

1 **Oxidative stress and abdominal aortic aneurysm: Potential treatment targets.**

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34 **Abstract**

35

36 Abdominal aortic aneurysm (AAA) is a significant cause of mortality in older adults. A key
37 mechanism implicated in AAA pathogenesis is inflammation and the associated production of
38 reactive oxygen species (ROS) and oxidative stress. These have been suggested to promote
39 degradation of the extracellular matrix and vascular smooth muscle apoptosis. Experimental and
40 human association studies suggest that ROS can be favourably modified to limit AAA formation and
41 progression. In this article, we discuss mechanisms potentially linking ROS to AAA pathogenesis and
42 highlight potential treatment strategies targeting ROS. Currently, none of these strategies have been
43 shown to be effective in clinical practice.

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47 Key words- abdominal aortic aneurysm, pharmacotherapy, oxidative stress, clinical trial, and animal
48 models

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67 **Introduction**

68 Abdominal aortic aneurysm (AAA) is a degenerative disease of the aorta common in people aged >
69 65 years.(1, 2) AAA is usually asymptomatic until rupture which is frequently fatal.(1-4) However,
70 rupture of small AAAs is rare.(5) The main focus of AAA management is to prevent rupture,
71 therefore current guidelines recommend that patients with large AAAs (>5-5.5cm) undergo
72 endovascular stent graft or open surgical repair.(4, 6) Patients with small AAAs undergo regular
73 imaging to monitor AAA diameter, although up to 70% of these individuals eventually require AAA
74 repair.(2)

75 AAA is believed to result from an aberrant interaction between genetic factors and the environment
76 which aggravates the normal ageing processes.(1, 2) One of the key features of AAA is vascular wall
77 inflammation associated with significant production of reactive oxygen species (ROS).(3, 6) ROS,
78 which include hydrogen peroxide (H₂O₂), superoxide (O₂⁻), and hydroxyl radical (·OH) are oxygen-
79 derived chemical molecules with high reactivity.(7, 8) Reports from recent clinical and experimental
80 investigations suggest that oxidative stress, i.e. production of ROS in excess of antioxidant protection,
81 is involved in the vascular degeneration found in AAA.(9-11) Imbalance in the activity of endogenous
82 pro-oxidative enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NOX) and
83 xanthine oxidase (XO), the mitochondrial respiratory chain and the antioxidant enzymes such as
84 glutathione peroxidase, heme oxygenase (HO), superoxide dismutase (SOD), thioredoxin (TRX), and
85 catalase results in excessive ROS.(12, 13) This is implicated in vascular cell dysfunction, lipid and
86 protein peroxidation, and deoxyribonucleic acid (DNA) damage which can result in permanent
87 cellular damage and death.(7, 12, 13) ROS regulate the degradation and remodelling of the
88 extracellular matrix (ECM) by upregulating proteolytic enzymes such as matrix metalloproteinases
89 (MMPs), (14) activating signalling kinases and transcription factors such as nuclear factor kappa beta
90 (NF-κB) and activator protein 1 (AP-1),(15-17) and promoting vascular smooth muscle cell (VSMC)
91 apoptosis.(18, 19) ROS also regulate fibroblast proliferation and macrophage and mononuclear
92 lymphocyte infiltration.(7, 20, 21)

93 In this article we discuss mechanisms potentially linking ROS to AAA pathogenesis and review
94 potential treatment strategies targeting ROS in the management of AAA based on experimental and
95 human studies.

96

97 **Literature Search**

98 A literature search was conducted to identify studies assessing antioxidants as therapeutic targets for
99 AAA using the Embase (1980), MEDLINE (1966), SCOPUS (1996), Web of Science (1965), and
100 Cochrane Library databases (1992) from inception to the 25th of May, 2015. The following search
101 terms were applied either as single or combined searches: “abdominal aortic aneurysm” OR “AAA”,
102 [Title/Abstract] AND “antioxidant treatment” OR “antioxidant targets” OR “antioxidant therapy”,
103 AND/OR “clinical studies” OR “human studies”, AND/OR “animal studies” OR “experimental
104 studies”. Abstracts were analysed for relevance and studies describing the therapeutic potential of
105 antioxidants in AAA pathogenesis were retrieved. Human and animal studies investigating the
106 therapeutic potential of antioxidants in AAA were included. Included article references were hand
107 searched for relevant publications meeting the inclusion criteria. Studies excluded include those in
108 languages other than English and studies unrelated to oxidative stress.

109

110 **Evidence linking ROS with AAA**

111 ROS such as NO and O₂⁻ are produced by all vascular cell types principally via membrane-associated-
112 specific enzymes such as NOX, XO, and nitric oxide synthase (NOS). (7, 13) Both animal and human
113 studies have associated elevated concentrations of ROS, or surrogate markers of ROS with AAA. (11,
114 22-24)

115

116 **Animal studies**

117 Evidence from different animal models implicates ROS in AAA pathogenesis. Nakahashi and
118 colleagues reported that HO-1 expression was significantly upregulated within the elastase-induced
119 rat model of AAA. (24) They further demonstrated the localisation of HO-1 to infiltrative
120 macrophages within the aneurysmal aortic wall. Similarly, iNOS produced NO has been reported to
121 exacerbate experimental AAA development.(25) Lizarbe *et al.* reported a reduction in aortic diameter
122 and MMP-13 expression in mice administered the iNOS inhibitor, 1400 W.(14) In the angiotensin II
123 (AngII)-induced mouse model of AAA, 8-isoprostane,(23) and 8-hydroxy-2' -deoxyguanosine (8-
124 OHdG), (9) concentrations (markers of oxidative stress) have been reported to be high within the
125 aneurysmal aorta. Similarly, high 8-OHdG content and glutathione peroxidase expression were
126 reported within the calcium chloride (CaCl₂)-induced mouse model of AAA. (26) Infiltrating
127 inflammatory cells and their products have been reported to be involved in aortic wall degradation and
128 ensuing AAA formation.(3, 27) (28)

