Angiotensin-converting enzyme inhibitors and risk of age-related macular degeneration in individuals with hypertension

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Aims: Several observational studies have examined the potential protective effect of angiotensin-converting enzyme inhibitor (ACE-I) use on the risk of age-related macular degeneration (AMD) and have reported contradictory results owing to confounding and time-related biases. We aimed to assess the risk of AMD in a base cohort of patients aged 40 years and above with hypertension among new users of ACE-I compared to an active comparator cohort of new users of calcium channel blockers (CCB) using data obtained from IQVIA Medical Research Data, a primary care database in the UK.

Methods: In this study, 53,832 and 43,106 new users of ACE-I and CCB were included between 1995 and 2019, respectively. In an on-treatment analysis, patients were followed up from the time of index drug initiation to the date of AMD diagnosis, loss to follow-up, discontinuation or switch to the comparator drug. A comprehensive range of covariates were used to estimate propensity scores to weight and match new users of ACE-I and CCB. Standardized mortality ratio weighted Cox proportional hazards model was used to estimate hazard ratios of developing AMD.

Results: During a median follow-up of 2 years (interquartile range 1–5 years), the incidence rate of AMD was 2.4 (95% confidence interval 2.2–2.6) and 2.2 (2.0–2.4) per 1000 person-years among the weighted new users of ACE-I and CCB, respectively. There was no association of ACE-I use on the risk of AMD compared to CCB use in either the propensity score weighted or matched, on-treatment analysis (adjusted hazard ratio: 1.07 [95% confidence interval 0.90–1.27] and 0.87 [0.71–1.07], respectively).

Conclusion: We found no evidence that the use of ACE-I is associated with risk of AMD in patients with hypertension.
1 | INTRODUCTION

As a leading cause of blindness worldwide, age-related macular degeneration (AMD) represents a significant public health issue. Globally AMD was estimated to affect 196 million individuals in 2020; this is expected to rise to 288 million by 2040 as a consequence of an ageing society. The gradual progression of the disease results in severe irreversible visual impairment or loss of vision. The impact of progressive vision loss caused by AMD incapacitates patients, most commonly among the elderly, hindering daily activities and profoundly reducing quality of life.

Despite major therapeutic advances in the management of neovascular AMD with vascular endothelial growth factor (VEGF) inhibitors, these treatments are not curative, and the burden of multiple clinic visits remains high, representing a significant cost for society. No approved treatment is available for the atrophic form of the disease. For this reason, there is urgent need for real-world evidence about medications that could reduce the risk of developing AMD, slow AMD progression or reduce AMD-associated blindness.

Hypertension is associated with increased risk of AMD. The association between antihypertensive medications and risk of AMD is less clear. Several preclinical studies have suggested that antihypertensive treatments, especially medications that inhibit the renin-angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACE-I) could have a protective effect against the development of AMD. Through the inhibition of angiotensin II receptors expressed in the ocular tissues and the corresponding inflammatory response, animal studies have shown that deregulation of RAS can protect against retinal vascular inflammation and choroidal neovascularisation. However, population-based observational studies have for the most part found no statistically significant associations between the use of ACE-I and the development of AMD.

In contrast, a cross-sectional study in the USA reported a lower odds of AMD among hypertensive patients who took RAS inhibitors for over 5 years, while, conversely, a nested case–control study in Canada among patients who had undergone revascularisation interventions found an increased odds of developing AMD in patients who were current users of ACE-I.

However, previous observational studies have a number of limitations: the majority lacked an active comparator and may therefore be subject to bias and confounding by indication; some were limited by small sample size or lack of ethnic diversity; and only a limited number of comorbidities were adjusted for as potential confounders in evaluating the risk of AMD.

In view of the limitations and inconclusive findings of previous studies, large-scale epidemiological studies with adjustment for a range of potential confounding factors are needed. Therefore, the aim of our study was to evaluate the relationship between the use of ACE-I and the subsequent development of AMD in hypertensive patients in a large primary care cohort in the UK.

2 | METHODS

2.1 | Data source

Data for this study were taken from IQVIA Medical Research Data (IMRD) in the UK, a nationally representative, pseudonymised primary care database comprising routinely collected data for almost 16 million patients from more than 800 general practices. Due to the comprehensive availability of data on diagnoses (coded using the Read code classification system), prescriptions (coded according to the British National Formulary), laboratory test results, referrals and patient demographics, the database is suitable for performing high-quality real world evidence studies. The Quality and Outcomes

KEYWORDS

age-related macular degeneration, angiotensin-converting enzyme inhibitors, hypertension

What is already known about this subject

• Several observational studies have examined the potential protective effect of angiotensin-converting enzyme inhibitor (ACE-I) use on the risk of age-related macular degeneration (AMD) and have reported contradictory results owing to confounding and time-related biases.
• In view of their limitations and inconclusive findings, large-scale, methodologically rigorous pharmcoepidemiological study is needed to assess the effectiveness of ACE-I in protection against AMD.

What this study adds

• In this retrospective population based cohort study of hypertensive patients aged 40 and above, using an active comparator, new user design with propensity score weighting and matching, we included 53 832 and 43 106 new users of ACE-I and calcium channel blockers, respectively
• The incidence rate of developing AMD was 2.40 and 2.19 per 1000 person years, no evidence of protective effect of ACE-I on developing AMD in patients with hypertension
Framework is a payment incentive scheme that rewards general practices for achieving set targets on maintaining records and appropriate management of patients with specific chronic illnesses, including hypertension; this leads to a high level of data quality for these conditions.

