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SYSTEMATIC REVIEW

Systematic Review Examining the Association Between Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Prescription and Abdominal Aortic Aneurysm Growth and Events

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WHAT THIS PAPER ADDS

There are conflicting reports about whether angiotensin II blockade is effective at limiting abdominal aortic aneurysm (AAA) growth and events. This systematic review and meta-analysis found that angiotensin converting enzyme inhibitor prescription was associated with a significantly lower risk of AAA rupture and AAA related events but was not associated with significantly slower AAA growth or reduced risk of AAA repair. There was no significant association between prescription of an angiotensin receptor blocker and AAA growth or events. These findings were based on a very low certainty of evidence.

Objective: Whether angiotensin II blockade is an effective medical treatment for abdominal aortic aneurysms (AAAs) has not been established. This systematic review and meta-analysis aimed to determine the association between angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) prescription and AAA growth and events.

Data sources: MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library databases were searched from their inception to 4 January 2024, with no language restrictions.

Review Methods: The five databases were searched for randomised controlled trials (RCTs) and observational studies reporting the association between ACEi or ARB prescription and AAA growth, repair, or rupture. The primary outcome was AAA growth, with secondary outcomes of AAA rupture, AAA repair, and AAA related events (rupture and repair combined). Risk of bias was assessed using the Risk of Bias 2 tool for RCTs and with a modified Newcastle—Ottawa scale for observational studies. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). Random effects models were used for meta-analyses.

Results: Eleven studies (two RCTs, eight observational studies, and one meta-analysis of individual patient data from seven populations) involving 58 022 patients were included. ACEi prescription was not associated with a statistically significant reduction in AAA growth (standard mean difference 0.01 mm/year, 95% confidence interval [CI] −0.26 − 0.28; $p = .93$; $I^2 = 98\%$) or AAA repair (odds ratio [OR] 0.73, 95% CI 0.50 − 1.09; $p = .65$; $I^2 = 61\%$), but was associated with a statistically significantly lower risk of AAA rupture (OR 0.87, 95% CI 0.81 − 0.93; $p < .001$; $I^2 = 26\%$) and AAA related events (OR 0.82, 95% CI 0.72 − 0.95; $p = .006$; $I^2 = 80\%$). ARB prescription was not associated with significantly reduced AAA growth or a lower risk of AAA related events. The two RCTs had a low risk of bias, with one observational study having low, seven moderate, and one high risk of bias. All of the findings had a very low certainty of evidence based on the GRADE analysis.

Conclusion: There was no association between ACEi or ARB prescription and AAA growth, but ACEi prescription was associated with a reduced risk of AAA rupture and AAA related events with very low certainty of evidence.

Keywords: AAA event, Abdominal aortic aneurysm, Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker, Growth, Rupture
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INTRODUCTION

Clinical guidelines recommend that small, asymptomatic abdominal aortic aneurysms (AAAs) are treated conservatively with surveillance imaging until the aortic diameter reaches $\geq$ 55 mm in men and $\geq$ 50 mm in women.[1,2] Approximately 70% of small AAAs expand during long term follow up to the threshold for surgical repair.[3–5] There is an unmet need for medical therapies to slow AAA growth and to reduce the risk of aneurysm rupture and the need for AAA repair (defined together as AAA related events).[6,7] Surveys and consultations with patients and vascular surgeons have identified that finding medical therapies for AAAs is a research priority.[8,9] Metformin, antibiotics, statins, antithrombotics, and antihypertensive drugs have been investigated as potential AAA therapies, but there is currently no high quality evidence to suggest their efficacy in limiting AAA growth and events.[6,10,11]

Excessive extracellular matrix remodelling is strongly implicated in AAA pathogenesis.[12] Numerous studies have implicated the matrix metalloproteinase (MMP) family of enzymes in elastin and collagen degradation of the tunica media typically found in AAAs.[13,14] Studies in animal models suggest that angiotensin II promotes AAA formation by stimulating activation of MMPs and aortic inflammation.[15] Subcutaneous angiotensin II infusion is a method of inducing aortic expansion and rupture in mice.[6,12] Studies in mouse models suggest that angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) drugs limit aortic expansion, but the translational relevance to patients with AAA is unknown.[16,17]