129

130 **Human associated studies**

131 Dubick and colleagues reported low levels of vitamin C, and lower copper-zinc SOD (CuZnSOD)
132 activity in aortic tissue samples from 29 patients with AAA and 14 patients with atherosclerotic
133 occlusive disease (AOD) compared to non-diseased control aortas.(29) SOD is a family of
134 metalloenzymes including CuZnSOD, manganese SOD (MnSOD), and extracellular SOD (EcSOD)
135 that catalyses the dismutation of O₂⁻ into oxygen and H₂O₂ thereby maintaining vascular NO
136 concentrations.(30, 31) High MnSOD and low CuZnSOD activities were observed in a study
137 evaluating the effect of hypertension on aortic antioxidant status in human AAA and AOD.(42) In
138 contrast, a separate study suggested that both CuZnSOD and MnSOD activities were lower in infra-
139 renal aortic biopsies collected from patients with intact and ruptured AAAs compared to non-
140 aneurysmal organ donors.(32) This study also suggested that glutathione reductase and glutathione
141 peroxidase were downregulated whilst lipid peroxidation products were high in AAA patients,
142 particularly those with ruptured aneurysms, compared to controls.(32) Aberrant lipid peroxidation has
143 been associated with aortic cell apoptosis and necrosis, (discussed in (33, 34)) which potentially
144 promotes aortic weakening and AAA. Evidence also suggests that dysregulated antioxidant protective
145 mechanisms,(35-42) and/or low levels of exogenous antioxidants (vitamin C, vitamin E) can
146 exacerbate ROS activity.(7, 13, 43) In addition, Miller *et al.* reported high expression of O₂⁻ and NOX
147 activity in biopsies of human aneurysmal aortas compared with biopsies from adjacent non-
148 aneurysmal aortas.(11) Zhang *et al.* reported high iNOS expression in the media and adventitia of
149 human AAA tissues compared to controls.(44) They suggested that iNOS promotes AAA progression
150 by selectively stimulating the formation and activity of the NO-derived oxidant peroxynitrite (ONOO⁻
151) with consequent aortic oxidative injury and AAA.(44)

152 Collectively, these studies suggest that oxidative stress is associated with the presence of AAA. It
153 remains to be shown whether targeting ROS or their modulators would be an effective strategy in
154 managing AAA.

155

156 **Potential mechanisms linking oxidative stress with AAA and associated therapeutic targets**

157 Sies defined oxidative stress as an imbalance between ROS and antioxidants in favour of the oxidants
158 leading to cellular injury and damage.(45) There is a close association between oxidative stress and
159 inflammation as evidence suggests that oxidative stress induces inflammation, which in turn
160 potentiates oxidative stress with resultant injury to tissues.(11, 46, 47) The human body is equipped to
161 maintain the oxidant-antioxidant balance to avoid injury in physiological conditions, but potentially
162 not in pathophysiological conditions like AAA (discussed in (45, 48)).

163 A number of endogenous enzyme systems regulating oxidative stress in AAA have been researched in
164 both pre-clinical and clinical studies in the past decade (Figure 1). The following sections summarise
165 the potential mechanisms linking these pathways to AAA and strategies which potentially, may be
166 used therapeutically to limit AAA (Figure 2).

167

168 **Xanthine and NADPH oxidases**

169 NOX activity has been reported to be markedly elevated by stimuli thought to be key in the
170 pathogenesis of AAA such as Ang II, TNF- α , mechanical stretch, and endothelin-1 acting both
171 through transcriptional pathways and posttranslational modification of oxidase regulatory subunits.(7,
172 49) Ang II for example, has been reported to induce mitochondrial dysfunction via a protein kinase
173 C-dependent pathway by activating NOX and forming NO, ONOO⁻, and O₂⁻ (Figure 2).(50)
174 Oxidative stress has been reported to enhance expression of angiotensin converting enzyme (ACE)
175 which is responsible for the conversion of angiotensin I (Ang I) to Ang II.(51) In addition, mice
176 overexpressing the NOX catalytic subunit Nox1 within VSMC are reported to have an enhanced
177 response to Ang II, exhibit increased O₂⁻ and H₂O₂ production and have aortic thickening.(52, 53)
178 Thomas *et al.* employing the Ang II-infused mouse model of AAA reported that deletion of p47phox,
179 a cytosolic subunit of NOX, abrogated NOX activity, reduced production of ROS within the aorta and
180 within infiltrating leukocytes, and significantly reduced the incidence and progression of AAA.(54) In
181 contrast, inhibition of Nox1 has been associated with resistance to aortic dissection and AAA
182 development in mouse models.(55) However, a deficiency in another NOX catalytic subunit, Nox2
183 was reported to exacerbate Ang II-induced AAA in mice and promote interleukin-1 beta (IL-1 β) and
184 MMP-9 expression.(56) Inhibition of IL-1 β or IL-1 β receptor expression has been reported to confer
185 AAA resistance in mouse models.(57)

186 XO is also a H₂O₂ and O₂⁻ generating enzyme formed from the proteolytic breakdown of xanthine
187 dehydrogenase.(13) Experimental evidence suggests XO is expressed by aortic endothelial cells in a
188 NOX dependent manner,(58) and is actively involved in lipid peroxidation and damage to the ECM
189 (discussed in (59)). However there are limited studies investigating the specific role of XO in AAA
190 pathogenesis.

191 Taken together, these studies suggest a potential mechanism by which NOX may modulate AAA
192 pathogenesis via effects on the renin-angiotensin system (RAS), inflammatory cytokines and MMPs.

193 Zhang *et al.* reported that cilostazol, a phosphodiesterase III inhibitor that selectively targets cyclic
194 adenosine monophosphate (cAMP), inhibited AAA development in an elastase-induced rat model.
195 (60) Cilostazol is a 2-oxo-quinoline derivative with antithrombotic, vasodilator, antimitogenic and
196 cardiogenic properties and is indicated for intermittent claudication in patients with peripheral arterial
197 disease.(61) Cilostazol was shown to significantly reduce NOX activity and ROS concentration with
198 consequent inhibition of MMP-2 and MMP-9 expression, and NF- κ B activation ($P < 0.05$).(60) In a
199 CaCl_2 mouse model of AAA, mice orally administered apocynin (a NOX inhibitor) were shown to
200 have reduced MMP-2, MMP-9 and NO metabolite (NO_2 and NO_3) expression within aortic tissues,
201 and decreased aneurysm formation compared to controls.(18) In contrast, Kigawa *et al.* reported that
202 mice deficient in NOX demonstrated increased incidence of AAA, albeit with decreased ROS
203 expression, within an Ang II-induced low-density lipoprotein receptor knock-out ($\text{Ldlr}^{-/-}$) mouse
204 model of AAA.(56) Collectively, these studies suggest that medication targeting both NOX and XO
205 pathways may limit AAA formation and progression, although more studies are needed to validate
206 these findings.

