Preservative-free versus preserved glaucoma eye drops and occurrence of glaucoma surgery. A retrospective study based on the French national health insurance information system, 2008-2016

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ABSTRACT.

Purpose: **Preservatives contained in glaucoma eye drops have been shown to have a deleterious impact on the ocular surface. We aimed to assess the association between preservative exposure and the occurrence of further glaucoma surgery among patients with glaucoma or ocular hypertension in France.**

Methods: **The study concerned all patients who first received glaucoma eye drop treatments in a French medical-administrative database (EGB) between 2008 and 2015. Three groups were created according to the level of preservative exposure during the whole follow-up: '0% preservatives', 'mixed' and '100% preservatives'. The occurrence of glaucoma surgery was estimated according to preservative exposure indicators in Cox multivariate models adjusted on age, sex, number of glaucoma eye drops simultaneously used, systemic antihypertensive treatment and duration of treatment.**

Results: **The sample consisted of 12 454 patients. The median (interquartile range) follow-up was 4.1 (1.7–6.1) years. A total of 231 (1.9%) patients underwent glaucoma surgery during follow-up. On multivariable analysis, the risk of glaucoma surgery was increased for the 'mixed' group (hazard ratio [HR] = 3.94 [95% CI, 1.54–10.05]) and for the '100% preservative' group (HR = 7.97 [95% CI, 3.07–20.67]) when compared with the 0% preservative group.**

Conclusion: **We found an association between exposure to glaucoma eye drop preservatives and the prevalence of further glaucoma surgery. While these data might be used to support the consideration of routine use of preservative-free drops, in the absence of a randomized clinical trial, they cannot prove a direct cause-and-effect relationship between preservative-free glaucoma eye drops and further glaucoma surgery.**

Key words: glaucoma – ocular hypertension – preservatives

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Introduction

The number of people with glaucoma worldwide in 2040 is estimated to be about 111 million (Tham et al. 2014). Glaucoma is the first cause of irreversible blindness and represents about 6% of all blindness cases worldwide (Bourne et al. 2018). Long-term ocular hypertension is a significant but reversible risk factor for glaucoma (Jonas et al. 2017).

The elevation of intraocular pressure (IOP) in primary open-angle glaucoma (POAG) is attributed to an increase in trabecular meshwork (TM) outflow resistance to aqueous humour (AH), resulting from trabecular degeneration, a process still misunderstood but associated with TM cell apoptosis, changes in extracellular matrix, oxidative stress and increased cytokines in AH (Baudouin et al., 2012a,2012b).

Patients treated for primary open-angle glaucoma or ocular hypertension often present with ocular surface diseases, more often and more severely when they receive more drugs and presenting more severe glaucoma (Baudouin et al., 2012a,2012b). This may have negative consequences on adherence to treatment and quality of life (Skalicky, Goldberg & McCluskey 2012). Such adverse effects can be due to therapeutic and/or additive agents, particularly preservatives that are

added to guarantee the conservation and stabilization of the product. The contribution of preservatives to ocular adverse effects, especially benzalkonium chloride (BAK), the most widely used preservative in glaucoma eye drop formulations, remains debated. As a quaternary ammonium, BAK has been shown to cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier and damage to deeper ocular tissues (Baudouin et al. 2010; Aguayo Bonniard et al. 2016). Clinically, these effects result in various symptoms such as irritation, dry eye, allergy and subconjunctival fibrosis (Baudouin et al. 2010) leading to an increased risk of failure if surgery performed (Broadway et al. 1994).

As for other preservatives such as SofZia, Purite or Polyquad, their tolerability advantage over BAK is uncertain and several recent publications have demonstrated toxic and inflammatory effects on the ocular surface (Meloni et al. 2010; Meloni, Balzaretti & Ceriotti 2019).

The other main side-effect of preservatives applied to the ocular surface is its infiltration into the eye and its accumulation in deeper ocular structures such as the TM, especially after repeated use of several preservative-containing eye drops over years, causing harmful effects to this structure (Hamard et al. 2002; Baudouin et al., 2012a,2012b).

The benefits of PF eye drops in terms of reducing adverse effects and thus improving quality of life for patients have been widely demonstrated in experimental trials (Jaenen et al. 2007). A limited number of observational studies also support the use of preservative-free treatments (Munoz Negrete, Lemij & Erb 2017; Economou et al. 2018). Our hypothesis is that preserved glaucoma eye drop side-effects on ocular surface and trabecular meshwork induce failure in IOP control thus higher recourse to glaucoma surgery. The present study was based on a French medical-administrative database, and the objective was to assess the association of preserved glaucoma eye drops with the occurrence for further glaucoma surgery among patients with POAG or ocular hypertension in France between 2008 and 2016.

