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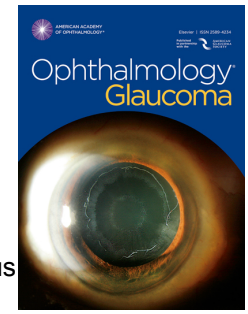

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PII: S2589-4196(25)00043-2

DOI: https://doi.org/10.1016/j.ogla.2025.03.002

Reference: OGLA 675

To appear in: *OPHTHALMOLOGY GLAUCOMA*

Received Date: 12 February 2025

Revised Date: 3 March 2025

Accepted Date: 7 March 2025

Please cite this article as: Montesano G, Rabiolo A, Garway-Heath DF, Fu DJ, Gazzard G, Ometto G, Crabb DP, Khawaja AP, Association of systemic calcium channel blockers use with visual field progression in a large real-world cohort from glaucoma clinics, *OPHTHALMOLOGY GLAUCOMA* (2025), doi: https://doi.org/10.1016/j.ogla.2025.03.002.

Association of systemic calcium channel blockers use with visual field progression in a large real-world cohort from glaucoma clinics

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Meeting Presentation: This research was presented at the Association for Research in Vision and Ophthalmology (ARVO) 2024 annual meeting (paper presentation)

Financial support: this work and GM are supported by funding from Glaucoma UK and the Royal College of Ophthalmologists. APK is supported by a UK Research and Innovation Future Leaders Fellowship, an Alcon Research Institute Young Investigator Award and a Lister Institute for Preventive Medicine Award. This research was supported by the NIHR Biomedical Research Centre at Moorfields Eye Hospital and the UCL Institute of Ophthalmology.

Conflict of Interest: COIs exist for the authors and are provided in the respective ICMJE COI forms. None are relevant to this research.

Running head: Calcium channel blockers and visual field progression

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Abstract

Purpose: to test the association between use of calcium channel blocker (CCB) medications and the rate of visual field (VF) progression in a large cohort of patients from five glaucoma clinics.

Design: retrospective, longitudinal case-control study.

Subjects: patients attending five glaucoma clinics in the United Kingdom using the same Electronic Medical Record (EMR) system.

Methods: for the main analysis, we selected one eye of patients with at least 5 reliable (false positive errors < 15%) VFs over at least 4 years. The use of systemic medications was derived from the EMR system. CCB users were identified as cases. Propensity Score Matching (PMS) and multivariable analyses (MV) were used to adjust for confounders. A Directed Acyclic Graph (DAG) of the relevant variables guided the selection of covariates. Linear mixed effect models (LMMs) were used to test the effect on the rate of VF Mean Deviation (MD) associated with CCB use and other covariates (for the MV analysis). Sensitivity analyses were conducted with different inclusion criteria and cut-offs on the estimated duration of CCB use.

Main Outcome Measure: mean difference in the rate of VF MD progression between CCB users and controls.

Results: the main analysis included 14,475 eyes (1,942 from CCB users) which met the selection criteria (one eye per patient). The Median [Interquartile Range] VF series length was 8 [6, 11] tests, with a follow-up of 8.6 [6, 11.5] and 8.2 [5.9, 11.2] years in CCB users and controls respectively. One-to-one PSM pairing with controls was achieved for all CCB users. The estimated rate of MD progression was -0.31 [-0.33, -0.28] dB/year (Mean [95%-Confidence Intervals]) in the CCB users and -0.35 [-0.37, -0.33] dB/year in the matched controls (p = 0.016). This significant difference was confirmed with the MV analysis, including all controls (p = 0.020). All sensitivity analyses confirmed the main results.

Conclusions: CCB use was statistically significantly associated with a slower rate of VF deterioration, after multivariable adjustment. The estimated difference was small and likely not clinically significant but may be influenced by the limited information on the duration of CCB exposure in this cohort.

Calcium channel blockers (CCBs) are some of the most commonly prescribed medications for cardiovascular conditions. Up to 40% of patients with systemic hypertension are prescribed a CCB[1] to control their blood pressure. In the United Kingdom (UK), CCBs make up approximately 4% of all primary-care prescriptions[2]. Because the incidence of both systemic hypertension[3] and glaucoma[4] increases with age, and the known association between these two conditions[5, 6], many patients who are at risk of, or have, glaucoma are likely to be prescribed CCBs.

The effect of systemic CCBs on glaucoma is controversial. Many large observational investigations have consistently shown an association between CCB use and increased risk of receiving a glaucoma diagnosis[7-11], replicating this result across different cohorts. Other studies have also shown an association between CCB use and glaucoma-related traits, such as thinner inner retinal layers on optical coherence tomography (OCT) imaging[10, 12]. On the other hand, studies investigating the association between CCBs and disease progression in patients with glaucoma have shown either no association[13] or a protective association[14-17], especially in normal tension glaucoma (NTG). Two of the studies showing a protective effect were small randomised clinical trials (RCTs)[14, 15].

