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Compendium: Pharmacologic Management of Aneurysms

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Abstract

Current management of aortic aneurysms relies exclusively on prophylactic operative repair of larger aneurysms. Great potential exists for successful medical therapy that halts or reduces aneurysm progression and hence alleviates or postpones the need for surgical repair. Preclinical studies in the context of abdominal aortic aneurysm (AAA) identified hundreds of candidate strategies for stabilization, and data from pre-operative clinical intervention studies show that interventions in the pathways of the activated inflammatory and proteolytic cascades in enlarging AAA are feasible. Similarly, extensive series of studies in the murine models of Marfan syndrome-related aortapathy inherited aortic root aneurysm support the concept of pharmaceutical aorta stabilization in Marfan syndrome.

Although some clinical studies report successful medical stabilization of growing aortic aneurysms and aortic root stabilization in Marfan syndrome, these claims are not consistently confirmed in larger and controlled studies. Consequently, no medical therapy can be recommended for the stabilization of aortic aneurysms.

The discrepancy between preclinical successes and clinical trial failures implies shortcomings in the available models of aneurysm disease, and perhaps incomplete understanding of the pathologic processes involved in later stages of aortic aneurysm progression. Preclinical models more reflective of human pathophysiology, identification of biomarkers to predict severity of disease progression, and improved design of clinical trials may more rapidly advance the opportunities in this important field.

Summary

The inconsistent correlations of preclinical successes and clinical trial results provide impetus for major advances in research innovation of aortic aneurysm. There are several explanations for this translational gap, including inadequate animal models, incomplete understanding of late stage human pathogenesis, and poorly-designed, underpowered clinical trials. Development of humanized models, advancing beyond early chemically-provoked models to those consistently demonstrating sequential dilation and rupture, addressing dysfunctional repair mechanisms,

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clinical studies utilizing digitized pharmaceutical histories and extensive prior radiographic records of aneurysm size to explore relationships without the heavy expense of prospective trials, imaging and genetic biomarkers predicting stability or rapid progression of aneurysm enlargement, run-in periods ensuring populations with active aortic enlargement prior to randomization of subjects, greater attention to concomitant medical therapy of cardiovascular risk factors, and longer follow up with clinical endpoints in clinical trials are all areas of opportunity in this important field.

Keywords

Aneurysm; Pharmacology; abdominal aortic aneurysm; Marfan syndrome; aneurysm; growth; pharmacologic treatment

An aneurysm is a localized dilatation of larger blood vessels that is related to regional weakening of the wall structure.[1] Although the large majority of aneurysms presents within arterial tree, venous aneurysms do occur. Aneurysms are generally associated with rupture and a life-threatening haemorrhage, yet some aneurysms (in particular popliteal[2] and venous aneurysms)[3] typically manifest through symptoms of acute thrombosis and embolism.

There are several classification systems for aneurysms. From the perspective of medical therapy the most helpful attribution is that of primary and secondary aneurysms. Primary aneurysms relate to a matrix defect in vessel wall (i.e. fibrillin deficiency in Marfan syndrome, Collagen III deficiency in the vascular type Ehlers Danlos syndrome,[4] and unknown defect(s) in aneurysms associated with bicuspid aortic valves).[5,6] Secondary aneurysms relate to extensive matrix turnover and pathological vessel wall remodelling[5,7] in response to a primary inflammatory insult (i.e. infection, immune diseases (Kawasaki Syndrome, Giant Cell Arthritis, Behçet syndrome),[8] and the degenerative abdominal aortic aneurysm (AAA)).[1]

Although aneurysms occur throughout the vascular tree, there is a remarkable topographic distribution for most aneurysms (i.e. descending thoracic aorta for giant cell arteritis, infrarenal aorta in AAA disease etc.).[9] Although this may be caused by local hemodynamic patterns and associated wall stresses, it likely could reflect the different embryologic origins of the vascular tree,[9] which result in a persistent regional diversity in microvascular endothelium,[10] mesenchymal cell characteristics[11,12,13] and immunologic make-up[14,15]. The remarkable regional diversity in susceptibility is clearly illustrated by the iliac trajectory: unlike the adjacent common iliac, internal iliac, and common femoral arteries; the external iliac artery is remarkably resistant to degenerative aneurysms.

The focus of this compendium will be on the perspectives for medical therapy in the context of AAA and aneurysms associated with Marfan's syndrome as clinical intervention data is available for these aneurysms. Systemic immune suppression in the context of auto-immune diseases such as Kawasaki syndrome and giant cell arteritis, and antibiotic strategies for infection-related aneurysms (Q-fever, bacterial) are beyond the scope of this paper.

The Abdominal Aortic Aneurysm (AAA)

An AAA is a localized dilatation caused by segmental weakening of the terminal aorta segment. The prevalence of the disease depends on the population studied, with reported prevalences varying between 1.4 and 12.4%.[16] The disease carries a complex genetic predisposition[17,18] and predominantly affects elderly men with a history of smoking.[19]

AAA's are generally asymptomatic, and are usually diagnosed by screening or as an incidental finding. The natural history of the disease is that of slow progression and ultimate rupture.[20] Ruptured AAA is a dramatic catastrophe, and aortic emergencies constitute one of the leading causes of acute death in elderly males.[1,16] Risk of rupture is minimal in small aneurysms (i.e. less than 50 mm), but progressively increases with enlarging AAA size--estimated annual rupture risks are less than 1% for AAA with a diameter of 50 mm to over 30% for an AAA exceeding 80 mm diameter.[21]

AAA management has been centred for decades on surgical repair of larger aneurysms to mitigate the risks of rupture. Multiple trials have shown no benefit of repair of AAA at sizes below 55 mm diameter, and consequently current guidelines advise watchful waiting for aneurysms smaller than 55 mm and preventive repair once the AAA grows over 55 mm, [1,19,21] possibly with a slightly lower intervention threshold for repair in women.[22]