207

208 **Lipoxygenases**

209 Lipoxygenases are non-heme iron-containing enzymes that catalyze the stereospecific deoxygenation
210 of polyunsaturated fatty acids with a 1, 4-cis, cis-pentadiene structure (62, 63) and are also proficient
211 in the generation of ROS, or augmenting leukocyte ROS production.(8, 64) Lipoxygenases are
212 required for the biosynthesis of leukotrienes, which are key inflammatory and chemotactic
213 mediators.(65) For example, inhibition of lipoxygenases including 5- lipoxygenase (5-LO) has been
214 reported to reduce the expression of MMP-2 and -9, and phagocytic macrophage infiltration.(66-68)
215 The proteolytic breakdown of the ECM by MMPs has been reported to be one of the key mechanism
216 involved in AAA pathogenesis (for a detailed review of MMPs and AAA, please see (69)). It has been
217 suggested that by promoting inflammation and the proteolytic degradation of the ECM via effects on
218 MMPs expression and recruitment of inflammatory cells, lipoxygenases may play a role in inducing
219 AAA formation.

220 A growing body of evidence has implicated lipoxygenases in the pathogenesis of AAA as illustrated
221 in Table 1.(46, 66, 67) A recent study by Bhamidipati *et al.* using an elastase perfused- and an Ang II-
222 infused $\text{Ldlr}^{-/-}$ mouse models of AAA demonstrated that 5- lipoxygenase (5-LO) inhibition attenuated
223 AAA formation and progression.(67) The authors reported that genetic deletion of 5-LO within the
224 elastase infused mouse model resulted in a 71% reduction in aortic dilatation compared with wild-
225 type controls. Mice administered 30 mg/kg/day of AZD4407 (a selective 5-LO inhibitor) were also
226 shown to be resistant to AAA formation and progression associated with decreased MMP-9 enzymatic
227 activity and immune cell infiltration within aortic tissue. These findings were further strengthened
228 through studies within the Ang II-infused $\text{Ldlr}^{-/-}$ mouse model of AAA, where they reported that
229 administration of AZD4407 within the chow for 28 days inhibited 5-LO activity within the circulation
230 resulting in a 54% reduction in aneurysm formation compared to control.(67)

231 Edaravone (3-methyl-1-phenyl-2-pyrazoline-5-one), a powerful antioxidant indicated as a therapeutic
232 agent for acute cerebral infarction,(70) was reported to significantly reduce the expression of MMP-2,
233 MMP-9 and ROS, and abrogate AAA formation and expansion in the combined elastase-induced and
234 CaCl_2 -induced rat model of AAA.(71) In addition, earlier studies by Zhao *et al.* found that $\text{ApoE}^{-/-}$
235 mice lacking 5-LO genes and fed a cholic acid-rich diet demonstrated a reduced incidence of
236 AAA.(66) Consistent with this, Ang II-infused $\text{ApoE}^{-/-}$ mice deficient in leukotriene B4 receptor 1

237 (BLT1) were shown to exhibit decreased incidence and size of AAA.(72) In a similar model, a BLT
238 antagonist (CP-105,696) limited AAA formation when administered at the same time as Ang II
239 infusion, but did not limit progression of established aneurysms. (68). Cao *et al.* employing the Ang
240 II-infused ApoE^{-/-} mouse model of AAA, reported that mice deficient in 5-LO or administered a 5-LO
241 activating protein (FLAP) inhibitor (MK-0591) had a similar incidence of AAA development to
242 controls.(73)

243 A human association study reported higher expressions of leukotriene C4 synthase (LTC4S), 5-LO
244 and FLAP within aneurysmal aortas compared to non-aneurysmal donor aortas.(74) Others have also
245 reported high production of leukotriene B4 (LTB4) by polymorphonuclear leukocytes localised within
246 intra-luminal thrombus samples collected from patients undergoing aneurysm repair.(75) A study
247 involving 613 men aged ≥65 with AAA and 707 randomly selected age-matched controls failed to
248 find an association between 7 single nucleotide polymorphisms in ALOX5AP, the gene encoding
249 FLAP, with human AAA.(76) Together, these reports fail to show a consistent role of lipoxygenase in
250 human and experimental AAA.

251

252 **Cyclooxygenases**

253 Cyclooxygenases (COX) are the key enzymes involved in the conversion of arachidonic acid to
254 prostaglandins.(77) It has been reported that COX-2 and its metabolite, prostaglandin E2 (PGE2), are
255 highly expressed within aneurysmal tissue and exacerbate VSMC apoptosis.(78-80) COX-2
256 expression was also reported to be associated with increased macrophage infiltration,(81) and
257 increased MMP-2 expression and aortic remodelling. Collectively, this information suggests that
258 COX-2 may play a significant role in AAA pathogenesis via effects on VSMC integrity and
259 inflammation, stimulating interest in treatments targeting the COX pathway as a means of limiting
260 AAA. Celecoxib, a nonsteroidal anti-inflammatory drug (NSAID), and a selective COX-2 inhibitor,
261 was reported to reduce the incidence and severity of AAA within the Ang II-induced mouse model in
262 both hyperlipidaemic and nonhyperlipidaemic mice.(82) In the same mouse model of AAA, Gitlin *et al.*
263 reported that mice with genetic deletion of COX-2 failed to develop AAA. They reported a 73%
264 and 90% reduction in AAA incidence following 7 and 21 days of Ang II infusion respectively and a
265 marked decrease in the aortic expression of the macrophage marker CD68, MCP-1 and macrophage
266 inflammatory protein-1alpha (MIP-1α).(81) This is in contrast to the study by Cao *et al.* reporting that
267 genetic deletion of COX-2 had no significant effect on AAA development within the Ang II-induced
268 AAA mouse model.(83) However, two recent studies provide evidence that mice administered
269 celecoxib have decreased AAA progression and rupture within the Ang II infused mouse model of
270 AAA.(84, 85) Another selective COX-2 inhibitor, MF-tricyclic, was reported to inhibit MMP-9
271 expression and consequently AAA growth within an elastase-induced rat model of AAA.(86) In
272 support, two other studies employing the same elastase-induced rat model of AAA reported that
273 indomethacin (a non-selective COX-2 inhibitor) significantly inhibited PGE₂ and MMP-9 expression
274 thereby preserving elastin integrity and reducing AAA expansion with no effect on the inflammatory
275 infiltrate.(87, 88) Conversely, Armstrong and colleagues reported that indomethacin and rofecoxib (a
276 selective COX-2 inhibitor) failed to impede aneurysm expansion within the elastase-induced AAA rat
277 model.(89) Furthermore, in a small case-control study involving 15 subjects on NSAIDs and 63
278 patients without NSAID, it was reported that AAA growth was significantly reduced in patients
279 receiving NSAIDs compared to controls without NSAIDs.(80) COX inhibitors have been associated
280 with increased incidence of cardiovascular events (myocardial infarction stroke and cardiovascular
281 death), and it is therefore unclear whether they would be safe to give patients with AAA.(90, 91) The

282 conflicting evidence from experimental studies regarding their therapeutic potential does not currently
283 support their trialling in AAA patients. A summary of studies investigating the role of COX in AAA
284 pathogenesis is given in Table 2.