Two small randomised controlled trials (RCTs) have examined the effect of drugs blocking the renin–angiotensin pathway on the growth of small AAAs. The Telmisartan in the Management of Abdominal Aortic Aneurysm (TEDY) trial and the Aortic Aneurysmal Regression of Dilation: Value of ACE Inhibition on Risk (AARDVARK) trial investigated the effect of telmisartan and perindopril on AAA growth.[18,19] Neither study found a significant effect of the drugs tested, but both trials were underpowered to show a small or moderate treatment effect.[18,19] There have also been multiple observational studies examining the association between ACEi and ARB prescription with AAA outcomes, but these have reported conflicting findings.[11,12]

The aim of this study was to collate the available evidence and to perform an up to date systematic review and meta-analysis of the association between ACEi or ARB prescription and AAA growth and AAA related events.

METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] The study protocol was registered with the PROSPERO database in January 2023 (CRD42023415456).

Literature search

A literature search was conducted to identify human studies that investigated whether ACEi and ARB drugs reduced AAA growth and lowered the risk of AAA rupture and repair. MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library databases were searched from their inception to 4 January 2024, with no language restrictions. A senior librarian was consulted to help formulate the search strategy. The database searches were supplemented by reviewing the reference lists of included studies to identify additional articles. The search strategy was: (angiotensin converting enzyme OR ACE inhibitor OR ACE OR angiotensin receptor OR angiotensin receptor blocker OR ARB OR angiotensin blockade) AND (AAA OR abdominal aortic aneurysm OR aortic aneurysm) AND (size OR growth OR repair OR surgery OR rupture). The full search strategy with MeSH terms is included in the Supplementary Material.

Two independent researchers (K.T. and K.G.) searched for eligible studies, which were collated with duplicates removed. To be included, studies needed to be RCTs or observational studies examining the effect of ACEi or ARBs on AAA growth and/or the risk of AAA rupture or surgical repair. Aneurysm surveillance studies that reported ACEi and ARB prescription data were also included. Both retrospective and prospective studies were eligible. No studies were excluded based on sample size. Unpublished studies and those that were currently underway were not included. Conference abstracts and studies without full texts were not included. Studies could be included in the meta-analysis if AAA growth data were reported as a standardised mean difference (SMD) with 95% confidence interval (CI) or as unadjusted growth rates. If data were in neither format, they were excluded from the study and analyses. If multiple studies had overlapping data, the more recent publication was selected for the meta-analysis, with the smaller older series excluded. This is on the assumption that the more recent study would have the most updated outcome data.

Eligible patients were those with AAA, defined as abdominal aortic diameter $\geq$ 30 mm. The primary outcome was AAA growth. Secondary outcomes were AAA rupture alone, AAA repair alone, and AAA related events (i.e., combined outcomes of AAA rupture and repair).

Data collection

Two investigators (K.T. and S.T.) independently collected data from the eligible studies by completing a pre-designed form. The following data were collected: sample size; risk factors (age, sex, smoking history, hypertension, diabetes); follow up period; drug or drug class investigated; rate of AAA growth; number of AAA ruptures; and AAA repair. If additional data were required, the corresponding author of the study was contacted.

Risk of bias assessment

Two investigators (K.T. and K.G.) independently evaluated the included studies for methodological quality and

potential risk of bias. For observational studies, a quality assessment tool was developed based on a modification of the Newcastle—Ottawa scale (Supplementary Table S1).[21] This tool included a scoring system whereby two points were given if a criterion was fulfilled, one point if only partially fulfilled, or 0 points if it was not fulfilled. The total score was expressed as a percentage, with $< 50\%$, $50 - 70\%$, and $> 70\%$ representing high, moderate, and low risk of bias, respectively. The quality measures this tool assessed included: study objective; design; sample size estimation; patient characteristics; AAA imaging modality; AAA size assessment; definition of rupture; accounting for confounding variables; and prospective or retrospective design. RCTs were assessed with the Cochrane Risk of Bias 2 (RoB2) tool.

The collected data and quality assessment were cross-checked between investigators, and discrepancies were resolved through discussion. If consensus could not be reached, then a mediating investigator (J.G.) was consulted for resolution.

