Published in final edited form as:

Biomed Pharmacother. 2022 September ; 153: 113340. doi:10.1016/j.biopha.2022.113340.

Development of pharmacotherapies for abdominal aortic aneurysms

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Abstract

The cardiovascular field is still searching for a treatment for abdominal aortic aneurysms (AAA). This inflammatory disease often goes undiagnosed until a late stage and associated rupture has a high mortality rate. No pharmacological treatment options are available. Three hallmark factors of AAA pathology include inflammation, extracellular matrix remodeling, and vascular smooth muscle dysfunction. Here we discuss drugs for AAA treatment that have been studied in clinical trials by examining the drug targets and data present for each drug's ability to regulate the aforementioned three hallmark pathways in AAA progression. Historically, drugs that were examined in interventional clinical trials for treatment of AAA were repurposed therapeutics. Novel treatments (biologics, small-molecule compounds etc.) have not been able to reach the clinic, stalling out in pre-clinical studies. Here we discuss the backgrounds of previous investigational drugs in hopes of better informing future development of potential therapeutics. Overall, the highlighted themes discussed here stress the importance of both centralized anti-inflammatory drug targets and rigor of translatability. Exceedingly few murine studies have examined an intervention-based drug treatment in halting further growth of an established AAA despite interventional treatment being the therapeutic approach taken to treat AAA in a clinical setting. Additionally, data suggest that a potentially successful drug target may be a central inflammatory biomarker. Specifically, one that can effectively modulate all three hallmark factors of AAA formation, not just inflammation. It is suggested that inhibiting PGE_2 formation with an mPGES-1 inhibitor is a leading drug target for AAA treatment to this end.

Keywords

Abdominal aortic aneurysms; Inflammation; Pharmacotherapy

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Introduction

Abdominal aortic aneurysms (AAA) result from the permanent expansion and weakening of the abdominal aortic wall. In humans, AAA criterion is a focal dilation of ≥ 3.0 cm that develops in the infrarenal region of the abdominal aorta [1,2]. The male gender and having a history of smoking are two of the leading risk factors for the disease [3]. Other risk factors for the development of AAA include obesity, genetic predisposition, older age, and a family history [1–3]. Rupture is the most severe consequence of this disease. Once an AAA ruptures, a patient's chance of survival decreases significantly [1–3]. 2% of yearly deaths in the USA are related to AAA [4]. While the rupture of even a large AAA is not a certainty, patients with a large dilation and those with a rapidly expanding AAA are at the greatest risk [1,3,5]. An AAA with a diameter of more than 8.0 cm has a 30–50% chance of rupture within the year and those with growth of 0.5 ≥ cm per six months present a high risk of rupture [3,5,6]. Unfortunately, about 50% of those with a ruptured AAA make it to the hospital alive and only 50% of those who continue on to emergency surgery survive the reparative procedure [6]. There are currently no FDA-approved drugs for the treatment of AAAs.

Formation and progression of AAA is multifaceted, involving numerous signaling cascades and risk factors. However, the field has reached a general consensus on three token features of the disease: extra-cellular matrix (ECM) degradation, dysfunction of vascular smooth muscle cells (VSMC), and persistent inflammation [1,4]. The aortic wall's structural strength is mainly due to ECM proteins like collagen and elastin. Aberrant degradation of the ECM by various factors can lead to weakening of the vessel, promoting AAA formation [7]. The ECM also supports layers of VSMCs that comprise the medial section of the aortic wall. Multiple factors have been identified in VSMC dysfunction that trigger phenotypic switches, cell death, and senescence seen in AAA pathology [8]. The integrity of the aortic wall incurs further loss with these changes in VSMC homeostasis. Chronic inflammation is thought to be a main factor in AAA formation and driver of the other two processes [1].

Drug development for the treatment of AAA has become increasingly difficult as we continue to expand on our knowledgebase. There has been continuous growth in the identification of pathways, molecules, and mechanisms that contribute to AAA formation and progression. With these advancements comes incertitude as to what, of the ever-growing list, is a druggable target with the potential to be successful. We find that clinically investigated AAA pharmacotherapies in USA registered trials (Clinicaltrials.gov) can be roughly classified into three overarching groups based on their primary molecular targets: inflammation, VSMC regulation, and ECM remodeling. Fig. 1 depicts these three groups representative of the three main pathways in AAA formation.

Several approaches have been used to bring potential therapeutics into clinical trials. One comes from an epidemiological perspective using patient population studies to examine comorbidities and co-prescriptions. Diabetes, despite being a risk factor for various cardiovascular diseases, is a protective factor for AAA [9]. This finding prompted further thought that it may actually be metformin treatment, rather than diabetes, that is protective. Later evidence unveiled a role of metformin in regulation of VSMCs and inflammation

in relation to AAA [10]. Examples of other drugs that have been investigated based on epidemiological evidence are antihypertensives and ticagrelor (anti--platelet) [11,12].

Doxycycline, a tetracycline antibiotic, has alternative action as a broad-spectrum matrix metalloproteinase (MMP) inhibitor that is independent of its antimicrobial mechanisms [7]. To our best knowledge, it is the only clinically investigated drug that falls into the group chiefly intending to treat AAA by controlling ECM degradation (Fig. 1). One of the biggest targets in AAA treatment has been inflammation. Ticagrelor, pemirolast (CRD007, mast cell stabilizer), stem cell therapy (mesenchymal stem cells), and canakinumab (ACZ885, human anti-IL-1β monoclonal antibody) have been clinically investigated in halting AAA progression using modulation of inflammation [13–16]. Both metformin and cyclosporin A, an immunomodulator, seem to fall under both the inflammation and VSMC groups. We have not identified a clinically investigated drug that falls into the sweet spot at the center of the three pathways – a drug with a mechanism of action that is purposefully used to modulate all three pathways to treat AAA.

This narrative review attempts to summarize investigational compounds for the treatment of AAA studied in USA registered clinical trials and each drug's associated preclinical data. Clinical studies selected for this review were trials registered in the USA's Clinicaltrials.gov database. Inclusion criteria were human studies for the condition of non-ruptured "abdominal aortic aneurysm" that examined a drug intervention to treat the condition. Availability of trial results and current status were not criteria. Owing to the interest and rigor of work done with doxycycline's effect on AAA, all available doxycycline studies in humans from PubMed.gov were included in the review if they included conclusive data related to MMPs, inflammatory markers, or aortic size measurements. Finally, after all drugs were identified, preclinical studies were selected from PubMed.gov of those that used one or more of the identified drugs to treat AAA in a murine model. Preclinical studies that did not have aortic size measurements were excluded.

Here we will analyze the evidence present, rodent and human, for each included drug's effect on the three primary pathways in AAA formation in addition to effect on AAA size. Further, we utilize a general categorization of the drugs (Fig. 1) to aid in visualizing exploration of drug targets in each of the three areas. Accruing evidence in the field suggests that inflammation is a main driver of AAA formation and that it is these pro-inflammatory factors that promote the other two hallmark pathways, VSMC dysfunction and remodeling of the ECM [1,2]. This points towards the idea that a drug may show promise in preclinical models if it targets one of these factors however, if it cannot effectively modulate the other two factors as well, it will most likely not be successful in a clinical setting, contributing to continued translational short-comings [3]. We aim to learn from the retroactive analysis of these AAA studies to advance future pharmacotherapies.

2. Screening and treatment

2.1. Prevalence and detection of AAA

The reported prevalence and mortality of AAA is highly variable and depends on the population being examined. Inconsistent reporting and variation in the rates of detection

contribute to inaccurate reporting of AAA prevalence and mortality [17]. In general, the reported incidence rate ranges from 1% to 12.7% [3,17]. One predictive scoring system estimated a prevalence of AAA in men aged 65–79 years at 2.8% [2,18]. Furthermore, the annual rate of new diagnoses in Western populations is reported to be between 0.4%– 0.67% [4,19].

Ultrasonography is a primary mode of observation for AAAs due to its high sensitivity (95%) and specificity (100%) [6]. Routine ultrasound screening is recommended for men over 65 who have ever smoked and is primarily the procedure by which most AAAs are detected [6,20]. Those with a normal preliminary ultrasound screen are not recommended to receive additional follow-up. Patients who have an AAA between 3.0 and 3.9 cm are recommended to receive a follow-up every 2–3 years and those between 4.0 and 5.4 cm are recommended to receive a follow-up every 6 months [21,22]. Once an AAA grows to 5.5 cm or larger for men or 5.0 cm or larger for women, the patient is referred for surgical intervention. Detection is often incidental due to the asymptomatic nature of the disease. About 30% of asymptomatic AAAs are discovered during routine physicals [6]. Although surgical intervention is not without risk, surgical treatment of large AAAs reduces the risk of rupture and resulting mortality.

2.2. Treatment and management options

Management options for AAAs are extremely limited. Surgical intervention is only recommended for patients with large asymptomatic AAAs (≥ 5.5 cm for men or ≥ 5.0 cm for women), symptomatic AAAs of any size, or ruptured AAAs [1]. Patients can choose either endovascular aneurysm repair (EVAR) or open repair. Both are designed to insert a graft or stent in the affected area of the aorta. As compared to open surgery, minimally invasive EVAR enters the aorta via blood vessels in the groin. This method is usually preferred over open repair for its shorter recovery time and lower mortality rate [1,6]. Thirty-day surgical mortality rates for EVAR vary from 2.7% to 5.8% [6]. However, when the EVAR1 [23], DREAM [24], and OVER [25] clinical trials examined surgical outcomes, no statistically significant difference was found in long-term (> 2 years) AAA-related mortality between the two surgical methods [1,4,26].

The other management option for patients is continued monitoring of the AAA's size progression. Those who have low-risk or small AAAs are not candidates for elective surgery and are without active treatment options. Continued surveillance of the condition has been associated with a reduced quality of life for these patients [1]. Ultimately, an approved pharmacotherapy is desperately needed for the treatment of AAAs. A plethora of research has gone into understanding the etiology and mechanisms behind AAA development. While numerous compounds have been examined in both animal studies and clinical trials, none have shown the ability to significantly limit disease progression in humans. Recently, doxycycline has been on the forefront of AAA clinical research. Despite some promising preclinical data, none of the clinical trials examining the efficacy of doxycycline for treating AAAs have shown a significant therapeutic effect.

3. Etiology and pathogenesis of AAA

3.1. Mechanisms of AAA formation and progression

The etiology of AAAs is complex and involves numerous potential mechanisms that contribute to development and progression of the disease in humans. However, three main mechanisms have been generally accepted as major contributors in this disease [2,27–29]. These include chronic inflammation, ECM remodeling, and VSMC dysfunction.

One characteristic of AAAs is the infiltration of immune cells including macrophages, neutrophils, B cells, and T cells [29,30]. Monocyte-derived macrophages are thought to be the predominant infiltrating cell type in the diseased vessel wall [30]. These macrophages can both produce and respond to pro-inflammatory signals. Exactly how initial recruitment of immune cells to the aortic wall unfolds is not completely clear. It is suggested that peptides derived from fragmentation of ECM proteins can recruit immune cells to the initial site of injury [31]. Newer evidence demonstrates that endothelial cell secreted interleukin (IL)– 6 potentially enhances CD14 receptor mediated recruitment of monocytes to the aortic wall [32]. Chemokine (C-C motif) ligand 3 secretion is also able to recruit monocytes that differentiate into macrophages in a high M1/M2 ratio [33]. Once inside the wall, infiltrating macrophages can cause further inflammation, recruitment, and ECM degradation through release of chemokines, cytokines, and MMPs [30]. In this way, a positive feedback loop forms to amplify inflammation in the aortic wall. Many more cytokines, chemokines, prostaglandins, and tumor necrosis factors have been associated with furthering AAA progression after initiation.

Normal remodeling in the ECM is done by MMP enzymes. MMPs are secreted endopeptidases that cleave collagen and elastin fibrils. Tight regulation of MMPs at multiple levels keeps the remodeling system in check. Key points of control include the conversion of zymogens to active MMPs, regulation of gene expression, and levels of tissue inhibitors of metalloproteinases (TIMPs). Increases in MMP activity excessively degrades elastin and collagen, thereby weakening the aortic wall [1,29]. Elastin fragmentation is commonly seen in the wall of mouse and human aneurysms. Data suggest that infiltrating immune cells are the largest source of MMPs in the aortic wall but it is controversial if MMPs are required for recruitment of these immune cells [34–36]. Overall, it is thought that extensive ECM degradation occurs in large part after initial recruitment of inflammatory cells. This remodeling contributes to loss of structural integrity in the aortic wall leading to dilation of the aorta and formation of an AAA.

VSMC dysfunction is another major factor in AAA etiology. Healthy VSMCs in the aorta hold a contractile phenotype to maintain vascular tone. However, these cells are not terminally differentiated and demonstrate plasticity by undergoing phenotypic switching due to inflammation early in AAA formation [8,37,38]. TGF- β is an important regulator of VSMC phenotype and function and thought to play a role in the switch seen in AAA [37,39]. Additionally, infiltrating macrophages can induce MMP secretion in VSMCs contributing to ECM degradation [40]. Large amounts of VSMC apoptosis are also seen in later stages of AAA progression and can be caused by loss of ECM structure and inflammatory molecules such as interleukins [8]. An increase in the synthetic phenotype

and death of VSMCs in the arterial wall contributes to further loss of the vessel's structural support leading to dilation of the aorta, thrombus formation, and potential aortic rupture [1,29].

Genetics also plays a role in AAA susceptibility [41]. One study comparing monozygotic and dizygotic twins suggested that genes accounted for 77% of the variance in development of AAAs in humans [42]. Family history increases the chance of developing an AAA, having a larger diameter aneurysm, and the possibility of small (< 5.0 cm) AAA rupture [1,2]. mRNA levels of numerous genes have been found to be altered in AAA tissue [1,2]. In addition, miRNAs have also been shown to have altered expression levels in this disease state [29]. Exactly how genetics and gene regulation influence disease progression in humans remains to be precisely defined. Polymorphisms in both MMP and TIMP genes have been identified as associated with AAA in humans. One such is a 5 A/6 A polymorphism in the promoter region of the MMP-3 gene where an insertion causes higher response to IL-1 [43,44].

3.2. Theories in human AAA development: atherosclerosis-driven and inflammation-driven

Two of the more widely acknowledged theories in human AAA pathogenesis and etiology are the atherosclerosis-driven theory and the inflammation-driven theory of AAA formation [1]. Historically, AAA was thought to be arterial remodeling in response to atherosclerosis [4, 45–47]. Hemodynamic stimuli triggered by the atherosclerotic plaque induces positive remodeling of the aorta, thereby increasing the vascular wall diameter [45]. This enlargement is compensatory for the changes in shear stress inside the aortic lumen [45,48]. In addition to being a risk factor in the disease, most AAA patients have some atherosclerosis present [1,2,49]. Despite the association observed between AAA and atherosclerosis, there is limited clinical evidence demonstrating causation due to a lack of correlation in the severity of these two diseases [1,4, 46,47,49–52]. They are now seen as both having multiple common risk factors instead of being interdependent. However, statin drugs (anti--hyperlipidemics) are associated with a reduction in AAA growth rate in humans [53,54].

The inflammation-driven (mediated) theory is another theory of AAA pathogenesis [1]. Numerous studies in recent years have solidified a role for inflammation in AAA development. There is significant evidence which suggests that persistent inflammation in the aorta is a primary driver of ECM degradation and VSMC apoptosis, completing the triad of AAA etiology (Fig. 2). In this way, key inflammatory markers are optimal targets for pharmacotherapy development. Pro-inflammatory cells such as T cells, B cells, and macrophages penetrate the aortic wall, emanating an inflammatory cascade in the tissues [1,27,29,30, 55–65]. Signaling molecules such as prostaglandins may increase the production of reactive oxygen species and promote apoptosis in aortic VSMCs, endothelial cells, and mast cells to trigger additional dysfunction [1,4,28,55,56,66–69]. Further, inflammatory cells can secrete MMPs that degrade the aortic wall's supportive matrix [30,56,68,70]. Numerous studies identify a role for inflammation in animal models of AAA but there is still debate as to whether inflammation is the trigger for or a response to

AAA formation in humans. Nevertheless, the inflammation-driven theory remains a leading concept in the field.

4. Animal models of AAA

Comprehensive reviews of mouse models of AAA are available [71–73]. To recapitulate, two more popular murine models used in AAA research are the elastase perfusion model and the angiotensin (Ang)II infusion model [73]. In the former, the abdominal aorta is locally infused with porcine pancreatic elastase (elastase or PPE). Severe degradation of the ECM occurs, triggering an inflammatory response and MMP upregulation [74,75]. A nondissecting AAA will typically form in two weeks, making this a suitable model for prevention studies. Marked macrophage infiltration and increased MMP expression seen in the aorta closely parallels human pathology [72,76]. One disadvantage of the elastase model is that the size and severity of the AAAs that form varies greatly [77].

In the AngII infusion model, AngII is administered for a prolonged period via a subcutaneous osmotic pump [78]. Genetically modified (*ApoE* −/− or *LDLR* −/−) mice are more susceptible to AAA formation with AngII infusion as compared to C57BL/6 mice [78,79]. The AngII infusion triggers a pro-inflammatory cascade that drives SMC apoptosis, ECM degradation, and aortic dilation [74,80,81]. An AAA will continue to expand until AngII infusion is discontinued, thereby making this model more appealing for intervention-based studies.

The AngII model appears to resemble human pathology more closely in some of the features it induces such as luminal expansion, thrombosis, ECM degradation, and prominent inflammatory markers [1,73,74, 80–82]. However, it shows dissection of the medial aorta, whereas the human condition presents as nondissecting AAA. It is also noted that these AAA form in the supra-renal region of the abdominal aorta while humans develop AAA in the infra-renal area. The AngII model is often considered more intense than other models, making it sometimes less favorable for pharmacology-related studies [72,73]. Like in the elastase model, a portion of the perfused mice will not form an AAA.

The calcium chloride ($CaCl_2$)-induced model of AAA is also frequently used. Here, $CaCl_2$ is applied directly to the infra-renal aorta [83]. Fragmentation of the elastin network is seen throughout the medial layer of the aortic wall and in concert with precipitation of calcium, triggers inflammatory infiltration and formation of a nondissecting AAA [72,83]. Subsequent dilation of the aorta is observed varying from 48% to 110% [72,83]. Severity of this model is mild and it does not present with two features commonly seen in human AAA, a thrombus and aortic rupture.