The two surgical options for repair are: open repair (through a trans-peritoneal or retroperitoneal approach) or endovascular repair (EVAR) (through a trans-arterial approach). [19,21] Decisions for the type of repair are dictated by AAA-specific features such as neck characteristics and proximity to major important branches, as well as by patients' preferences and characteristics such as frailty and obesity.[19,21] The majority of patients is currently managed by EVAR. Open repair comes with significant higher perioperative mortality and morbidity; registry-based studies report 30-day mortality rates of approximately 4–5% for men and 6–8% for women,[22,23] and perioperative morbidity of open repair is considerable.[19] However, open repair has an established long-term durability, although incisional hernia remains a common cause of late reintervention.[19] EVAR has superior short-term outcomes, but comes with higher rates of aortic re-intervention, and possibly higher costs.[24] Moreover, there is emerging concern in the published literature about the mid and long-term durability of EVAR with possibly excess late mortality in patients that received EVAR.[25,26]

Considering the fact that the sole indication for elective AAA repair is rupture prevention,[19] it has been pointed out that medical stabilization of small diameter aneurysms --keep small aneurysms small and thereby prevent or reduce the need for surgical repair--could be advantageous. This has natural appeal to patients and from an economic point of view.[27] Moreover, medical aneurysm stabilization could be beneficial as add-on strategy in patients considered at high risk for endoleak.[28] It is conceivable that in patients who have aneurysm neck prone to dilation, that stabilization of the neck could reduce the incidence of late type Ia endoleak. All in all, medical AAA stabilization has been brought forward as an unmet medical need.[29]

Targets for medical AAA therapy.

Candidate targets for therapy are dictated by the prevailing concepts of the processes driving AAA disease progression. It is generally assumed that AAA progression is driven by a localized inflammatory response and an accompanying proteolytic imbalance.[20,30] Consequently, proposed interventions directly or indirectly aim at targeting aspects of the inflammatory response, or at rectifying the proteolytic imbalance. The pertinence of these strategies is supported by a wealth of preclinical studies. The vast majority of these are performed in the 'standard' rodent models of AAA disease: the 'elastase' model, the '$CaCl_2$' model or the Angiotensin/LDLR$^{-/-}$ model.[31,32]

The elastase model is based on a transient exposure (generally brief intra-aortic exposure) of an isolated infra-renal aorta segment with porcine pancreatic elastase.[33] The rationale behind the model is the notion that loss of elastin is one of the most notable features of AAA disease. Yet, although the disease is undoubtedly characterized by extensive loss of elastin, it is important to point out that loss of elastin per se is not responsible for the critical wall failure in AAA. First of all, loss of elastin is a very early phenomenon in clinical AAA development, and the elastolysis is virtually complete before the disease reaches the critical 55 mm diameter threshold.[34] Secondly, clinical experience shows that chemical or surgical (endarteriectomy) does not result aneurysm formation.[35,36] The validity of this clinical observation is supported by experimental data that show that although elastin critically contributes to the elastic recoil of the aortic wall, it does not contribute to the resilience of the wall. In fact, studies by Dobrin et al show that the resilience of the wall essentially relies on vascular collagen.[37] This phenomenon is also reflected in the dynamics of the elastase model in which exposure to pure elastin does not immediately induce AAA formation,[38] and in which the initial response following porcine pancreatic elastin preparations is a small increase in aortic diameter, presumably reflecting loss of elastic recoil.[39] The actual aneurysm formation is secondary and reflects a delayed, secondary response, resulting from a secondary inflammatory response.[37]

Although the model is referred as the 'elastase' model, exposure to pure pancreatic elastase does not elicit aneurysm formation.[38] As such contaminants of the porcine pancreatic elastase preparation appear crucial for AAA induction. Further, the model is dependent on the genetic background of the mouse with a strict requirement for strains with Th1 dominated inflammatory responses,[39] underscoring the relevance of the inflammatory response in model.

AAA formation in the elastase models follow a typical pattern with the initial moderate dilatation resulting from loss of elastic recoil, followed by a secondary dilatation, the actual aneurysm formation approximately one week after the elastase induction presumably as result of a secondary inflammatory response. The ultimately dilatation reached varies between 150–200%.[39] A major criticism of the model is the fact that the model regresses ('heals') and is not associated with rupture,[31] although early ruptures were observed after preventive IL-6 neutralization.[40] Other reports show that interference with the healing response either by TGFβ neutralization[41] or 3-aminopropionitrile feeding induced LOX-inhibition[42] elicit rupture in the model.

The second most commonly used model of AAA disease is generally referred to as the '$CaCl_2$' model. In this model, AAA formation is induced by local calcium salt exposure of an isolated infrarenal aorta segment.[31] Although the model is scrutinized by some as a minimal model,[31] there is a wide variety in Ca^{++} concentrations used, and there are indications that $CaPO_4$ rather than the traditional $CaCl_2$ results in superior AAA formation.[43] Like the traditional elastase model, the model does not proceed to rupture.

Ruptures form an integral aspect of the third most commonly used model, the Angiotensin (II)/Apolipoprotein–E deficient mouse.[31,32] This model is based on the observation that chronic angiotensin infusion in apolipoprotein E-deficient mice results in aneurysms in the aortic tree. Although the model is commonly referred to as an aneurysm model, it is now clear that the model should be referred to as a model of aortic dissection.[44,45] Hence, conclusions based on the angiotensin model may not, or only partially translate to human AAA disease.

Based on experiments in these three models several hundred targets[31] have been proposed to limit aneurysm growth. Although a detailed review of the interventions is beyond the scope of this paper, successfully targeted main clusters for intervention include: vascular inflammation, tissue remodelling, blood pressure regulation and lipid metabolism. An overview of the reported main clusters, and illustrative exemplary studies are provided in table 1.