Statistical analyses

Unadjusted data were used from the included studies. In line with a previous study, a minimum of three studies investigating the association of either drug with any of the individual outcomes was required for a meta-analysis to be performed.[21] Separate analyses were performed for ACEi and ARB drugs due to their distinct mechanisms of action and physiological effects. In studies where growth rates of participants with and without ACEi or ARB treatments were reported, the SMD and standard error (SE) was initially computed by developing a random effects model. Subsequently, this computed SMD was incorporated alongside other studies where the SMD $\pm$ SE estimates were directly reported. The integration of both computed and directly reported SMD values allowed for a comprehensive and combined examination of the effect sizes across all studies included in the analysis. This approach was the best possible method for robust assessment of SMD estimates. In studies providing CIs, the logarithm of the upper and lower CI bounds was determined, and the difference between these logarithmic values was computed. This difference was subsequently divided by 3.92 to incorporate the 95% CI, yielding an estimated SE. Meta-analyses were performed using the inverse variance method with random effects models owing to the expected heterogeneity between studies. The meta-analysis of AAA growth rate outcomes was reported as summary estimates of SMD with 95% CI. The Sidik—Jonkman method (τ^2) and the I^2 statistic were calculated to assess heterogeneity between the studies. Risk of AAA related events, AAA rupture, and surgical repair were reported as the odds ratio (OR) with 95% CI. If the raw data or OR were not available, the OR was calculated from hazard ratio (HR) using the formula $OR = HR(1 - p)$, where p is the probability of an event in the control group, using a control event rate of 5%. Results were visually represented using Forest plots for all outcomes. All analyses were performed using R software 4.2.3 using meta and dmetaR packages. Statistical significance was interpreted at a p value of $\leq .050$. The certainty of evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) using the GRADEpro guideline development tool. Publication bias was assessed for an individual outcome if the analysis contained ten or more studies, as per the *Cochrane Handbook for Systematic Reviews of Interventions*.[22]

RESULTS

Characteristics of included studies

A total of 2 851 citations were identified with the search strategy. Twelve studies met the eligibility criteria, but one was excluded[23] because it contained duplicate data from the Chichester AAA screening programme.[24] Ultimately, 11 studies were included involving 58 022 patients with AAA who had either been prescribed ACEi or ARB or had been prescribed neither drug (regarded as controls) (Fig. 1). The studies included two RCTs,[18,19] two case control studies,[25,26], and six cohort studies (Table 1).[27—32] An additional meta-analysis of seven different series was also included,[33] which analysed individual patient data

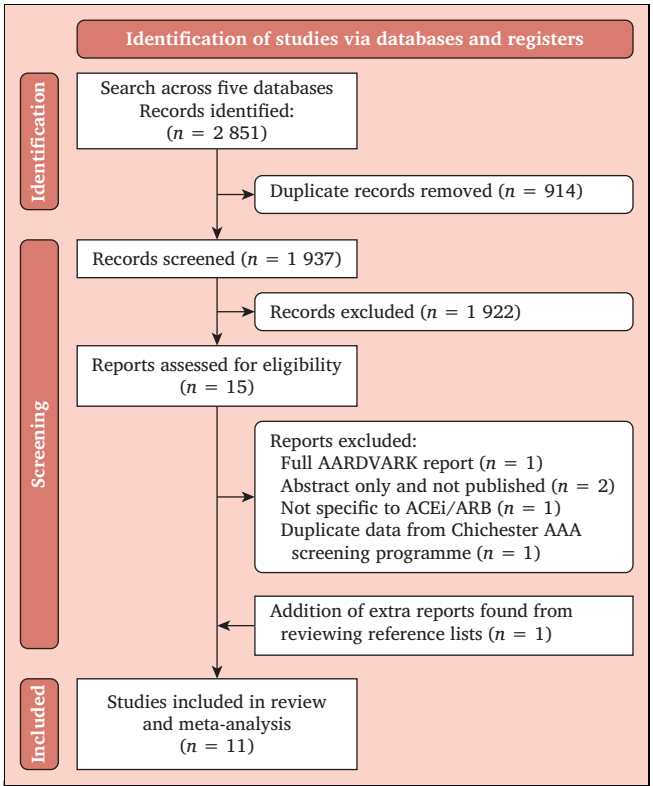

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart illustrating selection of the 11 studies included in this systematic review and meta-analysis examining whether angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) were associated with reduced abdominal aortic aneurysm (AAA) growth and events. The full AARDVARK report was excluded because it contained no additional data compared with the abbreviated report.

from seven surveillance programmes, including one unpublished series.