Advancement of the field has led to newer adaptations of classical AAA models (elastase, AngII, $CaCl_2$) in the pursuit of one that more closely resemble the human condition. For example, systemic neutralization of transforming growth factor β (TGF- β) with an antibody has been shown to exacerbate AAA formation in AngII-infused mice [71,84]. It has also been shown in the elastase model where it produced marked human features and a high rate of rupture within the first 14 days [85].

Several strains of transgenic mice can be used in AAA studies either alone or combined with other methods to induce AAA formation like that above. Blotchy mice have a mutation in the *Mottled* gene, causing ineffective cross-linking of ECM proteins and leading to spontaneous formation of aneurysms [86]. However, these are most frequently in the thoracic aorta. LOX deficient mice are also unable to effectively cross-link collagen and elastin. They spontaneously develop aneurysms as well but the knockout is associated with high perinatal death, restricting use as a model of AAA [87]. As such, the oral LOX inhibitor β3-aminopropionitriel (BAPN) is used in conjunction with the AngII or elastase models to create intense AAA [88].

Hyperlipidemic mice, specifically *ApoE−/−* and *LDLR−/−*, have a strong predisposition to AAA formation and can be combined with a high-fat diet (HFD) and/or chemical induction methods. Black6 mice (C57BL/6) are less responsive to AAA formation models compared to *ApoE−/−* and *LDLR−/−* strains [71,72]. The role of hyperlipidemia and atherosclerosis in AAA etiology is heavily debated. Even so, normo-lipidemic mice can still produce models of AAA like in the example of Nrf2 inactivated mice or mice with *HO-1−/−* promoted rupture [89,90].

All AAA models have advantages and disadvantages that should be considered when forming an experimental design. Elastase is a nondissecting model whereas AngII infusion is. A robust mouse model of AAA should reflect human characteristics such as fibrosis, thrombus, changes in hemodynamics, immune response, calcification, and rupture [76]. The field is still searching for a robust animal model of AAA that accurately captures the disease features seen in humans. Generally, rodent models develop relatively fast compared to the chronic and long-term progression of the human disease. How fast the model develops and what characteristics of human AAA it reflects should be considered in selecting a model for studies. In the case of experimental pharmacological studies, the intended timing of drug administration is also a factor in choosing a model.

5. Doxycycline as an investigational pharmacotherapy for the treatment of AAA

5.1. MMP inhibition by doxycycline

Doxycycline, a tetracycline antibiotic, has been of immense interest for the treatment of AAAs for some time, often thought to be a lead drug candidate for AAA treatment. A significant amount of work has been done to investigate its therapeutic potential in the area. Apart from its use as an antibiotic, doxycycline is an MMP inhibitor, reduces MMP expression and secretion, and regulates TIMPs at doses below that of its antimicrobial activity [7,91–94]. After this alternative action was discovered in the late 80′ s and early 90′ s, additional evidence grew for the involvement of MMPs in AAA formation [7,95–98]. Doxycycline has since been examined in various animal models of AAA based on the now established role of MMPs in AAA pathogenesis.

Justification for doxycycline’s use was based on its inhibitory effect of MMPs; Specifically, MMP-9 which is frequently considered one of the more important MMPs in AAA etiology

[29,99]. However, there is sparse information on exact IC_{50} values of doxycycline against MMPs. It is thought that the tetracycline class interacts with chelated Zn^{2+} in the catalytic domain of MMPs [100]. An IC_{50} for MMPs can vary depending on the specific mechanism of action (e.g. mRNA regulation, enzymatic inhibition, TIMPs), the MMP subtype, species, and origin cell-type (e.g. fibroblast, neutrophil, macrophage, smooth muscle cell). Those values for inhibition of MMP expression are believed to be lower than those needed for modulation of enzymatic activity [7,101,102]. To the best of our knowledge, a recent comprehensive review of doxycycline's pharmacokinetic characteristics pertaining to all human MMPs is not available. Supportive data exist for effective MMP regulation by doxycycline in animal models of AAA. Evidence for the ability to regulate AAA formation, inflammation, and apoptosis in animals, however, is mixed.

5.2. Preclinical studies with doxycycline

Since the initial animal study in 1996, a multitude of preclinical research has been conducted using doxycycline to alter AAA growth (Table 1). The vast majority of the published doxycycline murine studies have used a prevention-based treatment approach (i.e. doxycycline was administered starting prior to or with induction of AAA formation) [81, 93,103–106]. This may present an issue when the drug is eventually translated into the clinic because AAA is not prophylactically treated in humans. Relatively few murine studies have been conducted using doxycycline to treat an established AAA and those that have obtained mixed results [104,107].

In the first study to examine interventional treatment with doxycycline on AAA, Xie et al. infused *LDLR*−/− mice with AngII (1000 ng/kg/min) for 28 days [107]. Mice were then divided into control and treatment groups with equal aortic diameters after in vivo measurement with ultrasonography [107]. Doxycycline (100 mg/kg daily) was administered in drinking water to the treatment group for an additional 56 days [107]. At the study's conclusion there was no difference in maximal aortic diameter between the treatment and control groups [107].

A second 2017 study by Yu et al. started doxycycline administration (15 mg/kg daily, IP) in 6–8 week old C57BL/6 mice at 14 days post-elastase infusion [104]. On day 28, there was a significant difference in maximal aortic diameter and incidence between the doxycycline and control groups [104]. The study concluded that doxycycline treatment could reverse aortic dilation in these mice [104]. However, the only aortic diameter measurements described in the study are *ex vivo* measurements of harvested aortic tissue on day 28 [104]. Without confirmation of aortic diameter on the first day of doxycycline treatment (day 14), conclusions of reversing dilation cannot be substantiated.

5.3. Clinical studies with doxycycline

Several studies have been conducted around the world assessing doxycycline's effect on AAA growth in humans (Table 2). Conflicting data has been reported on MMPs between several of these human studies. A randomized, double-blind, placebo-controlled trial (NCT01756833) by Baxter et al. (2020), known as the N-TA^3CTrial, did not observe any significant changes in blood MMP-9 protein levels with twice daily 100

mg doxycycline for two years [108,109]. In another randomized, double-blind, placebo-controlled study, Ding et al. did not observe any significant changes in aneurysm wall MMP-9 zymogen or mRNA levels with doxycycline treatment at 100 mg/day for one month [110]. Alternatively, Lindeman et al. (a randomized, single-blind, placebo-controlled study) observed a significant effect of doxycycline (50, 100, and 300 mg/day for 2 weeks) on MMP-9 zymogen levels in aneurysm tissue (but not MMP-9 mRNA) [111]. In a prospective Phase II study, the group Baxter et al. (2002) saw a significant reduction in blood MMP-9 protein levels after a six month treatment with twice daily 100 mg doxycycline [112]. Finally, Curci et al. examined a treatment of 100 mg doxycycline twice daily for one week and found a significant decrease in MMP-9 protein and mRNA levels in aneurysm wall tissues [113].

These studies had differing lengths of treatment as well as different MMP-related measures. At a dose of 100 mg doxycycline twice daily, blood MMP-9 protein levels were reported to be significantly and not significantly decreased after six months and two years, respectively [108,112]. Zymogen and mRNA levels were also assessed in aneurysm wall tissue samples with mixed results [110,111,113]. Inter-study differences in factors such as patient medication adherence and heterogenicity of tissue samples are possible. Doxycycline's IC_{50} against MMP-9 varies for regulation of enzymatic activity, protein, zymogen, and mRNA levels; therefor, differing PK/PD profiles may be needed for each of these factors [7101,102].

Consistent results have also been found in these studies regarding inflammation related factors like C-reactive protein (CRP). The N-TA^{3}CTrial (NCT01756833) found a significant decrease in blood CRP levels with two years of 100 mg twice daily doxycycline treatment compared to the placebo group while another (randomized, double-blind, placebo-controlled pilot) study, using 150 mg/day doxycycline for three months, also found a reduction in blood CRP levels at a three month follow-up after treatment end [108,114].

Further, the Dutch PHAST (Pharmaceutical Aneurysm Stabilization Trial) study assessed 100 mg of doxycycline daily for 18 months and found that the drug treatment group had significantly larger AAA growth versus the placebo group ($P = 0.016$) [115]. The data were considered not clinically relevant on the basis that the growth was less than the protocol's pre-specified 1.3 mm/year definition [115]. The evaluated dose was based on previous studies showing a dose equivalence between 50 mg, 100 mg, and 300 mg doxycycline per day [111, 115]. Retrospective remarks regarding the trial propose that the dose may have been too low to see an effect [115]. There has been only one Clinicaltrials.gov registered clinical trial examining the effect of doxycycline treatment on AAA growth, the phase-IIb N-TA^{3}CT (NCT01756833) [109]. This placebo-controlled, double-blind trial of 261 randomized patients examined the efficacy of doxycycline intervention for the treatment of small AAAs [108]. In the study, patients with small infrarenal aneurysms (maximum transverse abdominal aorta diameter of 3.5–5.0 cm in men and 3.5–4.5 cm in women) were identified by computed tomography, and treated with either placebo or 100 mg BID, PO doxycycline [108,109]. After two years of either treatment, AAAs were again analyzed with computed tomography to compare changes in AAA sizes between the groups. The study found that there was no significant difference in the change in AAA size between the

placebo group and doxycycline treatment group after two years [108,109]. Notably, there were no reported AAA ruptures in the study during two-year follow-ups however, there were three deaths (2%) in the doxycycline group and four (3%) in the placebo group.

The prospective phase II study was conducted in 2002 with the 33 patients in the treatment group getting 100 mg BID, PO doxycycline for six months [112]. Results from this pilot study showed no significant effect of doxycycline treatment on AAA growth [112]. The phase-IIb N-TA^{3}CT was launched in May 2013, later concluding in January 2017 [109,116]. Additionally, we recall the two mouse studies that have used doxycycline as an intervention-based treatment for AAA [104, 107]. The later 2017 study by Yu et al. examined doxycycline treatment at 15 mg/kg IP every other day for two weeks, starting 14 days after AAA induction by elastase perfusion [104]. *Ex vivo* abdominal aorta measurements at day 28 showed a significant difference in maximal diameters between the treatment and control groups [104]. The earlier study in 2012 by Xie et al. used LDL receptor knock-out mice on a high fat diet with AngII infusion for 28 days to establish AAA [107]. 100 mg/kg/day doxycycline in drinking water was administered from day 28 (four weeks) through 12 weeks with continued AngII infusion [107]. *Ex vivo* abdominal aorta measurements at week 12 indicated no difference in maximal diameter versus control [107]. Potential differences in conclusions could stem from the two models used to establish AAA in these mice where the AngII AAA formed were more serious than those produced by elastase perfusion.

Primarily, the N-TA^{3}CT was first posted to the database on December 28th of 2012, actually starting in May 2013 [109]. Supportive animal data successfully using doxycycline as an intervention-based treatment comes from an elastase model in the 2017 Yu et al. study [104]. Until 2017, preclinical studies with doxycycline had only examined its ability to stop formation of an AAA, which it did successfully.

6. Experimental therapeutics for AAA treatment

Numerous drugs have been examined in clinical trials to halt AAA progression, but so far none have proved successful. To our best knowledge, all of the examined drugs have been repurposed FDA-approved pharmaceuticals – no novel drugs designed to treat AAA have made it to clinical trial thus far. Here we examine these treatments and for each drug, preclinical data and the clinical data available from the trial(s) (Table 3). Specifically, trials that are registered in the US National Library of Medicine's National Clinical Trials database on Clinicaltrials.gov. Further, we discuss evidence for each drug in relation to the AAA triad, inflammation, ECM degradation, and VSMC regulation. Fig. 1 depicts where each drug is categorized in terms of the primary target in regulating AAA formation and progression.

Both pemirolast (CRD007) and canakinumab (ACZ885) are included in Fig. 1 but are not discussed at length here. Primary targets of the drugs are readily published as mast cell stabilizer and human anti-IL-1β monoclonal antibody, respectively [13,14,117]. However, we have been unable to find information in animal models of AAA for either drug [13, 14]. Each has had one related clinical trial investigating its use as a treatment for AAA but neither clinical trial observed an effect on AAA growth [13,14,117,118].

6.1. Antihypertensives

High blood pressure is a modifiable risk factor for AAA. Individuals with AAA are also likely to have hypertension, so it is common for a patient with an AAA to be taking an antihypertensive. Several medications in this group have been examined in clinical trials to reduce AAA growth including amlodipine, perindopril, eplerenone, valsartan, telmisartan, and atenolol. The thought was that by reducing blood pressure, a risk factor, a reduction in AAA growth could be seen [119]. In addition to sartans, amlodipine may be one of the more studied anti-hypertensive in AAA treatment; it works by antagonizing trans-membrane calcium channels in VSMCs thereby reducing ion influx and contractility of the vascular muscles. Additionally, evidence has demonstrated its ability to slow atherosclerosis progression. Very limited and conflicting data shows antihypertensive drug influence on inflammation, ECM degradation, and VSMC dysfunction in relation to AAA.

Building off of a 1998 study showing amlodipine's ability to increase elastin degradation in vitro, Wilmink et al. sought to examine a possible association between antihypertensive drugs and AAA [120,121]. It was revealed that calcium channel blockers were an independent risk factor for AAA [121]. Since then, three groups have investigated the effect of amlodipine on mouse AAA progression. Two found that amlodipine administration was able to prevent AAA formation while one group concluded that it did not [119,122,123]. At a dose of 5 mg/kg/day, amlodipine prevented signs of AAA associated inflammation in aortic tissues in two independent studies. Significant macrophage infiltration and adventitial inflammation were suppressed in the AngII + BAPN (Black6 mice) and AngII + high fat diet (*LDLR* −/−) mouse models of AAA, respectively [119,122]. There was also no significant elastin fiber or medial degradation observed in the suprarenal aorta [119,122].

Conversely, a third study examining the effect of antihypertensive administration on AAA in mice found that amlodipine alone did not prevent AAA formation in the AngII model (*ApoE* −/−) [123]. Amlodipine (1 mg/kg/day) treated mice had comparable levels to untreated AngII mice in regards to increases in elastic lamellae degradation, macrophage accumulation, T-lymphocyte infiltration, apoptotic cells, MMP-2 activity, and rho-kinase activity [123]. Combination treatment of amlodipine (1 mg/kg/day) and atorvastatin (10 mg/kg/day) did prevent a lot of the listed increases. Differences in these results may be due to differing drug doses (5 mg/kg/day versus 1 mg/kg/day) and/or mouse models of AAA. There does not seem to be any studies examining an interventional treatment with an antihypertensive. It appears the amlodipine may be able to affect some aspects of inflammation and ECM degradation. There is incomplete data for other factors such as pro-inflammatory cytokines and other MMPs such as MMP-9. Of note, there is no data supporting VSMC regulation at the higher effective dose of amlodipine at 5 mg/kg/day. A combination therapy may be more promising than a monotherapy in this area.

In humans, the AARDVARK trial (NCT01118520) used amlodipine as a non-ACE (angiotensin converting enzyme) inhibitor comparison to perindopril (ACE inhibitor) in an effect on AAA growth. The study found no significant effect of either drug intervention on small AAA growth over 2 years [12]. Similarly, the TEDY trial found no effect of telmisartan (angiotensin receptor blocker) on slowing small AAA growth though, the study

was admittedly under powered [124]. Results are still pending for a study using eplerenone (NCT02345590) and one using valsartan and atenolol (NCT01904981) [125,126].

Originally, beta-blockers (mainly atenolol and propranolol) were thought to slow AAA growth in rats and humans [127–130]. More recent analyses have provided counter-evidence to the previous conclusion [131,132]. Pertinent clinical studies outside of Clinicaltrials.gov suggest no effect of propranolol on halting AAA growth rates [133–135]. The trials have been mostly underpowered and had high study withdrawal rates due to intolerance of propranolol. Findings from human propranolol studies are largely in agreement with those of other investigated anti-hypertensives.

6.2. Ticagrelor

An intraluminal thrombus is often present in human AAA. Suggestions have been made that it plays a role in progression of the disease but exactly how has not been decided. Ticagrelor (AZD6140) is a first-in-class antiplatelet therapy used to prevent blood clots in various disorders [136]. It reversibly binds to $P2Y_{12}$ receptors unlike is predecessors, thienopyridines, which bind irreversibly, at an IC_{50} = 0.005 μM against platelet aggregation *in vitro* [136]. The antagonism of the receptor works by preventing activation of ADP, but the interaction appears to be non-competitive, indicating different binding sites on the receptor [136]. $P2Y_{12}$ receptors are expressed on platelets to enhance aggregation and stabilization, triggering thrombus formation.

In a xenograft model of AAA in Lewis rats, ticagrelor was able to reduce aortic dilation compared to controls [137]. However, there appears to have been no significant preventative effect of drug on formation rates – at day 10, there was a 97.3% increase in external aneurysmal diameter from baseline compared to a 104.6% increase in the control group [137]. Drug treatment significantly reduced leukocyte and macrophage infiltration into the intraluminal thrombus but did not affect macrophage levels in the aneurysm wall. Also seen was a decrease in MMP-9 expression in both the thrombus and wall, a decrease in activation of pro-MMP-2 to MMP-2, and improvement in elastic fibers. There was an effect seen on SMC colonization in the thrombus but not the wall. From what we have found, there appears to be a large lack of knowledge in how ticagrelor affects AAA formation and progression.

6.3. Cyclosporin A

Cyclosporin A (CsA), an immunomodulator, is a potent regulator of both transforming growth factor beta 1 (TGF-β1) and calcineurin [138]. Once inside T cells it binds to cyclophilin where the complex then joins the catalytic subunit of calcineurin. This inhibition prevents the activation of downstream transcription factors that can activate T cells. However, CsA does not alter other pathways of T cell activation that are Ca^{2+} independent [138]. CsA is also able to induce the synthesis of TGF-β1 [138]. Data show a role for TGF-β1 in ECM remodeling and cell apoptosis in addition to being able to alter AAA growth [139,140].

