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Survival of medical treatment success in primary open-angle glaucoma and ocular hypertension

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ABSTRACT

Background/aims Topical agents to lower intraocular pressure (IOP) are the most common initial therapeutic measure in glaucoma prevention. This study aims to assess treatment success duration among patients initiating or intensifying topical glaucoma medication.

Methods Medical records (2013–2018) for adults initiating/intensifying topical glaucoma medication were extracted from five secondary-care and tertiary-care UK ophthalmology centres. Main study outcomes were time from treatment initiation/intensification to treatment failure (<20% IOP reduction or IOP >21 mm Hg at consecutive clinic visits, or intensification of glaucoma treatment) and time from treatment change to subsequent treatment intensification.

Results Study eyes (n=6587) underwent treatment intensification 0-to-1 glaucoma drop (5358 events), 1-to-2 drops (1469 events) and 2-to-3 drops (857 events) during the observation period. Median time to treatment failure was 1.60 (95% CI 1.57 to 1.65), 1.00 (95% CI 0.94 to 1.07) and 0.92 (95% CI 0.81 to 1.02) years following escalation 0-to-1, 1-to-2 and 2-to-3 drops, respectively. Median time to treatment intensification (non-IOP–based criterion) was 4.68 (95% CI 4.50 to 5.08) years for treatment initiators, 3.83 (95% CI 3.36 to 4.08) years on escalation 1-to-2 drops and 4.35 (95% CI 3.82 to 4.88) years on escalation 2-to-3 drops. On multivariable regression, significant risk factors for both treatment failure and intensification were lower baseline visual field mean deviation, primary open-angle glaucoma and lower eyedrop count in the fellow eye; lower baseline IOP was associated with treatment failure, higher baseline IOP with treatment intensification.

Conclusion Large-scale survival analyses provide the expected duration of treatment success from topical glaucoma medication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The most common initial therapeutic measure in glaucoma prevention is administration of topical intraocular pressure (IOP)-lowering agents, as IOP is the most important modifiable risk factor for development and progression of primary open-angle glaucoma. However, continued maintenance of adequate IOP control often requires treatment intensification.

WHAT THIS STUDY ADDS

⇒ Data on treatment persistence and escalation rates with topical glaucoma medication are not often collected systematically. In our analysis of electronic medical records from a large cohort of UK patients initiating or intensifying their treatment with topical IOP-lowering agents, we show that IOP remained adequately controlled for a median of 1.6, 1.0 and 0.9 years following escalation from 0 to 1, 1–2 and 2–3 agents, respectively.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Information on the longevity of the IOP-lowering effect with topical glaucoma medication underpins informed choices in treatment planning, benefiting healthcare providers, healthcare planners, surgeons and patients.

INTRODUCTION

Intraocular pressure (IOP) is the most important modifiable risk factor for development and progression of primary open-angle glaucoma (POAG).[1] Lowering IOP remains the only proven treatment to delay conversion of ocular hypertension (OHT) to POAG,[2] and to slow disease progression in established glaucoma.[3–5]

Topical IOP-lowering medication is the most common initial therapeutic approach to the management of OHT and POAG. However, continued maintenance of adequate IOP control often requires treatment intensification. If acceptable IOP levels are not achieved with a single topical medication, adding or switching to medications with complementary mechanisms of action is recommended.[6] In the UK, the National Institute for Health and Care Excellence recommends that a prostaglandin analogue be used as the initial agent, with the option of medication switch to, or augmentation with, a beta-blocker, carbonic anhydrase inhibitor or sympathomimetic if IOP control proves inadequate.[7]

The survival (or duration) of successful IOP reduction provided by topical glaucoma medication is less well established than that of non-medical interventions such as laser trabeculoplasty and incisional glaucoma surgery. For glaucoma procedures, studies have reported success rates of IOP-lowering at multiple postprocedure timepoints: these comprise complete success (sufficient IOP-lowering without the need for concurrent glaucoma medication)

and qualified success (glaucoma medications required). Information on the longevity of the IOP-lowering effect that can be expected with topical glaucoma medication would be integral to informing treatment strategy and prognosis and therefore of interest to healthcare providers, healthcare planners, surgeons and patients. However, few studies have examined how long IOP-lowering success lasts with glaucoma medication. Studies assessing longitudinal patterns of glaucoma medication use offer limited insight into the rates and trajectories of treatment intensification in real-world practice.[8–11] Accordingly, the objective of this study was to quantify the survival of treatment success and IOP control among patients with OHT and POAG receiving topical glaucoma medication in clinical practice in the UK and to identify risk factors for treatment failure or intensification.

MATERIALS AND METHODS

Study design and data source

This multicentre, retrospective cohort study included patients with OHT and POAG undergoing topical glaucoma therapy at five secondary-care and tertiary-care ophthalmology centres in the UK that use Medisoft Ophthalmology (Medisoft, Leeds, UK) to electronically record ophthalmic clinical care data, as previously described.[12] The socioeconomic status of the area where the centre was located was assessed using the English Index of Multiple Deprivation (IMD).[13]

Cohort selection

This study included patients who met the following criteria: attended a glaucoma clinic between 1 January 2013 and 31 December 2018 ('observation period') with at least one follow-up visit with an accompanying IOP measurement during the following 2 years; ≥18 years of age at first visit; diagnosis of either OHT or POAG; underwent a change in topical glaucoma medication(s), comprising treatment initiation (from 0 to 1 agent) and/or treatment intensification (from 1 to 2 agents or from 2 to 3 agents) during the observation period. To capture patients at the beginning of the treatment pathway, eyes that underwent an IOP-lowering glaucoma procedure (either laser or surgical) prior to the index visit were excluded. Those who underwent prior cataract surgery were included.