The screening and study selection process is detailed in a PRISMA flowchart in Figure 1. The baseline characteristics of the patients are shown in Supplementary Table S2.

Risk of bias of included studies

The two RCTs were deemed low risk of bias based on the RoB2 tool, each being low risk in all five categories (Supplementary Table S3).[18,19] Of the observational studies, one was deemed low risk of bias,[28] seven moderate risk of bias,[25,27,29–33] and one high risk of bias (Supplementary Table S4).[26]

All the observational studies had a clear primary objective and were of retrospective design, except one that was prospective.[32] Six of these studies used computed tomography or ultrasonography to study AAA growth.[28–33] Thorough description of AAA diameter measurement was only reported in one study.[31] All studies, except one,[33] compared the baseline characteristics of patients. All studies, except two that did not perform adjusted analyses,[31,32] described how confounders were accounted for in the analyses. None of the studies appropriately defined AAA rupture. Based on the quality assessment tool, the observational studies had a mean quality score of 56.3 ± 9.3%.

Association between angiotensin converting enzyme inhibitor prescription and abdominal aortic aneurysm growth and events

Six studies, including 12 individual series, reported the association between ACEi prescription and AAA growth.[19,28–30,32,33] Only two of these studies compared baseline patient characteristics between the medication and control groups, with

Table 1. Characteristics of the 11 included randomised controlled trials (RCTs) or observational studies investigating whether angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) were associated with a reduction in abdominal aortic aneurysm (AAA) growth and events.

Author	Year	*n*	Design	Drug	Imaging	Outcome	AAA growth rate − mm/y	AAA events	*p* value
Bicknell *et al.*[19]	2016	152	RCT	ACEi	US	Growth	1.77 ± 0.2 *vs.* 1.68 ± 0.2	–	.78
Golledge *et al.*[18]	2020	210	RCT	ARB	US + CTA	Growth	1.68 ± 0.35 *vs.* 1.78 ± 0.34	–	.66
						Repair	–	RR 1.35 (95% CI 0.54–3.35)	.52
Hackam *et al.*[25]	2006	15 326	Case control	ACEi	–	Rupture	–	OR 0.82 (95% CI 0.74–0.90)	<.001
Gellatly *et al.*[32]	2024	3 670	Cohort study	ACEi	US	Growth	−0.234 (95% CI −0.313 – −0.173)	–	<.001
				ARB			−0.253 (95% CI −0.333 – −0.173)	–	<.001
Kortekaas *et al.*[31]	2014	286	Cohort study	ACEi	US	Growth	−0.24 (95% CI −0.90–0.45)	–	>.050
Kristensen *et al.*[27]	2015	9 441	Cohort study	ACEi	US + CTA	Repair	–	HR 0.86 (95% CI 0.74–0.99)	.040
				ARB			–	HR 1.02 (95% CI 0.84–1.23)	.87
Lederle *et al.*[28]	2015	2 428	Cohort study	ACEi	US + CTA	Growth	2.0 *vs.* 2.1	–	.61
				ARB			1.8 *vs.* 1.9	–	.82
Sweeting *et al.*[29]	2010	1 701	Cohort study	ACEi	US	Growth	3.37 *vs.* 2.74	–	.009
Sweeting *et al.*[33] *	2012	2 682	Meta-analysis of IPD	ACEi	US + CTA	Growth	−0.125	–	.38
Thompson *et al.*[30]	2010	1 269	Cohort study	ACEi	US	Growth	2.04 ± 0.24 *vs.* 1.76 ± 0.27	–	.17
				ARB			1.96 ± 0.23 *vs.* 1.03 ± 0.48	–	.040
Wemmelund *et al.*[26]	2016	20 857	Case control	ACEi	–	Rupture	–	OR 1.02 (95% CI 0.88–1.19)	–
				ARB			–	OR 1.02 (95% CI 0.83–1.26)	–

AAA = abdominal aortic aneurysm; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; CTA = computed tomography angiography; HR = hazard ratio; IPD = individual patient data; OR = odds ratio; RCT = randomised controlled trial; RR = relative risk; US = ultrasound.