Data built a case for CsA's application to AAA treatment through modulation of ECM degradation factors and VSMC apoptosis via TGF-β1. In one study, *in vitro* AAA patient tissue samples have shown decreased MMP-9 secretion after treatment with 1 μg/mL CsA

for 24 h [141]. In the mouse $CaCl_2$ model, CsA was able to preserve elastin structure in the aortic wall, prevent VSMC loss, and reduce MMP-9 levels. However, there was not any data related to inflammatory factors reported. Also examined in this manuscript was the effect of a 7-day intervention of CsA, two weeks after elastase perfusion in rats. Seen seven weeks after treatment end, was a decrease in macrophage density and T lymphocyte infiltration. This study appears to be the only one examining the effect of intervention based CsA treatment on AAA progression in animals.

Of interesting note, it is known that AngII induces TGF-β1 [142,143]. A paradox forms with the meeting of the AngII mouse model of AAA and CsA treatment for AAA. While we are not sure exactly how, AngII infusion is able to produce intense AAA in a mouse model. It becomes contemplative how CsA may be able to halt AAA formation through TGF-β1 while AngII is able to induce AAA formation. To our knowledge, there are no studies examining CsA treatment in the AngII mouse model of AAA. While the results of the single CsA-AAA clinical trial are currently unknown, data are inconsistent for CsA's holistic ability to regulate all three major pathways [1]. It can both inhibit T cell activation and recruit macrophages; its intended upregulation of TGF-β1 has the potential to both increase and decrease MMP levels [144–146]. There is also large toxicity concerns surrounding CsA administration.

6.4. Metformin

Aside from its anti-hyperglycemic mechanisms, metformin is an agonist of AMP-activated protein kinase (AMPK) [147]. A significant downstream target of activated AMPK is inhibition of mechanistic target of rapamycin (mTOR). Together, AMPK and mTOR are major regulators of VSMC function and macrophages, deeming metformin primarily a modulator of both inflammation and VSMC function in the context of AAA [10,147,148].

In animal models of AAA, there have been no studies examining interventional metformin treatment effect of AAA progression. Several studies though, have conducting experiments preventing AAA formation and progression with metformin. At the highest dose of 300 mg/kg/day in drinking water with the AngII mouse model, one study concluded no effect of metformin pretreatment on aortic diameter or AAA incidence after four weeks [149]. Another similar study found that metformin treatment at that dose, starting day 0 of AngII infusion, significantly reduced aortic diameter and AAA incidence compared to positive controls (infusion length not clear) [150]. However, there was also a significant difference between the metformin group and the negative control mice (without AngII infusion). While this study used *ApoE−/−* mice, Tyagi and colleagues, who found no significance, used *LDLR−/−* mice on a high fat diet (both with AngII infusion) [149,150]. This difference highlights a potential influence of blood glucose levels in AAA formation.

AAA *in vivo* data are consistent in metformin's ability to decrease macrophage infiltration into the aortic wall [10,147,148,150,151]. Interestingly, the effect of metformin on pro-inflammatory cytokines is conflicting. Yang et al. reported a significant reduction in IL-6, IL-1β, and TNF-α expression in mouse AAA tissues versus positive controls [150]. Alternatively, one group observed no significant difference between metformin treated mouse tissue and positive controls when comparing expression of IL-1β, IL-4, IL-16, and

INF-γ – in fact, an increase compared to PBS infused negative control mice was seen with metformin administration [152]. While these two studies both used the AngII infusion + *ApoE−/−* mouse model of AAA, one used 300 mg/kg/day in drinking water while the latter used 100 mg/kg/day with differing lengths of pretreatment, making comparative analysis difficult [150,152].

In the AngII infusion model in *ApoE−/−* mice, metformin administration in drinking water at both 100 mg/kg/day and 300 mg/kg/day has shown attenuation of VSMC less and aortic cell apoptosis after four weeks [148,150]. Concurrently, collagen and elastin were preserved in the aortic wall. These VSMC and ECM findings have been replicated in the elastase model of AAA [147,151]. On the other hand, conclusions regarding metformin administration's effect on MMPs in the AAA wall are not in agreement. Some groups have found a reduction in the activity and mRNA levels of both MMP-2 and MMP-9 while others did not see a significant change [10,148,150,152]. In fact, one group did not see any increase in MMP-2 expression in the AngII positive controls, something regularly seen in other studies [10].

The overall case to metformin's ability to regulate inflammation, VSMCs, and ECM remodeling in AAA murine models is somewhat mixed. The evidence for VSMC function and ECM structural proteins seems to be consistent. However, inflammation and MMP related data are conflicting. There are currently three enrolling clinical trials investigating metformin treatment and AAA growth [153–155].

6.5. Stem cells

Evidence of the use of stem cells for the treatment of AAA has been previously reviewed, with some new experiments since [156–163]. Mesenchymal stem cells (MSC) have been the most frequently examined stem cells for treatment of AAA. Overall, initial results have been encouraging to this end with the goal of using the anti-inflammatory properties of MSC. Indeed, many of these studies have shown a significant effect of treatment on inflammation, ECM degradation, and VSMC regulation [156]. However, there exists some evidence that stem cells may actually be proinflammatory in human AAA [164].

Prevention of AAA formation has been well studied in this area but only one intervention-based study has been reported [163]. After AngII infusion for 28 days, MSC treatment (1×10^6 bone marrow-MSC via tail vein injection) was able to significantly reduce aortic diameter at two and four weeks after a single administration [16]. However, this effect was lost at eight weeks where there was no difference in aortic diameter between the MSC treated and saline groups with 100% incidence in both groups. This suggests a possible temporal element to MSC treatment.

The only clinical trial examining this was terminated due to slow enrollment [16]. Application of stem cells for the treatment of AAA appears promising. However, there are many considerations that come before any advanced work in the area [165]. First, while MSC seem to be a popular choice among researchers, there are a plethora of stem cell types. MSC alone can be derived from numerous tissues such as bone marrow and adipose tissue. These are also not cells that are terminally differentiated, posing a particularly complex

problem involving controlling differentiation *in vivo*. The source of the cells must also be considered (autologous vs. allogenic). Finally, dosing of stem cells can be very broad. There are variations in route of administration, quantity of stem cells, frequency of dosing, and targeting to the site of action. As such, this area has great potential for further research.

6.6. Fibrates

The fibrate class of drugs, including fenofibrate, is used to treat hypercholesteremia or dyslipidemia through agonism of peroxisome proliferator-activated receptor alpha (PPARα) [166,167]. Mouse studies previously showed that fenofibrate is capable of reducing aortic dilation in AAA mice, potentially via downregulation of osteopontin [168–170]. Mice receiving fenofibrate also had significantly less macrophage infiltration in the aortic wall and apoptosis compared to controls in the AngII mouse model of AAA (*ApoE* −/− and *LDLR*−/− on HFD) [169,170]. Two recent human studies of note outside of Clinicaltrials.gov investigated the effect of fenofibrate administration on AAA growth rate, the Fenofibrate in the management of AbdoMinal aortic aneurysm (FAME)– 2 and FAME trials [167,171–173]. FAME-2 found that after six months of fenofibrate administration (145 mg daily) there was no significant effect on serum osteopontin levels or AAA growth rate compared to placebo in those with small AAA (35 – 49 mm) [171,172]. The subsequent FAME trial examined the same dose administered for two weeks prior to AAA surgery (≥ 50 mm) [167,173]. Samples collected at the time of surgery showed no significant effect of fenofibrate on osteopontin concentrations in the aortic wall or serum as well as infiltrating macrophage levels in the aortic wall (primary endpoints) [167]. Additionally, no difference was seen in tissue MMP-9 and MMP-2 activity or serum levels [167].

7. Translation of preclinical studies

A wide range of drugs have been examined in Clinicaltrials.gov registered clinical trials for the treatment of AAA (Table 3). While the majority of these are still ongoing, it is important to examine the translatability of a drug's preclinical and clinical results in the context of AAA (Table 3). For two of the drugs with available results, amlodipine and ticagrelor's preclinical studies showed mixed results but failed to translate to clinical efficacy [11,12,15,119,122,123,137,174]. Notably, preclinical work for both drugs was solely focused on AAA prevention and not interventional treatment.

Limited data exists demonstrating efficacy for a drug in halting the growth of an established AAA. Of the research reported in Table 3, two drugs had intervention-based treatment data in preclinical models before going into clinical trials, a stem cell treatment and a cyclosporin (e) A study [141,163]. The 2014 murine stem cell therapy investigation did not show any difference between the treatments with 100% AAA incidence in both groups at eight weeks [163]. In the CsA study, there was a 14% increase in the external aortic diameter compared to 45% in the control group, a significant difference [141].

While the difference between AAA size of the above treatment groups may be significant, it is not necessarily clinically relevant. In the clinic, ≥ 50% expansion of the aorta is considered an aneurysm. Several stem cell therapy studies have shown the treatment group had an average expansion of ≥ 50% or a high rate of incidence but the findings

were still significantly less compared to the control group [157,159,175, 176]. One 2013 study reported an 82% maximum aortic dilation in the treatment group compared to 140% in the control group [176]. While this finding was statistically significant, it is not necessarily clinically relevant. The treatment group still had an aortic expansion of over 50%, classifying it as an AAA. It may be a relevant finding when compared to the control group of the study but when translated, it does not provide effective treatment to those in the clinic.

Doxycycline progressed into clinical testing with mixed results for its ability to limit the progression of an already formed aneurysm with intervention-based treatments. The drug was potentially unproven in its ability to halt further growth of an AAA. At this time, all human investigations into the effects of doxycycline on AAA have not shown a clinically relevant effect on halting further aneurysm growth (Table 2).

Final results from the N-TA^{3}CT were published recently in 2020 [108]. Supportive animal data cited came from three encouraging doxycycline studies that used the calcium chloride application model and elastase infusion model of AAA [93,94,177]. The N-TA^{3}CT's concluding data showing lack of effectiveness of doxycycline in the study grants space for a retrospective comparison of different AAA animal models to determine which model most closely reproduces the clinical findings of the trial [108]. As stated previously, the majority of animal studies examining the effects of doxycycline on AAAs utilized a pretreatment methodology. However, the two studies in mice previously mentioned, one using elastase-induced AAAs (Yu et al.) and the other using AngII-induced AAAs (Xie et al.), examined the effect of doxycycline treatment that was begun after AAA formation had been initiated [104,107]. This therapeutic approach is what was used in the clinical trial. Of these two mouse studies, the AngII-induced AAA model produced results more closely aligned with the inability of doxycycline to reduce AAA progression seen in N-TA^{3}CT [107,108]. Going forward, this may contribute to our growing understanding of which animal AAA model to use to obtain better translational results [3].

One of the leading ideas of AAA etiology is the inflammation-driven theory and a majority of clinically investigated drugs for the disease have attempted to target inflammation in some capacity. Doxycycline's intended mechanism of action is altering MMP production, secretion, and/or activity [178]. A limited number of animal studies using doxycycline (Table 1) have examined inflammatory factors alongside changes in AAA size [104,105,179]. The collective data show that with doxycycline administration there is a significant change in inflammatory factor regulation in correlation with reduction in AAA sizes [104,105, 179]. To this end, it is possible that positive effects we may see from doxycycline on AAA size in preclinical models may not be due to its MMP-related activity but anti-inflammatory actions.

Although doxycycline is not effective for reducing the progression of fully formed AAAs in the AngII-induced AAA model, other reports have described beneficial effects of other treatments initiated after the formation of AngII-induced AAAs in mice. In one of these studies, after an AngII infusion was completed, an 8-week treatment with an inhibitor of c-Jun N-terminal kinase (JNK) was begun [180]. This study showed that the JNK inhibitor

treatment significantly decreased the internal diameter of the abdominal aorta, as compared to 8 weeks of vehicle treatment [180]. However, the mean internal abdominal aorta diameter of the 8-week vehicle-treated mice was not larger than the mean internal abdominal aorta diameter of the same mice at the end of the AngII infusion before vehicle treatment [180]. Therefore, in this study, there was no increase in AAA size during the 8-week vehicle treatment, thereby indicating that in the absence of continued AngII infusion the effect of the drug treatment would not be the result of inhibiting AAA progression, but rather, an increase in regression of AAAs that do not enlarge [180].

In contrast to examining the effects of drug treatment initiated after the completion of AngII infusion, some studies have examined drug treatment that starts after the formation of AAAs with continued AngII infusion throughout the drug administration [180]. For example, one of us has previously reported that treatment with the cyclooxygenase (COX)–2 inhibitor celecoxib significantly reduced progression of AngII-induced AAAs in both hyperlipidemic and non-hyperlipidemic mice [181,182]. COX-2 inhibitor treatment that was started one week after the initiation of a six week AngII infusion significantly decreased AAA incidence, external abdominal aorta diameter, and death resulting from aortic rupture [181]. Furthermore, the study also examined the effect of COX-2 inhibitor treatment that was begun on fully-formed AAAs three weeks after the start of AngII infusion [181]. Even though significant AAA formation had occurred before COX-2 inhibitor treatment was started, the COX-2 inhibitor treatment significantly decreased AAA incidence and external abdominal aorta diameter, when analyzed after completion of an eight-week AngII infusion [181].

8. Future perspectives

The aforementioned issues highlight the importance of both anti-inflammatory drug targets and translational work in the search for an AAA treatment. While foundational studies and the capability of a drug to prevent formation is crucial, it must also be shown that it can affect late-stage AAA [183]. Prevention is important but intervention-based treatments are the most common cases in the clinical setting. These discovered AAAs are often at high-risk of rupture and a greater concern than prophylactic treatment. Further, it seems that the AngII mouse model of AAA is more reflective of the clinical success of a drug candidate.

Cumulative data has constructed a theorem that the prostaglandin E_2 (PGE_2) pathway may be a main contributor of AAAs [184–186]. In human AAAs, COX-2 expression is associated with a significant increase in the production of PGE_2, which has been proposed to contribute to human AAA progression [187,188]. The enzyme down-stream of COX-2 that is primarily responsible for the synthesis of PGE_2, which contributes to the formation of AngII-induced AAAs in mice, is microsomal prostaglandin E synthase-1 (mPGES-1) [189]. PGE_2 and its EP_4 receptor are upregulated in AAA with evidence demonstrating modulation of this pathway's influence on AAA formation, ECM degradation, and VSMC apoptosis [184,186,190,191]. Because of the adverse effects associated with the use of non-selective and COX-2-selective inhibitors, mPGES-1 has been proposed as an alternative target for the development of novel anti-inflammatory agents which lack the adverse effects of COX inhibitors [192–196]. The findings of significant PGE_2 production in human AAAs, together

with the experimental effectiveness of mPGES-1 inhibition for the modulation of AAA progression in mouse models, suggest that mPGES-1 may provide an effective target for the treatment of AAAs in humans without the adverse effects of COX inhibitors [181, 182,187–189].

The inflammation-driven theory is becoming more well-regarded and the field is starting to consider the growing body of evidence for a novel anti-inflammatory treatment of AAA [1,28,29,61,197]. Inflammation has support as potentially the “conductor” of AAA, “orchestrating” ECM degradation and pro-apoptotic pathways. It would be interesting to develop novel anti-inflammatory drug candidates to such end. Specifically, we find the growing evidence for microsomal mPGES-1 as a drug target for AAA encouraging [29,186,188,198,199]. However, targeting inflammation alone is not enough. Current work supports the idea that PGE_2 may be a critical central biomarker in inflammation. mPGES-1 and PGE_2 have a body of evidence demonstrating the ability to regulate inflammation, VSMC dysfunction, and ECM remodeling. Together, this makes the target appealing in its potential to tackle all three of the major pathways in AAA formation.

9. Conclusions

We have discussed drugs examined to treat AAA and their studies done in both humans and animals. There was a focus on the data present for each drug’s ability to modulate three hallmark features of AAA: inflammation, VSMC regulation, and remodeling of the ECM. We found that these drugs had mixed evidence for these three aspects and have considered why they did not show efficacy in their respective clinical trials. Evidence lends to an anti-inflammatory drug holding great potential for the treatment of AAA. Drug targets seen in the clinic show a trend towards anti-inflammatory mechanisms of action in the pursuit of a pharmacotherapy. It seems that identifying a central biomarker of inflammation that is proven to also effectively modulate ECM degradation and VSMC dysfunction is of high importance. Subsequently, this may be a very promising target for the treatment of AAA.

Intervention-based drug treatment is highly under-utilized in pre-clinical work. For the vast majority of drugs examined, crucial animal data is not robust in showing an ability to prevent further growth of an AAA. This approach being the application of a successful AAA drug in the clinic setting where growth of an established AAA needs to be halted. To our best knowledge, all drugs examined in the clinic had two or less preclinical studies examining an interventional drug treatment (doxycycline was the only one with two) – some had none. Additionally, we do not have an animal model that completely represents human AAA pathology. However, it seems that the AngII infusion model is most reflective of results later obtained in the clinic. Inhibiting PGE_2 formation, mainly with an mPGES-1 inhibitor, may be one of the leading drug targets for AAA treatment. Accruing evidence for an mPGES-1 inhibitor in altering AAA formation is backed by data exhibiting the target’s ability to alter the other two crucial pathways in AAA etiology.

Funding

This work was supported in part by the funding of the Molecular Modeling and Biopharmaceutical Center at the University of Kentucky College of Pharmacy; the National Science Foundation [Grant CHE-1111761]; and the National Institutes of Health [Grant P20 GM130456].

Data Availability

No data was used for the research described in the article.