2.2 | Study design and population

We performed a population-based, open cohort study, with the active comparator, new user design. The study period was from 1 January 1995 to 25 September 2019. In an open cohort study, participants can enter and leave the cohort at any time point during the study period. Practices were eligible for inclusion 1 year after installation of the Vision software system for computerization of medical records or 1 year after achieving acceptable mortality reporting, whichever was the latest. Patients became eligible for inclusion once they had been registered with an eligible general practice for at least a year, to ensure sufficient recording of baseline data and limit the possibility of prevalent user bias. From the eligible cohort, we identified patients aged 40 years and above with a clinically coded diagnosis of hypertension. Among them, we identified patients who were users of either ACE-I (exposure drug) or calcium channel blockers (CCB; comparator drug). CCB were chosen as the comparator drug to minimize confounding by indication bias as both ACE-I and CCB are first line therapy drugs for stage 1 hypertension.

Patients’ index date was defined as 1 year (latency period) after initiating ACE-I or CCB. Patients who discontinued use of the index drug or switched to the comparator drug within the first year of the index drug initiation were excluded as they may represent patients with a contraindication. We also excluded patients who concurrently initiated both ACE-I and CCB and those with a diagnosis of AMD prior to index date. The 1-year latency period was used to exclude patients who were diagnosed with AMD soon after treatment initiation for 2 reasons: (i) they may represent patients with prevalent AMD; and (ii) the drug is unlikely to confer a protective effect in such a short period.

2.3 | Exposure definition

Patients were included in the cohort if they were continuously exposed to the index drug during the latency period. Due to the unavailability of dose-duration information, each prescription was assumed to last for 28 days. In cases where there were 2 prescription records within 28 days, the additional prescription days from the first prescription were carried over to the next prescription, with a cap to carry-over of 14 days. A gap of >28 days plus the carry over days between 2 prescriptions of the drug was considered as drug discontinuation. A grace follow-up period of 1 year was allowed after discontinuation of the index drug (1 year after the last prescription date of the index drug plus carry over days, if relevant); this was because the protective effect of ACE-I was expected to be observed for up to a year after discontinuation.

2.4 | Follow-up period

Included patients were followed up from index date until the earliest of the following end points: date of AMD diagnosis (identified using Read codes; Table S1); treatment discontinuation (including the grace period); switch to the comparator drug, censoring due to death from any cause, transfer out of the general practice; last date of practice providing data to IMRD; or the end of the study period (25 September 2019).

2.5 | Covariates

The covariates included in the propensity score models were: (i) demographic variables, including age at index, sex, hypertension duration at index, ethnicity, Townsend deprivation quintile, calendar year (in 5-y bands); (ii) lifestyle variables, including body mass index (BMI), smoking status, drinking status; (iii) Charlson comorbidity index; (iv) individual baseline comorbidities, including heart failure, ischaemic heart disease, stroke/transient ischaemic attack, peripheral vascular disease, angina, atherosclerosis, type 1 diabetes, type 2 diabetes, depression, gout, osteoarthritis, rheumatoid arthritis, skin cancer, cataract, cataract surgery, thyroid disorders; (v) physiological measurements (latest available at baseline), including systolic blood pressure (BP), diastolic BP; (vi) laboratory measurements (latest available at baseline), including estimated glomerular filtration rate (eGFR), HbA1c categories (categorized as <6.5%, 6.5–7.5%, 7.5–8.5%, ≥8.5% and missing), low-density lipoprotein categories (categorized as <3 mmol/L, >3 mmol/L and missing), high-density lipoprotein categories (categorized as ≤1 mmol/L, >1 mmol/L and missing), total cholesterol categories (categorized as ≤5 mmol/L, >5 mmol/L and missing), triglyceride categories (categorized as ≤2.3 mmol/L, >2.3 mmol/L and missing), and albumin–creatinine ratio categories (categorized as <3, 3–30, >30 and missing); (vii) other antihypertensive medication use, including angiotensin receptor blockers, β blockers, blockers, potassium-sparing diuretics, loop diuretics, thiazide diuretics, and other diuretics; (viii) other medication use, including antplatelets, anticoagulants, hypnotics, hormonal contraceptives, nonsteroidal anti-inflammatory drugs, aspirin, insulin, acarbose, sulfonyl urea, GLP1 agonists, DPP4 inhibitors, SGLT2 inhibitors, glitazones, glinides and metformin. All covariate data were collected prior to treatment initiation.

2.6 | Missing data

Multiple imputation using chained equations with predictive mean matching was performed to impute missing systolic and diastolic BP, BMI and eGFR.
2.7 | Statistical analysis

Propensity score models were run separately for 5 sub-groups of 5-year calendar bands comprising the study period (1995–1999, 2000–2004, 2005–2009, 2010–2014, 2014–2019), generating calendar time-specific propensity scores at the time of first prescription of the exposure or comparator drug. Furthermore, the propensity score models were run separately on 5 imputed datasets and all estimates were combined using Rubin’s rule. A standardized morbidity ratio (SMR) weighting that assigned patients in the ACE-I a weight of 1 and patients in the CCB cohort a weight of (propensity score [PS]/[1 – PS]) was used to standardize the observed distribution of covariates between the ACE-I and CCB groups. Using this method, patients in the CCB cohort with higher and lower propensity to be new users of ACE-I are up- and down-weighted, respectively, to create a pseudo CCB cohort. SMR-weighted comparison of the covariates between the pseudo-cohorts of new users of ACE-I and CCB was described. SMR-weighted Cox proportional hazards models were used to estimate unadjusted and adjusted hazard ratios (aHRs) and 95% confidence intervals for incident development of AMD in the ACE-I group compared to the CCB group. The adjusted model included the following covariates: age, sex, Townsend deprivation quintile, ethnicity, smoking status, calendar year bands, BMI, eGFR, systolic and diastolic BP, and hypertension duration to account for any residual confounding. SMR-weighted Kaplan–Meier curves were plotted to evaluate the proportional hazards assumption.