The available literature is dominated by positive studies, few studies report disease aggravation[46,47] or failure of the studied intervention.[48,49,50,51] With respect to the latter, most failing interventions are included as a secondary finding presented along with a successful primary finding, raising the possibility that the available literature is biased by selective reporting of positive findings[52] and type-I errors (false positive conclusions). Strong support for the latter stems from a very elegant evaluation by Trachet et al.[53] The authors performed a meta-analysis of the incidence of dissecting aneurysms, and the mortality rates in the control arm of 194 papers applying the angiotensin model. The analysis indicated a strong inverse relationship between the aneurysm incidence and mortality rate of the control group, and the final conclusions of the study (median dissecting AAA incidence: 73% in studies reporting interventions claimed to reduce AAA formation, 56% in descriptive studies) vs. 35% for interventions claimed to enhance AAA formation.[53] Reported median mortality rates followed the similar inverse trend: respectively: 25, 19 and 13%).[53]

Medical therapy for AAA patients

There are two indications for medical therapy in AAA: cardiovascular risk management and pharmaceutical AAA stabilization.

Epidemiological[105,106] and cohort studies[107,108,109] characterise an AAA as a strong cardiovascular risk factor. In fact, in patients deemed unfit for repair, the risk of dying from non-aneurysm-related (in particular cardiovascular) causes by far exceeds the risk of dying from the AAA.[110] The profound impact of an AAA on overall survival is further illustrated

by the relative-survival analysis included in a meta-analysis of patient-survival following open or endovascular repair.[111] The observed 0.76 10-year relative survival ratio for patients who had their AAA repaired clearly illustrates the profound indirect risk of AAA disease.[111]

Level IIb evidences suggests that cardiovascular risk management is effective in AAA patients,[112,113] hence there is a case for cardiovascular risk management for all AAA patients, irrespective of a possible impact of the risk management on aneurysm progression. Logically, improvement in survival due to reduced cardiovascular risk not only improves the cost-effectiveness of AAA repair, but longer survival will maximize the benefits of an effective pharmaceutical stabilization program.

Preclinical models show the potential of lipid lowering,[86–90] antihypertensive therapy[80–84] and platelet aggregation inhibitors[67] in quenching experimental AAA development. Yet, there is little evidence for a beneficial effect of these strategies on clinical AAA progression and stability. The first studies exploring the potential of pharmaceutical therapy for AAA progression were based on observed beneficial associations between β-blocker use and aneurysm progression in two small (n of 12 and 38) case control studies.[114,115] These studies were then followed by a further case control[116] and cohort study,[117] and later by two randomized trials.[118,119] All these later studies were not confirmative, although the interpretation of the randomized controlled trials is compromised by the poor tolerability of the β-blocker used (propanol) which resulted in a 42% drop out rate in the treatment arm.[119]

The ACE-inhibitors are the second class of anti-hypertensive drugs that received significant attention in the context of AAA stabilization. Enthusiasm was spurred by supportive evidence from experimental studies,[82,83] and a population-based case-control study that reported an beneficial association between ACE inhibitor use and risk of rupture).[120] This study was followed by a series of non-confirmative studies,[121,122,123] one of them suggesting at an adverse association between ACE-inhibitor use and AAA progression.[123] These controversies were ultimately addressed in the AARDVARK study.[124] This study concluded that, despite more effective blood pressure lowering, the ACE-inhibitor perindopril did not show significant impact on aneurysm growth (compared to both placebo alone and to combined placebo and amlodipine (a Ca^{++} antagonist)). A shortcoming of the AARDVARK study is the lower than anticipated aneurysm growth. As such the trial may lack the sensitivity to detect minor effect sizes. Although the authors attribute this shortcoming to the high level medical cardiac risk management in the population studied,[124] it is likely that the lower than anticipated growth reflects inclusion of a disproportionate group of patients with relatively small AAAs (approx. 35 mm).

At this point the potential of the type 1 angiotensin-receptor antagonist Telmisartan is under investigation in the TEDY study.[125] The rationale for this study is the fact that AT_1-receptor antagonists interfere with the negative aspects of angiotensin signalling, but preserve signalling through the ATR1-receptor which is associated with vascular protective activity.[126,127] Along these lines, beneficial associations have been reported between type 1 AT-receptor antagonist use and AAA progression.[128]

The overall conclusion for antihypertensive therapies is that the available clinical studies refute β-blockers or ACE-inhibitors as pharmaceutical strategies for AAA stabilization. This indirectly confirms absence of a direct association between blood pressure and AAA progression.

The potential of statins has been evaluated in 12 studies. Results of these studies are mixed with six studies hinting at a beneficial association between statin use and AAA progression,[129,130,131,132,133,134] and another six studies failing to show an association between statin use and aneurysm progression.[117,122,123,135,136,137] Conclusion from the studies segregate, with the older and smaller studies being confirmative, and the later and larger studies being non-confirmative. On this basis, while the cardiovascular risk benefits of statins are impressive, there is no role for statins as a pharmaceutical strategy stabilizing AAA.

An effect of antiplatelet therapy on aneurysm progression has been explored in six studies. Beneficial effects have been observed in medium sized cohort study (n=148) of patients under surveillance of a 40–49 mm AAA.[138] Unfortunately, the validity of the study is challenged by the unrealistic high growth rate in the control group (5.2 mm/year; anticipated growth rate 2–3 mm/year[139]. A potential effect for combined aspirin-statin treatment has been observed in a sub-analysis of a study evaluating the effect of azithromycin on AAA progression.[140] A benefit for NSAIDs has been reported on the basis of a very small (n=19) study reportedly patients using NSAID showed reduced AAA progression.[141]

In contrast, three larger studies (the UK small aneurysm trial,[123] the ADAM study[117] and an Australian cohort study[136]) all fail to confirm a beneficial effect of anti-platelet therapy on AAA progression.

Well-established negative (beneficial) associations exist between diabetic disease and AAA growth rate.[142] Although this has been attributed to diabetes-related factors such as matrix stabilization by enhanced glycation and modulation of inflammation,[143] there are indications that this negative (protective) association relate to off-targets effect of metformin, a biguanide antidiabetic that is first-line medication for type II diabetes. Indeed, metformin use but other classes of anti-diabetic drug associated with reduced AAA growth rate.[144,145] At this point two trials are planned to test an effect of metformin on AAA growth. (Prof. Ron L. Dalman, personal communication)

Above clinical studies all evaluated potential off-target (so called pleiotropic) effects on AAA progression of drugs that are part of regular cardiovascular risk management. A further series of trials evaluate disease-specific targets that were defined on basis of the current understanding of AAA disease.