* Sweeting *et al.* (2012) included data from seven separate series (4 909 patients), six of which were included in the growth analysis (2 682 patients), excluding one series due to data duplication (2 227 patients).

similar risk factor profiles in the two groups.[19,29] Two cohort studies and one unpublished AAA surveillance series (Leeds, UK) found significant associations between ACEi prescription and a reduction in AAA growth compared with patients who were not prescribed these drugs.[31,32] However, one RCT and one retrospective observational study found no difference between these patient groups,[19,29] as did five series that were included in Sweeting *et al.*'s 2012 meta-analysis.[33] Two retrospective observational studies reported faster AAA growth in patients who had been prescribed ACEi compared with controls.[28,30]

Four studies reported the association between ACEi prescription and AAA related events.[19,25–27] Two of these studies compared the baseline characteristics and risk factors of the patients in both groups and found no significant differences.[19,27] One RCT reported similar rates of AAA events in patients who were and were not prescribed ACEi.[19] Two of the seven cohorts presented by Sweeting *et al.* examined the association between the ACEi prescription and AAA related events, neither of which showed a significant association.[33] Two retrospective studies found that there was an association between ACEi prescription and a lower risk of AAA rupture.[25,26] Another retrospective observational study associated ACEi prescription with a 14% reduced risk of AAA repair.[27]

The meta-analysis of AAA growth included seven studies.[19,28–33] The 2012 study by Sweeting *et al.* comprised of datasets from seven series, of which the SMD of each was available and included individually in the meta-analysis.[33] The UK Small Aneurysm Trial (UKSAT) data included in Sweeting *et al.*'s 2012 study,[33] which was extracted from the publication authored by Brady *et al.*, overlapped with their earlier study from 2010.[29] Therefore, the data reported by Brady *et al.* were excluded from the analyses to prevent data duplication because the Sweeting *et al.* article was published more recently and would have more up to date data.

The primary analysis suggested no statistically significant difference in AAA growth rate in patients prescribed ACEi compared with controls (SMD 0.01 mm/year, 95% CI −0.26 − 0.28; $p = .93$; $I^2 = 98\%$) (Fig. 2). Patients who were prescribed ACEi had a statistically significantly lower risk of AAA related events (OR 0.82, 95% CI 0.72 − 0.95; $p = .006$; $I^2 = 80\%$) and lower risk of AAA rupture (OR 0.87, 95% CI 0.81 − 0.93; $p < .001$; $I^2 = 26\%$) compared with patients who were not prescribed ACEi (Fig. 3). There was no significant association between ACEi prescription and the risk of AAA repair (Fig. 3).

Association between angiotensin receptor blocker prescription and abdominal aortic aneurysm growth and events

Four studies reported the association between ARB prescription and AAA growth.[18,28,30,32] Only one study compared baseline patient characteristics between groups and found no significant differences.[18] A RCT found that ARB prescription was not significantly associated with AAA growth,[18] whilst there were mixed findings in multiple retrospective cohort studies, with two suggesting an association with reduced growth rate,[28,32] and one suggesting that ARB prescription was not associated with quicker AAA growth.[30]

Three studies reported the relationship between ARB prescription and AAA related events.[18,26,27] There were no significant differences in baseline characteristics of the two groups in all three studies. One RCT reported no significant difference in the risk of AAA repair in patients who were and were not prescribed ARB drugs,[18] whilst a retrospective cohort study suggested that ARB prescription was associated with a higher risk of AAA repair.[27] Wemmelund *et al.*'s retrospective cohort study suggested no significant association between ARB prescription and AAA rupture.[26]

The meta-analysis showed that there was no statistically significant association between ARB prescription and AAA growth (SMD 0.34 mm/year, 95% CI −0.77 − 1.44; $I^2 = 100\%$) (Fig. 4). There was also no statistically significant