All analyses were performed in Stata version 16 and P-values <.05 were considered statistically significant.

2.8 | Sensitivity analysis

A sensitivity analysis was performed using PS-matched pairs of new users of ACE-I and CCB using the nearest-neighbour algorithm, considering caliper of width equal to 0.2. We matched without replacement.

A secondary analysis was performed using the intention-to-treat analysis instead of the on-treatment primary analysis to deal with potential informative censoring. In this, we did not censor due to discontinuation of the index drug or switch to the comparator drug, with such patients remaining into the cohort until meeting 1 of the other exit criteria.

2.9 | Posthoc analysis

A posthoc on-treatment analysis was performed with a grace follow-up period of 6 months instead of 1 year post discontinuation of the index drug. In addition, a second posthoc analysis was performed by restricting to patients who became new users of ACE-I or CCB on or after 1st January 2004, since the hypertension management guideline by the British Hypertension Society was modified and effectively implemented in 2004.

2.10 | Ethics statement

Use of IQVIA data for research was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. This study underwent independent scientific review for this analysis and approval was obtained from the Scientific Review Committee in September 2020 (SRC reference number 20SRC033).

3 | RESULTS

3.1 | Baseline characteristics

The cohort eligibility was met by 1,511,034 patients aged 18 years and above with a diagnosis of hypertension. After applying the inclusion and exclusion criteria, the ACE-I and CCB cohorts comprised 53,832 and 43,106 patients, respectively (Figure 1).

Tables 1 and 2 show the baseline characteristics of patients in the ACE-I and CCB cohort, before and after SMR weighting and after PS matching. Patients in the ACE-I cohort were younger (mean [standard deviation, SD]: 62.58 [12.41] vs. 68.07 [10.84] y), more likely to be male (50.4% vs. 43.8%), and less likely to be from ethnic minorities, especially black Afro-Caribbean (0.2% vs. 1.0%). They also had lower comorbidity score (mean [SD] Charlson comorbidity index 2.58 [1.86] vs. 3.01 [1.65]), although a higher proportion had cardiovascular diseases or diabetes at baseline. Patients in the ACE-I cohort had lower mean systolic BP, but higher levels of eGFR and albumin–creatinine ratio. They were less likely to be past or current users of angiotensin receptor blockers and α blockers, but more likely to be past or current users of other antihypertensive drugs.

After SMR weighting, the overall distribution of the baseline covariates between the ACE-I and CCB cohorts were similar. After PS matching, 27,240 matched ACE-I–CCB pairs were obtained and the PS score distribution between the matched cohorts was similar (Tables S2 and S3).

3.2 | Hazard of AMD

Table 3 shows the results of the primary and sensitivity analyses. In the primary on-treatment analysis, 487 (0.9%) and 443 (0.8%) of the weighted patients in the ACE-I and CCB cohort developed AMD during a cumulative weighted follow-up of 202,699 and 201,243 person-years, respectively. The median follow-up in both the cohorts was 2.00 years (interquartile range [IQR] 1.00–5.00). This provided a crude AMD incidence rate of 2.40 and 2.19 per 1000 person-years among the new users of ACE-I and CCBs, respectively, with an HR of 1.09 (95% confidence interval [CI] 0.92–1.28). After adjustment for covariates mentioned in the statistical analysis section, the HR remained similar (aHR 1.07, 95% CI 0.90–1.27).

In the intention to treat analysis, 713 (1.3%) and 659 (1.2%) weighted patients in the ACE-I and CCB cohorts developed AMD. The median follow-up in the ACE-I and CCB cohorts in this analysis
were 5.00 (IQR 2.00–8.00) and 4.00 (IQR 2.00–8.00) years, respectively. The crude incidence rates, unadjusted and adjusted HRs were similar to the primary on-treatment analysis.

In the propensity score matched sensitivity analysis (Table 3), 256 (0.9%) and 286 (1.1%) patients in the ACE-I and CCB cohorts developed AMD during a follow-up of 99,454 and 103,004 person-years, respectively, giving a crude AMD incidence rate of 2.6 and 2.7 per 1000 person-years, respectively. The unadjusted HR was 0.92 (95% CI 0.78–1.10) and, after adjustment, the aHR was 0.87 (95% CI 0.71–1.07). In the intention to treat analysis, the results were similar (aHR 0.88 [0.76–1.04]).

In the 2 posthoc analyses, where we restricted the grace period to 6 months after index drug discontinuation and restricted the sample to new users of ACE-I or CCB to those first prescribed the drug on or after 1 January 2004, we observed similar findings (Tables S4 and S5).

**FIGURE 1** Study flow diagram describing the cohort selection. ACE-I, angiotensin converting enzyme-inhibitors; CCB, calcium channel blockers; age-related macular degeneration

4 | DISCUSSION

We found no evidence of a close temporal association between use of ACE-I for at least 12 months continuously, compared to use of CCBs for the same duration, and risk of subsequent development of AMD in this UK cohort of patients aged 40 years and above with hypertension. Both on-treatment and intention-to-treat analysis in both propensity score matched and weighted cohorts yielded null effects.