Abbreviations:

AAA	abdominal aortic aneurysms
ACE	angiotensin converting enzyme
AMPK	AMP-activated protein kinase
AngII	angiotensin II
ApoE	apolipoprotein E
Black6	C57BL/6 J
COX	cycloxygenase
CRP	C-reactive protein
ECM	extra cellular matrix
EVAR	endovascular aneurysm repair
HFD	high fat diet
IL	interleukin
INF	interferon
LDLR	low-density lipoprotein receptor
MMP	matrix metalloproteinase
mPGES-1	microsomal prostaglandin E synthase 1
MSC	mesenchymal stem cells
PGE_2	prostaglandin E_2
PPARα	peroxisome proliferator-activated receptor alpha
TGF	transforming growth factor
TIMPs	tissue inhibitors of metalloproteinases
TNF	tumor necrosis factor

VSMC	vascular smooth muscle cells

REFERENCES

[1]. Golledge J, Abdominal aortic aneurysm: update on pathogenesis and medical treatments, Nat. Rev. Cardiol 16 (4) (2019) 225–242, 10.1038/s41569-018-0114-9. [PubMed: 30443031]

[2]. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G, Understanding the pathogenesis of abdominal aortic aneurysms, Expert Rev. Cardiovasc Ther 13 (9) (2015) 975–987, 10.1586/14779072.2015.1074861. [PubMed: 26308600]

[3]. Lindeman JH, Matsumura JS, Pharmacologic management of aneurysms, Circ. Res 124 (4) (2019) 631–646, 10.1161/CIRCRESAHA.118.312439. [PubMed: 30763216]

[4]. Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM, Pathophysiology and epidemiology of abdominal aortic aneurysms, Nat. Rev. Cardiol 8 (2) (2011) 92–102, 10.1038/nrcardio.2010.180. [PubMed: 21079638]

[5]. Lederle FA, Johnson GR, Wilson SE, Ballard DJ, Jordan WD Jr., Blebea J, Littooy FN, Freischlag JA, Bandyk D, Rapp JH, Salam AA, Veterans affairs cooperative study, i., rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair, JAMA 287 (22) (2002) 2968–2972, 10.1001/jama.287.22.2968. [PubMed: 12052126]

[6]. Aggarwal S, Qamar A, Sharma V, Sharma A, Abdominal aortic aneurysm: a comprehensive review, Exp. Clin. Cardiol 16 (1) (2011) 11–15. [PubMed: 21523201]

[7]. Hanemaaijer R, van Lent N, Sorsa T, Salo T, Yrj O, Konttinen T, Lindeman JH, Inhibition of matrix metalloproteinases (MMPs) by tetracyclines, in: Nelson M, Hillen W, Greenwald AA (Eds.), Tetracyclines in Biology, Chemistry and Medicine, Birkhauser Verlag, Switzerland, 2001, pp. 267–281.

[8]. Lu H, Du W, Ren L, Hamblin MH, Becker RC, Chen YE, Fan Y, Vascular smooth muscle cells in aortic aneurysm: from genetics to mechanisms, J. Am. Heart Assoc 10 (24) (2021), e023601, 10.1161/JAHA.121.023601. [PubMed: 34796717]

[9]. De Rango P, Farchioni L, Fiorucci B, Lenti M, Diabetes and abdominal aortic aneurysms, Eur. J. Vasc. Endovasc. Surg 47 (3) (2014) 243–261, 10.1016/j.ejvs.2013.12.007. [PubMed: 24447529]

[10]. Vasamsetti SB, Karnewar S, Kanugula AK, Thatipalli AR, Kumar JM, Kotamraju S, Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: potential role in atherosclerosis, Diabetes 64 (6) (2015) 2028–2041, 10.2337/db14-1225. [PubMed: 25552600]

[11]. Wanhainen A, Mani K, Kullberg J, Svensjo S, Bersztel A, Karlsson L, Holst J, Gottsater A, Linne A, Gillgren P, Langenskiold M, Hultgren R, Roy J, Gilgen NP, Ahlstrom H, Lederle FA, Bjorck M, The effect of ticagrelor on growth of small abdominal aortic aneurysms-a randomized controlled trial, Cardiovasc Res 116 (2) (2020) 450–456, 10.1093/cvr/cvz133. [PubMed: 31135888]

[12]. Kiru G, Bicknell C, Falaschetti E, Powell J, Poulter N, An evaluation of the effect of an angiotensin-converting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: a randomised placebo-controlled trial (AARDVARK), Health Technol. Assess 20 (59) (2016) 1–180, 10.3310/hta20590.

[13]. Medicine, U.N.L. o, CRD007 for the Treatment of Abdominal Aorta Aneurysm (The AORTA Trial). ⟨https://clinicaltrials.gov/ct2/show/NCT01354184⟩: Clinicaltrials.gov, 2011.

[14]. Medicine, U.N.L. o, ACZ885 for the Treatment of Abdominal Aortic Aneurysm (AAA). ⟨https://clinicaltrials.gov/ct2/show/NCT02007252⟩: Clinicaltrials.gov, 2013.

[15]. Medicine, U.N.L. o, The Efficacy of Ticagrelor on Abdominal Aortic Aneurysm (AAA) Expansion. ⟨https://ClinicalTrials.gopev/show/NCT02070653⟩: Clinicaltrials.gov, 2014.

[16]. Medicine, U.N.L. o, Safety and Efficacy of Allogeneic MSCs in Promoting T-regulatory Cells in Patients With Small Abdominal Aortic Aneurysms. ⟨https://ClinicalTrials.gov/show/NCT02846883⟩: Clinicaltrials.gov 2016.

[17]. Stather PW, Sidloff DA, Rhema IA, Choke E, Bown MJ, Sayers RD, A review of current reporting of abdominal aortic aneurysm mortality and prevalence in the literature, Eur. J. Vasc. Endovasc. Surg 47 (3) (2014) 240–242, 10.1016/j.ejvs.2013.11.007. [PubMed: 24368205]

[18]. Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, Gelijns AC, Greco G, Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals, J. Vasc. Surg 52 (3) (2010) 539–548, 10.1016/j.jvs.2010.05.090. [PubMed: 20630687]

[19]. Chung J, Epidemiology, risk factors, pathogenesis, and natural history of abdominal aortic aneurysm. In UpToDate, Post TW, Ed. UpToDate: Waltham, MA, 2020.

[20]. Guirguis-Blake JM, Beil TL, Senger CA, Coppola EL, Primary care screening for abdominal aortic aneurysm: updated evidence report and systematic review for the us preventive services task force, JAMA 322 (22) (2019) 2219–2238, 10.1001/jama.2019.17021. [PubMed: 31821436]

[21]. Morioka C, Meng F, Taira R, Sayre J, Zimmerman P, Ishimitsu D, Huang J, Shen L, El-Saden S, Automatic classification of ultrasound screening examinations of the abdominal aorta, J. Digit Imaging 29 (6) (2016) 742–748, 10.1007/s10278-016-9889-6. [PubMed: 27400914]

[22]. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, Mastracci TM, Mell M, Murad MH, Nguyen LL, Oderich GS, Patel MS, Schermerhorn ML, Starnes BW, The society for vascular surgery practice guidelines on the care of patients with an abdominal aortic aneurysm, e2, J. Vasc. Surg 67 (1) (2018) 2–77, 10.1016/j.jvs.2017.10.044. [PubMed: 29268916]

[23]. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM, Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial, Lancet 388 (10058) (2016) 2366–2374, 10.1016/s0140-6736(16)31135-7. [PubMed: 27743617]

[24]. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, Buskens E, Grobbee DE, Blankensteijn JD, Dutch randomized endovascular aneurysm management trial, G., A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms, N. Engl. J. Med 351 (16) (2004) 1607–1618, 10.1056/NEJMoa042002. [PubMed: 15483279]

[25]. Lederle FA, Kyriakides TC, Stroupe KT, Freischlag JA, Padberg FT Jr., Matsumura JS, Huo Z, Johnson GR, O.V.A.C.S. Group, Open versus endovascular repair of abdominal aortic aneurysm, N. Engl. J. Med 380 (22) (2019) 2126–2135, 10.1056/NEJMoa1715955. [PubMed: 31141634]

[26]. United Kingdom ETI, Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ, Endovascular versus open repair of abdominal aortic aneurysm, N. Engl. J. Med 362 (20) (2010) 1863–1871, 10.1056/NEJMoa0909305. [PubMed: 20382983]

[27]. Yoshimura K, Morikage N, Nishino-Fujimoto S, Furutani A, Shirasawa B, Hamano K, Current status and perspectives on pharmacologic therapy for abdominal aortic aneurysm, Curr. Drug Targets 19 (11) (2018) 1265–1275, 10.2174/1389450119666171227223331. [PubMed: 29284386]

[28]. Nanda S, Sharma SG, Longo S, Molecular targets and abdominal aortic aneurysms, Recent Pat. Cardiovasc Drug Disco 4 (2) (2009) 150–159, 10.2174/157489009788452940.

[29]. Lu H, Rateri DL, Bruemmer D, Cassis LA, Daugherty A, Novel mechanisms of abdominal aortic aneurysms, Curr. Atheroscler. Rep 14 (5) (2012) 402–412, 10.1007/s11883-012-0271-y. [PubMed: 22833280]

[30]. Raffort J, Lareyre F, Clement M, Hassen-Khodja R, Chinetti G, Mallat Z, Monocytes and macrophages in abdominal aortic aneurysm, Nat. Rev. Cardiol 14 (8) (2017) 457–471, 10.1038/nrcardio.2017.52. [PubMed: 28406184]

[31]. Hance KA, Tataria M, Ziporin SJ, Lee JK, Thompson RW, Monocyte chemotactic activity in human abdominal aortic aneurysms: role of elastin degradation peptides and the 67-kD cell surface elastin receptor, J. Vasc. Surg 35 (2) (2002) 254–261, 10.1067/mva.2002.120382. [PubMed: 11854722]

[32]. Blomkalns AL, Gavrila D, Thomas M, Neltner BS, Blanco VM, Benjamin SB, McCormick ML, Stoll LL, Denning GM, Collins SP, Qin Z, Daugherty A, Cassis LA, Thompson RW, Weiss RM, Lindower PD, Pinney SM, Chatterjee T, Weintraub NL, CD14 directs adventitial macrophage precursor recruitment: role in early abdominal aortic aneurysm formation, J. Am. Heart Assoc 2 (2) (2013), e000065, 10.1161/JAHA.112.000065. [PubMed: 23537804]

[33]. Ishida Y, Kuninaka Y, Nosaka M, Kimura A, Taruya A, Furuta M, Mukaida N, Kondo T, Prevention of CaCl2-induced aortic inflammation and subsequent aneurysm formation by the CCL3-CCR5 axis, Nat. Commun 11 (1) (2020) 5994, 10.1038/s41467-020-19763-0.

[34]. Reeps C, Pelisek J, Seidl S, Schuster T, Zimmermann A, Kuehnl A, Eckstein H-H, Inflammatory infiltrates and neovessels are relevant sources of MMPs in abdominal aortic aneurysm wall, Pathobiology 76 (5) (2009) 243–252, 10.1159/000228900. [PubMed: 19816084]

[35]. Gong Y, Hart E, Shchurin A, Hoover-Plow J, Inflammatory macrophage migration requires MMP-9 activation by plasminogen in mice, J. Clin. Investig 118 (9) (2008) 3012–3024, 10.1172/jci32750. [PubMed: 18677407]

[36]. Xiong W, Knispel R, Mactaggart J, Greiner TC, Weiss SJ, Baxter BT, Membrane-type 1 matrix metalloproteinase regulates macrophage-dependent elastolytic activity and aneurysm formation in vivo, J. Biol. Chem 284 (3) (2009) 1765–1771, 10.1074/jbc.m806239200. [PubMed: 19010778]

[37]. Petsophonsakul P, Furmanik M, Forsythe R, Dweck M, Schurink GW, Natour E, Reutelingsperger C, Jacobs M, Mees B, Schurgers L, Role of vascular smooth muscle cell phenotypic switching and calcification in aortic aneurysm formation, Arterioscler., Thromb., Vasc. Biol 39 (7) (2019) 1351–1368, 10.1161/atvbaha.119.312787. [PubMed: 31144989]

[38]. Ailawadi G, Moehle CW, Pei H, Walton SP, Yang Z, Kron IL, Lau CL, Owens GK, Smooth muscle phenotypic modulation is an early event in aortic aneurysms, J. Thorac. Cardiovasc. Surg 138 (6) (2009) 1392–1399, 10.1016/j.jtcvs.2009.07.075. [PubMed: 19931668]

[39]. Chen P-Y, Qin L, Li G, Malagon-Lopez J, Wang Z, Bergaya S, Gujja S, Caulk AW, Murtada S-I, Zhang X, Zhuang ZW, Rao DA, Wang G, Tobiasova Z, Jiang B, Montgomery RR, Sun L, Sun H, Fisher EA, Gulcher JR, Fernandez-Hernando C, Humphrey JD, Tellides G, Chittenden TW, Simons M, Smooth muscle cell reprogramming in aortic aneurysms, Cell Stem Cell 26 (4) (2020) 542–557.e11, 10.1016/j.stem.2020.02.013. [PubMed: 32243809]

[40]. Hadi T, Boytard L, Silvestro M, Alebrahim D, Jacob S, Feinstein J, Barone K, Spiro W, Hutchison S, Simon R, Rateri D, Pinet F, Fenyo D, Adelman M, Moore KJ, Eltzschig HK, Daugherty A, Ramkhelawon B, Macrophage-derived netrin-1 promotes abdominal aortic aneurysm formation by activating MMP3 in vascular smooth muscle cells, Nat. Commun 9 (1) (2018), 10.1038/s41467-018-07495-1.

[41]. Estrelinha M, Hinterseher I, Kuivaniemi H, Gene expression studies in human abdominal aortic aneurysm, Rev. Vasc. Med 2 (3) (2014) 77–82, 10.1016/j.rvm.2014.02.001.

[42]. Joergensen TM, Christensen K, Lindholt JS, Larsen LA, Green A, Houlind K (Eds.), Eur. J. Vasc. Endovasc. Surg 52 (1) (2016) 41–46, 10.1016/j.ejvs.2016.03.012. [PubMed: 27107486]

[43]. Saracini C, Bolli P, Sticchi E, Pratesi G, Pulli R, Sofi F, Pratesi C, Gensini GF, Abbate R, Giusti B, Polymorphisms of genes involved in extracellular matrix remodeling and abdominal aortic aneurysm, J. Vasc. Surg 55 (1) (2012) 171–179.e2, 10.1016/j.jvs.2011.07.051. [PubMed: 22094117]

[44]. Deguara J, Burnand KG, Berg J, Green P, Lewis CM, Chinien G, Waltham M, Taylor P, Stern RF, Solomon E, Smith A, An increased frequency of the 5A allele in the promoter region of the MMP3 gene is associated with abdominal aortic aneurysms, Hum. Mol. Genet 16 (24) (2007) 3002–3007, 10.1093/hmg/ddm258. [PubMed: 17875574]

[45]. Ward MR, Pasterkamp G, Yeung AC, Borst C, Arterial remodeling. Mechanisms and clinical implications, Circulation 102 (10) (2000) 1186–1191, 10.1161/01.cir.102.10.1186. [PubMed: 10973850]

[46]. Golledge J, Norman PE, Atherosclerosis and abdominal aortic aneurysm: cause, response, or common risk factors? Arterioscler. Thromb. Vasc. Biol 30 (6) (2010) 1075–1077, 10.1161/ATVBAHA.110.206573. [PubMed: 20484703]

[47]. Toghill BJ, Saratzis A, Bown MJ, Abdominal aortic aneurysm-an independent disease to atherosclerosis? Cardiovasc Pathol 27 (2017) 71–75, 10.1016/j.carpath.2017.01.008. [PubMed: 28189002]

[48]. Boyd AJ, Kuhn DC, Lozowy RJ, Kulbisky GP, Low wall shear stress predominates at sites of abdominal aortic aneurysm rupture, J. Vasc. Surg 63 (6) (2016) 1613–1619, 10.1016/j.jvs.2015.01.040. [PubMed: 25752691]

[49]. Wassef M, Upchurch GR Jr., Kuivaniemi H, Thompson RW, Tilson MD 3rd, Challenges and opportunities in abdominal aortic aneurysm research, J. Vasc. Surg 45 (1) (2007) 192–198, 10.1016/j.jvs.2006.09.004. [PubMed: 17210410]

[50]. Takagi H, Umemoto T, Group A, Association of peripheral artery disease with abdominal aortic aneurysm growth, J. Vasc. Surg 64 (2) (2016) 506–513, 10.1016/j.jvs.2016.01.059. [PubMed: 27316409]

[51]. Kaschina E, Scholz H, Steckelings UM, Sommerfeld M, Kemnitz UR, Artuc M, Schmidt S, Unger T, Transition from atherosclerosis to aortic aneurysm in humans coincides with an increased expression of RAS components, Atherosclerosis 205 (2) (2009) 396–403, 10.1016/j.atherosclerosis.2009.01.003. [PubMed: 19193379]

[52]. Johnsen SH, Forsdahl SH, Singh K, Jacobsen BK, Atherosclerosis in abdominal aortic aneurysms: a causal event or a process running in parallel? The Tromso study, Arterioscler. Thromb. Vasc. Biol 30 (6) (2010) 1263–1268, 10.1161/ATVBAHA.110.203588. [PubMed: 20360536]

[53]. Salata K, Syed M, Hussain MA, d Mestral C, Greco E, Mamdani M, Tu JV, Forbes TL, Bhatt DL, Verma S, Al-Omran M, Statins reduce abdominal aortic aneurysm growth, rupture, and perioperative mortality: a systematic review and meta-analysis, J. Am. Heart Assoc 7 (19) (2018), e008657, 10.1161/JAHA.118.008657. [PubMed: 30371297]

[54]. Takagi H, Matsui M, Umemoto T, A meta-analysis of clinical studies of statins for prevention of abdominal aortic aneurysm expansion, J. Vasc. Surg 52 (6) (2010) 1675–1681, 10.1016/j.jvs.2010.04.082. [PubMed: 20638223]

[55]. Dobrin PB, Baumgartner N, Anidjar S, Chejfec G, Mrkvicka R, Inflammatory aspects of experimental aneurysms. Effect of methylprednisolone and cyclosporine, Ann. N. Y Acad. Sci 800 (1996) 74–88, 10.1111/j.1749-6632.1996.tb33300.x. [PubMed: 8958984]

[56]. Wu QY, Cheng Z, Zhou YZ, Zhao Y, Li JM, Zhou XM, Peng HL, Zhang GS, Liao XB, Fu XM, A novel STAT3 inhibitor attenuates angiotensin II-induced abdominal aortic aneurysm progression in mice through modulating vascular inflammation and autophagy, Cell Death Dis 11 (2) (2020) 131, 10.1038/s41419-020-2326-2. [PubMed: 32071300]

[57]. Suehiro C, Suzuki J, Hamaguchi M, Takahashi K, Nagao T, Sakaue T, Uetani T, Aono J, Ikeda S, Okura T, Okamura H, Yamaguchi O, Deletion of interleukin-18 attenuates abdominal aortic aneurysm formation, Atherosclerosis 289 (2019) 14–20, 10.1016/j.atherosclerosis.2019.08.003. [PubMed: 31445353]

[58]. Liu Q, Wang Q, Li H, Embelin inhibits abdominal aortic aneurysm through decreasing IL6induced STAT3 and NFkappaB inactivation, Mol. Med Rep 18 (2) (2018) 2365–2372, 10.3892/mmr.2018.9221. [PubMed: 29956759]

[59]. Batra R, Suh MK, Carson JS, Dale MA, Meisinger TM, Fitzgerald M, Opperman PJ, Luo J, Pipinos II, Xiong W, Baxter BT, IL-1beta (Interleukin-1beta) and TNF-alpha (Tumor Necrosis Factor-alpha) impact abdominal aortic aneurysm formation by differential effects on macrophage polarization, Arterioscler. Thromb. Vasc. Biol 38 (2) (2018) 457–463, 10.1161/ATVBAHA.117.310333. [PubMed: 29217508]

[60]. Businaro R, Azzara G, Cannizzaro C, Coris M, Di Gioia C, Di Cristofano C, Massoni F, Cassese M, Ricci S, Immunolocalization of pro-inflammatory cytokines within human aortic aneurysms, Ital. J. Anat. Embryol (2013) 118, 10.13128/IJAE-13940.