One eye per patient was taken forward for analysis ('study eye') (online supplemental materials 1). The first clinic visit at which topical glaucoma treatment was either initiated or intensified was taken as the index or baseline event. Study cohorts were differentiated by the treatment change occurring at the index event: (1) escalation from 0 to 1 class of topical glaucoma medication (treatment initiation), (2) from 1 to 2 classes of medication and (3) from 2 to 3 classes of medication.

Study outcomes

The primary outcome was the duration of adequate IOP-lowering effect following treatment change, that is, the time from index event to waning of treatment effect, as defined by one of the following: a <20% reduction in IOP from index level at two consecutive clinic visits; IOP >21 mm Hg at two consecutive clinic visits; or subsequent intensification of glaucoma treatment, both medical (an increase in number of prescribed agents) and non-medical (undergoing an IOP-lowering procedure).[12] Cohorts were censored at subsequent treatment intensifications (see online supplemental materials 2). The secondary outcome was the time from treatment change to subsequent treatment intensification regardless of the recorded IOP, defined as a further increase in the number of topical glaucoma agents or receipt of an IOP-lowering procedure.

Table 1 Baseline demographic and clinical characteristics of study cohorts categorised by treatment initiation or intensification event

	Cohort 1 0→1 medications (n=5358)	Cohort 2 1→2 medications (n=1469)	Cohort 3 2→3 medications (n=857)
Age, years			
Mean (SD)	71.5 (12.0)	73.4 (11.2)	75.6 (10.9)
Sex, women, n (%)	2702 (50.4)	753 (51.3)	437 (51.0)
Ethnicity, n (%)			
Caucasian	4888 (91.2)	1367 (93.1)	813 (94.9)
Asian	64 (1.2)	16 (1.1)	8 (0.9)
Black	58 (1.1)	21 (1.4)	6 (0.7)
Other	49 (0.9)	10 (0.7)	9 (1.1)
Unspecified	299 (5.6)	55 (3.7)	21 (2.5)
Index of Multiple Deprivation, mean (SD)	6.2 (2.9)	6.2 (2.9)	6.4 (2.9)
Diagnosis, n (%)			
POAG	3494 (65.2)	1072 (73.0)	719 (83.9)
OHT	1864 (34.8)	397 (27.0)	138 (16.1)
Baseline IOP of study eye, mm Hg			
Mean (SD)	20.3 (6.6)	20.8 (5.8)	20.6 (6.1)
Visual field MD of study eye, dB			
Mean (SD)	n=4309–4.3 (5.6)	n=1229–6.2 (6.1)	n=711–8.0 (6.9)
Visual acuity of study eye, LogMAR			
Mean (SD)	n=30 960.19 (0.32)	n=9240.20 (0.32)	n=5090.27 (0.40)

IOP, intraocular pressure; LogMAR, logarithm of the minimum angle of resolution; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma.;

Statistical analyses

For each outcome, hazards were modelled with Kaplan-Meier survival analyses. Univariable and multivariable Cox regression was used to assess associations between the study outcomes and study variables: age, sex, ethnicity, IMD, glaucoma-related diagnosis, index IOP, index visual field mean deviation (MD) and number of medications administered in the fellow eye. All data analyses were performed using R statistical software.[14] The Hodapp *et al* classification system was used to report degree of visual field VF impairment: was classified as mild (MD >−6 dB), moderate (MD −6 dB to −12 dB) or advanced (MD <−12 dB).[15]

RESULTS

Study cohorts and baseline characteristics

Between January 2013 and December 2018, 6587 unique eyes of 6587 patients met the study eligibility criteria. Non-overlapping treatment periods were split between three treatment event groups: initiation of topical glaucoma medication (0-to-1; n=5358); escalation from 1 to 2 agents (1-to-2; n=1469) and escalation from 2 to 3 agents (2-to-3; n=857). Baseline demographic and clinical characteristics of the study cohorts are summarised in table 1. Topical glaucoma treatment was most frequently initiated with a prostaglandin analogue (86.9%); prostaglandin analogue and β-blocker (54.5%) for 2-class therapy and prostaglandin analogue, carbonic anhydrase inhibitor and β-blocker (70.4%) for 3-drop therapy (online supplemental materials 3—eTable 1).