Our findings align with several smaller population-based observational studies conducted internationally (sample size ranging from 2982 to 25,608), some with slightly longer mean follow-up durations, which have also reported no statistically significant association between the use of ACE-I and the development of AMD (studies are summarised in Table S6).22–25,41 Our study included 53,832 patients receiving ACE-I, an order of magnitude more patients than explored in
### TABLE 1  Baseline characteristics: demographic characteristics and comorbidities among new users of ACE-I and weighted pseudo cohort of new users of CCB

| Number of patients | Baseline characteristics of the original dataset | Baseline characteristics after imputation and SMR weighting |
|--------------------|-------------------------------------------------|----------------------------------------------------------|
|                    | ACE-I \(n = 53\,832\) | CCB \(n = 43\,106\) | Std Diff | ACE-I \(n = 53\,832\) | CCB \(n = 54\,149\) | Std Diff |
| **Age (y), mean (SD)** | 62.58 (12.41) | 68.07 (10.84) | 0.470 | 62.58 (12.41) | 63.17 (11.67) | 0.051 |
| **Male sex, n (%)** | 27 154 (50.44) | 18 883 (43.81) | 0.133 | 27 154 (50.44) | 21 216 (49.22) | 0.025 |
| **Hypertension duration (y), mean (SD)** | 3.91 (6.55) | 4.06 (6.78) | 0.023 | 3.91 (6.55) | 4.23 (6.83) | 0.049 |
| **Ethnicity, n (%)** |  |  |  |  |  |  |
| White | 23 275 (43.24) | 18 471 (42.85) | 0.002 | 23 275 (43.24) | 18 762 (43.52) | 0.006 |
| Mixed race | 122 (0.23) | 132 (0.31) |  | 122 (0.23) | 95 (0.22) |  |
| Other race | 28 (0.05) | 59 (0.14) |  | 28 (0.05) | 26 (0.06) |  |
| Black | 117 (0.22) | 447 (1.04) |  | 117 (0.22) | 99 (0.23) |  |
| South Asian | 399 (0.74) | 400 (0.93) |  | 399 (0.74) | 372 (0.86) |  |
| Missing | 29 891 (55.53) | 23 597 (54.74) |  | 29 891 (55.53) | 23 751 (55.10) |  |
| **Townsend, n (%)** |  |  |  |  |  |  |
| Townsend 1 | 11 528 (21.41) | 9140 (21.20) | 0.019 | 11 528 (21.41) | 8989 (20.85) | 0.029 |
| Townsend 2 | 10 402 (19.32) | 8457 (19.62) | 10 402 (19.32) | 7990 (18.54) |  |
| Townsend 3 | 9806 (18.22) | 7581 (17.59) | 9806 (18.22) | 7782 (18.05) |  |
| Townsend 4 | 7938 (14.75) | 6025 (13.98) | 7938 (14.75) | 6625 (15.37) |  |
| Townsend 5 | 5221 (9.70) | 4143 (9.61) | 5221 (9.70) | 4199 (9.74) |  |
| Missing | 8937 (16.60) | 7760 (18.00) | 8937 (16.60) | 7519 (17.44) |  |
| **Calendar year, n (%)** | 53 832 (100.00) | 43 106 (100.00) | 0.236 | 53 832 (100.00) | 43 106 (100.00) | 0.018 |
| 1995–2000 | 1521 (2.83) | 1268 (2.94) | 1521 (2.83) | 1175 (2.73) |  |
| 2001–2005 | 12 953 (24.06) | 8481 (19.67) | 12 953 (24.06) | 10 453 (24.25) |  |
| 2006–2010 | 22 371 (41.56) | 14 041 (32.57) | 22 371 (41.56) | 17 417 (40.40) |  |
| 2011–2015 | 12 972 (24.10) | 13 610 (31.57) | 12 972 (24.10) | 10 529 (24.42) |  |
| 2016–2020 | 4015 (7.46) | 7760 (18.00) | 4015 (7.46) | 3532 (8.19) |  |
| **Lifestyle variables** |  |  |  |  |  |  |
| **BMI (kg/m^2)** | 29.40 (6.06) | 27.73 (5.37) | 0.292 | 29.40 (6.06) | 29.42 (6.53) | 0.021 |
| Mean (SD) | 4374 (8.13) | 4153 (9.63) |  |  |  |
| **BMI missing, n (%)** | 4374 (8.13) | 4153 (9.63) |  | 4374 (8.13) | 4153 (9.63) |  |
| **Smoking status, n (%)** |  |  |  |  |  |  |
| Nonsmoker | 27 927 (51.88) | 22 536 (52.28) | 0.009 | 27 927 (51.88) | 22 102 (51.27) | 0.009 |
| Ex-smoker | 16 006 (29.73) | 12 626 (29.29) | 16 006 (29.73) | 13 037 (30.24) |  |
| Current smoker | 8962 (16.65) | 7121 (16.52) | 8962 (16.65) | 7183 (16.66) |  |
| Missing | 937 (1.74) | 823 (1.91) | 937 (1.74) | 783 (1.82) |  |
| **Drinking status, n (%)** |  |  |  |  |  |  |
| Nondrinker | 8519 (15.83) | 7566 (17.55) | 0.053 | 8519 (15.83) | 7612 (17.66) | 0.036 |
| Ex-drinker | 1305 (2.42) | 1084 (2.51) | 1305 (2.42) | 1099 (2.55) |  |
| Current drinker | 39 030 (72.50) | 30 172 (69.99) | 39 030 (72.50) | 30 395 (70.51) |  |
| Missing | 4978 (9.25) | 4284 (9.94) | 4978 (9.25) | 3999 (9.28) |  |
| **Comorbidities at baseline** |  |  |  |  |  |  |
| **Charlson comorbidity index, mean (SD)** | 2.58 (1.86) | 3.01 (1.65) | 0.243 | 2.58 (1.86) | 2.71 (1.91) | 0.075 |
| **Individual comorbidities, n (%)** |  |  |  |  |  |  |
| Heart failure | 1973 (3.67) | 344 (0.80) | 0.195 | 1973 (3.67) | 2418 (5.61) | 0.132 |
| Ischaemic heart disease | 5053 (9.39) | 2339 (5.43) | 152 | 5053 (9.39) | 5250 (12.18) | 0.107 |
| Stroke/TIA | 3816 (7.09) | 2764 (6.41) | 0.027 | 3816 (7.09) | 3710 (8.61) | 0.061 |
previous population-based studies; furthermore, unlike most of the earlier population-based surveys, we included only patients with at least 12 months of continuous medication exposure prior to AMD diagnosis, as indicated by monthly repeat prescription.