A presumed role for persistent chlamydia infection in the perpetuation of vascular disease including AAA at the millennium époque resulted in three studies with aimed at anti-chlamydia eradication. Two small trials with respectively a single four week course of the antibiotic roxithromycin[146] or repeated (annual) four week courses of roxithromycin[147] reported borderline benefits on aneurysm progression. However, this was not confirmed in a larger study with azithromycin that did not identify an effect of sixteen weeks of macrolide treatment on AAA progression.[148]

A further series of clinical studies aimed at targeting specific aspects of the vascular inflammation and proteolytic imbalance in AAA. In this respect, there is a longstanding interest in the tetracycline antibiotic doxycycline. Independent of its antibiotic properties doxycycline has been shown to reduce the expression of matrix metalloproteinases,[149] and to quench their activity.[150] Doxycycline effectively interferes with aneurysm formation in some[151,152] but not all[48] models of aneurysm formation, and clinical studies showed that doxycycline treatment reduces aortic wall MMP content and improves the proteolytic imbalance through its effect on aneurysm wall protease inhibitor levels.[153,154] Three studies[155,156,157] evaluated the effect of doxycycline treatment on aneurysm progression, and a fourth multi-centre randomized trial (Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^3CT) is ongoing.[158] A first study small study (n=32) evaluated patients after three months of doxycycline eradication therapy with the intent of testing the persistent chlamydia infection hypothesis.[155] The report claims an effect of doxycycline therapy on aneurysm progression in the 6–12, and 12–18 month follow up intervals but no effect was seen for the initial 0–6 month interval and for the overall study period. The second, open phase II study tested the safety and feasibility of six months of doxycycline therapy in AAA patients.[156] The study showed that chronic doxycycline treatment is feasible and well-tolerated, and it was concluded that aortic wall MMP-9 levels and AAA progression compared favourably to those of historic controls not receiving treatment. In contrast, data the Pharmaceutical Aneurysm Stabilization Trial[157] testing the effect of eighteen months doxycycline (100 mg/day) failed to show a benefit of doxycycline therapy on AAA progression; on the contrary, doxycycline treatment resulted in a clinically insignificant acceleration of AAA growth. Although earlier dose-finding study found dose-equivalence for low, regular and high dose (respectively 50, 100 or 300 mg/day) doxycycline on all parameters tested,[159,160] It has been argued that the dose used in the PHAST study is too low to elicit an effect. As such the results of the N-TA^3CT study that tests the benefit of 200 mg/day[158] are eagerly awaited.

A potential benefit of mast cell inhibition through the potent mast-cell stabilizer pemirolast[161] was tested in the AORTA trial.[162] Study results show that twelve months of mast cell inhibition is safe, but the mast cell inhibition did not influence AAA progression.[162]

The ACZ885 (Canakinumab) for the Treatment of Abdominal Aortic Aneurysm (AAA) study[163] tested the effect of IL-1β neutralization through subcutaneous Canakinumab (150 mg) once per month for twelve months. The study enrolled 65 patients and one year growth data was obtained for 20 participants in the placebo group and 23 in the Canakinumab group. AAA progression (2.5 mm/year) was similar for both groups, and the trial was terminated for reasons of futility.[163]

Apart from these studies on diameter changes, there is data available for surrogate endpoints (aneurysm wall inflammation). In a small study (6 cases, 10 controls) Motoki et al[164] evaluated the effect of PPAR-γ agonist pioglitzone and observed a reduction in aortic wall TNFα and MMP-9 expression. The effects of the PPARα agonist fenofibrate on circulating inflammatory markers of inflammation have been studied in the Fame trial. A randomized study of 24 weeks treatment.[165] No effect was observed on the circulating markers

osteopontin or kallistatin. Although the authors report an absent effect on AAA growth,[165] it is important to point out that the trial was not adequately powered to detect such an effect.

A highly selective suppression of aneurysm wall inflammation was observed for the selective vitamin D receptor agonist paricalcitol. It was shown that a 2–4 week pre-operative paricalcitol treatment selectively interfered with aspects of NFAT2 mediated inflammation, [166] suggesting that the effects of vitamin D are mainly mediated by an effect on calcineurin-mediated inflammation. This notion was confirmed in in-vitro studies.[166] Although plasma lipids do not associate with incident AAA disease, there are weak associations between plasma LDL levels and AAA progression.[167] In this light, the observed superior effects of ezetimide/simvastatin over simvastatin alone on vascular inflammation merit attention,[168] yet it is unclear how these observations relate to the apparent absence of statins on AAA progression.[117, 122,123,135–137]

The above overview of preclinical successes and clinical failures points to a major paradox of numerous preclinical successes and clinical challenges. Preclinical studies identified hundreds of successful candidate interventions, yet this enormous investment has not produced any clinical application, and no medical therapy is currently available for the stabilization of growing AAA.

More important, the apparent translational gap between preclinical and clinical studies challenges our concepts of the processes underlying late stage AAA disease pathophysiology. Undoubtedly, AAA is associated with a sustained and comprehensive inflammatory response, uncontrolled protease activity and excess matrix turn-over.[5,20,154] Short-term pre-operative intervention studies in patients undergoing open repair all proved the potential of indomethacin[169], statins,[137,170,171,172,173,174,175,176,177] ACE-inhibitors[121] and doxycycline[154,159,160] to effectively quench vascular inflammation and protease activity. Yet, these effects are not followed by reduction of AAA progression. Along similar lines, bona fide anti-inflammatory strategies such as anti-IL-1beta therapy[163] and mast cell[162] stabilization failed to influence AAA progression. Interestingly, profound immune suppression in the context of solid organ transplantation even results in accelerated AAA progression.[178,179] Although these aforementioned observations do not exclude a role for inflammation and or protease activity in AAA initiation and progression, they imply involvement of additional, so far unidentified critical factors that are unresponsive to the anti-inflammatory/anti-proteolytic therapies.