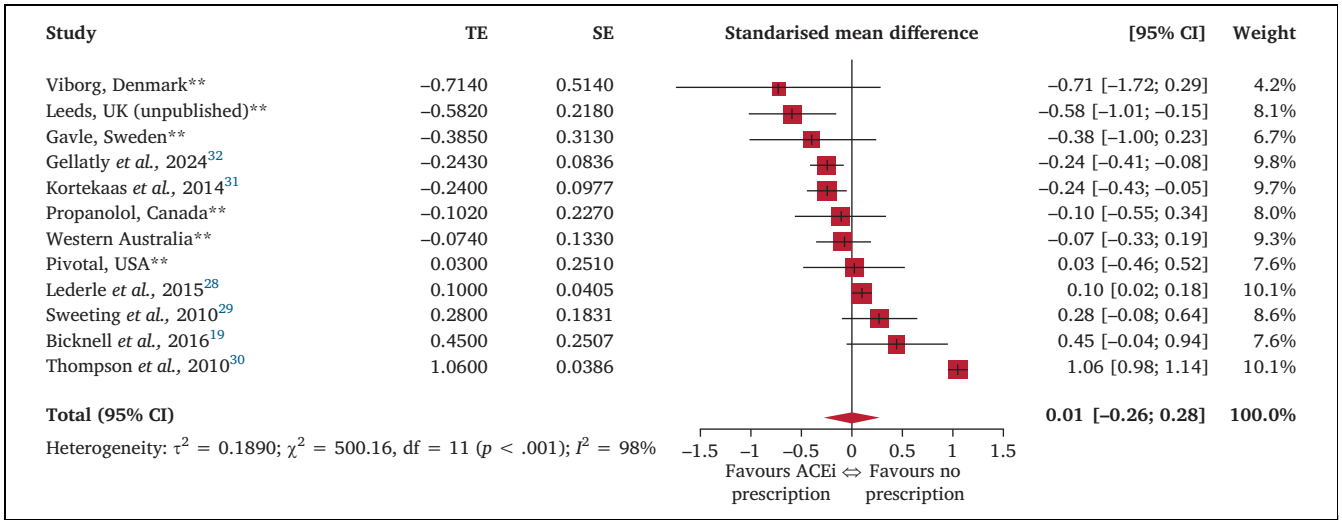

Figure 2. Forest plot illustrating meta-analysis of seven studies, including 12 series of 11 903 patients, examining whether angiotensin converting enzyme inhibitors (ACEi) were associated with abdominal aortic aneurysm growth. ** These data are from six series (from an original seven total series) that were extracted from a meta-analysis of individual patient data.[33] One of the original seven series was excluded (UK Small Aneurysm Trial [UKSAT]) owing to duplicate data. TE = total error; SE = standard error; CI = confidence interval.

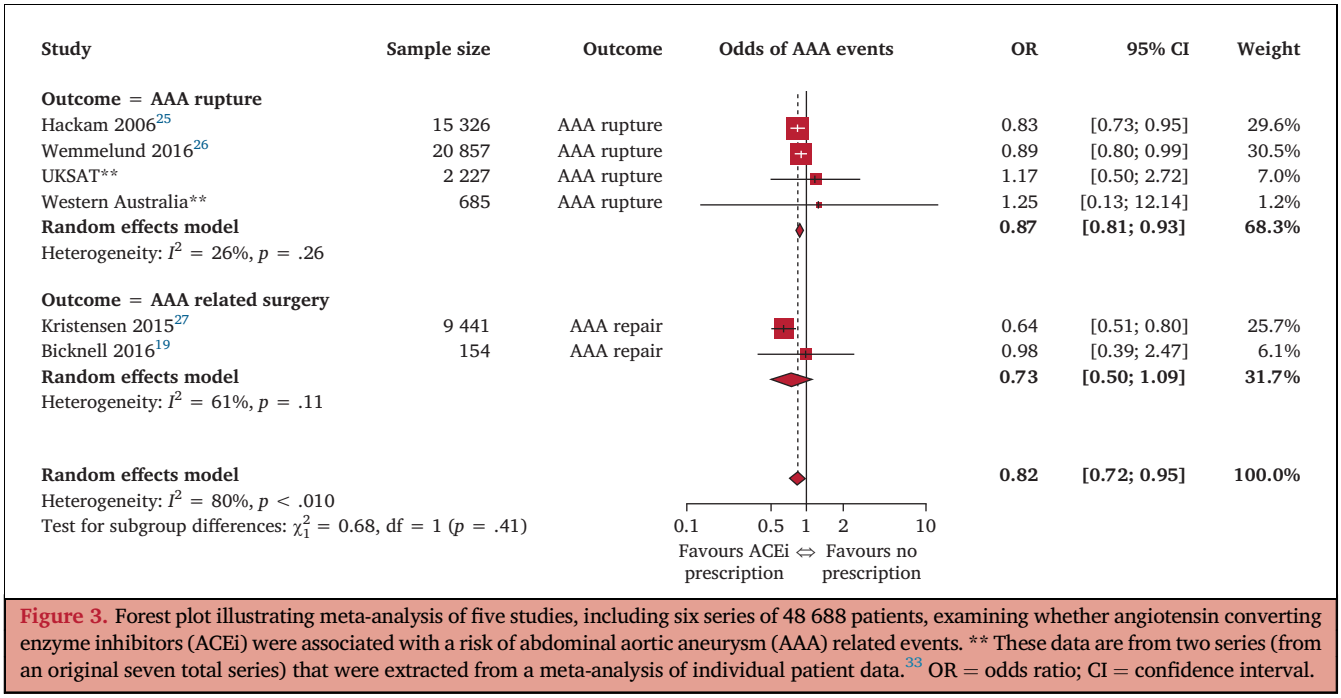

Figure 3. Forest plot illustrating meta-analysis of five studies, including six series of 48 688 patients, examining whether angiotensin converting enzyme inhibitors (ACEi) were associated with a risk of abdominal aortic aneurysm (AAA) related events. ** These data are from two series (from an original seven total series) that were extracted from a meta-analysis of individual patient data.[33] OR = odds ratio; CI = confidence interval.

association between ARB prescription and AAA related events (OR 1.24, 95% CI 0.41 — 3.77; I^2 = 95%) (Fig. 5).

Certainty of evidence

The GRADE summary is provided in Supplementary Tables S5 and S6 and suggested a very low certainty of evidence for all findings.

Publication bias

Sufficient studies were only available to examine publication bias for the meta-analysis assessing the association between ACEi prescription with AAA growth. The funnel plot was asymmetrical, suggesting the possibility of publication bias (Supplementary Figure S1).

DISCUSSION

Clinical guidelines do not specifically recommend prescription of ACEi and/or ARB drugs in patients with AAA.[1,2] This meta-analysis found low quality evidence for significant associations between ACEi prescription and reduced risk of AAA rupture and events. There was no significant association between ACEi prescription and AAA growth or between ARB prescription and AAA growth or events. Interpretation of these findings is limited by the low quality of the evidence because of high risk of bias, substantial heterogeneity, and the indirectness of findings.

One of the included observational studies was a meta-analysis of individual patient data from seven surveillance programmes, including the UK Small Aneurysm Trial (UKSAT) and the Positive Impact of Endovascular Options for Treating Aneurysms Early (PIVOTAL) trial.[33] In keeping with the overall finding of this study, the prior analysis suggested no significant effect of ACEi on AAA growth both in univariable and multivariable analyses.

The main finding of this meta-analysis was that ACEi prescription was associated with a reduced risk of AAA related events and rupture. This finding is in line with a recent review on the management of AAA, which included a meta-analysis of the effects of ACEi on AAA rupture, but this was not a systematic review.[34] In this previous analysis, ACEi

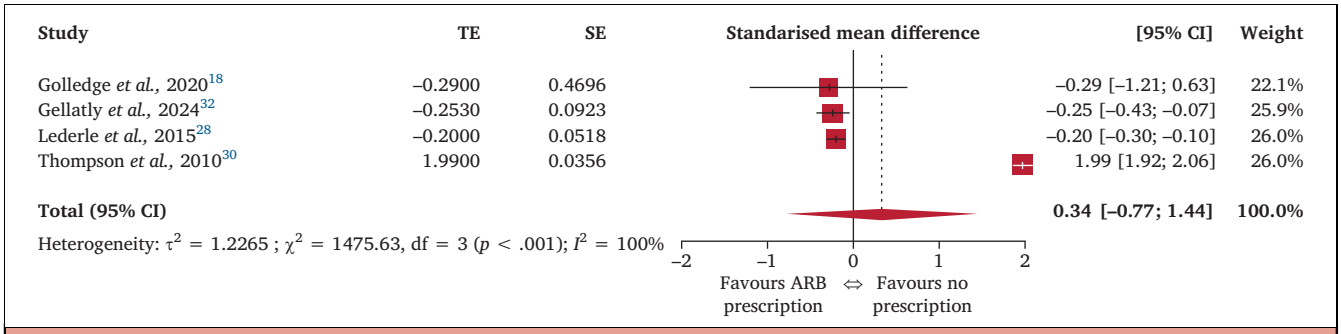

Figure 4. Forest plot illustrating meta-analysis of four studies, including 5 043 patients, examining whether angiotensin receptor blockers (ARB) were associated with abdominal aortic aneurysm growth. TE = total error; SE = standard error; CI = confidence interval.

