ORIGINAL ARTICLE

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

Anuradhaa Subramanian[1] ⬤ | Diana Han[1] ⬤ | Tasanee Braithwaite[1,2,3] |
Rasiah Thayakaran[1] | Dawit T. Zemedikun[1] | Krishna M. Gokhale[1] |
Wen Hwa Lee[4] | Jesse Coker[4] | Pearse A. Keane[5] | Alastair K. Denniston[5,6,7,8] |
Krishnarajah Nirantharakumar[1,7] | Laurent Azoulay[9,10,11] ⬤ | Nicola J. Adderley[1] ⬤

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[2]The School of Immunology and Microbial Sciences and The School of Life Course Sciences, Kings College London, London, UK

[3]The Medical Eye Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

[4]Action Against Age-Related Macular Degeneration, London, UK

[5]NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and Institute of Ophthalmology, University College London, London, UK

[6]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[7]Health Data Research UK (HDRUK), London, UK

[8]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

[9]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

[10]Centre for Clinical Epidemiology, Lady Davis Institute, Montreal, Canada

[11]Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

Correspondence
Krishnarajah Nirantharakumar, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.
Email: k.nirantharan@bham.ac.uk

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.[1] Globally AMD was estimated to affect 196 million individuals in 2020; this is expected to rise to 288 million by 2040[2] as a consequence of an ageing society.[3] 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.[4–7]

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.[8] 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.[9–14] 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.[15] 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[16,17] and choroidal neovascularisation.[18–21] 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.[22–25] 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,[26] 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.[27]

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[28] or lack of ethnic diversity[22,29,30]; and only a limited number of comorbidities were adjusted for as potential confounders in evaluating the risk of AMD.[25,26]

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

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

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, psuedonymised primary care database comprising routinely collected data for almost 16 million patients from more than 800 general practices.[31] 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

Framework[32] 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.[33] 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,[34] 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 the index drug during the latency period. Due to the unavailability of dose-duration information, each prescription was assumed to last for 28 days.[35] 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 for men, and categorized as ≥1.2 mmol/L, <1.2 mmol/L and missing for women), 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, α blockers, β blockers, potassium diuretics, loop diuretics, thiazide diuretics, and other diuretics; (viii) other medication use, including antiplatelets, 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.[36,37] Furthermore, the propensity score models were run separately on 5 imputed datasets and all estimates were combined using Rubin's rule.[38] 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])[39] 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 CCBs 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 calliper 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.[40]

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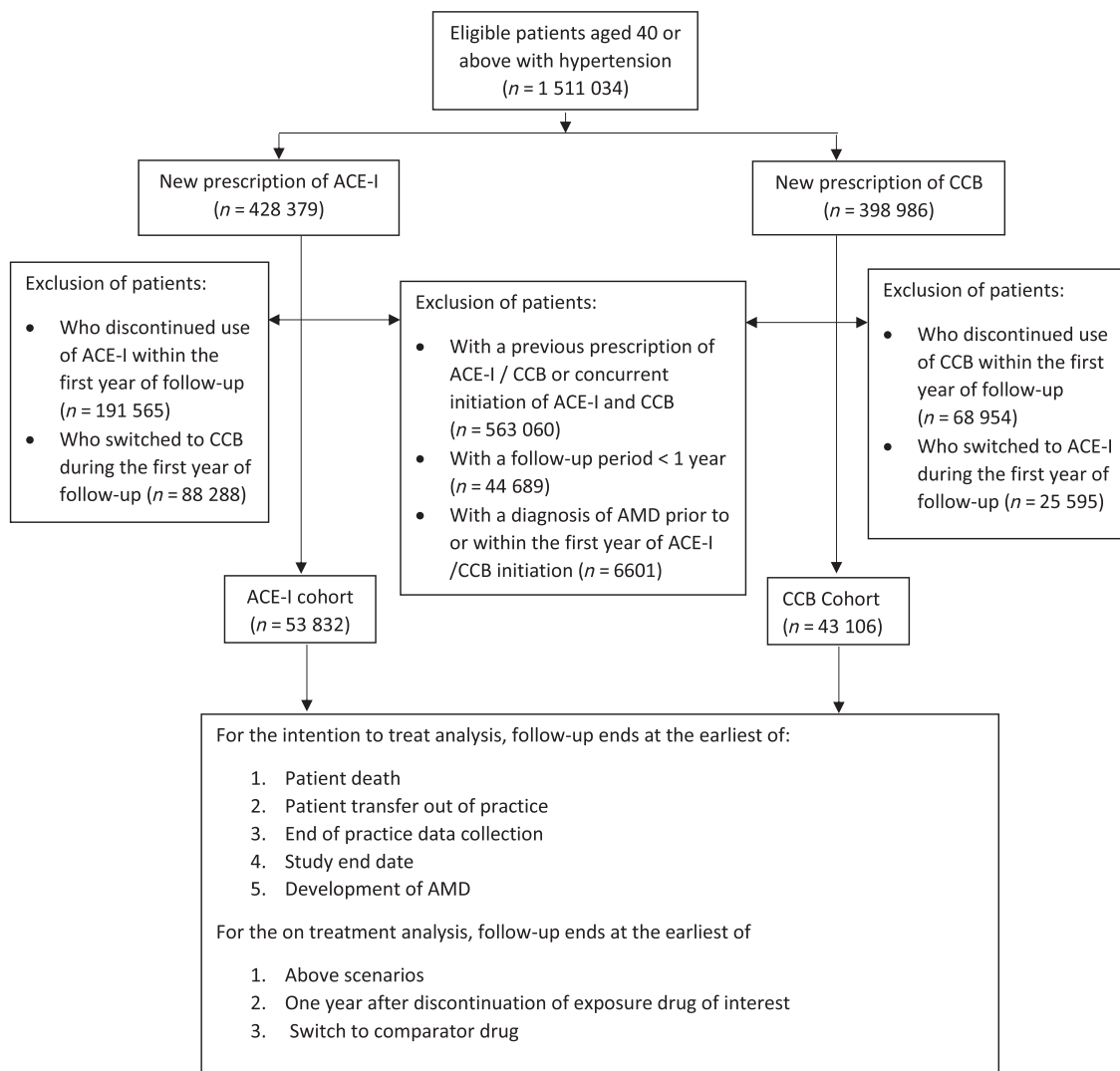
FIGURE 1 Study flow diagram describing the cohort selection. ACE-I, angiotensin converting enzyme-inhibitors; CCB, calcium channel blockers; age-related macular degeneration

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 matched 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).

4 | DISCUSSION

We found no evidence a of 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

	Baseline characteristics of the original dataset			Baseline characteristics after imputation and SMR weighting		
Number of patients	ACE-I (n = 53 832)	CCB (n = 43 106)	Std Diff	ACE-I (n = 53 832)	CCB[a] (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			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)	5706 (13.24)		4015 (7.46)	3532 (8.19)	
Lifestyle variables						
BMI (kg/m^2)						
Mean (SD)	29.40 (6.06)	27.73 (5.37)	0.292	29.30 (6.03)	29.42 (6.53)	0.021
BMI missing, n (%)	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)	0.152	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

TABLE 1 (Continued)

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[a] (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.

[a]Pseudo 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.

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[18] 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.[26] 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.[27,28]

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.[22,29]

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.[42] 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.

TABLE 2 Baseline characteristics: laboratory measurements and medication use among new users of ACE-I and weighted pseudo cohort of new users of CCB

	Baseline characteristics of the original dataset			Baseline characteristics after imputation and SMR weighting		
Number of patients	ACE-I (n = 53 832)	CCB (n = 43 106)	Std Diff	ACE-I (n = 53 832)	CCB[a] (n = 54 149)	Std Diff
Laboratory values						
Systolic BP			0.362			0.017
Mean (SD)	155.82 (19.43)	162.93 (19.88)		155.84 (19.44)	155.51 (19.64)	
Missing	191 (0.35)	123 (0.29)				
Diastolic BP			0.019			0.045
Mean (SD)	90.07 (12.12)	90.30 (11.85)		90.08 (12.12)	89.54 (12.03)	
Missing	189 (0.35)	120 (0.28)				
HbA1c categories (%), n (%)			0.123			0.026
<6.5	6304 (11.71)	6100 (14.15)		6304 (11.71)	5246 (12.17)	
6.5–7.5	2891 (5.37)	948 (2.20)		2891 (5.37)	2338 (5.42)	
7.5–8.5	1466 (2.72)	364 (0.84)		1466 (2.72)	1165 (2.70)	
≥8.5	1756 (3.26)	332 (0.77)		1756 (3.26)	1654 (3.84)	
Not recorded	41 415 (76.93)	35 362 (82.03)		41 415 (76.93)	32 702 (75.86)	
Low-density lipoprotein categories (mmol/L), n (%)			0.031			0.011
≤3	14 072 (26.14)	10 825 (25.11)		14 072 (26.14)	12 282 (28.49)	
>3	18 654 (34.65)	16 048 (37.23)		18 654 (34.65)	14 153 (32.83)	
Missing	21 106 (39.21)	16 233 (37.66)		21 106 (39.21)	16 670 (38.67)	
High-density lipoprotein categories (mmol/L), n (%)			0.014			0.004
Low	8749 (16.25)	5086 (11.80)		8749 (16.25)	7022 (16.29)	
High	29 877 (55.50)	25 602 (59.39)		29 877 (55.50)	23 983 (55.64)	
Missing	15 206 (28.25)	12 418 (28.81)		15 206 (28.25)	12 100 (28.07)	
Total cholesterol categories (mmol/L), n (%)			0.081			0.004
≤5	17 387 (32.30)	12 246 (28.41)		17 387 (32.30)	14 686 (34.07)	
>5	27 951 (51.92)	22 753 (52.78)		27 951 (51.92)	21 675 (50.28)	
Missing	8494 (15.78)	8107 (18.81)		8494 (15.78)	6744 (15.64)	
Triglyceride categories (mmol/L), n (%)			0.036			0.002
≤2.3	31 149 (57.86)	25 979 (60.27)		31 149 (57.86)	25 173 (58.40)	
>2.3	8104 (15.05)	4741 (11.00)		8104 (15.05)	6214 (14.41)	
Missing	14 579 (27.08)	12 386 (28.73)		14 579 (27.08)	11 719 (27.19)	
Glomerular filtration rate (mL/min/1,73 m2)			0.138			0.070
Mean (SD)	76.53 (18.37)	74.07 (17.15)		76.06 (18.43)	74.80 (18.57)	
Missing	7534 (14.00)	6681 (15.50)				
Albumin creatinine ratio categories, n (%)			0.104			0.021
<3	4332 (8.05)	2570 (5.96)		4332 (8.05)	3627 (8.42)	
3–30	1641 (3.05)	906 (2.10)		1641 (3.05)	1432 (3.32)	
>30	222 (0.41)	141 (0.33)		222 (0.41)	176 (0.41)	
Missing	47 637 (88.49)	39 489 (91.61)		47 637 (88.49)	37 869 (87.85)	
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