One of possible key factors is failing or defective compensatory repair. In fact, interference with compensatory repair mechanisms (stem cell function) may explain the apparent disastrous effects of intense immune suppression,[180] chemotherapy[181] and the unexpected negative effect of doxycycline therapy[157,182] on aneurysm growth. Moreover, there are clear indications for defective matrix repair in AAA. The disease is associated with complete loss of the normal aortic wall architecture, and the normal aortic matrix is replaced by a collagenous, fibrotic matrix.[154] Although a higher collagen cross-link content in AAA wall samples may imply more stable collagen,[183] this is actually not the case due to defects at the level of collagen fibril organization. In the healthy aortic matrix the collagen fibrils are laid down in supra-molecular, intertwined network structures. As a result, forces are distributed

over the wall. Loss of this network behaviour in AAA disease fundamentally impacts the mechanical stability of the wall[183] and may contribute to the aortic wall weakening in the disease.

Fatty degeneration was recently identified as another potential contributor to the weakening of the aneurysm wall.[184,185] Fatty degeneration is a known phenomenon in aging and chronically injured muscle,[186] and thought to be a consequence of impaired repair mechanism in the context of chronic injury.[187] Gene-expression studies on AAA wall specimens suggest that progressive adipocyte accumulation associated with rupture.[184,188]

Unfortunately, perpetual inflammatory cycle and the impaired compensatory repair that are hallmarks of human AAA are not captured in the rodent models of AAA disease. This shortcoming may largely reflect the spontaneous resolution of inflammation in these models and the superior endogenous healing responses of small animal models[189,190] as well as their inherent resistance to develop chronic fibrosis. In an attempt to create more relevant (viz. rupture prone) AAA models, modified models have been introduced in which interference with the primary healing responses resulted in AAA ruptures.[41,42] Yet, these models do not recapitulate the chronically impaired and dysregulated healing responses that characterize AAA disease. Absence of fibrotic repair in murine models of AAA disease also explains the apparent benefit of inducing fibrotic repair in stabilizing growing AAA in murine models.[191] Since the extensive fibrosis is a hallmark of human AAA disease, and that process of fibrosis results in deposition of a brittle, poor quality matrix,[154,183] it is questionable whether a profibrotic strategy will stabilize human AAA.

Considering the wealth of preclinical success and failing clinical attempts to identify molecular strategies for stabilizing AAA disease we must acknowledge that our understanding of AAA disease is far from complete, and that the available small animal models of the disease only partially mimic aspects of the human disease. There appears a recent trend to include (or demand) confirmative studies in a second animal model in preclinical studies. Considering the parallels between the different models, it is dubious whether this increases the likelihood of the findings being more translationally relevant. Future advancement of the field critically relies on an improved mechanistic insight in the processes that sustain the impaired and ultimately failing repair mechanisms in advanced clinical AAA disease.

Marfan Syndrome

Marfan syndrome is an autosomal-dominant, multisystem connective tissue disorder. The syndrome is caused by mutations in the Fbn-1 gene region located on chromosome 15, and is estimated to affect approximately 2–3/10000 individuals. Over 1000 different Fbn-1 mutations have been associated with the syndrome[195] and the syndrome has extreme heterogeneous genotype-phenotype variability[196] (see table 3 for the diagnostic criteria[197]). Ascending, and to a slighter lesser extent descending thoracic aorta aneurysms are among the primary disquieting features of the syndrome.[198,199]

The Fbn-1 gene codes for fibrillin, a structural connective tissue macromolecule that has been traditionally been considered a key chaperone in elastic fiber formation. However, involvement of tissues not containing elastin indicate roles far beyond that as a scaffold of elastin formation. Indeed, defects in the Fbn-1 gene associate with impaired collagen network formation[182], and fibrillin is a complex modulator of growth factor signalling and cell function.[200]

The aortapathy (thoracic aneurysms, dissections) is among the leading causes of premature death in Marfan patients. Although increased awareness, improved surgical techniques, and medical therapy have significantly improved prospects, Marfan syndrome still comes with significant aorta-related mortality.[201,202] In this respect, strong associations have been described between the gross genotype (dominant negative (abnormal fibrillin-1 protein) or haplo-insufficient (reduced fibrillin-1 protein)) and survival; with significant better outcomes in patients with dominant negative mutations.[203,204]

Aneurysms in Marfan syndrome are currently managed by medical therapy (β-blockers and possibly angiotensin-II receptor type 1 antagonists (AT2 inhibitors)), and preventive surgical repair once the aneurysm size exceeds 50 mm.[205] Although medical therapy preventing aortic dilatation has a prominent role in the current guidelines, it is important to note that the level of evidence is low.

Recommendations for β-blocker therapy are actually based on a single, small open study that included 70 patients.[206] Conclusions from this study have recently been scrutinized on basis of its small size and considerable losses during follow up, and the fact that significance was only reached upon creating a composite end point.[207] In addition to this single intervention study, there are additional claims from a series of observational reports.