However, well-powered studies of the association between CCB use and rate of glaucoma progression are still lacking. In this work, we analysed real-world data from more than 14,000 patients followed in five glaucoma clinics across the UK. We investigated the association between systemic CCB use and the rate of visual field (VF) progression, adjusting for multiple confounders. We further report on the association of the rate of VF progression with the use of systemic medication classes and multiple patient characteristics.

Methods

Clinical cohort

Patient data from five National Health Service glaucoma clinics in England were extracted from an ophthalmic electronic medical record (EMR; Medisoft, Medisoft Ltd., Leeds, UK). This database was created in 2015 as part of the Royal College of Ophthalmologists National Ophthalmology Database audit[18]. All patient data were anonymized upon data extraction and stored in a secure database at City, University of London. Subsequent analyses of this dataset were approved by a research ethics committee of City, University of London, in accordance with the Declaration of Helsinki and the General Data Protection Regulation of the European Union. The dataset contained Humphrey Field Analyzer (HFA, Zeiss Meditec, Dublin, CA) VF data for 145,562 eyes of 73,990 patients. We selected tests performed with a 24-2 pattern and any SITA (Swedish Interactive Threshold Algorithm) strategy[19] with less than 15% false positive error rate[20]. A mixture of VF SITA Standard and Fast was allowed because the use of SITA Fast, despite its slightly lower precision, is unlikely to make a sizeable difference for measuring VF progression[21]. Series were truncated at the time of

glaucoma surgery (any incisional surgery or cyclodestructive procedure). Eyes which received glaucoma surgery before they earlier VF test were excluded. We excluded eyes with documented co-pathologies other than glaucoma. One eye per patient was selected when both were includible, preferring an eye with a manually entered diagnostic label of glaucoma for one eye, or at random when both eyes had the same label or no label.

For our main analysis, we selected series with at least 5 tests performed over at least 4 years. Following previous methodology for analyses on the same dataset[22-24], the series needed to contain at least two not necessarily consecutive VFs with a mean deviation (MD) < -2 dB (95% lower limits of normality for HFA[22]). This increased the likelihood of including eyes with perimetric defects from glaucoma during the course of their follow up, without relying on diagnostic labels reported by clinicians. A sensitivity analysis was conducted without applying this criterion (see later).

Other information recorded in the EMR was: baseline age, sex, self-reported ethnicity, Index of Multiple Deprivation (IMD)[25, 26], diabetic status, Best Corrected Visual Acuity (BCVA), Intraocular pressure (IOP), ocular medications, ocular diagnoses, ocular surgeries (with dates). Higher IMD scores indicate more deprivation. The IMD score was standardised for the multivariable analyses by subtracting the sample mean (15.6) and dividing by the sample standard deviation (11.9) calculated from the main analysis cohort, for consistency. More than 90% of the cohort reported "white" as their ethnicity. Because of the low representation of non-white patients in this cohorts, they were not further subdivided into more specific ethnic groups.

This selection led to the inclusion of 14,475 eyes (one per patient) and 133,505 VF tests. A detailed flowchart of the selection steps is reported in a **supplementary appendix**. Different selection strategies were assessed in our sensitivity analyses, which are summarised later.

Systemic medications

Medical staff could manually enter systemic medications into the EMR, as per standard clinical practice, recorded as active components or brand names. These were automatically classified by the EMR into broader categories. All classifications were manually reviewed. Brand names were converted into their active component names. All fixed combinations were split into their individual components. The categories that were identified for systemic medications are reported in **Table 1**. The category identified as "*Other anti-hypertensives*" included: Angiotensin Receptor Blockers (ARBs), Angiotensin Converting Enzyme inhibitors (ACEi), direct renin inhibitors, α2A-adrenergic agonists, α1-adrenergic blockers, direct vaso-dilators and medications for pulmonary hypertension.

The records include a start and end date for each medication. However, the recorded start dates do not necessarily represent the effective day the medication was initiated, but rather the first date it was recorded into the system. A separate field explicitly reporting the start of the medication was available but was often left empty. Exposure to medications for the main

analysis was, therefore, based on any report of the use of the medication in the EMR at any point in time. A sensitivity analysis for CCBs was conducted by requiring an estimated exposure for at least 20% of the VF follow-up time (see later).

Statistical analysis

This was a retrospective, longitudinal, case-control study. All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria). The primary outcome measure was the difference in the rate in VF progression, measured with a linear mixed model (LMM), associated with exposure to CCBs. All other results are to be considered exploratory. The STROBE checklist[27] for case-control studies is provided as **supplementary**.

The outcome variable of the LMM was the MD, regressed over time as a continuous variable (in years). The coefficient associated with time measured the rate of MD progression (in dB/year). An interaction term between time and use of medications, such as CCBs, modelled the difference in rate associated with exposure (the outcome measure for this study). Random intercepts and slopes modelled the variation in baseline damage and rate of MD progression across individuals. The LMMs were calculated using the *lme4*[28] and *lmerTest*[29] packages for R. The significance threshold was set at $p = 0.05$.