Methods

Data source

The French medico-administrative database was previously described in details (Daien et al. 2017). Data were extracted in December 2018 from the EGB (Echantillon Généraliste de Bénéficaires) database, a permanent 1/97th random sample of the national healthcare insurance database (SNIIRAM) that covers almost 99% of the French population (i.e. more than 66 million persons) and linked to the national hospital-discharge summary database (Programme de Médicalisation des Systèmes d'Information (PMSI)) and the national death registry. Available data include demographic data; presence of a long-term disease (ALD); outpatient medical expenses; medication (defined in a French system by Code Identifiant de Présentation [CIP] and Anatomique, Thérapeutique et Chimique [ATC] classification; number of packs dispensed, date of prescription and nature of prescriber, date of dispensing and dispensing pharmacy); date and nature of physician interactions, paramedical interventions, laboratory tests and medical procedures coded according to the Common Classification of Medical Procedures (CCAM); medical transports; days of paid sick leave; date and duration of hospitalizations as well as main, related and associated diagnoses coded with the International Classification of Diseases (ICD), 10th Revision and date of death.

Study population

The study concerned all patients who first received glaucoma eye drop treatments in the EGB database between 1 January 2008 and 31 December 2015, and at least 3 months of claim within the first year of follow-up. To select incident cases, patients with a history of medical or surgical glaucoma treatment within the 3 years before inclusion were excluded. Patients who underwent a surgery that could lead to glaucoma eye drop prescription within that 3-year period were also excluded on the basis of CCAM codes (cornea transplantation [BCFA007, BDFA001, BDLA002, BDLA003, BDMA002, BDMA008 and BEFA005], vitrectomy [BGFA001, BGFA005, BGFA006, BGFA009-011]). The study design is depicted Fig. 1 with various examples.

Preservative exposure estimate

Glaucoma eye drops dispensed during the follow-up (i.e. from the inclusion until surgery or end of follow-up) were extracted for each patient. According to these data, patients were divided into 3 groups according to the type of treatment: '0% preservatives' (patients who received preservative-free eye drops exclusively); 'mixed' (patients who received both preserved and preservative-free eye drops); and '100% preservatives' (patients who received preserved eye drops exclusively).

The length of exposure to preserved eye drops was also calculated for each patient by adding the duration of all the preserved treatment dispensed on different dates.

Data collected

The primary outcome was the occurrence of a surgical intervention for glaucoma, defined as any hospitalization with one of the following CCAM codes for glaucoma surgery: BEFA008 (trabeculectomy), BGFA014 (deep sclerectomy), BEPA003 (trabeculotomy performed via a sclerotomy) and BGFA900 (deep sclerectomy with viscocanaloplasty). We did not consider the code for drainage tubes (BEJB004) nor microinvasive glaucoma surgery since a specific code was not available within the study period. However, the number of these procedures was very low in France at this time (Bron et al. 2017). The following variables were also collected or calculated: age at inclusion, sex, duration of follow-up, systemic antihypertensive treatment, use of artificial tears and number of classes of glaucoma eye drops (alpha-adrenergic agonists, beta blockers, carbonic anhydrase inhibitors, cholinergic and/or prostaglandin analogs) simultaneously delivered at the end of the follow-up, that is during the last 6 months (considered as an indicator of disease severity).

Statistical analyses

We used Cox proportional hazards models to evaluate the association between preservative exposure and