The largest observational study is by Silverman et al.[208] The authors reported outcomes for 417 patients with ‘definite’ Marfan syndrome who were under surveillance in four referral centers. Groups were created on basis of β-blockers prescription. β-blocker usage was unknown for 84 patients, as result 191 patients taking β-blocker and 142 patients who had never taken β-blockers were evaluated. Despite the impressive study size, this study comes with significant points of concern. According to the authors: “Median cumulative probability of survival for patients who had taken β-blockers was 72 years compared with 70 years for patients who had never taken β-blockers ($p = 0.01$)”. Yet, the reported estimated life expectancies contrast with actual data in the manuscript, and with the data for other populations for the same time interval.[209] Moreover, it is important to point out that the number of patients with an age over 50 in the study was very limited,[208] and as a consequence that the study is underpowered to allow detection of a 2-year difference in life expectancy. A further issue with the study is the fact that authors did not address putative time-effects in their analysis. Although not fully clear from the text, it appears that the study covers the period between approx. 1970–1993. It is conceivable that improvements in surgical techniques coincided with the clinical implementation of β-blocker usage, making time is a major potential confounder in this study. As actually pointed out by the authors in the discussion: “it is very likely that increased awareness and improved diagnostic tools

resulted in progressively more mild cases of the Marfan syndrome being identified towards the end of the observation period".[208]

A further observational study[210] on an effect of β-blockers on aortapathy reports growth data for 113 juvenile Marfan patients from two centers. Different dosing schedules were used by the two centers: an intermediate dose in the first center (1.3 mg/kg (n=80 patients)) and a high dose in the second center (1.9 mg/kg (n=20 patients)). Thirteen individuals who "could not or would not take β-adrenergic blockade therapy" constituted the 'control group'.[210] On the basis of the slower rate of aortic root growth in individuals taking β-blockers, the authors recommended that "β-adrenergic blockade therapy in patients with Marfan syndrome should begin at the earliest age possible, and that the dose be adjusted to the largest dose β-adrenergic blockade therapy that is clinically tolerated".[210] Some concerns of this study include the authors report beneficial effects on the aorta growth rate; yet, this is actually not the case for the indexed growth rate (mm/m^2), for which favorable effects were only observed for the intermediate dose group and *not* for high dose group. Reviewing the manuscript[210] for a potential explanation(s) reveals that with similar mean end-of-follow up ages in the intermediate dose and control groups, mean end-of-follow up length in the intermediate dose group was 174 cm, but only 149 cm in the control group.[210] An extreme standard deviation in the control group (69 cm (versus 22 cm in the intermediate dose group))[210] implies severe skewing of the size distribution to the right in the control group, and consequently that the reported mean height overestimates the actual median height. This implies profound heterogeneity between control group and the treated groups, and consequently that the conclusions of the study may be prone to bias.

Beneficial effects are further reported by Ladouceur et al.[211] who retrospectively evaluated the effect of β-blockers in 155 young Marfan patients in whom the therapy was initiated before the age of 12 years. The authors concluded that: "β-blockade significantly decreased the rate of aortic dilatation at the level of the sinuses of Valsalva by a mean of 0.16 mm/year ($p<0.05$), an effect that increased with treatment duration".[211] Although the authors rightly point out that the increase in aortic dilatation was less in the treatment arm, this difference actually reflect the larger baseline diameter in group receiving β-blockers, as the actual aortic diameters at the age of 18 were actually similar in the two groups. The claim made by the authors that "a trend toward lower cardiac mortality, decreased need for preventive aortic surgery, and less dissection was observed"[211] is not justified by the data in the manuscript.

Conclusions from Ladouceur et al,[211] are not confirmed in a second smaller observational study in young Marfan patients.[212] This study included 63 children who were monitored for over 6 years. Thirty-four patients received β-adrenergic blockade therapy (Atenolol, 0.92 mg/kg), 29 patients not receiving β-blockers served as control. The authors concluded that: "This study found no difference in the rate of aortic root dilation in children with Marfan syndrome treated with β-blockers and those not treated".[212] Like the other reports this retrospective analysis is prone to bias. In particular the higher percentage of patients with a family history of Marfan syndrome in the untreated group (35% vs. 69% in the treated group) may indicate that groups were not balanced with respect to the severity or phenotype.

A further small open label study[213] non-randomly assigned 58 adolescent Marfan patients to β-blocker therapy (max. dose 2 mg/kg) or the ACE inhibitor Enalapril. It was concluded that ACE inhibition resulted in favorable hemodynamic changes, and a smaller increase in aortic root diameter (0.1 (1.0) vs 5.8 (5.2) mm (mean (sd)).[213] Given the study design, the small sample size and absence of a control group it is difficult to draw conclusions from this study. A report from Rossi-Foulkes et al.[214] compares outcomes for pre-adolescent patients on different antihypertensive therapy (β-blockers or Ca-antagonists). The authors reported that medication favorably influenced aortic growth,[214] but that it did not prevent complications. In the absence of a control group, and profound baseline differences in the medicated and non-medicated group this report should be considered inconclusive.

Taken together, this overview of reports on β-adrenergic blockade in Marfan syndrome shows a paucity of studies with adequate study designs and appropriate statistical approaches.[215] As a consequence, the currently available evidence does not provide a strong rationale for β-adrenergic blockade to prevent aortapathy in patients with Marfan syndrome.[216,217,218] An adequate evaluation taking into account the possibility that patient responses to β-adrenergic blockade are heterogeneous and relate to the underlying genotype[219,220] is missing

Observed excessive TGFβ signalling in the aortas of murine models of Marfan syndrome, and a preventive effect of interference with TGFβ signalling through neutralizing antibodies or the angiotensin II receptor antagonists in the model[221] fuelled optimism for angiotensin II receptor antagonists (“Sartans”) as a preventive treatment for aortapathy in Marfan syndrome.

Supportive observations from small (respectively 28, 20 and 18 patients) open studies in young Marfan patients,[222,223,224] and a small open label study on surrogate endpoints[225] were followed by one smaller and four larger randomized trials. A small Belgium trial enrolling 22 patients with Marfan syndrome failed to observe an add-on effect of Losartan when added to blocker therapy.[226]

Forteza et al. performed a larger randomized trial and randomized 5–60 year old Marfa patients to Losartan (n = 70) or atenolol (n = 70) (both dosed at 100 mg/day in individuals over 50 kg).[227] The trial results show similar aortic root and ascending aorta diameters progression in the 2 arms for the 3-year follow up.[227] In a French study, incorporating 303 Marfan patients aged 10 years and older, Millerton et al. assigned patients to Losartan or placebo next to their regular treatment (86% of the participants also used β-blockers).[228] It was concluded that 3-year Losartan therapy did not influence the aorta parameters tested or the need for surgery.[228] Unfortunately inclusion of both young and adult patients creates considerable heterogeneity both with regard to the genotype as to aortic dilation rates potentially interfering with the ability to detect suppression of growth.