[61]. Lindeman JH, Rabelink TJ, van Bockel JH, Immunosuppression and the abdominal aortic aneurysm: doctor Jekyll or Mister Hyde? Circulation 124 (18) (2011) e463–e465, 10.1161/CIRCULATIONAHA.110.008573. [PubMed: 22042930]

[62]. Usui F, Shirasuna K, Kimura H, Tatsumi K, Kawashima A, Karasawa T, Yoshimura K, Aoki H, Tsutsui H, Noda T, Sagara J, Taniguchi S, Takahashi M, Inflammasome activation by mitochondrial oxidative stress in macrophages leads to the development of angiotensin II-induced aortic aneurysm, Arterioscler. Thromb. Vasc. Biol 35 (1) (2015) 127–136, 10.1161/ATVBAHA.114.303763. [PubMed: 25378412]

[63]. Erhart P, Cakmak S, Grond-Ginsbach C, Hakimi M, Bockler D, Dihlmann S, Inflammasome activity in leucocytes decreases with abdominal aortic aneurysm progression, Int J. Mol. Med 44 (4) (2019) 1299–1308, 10.3892/ijmm.2019.4307. [PubMed: 31432101]

[64]. Zhou Y, Wu W, Lindholt JS, Sukhova GK, Libby P, Yu X, Shi GP, Regulatory T cells in human and angiotensin II-induced mouse abdominal aortic aneurysms, Cardiovasc Res 107 (1) (2015) 98–107, 10.1093/cvr/cvv119. [PubMed: 25824145]

[65]. Davis FM, Daugherty A, Lu HS, Updates of recent aortic aneurysm research, Arterioscler. Thromb. Vasc. Biol 39 (3) (2019) e83–e90, 10.1161/ATVBAHA.119.312000. [PubMed: 30811252]

[66]. Yin J, Xia W, Li Y, Guo C, Zhang Y, Huang S, Jia Z, Zhang A, COX-2 mediates PM2.5-induced apoptosis and inflammation in vascular endothelial cells, Am. J. Transl. Res 9 (9) (2017) 3967–3976. [PubMed: 28979673]

[67]. Kovarova M, Koller BH, PGE(2) promotes apoptosis induced by cytokine deprivation through EP3 receptor and induces Bim in mouse mast cells, PLoS One 9 (7) (2014), e102948, 10.1371/journal.pone.0102948. [PubMed: 25054560]

[68]. Dale MA, Ruhlman MK, Baxter BT, Inflammatory cell phenotypes in AAAs: their role and potential as targets for therapy, Arterioscler. Thromb. Vasc. Biol 35 (8) (2015) 1746–1755, 10.1161/ATVBAHA.115.305269. [PubMed: 26044582]

[69]. Kovacevic M, Jonjic N, Stalekar H, Zaputovic L, Stifter S, Vitezic D, Apoptotic cell death and rupture of abdominal aortic aneurysm, Med Hypotheses 74 (5) (2010) 908–910, 10.1016/j.mehy.2009.10.021. [PubMed: 19896778]

[70]. Ozen G, Boumiza S, Deschildre C, Topal G, Longrois D, Jakobsson PJ, Michel JB, Jacob MP, Chahed K, Norel X, Inflammation increases MMP levels via PGE2 in human vascular wall and plasma of obese women, Int J. Obes. (Lond.) 43 (9) (2019) 1724–1734, 10.1038/s41366-018-0235-6. [PubMed: 30349011]

[71]. Golledge J, Krishna SM, Wang Y, Mouse models for abdominal aortic aneurysm, Br. J. Pharm 179 (5) (2022) 792–798, 10.1111/bph.15260.

[72]. Daugherty A, Cassis LA, Mouse models of abdominal aortic aneurysms, Arterioscler. Thromb. Vasc. Biol 24 (3) (2004) 429–434, 10.1161/01.ATV.0000118013.72016.ea. [PubMed: 14739119]

[73]. Sata M, Mouse Models Vasc. Dis (2016), 10.1007/978-4-431-55813-2.

[74]. Tedjawirja VN, de Waard V, Which mouse model of abdominal aortic aneurysm deserves triple a status? Eur. J. Vasc. Endovasc. Surg 58 (5) (2019) 777–778, 10.1016/j.ejvs.2019.07.008. [PubMed: 31427146]

[75]. Azuma J, Asagami T, Dalman R, Tsao PS, Creation of murine experimental abdominal aortic aneurysms with elastase, J. Vis. Exp (29) (2009), 10.3791/1280.

[76]. Busch A, Bleichert S, Ibrahim N, Wortmann M, Eckstein H-H, Brostjan C, Wagenhäuser MU, Goergen CJ, Maegdefessel L, Translating mouse models of abdominal aortic aneurysm to the translational needs of vascular surgery, JVS: Vasc. Sci (2021), 10.1016/j.jvssci.2021.01.002.

[77]. Carsten CG 3rd, Calton WC, Johanning JM, Armstrong PJ, Franklin DP, Carey DJ, Elmore JR, Elastase is not sufficient to induce experimental abdominal aortic aneurysms, J. Vasc. Surg 33 (6) (2001) 1255–1262, 10.1067/mva.2001.112706. [PubMed: 11389426]

[78]. Daugherty A, Manning MW, Cassis LA, Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice, J. Clin. Invest 105 (11) (2000) 1605–1612, 10.1172/JCI7818. [PubMed: 10841519]

[79]. Trachet B, Fraga-Silva RA, Jacquet PA, Stergiopulos N, Segers P, Incidence, severity, mortality, and confounding factors for dissecting AAA detection in angiotensin II-infused mice: a meta-analysis, Cardiovasc Res 108 (1) (2015) 159–170, 10.1093/cvr/cvv215. [PubMed: 26307626]

[80]. Fashandi AZ, Hawkins RB, Salmon MD, Spinosa MD, Montgomery WG, Cullen JM, Lu G, Su G, Ailawadi G, Upchurch GR Jr., A novel reproducible model of aortic aneurysm rupture, Surgery 163 (2) (2018) 397–403, 10.1016/j.surg.2017.10.003. [PubMed: 29195736]

[81]. Manning MW, Cassis LA, Daugherty A, Differential effects of doxycycline, a broad-spectrum matrix metalloproteinase inhibitor, on angiotensin II-induced atherosclerosis and abdominal aortic aneurysms, Arterioscler. Thromb. Vasc. Biol 23 (3) (2003) 483–488, 10.1161/01.ATV.0000058404.92759.32. [PubMed: 12615694]

[82]. Senemaud J, Caligiuri G, Etienne H, Delbosc S, Michel JB, Coscas R, Translational relevance and recent advances of animal models of abdominal aortic aneurysm, Arterioscler. Thromb. Vasc. Biol 37 (3) (2017) 401–404, 10.1161/ATVBAHA.116.308534. [PubMed: 28062500]

[83]. Chiou AC, Chiu B, Pearce WH, Murine aortic aneurysm produced by periarterial application of calcium chloride, J. Surg. Res 99 (2) (2001) 371–376, 10.1006/jsre.2001.6207. [PubMed: 11469913]

[84]. Angelov SN, Hu JH, Wei H, Airhart N, Shi M, Dichek DA, TGF-β (Transforming Growth Factor-β) signaling protects the thoracic and abdominal aorta from angiotensin II-induced pathology by distinct mechanisms, Arterioscler. Thromb. Vasc. Biol 37 (11) (2017) 2102–2113, 10.1161/atvbaha.117.309401. [PubMed: 28729364]

[85]. Lareyre F, Clément M, Raffort J, Pohlod S, Patel M, Esposito B, Master L, Finigan A, Vandestienne M, Stergiopulos N, Taleb S, Trachet B, Mallat Z, TGFβ (transforming growth factor-β) blockade induces a human-like disease in a nondissecting mouse model of abdominal aortic aneurysm, Arterioscler. Thromb. Vasc. Biol 37 (11) (2017) 2171–2181, 10.1161/atvbaha.117.309999. [PubMed: 28912363]

[86]. Andrews EJ, White WJ, Bullock LP, Spontaneous aortic aneurysms in blotchy mice, Am. J. Pathol 78 (2) (1975) 199–210. [PubMed: 1115218]

[87]. Mäki JM, Räsänen J, Tikkanen H, Sormunen R, Mäkikallio K, Kivirikko KI, Soininen R, Inactivation of the lysyl oxidase gene Lox leads to aortic aneurysms, cardiovascular dysfunction, and perinatal death in mice, Circulation 106 (19) (2002) 2503–2509, 10.1161/01.cir.0000038109.84500.1e. [PubMed: 12417550]

[88]. Lu G, Su G, Davis JP, Schaheen B, Downs E, Roy RJ, Ailawadi G, Upchurch GR Jr., A novel chronic advanced stage abdominal aortic aneurysm murine model, J. Vasc. Surg 66 (1) (2017) 232–242.e4, 10.1016/j.jvs.2016.07.105. [PubMed: 28274752]

[89]. Kopacz A, Werner E, Grochot-Przęczek A, Klóska D, Hajduk K, Neumayer C, Józkowicz A, Piechota-Polanczyk A, Simvastatin Attenuates abdominal aortic aneurysm formation favoured by lack of Nrf2 transcriptional activity, Oxid. Med. Cell. Longev 2020 (2020) 6340190, 10.1155/2020/6340190.

[90]. Kopacz A, Klóska D, Werner E, Hajduk K, Grochot-Przęczek A, Józkowicz A, Piechota-Polańczyk A, A dual role of heme oxygenase-1 in angiotensin II-induced abdominal aortic aneurysm in the normolipidemic mice, Cells 10 (1) (2021), 10.3390/cells10010163.

[91]. Sapadin AN, Fleischmajer R, Tetracyclines: nonantibiotic properties and their clinical implications, J. Am. Acad. Dermatol 54 (2) (2006) 258–265, 10.1016/j.jaad.2005.10.004. [PubMed: 16443056]

[92]. Mata KM, Fernandes CR, Tefe-Silva C, Ramos SG, Doxycycline balance the TIMPs 1 and 2 expressions in a new model of abdominal aortic aneurysms, J. Immunol. Sci 2 (6) (2018) 4–8.

[93]. Curci JA, Petrinec D, Liao S, Gulob LM, Thompson RW, Pharmacologic suppression of experimental abdominal aortic aneurysms: A comparison of doxycycline and four chemically modified tetracyclines, J. Vasc. Surg 25 (1998) 1082–1093.

[94]. Prall AK, Longo GM, Mayhan WG, Waltke EA, Fleckten B, Thompson RW, Baxter BT, Doxycycline in patients with abdominal aortic aneurysms and in mice: comparison of serum levels and effect on aneurysm growth in mice, J. Vasc. Surg 35 (5) (2002) 923–929, 10.1067/mva.2002.123757. [PubMed: 12021708]

[95]. Golub LM, Wolff M, Lee HM, McNamara TF, Ramamurthy NS, Zambon J, Ciancio S, Further evidence that tetracyclines inhibit collagenase activity in human crevicular fluid and from other mammalian sources, J. Periodontal Res 20 (1) (1985) 12–23, 10.1111/j.1600-0765.1985.tb00405.x. [PubMed: 2983061]

[96]. Golub LM, Lee HM, Lehrer G, Nemiroff A, McNamara TF, Kaplan R, Ramamurthy NS, Minocycline reduces gingival collagenolytic activity during diabetes. Preliminary observations and a proposed new mechanism of action, J. Periodontal Res 18 (5) (1983) 516–526, 10.1111/j.1600-0765.1983.tb00388.x. [PubMed: 6315909]

[97]. Golub LM, Lee HM, Ryan ME, Giannobile WV, Payne J, Sorsa T, Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms, Adv. Dent. Res 12 (2) (1998) 12–26, 10.1177/08959374980120010501. [PubMed: 9972117]

[98]. Smith GN Jr., Mickler EA, Hasty KA, Brandt KD, Specificity of inhibition of matrix metalloproteinase activity by doxycycline: Relationship to structure of the enzyme. Arthritis &, Rheumatism 42 (6) (1999) 1140–1146, 10.1002/1529-0131(199906)42:6<1140::Aid-anr10>3.0.Co;2-7. [PubMed: 10366106]

[99]. Paghdar S, Khan TM, Patel NP, Chandrasekaran S, De Sousa JFM, Tsouklidis N, Doxycycline therapy for abdominal aortic aneurysm: inhibitory effect on matrix metalloproteinases, Cureus 13 (5) (2021), e14966, 10.7759/cureus.14966. [PubMed: 34123662]

[100]. Griffin MO, Fricovsky E, Ceballos G, Villarreal F, Tetracyclines: a pleitropic family of compounds with promising therapeutic properties. Review of the literature, Am. J. Physiol. Cell Physiol 299 (3) (2010) C539–C548, 10.1152/ajpcell.00047.2010. [PubMed: 20592239]

[101]. Hanemaaijer R, Visser H, Koolwijk P, Sorsa T, Salo T, Golub LM, van Hinsbergh VW, Inhibition of MMP synthesis by doxycycline and chemically modified tetracyclines (CMTs) in human endothelial cells, Adv. Dent. Res 12 (2) (1998) 114–118, 10.1177/08959374980120010301. [PubMed: 9972133]

[102]. Sadowski T, Steinmeyer J, Effects of tetracyclines on the production of matrix metalloproteinases and plasminogen activators as well as of their natural inhibitors, tissue inhibitor of metalloproteinases-1 and plasminogen activator inhibitor-1, Inflamm. Res 50 (3) (2001) 175–182, 10.1007/s000110050742. [PubMed: 11339506]

[103]. Turner GH, Olzinski AR, Bernard RE, Aravindhan K, Karr HW, Mirabile RC, Willette RN, Gough PJ, Jucker BM, In vivo serial assessment of aortic aneurysm formation in apolipoprotein E-deficient mice via MRI, Circ. Cardiovasc Imaging 1 (3) (2008) 220–226, 10.1161/CIRCIMAGING.108.787358. [PubMed: 19808546]

[104]. Yu M, Chen C, Cao Y, Qi R, Inhibitory effects of doxycycline on the onset and progression of abdominal aortic aneurysm and its related mechanisms, Eur. J. Pharm 811 (2017) 101–109, 10.1016/j.ejphar.2017.05.041.

[105]. Mata KM, Tefe-Silva C, Floriano EM, Fernandes CR, Rizzi E, Gerlach RF, Mazzuca MQ, Ramos SG, Interference of doxycycline pretreatment in a model of abdominal aortic aneurysms, Cardiovasc Pathol 24 (2) (2015) 110–120, 10.1016/j.carpath.2014.10.004. [PubMed: 25466491]

[106]. Bartoli MA, Parodi FE, Chu J, Pagano MB, Mao D, Baxter BT, Buckley C, Ennis TL, Thompson RW, Localized administration of doxycycline suppresses aortic dilatation in an experimental mouse model of abdominal aortic aneurysm, Ann. Vasc. Surg 20 (2) (2006) 228–236, 10.1007/s10016-006-9017-z. [PubMed: 16572291]

[107]. Xie X, Lu H, Moorleghen JJ, Howatt DA, Rateri DL, Cassis LA, Daugherty A, Doxycycline does not influence established abdominal aortic aneurysms in angiotensin II-infused mice, PLoS One 7 (9) (2012), e46411, 10.1371/journal.pone.0046411. [PubMed: 23029514]

[108]. Baxter BT, Matsumura J, Curci JA, McBride R, Larson L, Blackwelder W, Lam D, Wijesinha M, Terrin M, Investigators NTC, Effect of doxycycline on aneurysm growth among patients with small infrarenal abdominal aortic aneurysms: a randomized clinical trial, JAMA 323 (20) (2020) 2029–2038, 10.1001/jama.2020.5230. [PubMed: 32453369]

[109]. Medicine, U.N.L. o, Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial. ⟨https://ClinicalTrials.gov/show/NCT01756833⟩: Clinicaltrials.gov, 2021.