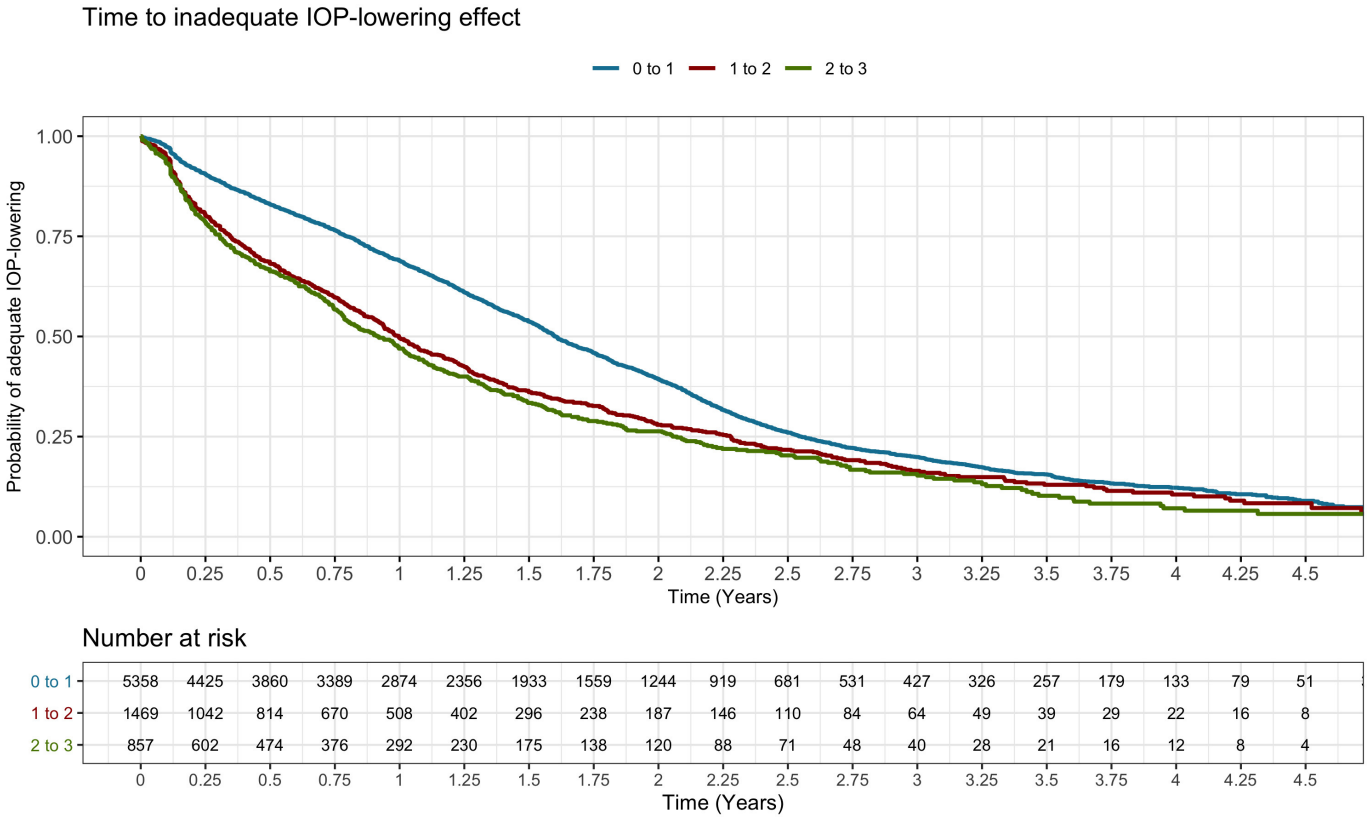

Figure 1 Kaplan-Meier curve of time to inadequate intraocular pressure (IOP)-lowering effect following topical glaucoma treatment initiation or intensification. Kaplan-Meier estimates of reaching inadequate IOP-lowering effect, defined as time to: IOP reduction <20% at two consecutive visits; or IOP >21 mm Hg at two consecutive visits; or medication Intensification; or IOP-lowering glaucoma procedure. Treatment events considered were as follows: escalation from 0 to 1 class of topical glaucoma medication (treatment initiation; blue); from 1 to 2 classes of medication (red) and from 2 to 3 classes of medication (green). Median outcome time and the 95% CI are displayed here for each cohort.

Duration of adequate IOP control following treatment initiation and intensification

First, we examined the time to treatment failure, as defined by either an inadequate IOP response (IOP reduction <20% from index level or IOP >21 mm Hg at two consecutive clinic visits) or a subsequent intensification of treatment. In the Kaplan-Meier analysis, treatment success survival was longest for the 0-to-1 drop cohort, followed by the 1-to-2 drop cohort, and was shortest for the 2-to-3 drop cohort (figure 1). The median time to treatment failure, which represents the timepoint corresponding to a 50% probability of treatment failure, was 1.60 (95% CI 1.57 to 1.65) years for study eyes initiating treatment (0-to-1 drop cohort), 1.00 (95% CI 0.94 to 1.07) years for eyes in the 1-to-2 drop cohort and 0.92 (95% CI 0.81 to 1.02) years for eyes in the 2-to-3 drop cohort. Similarly, the lowest probabilities of treatment failure at 1 and 2 years were observed for the 0-to-1 drop cohort (31% (95% CI 30% to 33%) and 61% (95% CI 59% to 62%), respectively), followed by the 1-to-2 drop cohort (51% (95% CI 47% to 53%) and 72% (95% CI 69% to 75%), respectively) and the 2-to-3 drop cohort (53% (95% CI 51% to 57%) and 74% (95% CI 71% to 77%), respectively).

Risk factors for inadequate IOP response to topical glaucoma medication

Univariable associations with treatment failure are summarised in table 2. A lower number of baseline topical glaucoma agents in the fellow eye was associated with treatment failure in each of the cohorts: 0-to-1 drop, HR 0.60 (95% CI 0.44 to 0.81; $p=9.2\times10^{-4}$); 1-to-2 drops, HR 0.79 (95% CI 0.72 to 0.87; $p=5.3\times10^{-7}$) and 2-to-3 drops, HR 0.90 (95% CI 0.83 to 0.97; $p=5.6\times10^{-3}$).

Patients with OHT were less likely than patients with POAG to fail medical treatment after initiation of monotherapy (HR 0.24, 95% CI 0.10 to 0.60; $p=2.3\times10^{-3}$) and escalation from 1 to 2 agents (HR 0.81, 95% CI 0.70 to 0.94; $p=6.5\times10^{-3}$) but not after subsequent treatment intensification from 2 to 3 agents (HR 1.13, 95% CI 0.89 to 1.44; p=0.30). Moreover, associations between greater visual field loss at baseline (ie, lower or more negative visual field MD) and greater likelihood of treatment failure were observed in the 0-to-1 drop cohort (HR per dB 0.90, 95% CI 0.87 to 0.93; $p=3.3\times10^{-10}$) and the 1-to-2 drop cohort (HR per dB 0.98, 95% CI 0.96 to 0.99; $p=1.8\times10^{-5}$), but not in the 2-to-3 drop cohort (HR per dB 1.00, 95% CI 0.98 to 1.01; p=0.67).