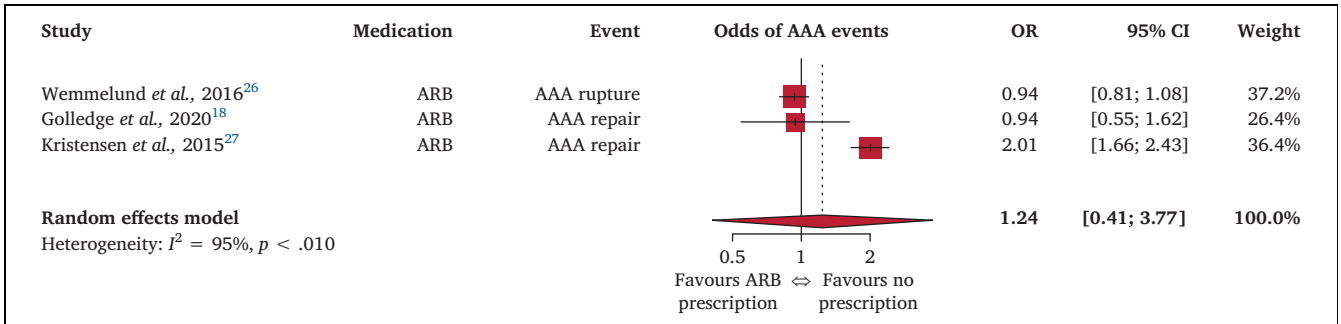

Figure 5. Forest plot illustrating meta-analysis of three studies, including 30 508 patients, examining whether angiotensin receptor blockers (ARB) were associated with a risk of abdominal aortic aneurysm (AAA) related events. OR = odds ratio; CI = confidence interval.

prescription was associated with an 18% reduced risk of AAA rupture,[34] similar to the 13% reduction shown in the current analysis. The current analysis included nine further cohorts and 22 510 more patients than the most recent prior systematic review.[35] Another large population based, retrospective cohort study from the Netherlands also supports the findings of this study and suggested that ACEi prescription was associated with a 14% lower likelihood of requiring AAA repair.[27] Epidemiological studies have shown that hypertension is a risk factor for the development of AAA and is associated with a higher risk of AAA rupture, although it has not been associated with AAA growth.[36] It is possible that ACEi drugs reduce the risk of AAA rupture by lowering blood pressure. ACEi prescription was associated with significantly fewer AAA related events but not a lower risk of AAA repair alone.

There were no significant associations between ARB prescription and AAA growth or AAA related events.

The findings of this meta-analysis suggest that ACEi may reduce the risk of AAA rupture and AAA related events, but this must be interpreted with an understanding of the strengths and limitations of the analysis. This study is the largest systematic review and meta-analysis examining the association between ACEi or ARB and AAA growth and events. Limitations include that most of the data are from retrospective observational studies, which are subject to recording bias. Furthermore, the data are limited by significant heterogeneity, high risk of bias, small sample sizes, and difficulty accounting for confounding factors. Owing to the small number of studies available, it was not possible to perform subanalyses separately assessing RCTs and observation studies. Similarly, there were insufficient studies to assess publication bias for most analyses. Furthermore, due to the low event rate and the small number of studies reporting AAA rupture, the findings could be at risk of type II error. The majority of the studies had a disproportionate number of men compared with women, with men making up 69% of the included patients, and the findings may not be generalisable to women.

Conclusion

This meta-analysis found no association between ACEi or ARB prescription and AAA growth, but ACEi prescription was associated with reduced risk of AAA rupture and events with a very low certainty of evidence. The findings may provide support for using ACEi as preferred treatments of hypertension in patients with AAA.

CONFLICTS OF INTEREST STATEMENT AND FUNDING

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2024.03.034.

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