreement that a given treatment or procedure in beneficial, useful, effective.)	B (Data derived from a single randomized clinical trial or large non-randomized studies.)
		Consider the use of statins and ACE inhibitors to reduce aortic complications in patients with small AAAs.	IIb (Usefulness/efficacy is less well established by evidence/opinion.)	B (Data derived from a single randomized clinical trial or large non-randomized studies.)
SVS [72]	2009	Encourage smoking cessation to reduce the risk of AAA growth and rupture.	Strong	High
		Consider the use of statins to reduce the risk of AAA growth.	Weak	Low
		Uncertain benefits for the use of doxycycline, roxithromycin, ACE inhibitors, and ARBs for reducing the risk of AAA expansion and rupture.	Weak	Low
		Do not use β-blockers to reduce the risk of AAA expansion and rupture.	Strong	Moderate

AAA = abdominal aortic aneurysm; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ESC = European Society of Cardiology; SVS = Society for Vascular Surgery.

Table 6. Possible future roles of pharmacologic treatments in the management of AAA.

Level of Prevention	Target Population	Treatment Goal	Possible Treatment Strategies
Primary prevention	At-risk patients	Reduce the incidence of AAA.	Use pharmacologic treatment of risk factors for AAA, such as hypertension and hypercholesterolemia.
Secondary prevention	Patients with small AAAs	Reduce the progression of AAA and the risk of surgical referral.	Use pharmacologic therapy to stop or slow the progression of AAA.
Tertiary prevention	Patients with large AAAs	Reduce AAA-related complications and mortality.	Use adjuvant pharmacologic treatment to reduce peri- and postoperative complications and to improve EVAR results.

AAA = abdominal aortic aneurysm; EVAR = endovascular aneurysm repair.

Table 7. Challenges to using pharmacotherapy to prevent AAA progression.

Current Concerns	Possible Strategies to Address These Concerns
Appropriate drug targets may not have been identified.	Consider the appropriate use of animal models and human tissue samples to gain a better understanding of human AAA pathophysiology and pathogenesis.
Few pharmacokinetic approaches have been used.	Develop AAA-targeted DDSs to more effectively concentrate drugs at the site of the AAA.
Pharmacotherapy may not take the heterogeneity of human AAA into account.	Use appropriate biomarkers to develop personalized medicine for patients with AAA.

AAA = abdominal aortic aneurysm; DDS = drug delivery system.

have decreased in recent years. To gain a better understanding of human AAA pathophysiology and pathogenesis, continued efforts are essential, including the appropriate use and interpretation of animal models and full utilization of human samples. Second, it is important for pharmacotherapy to be sufficiently concentrated at the AAA site, but few pharmacokinetic approaches have been tested. Golledge *et al.* suggested that inappropriate dosage may underlie the negative findings in previous clinical trials [5]. Since AAA is predominately localized to a limited site on the aorta, it is reasonable to strive for local delivery of therapeutic agents in order to increase therapeutic efficacy and reduce systemic side effects. The efficacy of local administration was previously reported using doxycycline in rodent models of AAA [74, 75]. Notably, Nosoudi *et al.* recently reported the effects of AAA-targeted delivery of drugs using nanoparticles [27, 29], which seems to represent an attractive strategy for inhibiting AAA progression. Third, there is a possibility that the heterogeneity of human AAA might not be fully appreciated or taken into account when testing therapeutic agents, since patients with AAA are heterogeneous in terms of their characteristics, clinical history, and genetic background [10, 76]. In addition, human AAA tissue itself is spatiotemporally heterogeneous in terms of histopathological characteristics [7]. Therefore, it may be better to stratify AAA patients according to the predominant biological activities; towards this end, we must identify biomarkers that accurately reflect biological activity in AAA. If we can optimize therapeutic regimens for individual patients using biomarkers (personalized medicine), we may be able to achieve more effective outcomes with pharmacologic therapy and prevent or slow AAA progression.

3.3. Pharmacologic Therapy for Tertiary Prevention

In tertiary prevention, the goal of pharmacotherapy is to reduce AAA-related complications and mortality in patients with AAAs measuring 5.5 cm or larger. In the absence of significant co-morbidities, these patients should undergo surgical repair. Accordingly, pharmacotherapy for tertiary prevention is expected to serve as an adjuvant treatment to reduce peri- and postoperative complications as well as to improve the results of EVAR. The ESVS guidelines [2] already recommend that statins be started one month prior to surgical intervention to reduce cardiovascular morbidity, since statin therapy improves perioperative and postoperative outcomes after AAA repair [77-79]. β-blockers are also recommended for patients with ischemic heart disease, and these can be started one month before the intervention [2, 71]. Because AAA patients often have several comorbidities that significantly affect the outcome of AAA repair, preoperative care strategies, especially pharmacotherapy, may help improve post-intervention morbidity and mortality.

Notably, ongoing aortic wall degeneration and the subsequent failure of aneurysm exclusion, such as endoleaks, is a major concern after EVAR. To address this concern, adjuvant pharmacotherapy concomitant to or after EVAR could provide an ideal solution. Several studies have suggested a potential association between aneurysm sac regression and treatment with drugs like statins [80, 81], doxycycline [82], calcium channel blockers [83], and tranexamic acid [84]. However, the use of pharmacotherapy remains controversial because of inconsistent results [85]. Further studies are needed to clarify the role of adjuvant pharmacotherapy in enhancing sac regression and in reducing the risk of

endoleaks after EVAR. The combination of local drug delivery plus EVAR has promise in terms of utilizing pharmacotherapy as an adjuvant treatment. Indeed, we [86] and others [87] have filed patent applications for devices that comprise a stent graft and a drug delivery system. Progress in this area could drive the development of less invasive therapeutic strategies for AAA treatment.

CONCLUSION

Research conducted over the last 25 years has substantially deepened our understanding of the pathophysiology underlying AAA. However, this understanding has not translated into the development of pharmacologic therapies that improve the outcomes of AAA patients. Going forward, strategic approaches must be developed to continue to make progress in AAA research in order to offer effective pharmacotherapy to patients in addition to open repair and EVAR.

LIST OF ABBREVIATIONS

AAA	=	Abdominal aortic aneurysm
ACC	=	American College of Cardiology
ACE	=	Angiotensin-converting enzyme
AHA	=	American Heart Association
Ang II	=	Angiotensin II
Apoe-/-	=	Apolipoprotein E deficient
ARB	=	Angiotensin receptor blocker
B2R	=	Kinin B2 receptor
COX-2	=	Cyclooxygenase-2
CT	=	Computed tomography
DDS	=	Drug delivery system
ECM	=	Extracellular matrix
EP4	=	Prostanoid receptor EP4
ERK	=	Extracellular signal-regulated kinase
ESC	=	European Society of Cardiology
ESVE	=	European Society for Vascular Surgery
EVAR	=	Endovascular aneurysm repair
FAK	=	Focal adhesion kinase
HGF	=	Hepatocyte growth factor
HMG-CoA	=	3-hydroxy-3-methylglutaryl-coenzyme A
IL-1β	=	Interleukin-1β
IL-6	=	Interleukin-6
IL-10	=	Interleukin-10
JNK	=	c-Jun N-terminal kinase
Ldlr-/-	=	Low density lipoprotein receptor deficient
LNA	=	Locked nucleic acid
MCP	=	Monocyte chemotactic protein
MMP	=	Matrix metalloproteinase
MRI	=	Magnetic resonance imaging
mTOR	=	Mammalian target of rapamycin
NF-κB	=	Nuclear factor-κB
NS	=	Not significant
OPG	=	Osteoprotegerin
PATI	=	Propranolol aneurysm trial investigators
PGE2	=	Prostaglandin E2
PGG	=	Pentagalloyl glucose
PMA	=	Phorbol myristate acetate
PPARγ	=	Peroxisome proliferator-activated receptor-γ
QOL	=	Quality of life
RCT	=	Randomized controlled trial
ROS	=	Reactive oxygen species
SDF-1	=	Stromal cell-derived factor 1
SVS	=	Society for Vascular Surgery
TGF-β1	=	Transforming growth factor-β1
TIMP-3	=	Tissue inhibitor of metalloproteinase-3
TLR2	=	Toll-like receptor2
TNF-α	=	Tumor necrosis factor-α
US	=	Ultrasonography
VSMC	=	Vascular smooth muscle cell

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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