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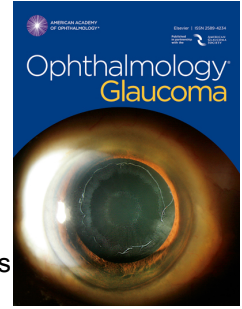
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# Journal Pre-proof

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

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**Running head:** Calcium channel blockers and visual field progression

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# 1 Abstract

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

5 **Design:** retrospective, longitudinal case-control study.

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

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

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

19 **Results:** the main analysis included 14,475 eyes (1,942 from CCB users) which met the  
20 selection criteria (one eye per patient). The Median [Interquartile Range] VF series length  
21 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  
22 controls respectively. One-to-one PSM pairing with controls was achieved for all CCB users.  
23 The estimated rate of MD progression was -0.31 [-0.33, -0.28] dB/year (Mean [95%-  
24 Confidence Intervals]) in the CCB users and -0.35 [-0.37, -0.33] dB/year in the matched  
25 controls (p = 0.016). This significant difference was confirmed with the MV analysis,  
26 including all controls (p = 0.020). All sensitivity analyses confirmed the main results.

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

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

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

47 However, well-powered studies of the association between CCB use and rate of glaucoma  
48 progression are still lacking. In this work, we analysed real-world data from more than  
49 14,000 patients followed in five glaucoma clinics across the UK. We investigated the  
50 association between systemic CCB use and the rate of visual field (VF) progression, adjusting  
51 for multiple confounders. We further report on the association of the rate of VF progression  
52 with the use of systemic medication classes and multiple patient characteristics.

## 53 Methods

### 54 Clinical cohort

55 Patient data from five National Health Service glaucoma clinics in England were extracted  
56 from an ophthalmic electronic medical record (EMR; Medisoft, Medisoft Ltd., Leeds, UK).  
57 This database was created in 2015 as part of the Royal College of Ophthalmologists National  
58 Ophthalmology Database audit<sup>18</sup>. All patient data were anonymized upon data extraction  
59 and stored in a secure database at City, University of London. Subsequent analyses of this  
60 dataset were approved by a research ethics committee of City, University of London, in  
61 accordance with the Declaration of Helsinki and the General Data Protection Regulation of  
62 the European Union. The dataset contained Humphrey Field Analyzer (HFA, Zeiss Meditec,  
63 Dublin, CA) VF data for 145,562 eyes of 73,990 patients. We selected tests performed with a  
64 24-2 pattern and any SITA (Swedish Interactive Threshold Algorithm) strategy<sup>19</sup> with less  
65 than 15% false positive error rate<sup>20</sup>. A mixture of VF SITA Standard and Fast was allowed  
66 because the use of SITA Fast, despite its slightly lower precision, is unlikely to make a  
67 sizeable difference for measuring VF progression<sup>21</sup>. Series were truncated at the time of

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

73 For our main analysis, we selected series with at least 5 tests performed over at least 4  
74 years. Following previous methodology for analyses on the same dataset<sup>22-24</sup>, the series  
75 needed to contain at least two not necessarily consecutive VFs with a mean deviation (MD)  
76  $< -2$  dB (95% lower limits of normality for HFA<sup>22</sup>). This increased the likelihood of including  
77 eyes with perimetric defects from glaucoma during the course of their follow up, without  
78 relying on diagnostic labels reported by clinicians. A sensitivity analysis was conducted  
79 without applying this criterion (see later).

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

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

## 92 Systemic medications

93 Medical staff could manually enter systemic medications into the EMR, as per standard  
94 clinical practice, recorded as active components or brand names. These were automatically  
95 classified by the EMR into broader categories. All classifications were manually reviewed.  
96 Brand names were converted into their active component names. All fixed combinations  
97 were split into their individual components. The categories that were identified for systemic  
98 medications are reported in **Table 1**. The category identified as “*Other anti-hypertensives*”  
99 included: Angiotensin Receptor Blockers (ARBs), Angiotensin Converting Enzyme inhibitors  
100 (ACEi), direct renin inhibitors,  $\alpha$ 2A-adrenergic agonists,  $\alpha$ 1-adrenergic blockers, direct vaso-  
101 dilators and medications for pulmonary hypertension.

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

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

## 109 Statistical analysis

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

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

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

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

158 Missing data were imputed using the method of Multivariable Imputation by Chained  
159 Equations (MICE), as implemented in the *mice*<sup>32</sup> package for R, using all available  
160 demographics. Single imputation was chosen because of the low percentage of missing data  
161 (< 10%, see **Results**), to reduce computational complexity and to generate a unique dataset  
162 that could be adapted for both PMS and the multivariable analyses.