Multivariable adjusted associations with treatment failure were also carried out (online supplemental materials—eTable 2). A lower number of baseline topical glaucoma agents in the fellow eye remained associated with treatment failure following treatment intensification from 1-to-2 drops (HR 0.80 (95% CI 0.72 to 0.88); $p=5.2\times10^{-5}$) and from 2-to-3 drops (HR 0.91 (95% CI 0.83 to 0.99); $p=3.3\times10^{-3}$) but not following treatment initiation (HR 1.00 (95% CI 0.91 to 1.10); p=0.99). In comparison to POAG, OHT was still significantly associated with treatment success in the 0-to-1 drop cohort (HR 0.86 (95% CI 0.78 to 0.95); $p=2.9\times10^{-3}$) but not in the 1-to-2 drop cohort (HR 1.06 (95% CI 0.87 to 1.28); p=0.57). As observed in univariable

Table 2 Univariable associations (unadjusted) of inadequate IOP response to topical glaucoma medication

	Cohort 1 0→1 medications (n=5358)	Cohort 2 1→2 medications (n=1469)	Cohort 3 2→3 medications (n=857)
Covariable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age at baseline (decade)	0.94 (0.75 to 1.17)	1.00 (0.95 to 1.06)	0.94 (0.87 to 1.01)
Sex: men versus women	0.67 (0.40 to 1.11)	0.87 (0.76 to 0.99)	0.91 (0.77 to 1.07)
Ethnicity: black versus white	0.85 (0.12 to 6.11)	0.54 (0.30 to 0.98)*	0.98 (0.32 to 3.06)
Ethnicity: Asian versus white	0.76 (0.52 to 1.10)	1.29 (0.71 to 2.34)	1.27 (0.57 to 2.83)
Ethnicity: other versus white	0.92 (0.66 to 1.30)	0.84 (0.35 to 2.01)	0.37 (0.12 to 1.14)
Ethnicity: unspecified versus white	1.61 (0.50 to 5.14)	0.56 (0.37 to 0.86)**	0.60 (0.32 to 1.13)
Index of Multiple Deprivation (decile)	0.97 (0.89 to 1.05)	1.00 (0.98 to 1.02)	1.01 (0.98 to 1.04)
Diagnosis: OHT versus POAG	0.24 (0.10 to 0.60)**	0.81 (0.70 to 0.94)**	1.13 (0.89 to 1.44)
Baseline visual field MD of study eye, dB	0.90 (0.87 to 0.93)***	0.98 (0.96 to 0.99)***	1.00 (0.98 to 1.01)
Baseline IOP of study eye, mm Hg	1.03 (0.98 to 1.07)	0.97 (0.96 to 0.98)***	0.99 (0.98 to 1.01)
Baseline eyedrop count in fellow eye	0.60 (0.44 to 0.81)***	0.79 (0.72 to 0.87)***	0.90 (0.83 to 0.97)**

*p≤0.05.
**p≤0.01.
***p≤0.001.
IOP, intraocular pressure; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

associations, higher baseline visual field MD was associated with treatment success for both the 0-to-1 drop cohort (HR 0.98 (95% CI 0.97 to 0.98); $p=1.3\times10^{-3}$) and the 1-to-2 drop cohort (HR 0.98, 95% CI 0.97 to 0.99; $p=1.0\times10^{-3}$). Higher baseline IOP was associated with treatment success in each of the cohorts: 0-to-1 drop, HR 0.97 (95% CI 0.97 to 0.98; $p=2.2\times10^{-12}$); 1-to-2 drops, HR 0.97 (95% CI 0.95 to 0.98; $p=1.1\times10^{-4}$) and 2-to-3 drops, HR 0.98 (95% CI 0.96 to 1.00, p=0.046).

Time to subsequent treatment escalation

Next, we examined the duration between treatment initiation or intensification and subsequent treatment escalation, as defined by a further increase in the number of topical glaucoma agents or receipt of an IOP-lowering procedure. The median time to treatment escalation was longer than the median time to treatment failure based on IOP-specific criteria: 4.68 (95% CI 4.50 to 5.08) years in the 0-to-1 drop cohort; 3.83 (95% CI 3.36 to 4.08) years in the 1-to-2 drop cohort and 4.35 (95% CI 3.82 to 4.88) years in the 2-to-3 drop cohort (figure 2).

Risk factors for treatment escalation

Univariable regressions identified higher baseline IOP and lower visual field MD to be strongly associated with subsequent treatment escalation across each of the cohorts: 0-to-1 drop cohort (baseline IOP, HR 1.05 (95% CI 1.04 to 1.06), $p=1.8\times10^{-42}$; baseline visual field MD, HR 0.95 (95% CI 0.94 to 0.96), $p=1.8\times10^{-33}$); 1-to-2 drop cohort (baseline IOP, HR 1.03 (95% CI 1.01 to 1.05), $p=2.7\times10^{-3}$; baseline visual field MD, HR 0.95 (95% CI 0.94 to 0.97), $p=8.3\times10^{-11}$) and 2-to-3 drop cohort (baseline IOP, HR 1.06 (95% CI 1.04 to 1.08), $p=7.6\times10^{-9}$; baseline visual field MD, HR 0.98 (95% CI 0.96 to 1.00), p=0.032) (table 3). In comparison to POAG, patients with OHT were less likely to undergo subsequent treatment escalation in the 0-to-1 drop cohort (HR 0.66 (95% CI 0.59 to 0.74); $p=1.0\times10^{-11}$) and the 1-to-2 drop cohort (HR 0.60 (95% CI 0.46 to 0.77); $p=9.2\times10^{-5}$) but not in the 2-to-3 drop cohort (HR 0.98 (95% CI 0.66 to 1.46); p=9.2). Each of the statistically significant associations remained as such when evaluated with multivariable-adjusted regression (online supplemental materials—eTable 3).