285

286 **Nitric oxide synthases**

287 The family of NOS including inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal NOS
288 (nNOS) are capable of generating NO and L-citrulline by catalysing the oxidation of L-arginine. Both
289 eNOS and nNOS are selectively expressed whereas iNOS is widely distributed within multiple cell
290 types.(12, 92) NO is an important regulator of cardiovascular homeostasis, however evidence suggest
291 that under specific conditions, exaggerated production of NO by iNOS may lead to tissue damage
292 through several mechanisms including the formation of reactive nitrogen species.(93) In addition,
293 uncoupling of eNOS from its cofactors is associated with increased generation of O_2^- .(93, 94) and
294 consequent tissue damage which has been suggested to be relevant in AAA pathogenesis.(94, 95)

295 A number of medications which were not developed to modulate NOS have been suggested to have
296 pleiotropic effects on NOS which in part explain their ability to limit AAA within experimental
297 models (Table 3). For example a number of studies suggest that statin therapy may limit AAA
298 development due to its antioxidant and anti-inflammatory effects.(96-102) In an elastase induced rat
299 model of AAA, Kalyanasundaram *et al.* reported that simvastatin administration resulted in the
300 downregulation of several oxidative stress-related genes including SOD2, HO-1, NOS3 and
301 thioredoxin reductase 1 (TRXR1) with consequent AAA inhibition.(96) Simvastatin was also shown
302 to reduce NF- κ B, MMP-9 and MMP3 expression.(96) This is supported by the study by Steinmetz *et al.*
303 which demonstrated that simvastatin inhibited AAA formation independent of serum cholesterol
304 levels in the C57BL/6 wild type and the ApoE^{-/-} mice using the elastase-infused mice model of
305 AAA.(97) They reported a simvastatin-mediated decrease in MMP-9 and increase in TIMP-1
306 expression, but did not measure any ROS.(97) In contrast, others have reported that simvastatin had
307 no significant effect on aortic diameter within the Ang II-induced mouse model of AAA.(103) In two
308 previous studies, fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR α) activator
309 used clinically to reduce triglycerides, was shown to abrogate Ang II-induced AAA within Ldlr^{-/-} and
310 ApoE^{-/-} mice.(104, 105) Fenofibrate upregulated eNOS within the tunica intima and iNOS within the
311 tunica media and adventitia associated with reduced Ang II induced AAA formation.(105) In addition,
312 within a CaCl₂ mouse model of AAA, iNOS deficient mice were shown to be partly resistant to AAA
313 formation associated with decreased MMP-2, MMP-9 and NO expression within aortic tissues.(18)
314 In contrast, Gao *et al.* reported that mice deficient in the eNOS cofactor tetrahydrobiopterin (H4B)
315 were prone to Ang II-induced AAA formation.(94) They reported that oral folic acid treatment
316 upregulates the expression and activity of the H4B salvage enzyme dihydrofolate reductase within the
317 endothelium, restores eNOS function and inhibited AAA formation.(94) In a further study employing
318 the Ang II infused ApoE^{-/-} mice model of AAA, Siu and colleagues also demonstrated that oral
319 administration of folic acid limited aortic elastin degradation, macrophage infiltration and
320 significantly inhibited AAA expansion by upregulating eNOS activity.(95) Similarly, deletion of the
321 eNOS gene within ApoE^{-/-} mice has been associated with increased AAA formation.(106) These
322 studies suggest that due to the complexity of these enzymes, the underlying difference in the animal
323 models involved, and the inconsistent findings it is currently unclear how NOS regulation is involved
324 in AAA pathogenesis.

325

326 **Heme oxygenases and thioredoxin**

327 HO-1 is an enzyme that reduces oxidative stress by catalysing heme to carbon monoxide, biliverdin,
328 bilirubin, and free ferrous iron.(12, 13, 107, 108) The endogenously produced carbon monoxide is
329 reported to serve as a second messenger influencing cellular proliferation, inflammation, and
330 apoptosis.(109)

331 Nakahashi *et al.* were the first to suggest that HO-1 may be beneficial in limiting AAA
332 development.(24) The authors conducted a microarray analysis to investigate aortic gene expression
333 following a femoral arteriovenous fistula to increase laminar shear and wall strain within an elastase-
334 induced rat model of AAA. They found that flow loading decreased AAA diameter and upregulated
335 HO-1 expression.(24)

336 Two contradictory case-control studies were found examining the relationship between the HO-1 gene
337 promoter region and AAA prevalence in humans.(110, 111) Short (<25 GT) dinucleotide repeats
338 within the HO-1 gene promoter region are associated with greater HO-1 expression whilst longer (\geq 25
339 GT) dinucleotide repeats are associated with lower HO-1 expression in response to recognised
340 stimuli. (112) A study by Schillinger and colleagues suggested that patients with AAA were less
341 frequently carriers of short (< 25 GT) repeats within the HO-1 gene promoter compared to
342 atherosclerotic or healthy controls. The findings suggested that short (<25 GT) dinucleotide repeats
343 within the HO-1 gene promoter region associated with increased HO-1 expression protected against
344 AAA.(110) In contrast, a more recent study by Gregorek *et al.* found more short (< 25 GT) repeats
345 within the HO-1 gene promoter alleles in AAA patients compared to healthy non-aneurysmal
346 controls.(111) Both studies have limitations that may have influenced the results, such as, the small
347 sample sizes (70 AAA patients in the study of Schillinger *et al.* and 117 in the investigation of
348 Gregorek and colleagues), the relatively wide 95 % confidence interval in both studies, and lack of
349 validation of findings. Therefore, it remains to be seen what role HO-1 plays in AAA formation and
350 progression.