Similarly, in a cross-sectional analysis, Ren et al. found no association between ACE-I use and subsequent risk of AMD, including early or late AMD, but reported a protective effect in patients taking any RAS inhibitor for >5 years. Conversely, a nested case-control study in Canada among patients who had undergone revascularisation interventions and a census study in Australia found an increased odds of developing AMD in patients who were current users of ACE-I. It is possible that the choice of comparator drug may have affected the findings. Although, it is unlikely that any protective effect of ACE-I were masked by CCB as several studies have shown effect estimates in the direction of an increased risk of AMD among users of CCB.

4.1 Strengths and limitations

To our knowledge, this is the largest study using real world evidence to study the effect of ACE-I on the development of AMD. The new-user design is a real strength to the study that limits the possibility of survivor bias associated with the inclusion of prevalent users of the drug. The richness of the data source allowed us to estimate the propensity scores of ACE-I prescriptions using a comprehensive range of covariates. The SMR-weighted Cox proportional hazards model allowed us to retain the full sample size through a pseudo-population, while minimising confounding by indication. Our study design was rigorous in terms of: (i) inclusion of an active-comparator drug used at the same disease stage; (ii) accounting for the lag time between the onset of the disease and its diagnosis within primary care; (iii) accounting for the continuing protective effect of ACE-I use up to a year after discontinuation; and (iv) exclusion of patients who were de-prescribed the index drug within the latency period.

One of the major limitations of the study is the short median follow-up duration available for analysis, following the initiation and continuous prescription of the drug under investigation for a period of at least 12 months. In addition, there may be under-recording of early AMD/age-related maculopathy within this primary care population, as, whilst visually significant AMD diagnosis is predominantly made in the hospital eye service, the diagnosis of age-related maculopathy may be made in various additional care settings (e.g. optometry practices), and general practice records may not be complete. Furthermore, the codes for AMD outcome were mostly nonspecific and did not distinguish between wet and dry AMD. Therefore, we were unable to explore any difference in effect of ACE-I on these 2 different types of AMD. There is also the possibility of exposure misclassification arising for several reasons, including patient nonadherence and receiving prescriptions from specialists.

| Number of patients | Baseline characteristics of the original dataset | Baseline characteristics after imputation and SMR weighting |
|--------------------|-----------------------------------------------|---------------------------------------------------------|
|                    | ACE-I (n = 53 832) | CCB (n = 43 106) | Std Diff | ACE-I (n = 53 832) | CCBa (n = 54 149) | Std Diff |
| Peripheral vascular disease | 1207 (2.24) | 1363 (3.16) | 0.057 | 1207 (2.24) | 1229 (2.85) | 0.038 |
| Angina | 2227 (4.14) | 1584 (3.67) | 0.024 | 2227 (4.14) | 2197 (5.10) | 0.049 |
| Atherosclerosis | 5017 (9.32) | 2310 (5.36) | 0.152 | 5017 (9.32) | 5213 (12.09) | 0.107 |
| Type 2 diabetes | 9143 (16.98) | 2310 (5.36) | 0.375 | 9143 (16.98) | 7515 (17.43) | 0.015 |
| Type 1 diabetes | 472 (0.88) | 74 (0.17) | 0.098 | 472 (0.88) | 302 (0.70) | 0.024 |
| Depression | 11 029 (20.49) | 8560 (19.86) | 0.016 | 11 029 (20.49) | 9187 (21.31) | 0.021 |
| Gout | 2718 (5.05) | 2193 (5.09) | 0.002 | 2718 (5.05) | 2785 (6.46) | 0.064 |
| Osteoarthritis | 12 385 (23.01) | 12 178 (28.25) | 0.120 | 12 385 (23.01) | 10 081 (23.39) | 0.009 |
| Rheumatoid arthritis | 236 (0.44) | 306 (0.71) | 0.036 | 236 (0.44) | 206 (0.48) | 0.005 |
| Skin cancer | 1834 (3.41) | 2102 (4.88) | 0.074 | 1834 (3.41) | 1403 (3.26) | 0.008 |
| Cataract | 2855 (5.30) | 3150 (7.31) | 0.083 | 2855 (5.30) | 2519 (5.84) | 0.022 |
| Cataract surgery | 1903 (3.54) | 2150 (4.99) | 0.072 | 1903 (3.54) | 1751 (4.06) | 0.026 |
| Thyroid disorders | 4403 (8.18) | 3841 (8.91) | 0.026 | 4403 (8.18) | 3966 (9.20) | 0.037 |