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

## 168 Sensitivity and supplementary analyses

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

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

181 since they have been both associated with a reduced chance of progression in some  
182 subgroup of patients<sup>13</sup>.

## 183 Results

### 184 Cohort characteristics

185 We identified 1,942 out of 14,475 (13%) patients exposed to systemic CCBs. Of these, 87%  
186 were using dihydropyridines (54% amlodipine) and 13% using non-dihydropyridines (10%  
187 diltiazem, 3% verapamil). The average exposure among CCB users was 32% (Median  
188 [Interquartile Range] 23 [0, 52]%). The characteristics of the exposed cohort, of all controls  
189 and of the 1,942 matched controls identified via PSM are reported in **Table 1**. All variables  
190 considered for PSM were well balanced between CCB users and matched controls. A  
191 statistically significant difference ( $p < 0.05$ ) was still present for baseline age, but both the  
192 median and the interquartile range were very similar, differing at most by 1 year. Some  
193 variables, such as the highest IOP, the average IOP and the baseline BCVA were also well  
194 balanced, despite not having been considered for PSM. Other variables, such as the length  
195 of the follow up and the number of tests, showed a strongly statistically significant  
196 difference ( $p < 0.01$ ) but were very similar in their median and IQR. Missing data were  
197 imputed for age (1/14,475,  $< 0.01\%$ ), IMD score (691/14,475, 4.8%), diabetes type  
198 (287/1,980, 14.5% of diabetic patients, 2% of the total), ethnicity (1,157/14,475, 8%) and  
199 baseline VA (1,031/14,475, 7.1%).

### 200 Associations with rate of progression

201 The results of the analysis on CCB-exposed and PSM-matched controls are reported in **Table**  
202 **2**. Exposure to CCBs was associated with a significantly slower rate of progression ( $p =$   
203 0.016). No difference was found in the estimated baseline MD, as expected from the PSM  
204 (see **Table 1**). The analysis was also repeated by excluding 116 eyes that had a diagnostic  
205 label suggestive of an angle closure mechanism, with no material difference in the results.

206 These results were also confirmed by the multivariable analysis (**Figure 1**). The estimated  
207 rate for the 'reference' patient was -0.34 [-0.41, -0.28] dB/year (Mean [95% Confidence  
208 Interval]), very similar to the estimated rate for the matched control group obtained with  
209 PSM (**Table 2**). The estimated difference in rate associated with the use of CCBs was 0.03  
210 [0.01, 0.06] dB/year ( $p = 0.020$ ) similar to the difference in **Table 2**. Similar results were  
211 obtained by including or excluding patients with a diagnostic label suggestive of angle  
212 closure ( $p=0.025$ ). Other significant detrimental associations were found with older baseline  
213 age, higher baseline PSD, more positive baseline MD, presence of diabetes and use of  
214 systemic corticosteroids. Female sex was associated with a slower rate of MD progression ( $p$   
215 = 0.048) in the full cohort. A table with the results from the multivariable LMM is reported in  
216 the **supplementary appendix**.

217 The secondary and sensitivity analyses confirmed these results and are reported in detail in  
218 the **supplementary appendix**. Similar results were obtained by redefining the use of CCBs as  
219 an estimated exposure of at least 20% (CCB users=1,044,  $p=0.005$  for PSM analysis) and by  
220 removing patients on non-dihydropyridines (258/1942 CCB users,  $p = 0.034$ ). The ‘dose-  
221 response’ analysis showed a significant positive association with the exposure fraction (0.13  
222 [0.07, 0.19] dB/year per fraction point,  $p < 0.001$ , **supplementary appendix**), which was  
223 maintained after restricting the analysis to the 1,044 CCB users (0.16 [0.08, 0.24] dB/year  
224 per fraction point,  $p < 0.001$ ). CCBs were also significantly associated with slower rates of  
225 MD progression ( $p=0.004$  for PSM analysis) when all patients with at least 2 reliable VFs over  
226 1 year prior to glaucoma surgery were included ( $N = 36,146$ , CCB users = 5,104). Other  
227 associations in the multivariable LMM became significant with this extended cohort (see  
228 **supplementary appendix**). ARBs, but not ACEis, were also found to have significant  
229 association with slower rates of progression ( $p=0.015$ , multivariable analysis), when  
230 analysed separately from other anti-hypertensives in the main selection cohort  
231 (**supplementary appendix**).

## 232 Discussion

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

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

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

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

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

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

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

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

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

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

333 While these mechanisms can explain the association with a slower rate of VF progression,  
334 they do not justify the higher risk of developing glaucoma associated with the use of CCBs.  
335 The main proposed explanation for this detrimental association is a complex effect on  
336 systemic blood pressure of some CCBs, especially when used in combination with other anti-  
337 hypertensive medications<sup>10</sup>. However, this explanation is not supported by our results: most  
338 of the patients in our cohort were on CCBs known for their hypotensive properties, such as  
339 amlodipine (54%), and a large proportion of CCB users were on other anti-hypertensive  
340 medications, beta-blockers or diuretics (see **Table 1**). Despite this, CCBs were associated with  
341 a slower rate of VF progression. Interestingly, the estimated association in the multivariable  
342 analysis remained essentially unchanged when patients on non-dihydropyridines were  
343 excluded from the analysis (0.031 [0.002, 0.060],  $p = 0.034$ , see **supplementary appendix**).  
344 Whatever the mechanism, it is likely to be IOP-independent. Despite some evidence of IOP  
345 reduction with CCBs use<sup>46, 47</sup>, other studies have failed to replicate this effect<sup>48</sup>. Notably, such  
346 a lack of association between IOP and CCBs was also reported in a large-scale investigation  
347 on the cohort from the UK Biobank<sup>10</sup>. There was no difference in IOP in our cohort (see **Table**  
348 **1**).

349 Despite its strengths, mainly the very large sample size and the long follow-up (**Table 1**), this  
350 study has limitations, largely derived from its retrospective nature. Our sensitivity and  
351 secondary analyses were designed to mitigate these limitations. One limitation was the lack  
352 of clear diagnostic labels. More than half of the eyes included in the main analysis had not  
353 been explicitly labelled as 'glaucoma' in the EMR. This is despite having selected patients  
354 followed for at least 4 years with at least two tests with an MD < -2 dB. This criterion has  
355 been previously used on this dataset to minimise the inclusion of glaucoma suspects and  
356 ocular hypertensives<sup>22-24</sup>, but is clearly not a replacement for a definitive diagnosis. However,  
357 many similar investigations relying on retrospective analysis of medical records or self-  
358 reported diagnosis suffer from the same limitation. On the other hand, the selection criteria  
359 might have excluded eyes with very early glaucoma or patients with fewer tests prior to  
360 surgery, such as fast progressors. Our primary analysis required 5 VFs over at least 4 years;  
361 13% of this cohort were using CCBs. This was no different from the proportion of CCB users  
362 (12%) in a larger cohort of patients with at least 2 VFs over 1 year (but fewer than 5 VFs over  
363 4 years), indicating that CCB use was not associated with a shorter follow-up. We included  
364 this larger cohort in a sensitivity analysis and obtained similar results (**supplementary**  
365 **appendix**). Our main analysis also truncated VF series at the time of glaucoma surgery, to  
366 minimise the systematic bias in the slopes of fast progressing eyes prior to surgery. Cataract  
367 surgery might also affect VF metrics such as MD. However, cataract surgery is usually not  
368 offered with the specific goal of treating glaucoma and is therefore unlikely to be more  
369 commonly performed in fast progressing patients. Regardless, cataract surgery and phakic  
370 status were actively controlled for in our PS matching and multivariable analyses. The effect  
371 was not significant in our main multivariable analysis ( $p = 0.8$ ).

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

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

## 408 Figure legends

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

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

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543

	CCB users N = 1,942 <sup>a</sup>	Matched controls N = 1,942 <sup>a</sup>	p-value <sup>b</sup>	All controls N = 12,533 <sup>a</sup>	p-value <sup>b</sup>
<b>Demographics</b>					
Age (years) <sup>c</sup>	71 (65, 77)	72 (65, 78)	0.038	68 (59, 75)	<0.001
Sex <sup>c</sup>			0.460		0.901
Female	1,016 (52%)	1,039 (54%)		6,538 (52%)	
Male	926 (48%)	903 (46%)		5,995 (48%)	
Ethnicity <sup>c</sup>			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 <sup>c</sup>	12 (7, 22)	12 (7, 22)	0.462	12 (7, 20)	0.124
Diabetes <sup>c</sup>			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 <sup>c</sup>			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) <sup>c</sup>	-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) <sup>c</sup>	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 <sup>c</sup>			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%)	
<b>Medications</b>					
Diuretics <sup>c</sup>	768 (40%)	749 (39%)	0.532	1,585 (13%)	<0.001
Other anti-hypertensives <sup>c</sup>	1,191 (61%)	1,185 (61%)	0.843	2,231 (18%)	<0.001
Nitrates <sup>c</sup>	180 (9.3%)	158 (8.1%)	0.210	289 (2.3%)	<0.001
Statins <sup>c</sup>	996 (51%)	993 (51%)	0.923	2,137 (17%)	<0.001
Corticosteroids <sup>c</sup>	226 (12%)	225 (12%)	0.960	651 (5.2%)	<0.001
Beta blockers <sup>c</sup>	475 (24%)	469 (24%)	0.822	1,184 (9.4%)	<0.001
Psychoactive drugs <sup>c</sup>	309 (16%)	369 (19%)	0.011	1,104 (8.8%)	<0.001
Metformin <sup>c</sup>	236 (12%)	228 (12%)	0.692	519 (4.1%)	<0.001