351 Thioredoxin (TRX) is a thiol oxidoreductase and regulator of signal transduction found in endothelial
352 cells and VSMC.(41) Functionally, TRX has been suggested to modulate NOX-mediated generation
353 of O_2^- via interaction with p40Phox,(113) and to decrease IL-1 β expression by monocyte-derived
354 macrophages during inflammation.(114) These effects are potentially partly mediated by
355 downregulating macrophage inhibitory factor (MIF).(115)

356 Only one study was found investigating TRX in AAA patients.(22) In a multicentre cohort study, the
357 authors reported that TRX was present at higher concentrations in the serum of patients with AAA
358 and concentrations were correlated with AAA diameter and growth rate.(22) More investigations into
359 the importance of TRX in AAA using experimental and human association studies are needed to
360 further elucidate the role of TRX.

361

362 **Superoxide dismutases and catalases**

363 The efficacy of the SOD system has been reported to rely on the ability of catalase or glutathione
364 peroxidase to subsequently catalyse the decomposition of H_2O_2 to water and oxygen, and inhibit the
365 conversion of H_2O_2 to the $\cdot OH$.(13) H_2O_2 has been reported to promote MMP-3, MMP-9 and MMP-12
366 expression,(116) which have been implicated in ECM degradation important in AAA. The ability of
367 the SOD system to balance H_2O_2 levels could be important in protecting against AAA.

368 Catalase is an enzyme responsible for the degradation of H₂O₂ to water and oxygen and has
369 cardiovascular protective effects,(117) including inhibition of Ang II-induced aortic thickening.(37)
370 Patients with AAA have been reported to have low catalase expression within circulating neutrophils
371 and plasma.(118) Catalase has been reported to abrogate the H₂O₂-mediated increases in MMP
372 expression and inflammatory cytokine secretion. (117, 119)

373 Several studies have investigated the relationship between SOD, catalases and AAA as shown in
374 Table 4.(119-124) In a study, employing an elastase-induced rat model of AAA, Sinha *et al.* reported
375 a significant increase in MnSOD levels and MMP-9 activity in aneurysmal aortas during the early
376 stages of aneurysm formation. CuZnSOD and EcSOD levels were similar in AAAs and control
377 aortas.(120) The authors reported that a SOD mimetic, TEMPOL, increased MMP-2 and MMP-9
378 activity by more than 2-fold in aortic explant cultures, and suggested that strategies aimed at
379 inhibiting oxidative stress during AAA formation should focus on MnSOD.(120) In a recent study
380 employing the CaCl₂ induced mouse model of AAA, a standardised extract from *Ginkgo biloba*, EGb
381 761, reported to possess antioxidant and free radical scavenging properties,(125) was shown to
382 significantly reduce NF- κ B protein expression, MMP-2 and MMP-9 activities within the aorta, inhibit
383 SOD and catalase activity, and decrease aneurysm size.(126) Other studies however report that
384 increased SOD is beneficial against AAA formation.(121) For example, another natural product,
385 diferuloylmethane (curcumin), a phenol found in the dietary spice turmeric,(127) has been reported to
386 exert anti-inflammatory effects via inhibition of ROS production and enhanced SOD expression.(121)
387 Curcumin was also reported to inhibit aneurysm formation.(128) An initial study using the elastase-
388 induced mouse model of AAA showed that curcumin inhibited AAA formation by decreasing aortic
389 inflammation and MMP-9 expression.(129) Similarly, in the Ang II-induced mouse model of AAA,
390 Hao *et al.* reported that oral administration of curcumin significantly decreased aortic macrophage
391 infiltration, MCP-1 and TNF- α concentrations and AAA incidence, and increased SOD activity.(121)
392 Cobalt chloride (CoCl₂), an inhibitor of the hypoxia-inducible factor alpha (HIF-1 α) degrading prolyl
393 hydroxylase domain protein,(130) was reported to restore SOD and catalase expression within a
394 CaCl₂ model of AAA, and inhibit NF- κ B phosphorylation, cytokine expression and consequent AAA
395 formation.(123) Taken together, there is no consistent evidence on the role of SOD in AAA
396 pathogenesis.

397 A study examining the effect of tamoxifen, a selective oestrogen receptor modulator with potent
398 antioxidant and vasodilator properties,(131) demonstrated that rats receiving 10mg/kg/day of
399 tamoxifen subcutaneously exhibited a marked increase in aortic catalase expression associated with
400 significant inhibition of neutrophil infiltration and AAA expansion compared to controls within the
401 elastase-induced rat model of AAA.(124) The direct irreversible catalase inhibitor 3-amino-1, 2, 4-
402 triazole (AT) was shown to significantly abrogate the aneurysm inhibitory effect of tamoxifen by
403 roughly 30%.(124) In addition, transgenic ApoE^{-/-} mice overexpressing the human catalase gene
404 within VSMC where shown to be resistant to Ang II induced aortic wall remodelling thought to be
405 involved in early AAA formation.(132) This finding was supported by a similar study within the
406 CaCl₂ induced mice model of AAA, where both transgenic mice over expressing catalase and mice
407 administered polyethylene glycol-catalase (PEG-catalase) where shown to exhibit decreased MMP
408 activity, decreased VSMC apoptosis and decreased AAA formation.(119) However, mice transgenic
409 for catalase did not have altered H₂O₂ concentrations.(119) These studies suggest that upregulating
410 aortic catalase activity is a putative mechanism to limit AAA progression.

411

412

413 **Studies investigating exogenous and phenolic antioxidants**

414 Exogenous antioxidants including folic acid, vitamin C (ascorbic acid), and vitamin E (α -Tocopherol)
415 are reported to modulate ROS production with implications for AAA pathogenesis.(23, 133-136) For
416 example, vitamin E which has been reported to also inhibit COX expression,(133) has been shown to
417 inhibit AAA formation in two different rodent models of AAA.(23, 24, 137) In the Ang II-induced
418 ApoE^{-/-} mice model of AAA, Gavrilu *et al.* reported decreased concentrations of markers of oxidative
419 stress and aortic macrophage infiltration along with reduction in maximum AAA diameter and
420 incidence of rupture in mice receiving vitamin E.(23) Gopal *et al.* reported that dietary
421 supplementation with vitamin E and β -carotene confers substantial protection against Ang II induced
422 AAA formation. (137) In an elastase-induced rat model of AAA, Nakahashi and colleagues reported
423 that rats receiving vitamin E had significantly decreased AAA expansion compared to controls.(24)
424 Unfortunately in a randomised double-blind placebo-controlled trial, Tornwall *et al.* failed to show
425 any significant association between vitamin E supplementation and the incidence of AAA.(138) The
426 latter study did not include aortic imaging and simply relied on the clinical presentation of AAA. This
427 study does not therefore rule out a benefit of vitamin E in limiting AAA growth.