[110]. Ding R, McGuinness CL, Burnand KG, Sullivan E, Smith A, Matrix metalloproteinases in the aneurysm wall of patients treated with low-dose doxycycline, Vascular 13 (5) (2005) 290–297, 10.1258/rsmvasc.13.5.290. [PubMed: 16288704]

[111]. Lindeman JH, Abdul-Hussien H, van Bockel JH, Wolterbeek R, Kleemann R, Clinical trial of doxycycline for matrix metalloproteinase-9 inhibition in patients with an abdominal aneurysm: doxycycline selectively depletes aortic wall neutrophils and cytotoxic T cells, Circulation 119 (16) (2009) 2209–2216, 10.1161/CIRCULATIONAHA.108.806505. [PubMed: 19364980]

[112]. Baxter BT, Pearce WH, Waltke EA, Littooy FN, Hallett JW Jr., Kent KC, Upchurch GR Jr., Chaikof EL, Mills JL, Fleckten B, Longo GM, Lee JK, Thompson RW, Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: report of a prospective (Phase II) multicenter study, J. Vasc. Surg (2002) 1–12, 10.1067/mva.2002.125018. [PubMed: 12096249]

[113]. Curci JA, Mao D, Bohner DG, Allen BT, Rubin BG, Reilly JM, Sicard GA, Thompson RW, Preoperative treatment with doxycycline reduces aortic wall expression and activation of matrix metalloproteinases in patients with abdominal aortic aneurysms, J. Vasc. Surg 31 (2) (2000) 325–342, 10.1016/s0741-5214(00)90163-0. [PubMed: 10664501]

[114]. Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, Saikku P, Juvonen T, Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study, J. Vasc. Surg 34 (4) (2001) 606–610, 10.1067/mva.2001.117891. [PubMed: 11668312]

[115]. Meijer CA, Stijnen T, Wasser MN, Hamming JF, van Bockel JH, Lindeman JH, Pharmaceutical G Aneurysm Stabilisation Trial Study, Doxycycline for stabilization of abdominal aortic aneurysms: a randomized trial, Ann. Intern Med 159 (12) (2013) 815–823, 10.7326/0003-4819-159-12-201312170-00007. [PubMed: 24490266]

[116]. Baxter BT, Matsumura J, Curci J, McBride R, Blackwelder WC, Liu X, Larson L, Terrin ML, Investigators NT, Non-invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA(3)CT): Design of a Phase IIb, placebo-controlled, double-blind, randomized clinical trial of doxycycline for the reduction of growth of small abdominal aortic aneurysm, Conte Clin. Trials 48 (2016) 91–98, 10.1016/j.cct.2016.03.008.

[117]. Sillesen H, Eldrup N, Hultgren R, Lindeman J, Bredahl K, Thompson M, Wanhainen A, Wingren U, Swedenborg J, Wanhainen A, Hultgren R, Janson I, Wingren U, Hellberg A, Larzon T, Drott C, Holst J, Sillesen H, Eldrup N, Jepsen J, Lindholdt J, Grønholdt ML, Thompson M, McCullum C, Randomized clinical trial of mast cell inhibition in patients with a medium-sized abdominal aortic aneurysm, Br. J. Surg 102 (8) (2015) 894–901, 10.1002/bjs.9824. [PubMed: 25963302]

[118]. Novartis, CACZ885×2201. Novartis Clincial Trial Results, 2016.

[119]. Kanematsu Y, Kanematsu M, Kurihara C, Tsou TL, Nuki Y, Liang EI, Makino H, Hashimoto T, Pharmacologically induced thoracic and abdominal aortic aneurysms in mice, Hypertension 55 (5) (2010) 1267–1274, 10.1161/HYPERTENSIONAHA.109.140558. [PubMed: 20212272]

[120]. Boyle JR, Loftus IM, Goodall S, Crowther M, Bell PR, Thompson MM, Amlodipine potentiates metalloproteinase activity and accelerates elastin degradation in a model of aneurysmal disease, Eur. J. Vasc. Endovasc. Surg 16 (5) (1998) 408–414, 10.1016/s1078-5884(98)80008-7. [PubMed: 9854552]

[121]. Wilmink ABM, Vardulaki KA, Hubbard CSF, Day NE, Ashton HA, Scott AP, Quick CRG, Are antihypertensive drugs associated with abdominal aortic aneurysms? J. Vasc. Surg 36 (4) (2002) 751–757, 10.1067/mva.2002.126550. [PubMed: 12368736]

[122]. Chen X, Rateri DL, Howatt DA, Balakrishnan A, Moorleghen JJ, Morris AJ, Charnigo R, Cassis LA, Daugherty A, Amlodipine reduces AngII-induced aortic aneurysms and atherosclerosis in hypercholesterolemic mice, PLoS One 8 (11) (2013), e81743, 10.1371/journal.pone.0081743. [PubMed: 24244746]

[123]. Takahashi K, Matsumoto Y, Doe Z, Kanazawa M, Satoh K, Shimizu T, Sato A, Fukumoto Y, Shimokawa H, Combination therapy with atorvastatin and amlodipine suppresses angiotensin II-induced aortic aneurysm formation, PLoS One 8 (8) (2013), e72558, 10.1371/journal.pone.0072558. [PubMed: 23967318]

[124]. Golledge J, Pinchbeck J, Tomee SM, Rowbotham SE, Singh TP, Moxon JV, Jenkins JS, Lindeman JH, Dalman RL, McDonnell L, Fitridge R, Morris DR, Efficacy of telmisartan to slow growth of small abdominal aortic aneurysms, JAMA Cardiol 5 (12) (2020) 1374, 10.1001/jamacardio.2020.3524. [PubMed: 32845283]

[125]. Medicine, U.N.L. o, Comparison of Beta-blocker Versus Angiotensin Receptor Blocker for Suppression of Aneurysm Expansion in Patients With Small Abdominal Aortic Aneurysm and Hypertension (BASE Trial). ⟨https://ClinicalTrials.gov/show/NCT01904981⟩: Clinicaltrials.gov, 2013.

[126]. Medicine, U.N.L. o, Eplerenone in the Management of Abdominal Aortic Aneurysms. ⟨https://ClinicalTrials.gov/show/NCT02345590⟩: Clinicaltrials.gov, 2015.

[127]. Gadowski GR, Pilcher DB, Ricci MA, Abdominal aortic aneurysm expansion rate: effect of size and beta-adrenergic blockade, J. Vasc. Surg 19 (4) (1994) 727–731, 10.1016/s0741-5214(94)70048-6. [PubMed: 7909340]

[128]. Englund R, Hudson P, Hanel K, Stanton A, Expansion rates of small abdominal aortic aneurysms, ANZ J. Surg 68 (1) (1998) 21–24, 10.1111/j.1445-2197.1998.tb04630.x.

[129]. Slaiby JM, Ricci MA, Gadowski GR, Hendley ED, Pilcher DB, Expansion of aortic aneurysms is reduced by propranolol in a hypertensive rat model, J. Vasc. Surg 20 (2) (1994) 178–183, 10.1016/0741-5214(94)90004-3. [PubMed: 8040940]

[130]. Leach SD, Toole AL, Stern H, DeNatale RW, Tilson MD, Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms, Arch. Surg 123 (5) (1988) 606–609, 10.1001/archsurg.1988.01400290092015. [PubMed: 2895995]

[131]. Bhak RH, Wininger M, Johnson GR, Lederle FA, Messina LM, Ballard DJ, Wilson SE, Factors associated with small abdominal aortic aneurysm expansion rate, JAMA Surg 150 (1) (2015) 44, 10.1001/jamasurg.2014.2025. [PubMed: 25389641]

[132]. Rughani G, Robertson L, Clarke M, Medical treatment for small abdominal aortic aneurysms, Cochrane Database Syst. Rev 9 (2012) CD009536, 10.1002/14651858.CD009536.pub2.

[133]. Wilmink ABM, Hubbard CSFF, Day NE, Quick CRG, Effect of propanolol on the expansion of abdominal aortic aneurysms: a randomized study, Br. J. Surg 87 (4) (2002), 10.1046/j.1365-2168.2000.01420-23.x, 499–499.

[134]. Lindholt JS, Henneberg EW, Juul S, Fasting H, Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms, Int Angiol 18 (1) (1999) 52–57. [PubMed: 10392481]

[135]. Propranolol for small abdominal aortic aneurysms: results of a randomized trial, J. Vasc. Surg 35 (1) (2002) 72–79, 10.1067/mva.2002.121308. [PubMed: 11802135]

[136]. Capodanno D, Dharmashankar K, Angiolillo DJ, Mechanism of action and clinical development of ticagrelor, a novel platelet ADP P2Y12 receptor antagonist, Expert Rev. Cardiovasc Ther 8 (2) (2010) 151–158, 10.1586/erc.09.172. [PubMed: 20136601]

[137]. Dai J, Louedec L, Philippe M, Michel JB, Houard X, Effect of blocking platelet activation with AZD6140 on development of abdominal aortic aneurysm in a rat aneurysmal model, J. Vasc. Surg 49 (3) (2009) 719–727, 10.1016/j.jvs.2008.09.057. [PubMed: 19028049]

[138]. Matsuda S, Koyasu S, Mechanisms of action of cyclosporine, Immunopharmacology 47 (2–3) (2000) 119–125, 10.1016/s0162-3109(00)00192-2. [PubMed: 10878286]

[139]. Zhu SB, Zhu J, Zhou ZZ, Xi EP, Wang RP, Zhang Y, TGF-beta1 induces human aortic vascular smooth muscle cell phenotype switch through PI3K/AKT/ID2 signaling, Am. J. Transl. Res 7 (12) (2015) 2764–2774. [PubMed: 26885273]

[140]. Dai J, Losy F, Guinault A-M, Pages C, Anegon I, Desgranges P, Becquemin J-P, Allaire E, Overexpression of transforming growth factor-β1 stabilizes already-formed aortic aneurysms, Circulation 112 (7) (2005) 1008–1015, 10.1161/circulationaha.104.523357. [PubMed: 16103255]

[141]. Dai J, Michineau S, Franck G, Desgranges P, Becquemin JP, Gervais M, Allaire E, Long term stabilization of expanding aortic aneurysms by a short course of cyclosporine A through transforming growth factor-beta induction, PLoS One 6 (12) (2011), e28903, 10.1371/journal.pone.0028903. [PubMed: 22194945]

[142]. Wolf G, Renal injury due to renin-angiotensin-aldosterone system activation of the transforming growth factor-beta pathway, Kidney Int 70 (11) (2006) 1914–1919, 10.1038/sj.ki.5001846. [PubMed: 16985515]

[143]. Ruster C, Wolf G, Renin-angiotensin-aldosterone system and progression of renal disease, J. Am. Soc. Nephrol 17 (11) (2006) 2985–2991, 10.1681/ASN.2006040356. [PubMed: 17035613]

[144]. Yuan W, Varga J, Transforming growth factor-beta repression of matrix metalloproteinase-1 in dermal fibroblasts involves Smad3, J. Biol. Chem 276 (42) (2001) 38502–38510, 10.1074/jbc.M107081200. [PubMed: 11502752]

[145]. UríA JA, Jiménez MG, BalbíN M, Freije JMP, López-OtíN C, Differential effects of transforming growth factor-β on the expression of collagenase-1 and collagenase-3 in human fibroblasts, J. Biol. Chem 273 (16) (1998) 9769–9777, 10.1074/jbc.273.16.9769. [PubMed: 9545314]

[146]. Ishikawa F, Miyoshi H, Nose K, Shibanuma M, Transcriptional induction of MMP-10 by TGF-β, mediated by activation of MEF2A and downregulation of class IIa HDACs, Oncogene 29 (6) (2010) 909–919, 10.1038/onc.2009.387. [PubMed: 19935709]

[147]. He J, Li N, Fan Y, Zhao X, Liu C, Hu X, Metformin inhibits abdominal aortic aneurysm formation through the activation of the AMPK/mTOR signaling pathway, J. Vasc. Res 58 (3) (2021) 148–158, 10.1159/000513465. [PubMed: 33601368]

[148]. Wang Z, Guo J, Han X, Xue M, Wang W, Mi L, Sheng Y, Ma C, Wu J, Wu X, Metformin represses the pathophysiology of AAA by suppressing the activation of PI3K/AKT/mTOR/autophagy pathway in ApoE(−/−) mice, Cell Biosci 9 (2019) 68, 10.1186/s13578-019-0332-9. [PubMed: 31467666]

[149]. Tyagi S, Howatt D, Franklin M, Endean E, Lee E, Lu H, Daugherty A, Metformin does not attenuate angiotensin ii-induced abdominal aortic aneurysms in low-density lipoprotein receptor-deficient mice, J. Vasc. Surg 71 (1) (2020) e26–e27, 10.1016/j.jvs.2019.10.047.

[150]. Yang L, Shen L, Gao P, Li G, He Y, Wang M, Zhou H, Yuan H, Jin X, Wu X, Effect of AMPK signal pathway on pathogenesis of abdominal aortic aneurysms, Oncotarget 8 (54) (2017) 92827–92840, 10.18632/oncotarget.21608. [PubMed: 29190959]

[151]. Fujimura N, Xiong J, Kettler EB, Xuan H, Glover KJ, Mell MW, Xu B, Dalman RL, Metformin treatment status and abdominal aortic aneurysm disease progression, e8, J. Vasc. Surg 64 (1) (2016) 46–54, 10.1016/j.jvs.2016.02.020. [PubMed: 27106243]

[152]. Kunath A, Unosson J, Friederich-Persson M, Bjarnegard N, Becirovic-Agic M, Bjorck M, Mani K, Wanhainen A, Wagsater D, Inhibition of angiotensin-induced aortic aneurysm by metformin in apolipoprotein E-deficient mice, JVS Vasc. Sci 2 (2021) 33–42, 10.1016/j.jvssci.2020.11.031. [PubMed: 34617056]

[153]. Medicine, U.N.L. o, Metformin Therapy in Non-diabetic AAA Patients. ⟨https://ClinicalTrials.gov/show/NCT03507413⟩: Clinicaltrials.gov, 2018.

[154]. Medicine, U.N.L. o, Metformin for Abdominal Aortic Aneurysm Growth Inhibition (MAAAGI). ⟨https://clinicaltrials.gov/ct2/show/NCT04224051⟩: Clinicaltrials.gov, 2020.

[155]. Medicine, U.N.L. o, Limiting AAA With Metformin (LIMIT) Trial (LIMIT). ⟨https://clinicaltrials.gov/ct2/show/NCT04500756⟩: Clinicaltrials.gov, 2020.

[156]. Yamawaki-Ogata A, Hashizume R, Fu XM, Usui A, Narita Y, Mesenchymal stem cells for treatment of aortic aneurysms, World J. Stem Cells 6 (3) (2014) 278–287, 10.4252/wjsc.v6.i3.278. [PubMed: 25067996]

[157]. Davis JP, Salmon M, Pope NH, Lu G, Su G, Sharma AK, Ailawadi G, Upchurch GR Jr., Attenuation of aortic aneurysms with stem cells from different genders, J. Surg. Res 199 (1) (2015) 249–258, 10.1016/j.jss.2015.04.025. [PubMed: 25958166]

[158]. Hosoyama K, Wakao S, Kushida Y, Ogura F, Maeda K, Adachi O, Kawamoto S, Dezawa M, Saiki Y, Intravenously injected human multilineage-differentiating stress-enduring cells selectively engraft into mouse aortic aneurysms and attenuate dilatation by differentiating into multiple cell types, e4, J. Thorac. Cardiovasc Surg 155 (6) (2018) 2301–2313, 10.1016/j.jtcvs.2018.01.098. [PubMed: 29559260]

[159]. Park HS, Choi GH, Hahn S, Yoo YS, Lee JY, Lee T, Potential role of vascular smooth muscle cell-like progenitor cell therapy in the suppression of experimental abdominal aortic aneurysms, Biochem Biophys. Res Commun 431 (2) (2013) 326–331, 10.1016/j.bbrc.2012.12.099. [PubMed: 23291168]

[160]. Sharma AK, Salmon MD, Lu G, Su G, Pope NH, Smith JR, Weiss ML, Upchurch GR Jr., Mesenchymal stem cells attenuate NADPH oxidase-dependent high mobility group box 1 production and inhibit abdominal aortic aneurysms, Arterioscler. Thromb. Vasc. Biol 36 (5) (2016) 908–918, 10.1161/ATVBAHA.116.307373. [PubMed: 26988591]

[161]. Wen H, Wang M, Gong S, Li X, Meng J, Wen J, Wang Y, Zhang S, Xin S, Human umbilical cord mesenchymal stem cells attenuate abdominal aortic aneurysm progression in sprague-dawley rats: implication of vascular smooth muscle cell phenotypic modulation, Stem Cells Dev 29 (15) (2020) 981–993, 10.1089/scd.2020.0058. [PubMed: 32486904]

[162]. Xie J, Jones TJ, Feng D, Cook TG, Jester AA, Yi R, Jawed YT, Babbey C, March KL, Murphy MP, Human adipose-derived stem cells suppress elastase-induced murine abdominal aortic inflammation and aneurysm expansion through paracrine factors, Cell Transpl 26 (2) (2017) 173–189, 10.3727/096368916×692212.

[163]. Yamawaki-Ogata A, Fu X, Hashizume R, Fujimoto KL, Araki Y, Oshima H, Narita Y, Usui A, Therapeutic potential of bone marrow-derived mesenchymal stem cells in formed aortic aneurysms of a mouse model, Eur. J. Cardiothorac. Surg 45 (5) (2014) e156–e165, 10.1093/ejcts/ezu018. [PubMed: 24554076]

[164]. Ryer EJ, Garvin RP, Schworer CM, Bernard-Eckroth KR, Tromp G, Franklin DP, Elmore JR, Kuivaniemi H, Proinflammatory role of stem cells in abdominal aortic aneurysms, e4, J. Vasc. Surg 62 (5) (2015) 1303–1311, 10.1016/j.jvs.2014.04.067. [PubMed: 24997808]

[165]. Herberts CA, Kwa MS, Hermsen HP, Risk factors in the development of stem cell therapy, J. Transl. Med 9 (1) (2011) 29, 10.1186/1479-5876-9-29. [PubMed: 21418664]

[166]. Amioka N, Miyoshi T, Fibrates: a possible treatment option for patients with abdominal aortic aneurysm? Biomolecules 12 (1) (2022) 74, 10.3390/biom12010074. [PubMed: 35053222]

[167]. Moxon JV, Rowbotham SE, Pinchbeck JL, Lazzaroni SM, Morton SK, Moran CS, Quigley F, Jenkins JS, Reid CM, Cavaye D, Jaeggi R, Golledge J, A randomised controlled trial assessing the effects of peri-operative fenofibrate administration on abdominal aortic aneurysm pathology: outcomes from the FAME trial, Eur. J. Vasc. Endovasc. Surg 60 (3) (2020) 452–460, 10.1016/j.ejvs.2020.06.006. [PubMed: 32703634]

[168]. Bruemmer D, Collins AR, Noh G, Wang W, Territo M, Arias-Magallona S, Fishbein MC, Blaschke F, Kintscher U, Graf K, Law RE, Hsueh WA, Angiotensin II–accelerated atherosclerosis and aneurysm formation is attenuated in osteopontin-deficient mice 112 (9) (2003) 1318–1331, 10.1172/jci18141.