Because of the retrospective observational nature of this study, covariate adjustment was required to increase precision and reduce the risk of bias in the estimated association between CBBs and the rate of VF progression. The choice of covariates for adjustment was based on a directed acyclic graph (DAG, provided as **supplementary**). The DAG lays out the assumptions about possible direct and indirect correlations and causal links between the variables in the dataset. Various algorithms exist to find optimal solutions for a DAG, which return valid sets of adjustment variables to minimise the effect of confounders and avoid sources of collider bias when estimating the association between a specific exposures and outcomes. Note that, even with the same DAG, different adjustment sets may be required to estimate associations between different exposures and outcomes. For this study, we used the maximal (most extensive) valid set of covariates calculated with the package *dagitty*[30] for R based on the assumed DAG (the *canonical* set in the terminology of the software package). The DAG and the adjustment set was defined and locked before the analysis. The model was therefore fully pre-specified before the analysis. Of note, the IOP and number of medications were not selected as covariates, because in a clinical context they are influenced by VF progression (faster progressing patients are more heavily treated to lower IOPs than stable patients). Inclusion of these covariates could therefore introduce a collider bias. There was, however, no difference in IOP between CCB users and controls (see **Table 1**). It is also interesting to note that, based on the assumed DAG, the same adjustment set could be used to estimate the association between the systemic medications included in the analysis and VF progression.

Covariate adjustment was carried out with two different methods. For the main analysis, we performed a propensity score matching (PSM) to generate a control group (CCB non-users) matched 1:1 to the exposed group (CCB users) according to the adjustment set of covariates. We used the package *MatchIt*[31] for R (logistic model). For PSM, we also imposed a strict 1:1 matching for the diagnostic labels, so that we could perform a fully matched analysis with and without patients with diagnostic labels compatible with primary angle closure disease (PACD). The proportion of eyes labelled as primary open angle glaucoma (POAG) or other (which included those with no label) were also balanced. The LMM for the comparison between exposed and matched controls included only one interaction term between time and CCB use (binary), modelling the observed difference in rate of progression associated with exposure to CCBs. For the secondary analysis, a multivariable LMM was used. This analysis included all eyes that met the criteria for analysis. The LMM included the covariates via multiple interaction terms between time and each covariate of interest. Similarly to the CCBs in the main analysis, each interaction term coefficient measured the change in rate of progression associated with each covariate.

Missing data were imputed using the method of Multivariable Imputation by Chained Equations (MICE), as implemented in the *mice*[32] package for R, using all available demographics. Single imputation was chosen because of the low percentage of missing data (< 10%, see **Results**), to reduce computational complexity and to generate a unique dataset that could be adapted for both PMS and the multivariable analyses.

An indicative minimum sample size was determined for the main analysis using the methodology described in Montesano et al.[33], assuming one test every year for 8 years, a standard deviation for the MD of 1.97 dB[33] and an average rate of progression of -0.38 dB/year[33]. A sample of 1,500 eyes per group provided 92% power to detect a 15% difference in rate of progression at a significance level of $p < 0.05$.

Sensitivity and supplementary analyses

Additional analyses were carried out to assess the sensitivity of our results to changes in the selection criteria and assumptions regarding the exposure to CCBs. These are reported as **supplementary material**:

1. Inclusion of all eyes with at least 2 reliable VFs over one year of follow-up prior to any glaucoma surgery
2. Multivariable analysis with continuous-valued exposure to CCBs in the main selection cohort
3. Multivariable analysis excluding patients on non-dihydropyridines in the main analysis cohort
4. Exposure to CCBs defined as exposure for at least 20% of the follow-up time
5. Multivariable analysis isolating the effect of Angiotensin Receptor Blockers (ARBs) and Angiotensin Converting Enzyme Inhibitors (ACEi) in the main analysis cohort,

since they have been both associated with a reduced chance of progression in some subgroup of patients[13].

Results

Cohort characteristics

We identified 1,942 out of 14,475 (13%) patients exposed to systemic CCBs. Of these, 87% were using dihydropyridines (54% amlodipine) and 13% using non-dihydropyridines (10% diltiazem, 3% verapamil). The average exposure among CCB users was 32% (Median [Interquartile Range] 23 [0, 52]%). The characteristics of the exposed cohort, of all controls and of the 1,942 matched controls identified via PSM are reported in **Table 1**. All variables considered for PSM were well balanced between CCB users and matched controls. A statistically significant difference ($p < 0.05$) was still present for baseline age, but both the median and the interquartile range were very similar, differing at most by 1 year. Some variables, such as the highest IOP, the average IOP and the baseline BCVA were also well balanced, despite not having been considered for PSM. Other variables, such as the length of the follow up and the number of tests, showed a strongly statistically significant difference ($p < 0.01$) but were very similar in their median and IQR. Missing data were imputed for age (1/14,475, < 0.01%), IMD score (691/14,475, 4.8%), diabetes type (287/1,980, 14.5% of diabetic patients, 2% of the total), ethnicity (1,157/14,475, 8%) and baseline VA (1,031/14,475, 7.1%).