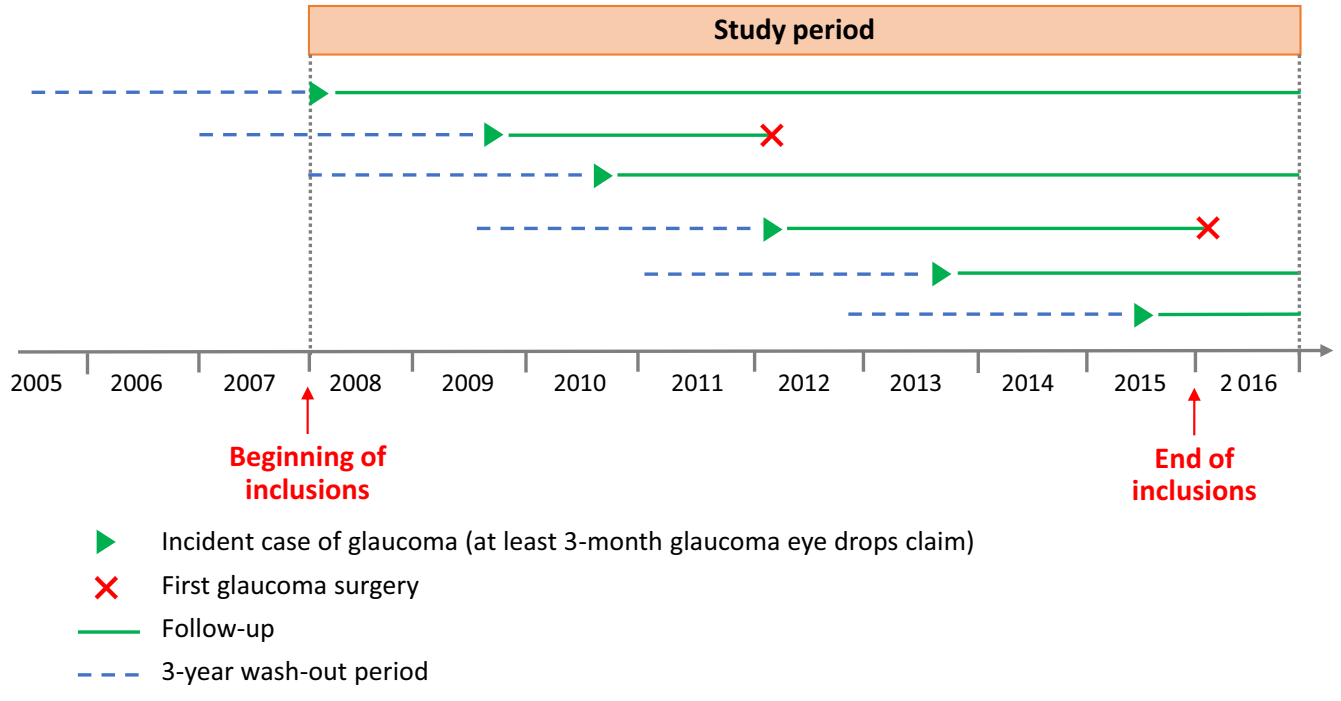

Fig. 1. Scheme of the study design.

glaucoma surgery incidence. Patients who did not undergo surgery were censored at date of death or on 31 December 2016. Adjusted Hazard Ratios (HRs) and 95% confidence intervals (CIs) of glaucoma surgery were estimated according to preservative exposure, the '0% preservative' group being the reference. Analyses were adjusted on time on study (timescale), age at diagnosis, sex, number of classes of glaucoma medication (as indicator of glaucoma severity), systemic antihypertensive treatment and preserved treatment duration (since the rate of preserved treatment did not take into account the exposure duration).

Results

Study sample

Between 1 January 2008 and 31 December 2015, a total of 33 914 individuals ≥18 years old had at least one claim for glaucoma eye drops; 21 410 received at least 3 months of treatment within the first year of follow-up and were therefore eligible for the study, and 12 570 could be considered as incident cases because they did not receive any glaucoma treatment within the 3 years before inclusion. Furthermore, 84 individuals were excluded because they had surgery within the 3 previous years that could lead to glaucoma eye drops use and 32 because they underwent surgery within 3 months after the first claim. Therefore, 12 454 individuals were considered for analysis (Figure 2).

Patient characteristics

Among the 12 454 individuals, 231 (1.9%) underwent at least one glaucoma surgery, of whom 80 (34.6%) had at least 2 surgeries (on the same eye or the fellow eye). General characteristics of individuals according to surgery and in the whole sample are displayed in Table 1.

Mean age at inclusion was 67.1 (SD = 13.7) years, and more than half of the individuals were women. Within the last 6 months of follow-up, most of patients without surgery received no treatment or only one glaucoma eye drop whereas in the surgery group, more than two-thirds (n = 162, 70.3%) received 3 or more simultaneous glaucoma eye drops. Almost half of patients exclusively received preserved eye drops (n = 6170; 49.5%), one third both preserved and PF eye drops (n = 4368; 35.1%), and the remaining patients exclusively PF eye drops (n = 1916; 15.4%). It is worth noting that PF glaucoma eye drops were not so developed during the investigated study period, that is, from 2008 to 2016.