Notably, with univariable analyses, the number of topical glaucoma agents in the fellow eye was significantly associated with treatment escalation for each of the cohorts: 0-to-1 drop cohort, HR 0.84 (95% CI 0.75 to 0.94; $p=3.1\times10^{-3}$); 1-to-2 drop cohort, HR 0.77 (95% CI 0.67 to 0.88; $p=1.9\times10^{-4}$) and 2-to-3 drop cohort, HR 0.86 (95% CI 0.76 to 0.97; p=0.017). However, this association was not statistically significant for the 0-to-1 drop cohort (HR 1.02 (95% CI 0.90 to 1.16); p=0.79) or the 2-to-3 drop cohort (HR 0.93 (95% CI 0.81 to 1.06); p=0.29) cohorts when queried with multivariable regression.

DISCUSSION

Key findings

Robust measurement of relevant long-term clinical outcomes in glaucoma presents a major challenge. This retrospective analysis of Medisoft EMR (Electronic Medical Record) data from patients attending UK glaucoma clinics for the management of OHT or POAG provides insight into the duration of IOP control following initiation or intensification of topical glaucoma medication in clinical practice, and the timescale until subsequent treatment escalation. In this large, real-world UK cohort, adequate IOP control was maintained for a median of 1.6, 1.0 and 0.9 years after escalation from 0 to 1, from 1 to 2 and from 2 to 3 topical agents, respectively. Treatment failure, as defined by waning of IOP-lowering effect, was strongly associated with greater visual field loss at baseline and a diagnosis of POAG compared with OHT.

Prespecified IOP reduction targets serve as objective measures of treatment success/failure. However, comparisons of treatment response rates between individual glaucoma studies are complicated by the fact that such targets are only occasionally employed as efficacy endpoints, and in such cases, the numerical targets may differ between studies. Despite this, the likelihood of treatment failure observed among treatment initiators (0-to-1 drop cohort) in our analysis (31% and 61% probability at 1 and 2 years, respectively) aligns with reports from randomised controlled trials of topical glaucoma medication.[16 17]

Our analyses identified greater visual field loss at baseline, lower baseline IOP, existing POAG and use of a lower number of baseline topical glaucoma agents in the fellow eye as predictors