Associations with rate of progression

The results of the analysis on CCB-exposed and PSM-matched controls are reported in **Table 2**. Exposure to CCBs was associated with a significantly slower rate of progression ($p = 0.016$). No difference was found in the estimated baseline MD, as expected from the PSM (see **Table 1**). The analysis was also repeated by excluding 116 eyes that had a diagnostic label suggestive of an angle closure mechanism, with no material difference in the results.

These results were also confirmed by the multivariable analysis (**Figure 1**). The estimated rate for the 'reference' patient was -0.34 [-0.41, -0.28] dB/year (Mean [95% Confidence Interval]), very similar to the estimated rate for the matched control group obtained with PSM (**Table 2**). The estimated difference in rate associated with the use of CCBs was 0.03 [0.01, 0.06] dB/year ($p = 0.020$) similar to the difference in **Table 2**. Similar results were obtained by including or excluding patients with a diagnostic label suggestive of angle closure ($p=0.025$). Other significant detrimental associations were found with older baseline age, higher baseline PSD, more positive baseline MD, presence of diabetes and use of systemic corticosteroids. Female sex was associated with a slower rate of MD progression ($p = 0.048$) in the full cohort. A table with the results from the multivariable LMM is reported in the **supplementary appendix**.

The secondary and sensitivity analyses confirmed these results and are reported in detail in the **supplementary appendix**. Similar results were obtained by redefining the use of CCBs as an estimated exposure of at least 20% (CCB users=1,044, p=0.005 for PSM analysis) and by removing patients on non-dihydropyridines (258/1942 CCB users, p = 0.034). The 'dose-response' analysis showed a significant positive association with the exposure fraction (0.13 [0.07, 0.19] dB/year per fraction point, p < 0.001, **supplementary appendix**), which was maintained after restricting the analysis to the 1,044 CCB users (0.16 [0.08, 0.24] dB/year per fraction point, p < 0.001). CCBs were also significantly associated with slower rates of MD progression (p=0.004 for PSM analysis) when all patients with at least 2 reliable VFs over 1 year prior to glaucoma surgery were included (N = 36,146, CCB users = 5,104). Other associations in the multivariable LMM became significant with this extended cohort (see **supplementary appendix**). ARBs, but not ACEis, were also found to have significant association with slower rates of progression (p=0.015, multivariable analysis), when analysed separately from other anti-hypertensives in the main selection cohort (**supplementary appendix**).

Discussion

In this work, we analysed the association between exposure to systemic CCB use and rate of VF loss in a large real-world cohort of patients from glaucoma clinics in the UK. We found a significant association of CCB use with a marginally slower rate of progression, after adjusting for multiple confounders. We confirmed this finding with additional sensitivity analyses, using either less stringent criteria for inclusion of patients in the analysed cohort or more stringent criteria for the definition of CCB exposure. All analyses, however, confirmed an estimated small average difference in the rate of VF deterioration between CCB users and controls, which is likely not clinically significant. However, this should be interpreted in the context of the limited information regarding CCB exposure in this cohort, which might dilute the magnitude of the true association.

This is the first large-scale real-world analysis of the association between systemic CCB and VF progression. Our findings are in general agreement with previous literature looking at the association of CCB use and the rate of VF progression. Koseki et al. published the results of two small placebo-controlled RCTs investigating the effect of brovincamine[14] and nilvadipine[15] on the rate of VF progression in patients with NTG. Both studies found a significant neuroprotective effect of the CCB under study. They also investigated the difference in the rate of MD progression with LMMs. The effect was much larger (0.7 dB/year or 90% reduction with brovincamine and 0.26 dB/year or 96% reduction with nilvadipine) compared to our results (0.04 dB/year or 11% reduction in those exposed to CCBs). These differences can be explained by several factors, primarily the retrospective observational nature of our study. In fact, for most of the patients in our cohort, we had very little information regarding the period of exposure and the dosage of CCBs. There were also

significant differences in the study cohorts, because Koseki et al. recruited NTG patients who were randomised to CCB treatment, rather than a varied real-world cohort of patients from glaucoma clinics who were prescribed CCBs as treatment for other systemic conditions.

Daugeliene et al.[16] published a small retrospective analysis on 47 NTG patients (24 taking CCBs) and reported a significant protective association between CCB use and rate of MD progression (0.25 dB/year or 47% slower). Pappelis et al.[13] analysed a larger cohort of 250 patients with POAG and 112 glaucoma suspects. In contrast to Daugeliene et al. and our results, they found no significant association between any of the systemic medications (including CCBs) and the rate of MD progression. There are however important differences between our analysis and Pappelis et al. For example, they used a quantile regression on the median rate, which would be relatively insensitive to changes in the negative tail of the distribution of RoPs and would not account for the length of the test series. Moreover, they selected their variables based on the Akaike Information Criterion[34]. Optimising prediction, however, does not generally lead to estimating an unbiased association between specific exposures and outcomes[35]. For example, adjusting for number of medications and treated IOP, which are known to be reactive to VF progression in clinical practice (i.e. fast progressing patients will be treated more aggressively to a lower IOP) carries the risk of introducing a collider bias[30, 35].