For the 12 454 patients included, 457 396 1-month treatments were delivered during the study period. The mean number of 1-month treatments per patient was 36.7 (SD = 33.7) for the whole period of follow-up, and the median (interquartile range) follow-up was 4.1 (1.7–6.1) years. Prostaglandin analogs and beta blockers were the most prevalent IOP-lowering drugs (58.8% and 44.1%, respectively).

Association between preservative in glaucoma eye drops and risk of surgery

The number of patients who underwent surgery was 5 in the 0% preservative group (0.26%), 102 in the mixed group (2.39%) and 124 in the 100% preservative group (2.01%). The Kaplan–Meier cumulative prevalence curve for glaucoma surgery by treatment group is presented in Fig. 3.

Both 'mixed' and '100% preservative' groups had higher risk than the '0% preservative' group. The occurrence of surgery was lowest for patients who received only PF glaucoma eye drops ('0%' preservative group) and not different for the two other groups ('mixed' and '100% preservatives').

Table 2 shows the results of multivariate Cox proportional hazards regression analysis with the group of treatment as the exposure indicator. Duration of preserved eye drops use

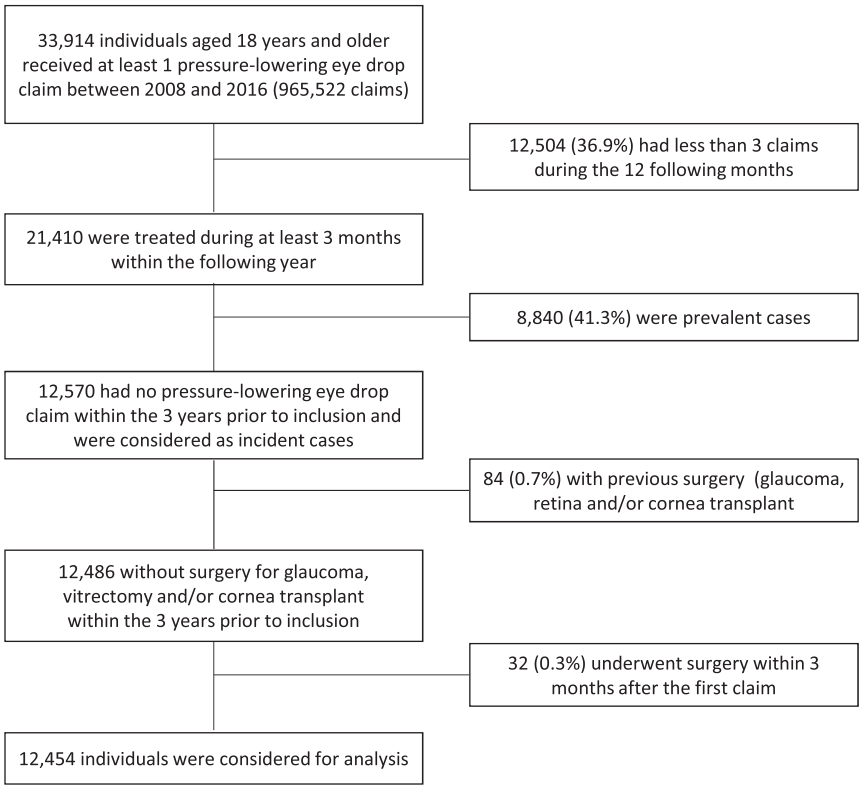

Fig. 2. Flow chart of participants in the study (n = 12 454).

Table 1. Characteristics of individuals considered for analysis (n = 12 454).

	Without surgery (n = 12 223)		With surgery (n = 231)		
	n	%	n	%	p
Age (SD)	67.2	(13.7)	66.8	(12.8)	0.36
Sex (women, %)	6716	(54.9)	103	(44.5)	<0.01
Systemic antihypertensive treatment (%)	7204	(58.9)	107	(46.5)	<0.001
N of glaucoma eye drops simultaneously used (within the last 6 months) (%)					
0	3358	(27.5)	4	(1.6)	<0.0001
1	5077	(41.5)	17	(7.4)	
2	2742	(22.4)	48	(20.7)	
≥3	1046	(8.6)	162	(70.3)	
Group of treatment (%)					
0% preservatives	1911	(15.6)	5	(2.2)	<0.0001
Mixed	4266	(34.9)	102	(44.2)	
100% preservatives	6046	(49.5)	124	(53.7)	

was integrated as a quadratic polynomial function because of an inverse U-shape relationship with surgery onset.