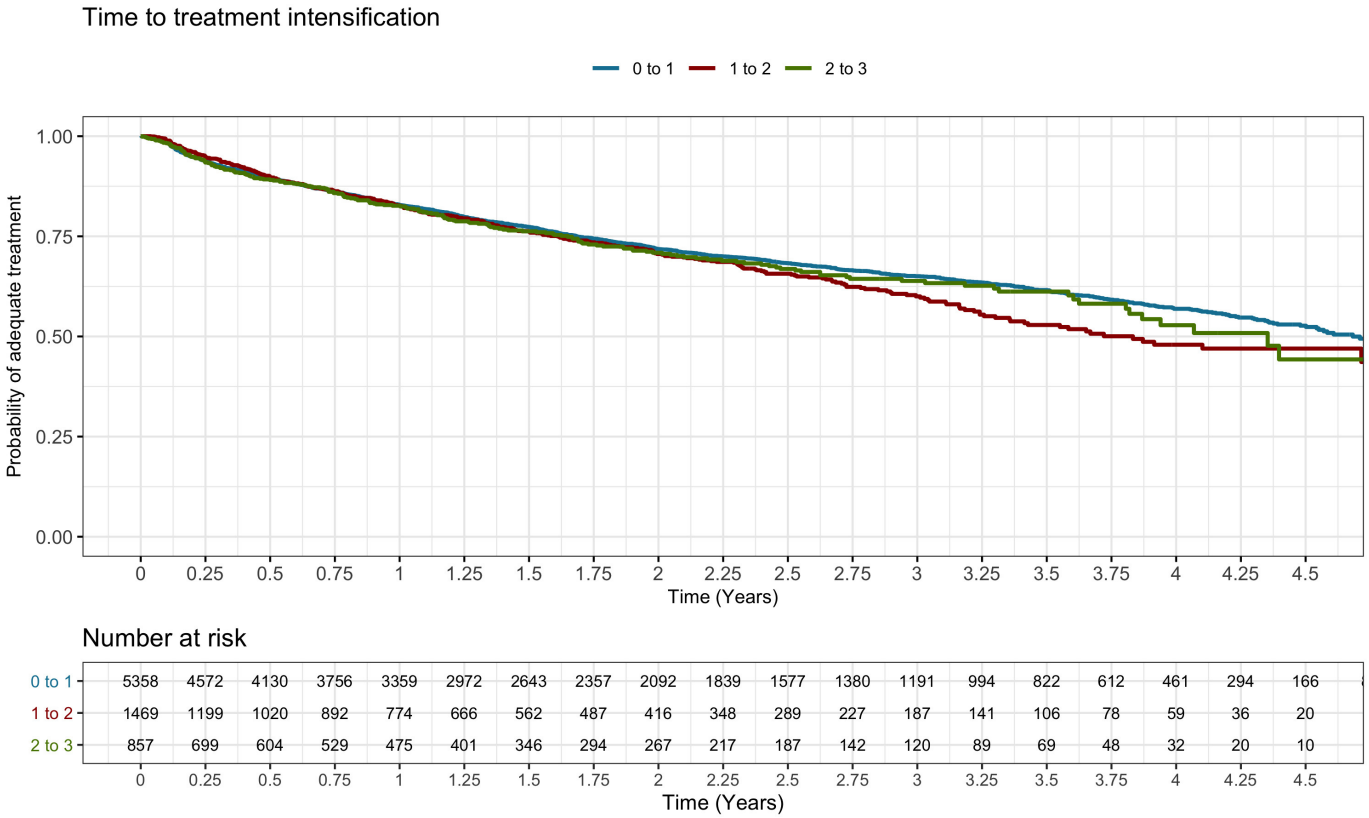

Figure 2 Kaplan-Meier curve of time from treatment initiation (escalation from 0 to 1 class of topical glaucoma medication (treatment initiation; blue)) or intensification (escalation from 1 to 2 classes of medication (red) and from 2 to 3 classes of medication (green)) to subsequent treatment intensification. Treatment intensification was defined as an increase in the number of medical glaucoma agents or intraocular pressure-lowering procedure conducted.

of treatment failure with topical glaucoma medication. The association between lower baseline IOP and treatment failure may be related to the difficulty of achieving and maintaining ≥20% IOP reduction in eyes with pre-existing low IOP. In contrast, lower baseline IOP was protective against treatment escalation. Higher IOP and worse visual field MD were identified as predictive baseline factors for disease progression (as determined by perimetric and photographic optic disc criteria) in the Early Manifest Glaucoma Trial.[18] For eyes with worse visual field damage, as well as eyes with existing POAG, the higher rate of treatment escalation may be related to the need to aggressively lower IOP, given that these eyes are at increased risk of glaucoma progression.

Data on treatment persistence and escalation rates with topical glaucoma medication are highly variable, and comparisons are complicated by differences in patient characteristics and

Table 3 Univariable associations (unadjusted) with initiation and intensification of glaucoma medication

	Cohort 1 0→1 medications (n=5358)	Cohort 2 1→2 medications (n=1469)	Cohort 3 2→3 medications (n=857)
Covariable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age at baseline (decade)	1.02 (0.98 to 1.07)	1.01 (0.92 to 1.11)	0.83 (0.74 to 0.93)**
Sex: men versus women	0.99 (0.89 to 1.10)	0.93 (0.76 to 1.14)	0.97 (0.74 to 1.27)
Ethnicity: black versus white	0.99 (0.89 to 1.10)	0.57 (0.21 to 1.52)	0.54 (0.08 to 3.85)
Ethnicity: Asian versus white	0.92 (0.55 to 1.53)	1.64 (0.68 to 3.96)	2.26 (0.72 to 7.07)
Ethnicity: other versus white	0.64 (0.32 to 1.30)	1.82 (0.62 to 4.89)	1.82 (0.68 to 4.89)
Ethnicity: unspecified versus white	1.05 (0.82 to 1.36)	0.60 (0.30 to 1.22)	1.06 (0.44 to 2.57)
Index of Multiple Deprivation (decile)	1.00 (0.98 to 1.02)	0.97 (0.94 to 1.00)	1.01 (0.96 to 1.06)
Diagnosis: OHT versus POAG	0.66 (0.59 to 0.74)***	0.60 (0.46 to 0.77)***	0.98 (0.66 to 1.46)
Baseline visual field MD of study eye, dB	0.95 (0.94 to 0.96)***	0.95 (0.94 to 0.97)***	0.98 (0.96 to 1.00)*
Baseline IOP of study eye, mm Hg	1.05 (1.04 to 1.06)***	1.03 (1.01 to 1.05)**	1.06 (1.04 to 1.08)***
Baseline eyedrop count in fellow eye	0.84 (0.75 to 0.94)**	0.77 (0.67 to 0.88)***	0.86 (0.76 to 0.97)*

*p≤0.05
**p≤0.01.
***p≤0.001.
IOP, intraocular pressure; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

follow-up durations. Retrospective chart review studies assessing time-to-change of initial topical IOP-lowering monotherapy in patients with OHT or open-angle glaucoma (OAG) point to varying rates of adjunctive treatment use and varying durations of treatment stability[8 10 19–21] which may be attributable to inter-study differences in inclusion criteria, definition of intensification, follow-up duration, medication adherence, disease severity and statistical techniques. The study closest to ours in terms of design—a retrospective US analysis of administrative claims data (2011–2017) obtained from a large cohort of OHT/OAG patients (n=48 402) who escalated to 1-, 2-, 3- or 4-drug therapy (index treatment regimen) and were followed for 2 years—reported median times to treatment intensification (defined as use of adjunctive medication or a laser/surgical procedure) of 273, 232, 219 and 227 days for the 1-, 2-, 3- and 4-drug cohorts, respectively, over the 24-month postindex period.[20] However, it is difficult to compare the glaucoma populations between the studies, and by extension the findings, as clinical severity parameters such as visual fields were not available from this analysis. By reporting these data for our cohort, we enable comparison and contextualisation with future studies.