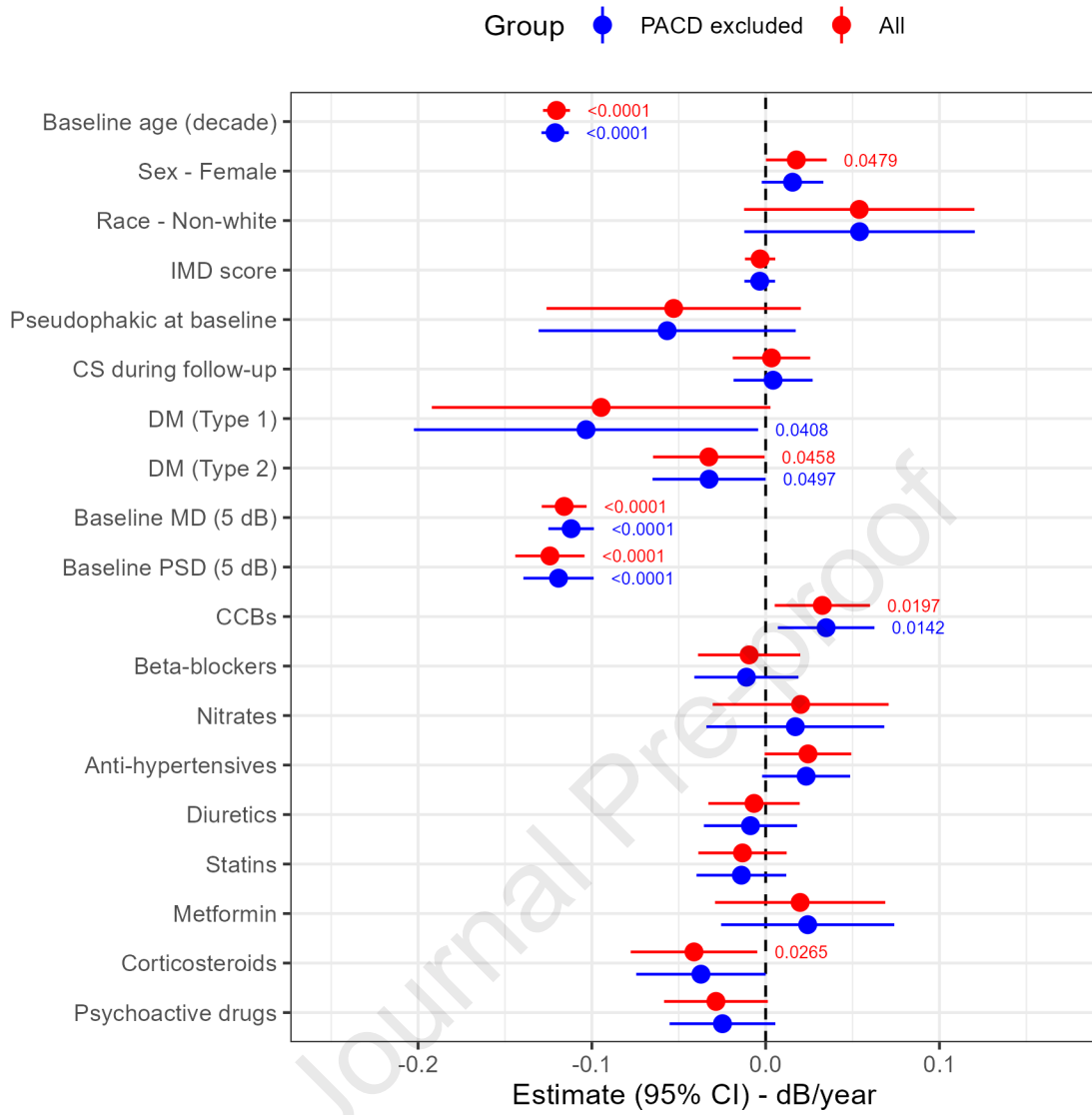
<sup>a</sup> Median (Interquartile Range); n (%); <sup>b</sup> Wilcoxon rank sum test; Pearson's Chi-squared test; <sup>c</sup> Included in propensity score matching

**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 <sup>1</sup>	Estimate	95% CI <sup>1</sup>	Estimate	95% CI <sup>1</sup>	p-value
<b>All</b>							
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
<b>PACD excluded</b>							
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

<sup>1</sup>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.

Journal Pre-proof