In our model, we overcome many of the previous limitations. We calculated the effect of CCB exposure (and other variables) on the mean rate of progression with LMMs. This is justified by previous evidence that most of the differences in the rates of VF progression across different populations or treatments are reflected by the negative tail of the distributions[36, 37]. Moreover, LMMs would account for different series length, by 'shrinking' the effect of shorter VF series[38]. Finally, our multivariable adjustments were based on a DAG accounting for known and potential associations between variables. The adjustment set was specified prior to the analysis to estimate the association between exposure and outcome. Based on the DAG, this did not include adjustments for IOP control to avoid collider-bias. However, no significant difference was found between CCB users and controls for any of the IOP related metrics (see **Table 1**).

One interesting finding from Pappelis et al. was the protective association between use of ACEis and ARBs and reduced risk of conversion to POAG in glaucoma suspects, as well as an association of ARBs with a slower rate of progression (although not significant, except in a more advanced age)[13]. Our analysis was designed to investigate the association between rate of VF progression and exposure to CCBs, but the same set of covariate adjustments could be used to explore the effect of other systemic medications according to the assumed DAG. In one **supplementary analysis**, we found a significant association between ARBs and a slower rate of MD progression, in agreement with Pappelis et al.[13].

Our results, and those reported by the studies discussed so far, are seemingly in contrast with many large-scale investigations associating CCB exposure to an increased risk of having

a glaucoma diagnosis[7-11] or glaucoma related traits[10, 12]. In these studies, the association between CCBs and glaucoma has been largely explored by assessing the likelihood of being diagnosed with POAG in comparison with a control group. POAG was defined using various criteria, ranging from a retrospective extraction of information from electronic medical records and insurance data[8, 10, 11], patients' self-reporting[10, 11], expert assessment[7, 9] or a combination of these three[9-11]. Regardless, all studies, including one meta-analysis[9], showed a significant and generally large increase in the risk of being diagnosed with glaucoma after multivariable adjustment, ranging from 1.23[9] to 1.8[7] fold-increase. This is also supported by the significant associations reported between CCB use and thinner inner retinal layers measured via OCT imaging[10, 12], after multivariable adjustments.

Reconciling these apparently contrasting findings is complicated and might not be possible with the current evidence. These studies are investigating different aspects of the problem, namely the risk of developing glaucoma as opposed to VF progression in patients who have POAG or, as in this study, are being monitored in glaucoma clinics. One explanation for the contrasting results is bias by indication. For example, in the UK, CCBs are prescribed as second-line treatment for uncontrolled hypertension or as a first-line treatment in patients with Black-African or Black Afro-Caribbean origin or older than 55 years[39]. These patients have a higher risk of developing glaucoma[4]. Although multivariable analyses adjust for age and ethnicity, controlling for complex indications is challenging, potentially linking CCBs to glaucoma despite a possible neuroprotective effect. This hypothesis would add significance to the small difference in rate found in our cohort, because it would suggest that CCBs have significantly reduced the rate of VF progression in a potentially fast progressing group of patients. Another alternative hypothesis is that CCBs might induce a type of damage to the optic nerve head that manifests features similar to glaucoma, leading to a diagnosis, but is in fact much less aggressive, resulting in a slower rate of progression when observed longitudinally in clinics. This would explain both the increased risk of a diagnosis of POAG and the apparent neuroprotective effect observed during the follow-up. Of course, this would only explain cases in which the treatment with CCBs was started before the initiation of the follow-up in a glaucoma clinic. However, precise information on the duration of the exposure is often lacking in most of these studies, including ours, and can only be truly assessed accurately in the context of RCTs[14, 15].

The association between CCBs and a higher risk of glaucoma is generally in contrast with their supposed neuroprotective effects. These are usually linked to inhibition of cell apoptosis via a reduction of calcium influx[40]. Moreover, studies in patients have shown a positive effect of CCBs on the blood flow and circulation of the optic nerve head[41-43], with some reported improvements in visual function[43]. This might contribute to the reported protective effect in NTG[14, 15]. Another supposed mechanism of action of CCBs is to protect and restore the functionality of mitochondria in neurons[40], which has also been shown, in vitro, for amlodipine[44] and in animal models of ocular hypertension for nilvadipine[45].

While these mechanisms can explain the association with a slower rate of VF progression, they do not justify the higher risk of developing glaucoma associated with the use of CCBs. The main proposed explanation for this detrimental association is a complex effect on systemic blood pressure of some CCBs, especially when used in combination with other anti-hypertensive medications[10]. However, this explanation is not supported by our results: most of the patients in our cohort were on CCBs known for their hypotensive properties, such as amlodipine (54%), and a large proportion of CCB users were on other anti-hypertensive medications, beta-blockers or diuretics (see **Table 1**). Despite this, CCBs were associated with a slower rate of VF progression. Interestingly, the estimated association in the multivariable analysis remained essentially unchanged when patients on non-dihydropyridines were excluded from the analysis (0.031 [0.002, 0.060], p = 0.034, see **supplementary appendix**). Whatever the mechanism, it is likely to be IOP-independent. Despite some evidence of IOP reduction with CCBs use[46, 47], other studies have failed to replicate this effect[48]. Notably, such a lack of association between IOP and CCBs was also reported in a large-scale investigation on the cohort from the UK Biobank[10]. There was no difference in IOP in our cohort (see **Table 1**).

Despite its strengths, mainly the very large sample size and the long follow-up (**Table 1**), this study has limitations, largely derived from its retrospective nature. Our sensitivity and secondary analyses were designed to mitigate these limitations. One limitation was the lack of clear diagnostic labels. More than half of the eyes included in the main analysis had not been explicitly labelled as 'glaucoma' in the EMR. This is despite having selected patients followed for at least 4 years with at least two tests with an MD < -2 dB. This criterion has been previously used on this dataset to minimise the inclusion of glaucoma suspects and ocular hypertensives[22-24], but is clearly not a replacement for a definitive diagnosis. However, many similar investigations relying on retrospective analysis of medical records or self-reported diagnosis suffer from the same limitation. On the other hand, the selection criteria might have excluded eyes with very early glaucoma or patients with fewer tests prior to surgery, such as fast progressors. Our primary analysis required 5 VFs over at least 4 years; 13% of this cohort were using CCBs. This was no different from the proportion of CCB users (12%) in a larger cohort of patients with at least 2 VFs over 1 year (but fewer than 5 VFs over 4 years), indicating that CCB use was not associated with a shorter follow-up. We included this larger cohort in a sensitivity analysis and obtained similar results (**supplementary appendix**). Our main analysis also truncated VF series at the time of glaucoma surgery, to minimise the systematic bias in the slopes of fast progressing eyes prior to surgery. Cataract surgery might also affect VF metrics such as MD. However, cataract surgery is usually not offered with the specific goal of treating glaucoma and is therefore unlikely to be more commonly performed in fast progressing patients. Regardless, cataract surgery and phakic status were actively controlled for in our PS matching and multivariable analyses. The effect was not significant in our main multivariable analysis (p = 0.8).

Another limitation was the lack of detailed information on the duration of CCB exposure and the dosage of all systemic medications. While the duration of exposure could be estimated from the date of first reporting, this estimate is necessarily imprecise (see **Methods**). However, a sensitivity analysis defining use of CCBs as exposure over at least 20% of the follow-up time confirmed our results, showing a larger difference in rate of progression (0.07 dB/year or 20% reduction, **supplementary appendix**). We further explored this 'dose-response' by performing and additional sensitivity analysis, replacing the binary CCB exposure with a continuous estimate of their exposure fraction (0 to 1). We found a significant positive association with the exposure fraction (0.13 [0.07, 0.19] dB/year per fraction point, $p < 0.001$, **supplementary appendix**), confirming our previous results. Note that this analysis would implicate a 0.13 dB/year slower rate of progression, on average, for patients on CCBs for 100% of their follow-up time. However, given the inherent uncertainty around our estimates of exposure duration, we caution against a strict interpretation of these results as a 'dose-response'. However, this could suggest that low-level exposure to CCB might have contributed to the small detected difference between CCB users and controls. Another important consideration is that the manual entry of medications by medical staff might be inaccurate, because omissions are impossible to detect. This cohort of patients also lacked ethnic diversity, because > 90% identified as white, and this limits the generalisability of the findings. Finally, one clear limitation is the lack of an accurate record of the general health of the participants, especially of their cardiovascular status. Some information, especially on the cardiovascular status, can be obtained indirectly from the use of other systemic medications (see the DAG in **supplementary appendix**). Large-scale studies of this kind would benefit from information from primary care providers, to allow for a more careful characterization of the patients' cohort.

In conclusion, we report evidence of an association between use of systemic CCBs and slower rate of VF progression in a very large cohort of patients from glaucoma clinics. While this is in agreement with most previous literature on VF progression, it is in apparent contrast with reported evidence of CCBs being linked to a higher risk of developing glaucoma. A comprehensive explanation for this discrepancy remains elusive. It is important to highlight, however, that while statistically significant, the small average estimated difference in rate of VF deterioration between CCB users and controls is unlikely to be clinically meaningful. This should be interpreted in the context of the limitations of this investigation, mainly the lack of precise data on general health and on the duration and dose of CCB exposure. Further analyses with better characterises cohorts might show different results in specific sub-groups. Ultimately, the magnitude of any potential effect, whether detrimental or protective, could only be estimated with carefully designed RCTs.

Figure legends

Figure 1. Results of the multivariable linear mixed model analysis. The graph reports the estimated effects for the interaction between each variable and time. This represents the additive effect of each variable on the rate

of progression of the mean deviation over time. The 95% Confidence Intervals are represented with horizontal bars. Significant p-values (< 0.05) are reported. For better visibility, the estimates are reported for 5 dB change for MD and PSD and by decade for baseline age. For this analysis, the 'reference' patient was 67 years old, white, male, not diabetic, average IMD score, 0 dB MD and PSD at baseline, phakic at baseline, no cataract surgery during follow-up, not on any of the included systemic medications. Age, baseline MD and baseline PSD were rescaled for better visibility. CCB = calcium channel blockers; DM = Diabetes Mellitus; MD = Mean Deviation; PSD = Pattern Standard Deviation; IMD = Index of Multiple deprivation. PACD = Primary Angle Closure Disease; CS = Cataract Surgery.

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	CCB users N = 1,942[a]	Matched controls N = 1,942[a]	p-value[b]	All controls N = 12,533[a]	p-value[b]
Demographics					
Age (years)[c]	71 (65, 77)	72 (65, 78)	0.038	68 (59, 75)	<0.001
Sex[c]			0.460		0.901
Female	1,016 (52%)	1,039 (54%)		6,538 (52%)	
Male	926 (48%)	903 (46%)		5,995 (48%)	
Ethnicity[c]			0.726		0.375
Non-white	39 (2.0%)	36 (1.9%)		216 (1.7%)	
White	1,903 (98%)	1,906 (98%)		12,317 (98%)	
IMD score[c]	12 (7, 22)	12 (7, 22)	0.462	12 (7, 20)	0.124
Diabetes[c]			0.443		<0.001
No diabetes	1,494 (77%)	1,518 (78%)		11,001 (88%)	
Type 1	26 (1.3%)	19 (1.0%)		88 (0.7%)	
Type 2	422 (22%)	405 (21%)		1,444 (12%)	
Cataract surgery[c]			0.564		<0.001
Phakic	1,231 (63%)	1,201 (62%)		10,096 (81%)	
Pseudophakic	62 (3.2%)	69 (3.6%)		203 (1.6%)	
CS during follow-up	649 (33%)	672 (35%)		2,234 (18%)	
Baseline MD (dB)[c]	-3.1 (-6.0, -1.6)	-3.1 (-5.9, -1.6)	0.708	-3.1 (-6.0, -1.6)	0.785
Baseline PSD (dB)[c]	2.71 (1.84, 5.73)	2.69 (1.83, 5.47)	0.472	2.6 (1.8, 5.8)	0.208
VF tests (N)	8.0 (6.0, 11.0)	8.0 (6.0, 11.0)	<0.001	8.0 (6.0, 11.0)	0.024
Follow-up (years)	8.57 (6.05, 11.52)	8.08 (5.87, 11.05)	0.001	8.20 (5.88, 11.24)	<0.001
Baseline VA (logMAR)	0.20 (0.00, 0.20)	0.20 (0.00, 0.30)	0.091	0.10 (0.00, 0.20)	<0.001
Average IOP (mmHg)	16.8 (14.7, 19.0)	16.7 (14.3, 19.1)	0.104	17.0 (14.7, 19.5)	0.190
Highest IOP (mmHg)	21 (18, 26)	21 (17, 25)	0.072	21 (18, 26)	0.616
Diagnostic label[c]			0.457		0.940
POAG	822 (42%)	784 (40%)		5,274 (42%)	
PACD	58 (3.0%)	58 (3.0%)		391 (3.1%)	
Other	1,062 (55%)	1,100 (57%)		6,868 (55%)	
Medications					
Diuretics[c]	768 (40%)	749 (39%)	0.532	1,585 (13%)	<0.001
Other anti-hypertensives[c]	1,191 (61%)	1,185 (61%)	0.843	2,231 (18%)	<0.001
Nitrates[c]	180 (9.3%)	158 (8.1%)	0.210	289 (2.3%)	<0.001
Statins[c]	996 (51%)	993 (51%)	0.923	2,137 (17%)	<0.001
Corticosteroids[c]	226 (12%)	225 (12%)	0.960	651 (5.2%)	<0.001
Beta blockers[c]	475 (24%)	469 (24%)	0.822	1,184 (9.4%)	<0.001
Psychoactive drugs[c]	309 (16%)	369 (19%)	0.011	1,104 (8.8%)	<0.001
Metformin[c]	236 (12%)	228 (12%)	0.692	519 (4.1%)	<0.001

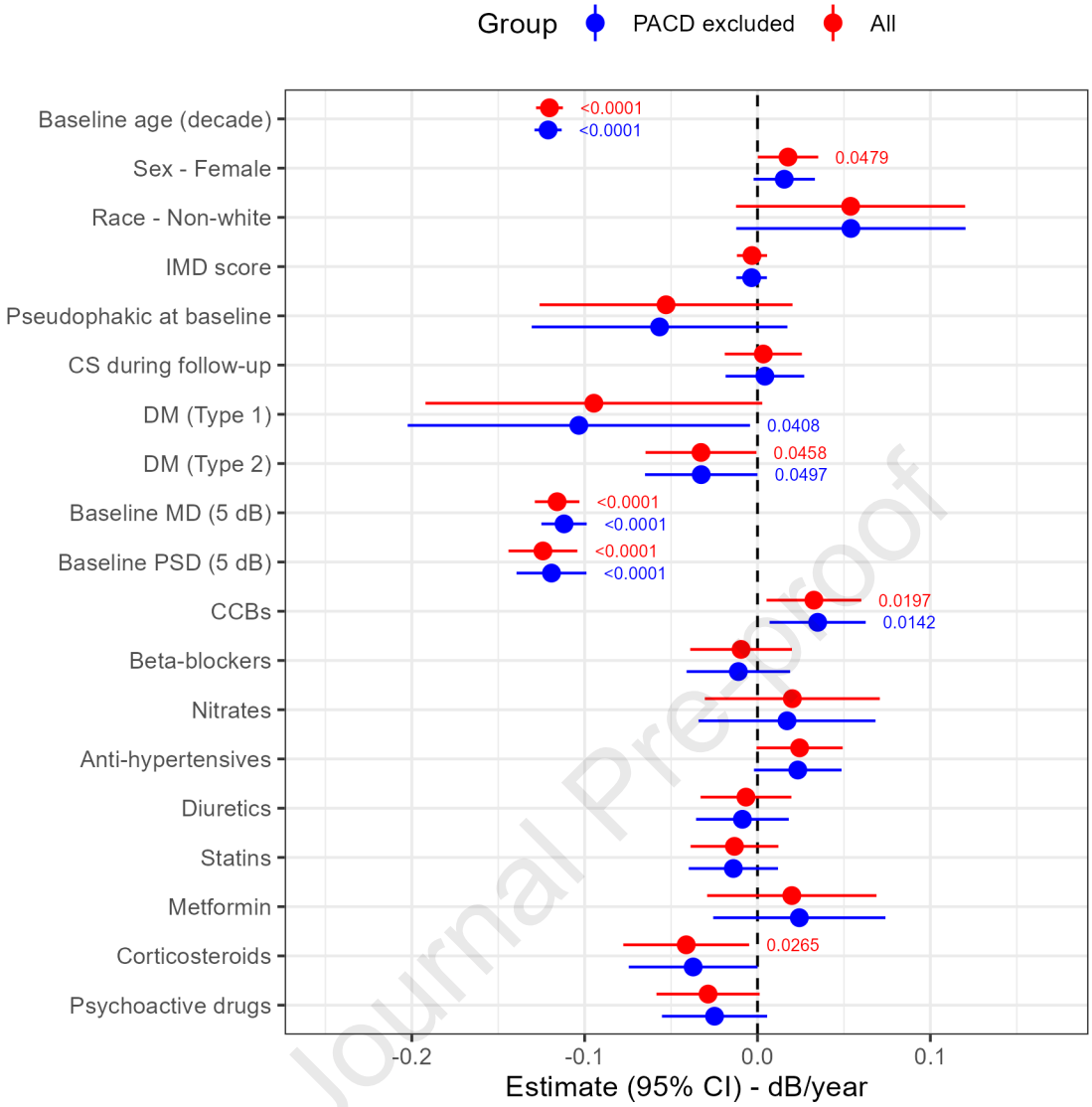
[a] Median (Interquartile Range); n (%); [b] Wilcoxon rank sum test; Pearson's Chi-squared test; [c] Included in propensity score matching

Table 1. Demographics for the main selection cohorts - at least 5 visual field (VF) tests over at least 4 years, with at least two non-consecutive mean deviation values < -2 dB. CCB = Calcium Channel Blocker; IOP = Intraocular Pressure (during follow-up); VA = Visual Acuity; MAR = Minimum Angle of Resolution; POAG = Primary Open Angle Glaucoma; PACD = Primary Angle Closure Disease; MD = Mean Deviation; PSD = Pattern Standard Deviation; IMD = Index of Multiple Deprivation; CS = Cataract Surgery; Other = Unclassified, not updated or classified as ocular hypertension/glaucoma suspect but meeting the selection criteria.

	Matched controls		CCB users		Differences		
	Estimate	**95% CI[1]**	**Estimate**	**95% CI[1]**	**Estimate**	**95% CI[1]**	**p-value**
All							
Baseline (dB)	-4.2	-4.5, -4.0	-4.4	-4.6, -4.1	-0.10	-0.41, 0.20	0.5
Rate of progression (dB/year)	-0.35	-0.37, -0.33	-0.31	-0.33, -0.28	0.04	0.01, 0.08	0.016
PACD excluded							
Baseline (dB)	-4.3	-4.5, -4.1	-4.4	-4.6, -4.1	-0.09	-0.40, 0.22	0.6
Rate of progression (dB/year)	-0.35	-0.37, -0.32	-0.31	-0.33, -0.28	0.04	0.01, 0.08	0.016

[1]CI = Confidence Interval

Table 2. Results from the linear mixed model comparing Calcium Channel Blocker (CCB, any exposure) users and matched controls. PACD = Primary Angle Closure Disease.



Systemic calcium channel blockers were significantly associated with a slower rate of visual field deterioration, after multivariable adjustment, in a large cohort of patients from glaucoma clinics.