We observed an association between the treatment group and occurrence of glaucoma surgery after adjustment on age, sex, number of glaucoma eye drops simultaneously used and duration of preserved eye drops use. The highest relative risk of surgery was observed for patients who had received preserved glaucoma eye drops exclusively ('100%' group) (HR: 7.97; 95% CI, 3.07–20.67) as compared with patients with no preserved drugs. Patients who had received both PF and preserved treatments ('mixed') had a medium risk (HR: 3.94; 95% CI, 1.54–10.05).

Discussion

This 9-year longitudinal cohort on the French medico-administrative database allow us to find an association between exposure to preserved glaucoma eye drops and the occurrence of further glaucoma surgery. The association remained significant after adjustment on treatment duration and the number of glaucoma eye drops simultaneously used. The relative risk of surgery for patients under preserved glaucoma eye drops exclusively ('100%' group) was 7.97 (95% CI, 3.07–20.67) as compared with patients with no preserved drugs. Patients who had received both PF and preserved treatments ('mixed') had a medium risk (HR: 3.94; 95% CI, 1.54–10.05) of surgery.

Patients' characteristics and delivered treatments in the present study were consistent with existing data on POAG epidemiology (Delcourt et al. 2006). The mean delay between first prescription of glaucoma eye drop and surgery was 2.3 years. This was shorter than the 7.7 years of delay found in another French study (Hollo, Schmidl & Hommer 2018); however, this short delay could be due to the study design, an open cohort, leading to an under-representation of individuals with long follow-up and subsequent long treatment period before surgery. Our statistical analysis using Cox model and censored data take into account various delay. Results regarding exposure to preserved treatments are also consistent with those previously reported (Ramli et al. 2015) with around 81% of patients consuming preservatives.

To our knowledge, the present study is the first to show an association between type of eye drops used (preserved versus preservative-free) and occurrence of glaucoma surgery. Even though the aim of the present study was not to assess the mechanisms of the influence of preservatives on the occurrence of further glaucoma surgery, there is a body of evidence in the literature which may be used for a fair and documented hypothesis. The switch from preserved to preservative-free eye drops resulted in an improvement of the Ocular Surface Disease Index (OSDI) (Henry et al. 2008), a decrease in conjunctival hyperaemia (Januleviciene et al. 2012; Denis 2016) and subjective complaints (Hommer et al. 2018), and an increase in tear film thickness and breakup time (Dubrulle et al. 2018). Dubrulle et al. (2018) also suggested that treating ocular surface disease improved

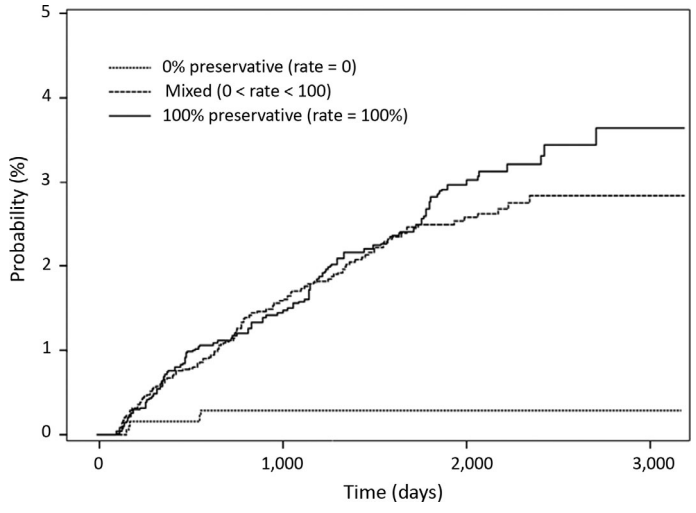

Fig. 3. Cumulative probability of undergoing glaucoma surgery stratified by type of glaucoma eye drop preservative exposure.