428 Vitamin C is considered to be one of the most efficient water-soluble antioxidant in human plasma
429 with the ability to scavenge ROS, regenerate α -tocopherol and reduce H4B preventing eNOS
430 uncoupling.(12, 43, 139) Shang *et al.* in a study using the elastase-induced rat model of AAA
431 demonstrated that daily intraperitoneal injection of vitamin C (100mg/ml) significantly decreased 8-
432 hydroxylguanine and 8-isoprostane (markers of oxidative stress), MMP-2, MMP-9 and IL-1 β
433 expression, upregulated TIMP-1 and -2 expression and abrogated AAA expansion by 26%.(10) In a
434 similar study employing the combined elastase and CaCl₂-induced rat model, vitamin C
435 administration was shown to limit AAA formation through downregulation of MMP-9, MCP-1, IL-
436 1 β , TNF α , CD68, and ROS (8-hydroxylguanine).(140)

437 Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a dietary polyphenol commonly found in red wine and
438 grape skin with antioxidant,(141-144) anti-inflammatory,(145) and anti-angiogenic(146) effects has
439 been reported to inhibit experimental AAA.(26, 147) In a CaCl₂ induced mice model of AAA,
440 resveratrol (at 100mg/kg/day) was reported to prevent AAA development by attenuating the
441 expression of glutathione peroxidase, MCP-1, TNF- α and CD68 and reducing the activity of MMP-9
442 and -2.(26) One limitation of this study was the effect of resveratrol at other doses or time points was
443 not reported especially since 100mg/kg/day is quite a large dose within mice. Palmieri *et al.* studied
444 the effect of resveratrol within the elastase-induced rat model of AAA.(147) They reported that male
445 Sprague-Dawley rats receiving 10 mg/kg/day resveratrol one week before until two weeks following
446 AAA induction exhibited significantly decreased CD62L-monocyte subset expansion, CD143
447 monocyte expression, TNF α expression and MMP-9 activity with consequent inhibition of AAA
448 development.(147) In addition, the polyphenolic flavonoid quercetin, which has antioxidant and anti-
449 inflammatory properties,(148) was reported to reduce the aortic expression of MMP-2, MMP-9, and
450 cathepsin, and limit macrophage infiltration with consequent decrease in AAA diameter.(149) In a
451 second experiment, the authors reported the inhibitory effects of quercetin on AAA incidence via
452 attenuation of oxidative stress and MMP activation was in part through the modulation of c-Jun N-
453 terminal kinase (JNK)/AP-1 signalling.(150)

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456 **The potential of modulating oxidative stress to limit AAA growth in patients**

457 The studies noted above provide good evidence that markers of oxidative stress are upregulated in
458 experimental and human AAA. The wide range of oxidative stress pathways upregulated and the
459 number of interactions between these makes it extremely complex to design interventions which can
460 effectively reduce aortic oxidative stress long-term (see Figure 2). This is particularly difficult where
461 high levels of oxidative stress are already present such as within established AAAs. Many of the
462 interventions which have been successful in experimental models have been applied prior to or at the
463 time of AAA induction. However, treatments are needed for established AAAs in patients.(151)
464 Recently a number of strategies which were successfully applied in animal models, such as
465 doxycycline mediated MMP inhibition and use of a mast cell inhibitor, have been reported to be
466 ineffective at limiting AAA growth in patients.(152, 153) It is currently not clear why previous
467 promising strategies to limit AAA growth have not been translated to patients, although suggested
468 reasons include poor design of previous animal studies, inappropriate animal models and ineffective
469 approaches to inhibiting the pathways that were targeted. Given that patients with AAA usually have
470 multiple co-morbidities any treatment to limit AAA growth would need to be very safe. Based on the
471 animal data presented in this review a number of non-toxic antioxidant approaches have potential to
472 limit AAA, such as vitamin E, vitamin C and polyphenolics (curcumin, quercetin, resveratrol).
473 Despite the promising experimental studies there are no clinical trial data to suggest that such simple
474 antioxidant therapies are effective. For example, a clinical trial failed to show any significant
475 association between vitamin E supplement and the incidence of AAA, although no aortic imaging was
476 included in this trial.(138) Whether such simple approaches to modifying oxidative stress can achieve
477 a sustained reduction in aortic oxidative stress is uncertain. Clinical trials to examine the value of
478 these agents in established AAAs are needed to answer this.

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493 **List of abbreviations**

5-LO	5-lipoxygenase
AAA	Abdominal aortic aneurysm
Ang II	angiotensin II
AP-1	Activator protein-1
ApoE ^{-/-}	apolipoprotein E deficient
CaCl ₂	Calcium chloride
cAMP	cyclic adenosine monophosphate
CoCl ₂	Cobalt chloride
COX	Cyclooxygenase
CuZnSOD	Copper-Zinc SOD
ECM	Extracellular matrix
EcSOD	Extracellular SOD
eNOS	Endothelial NOS
FLAP	5-lipoxygenase activating protein
H4B	Tetrahydrobiopterin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HO	Heme oxygenase
IL-1 β	interleukin-1 β
iNOS	Inducible NOS
JNK	c-Jun N-terminal kinase
MCP-1	Monocyte chemoattractant protein-1
MIP	Macrophage inflammatory protein
MMP	Matrix metalloproteinase
MnSOD	Manganese SOD

NADPH	Nicotinamide adenine dinucleotide phosphate
NF- κ B	nuclear factor- κ B
nNOS	Neuronal NOS
NO	Nitric oxide
NOS	Nitric oxide synthase
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
NSAID	nonsteroidal anti-inflammatory drug
PGE2	Prostaglandin E2
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TIMP-1	tissue inhibitor of metalloproteinase-1
TNF α	Tumor necrosis factor α
TNF- α	tumor necrosis factor- α
TRX	Thioredoxin
VSMC	Vascular smooth muscle cells
XO	Xanthine oxidase

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502 **Conflicts of Interest**

503 The authors declare no conflict of interest.

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939 **Figure legends**

940 **Figure 1 A Schematic diagram showing the critical balance between oxidants and antioxidants**
941 **in relation to AAA [modified from [(1)].**

942 Endogenous oxidant systems generate reactive oxygen species (ROS) whilst the antioxidants either
943 detoxify or scavenge ROS. A shift in the balance towards increased oxidant activity, leads to excess
944 ROS and resultant oxidative stress. Oxidative stress with associated tissue damage and other pro-
945 aneurysmal factors may result in AAA.