ACE-I, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; Std Diff, standardized difference; SD, standard deviation; SMR, standardized morbidity ratio; TIA, transient ischaemic attack.
aPseudo cohort of new users of CCB: using SMR weighting, users of CCB with higher and lower propensity to be new users of ACE-inhibitors are up- and down-weighted, respectively.
# Table 2: Baseline characteristics: laboratory measurements and medication use among new users of ACE-I and weighted pseudo cohort of new users of CCB

| Number of patients | Baseline characteristics of the original dataset | Baseline characteristics after imputation and SMR weighting |
|--------------------|-----------------------------------------------|----------------------------------------------------------|
|                    | ACE-I (n = 53 832) | CCB (n = 43 106) | Std Diff | ACE-I (n = 53 832) | CCB (n = 54 149) | Std Diff |
| Laboratory values  |                                              |                                                          |
| Systolic BP        |                                              |                                                          |
| Mean (SD)          | 155.82 (19.43) | 162.93 (19.88) | 0.362 | 155.84 (19.44) | 155.51 (19.64) | 0.017 |
| Missing            | 191 (0.35) | 123 (0.29) |                                              |
| Diastolic BP       |                                              |                                                          |
| Mean (SD)          | 90.07 (12.12) | 90.30 (11.85) | 0.019 | 90.08 (12.12) | 89.54 (12.03) | 0.045 |
| Missing            | 189 (0.35) | 120 (0.28) |                                              |
| HbA1c categories (%) |                                              |                                                          |
| <6.5               | 6304 (11.71) | 6100 (14.15) | 0.123 | 6304 (11.71) | 5246 (12.17) | 0.026 |
| 6.5–7.5            | 2891 (5.37) | 948 (2.20) |                                              |
| 7.5–8.5            | 1466 (2.72) | 364 (0.84) |                                              |
| ≥8.5               | 1756 (3.26) | 332 (0.77) |                                              |
| Not recorded       | 41 415 (76.93) | 35 362 (82.03) |                                              |
| Low-density lipoprotein categories (mmol/L), n (%) |                                              |                                                          |
| ≤3                 | 14 072 (26.14) | 10 825 (25.11) | 0.031 | 14 072 (26.14) | 12 282 (28.49) | 0.011 |
| >3                 | 18 654 (34.65) | 16 048 (37.23) |                                              |
| Missing            | 21 106 (39.21) | 16 233 (37.66) |                                              |
| High-density lipoprotein categories (mmol/L), n (%) |                                              |                                                          |
| Low                | 8749 (16.25) | 5086 (11.80) | 0.014 | 8749 (16.25) | 7022 (16.29) | 0.004 |
| High               | 29 877 (55.50) | 25 602 (59.39) |                                              |
| Missing            | 15 206 (28.25) | 16 760 (38.77) |                                              |
| Total cholesterol categories (mmol/L), n (%) |                                              |                                                          |
| ≤5                 | 17 387 (32.30) | 12 246 (28.41) | 0.081 | 17 387 (32.30) | 14 686 (34.07) | 0.004 |
| >5                 | 27 951 (51.92) | 22 753 (52.78) |                                              |
| Missing            | 8494 (15.78) | 8107 (18.81) |                                              |
| Triglyceride categories (mmol/L), n (%) |                                              |                                                          |
| ≤2.3               | 31 149 (57.86) | 25 979 (50.27) | 0.036 | 31 149 (57.86) | 25 173 (58.40) | 0.002 |
| >2.3               | 8104 (15.05) | 4741 (11.00) |                                              |
| Missing            | 14 579 (27.08) | 12 386 (28.73) |                                              |
| Glomerular filtration rate (mL/min/1.73 m2) |                                              |                                                          |
| Mean (SD)          | 76.53 (18.37) | 74.07 (17.15) | 0.138 | 76.06 (18.43) | 74.80 (18.57) | 0.070 |
| Missing            | 7534 (14.00) | 6681 (15.50) |                                              |
| Albumin creatinine ratio categories, n (%) |                                              |                                                          |
| <3                 | 4332 (8.05) | 2570 (5.96) | 0.104 | 4332 (8.05) | 3627 (8.42) | 0.021 |
| 3–30               | 1641 (3.05) | 906 (2.10) |                                              |
| >30                | 222 (0.41) | 141 (0.33) |                                              |
| Missing            | 47 637 (88.49) | 39 489 (91.61) |                                              |
| Other antihypertensive medication use, n (%) |                                              |                                                          |
| Angiotensin receptor blockers | 1622 (3.01) | 5134 (11.91) | 0.344 | 1622 (3.01) | 1861 (4.32) | 0.050 |
| Alpha blockers     | 1492 (2.77) | 1579 (3.66) | 0.051 | 1492 (2.77) | 1463 (3.39) | 0.035 |
| Beta blockers      | 18 931 (35.17) | 14 012 (32.51) | 0.056 | 18 931 (35.17) | 16 162 (37.49) | 0.049 |
| Potassium diuretics | 841 (1.56) | 321 (0.74) | 0.077 | 841 (1.56) | 1332 (3.09) | 0.143 |
| Loop diuretics     | 6169 (11.46) | 2891 (6.71) | 0.166 | 6169 (11.46) | 6430 (14.92) | 0.121 |
We included all drugs within the CCB drug class to define the comparator cohort, including those that are preferentially prescribed as a treatment for arrhythmia and ischaemic heart disease rather than as a treatment for hypertensive disorders. However, these constituted only 7.2% of all CCB prescriptions and the distribution of atrial fibrillation and ischaemic heart disease was similar between the exposed and the comparator cohorts after PS matching. Furthermore, we made assumptions regarding the duration of each prescription due to the unavailability of prescription duration data, although existing literature suggests prescriptions of drugs for the management of chronic disease in primary care are usually repeated every 28 days. As a result of the new user design, patients prescribed both ACE-I and CCB (either concurrently or at different time points) were excluded from the cohort. However, participants on other dual therapies (e.g. ACE-I or CCB in combination with β blockers or thiazide diuretics), representing those with more severe disease, were included; nevertheless, it is possible that the characteristics of patients prescribed dual therapy with ACE-I and CCB may differ from those prescribed other dual antihypertensive therapies.