Young Marfan patients were studied in a semi-blinded study by the US Marfan network. Six hundred and eight participants between 6 months to 25 years of age were allocated to atenolol (mean dose (sd) achieved: 2.7 (1.1) mg or Losartan (mean dose (sd) 1.3 (0.2) mg).[229] Again, the 3-year follow up showed equivalence for β-adrenergic blockade or

angiotensin receptor blockade. The fourth larger randomized trial is a multicentre, open-label, randomized controlled trial with blinded assessments performed in The Netherlands.[230] The COMPARE trial incorporates 233 adult participants (47% female) who were randomized to either Losartan (n = 116) or no additional treatment (n = 117). The study showed mixed effects with an effect of Losartan on root dilatation rate, but no effect on the more distal aspects of the aorta. Remarkably, a planned sub-analysis performed on the available data of the COMPARE trial[230] suggests that an effect of angiotensin-II receptor blockade may depend on the type of FBN-1 mutation since it was concluded that Losartan reduced only aortic root dilatation rate in haplo-insufficient patients, and not in dominant negative patients.[231]

According to the trial registries, there is currently one small (n=56) on-going 4-arm trial, The Oxford Marfan Trial Version which evaluates the effect of irbesartan (150–300 mg), doxycycline (100–200 mg) and a combination of both on markers of vascular dysfunction in the Marfan syndrome in patients over 13-year of age.[232]

With the exception of the potential beneficial effect in adult haplo-insufficient Marfan patients the clinical trials uniformly fail to show a benefit of type I angiotensin II receptor inhibition on the aortapathy in Marfan patients. Remarkably, opposite conclusions were drawn in a meta-analysis of the published prospective trials.[233] Evaluation of the meta-analysis appears to have weaknesses that resulted in an overestimation of the effect size. Specifically, the planned sub-analyses performed within the COMPARE trial[230] were included as separate studies, resulting in duplication of the positive data. Further, the weight distribution attributed to the studies included in the meta-analysis[233] may be incorrect.

These contrasting findings between promising preclinical data and the clinical data with respect to the angiotensin II receptor antagonism may reflect profound interspecies differences, not only with respect to aspects of the immune and inflammatory responses but also with respect to healing, as well as the significant heterogeneous character of aorta disease in Marfan's disease.[234] Most of the preclinical work is based on mice with hypomorphic FBN1 mutations: theFbn1C1039G/+ strain, with 50% of normal; and Fbn1mgR/mgR strain with 20% of normal fibrillin-1),[235] but alternative models are currently being developed.[236]

Given the extreme genotypical and phenotypical variation in Marfan syndrome observations, from a specific murine model may only be relevant to a subset of Marfan patients. Moreover, translatability of experimental findings can be further interfered by phenotypical aspects such age (disease stage) heterogeneity is indicated by the dimorphic effects of TGFβ neutralization in an experimental model of Marfan syndrome.[237] Clinical relevance of the genotypical heterogeneity as is implicated in the sub-analysis of the Compare trial that showed an exclusive benefit of Losartan in haplo-insufficient patients.[231] As such a re-evaluation of the negative trials taking along the lines of dominant negative and haplo-insufficient genotypes merits consideration.

Unfortunately, such a meta-analysis may be challenging as phenotyping was only available for one third of the patients in the large Atenolol vs Losartan trial performed by the Pediatric

Heart Network.[229] Genotype information is available for 84% of the participants in the Sartan trial (78% established FBN1 mutation)[228] and the trial by Forteza et al (82% FBN-1 mutation)[227], but information on type FBN1 is missing in the publications.

Interpretation of currently available randomized trials is further challenged by the substantial phenotypical heterogeneity in the patients studied (young vs adult patients), and by loss of sensitivity by use of Z-scores rather than root size as clinical end points.[238] A meta-analysis based on all individual patient data has been announced, but conclusions are awaited at the time of writing this overview.[239]

A further point of debate is the suggested pivotal role of TGF-β signalling in Marfan disease.[221] The rationale for angiotensin II receptor type 1 (ATR1) blocker in Marfan syndrome was based on a presumed excess TGF-β signalling as the underlying cause of aortapathy in Marfan syndrome. A critical question is whether this assumption is correct as excess TGF-β activation appears a common phenomenon in aortic aneurysm disease[240,241] and may actually be part of the compensatory healing or anti-inflammatory responses. Such a mechanism is supported by the observation that TGF-β upregulation in murine models of Marfan syndrome are secondary,[242,243,244,245] by the fatal consequences of TGF-β neutralizing in murine models of aneurysm,[41,246] and opposite contextual (disease state) effects of TGFβ on the aorta pathology in the Marfan mouse model.[237]

Taking into account the currently available data, there is insufficient evidence in support for either β-adrenergic blockade or ATR1 blocker for aortapathy in Marfan syndrome. The field would benefit from a meta-analysis (and sub analysis) of the available data from the Losartan trials. Such a meta-analysis has been announced,[247] but conclusions are awaited at the time of writing this overview. If this is not definitive, there is need for an adequately-powered, placebo-controlled global trial that would stratify or control multiple known confounders--including age, genetic heterogeneity of Marfan syndrome, and diverging effects on blood pressure and pulse.