946 Abbreviations: *may generate ROS, AAA= abdominal aortic aneurysm, COX= cyclooxygenase,
947 ECM= extracellular matrix, LO= lipoxygenase, HO= heme oxygenase, NOS= nitric oxide synthase,
948 NOX= nicotinamide adenine dinucleotide phosphate oxidase, ROS= reactive oxygen species, SOD=
949 superoxide dismutase, TRX= thioredoxin, VSMC= vascular smooth muscle cells, XO= xanthine
950 oxidase.

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952 **Figure 2 Overview of the mechanism leading to oxidative stress and potential treatments to limit**
953 **oxidative stress associated with AAA.**

954 AAA risk factors include smoking, male gender, advanced age and family history. Pro-inflammatory
955 agents include Ang II. ROS generating enzymes include eNOS, NOX, XO, LO, COX. ROS degrading
956 systems include SOD and catalase. O_2 is converted to O_2^- by NOX. SOD inactivates O_2^- forming
957 H_2O_2 , and catalase converts H_2O_2 to H_2O and O_2 . Under pro-aneurysmal conditions, H_2O_2 could be
958 converted to $\cdot OH$ by the Fenton and/or the Haber-Weiss reactions. In addition, O_2^- then combines
959 with NO produced by eNOS to form the highly reactive ONOO \cdot . The increase generation of ROS
960 within the aorta results in oxidative stress which leads to enhance ACE expression which promotes
961 Ang II production and resultant positive feedback activation of more pro-oxidant enzymes. Oxidative
962 stress also promotes mitochondria dysfunction, activates signalling molecules, and potentiates
963 inflammation. It also increases pro-inflammatory cytokine secretion with resultant recruitment of
964 effector immune cells, release of proteases, leading to ECM degradation, VSMC apoptosis and
965 consequent AAA development and progression. Key targets currently under investigation include: 1).
966 Preventing eNOS uncoupling using vitamins, 2). Preventing the production of O_2^- using NOX-
967 inhibitors, TRX or genetic approaches, 3). Blocking the COX-2 and/or LO pathways using vitamins
968 and NSAID, 4). Enhancing the effect of SOD using SOD mimetics, folic acid and polyphenolics, 5).
969 Applying catalase activators to improve the detoxification of H_2O_2 , 6). Using polyphenolics to inhibit
970 ROS-induced signalling and 7). Employing vitamins, polyphenolics and NSAID to scavenge ROS and
971 prevent oxidative stress.

972 Abbreviations: 5-LO= 5-lipoxygenase, AAA= abdominal aortic aneurysm, ACE= angiotensin
973 converting enzyme, Ang I= angiotensin I, Ang II= angiotensin II, AP-1= activator protein-1, COX=
974 cyclooxygenase, ECM= extracellular matrix, eNOS= endothelial nitric oxide synthase, Erk1/2=
975 extracellular signal-regulated kinase 1/2, Fe^{2+} = ferrous iron, Fe^{3+} = ferric iron, H_2O_2 = hydrogen
976 peroxide, IL-1 β = interleukin-1 beta, JNK= c-Jun N-terminal kinase, LO= lipoxygenase, MCP-1=

977 monocyte chemoattractant protein-1, MMP= matrix metalloproteinase, NF- κ B= nuclear factor kappa
978 beta, NO= nitric oxide, NOS= nitric oxide synthase, NSAIDS= nonsteroidal anti-inflammatory drugs,
979 NOX= nicotinamide adenine dinucleotide phosphate oxidase, O₂⁻= superoxide, [•]OH= hydroxyl
980 radical, ONOO[•] = peroxynitrite, ROS= reactive oxygen species, SOD= superoxide dismutase, TNF-
981 α = tumour necrosis factor- α , VSMC= vascular smooth muscle cells, XO= xanthine oxidase. Symbols
982 indicate: \uparrow increase; \downarrow decrease.

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1010 **Tables**1011 **Table 1** Overview of studies assessing the lipoxygenase pathway in AAA

Therapies	Key findings	AAA model	Reference
BLT1 inhibition (genetic).	Inhibition of the 5-LO metabolite, LTB ₄ mediated-inflammation. Decreased MMP-2 and -9 expression. Decreased inflammatory cell infiltrate and decreased AAA formation.	Ang II-infused ApoE ^{-/-} mouse model of AAA.	(72)
5-LO inhibition (genetic and pharmacological).	Decreased MMP-9 activity and effector immune cell recruitment. 71% (genetic) and 54% (pharmacological) reduction in aortic dilatation.	Elastase perfused- and Ang II-infused Ldlr ^{-/-} mouse models of AAA.	(67)
None.	Upregulated 5-LO, FLAP, and LTC ₄ S transcripts in aneurysmal aorta compared with non-aneurysmal control aortas.	Human.	(74)
5-LO inhibition (genetic deletion).	Decreased MMP-2 and MIP-1 α expression. Decreased AAA incidence.	Cholate fed ApoE ^{-/-} mice.	(66)
BLT1 inhibition (pharmacological)	Diminished macrophage accumulation, decreased incidence of AAA when administered at the same time as Ang II, but no significant effect on AAA size when administered 14 days after AAA induction.	Ang II-infused ApoE ^{-/-} mouse model of AAA.	(68)
Generalised ROS inhibition (endaravone).	Decreased MMP-2, MMP-9, and ROS expression. Reduced AAA formation (when administered from the onset of AAA induction), and expansion (when administered to already established AAAs).	Combined elastase-induced and CaCl ₂ -induced rat models of AAA.	(71)
5-LO inhibition (genetic and pharmacological).	No significant effect on aortic media inflammation or AAA development in 5-LO deficient mice or mice administered FLAP inhibitor (MK-0591).	Ang II-infused ApoE ^{-/-} mouse model of AAA.	(73)
None.	No association between 7 single nucleotide polymorphisms in ALOX5AP, the gene encoding FLAP with human AAA.	Human.	(76)

1012 Abbreviations: 5-LO= 5-lipoxygenase, Ang II= angiotensin-II, ApoE^{-/-} = apolipoprotein E-deficient,
 1013 BLT1= leukotriene B4 receptor-1, FLAP= 5-LO activating protein, CaCl₂= calcium chloride, Ldlr^{-/-} =
 1014 low density lipoprotein receptor knockout, LTB₄= leukotriene B₄, LTC₄S= leukotriene C₄ synthase,
 1015 MIP= macrophage inflammatory protein, MMP== matrix metalloproteinase, ROS= reactive oxygen
 1016 species.