TABLE 2 (Continued)

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[a] ($n = 54\ 149$)	Std Diff
Thiazide diuretics	19 313 (35.88)	15 864 (36.80)	0.019	19 313 (35.88)	16 285 (37.78)	0.040
Other diuretics	436 (0.81)	292 (0.68)	0.015	436 (0.81)	356 (0.83)	0.002
Other medication use, *n* (%)						
Antiplatelets	15 532 (28.85)	10 688 (24.79)	0.092	15 532 (28.85)	13 346 (30.96)	0.048
Anticoagulants	2787 (5.18)	1733 (4.02) drug	0.055	2787 (5.18)	3341 (7.75)	0.123
Hypnotics	8254 (15.33)	7163 (16.62)	0.035	8254 (15.33)	7104 (16.48)	0.031
Hormonal contraceptives	2511 (4.66)	884 (2.05)	0.145	2511 (4.66)	2043 (4.74)	0.004
NSAIDs	34 436 (63.97)	27 638 (64.12)	0.003	34 436 (63.97)	26 940 (62.50)	0.031
Aspirin	1038 (1.93)	762 (1.77)	0.012	1038 (1.93)	961 (2.23)	0.022
Insulin	1107 (2.06)	271 (0.63)	0.124	1107 (2.06)	930 (2.16)	0.009
Sulfonyl urea	3020 (5.61)	793 (1.84)	0.200	3020 (5.61)	2917 (6.77)	0.061
GLP1 agonists	133 (0.25)	43 (0.10)	0.035	133 (0.25)	64 (0.15)	0.024
DPP-4 inhibitors	403 (0.75)	165 (0.38)	0.049	403 (0.75)	383 (0.89)	0.019
SGLT-2 inhibitors	79 (0.15)	23 (0.05)	0.030	79 (0.15)	42 (0.10)	0.016
Glitazones	868 (1.61)	219 (0.51)	0.108	868 (1.61)	686 (1.59)	0.002
Glinides	92 (0.17)	16 (0.04)	0.042	92 (0.17)	38 (0.09)	0.026
Acarbose	133 (0.25)	31 (0.07)	0.044	133 (0.25)	79 (0.18)	0.016
Metformin	5816 (10.80)	1478 (3.43)	0.290	5816 (10.80)	4575 (10.61)	0.007

ACE-I, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; Std Diff, standardized difference; SMR, standardized morbidity ratio; BP, blood pressure; NSAIDs, nonsteroidal anti-inflammatory drug; GLP1–1, glucagon-like peptide-1; DPP-4, dipeptidyl-peptidase 4; SGLT-2, aodium/glucose cotransporter 2.

[a]Pseudo 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.

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[15] 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.

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

	SMR weighted analysis (primary analysis)		PS matched analysis (sensitivity analysis)	
	ACE-I	CCB[a]	ACE-I	CCB
On-treatment analysis (primary analysis)				
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)				
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.

[a]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.

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.

COMPETING INTERESTS

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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.

ORCID

Anuradhaa Subramanian https://orcid.org/0000-0001-8875-7363
Diana Han https://orcid.org/0000-0002-7435-0658
Laurent Azoulay https://orcid.org/0000-0001-5162-3556
Nicola J. Adderley https://orcid.org/0000-0003-0543-3254

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