Finally, despite performing SMR weighting and PS matching, there were differences between the exposed and the comparator cohort in terms of cardiovascular conditions and metabolic conditions at baseline after weighting and matching, respectively. This study cannot exclude the possibility that ACE-I may have a protective effect against the development of AMD when used for longer periods prior to the typical age of AMD onset. Unexplored by our analysis was whether there is any association between use of ACE-I and AMD progression or AMD-associated visual outcomes including blindness. Also unexplored was the possibility of whether both ACE-I and CCBs reduce risk of incident AMD, for instance through exerting comparable antihypertensive efficacy, compared to patients with untreated hypertension; this was not possible to assess using this type of analysis due to the likelihood of prescription by indication bias. Our analysis advances a methodological approach that addresses many of the potential sources of bias and confounding which may have influenced earlier studies. We hope this will facilitate future research in cohorts with longer periods of drug exposure and follow-up.

With AMD being a leading cause of sight loss and lack of preventive treatment options for at-risk groups, pharmacovigilance strategies maybe employed to screen commonly prescribed drugs in primary care to identify AMD protective signals, which can then be critically evaluated through rigorous pharmacoepidemiological, clinical and pharmacological evaluation.
This study provides no evidence that the use of ACE-I is associated with a decreased risk of AMD in patients with hypertension within a median follow-up period of 2 years. The results are in line with literature and remain consistent with rigorous sensitivity analyses. Further observational studies with longer follow-up period maybe beneficial.

ACKNOWLEDGEMENT
This research was funded by Action Against Age-related Macular Degeneration, Charity numbers 1 170 224 and SC048549.

CONTRIBUTORS
P.A.K., K.N. and A.K.D. conceived the research question. A.S., K.N. and N.J.A. designed the analysis. K.M.G. extracted analysable data. A.S. performed the analysis, with supervision and contributions by L.A., N.J.A. and K.N. A.S., D.H. and T.B. drafted the manuscript. All authors (A.S., D.H., T.B., R.T., D.T.Z., K.M.G., W.H.L., J.C., P.A.K., A.K.D., K.N., L.A. and N.J.A.) reviewed and revised the manuscript, provided critical feedback and agreed to its publication. N.J.A. and K.N. act as guarantors; the guarantors accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from IQVIA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of IQVIA.

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### 4.2 Conclusion

This study provides no evidence that the use of ACE-I is associated with a decreased risk of AMD in patients with hypertension within a median follow-up period of 2 years. The results are in line with literature and remain consistent with rigorous sensitivity analyses. Further observational studies with longer follow-up period maybe beneficial.

### ACKNOWLEDGEMENT

This research was funded by Action Against Age-related Macular Degeneration, Charity numbers 1 170 224 and SC048549.

### COMPETING INTERESTS

Drs Adderley, Nirantharakumar and Denniston reported a grant from Action Against Age-related Macular Degeneration during the conduct of the study. Dr Adderley reported receiving grants from Medical Research Council, National Institute for Health Research and National Institute for Health Research RFPB outside the submitted work. Dr Nirantharakumar reported receiving grants from Medical Research Council, National Institute for Health Research, AstraZeneca, MSD, Boehringer Ingelheim, Vifor, and Health Data Research UK and personal fees from Sanofi outside the submitted work. Dr Denniston reported receiving grant support from Health Data Research UK outside the submitted work. Dr Braithwaite reported receiving salary support from the patient charity Olivia’s Vision. No other disclosures were reported.

### TABLE 3

Crude and adjusted hazard ratios of AMD among new users of ACE-I compared to new users of CCB, in SMR-weighted and PS-matched analysis

| On-treatment analysis (primary analysis) | SMR weighted analysis (primary analysis) | PS matched analysis (sensitivity analysis) |
|-----------------------------------------|------------------------------------------|--------------------------------------------|
| **ACE-I** | **CCB** | **ACE-I** | **CCB** |
| AMD, n (%) | 487 (0.90) | 443 (0.82) | 256 (0.94) | 286 (1.05) |
| Number of patients, n | 53 832 | 54 149 | 27 240 | 27 240 |
| Total person-y of follow-up | 202 699 | 201 243 | 99 454 | 103 004 |
| Median follow-up (y) | 2.00 (1.00–5.00) | 2.00 (1.00–5.00) | 2.00 (1.00–5.00) | 2.00 (1.00–5.00) |
| Crude incidence rate/1000 person-y | 2.40 | 2.19 | 2.58 | 2.74 |
| Unadjusted HR (95% CI) | 1.09 (0.92–1.28); SE = 0.09 | 0.92 (0.78–1.10); SE = 0.09 |
| Adjusted HR (95% CI) | 1.07 (0.90–1.27); SE = 0.09 | 0.87 (0.71–1.07); SE = 0.10 |

| Intention to treat analysis (secondary analysis) | SMR weighted analysis (primary analysis) | PS matched analysis (sensitivity analysis) |
|-----------------------------------------------|------------------------------------------|--------------------------------------------|
| **ACE-I** | **CCB** | **ACE-I** | **CCB** |
| AMD, n (%) | 713 (1.32) | 659 (1.22) | 394 (1.45) | 428 (1.57) |
| Number of patients, n | 53 832 | 54 149 | 27 240 | 27 240 |
| Total person-y of follow-up | 303 758 | 301 188 | 147 302 | 151 074 |
| Median follow-up (y) | 5.00 (2.00–8.00) | 4.00 (2.00–8.00) | 4.00 (2.00–8.00) | 4.00 (2.00–8.00) |
| Crude incidence rate/1000 person-y | 2.35 | 2.18 | 2.67 | 2.78 |
| Unadjusted HR (95% CI) | 1.08 (0.93–1.24); SE = 0.07 | 0.95 (0.82–1.10); SE = 0.07 |
| Adjusted HR (95% CI) | 1.06 (0.91–1.22); SE = 0.07 | 0.88 (0.76–1.04); SE = 0.08 |

ACE-I, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; SMR, standardized mortality ratio; PS, propensity score; AMD, age-related macular degeneration; HR, hazard ratio; SE, standard error; CI, confidence interval.

*Pseudo cohort of new users of CCB: using SMR weighting, users of CCB with higher and lower propensity to be new users of ACE-I are up- and down-weighted, respectively.
REFERENCES

1. Bourne RRA, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: A systematic analysis. Lancet Glob Health. 2013;1(6):e339-e349.

2. Jonas JB, Cheung CMG, Panda-Jonas S. Updates on the Epidemiology of Age-Related Macular Degeneration. Asia-Pacific J Ophthalmol. 2017;6:493-497.

3. Jager RD, Mieler WF, Miller. Age-Related Macular Degeneration. N Engl J Med. 2008;358:2606-2617.

4. Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SL. The psychosocial impact of macular degeneration. Arch Ophthalmol. 1998;116:514-520.

5. Christophoridis JB, Tecce N, Dell’Omo R, Mastropasqua R, Veranolino M, Costagliola C. Age Related Macular Degeneration and Visual Disability. Curr Drug Targets. 2011;12:221-233. doi: 10.2174/138945011794182755

6. Brody BL, Gamst AC, Williams RA, et al. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. Ophthalmology. 2001;108:1893-1900. doi: 10.1016/S0161-6420(01)00754-0

7. Marback RF, Maia ODO, Morais FB, Takahashi WY. Quality of life in patients with age-related macular degeneration with monocular and binocular legal blindness. Clinics. 2007;62:573-578. doi: 10.1590/S1807-59322007000500007

8. KM K, U C, C O. Economic cost of age-related macular degeneration: a review of recent research. Drugs Aging. 2006;23:217-225.

9. Sperduto RD, Hiller R. Systemic Hypertension and Age-Related Macular Degeneration. Clinics. 2004;59:249-255. doi: 10.1016/S0161-6420(01)00754-0

10. KM K, U C, C O. Economic cost of age-related macular degeneration: a review of recent research. Drugs Aging. 2006;23:217-225.

11. Barro-Soria R, Stindl J, Müller C, et al. Angiotensin-2-Mediated Ca2+ Signaling in the Retinal Pigment Epithelium: Role of Angiotensin-Receptor- Associated-Protein and TRPV2 Channel. PloS ONE. 2012; 7(11):e49624. doi: 10.1371/journal.pone.0049624

12. Nagai N, Oike Y, Izumi-Nagai K, et al. Angiotensin II type 1 receptor-mediated inflammation is required for choroidal neovascularization. Arterioscler Thromb Vasc Biol. 2006;26:2252-2259.

13. Wu KHC, Wang JJ, Rochtchina E, Foran S, Ng MK, Mitchell P. Angiotensin-converting enzyme inhibitors (ACEIs) and age-related maculopathy (ARM): cross-sectional findings from the Blue Mountains Eye Study. Acta Ophthalmol Scand. 2004;82:298-303.

14. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascu- lar disease and its risk factors for age-related maculopathy: The Beaver Dam Eye Study. J Hypertens. 2001;19:1455-1462.

15. McCarty CA, Mukesh BN, Fu CL, Mitchell P, Wang JJ, Taylor HR. Risk factors for age-related maculopathy: The visual impairment project. Arch Ophthalmol. 2001;119:1455-1462.

16. Smith T, Otete H, Chauhan U, Fell C. GP incentives to GP incentives to...
Colon Cancer Chemotherapy. *Pharmacoepidemiol Drug Saf*. 2013;22:810-818.

37. Dusetzina SB, Mack CD, Stürmer T. Propensity Score Estimation to Address Calendar Time-Specific Channeling in Comparative Effectiveness Research of Second Generation Antipsychotics. *PLoS ONE*. 2013;8(5):e63973. doi:10.1371/journal.pone.0063973

38. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med*. 2019;38:5120-5132.

39. Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology*. 2003;14:680-686. doi:10.1097/01.EDE.0000081989.82616.7d

40. Williams B, Poulter NR, Brown MJ, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ Br Med J*. 2004;328(7440):634-640. doi:10.1136/bmj.328.7440.634

41. Thomas AS, Redd T, Hwang T. Effect of systemic beta-blockers, ace inhibitors, and angiotensin receptor blockers on development of choroidal neovascularization in patients with age-related macular degeneration. *Retina*. 2015;35(10):1964-1968. doi:10.1097/IAE.0000000000000603

42. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. *Am J Epidemiol*. 2003;158:915-920. doi:10.1093/aje/kwg231

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Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Subramanian A, Han D, Braithwaite T, et al. Angiotensin-converting enzyme inhibitors and risk of age-related macular degeneration in individuals with hypertension. *Br J Clin Pharmacol*. 2022;88(9):4199-4210. doi:10.1111/bcp.15366