Patients in our cohort remained on their index therapy for a median of 3.8–4.7 years, yet the median time to onset of inadequate IOP-lowering effect was 0.9–1.6 years; this lag exceeds that reported in other studies.[22] At first glance, this implies a delay between clinical indication and escalation, highlighting a window of opportunity for clinical review and intervention. However, there are considerations other than IOP—both clinical and patient-related factors—that inform the treatment escalation decision in the context of long-term disease management. For example, these analyses do not capture switches in topical medication to another within that class or another class. Treatment failure may also be due to treatment non-adherence, in which case providing support to the patient to comply with index therapy is more appropriate than escalating treatment. It is to be expected that recognition of treatment failure precedes escalation. In addition, the risks of starting additional treatment need to be balanced against the potential benefits: for some low-risk patients, <20% IOP reduction may be deemed more acceptable than the potential adverse effects of a new treatment. Supporting this is the fact that treatment escalation is more likely to occur in patients with worse visual field MD, who are considered to be at higher risk of disease progression. Further studies are required to understand at what point the lag between treatment failure and escalation becomes clinically significant.

Study strengths and limitations

Studies of topical drop efficacy mostly include carefully performed randomised controlled trials as they are well-placed for comparing treatments. However, cohort selection and ideal trial conditions can affect generalisability and thus not ideal for setting expectations for clinicians and patients in a real-world general clinic population. Analyses of real-world clinical data complement clinical trials by typically drawing on larger sample sizes and, accordingly, offering representative heterogeneity in patient profiles and healthcare delivery systems. Certain effects are also more likely to be represented in real-world studies than in clinical trials, such as regression to the mean. This is a key strength of this study: by examining the spectrum of glaucoma medical treatments and procedures provided in routine clinical care at five regional ophthalmology centres, the results can be considered generalisable to patients attending glaucoma clinics across the UK. Against this, our dataset is subject to more noise and bias as compared with a randomised controlled trial: data entry omissions and/or errors may occur, leading to avoidable cases of missing data or false group assignments (eg, a patient assigned as not using medication because none was recorded).

In this study, treatment failure was defined according to IOP criteria, without consideration of other features of glaucomatous progression such as optic disc morphology or visual field changes. We acknowledge that in clinical practice, treatment decisions consider functional and structural progression, with IOP being only one of several parameters to consider. Our data did not contain structured information on the reasons underlying treatment escalation. Moreover, cohort selection was defined to capture the natural progression of patients escalating from 0-to-1, 1-to-2 and 2-to-3 drops. Patients escalating at different intervals (eg, 0-to-2 or 1-to-3) are therefore not captured in this analysis. Future studies should also consider responsiveness to switches in treatment that are not captured by total number, including switches within a class; switches between classes; and switches from two distinct drops to combination formulations.

Conclusions

This retrospective analysis of a large real-world cohort of patients with OHT and POAG provides insight into the clinical effectiveness of topical IOP-lowering agents in clinical practice. Estimates of time to treatment failure and time to treatment escalation indicate a considerable difference between these two parameters. These data are relevant to physicians and patients who wish to understand their likely disease management course. Potential risk factors for both treatment failure and treatment intensification are identified, and these should be considered in the management of patients with OHT and POAG.

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Competing interests DJF reports consultancy fees/travel expenses from Allergan; AIM reports consultancy fees/travel expenses from Aerie, Allergan, Novartis, Pfizer, Thea and Visufarma UK; APK reports consultancy/lecture fees/travel expenses from Aerie, Allergan, Google Health, Grafton Optical, Novartis, Santen and Thea; EA is an employee of AbbVie Inc.; VS was an employee of AbbVie Inc. at the time of the study.

Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the guidelines of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (http://www.encepp.eu/index.shtml), the International Society for Pharmacoepidemiology (https://www.pharmacoepi.org/resources/guidelines_08027.cfm) and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study was exempt from the requirement for institutional review board approval and adherence to the tenets of the Declaration of Helsinki, as advised by the Moorfields Eye Hospital Research Management Committee, since it did not directly involve human subjects, identifiable human material or identifiable data.

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Data availability statement Data are available upon reasonable request. The curated anonymised dataset on deidentified participants will be available to researchers on application for data access and after sufficient regulatory approval is obtained and data transfer agreement is signed.

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Supplementary Materials

Contents

Supplementary Materials 1 - Cohort selection

One eye per patient was taken forward for analysis ("study eye") – namely, the first eye undergoing treatment initiation or intensification during the observation period. If both eyes underwent treatment changes simultaneously, the eye receiving the lower number of medications was taken forward since this eye had greater scope for subsequent treatment intensification. If the numbers of medications were identical for both eyes, the study eye was selected at random using the sample function of base R software, version 3.6.2 (R Foundation for Statistical Computing).

Supplementary Materials 2 - Study Outcomes

Cohorts were censored at subsequent treatment intensifications. Data from an individual eye could therefore be included in more than one treatment cohort in instances where multiple intensification events were noted within the observation period. For example, an eye starting treatment with 1 class of topical glaucoma medication in 2013 and progressing to 2 classes of medication in 2015 would separately contribute data for the period 2013–2015 to the 0-to-1 cohort and data for the period 2015–2017 to the 1-to-2 cohort. In these instances, the treatment periods for a given eye contributing to different cohorts are wholly distinct and therefore non-overlapping. In this way, each step in a patient's progression from zero to multiple drops contributes separately to the analyses. Progression from zero (i.e., treatment initiation falling with in the observation period) was possible for 22% (332/1469) of the 1-to-2 cohort and 5% (43/857) of the 2-to-3 cohort. Accordingly, treatment initiation dates cannot be directly reported for 78% (1137/1469) of those that increased from 1 to 2 topical agents and 95% (814/857) of those that increased from 2 to 3 agents as they fell before January 1, 2013.