[169]. Krishna SM, Seto SW, Moxon JV, Rush C, Walker PJ, Norman PE, Golledge J, Fenofibrate increases high-density lipoprotein and sphingosine 1 phosphate concentrations limiting abdominal aortic aneurysm progression in a mouse model, Am. J. Pathol 181 (2) (2012) 706–718, 10.1016/j.ajpath.2012.04.015. [PubMed: 22698985]

[170]. Golledge J, Cullen B, Rush C, Moran CS, Secomb E, Wood F, Daugherty A, Campbell JH, Norman PE, Peroxisome proliferator-activated receptor ligands reduce aortic dilatation in a mouse model of aortic aneurysm, Atherosclerosis 210 (1) (2010) 51–56, 10.1016/j.atherosclerosis.2009.10.027. [PubMed: 19926086]

[171]. Pinchbeck JL, Moxon JV, Rowbotham SE, Bourke M, Lazzaroni S, Morton SK, Matthews EO, Hendy K, Jones RE, Bourke B, Jaeggi R, Favot D, Quigley F, Jenkins JS, Reid CM, Velu R, Golledge J, Randomized placebo-controlled trial assessing the effect of 24–week fenofibrate therapy on circulating markers of abdominal aortic aneurysm: outcomes from the FAME-2 Trial, J. Am. Heart Assoc 7 (19) (2018), 10.1161/jaha.118.009866.

[172]. Rowbotham SE, Bourke B, Bourke M, Jaeggi R, Jenkins JS, Moxon JV, Pinchbeck JL, Reid CM, Velu R, Golledge J, Fenofibrate in the management of AbdoMinal aortic aneurysm (FAME)-2: the study protocol for a multi-centre, randomised, placebo-controlled trial, Int. J. Clin. Trials 3 (4) (2016) 217, 10.18203/2349-3259.ijct20163960.

[173]. Rowbotham SE, Cavaye D, Jaeggi R, Jenkins JS, Moran CS, Moxon JV, Pinchbeck JL, Quigley F, Reid CM, Golledge J, Fenofibrate in the management of AbdoMinal aortic anEurysm (FAME): study protocol for a randomised controlled trial, Trials 18 (1) (2017), 10.1186/s13063-016-1752-z.

[174]. Medicine, U.N.L. o, Evaluation of Effect of Angiotensin-converting Enzyme (ACE) Inhibitors on Small Aneurysm Growth Rate. ⟨https://ClinicalTrials.gov/show/NCT01118520⟩: Clinicaltrials.gov, 2021.

[175]. Fu XM, Yamawaki-Ogata A, Oshima H, Ueda Y, Usui A, Narita Y, Intravenous administration of mesenchymal stem cells prevents angiotensin II-induced aortic aneurysm formation in apolipoprotein E-deficient mouse, J. Transl. Med 11 (2013) 175, 10.1186/1479-5876-11-175. [PubMed: 23875706]

[176]. Schneider F, Saucy F, de Blic R, Dai J, Mohand F, Rouard H, Ricco JB, Becquemin JP, Gervais M, Allaire E, Bone marrow mesenchymal stem cells stabilize already-formed aortic aneurysms more efficiently than vascular smooth muscle cells in a rat model, Eur. J. Vasc. Endovasc. Surg 45 (6) (2013) 666–672, 10.1016/j.ejvs.2013.03.007. [PubMed: 23598054]

[177]. Petrinec D, Liao S, Holmes DR, Reilly JM, Parks WC, Thompson RW, Doxycycline inhibition of aneurysmal degeneration in an elastase-induced rat model of abdominal aortic aneurysm: preservation of aortic elastin associated with suppressed production of 92 kD gelatinase, J. Vasc. Surg 23 (2) (1996) 336–346, 10.1016/s0741-5214(96)70279-3. [PubMed: 8637112]

[178]. Liu J, Xiong W, Baca-Regen L, Nagase H, Baxter BT, Mechanism of inhibition of matrix metalloproteinase-2 expression by doxycycline in human aortic smooth muscle cells, J. Vasc. Surg 38 (6) (2003) 1376–1383, 10.1016/s0741-5214(03)01022-x. [PubMed: 14681644]

[179]. Sho E, Chu J, Sho M, Fernandes B, Judd D, Ganesan P, Kimura H, Dalman RL, Continuous periaortic infusion improves doxycycline efficacy in experimental aortic aneurysms, J. Vasc. Surg 39 (6) (2004) 1312–1321, 10.1016/j.jvs.2004.01.036. [PubMed: 15192574]

[180]. Yoshimura K, Aoki H, Ikeda Y, Fujii K, Akiyama N, Furutani A, Hoshii Y, Tanaka N, Ricci R, Ishihara T, Esato K, Hamano K, Matsuzaki M, Regression of abdominal aortic aneurysm by inhibition of c-Jun N-terminal kinase, Nat. Med 11 (12) (2005) 1330–1338, 10.1038/nm1335. [PubMed: 16311603]

[181]. Ghoshal S, Loftin CD, Cyclooxygenase-2 inhibition attenuates abdominal aortic aneurysm progression in hyperlipidemic mice, PLoS One 7 (11) (2012), e44369, 10.1371/journal.pone.0044369. [PubMed: 23209546]

[182]. Mukherjee K, Gitlin JM, Loftin CD, Effectiveness of cyclooxygenase-2 inhibition in limiting abdominal aortic aneurysm progression in mice correlates with a differentiated smooth muscle cell phenotype, J. Cardiovasc Pharm 60 (6) (2012) 520–529, 10.1097/FJC.0b013e318270b968.

[183]. Sawada H, Lu HS, Cassis LA, Daugherty A, Twenty years of studying AngII (Angiotensin II)-induced abdominal aortic pathologies in mice: continuing questions and challenges to provide insight into the human disease, Arterioscler. Thromb. Vasc. Biol 42 (3) (2022) 277–288, 10.1161/ATVBAHA.121.317058. [PubMed: 35045728]

[184]. Hiromi T, Yokoyama U, Kurotaki D, Mamun A, Ishiwata R, Ichikawa Y, Nishihara H, Umemura M, Fujita T, Yasuda S, Minami T, Goda M, Uchida K, Suzuki S, Takeuchi I, Masuda M, Breyer RM, Tamura T, Ishikawa Y, Excessive EP4 signaling in smooth muscle cells induces abdominal aortic aneurysm by amplifying inflammation, Arterioscler. Thromb. Vasc. Biol 40 (6) (2020) 1559–1573, 10.1161/ATVBAHA.120.314297. [PubMed: 32321307]

[185]. Lindholt JS, Kristensen KL, Burillo E, Martinez-Lopez D, Calvo C, Ros E, Martin-Ventura JL, Sala-Vila A, Arachidonic acid, but not omega-3 index, relates to the prevalence and progression of abdominal aortic aneurysm in a population-based study of Danish men, J. Am. Heart Assoc 7 (3) (2018), 10.1161/JAHA.117.007790.

[186]. Camacho M, Dilme J, Sola-Villa D, Rodriguez C, Bellmunt S, Siguero L, Alcolea S, Romero JM, Escudero JR, Martinez-Gonzalez J, Vila L, Microvascular COX-2/mPGES-1/EP-4 axis in human abdominal aortic aneurysm, J. Lipid Res 54 (12) (2013) 3506–3515, 10.1194/jlr.M042481. [PubMed: 24133193]

[187]. Holmes DR, Wester W, Thompson RW, Reilly JM, Prostaglandin E2 synthesis and cyclooxygenase expression in abdominal aortic aneurysms, J. Vasc. Surg 25 (5) (1997) 810–815, 10.1016/s0741-5214(97)70210-6. [PubMed: 9152308]

[188]. Walton LJ, Franklin IJ, Bayston T, Brown LC, Greenhalgh RM, Taylor GW, Powell JT, Inhibition of prostaglandin E2 synthesis in abdominal aortic aneurysms: implications for smooth muscle cell viability, inflammatory processes, and the expansion of abdominal aortic aneurysms, Circulation 100 (1) (1999) 48–54, 10.1161/01.cir.100.1.48. [PubMed: 10393680]

[189]. Wang M, Lee E, Song W, Ricciotti E, Rader DJ, Lawson JA, Pure E, FitzGerald GA, Microsomal prostaglandin E synthase-1 deletion suppresses oxidative stress and angiotensin II-induced abdominal aortic aneurysm formation, Circulation 117 (10) (2008) 1302–1309, 10.1161/CIRCULATIONAHA.107.731398. [PubMed: 18285567]

[190]. Yokoyama U, Ishiwata R, Jin MH, Kato Y, Suzuki O, Jin H, Ichikawa Y, Kumagaya S, Katayama Y, Fujita T, Okumura S, Sato M, Sugimoto Y, Aoki H, Suzuki S, Masuda M, Minamisawa S, Ishikawa Y, Inhibition of EP4 signaling attenuates aortic aneurysm formation, PLoS One 7 (5) (2012), e36724, 10.1371/journal.pone.0036724. [PubMed: 22570740]

[191]. Camacho M, Gerboles E, Escudero JR, Anton R, Garcia-Moll X, Vila L, Microsomal prostaglandin E synthase-1, which is not coupled to a particular cyclooxygenase isoenzyme, is essential for prostaglandin E(2) biosynthesis in vascular smooth muscle cells, J. Thromb. Haemost 5 (7) (2007) 1411–1419, 10.1111/j.1538-7836.2007.02555.x. [PubMed: 17403097]

[192]. Ding K, Zhou Z, Hou S, Yuan Y, Zhou S, Zheng X, Chen J, Loftin C, Zheng F, Zhan C-G, Structure-based discovery of mPGES-1 inhibitors suitable for preclinical testing in wild-type mice as a new generation of anti-inflammatory drugs, Sci. Rep 8 (2018) 5205, 10.1038/s41598-018-23482-4. [PubMed: 29581541]

[193]. Ding K, Zhou Z, Zhou S, Yuan Y, Kim K, Zhang T, Zheng X, Zheng F, Zhan CG, Design, synthesis, and discovery of 5-((1,3-diphenyl-1H-pyrazol-4-yl) methylene)pyrimidine-2,4,6(1H,3H,5H)-triones and related derivatives as novel inhibitors of mPGES-1, Bioorg. Med. Chem. Lett 28 (2018) 858–862. [PubMed: 29456107]

[194]. Zhou Z, Yuan Y, Zhou S, Ding K, Zheng F, Zhan C-G, Selective inhibitors of human mPGES-1 from structure-based computational screening, Biorg. Med. Chem. Lett 27 (2017) 3739–3743.

[195]. Zhou S, Zhou Z, Ding K, Yuan Y, Loftin C, Zheng F, Zhan C-G, DREAM-in-CDM approach and identification of a new generation of anti-inflammatory drug targeting mPGES-1, Sci. Rep 10 (2020) 10187, 10.1038/s41598-020-67283-0. [PubMed: 32576928]

[196]. Zhou S, Zhou Z, Ding K, Yuan Y, Zheng F, Zhan C-G, In silico observation of the conformational opening of the glutathione-binding site of microsomal prostaglandin E2 synthase-1, J. Chem. Inf. Model 59 (2019) 3839–3845. [PubMed: 31429562]

[197]. Davis FM, Rateri DL, Daugherty A, Abdominal aortic aneurysm: novel mechanisms and therapies, Curr. Opin. Cardiol 30 (6) (2015) 566–573, 10.1097/HCO.0000000000000216. [PubMed: 26352243]

[198]. Gomez I, Foudi N, Longrois D, Norel X, The role of prostaglandin E2 in human vascular inflammation, Prostaglandins Leukot. Ess. Fat. Acids 89 (2–3) (2013) 55–63, 10.1016/j.plefa.2013.04.004.

[199]. Weaver LM, Stewart MJ, Ding K, Zhou S, Loftin C, Zheng F, Zhan C-G, Abstract 13612: an mPGES-1 inhibitor halts abdominal aortic aneurysm formation in mice, Circulation 144 (Suppl_1) (2021), 10.1161/circ.144.suppl_1.13612.A13612-A13612.

[200]. Kaito K, Urayama H, Watanabe G, Doxycycline treatment in a model of early abdominal aortic aneurysm, Surg. Today 33 (6) (2003) 426–433, 10.1007/s10595-002-2513-0. [PubMed: 12768368]

[201]. Medicine, U.N.L. o, The Effect of Doxycycline on Matrix Metalloproteinase Expression and Activity in the Abdominal Aneurysm ⟨https://ClinicalTrials.gov/show/NCT00538967⟩: Clinicaltrials.gov, 2007.

[202]. Medicine, U.N.L. o, Cyclosporine A in Patients With Small Diameter Abdominal Aortic Aneurysms. ⟨https://ClinicalTrials.gov/show/NCT02225756⟩: Clinicaltrials.gov, 2014.

[203]. Liu S, Xie Z, Daugherty A, Cassis LA, Pearson KJ, Gong MC, Guo Z, Mineralocorticoid receptor agonists induce mouse aortic aneurysm formation and rupture in the presence of high salt, Arterioscler. Thromb. Vasc. Biol 33 (7) (2013) 1568–1579, 10.1161/ATVBAHA.112.300820. [PubMed: 23661677]

[204]. Kurobe H, Hirata Y, Matsuoka Y, Sugasawa N, Higashida M, Nakayama T, Maxfield MW, Yoshida Y, Shimabukuro M, Kitagawa T, Sata M, Protective effects of selective mineralocorticoid receptor antagonist against aortic aneurysm progression in a novel murine model, J. Surg. Res 185 (1) (2013) 455–462, 10.1016/j.jss.2013.05.002. [PubMed: 23731681]

[205]. Wang SK, Green LA, Gutwein AR, Drucker NA, Motaganahalli RL, Fajardo A, Babbey CM, Murphy MP, Rationale and design of the arrest trial investigating mesenchymal stem cells in the treatment of small abdominal aortic aneurysm, Ann. Vasc. Surg 47 (2018) 230–237, 10.1016/j.avsg.2017.08.044. [PubMed: 28916304]

[206]. Hashizume R, Yamawaki-Ogata A, Ueda Y, Wagner WR, Narita Y, Mesenchymal stem cells attenuate angiotensin II-induced aortic aneurysm growth in apolipoprotein E-deficient mice, J. Vasc. Surg 54 (6) (2011) 1743–1752, 10.1016/j.jvs.2011.06.109. [PubMed: 21908146]

[207]. Sharma AK, Lu G, Jester A, Johnston WF, Zhao Y, Hajzus VA, Saadatzadeh MR, Su G, Bhamidipati CM, Mehta GS, Kron IL, Laubach VE, Murphy MP, Ailawadi G, Upchurch GR Jr., Experimental abdominal aortic aneurysm formation is mediated by IL-17 and attenuated by mesenchymal stem cell treatment, Circulation 126 (11 Suppl 1) (2012) S38–S45, 10.1161/CIRCULATIONAHA.111.083451. [PubMed: 22965992]

[208]. Kaschina E, Schrader F, Sommerfeld M, Kemnitz UR, Grzesiak A, Krikov M, Unger T, Telmisartan prevents aneurysm progression in the rat by inhibiting proteolysis, apoptosis and inflammation, J. Hypertens. 26 (12) (2008) 2361–2373, 10.1097/HJH.0b013e328313e547. [PubMed: 19008714]

[209]. Morris DR, Cunningham MA, Ahimastos AA, Kingwell BA, Pappas E, Bourke M, Reid CM, Stijnen T, Dalman RL, Aalami OO, Lindeman JH, Norman PE, Walker PJ, Fitridge R, Bourke B, Dear AE, Pinchbeck J, Jaeggi R, Golledge J, TElmisartan in the management of abDominal aortic aneurYsm (TEDY): the study protocol for a randomized controlled trial, Trials 16 (2015) 274, 10.1186/s13063-015-0793-z. [PubMed: 26081587]

[210]. Medicine, U.N.L. o, Study of the Effectiveness of Telmisartan in Slowing the Progression of Abdominal Aortic Aneurysms. ⟨https://ClinicalTrials.gov/show/NCT01683084⟩: Clinicaltrials.gov, 2012.

[211]. Iida Y, Xu B, Schultz GM, Chow V, White JJ, Sulaimon S, Hezi-Yamit A, Peterson SR, Dalman RL, Efficacy and mechanism of angiotensin II receptor blocker treatment in experimental abdominal aortic aneurysms, PLoS One 7 (12) (2012), e49642, 10.1371/journal.pone.0049642. [PubMed: 23226500]

[212]. Matsumoto S, Kamide K, Banno F, Inoue N, Mochizuki N, Kawano Y, Miyata T, Impact of RGS2 deficiency on the therapeutic effect of telmisartan in angiotensin II-induced aortic aneurysm, Hypertens. Res 33 (12) (2010) 1244–1249, 10.1038/hr.2010.184. [PubMed: 20882024]

[213]. Fujiwara Y, Shiraya S, Miyake T, Yamakawa S, Aoki M, Makino H, Nishimura M, Morishita R, Inhibition of experimental abdominal aortic aneurysm in a rat model by the angiotensin receptor blocker valsartan, Int J. Mol. Med 22 (6) (2008) 703–708, 10.3892/ijmm_00000075. [PubMed: 19020766]

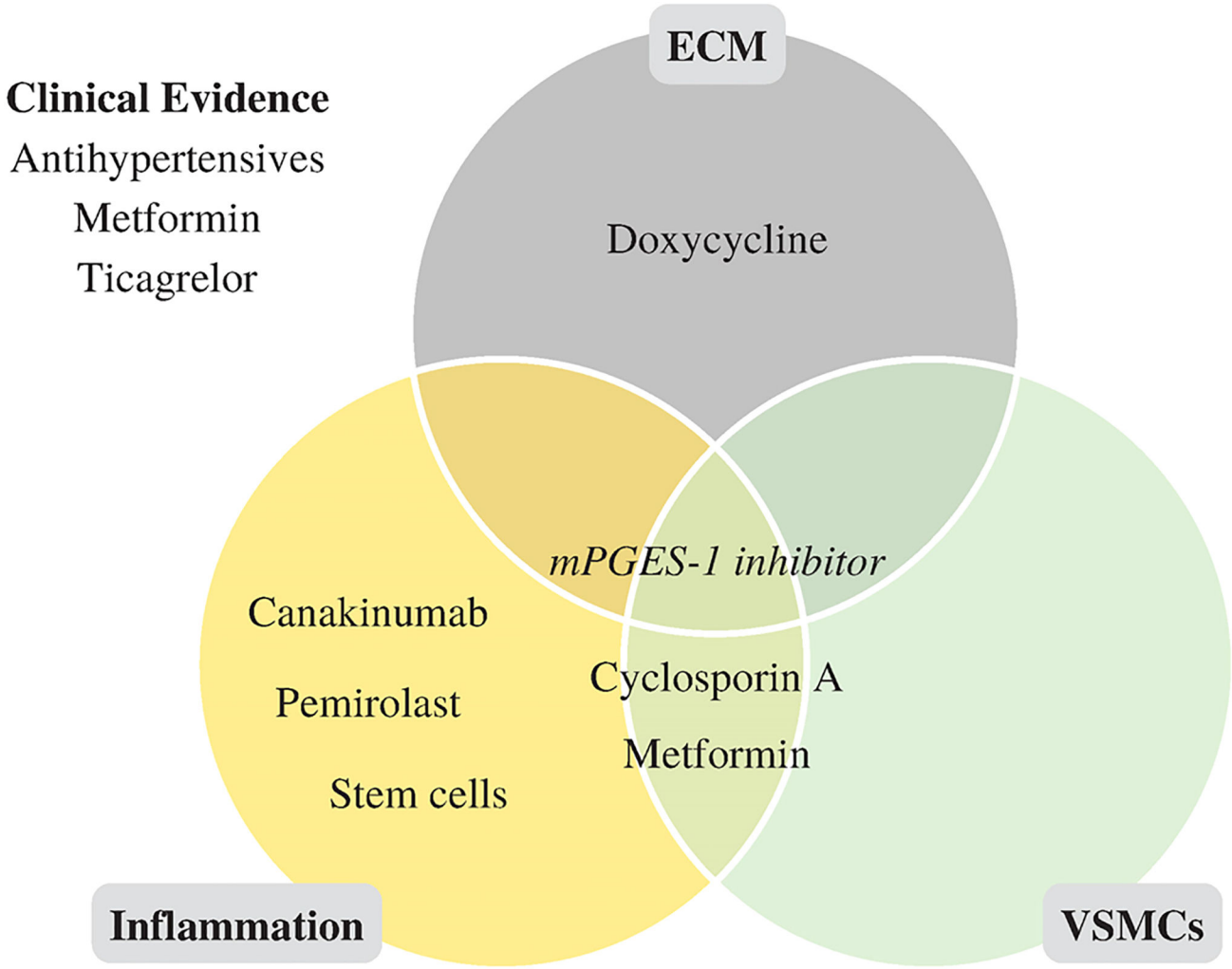

Fig. 1.

Categorization of drugs from AAA clinical trials from clinicaltrials.gov. A general categorization of drugs that have been examined in clinical trials for the treatment of AAA. Cataloging is done by the drug's primary target and mechanism of action in relation to the three areas described.

Created with Canva.com. VSMC, vascular smooth muscle cells; ECM, extracellular matrix; mPGES-1, microsomal prostaglandin E synthase-1.

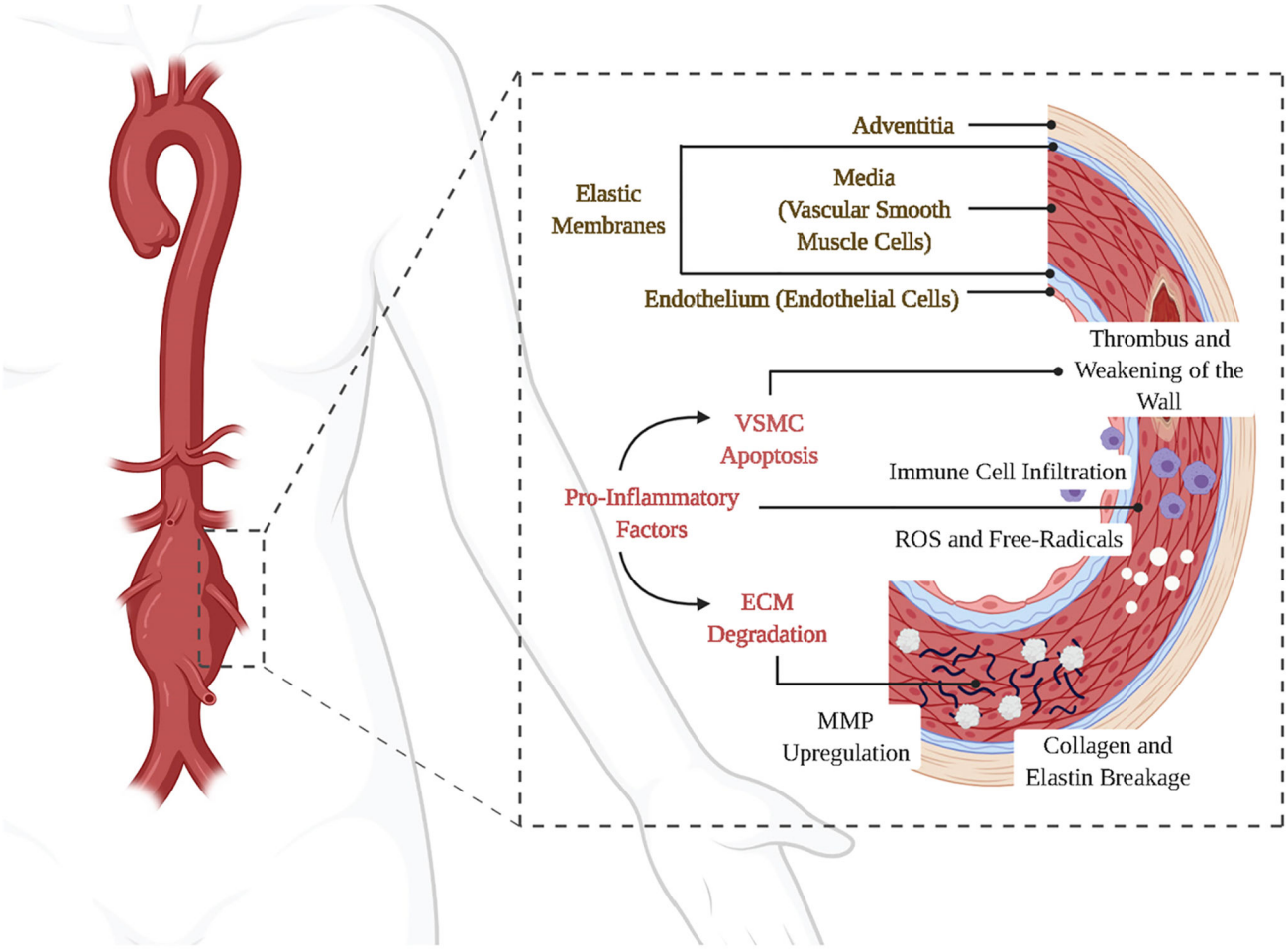

Fig. 2.

Mechanisms and etiology in the pathogenesis of AAA. In the inflammation-driven theory of AAA etiology, pro-inflammatory factors (such as prostaglandins) are the main drivers of the other two hallmarks of AAA formation in humans, VSMC apoptosis and ECM degradation. Subsequently, these three factors influence downstream signalers such as MMP upregulation, immune cell infiltration, and thrombus formation in the abdominal aortic wall. The outer-most layer of the aorta is the adventitia followed by the media and then the endothelium. The media is primarily composed of VSMCs and has elastic membranes on either side. Endothelial cells in the endothelium are in direct contact with blood in circulation.

Created with BioRender.com. AAA, abdominal aortic aneurysm; VSMC, vascular smooth muscle cells; ECM, extracellular matrix; ROS, reactive oxygen species; MMP, matrix metalloproteinase.

Table 1

Preclinical studies using doxycycline to treat AAA dilation.

Animal Model	Treatment	Dose	Inflammation Related Results	AAA Size Results
Elastase (SD rats)[179]	Intervention (not completely transparent)	30 mg/kg/day SC	100 cells/CSA medial layer macrophage density (vs. ~220) cells/CSA) *	3.86 mm diameter (vs. 5.25 mm) *
				86.2% increase in diameter (vs. 148%) *
AngII (*LDL*−/− mice on HFD)[81]	Prevention	30 mg/kg/day in drinking water	–	35% incidence (vs. 86%) *
AngII (*LDL*−/− mice on HFD)[107]	Intervention	100 mg/kg/day in drinking water	–	2.8 mm diameter (vs. 2.8 mm)# (exact numbers estimated from figures)
Elastase (Wistar rats)[177]	Prevention	25 mg/day SC	–	1.17 mm increase in diameter (vs. 2.69 mm) *
				16% incidence (vs. 100%) *
Elastase and thioglycolate (Wistar rats)[200]	Prevention	30 mg/kg/day SC	–	1.172 diameter growth ratio (vs. 1.067) *
AngII (*ApoE* −/− mice)[103]	Prevention	30 mg/kg/day in drinking water	–	47% incidence (vs. 71%) *
Elastase (Black6 mice)[104]	Prevention	30 mg/kg/day PO	Macrophage infiltration (numbers not reported)*	1.10 mm diameter (vs. 1.84 mm) *
				17% incidence (vs. 83%) *
		15 mg/kg/2days IP		0.98 mm diameter (vs. 1.84 mm) *
				0% incidence (vs. 83%) *
		30 mg/kg/2days PO	–	1.44 mm diameter (vs. 1.84 mm)#
				66% incidence (vs. 83%)#
	Intervention	15 mg/kg/2days IP	–	0% incidence (vs. 80%) *
Ligature induced stenosis (Wistar rats)[105]	Prevention	30 mg/kg/day PO	0.75 mm^2 macrophages (vs. 70 mm^2) * 5 mm^2 neutrophils (vs. 105 mm^2) * (exact numbers estimated from figures)	2.10 mm diameter (vs. 8.025 mm) * (exact numbers estimated from figures)
Elastase (Black6 mice)[106]	Prevention	100 mg/kg/day in drinking water	–	1.44 mm diameter (vs. 1.25 mm) *
				54% incidence (vs. 96%) *
Elastase (Wistar rats)[93]	Prevention	7.5 mg/kg/day SC	–	2.72 mm diameter (vs. 3.54 mm) *
				78% increase in diameter (vs. 126%) *

Animal Model	Treatment	Dose	Inflammation Related Results	AAA Size Results
		15 mg/kg/day SC		2.53 mm diameter (vs. 3.54 mm) *
				61% increase in diameter (vs. 126%) *
		30 mg/kg/day SC		2.28 mm diameter (vs. 3.54 mm) *
				51% increase in diameter (vs. 126%) *
		60 mg/kg/day SC		2.34 mm diameter (vs. 3.54 mm) *
				50% increase in diameter (vs. 126%) *

Results are shown as “treatment group (vs. control group)”.

Significant difference between groups is denoted with an asterisk (*);

Those without a significant difference are denoted with an octothorpe (#).

SD, Sprague-Dawley; AngII, angiotensin II; *LDL*, low-density lipoprotein; HFD, high-fat diet; *ApoE*, apolipoprotein E.

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Table 2

Human studies using doxycycline to treat abdominal aortic aneurysms.

Dose	Treatment Length	Enrolled Participants	Inflammation Related Results	MMP Related Results	AAA Size Results
100 mg BID [108, 109]	24 months	261	−0.089 difference between groups in slope per year for log(CRP) (mg/L)#	−0.001 difference between groups in slope per year for log(MMP-9) (ng/mL)#	0.36 cm increase in diameter (vs. 0.36 cm)#
50 mg; 100 mg; 300 mg[111, 201]	2 weeks	60	3.50 pg/mg IL-1β (vs. 4.27)# 148 pg/mg IL-6 (vs. 462) * 0.17 pg/mg TNF-α (vs. 0.24)#	MMP-9 protein levels (numbers not reported) −1.40 log(transcript) of MMP-9 (vs. −1.21)# −2.18 log(transcript) of MMP-12 (vs. −2.57)#	–
100 mg[115]	18 months	286	398 M2 macrophages (vs. 250) * 455 M1 macrophages (vs. 482)#	–	0.41 cm increase in diameter (vs. 0.33 cm)#
100 mg[110]	1 month	56	–	MMP-2 and MMP-9 protein, total activity, and mRNA levels (numbers not reported)#	–
150 mg[114]	3 months w/ 18-month follow-up	34	3.8 mg/L C-reactive protein at 6-month follow-up (vs. 5.66 mg/L) *	–	0.15 cm/year increase in diameter (vs. 0.3 cm)#
100 mg BID[113]	7 days	15	–	Total MMP-2 and MMP-9 activity (numbers not reported)#	–
100 mg BID[112]	6 months	36	–	−29.2% or – 52.5 ng/mL change in MMP-9 levels from baseline *	4.27 cm diameter vs. 4.1 cm at baseline#

Studies conducted after interventional surgery are not reported here. Results are shown as “group (vs. control group)”.

Significant difference between treatment groups is denoted with an asterisk (*);

Those without a significant difference are denoted with an octothorpe (#).

MMP; matrix metalloproteinase.

Table 3

Drugs examined in clinical trials (NCT, Clinicaltrials.gov) compared to the animal studies used to examine it.

Drug	Mechanism	Animal Model	Preclinical Results	Clinical Results
Amlodipine	Anti-hypertensive (Calcium channel blocker)	AngII (*LDLR*−/− on HFD) [122]	Prevention: 0.102 cm diameter (vs. 1.72 mm) *	0.181 cm growth rate (vs. 0.168 cm)#[12,174]
		AngII (*ApoE*−/−)[123]	Prevention: 0.174 cm diameter (vs. 1.97)#	
		AngII and BAPN (Black6 mice)[119]	Prevention: 0% incidence (vs. 49%) *	
Ticagrelor	Anti-platelet (P2Y12 ADP-receptor blocker)	Xenograft (Lewis rats) [137]	Prevention: 0.361 cm external diameter (vs. 5.21 mm) *	0.25 cm increase in diameter (vs. 0.18 cm)#[11,15]
Cyclosporin(e) A	Immunosuppressant (inhibits T cell activation, increases TGF-β1)	$CaCl_2$ (Black6 mice)[141]	Prevention: 0.072 cm external diameter (vs. 1.10 mm) *	Ongoing[202]
		Elastase (Wistar rats) [141]	Prevention: 32% increase in external diameter (vs. 126%) *	
		Xenograft (Fischer 344 rats)[141]	Intervention: 14% increase in external diameter (vs. 45%) *	
		Elastase (Wistar rats)[55]	Prevention: 0.268 cm external diameter (vs. 2.52 mm)#	
Eplerenone	Anti-hypertensive (mineralocorticoid receptor blocker)	Aldosterone and salt (Black6 mice)[203]	Prevention: 0.108 cm external aortic diameter (vs. 1.40 mm) *	Ongoing[126]
		AngII and BAPN (Black6 mice)[204]	Prevention: 30% incidence (vs. 88%)	
Metformin (non-diabetics only)	Anti-hyperglycemic (reduces hepatic glucose production, AMPK agonist)	Elastase (Black6 mice) [151]	Prevention: 40% incidence (vs. 100%)	Enrolling[154]
		AngII (*LDL*−/− mice on HFD)[149]	Prevention: 50% incidence (vs. 67%)#	
		AngII (*ApoE*−/− mice)[10]	Prevention: 17% incidence (vs. 83%)	
		AngII (*ApoE*−/− mice)[148]	Prevention: 25% incidence (vs. 78%)	Enrolling[155]
		AngII (*ApoE*−/− mice)[150]	Prevention: exact numbers not reported *	
		Elastase (SD rats)[147]	Prevention: 0.251 cm diameter (vs. 2.89 mm) *	Enrolling[153]
		AngII (*ApoE*−/− mice)[152]	Prevention: 45% incidence (vs. 100%)	
Stem Cells	Possible anti-inflammatory properties	Elastase (Black6 mice) [157]	Prevention: 80% aortic dilation (vs. 125%) *	Terminated[16,205]
		AngII (*ApoE*−/− mice)[175]	Prevention: 50% incidence (vs. 100%)	
		AngII (*ApoE*−/− mice)[206]	Prevention: 0.06 cm diameter (vs. 1.05 mm) *	
		CaCl2 and Elastase (SCID mice)[158]	Prevention: 0.20 cm diameter (vs. 2.15 mm)#	
		Elastase (SD rats)[159]	Prevention: 50% incidence (vs. 83%)	

Drug	Mechanism	Animal Model	Preclinical Results	Clinical Results
		Elastase (Black6 mice) [207]	Prevention: 82% aortic dilation (vs. 140%) *	
		Elastase (Black6 mice) [160]	Prevention: 99% dilation (vs. 135%) *	
		Xenograft (Fischer 344 rats)[176]	Prevention: 5% aortic dilation (vs. 85%) *	
		Elastase (Black6)[162]	Prevention: 0.075 cm diameter (vs. 1.0 mm) *	
		AngII (*ApoE*−/− mice)[163]	Intervention: 100% incidence (vs. 100%)#	
		Elastase (SD rats)[161]	Prevention: 56% dilation (vs. 95%) *	
Telmisartan	Anti-hypertensive (angiotensin receptor blocker)	Elastase (Brown Norway rats)[208]	Prevention: 0.165 cm diameter (vs. 2.02 mm) *	Ongoing[209,210]
		AngII (*ApoE*−/− mice)[211]	Prevention: 0% incidence (vs. 67%) *	
		Elastase (Black6 mice) [211]	Prevention: 0% incidence (vs. 100%)	
		AngII (wild-type mice) [212]	Prevention: 0.13 cm diameter (vs. 1.2 mm)#	
Valsartan	Anti-hypertensive (angiotensin receptor blocker)	Elastase (Wistar rats) [213]	Prevention: 0.20 cm internal diameter (vs. 2.75 mm) *	Ongoing[125]
Atenolol	Anti-hypertensive and other indications (beta-blocker)	–	–	Ongoing[125]

Animal models of AAA and the strains used are presented. Studies reported are those that examined AAA size. Results for preclinical and clinical trials are compared shown as “type of treatment: drug group (vs. control group)”.

Preclinical studies that had a significant difference between the drug and control groups are denoted with an asterisk (*);

Studies that did not are denoted with an octothorpe (#).

AngII, angiotensin II*; LDLR*, low-density lipoprotein receptor; HFD, high-fat diet; *ApoE*, apolipoprotein E; BAPN, beta-aminopropionitrile; SD, Sprague-Dawley.

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