Table 2. Multivariate Cox regression analyses of the prevalence of glaucoma surgery according to the group of treatment (n = 12 454)

	HR	95% CI	p
Age	1.00	[0.99–1.01]	0.76
Sex (women vs men)	0.89	[0.69–1.17]	0.41
Number of drug classes	4.78	[4.28–5.33]	<0.0001
Systemic antihypertensive treatment	0.78	[0.59–1.03]	0.08
Preserved glaucoma eye drop exposure	0.95	[0.93–0.97]	<0.0001
Group of treatment			<0.0001
0% preservatives (reference)	1.00	-	-
Mixed	3.94	[1.54–10.05]	0.004
100% preservatives	7.97	[3.07–20.67]	<0.0001

95% CI, 95% confidence interval; HR, hazard ratio.

intraocular pressure (the mean IOP significantly decreased by 36.2% with a mean number of IOP-lowering medications decreasing from 3.7 at baseline to 2.8; the Oxford score also decreased significantly by 76.5%) by stopping local inflammation. Mutual relationships between ocular surface and external filtration surgery were widely proven in vitro and in vivo (Baudouin 2017). Furthermore, preservative effects might not be restricted to the ocular surface and recent studies suggested that BAK could accumulate in the anterior chamber where it may also exert toxicity by producing inflammation (Stevens et al. 2012) and decrease trabecular meshwork (TM) cell viability via induction of apoptosis (Ammar & Kahook 2011a,2011b).

More recent studies found preserved medication trigger inflammatory effects and enhanced trabecular degeneration (Baudouin et al. 1999; Baudouin et al., 2012a,2012b; Batra, Tailor & Mohamed 2014; Dubrulle et al. 2018). The use of PF eye drops could therefore lead to a decreased risk of surgery by preserving the ocular surface and the trabecular meshwork, but also by improving compliance.

On the other hand, it is to be noted that preservatives, and notably, BAK, have been shown to have a promoting effect on corneal drug penetration for some authors (Kaur & Smitha 2002). Indeed, cornea is an effective barrier to drug penetration thanks to tight junctions which effectively seal the superficial epithelial cells layers. On a theoretical basis, BAK would act by breaking down this physiological and anatomical diffusion barrier (Green & Tonjum 1975). However, this potential positive interest of BAK has to be balanced. Its efficacy was proved for the enhancement of intraocular penetration of bimatoprost, a hydrophilic molecule, but this observation must not be generalized to the whole anti-glaucoma drugs (Katz et al. 2010). Indeed, Rouland et al. showed that the IOP-lowering effect of preservative-free latanoprost and BAK-preserved latanoprost was similar for this hydrophobic molecule, for which corneal penetration is naturally good and does not need potentiation (Rouland et al. 2013).

Medical-administrative data used for the present study were not initially collected for epidemiological purposes, which implies limitations that must be considered. Claims data give information on treatment deliveries but do not allow to check whether the patient is compliant or not. Only the dispensing of reimbursed drugs is recorded in the databases, and self-medication with over-the-counter drugs, such as artificial tears that are mostly preserved, cannot be measured. However, glaucoma eye drops cannot be delivered without a medical prescription, and all the deliveries performed at the national level should be contained in this database. Even though patients who underwent glaucoma surgery within the 3 years before the entry were excluded, we could have included patients whose former surgery became ineffective and thus who re started eye drops during the period of the study. This represents a selection bias but there is no reason why it is more represented in a group than in other. Preserved-free glaucoma eye drops were not available for all molecules at the time of the study. More severe glaucoma requiring more glaucoma eye drops were thus more at risk of preservative exposure. This confusion bias was considered in the statistical analysis by adjustment of preservative exposure on the number of glaucoma eye drops simultaneously used as an indicator of disease severity. We observed a significant proportion of patients without treatment before the time point of analysis. We can hypothesize it is related to a lower compliance at early stage of glaucoma or to a misclassification of glaucoma subjects, due to limits of medico-administrative data that are not recorded for epidemiological purpose. These data represent real-life exposure and adherence to glaucoma treatment.

Lastly, since the French population is mainly Caucasian, our results are not transferable to other parts of the world.

The strength of our study was the very large number of patients and the duration of the observed period. Furthermore, our data were based on daily clinical practices and are representative of the medico-administrative database,

which includes almost 99% of the French population; therefore, our results can be extrapolated nationwide. Finally, detailed information regarding the dose of pharmaceutical forms and the number of dispensed units and the packaging size was available and allowed us to sharpen our indicators.

In conclusion, we found an association between exposure to glaucoma eye drop preservatives and the prevalence of further glaucoma surgery. While these data might be used to support the consideration of routine use of preservative-free drops, in the absence of a randomized clinical trial, they cannot prove a direct cause-and-effect relationship between preservative-free glaucoma eye drops and further glaucoma surgery. This finding deserves further investigations.

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