Supplementary Materials 3 - eTable 1. Topical Glaucoma Medications Used for Treatment Initiation or Intensification in the Study Eye

	Cohort 1 **0 → 1 medications** (n=5358)	**Cohort 2** **1 → 2 medications** (n=1469)	**Cohort 3** **2 → 3 medications** (n=857)
Medication type, % patients			
AA	1.		
BB	6		
CAI	7.		
PGA	1		
Pilocarpine	4.1		
BB + AA	86.9	0.	
CAI + AA	0.2	8	
CAI + BB		2.	
PGA + AA		2	
PGA + BB		6.	
PGA + CAI		0	
Pilocarpine + CAI		7.1	
Pilocarpine + PGA		54.5	
CAI + BB + AA		28.9	3.9
PGA + BB + AA		0.1	7.9
PGA + CAI + AA		0.4	17.3
PGA + CAI + BB			70.4
Pilocarpine + CAI + AA			0.
Pilocarpine + CAI + BB			1
Pilocarpine + PGA + AA			0.
Pilocarpine + PGA + BB			1
			0.
			2
			0.1

AA, alpha agonist; BB, beta-blocker; CAI, carbonic anhydrase inhibitor; PGA, prostaglandin analogue.

Supplementary Materials 4 - eTable 2 Multivariable Associations (Unadjusted) of Inadequate IOP Response to Topical Glaucoma Medication

	Cohort 1 **0 → 1 medications** (n=5358)	**Cohort 2** **1 → 2 medications** (n=1469)	**Cohort 3** **2 → 3 medications** (n=857)
Covariable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age at baseline (decade)	1.00 (0.96–1.03)	0.92 (0.86–0.99)*	0.94 (0.86–1.03)
Sex: men *vs* women	0.98 (0.90–1.06)	0.86 (0.74–0.99)*	0.88 (0.73–1.06)
Ethnicity: Black *vs* White	0.61 (0.38–0.99)*	0.58 (0.27–1.24)	1.07 (0.26–4.33)
Ethnicity: Asian *vs* White	0.87 (0.61–1.25)	1.03 (0.53–2.01)	0.89 (0.28–2.81)
Ethnicity: other *vs* White	1.01 (0.62–1.66)	0.49 (0.16–1.54)	0.33 (0.10–1.03)
Ethnicity: unspecified *vs* White	0.91 (0.75–1.11)	0.56 (0.36–0.86)**	0.96 (0.45–2.02)
Index of Multiple Deprivation (decile)	1.01 (0.99–1.02)	1.00 (0.97–1.02)	1.00 (0.97–1.04)
Diagnosis: OHT *vs* POAG	0.86 (0.78–0.95)**	1.06 (0.87–1.28)	1.17 (0.88–1.55)
Baseline visual field MD of study eye, dB	0.98 (0.97–0.98)**	0.98 (0.97–0.99)***	1.00 (0.98–1.01)
Baseline IOP of study eye, mmHg	0.97 (0.97–0.98)***	0.97 (0.95–0.98)***	0.98 (0.96–1.00)*
Baseline eyedrop count in fellow eye	1.00 (0.91–1.10)	0.80 (0.72–0.88)***	0.91 (0.83–0.99)**

*P≤0.05; **P≤0.01; ***P≤0.001.

CI, confidence interval; dB, decibel; HR, hazard ratio; IOP, intraocular pressure; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

Supplementary Materials 5 - eTable 3 Multivariable Associations (Unadjusted) With Initiation and Intensification of Glaucoma Medication

	Cohort 1 **0 → 1 medications** (n=5358)	**Cohort 2** **1 → 2 medications** (n=1469)	**Cohort 3** **2 → 3 medications** (n=857)
Covariable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age at baseline (decade)	0.99 (0.94–1.04)	0.93 (0.83–1.03)	0.84 (0.83–1.03)
Sex: men *vs* women	1.04 (0.93–1.16)	0.88 (0.70–1.10)	0.84 (0.63–1.14)
Ethnicity: Black *vs* White	0.70 (0.37–1.31)	0.46 (0.11–1.87)	0.90 (0.13–6.58)
Ethnicity: Asian *vs* White	0.88 (0.51–1.52)	1.07 (0.40–2.90)	1.54 (0.37–6.36)
Ethnicity: other *vs* White	0.69 (0.33–1.45)	0.81 (0.20–3.29)	0.54 (0.20–3.29)
Ethnicity: unspecified *vs* White	1.05 (0.80–1.39)	0.67 (0.33–1.37)	0.99 (0.31–3.12)
Index of Multiple Deprivation (decile)	1.01 (0.99–1.03)	0.98 (0.94–1.02)	1.02 (0.96–1.07)
Diagnosis: OHT *vs* POAG	0.53 (0.46–0.62)***	0.62 (0.45–0.85)**	0.81 (0.51–1.29)
Baseline visual field MD of study eye, dB	0.96 (0.95–0.96)***	0.95 (0.94–0.97)***	0.96 (0.94–0.98)***
Baseline IOP of study eye, mmHg	1.07 (1.06–1.08)***	1.04 (1.02–1.06)***	1.07 (1.04–1.10)***
Baseline eyedrop count in fellow eye	1.02 (0.90–1.16)	0.81 (0.70–0.94)**	0.93 (0.81–1.06)

*P≤0.05; **P≤0.01; ***P≤0.001.

CI, confidence interval; dB, decibel; HR, hazard ratio; IOP, intraocular pressure; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma.