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\textsubscript{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 (CaCl₂)-induced model of AAA is also frequently used. Here, CaCl₂ 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, CaCl₂) 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-aminopropionitrile (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.
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$^3$CTrial, 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 heterogeneity of tissue samples are possible. Doxycycline’s IC₅₀ against MMP-9 varies for regulation of enzymatic activity, protein, zymogen, and mRNA levels; therefore, 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-TA³CTrial (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-TA³CT (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-TA³CT 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-TA³CT 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 transmembrane 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<sub>12</sub> receptors unlike is predecessors, thienopyridines, which bind irreversibly, at an IC<sub>50</sub> = 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<sub>12</sub> 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<sup>2+</sup> 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\textsubscript{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-\(\beta\)\textsubscript{1} [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-\(\beta\)\textsubscript{1} 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-\(\beta\)\textsubscript{1} 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\textsubscript{−/−} mice, Tyagi and colleagues, who found no significance, used LDLR\textsubscript{−/−} 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-1\(\beta\), and TNF-\(\alpha\) 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-1\(\beta\), 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 ×10⁶ 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 (c) 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^3CT 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^3CT’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^3CT [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\textsubscript{2} (PGE\textsubscript{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\textsubscript{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\textsubscript{2}, which contributes to the formation of AngII-induced AAAs in mice, is microsomal prostaglandin E synthase-1 (mPGES-1) [189]. PGE\textsubscript{2} and its EP\textsubscript{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\textsubscript{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:

| Abbreviation | Definition                      |
|--------------|---------------------------------|
| AAA          | abdominal aortic aneurysms      |
| ACE          | angiotensin converting enzyme   |
| AMPK         | AMP-activated protein kinase     |
| AngII        | angiotensin II                  |
| ApoE         | apolipoprotein E                |
| Black6       | C57BL/6 J                       |
| COX          | cyclooxygenase                  |
| 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          |
| PGE₂         | prostaglandin E₂                |
| PPARα        | peroxisome proliferator-activated receptor alpha |
| TGF          | transforming growth factor      |
| TIMPs        | tissue inhibitors of metalloproteinases |
| TNF          | tumor necrosis factor           |
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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.
Preclinical studies using doxycycline to treat AAA dilation.

| Animal Model                      | Treatment              | Dose               | Inflammation Related Results                                                                 | AAA Size Results                      |
|-----------------------------------|------------------------|--------------------|------------------------------------------------------------------------------------------------|---------------------------------------|
| Elastase (SD rats)⁷⁷⁹             | Intervention (not     | 30 mg/kg/day SC    | 100 cells/CSA medial layer macrophage density (vs. ~220 cells/CSA)                              | 3.86 mm diameter (vs. 5.25 mm)        |
|                                   | completely transparent |                    |                                                                                               | 86.2% increase in diameter (vs. 148%)  |
| AngII (LDL−/− mice on HFD)¹⁰⁷     | Prevention             | 30 mg/kg/day in drinking water | –                                                   | 35% incidence (vs. 86%)               |
| AngII (LDL−/− mice on HFD)        | Interventon            | 100 mg/kg/day in drinking water | –                                                   | 2.8 mm diameter (vs. 2.8 mm)           |
| Elastase (Wistar rats)¹⁷⁷          | Prevention             | 25 mg/day SC        | –                                                   | 1.17 mm increase in diameter (vs. 2.69 mm) |
| Elastase and thioglycolate (Wistar rats) [200] | Prevention             | 30 mg/kg/day SC      | –                                                   | 1.172 diameter growth ratio (vs. 1.067) |
| AngII (ApoE −/− mice)             | 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)        |
|                                   | Intervention           | 15 mg/kg/2days IP   | –                                                   | 17% incidence (vs. 83%)               |
|                                   |                        | 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)        |
|                                   |                        | 0% incidence (vs. 83%) | –                                                   | 66% incidence (vs. 83%)               |
| Ligature induced stenosis (Wistar rats)[105] | Prevention             | 30 mg/kg/day PO     | 0.75 \(\text{mm}^2\) macrophages (vs. 70 \(\text{mm}^2\)) + 5 \(\text{mm}^2\) neutrophils (vs. 105 \(\text{mm}^2\)) | 2.10 mm diameter (vs. 8.025 mm)       |
| Elastase (Black6 mice)[106]       | Prevention             | 100 mg/kg/day in drinking water | –                                                   | 1.44 mm diameter (vs. 1.25 mm)        |
| 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%) | –                                                   | 54% incidence (vs. 96%)               |

* indicates statistical significance compared to control group.
| 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.
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)                                                                  | −0.001 difference between groups in slope per year for log(MMP-9) (ng/mL)               | –                                    |
| 100 mg[115]    | 18 months        | 286                   | 148 pg/mg IL-6 (vs. 462)                                                                      | −1.40 log(transcript) of MMP-9 (vs. −1.21)                                              | –                                    |
|                |                  |                       | 0.17 pg/mg TNF-α (vs. 0.24)                                                                  | −2.18 log(transcript) of MMP-12 (vs. −2.57)                                             | –                                    |
|                |                  |                       | 398 M2 macrophages (vs. 250)                                                                  |                                                                                       | 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                  | −                                                                                             | MMP-2 and MMP-9 activity (numbers not reported)                                       | 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 activity (numbers not reported)                  | 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) #  |
|                  |                                                  |                               | Prevention: 0.174 cm diameter (vs. 1.97) #                |                                       |
|                  |                                                  |                               | 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           |
|                  |                                                  |                               | Prevention: 14% increase in external diameter (vs. 45%) * | (0.18 cm) #                            |
| Cyclosporine A   | Immunosuppressant (inhibits T cell activation, increases TGF-β1) | CaCl2 (Black6 mice) [141] | Prevention: 0.072 cm external diameter (vs. 1.10 mm) *    |                                       |
|                  |                                                  |                               | Prevention: 32% increase in external diameter (vs. 126%) * |                                       |
|                  |                                                  |                               | Prevention: 14% increase in external diameter (vs. 45%) * |                                       |
| 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]                        |
| Metformin (non-diabetics only) | Anti-hyperglycemic (reduces hepatic glucose production, AMPK agonist) | Elastase (Black6 mice) [151] | Prevention: 40% incidence (vs. 100%)                      | Enrolling [154]                     |
|                  |                                                  |                               | Prevention: 0% incidence (vs. 67%) #                      |                                       |
|                  |                                                  |                               | Prevention: 17% incidence (vs. 83%)                       |                                       |
|                  |                                                  |                               | Prevention: 25% incidence (vs. 78%)                       |                                       |
| Stem Cells       | Possible anti-inflammatory properties             | Elastase (Black6 mice) [157]  | Prevention: 0.251 cm diameter (vs. 2.89 mm) *             | Enrolling [153]                     |
|                  |                                                  |                               | Prevention: 45% incidence (vs. 100%)                      |                                       |
|                  |                                                  |                               | Prevention: 80% aortic dilation (vs. 125%) *               | Terminated [16,205]                  |
|                  |                                                  |                               | Prevention: 50% incidence (vs. 100%)                      |                                       |
|                  |                                                  |                               | Prevention: 0.06 cm diameter (vs. 1.05 mm) *               |                                       |
|                  |                                                  |                               | Prevention: 0.20 cm diameter (vs. 2.15 mm) #              |                                       |
## 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.

| Drug              | Mechanism                                      | Animal Model                      | Preclinical Results                                      | Clinical Results |
|-------------------|------------------------------------------------|-----------------------------------|----------------------------------------------------------|------------------|
| Telmisartan       | Anti-hypertensive (angiotensin receptor blocker) | Elastase (Brown Norway rats) [208] | Prevention: 0.16 cm diameter (vs. 0.20 cm) *            | Ongoing [209, 210] |
|                   |                                                 | Elastase (Brown Norway rats) [208] | Prevention: 0.165 cm diameter (vs. 2.02 cm) * Note: Ongoing studies are marked with asterisks. |
|                   |                                                 | Elastase (Black6 mice) [211]      | Prevention: 0% incidence (vs. 67%) *                     |                  |
|                   |                                                 | Elastase (Black6 mice) [211]      | Prevention: 0% incidence (vs. 100%)                      |                  |
|                   |                                                 | Elastase (black6) [160]           | Prevention: 82% aortic dilation (vs. 140%) *            |                  |
|                   |                                                 | Elastase (Black6 mice) [160]      | Prevention: 99% dilation (vs. 135%) *                   |                  |
|                   |                                                 | Elastase (Black6) [162]           | Prevention: 5% aortic dilation (vs. 85%) *              |                  |
|                   |                                                 | Elastase (Black6) [162]           | Prevention: 0.075 cm diameter (vs. 1.0 mm) *            |                  |
|                   |                                                 | AngII (ApoE−/− mice) [163]        | Prevention: 100% incidence (vs. 100%) #                |                  |
|                   |                                                 | Elastase (SD rats) [161]          | Prevention: 56% dilation (vs. 95%) *                     |                  |
| 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]    |

* Denotes a significant difference between the drug and control groups.
# Denotes no significant difference between the drug and control groups.