Currently available data indicate equivalence of β-adrenergic and ATR1 blockade. In light of the milder side effects and superior persistence,[248] ATR1 antagonists might be preferable.[249]

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Abbreviations

AAA	Abdominal Aortic Aneurysm
ACE	Angiotensin Converting Enzyme
AMPK	5’ adenosine monophosphate-activated protein kinase
AP-1	Activator Protein-1

ATR1:	angiotensin II receptor type 1
CCL-1	Chemokine (C-C motif) ligand
EGFR	Epidermal growth factor receptor
EVAR	Endovascular Aneurysm Repair
FBN1	Fibrillin-1
HDL	High Density Lipoprotein
IL-1β	Interleukin-1β
iNOS	inducible Nitric Oxide Synthetase
LDLR	Low density Lipoprotein Receptor
LOX	Lysyl Oxidase
MMP	Matrix Metalloproteinase
NFAT2	Nuclear Factor of Activated T-cells-2
NFκB	Nuclear Factor-κB
NOTCH	Notch homolog, translocation-associated
PPARα	peroxisome proliferator-activated receptors
RXR	retinoid X receptor
sd	standard deviation
TGF-β	Transforming Growth Factor-β
TNFα	Tumor Necrosis Factor-α

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Table 1.

Summary of successful experimental targets for pharmaceutical AAA stabilization.

Targeted cluster	Strategy
Anti-inflammatory	NFκB,[54] AP-1,[55] Rho kinase[56] inhibition IL1,[57] TNFα,[58] CCL-1[59] B-cell[60]; γδT-cell[61] depletion Neutrophil inhibition[62] Mast cell inhibition[63] Complement inhibition[64,65] Oxilipin inhibition[66,67] Immune suppression[68,69]
Protease inhibition	MMP inhibition[70,71] Cysteine protease inhibition[72,73] Serine protease inhibition[74,75]
Oxidative stress	Antioxidant enzymes[76,77] Secondary antioxidants[78,79]
Blood pressure lowering	B-blockers[80] Ca-Antagonists[81] ACE-inhibitors[82,83] ATR-1 antagonists[84] iNOS inhibition[85]
Lipid metabolism	Statins[86,87] HDL[88] RXR and PPARα/γ activation[89,90]
Cell Therapy	Mesenchymal stem cells[91,92] Fibroblasts[93]
Matrix/Morphogens	Interference with TGFβ signalling[94] Interference with NOTCH[95]/Wnt[96] signalling Thrombospontin inhibition[97] EGFR inhibition[98]
Metabolism	Inhibition of HIF1α[99] Activation of AMPK[100]
Nutriceuticals	Polyphenols[101] Phyto-oestrogens[102]
Sex hormones	Castration[103] Oestrogens[104]

Table 2.

Ongoing and planned medical intervention studies for AAA stabilization

Study acronym	Intervention	Read-out
Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^3CT)[158] NCT01756833	Doxycycline 100 mg bid or placebo	2-year AAA progression (CT scan), repair or rupture
TEDY[125] NCT01683084	Telmisartan (AT_1 receptor antagonist) 40 mg or placebo.	1-year AAA progression (US and CT scan), repair or rupture
VIVAAA NCT02846883	Mesenchymal stem cells	AAA inflammation (PET-CT)
Eplerenone in the Management of abdominal aortic aneurysms. NCT02345590	Eplerenone (selective aldosterone receptor antagonist) or placebo	Not specified
TicAAA NCT02070653	Placebo or none specified dose Ticagrelor (P2Y12 inhibitor)	1-year AAA progression, surgery or repair.
FAME[192] ACTRN12612001226897	Fenofibrate (PPARα agonist) 145mg or placebo 2–4 weeks prior to elective open repair	Aortic wall macrophage and osteopontin content
The Effect of Angiotensin II Type 1 Receptor Antagonists on the Size and Expansion Rate of Abdominal Aortas in Hypertensive Patients. NCT01670903	Comparison of patients treated with different classes of anti-hypertensives (AT1 receptor antagonists, ACE inhibitors, or non ARB/ACE)	Not specified
Metformin Therapy in Non-diabetic AAA Patients NCT03507413	Metformin (1000 mg BID) or placebo	1-year AAA progression (CT)
LIMIting AAA with MeTformin (LIMIT trial) Not yet registered.	Metformin or placebo	2-year AAA progression (CTA)
Inositol in the MAnaGemENt of abdominal aortic aneurysm (IMAGEN)[193]	Inositol or placebo	1-year AAA progression (sack volume (CT))
Aortic Aneurysm Repression with Mesenchymal Stem Cells (ARREST) trial.[194]	1 or 3 10^6 cells/kg allogenic mesenchymal cells or placebo	Phase I safety trial. Circulating cytokine levels and 18-FDG/PET

Table 3.

Revised Ghent criteria for diagnosing Marfan syndrome

In absence of a family history:
(1) Z -score for the aortic diameter at the sinuses of valva ≥ 2 or aortic root dissection AND ectopia lentis
(2) Z -score for the aortic diameter at the sinuses of valva ≥ 2 or aortic root dissection AND fibrillin-1 mutation
(3) Z -score for the aortic diameter at the sinuses of valva ≥ 2 or aortic root dissection AND Systemic score ≥7*
(4) ectopia lentis AND fibrillin-1 mutation AND aortic aneurysm
In the presence of a family history:
(5) ectopia lentis AND family history of Marfan syndrome (see 1–4)
(6) Systemic score ≥7 AND family history of Marfan syndrome (see 1–4)*
(7) Z -score for the aortic diameter at the sinuses of valva ≥ 2 (above 20 years old) or ≥3 in those below 20 years old) AND family history of Marfan syndrome*
*In the absence of discriminating features other syndromes.
Systemic score
• Wrist AND thumb sign – 3 (Wrist OR thumb sign – 1)
• Pectus carinatum deformity – 2 (pectus excavatum or chest asymmetry – 1)
• Hind foot deformity – 2 (plain pes planus – 1)
• Pneumothorax – 2
• Dural ectasia – 2
• Protrusio acetabuli – 2
• Reduced US/LS AND increased arm/height AND no severe scoliosis – 1
• Scoliosis or thoracolumbar kyphosis – 1
• Reduced elbow extension – 1
• Facial features (3/5) – 1 (dolichocephaly, enophtalmos, downslanting palpebral fissures, malar hyoplasia, retrognathia)
• Skin striae – 1
• Myopia >3 diopters – 1
• Mitral valve prolapse (all types) – 1
Maximum total: 20 points; score ≥7 indicates systemic involvement