1017 **Table 2** Studies assessing the association of the cyclooxygenase pathway with AAA

Therapies	Key findings	AAA model	Reference
COX-2 inhibition (pharmacological).	Decreased incidence and severity of AAA.	Ang II-infused mouse model of AAA.	(82) (84) (85)
COX-2 inhibition (genetic deletion).	Decreased MCP-1, MIP-1 α expression. Decreased macrophage infiltration. Decreased AAA formation.	Ang II-infused mouse model of AAA.	(81)
COX-2 inhibition (genetic deletion).	No significant effect on AAA incidence.	Ang II-infused ApoE ^{-/-} mouse model of AAA.	(83)
COX-2 inhibition (pharmacological).	Decreased MMP-9 expression and decreased AAA development. Decreased PGE ₂ and MMP-9 expression. Decreased inflammatory cell infiltration. Decreased AAA expansion.	Elastase-induced rat model of AAA.	(86) (87) (88)
COX-2 inhibition (pharmacological).	Decreased MMP-9 expression but no significant effect on AAA expansion.	Elastase-induced rat model of AAA.	(89)
None	Significant reduction in AAA growth in patients on NSAIDS compared to patients without NSAIDS.	Human case-control study.	(80)

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1019 Abbreviations: Ang II= angiotensin-II, ApoE^{-/-} = apolipoprotein E-deficient, COX-2=
 1020 cyclooxygenase-2, MCP= monocyte chemoattractant protein, MIP= macrophage inflammatory
 1021 protein, MMP= matrix metalloproteinase, NSAIDS= nonsteroidal anti-inflammatory drugs, PGE₂=
 1022 prostaglandin E-2, VSMC= vascular smooth muscle cell.

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1030 **Table 3** Overview of studies assessing the effects of medications known to affect NOS and/or direct
 1031 NOS inhibition in AAA

Therapies	Key findings	AAA model	Reference
Simvastatin	Decreased MMP-9, MMP-3, and NF- κ B expression. Increased TIMP-1 expression. Decreased AAA formation.	Elastase-induced mouse model of AAA.	(147) (Steinmetz 2005)
Simvastatin	Decreased macrophage infiltration. No significant effect on AAA diameter.	Ang II-infused ApoE ^{-/-} and Ldlr ^{-/-} mouse models of AAA.	(153) (Golledge 2010)
Fenofibrate	Decreased inflammatory cell and cytokine expression. Decreased VSMC apoptosis. Decreased AAA development.	Ang II-infused ApoE ^{-/-} and Ldlr ^{-/-} mouse models of AAA.	(105) (120)
iNOS inhibition (genetic).	Decreased MMP-9, MMP-2, and NO expression. Decreased AAA formation.	CaCl ₂ -induced mouse model of AAA.	(18)
H4B and eNOS inhibition (genetic).	Increased MMP-9, MMP-2 expression. Increased macrophage infiltration. Increased AAA formation. Folic acid administration blocked the AAA promoting effect of H4B deficiency.	Ang II-infused mouse model of AAA.	(94)
eNOS upregulation (pharmacological).	Decreased ECM degradation. Decreased macrophage infiltration. Decreased O ₂ ⁻ production. Decreased AAA expansion.	Ang II-infused mouse model of AAA.	(95)

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1033 Abbreviations: Ang II= angiotensin-II, ApoE^{-/-} = apolipoprotein E-deficient, CaCl₂= calcium
 1034 chloride, ECM= extracellular matrix, eNOS= endothelial nitric oxide synthase, H4B=
 1035 tetrahydrobiopterin, iNOS= inducible nitric oxide synthase, Ldlr^{-/-} = low density lipoprotein receptor
 1036 knockout, MMP= matrix metalloproteinase, NF- κ B= nuclear factor kappa beta, NO= nitric oxide,

1037 O₂⁻ = superoxide , TIMP-1= tissue inhibitor of matrix metalloproteinase-1, VSMC= vascular smooth
 1038 muscle cells.

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1041 **Table 4** Overview of studies assessing superoxide dismutase and/or catalase in AAA

Therapies	Key findings	AAA model	Reference
SOD inhibition (pharmacological).	Decreased MMP-2, MMP-9, and NF-κβ expression. Decreased SOD and catalase activity. Decreased AAA size.	CaCl ₂ -induced mouse model of AAA.	(126)
SOD upregulation (pharmacological).	Decreased aortic MCP-1, and TNF-α expression. Decreased macrophage infiltration. Increased SOD activity. Decreased AAA incidence.	Ang II-infused ApoE ^{-/-} mouse model of AAA.	(121)
None.	Higher catalase activity. Reduced NF-κβ expression. No effect on SOD activity and H ₂ O ₂ in AAA wall in vitro.	Human.	(122)
Catalase upregulation (pharmacological).	Decreased aortic neutrophil infiltration. Decreased AAA expansion in rats receiving tamoxifen to increase catalase expression. A catalase inhibitor (AT) blocked the AAA protective effects of tamoxifen.	Elastase-induced rat model of AAA.	(124)
Catalase upregulation (genetic).	Transgenic mice overexpressing catalase exhibited increased H ₂ O ₂ degradation and decreased aortic wall remodelling.	Ang II-infused mouse model of AAA.	(163) (Maiellaro_ rafferty, 2011)
Catalase upregulation (genetic and pharmacological).	Decreased MMP activity. Decreased VSMC apoptosis. Decreased AAA formation.	CaCl ₂ -induced mouse model of AAA.	(119)

1042 Abbreviations: Ang II= angiotensin-II, ApoE^{-/-} = apolipoprotein E-deficient, AT=3-amino-1, 2, 4-
 1043 triazole, CaCl₂= calcium chloride, H₂O₂= hydrogen peroxide, MMP== matrix metalloproteinase,
 1044 MnSOD= manganese superoxide dismutase, NF-κβ= nuclear factor kappa beta, SOD= superoxide
 1045 dismutase, TNF-α= tumor necrosis factor-α, VSMC= vascular smooth muscle cells.

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