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Statin use and the reoperation rates in glaucoma filtration surgery – population-based cohort study

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ABSTRACT.

Purpose: **To examine the association of systemic statin therapy and reoperation rate after glaucoma filtration surgery (GFS).**

Methods: **This is a population-based, historic cohort study of 2705 eyes undergoing GFS in Finland between July 2009 and December 2016. GFSs were identified from national administrative healthcare registers. Baseline sociodemographic and health characteristics were documented. Reoperation rates of GFS subgroups were analysed, with statin users compared to non-users. The outcomes were modelled using a Poisson regression model adjusted for age, sex, education, statin use, chronic comorbidities, and cataract surgery with incident rate ratios (IRR) as the main outcome measure.**

Results: **The cohort contained 2263 subjects with open-angle glaucoma (OAG), 823 men and 1440 women. Surgery was performed on 2705 eyes. First documented procedures: deep sclerectomy (DS) (n = 1601), trabeculectomy (TRE) (799) and glaucoma drainage device (GDD) implantation (305) respectively. In total, 438 secondary operations were performed during the 7.5-year (median 2.25 years) follow-up period. The reoperation rates were 19% after DS, 12% after TRE, and 13% after GDD. Of the surgical procedures, 32% were performed on eyes of patients receiving statin therapy. Statin users showed no difference in reoperation rates (IRR 1.06, CI 0.82–1.37). In subgroups, no difference was observed in the reoperation rates adjusted with statin use after filtration surgery (DS, TRE) (IRR 1.06, CI 0.8–1.40) or GDD implantation (0.57, CI 0.20–1.63).**

Conclusion: **Systemic statin therapy among surgically treated OAG patients had no impact on secondary surgery rates following DS, TRE or GDD implantation.**

Key words: clinical epidemiology – cohort study – glaucoma filtration surgery – medication – statin

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Introduction

Glaucoma is a neurodegenerative disease affecting primarily the nerve fibres that form the optic nerve, causing progressive visual field loss and listed as one of the leading causes of irreversible blindness (Flaxman et al. 2017). An estimated 76 million people globally are afflicted by glaucoma (Quigley & Broman 2006; Tham et al. 2014). Today, the only confirmed modifiable risk factor for development and progression of glaucoma is elevated intraocular pressure (IOP) (Heijl et al. 2002; Anderson & Normal Tension Glaucoma Study 2003). IOP-lowering treatments are the mainstay of glaucoma therapy including medication, laser, and surgery. Surgical treatments are employed when other treatment modalities are not tolerated by the patient or are insufficient to reach a required target pressure to prevent visual loss ('European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition – Chapter 3' 2017). Trabeculectomy and deep sclerectomy represent current practice in filtration surgery (Rodriguez-Una, Azuara-Blanco & King 2017; Vinod et al. 2017; Harju et al. 2018). The longstanding success of these procedures is highly dependent on the control of scarring after surgery, allowing a sustained outflow of aqueous humour under the conjunctiva (Seibold, Sherwood & Kahook 2012). At present, the antimetabolites 5-fluorouracil or

mitomycin-C are routinely applied to the surgical site during operation to reduce post-operative scarring (De Fendi et al. 2013). However, these agents carry a risk of local side effects and complications such as bleb leak, chronic hypotony and hypotony-related maculopathy, corneal epithelial toxicity, and bleb-related endophthalmitis (Lama & Fechtner 2003). Glaucoma surgeries face many challenges; results and durability vary, with repeat procedures common.

Statins are cholesterol lowering drugs broadly used in primary and secondary prevention of cardiovascular diseases, harbouring beneficial properties beyond those regarding cholesterol (Davies et al. 2016; Mohammad et al. 2019). Statins may play a beneficial role in mitigating many ocular conditions (Ooi et al. 2019). Statins have also shown pressure-independent neuroprotective qualities in reducing glaucoma progression (Leung et al. 2010; Marcus et al. 2012; Stein et al. 2012; Talwar, Musch & Stein 2017). Their regulatory impact on key signalling pathways relevant to scarring hold promise for novel therapies (Watts et al. 2005; Kuo et al. 2019). Of particular interest among statins' pleiotropic effects in terms of glaucoma surgery is the ability to modulate inflammation and fibrosis, notably by inhibiting cytokine TGF-β induced connective tissue growth factor expression and tissue contractility in human on human Tenon fibroblasts (Meyer-Ter-Vehn et al. 2008). One prospective animal study suggested that lovastatin might offer alternative antifibrotic treatment applied locally in GFS (Park, Yoo & Kim 2016). Statins inhibited pro-inflammatory cytokines in a cell model for proliferative vitreoretinopathy (Mysore et al. 2021). Clinically, statin users have been reported to undergo fewer reoperations for rhegmatogenous retinal detachment and overall fewer operations for thyroid related orbitopathy (Loukovaara et al. 2018; Reynolds, Del Monte & Archer 2018). However, the impact of systemic statin intake on limiting undesirable post-operative scarring after glaucoma surgery is unknown.

To date, no study has explicitly investigated the association between statins and long-term success of GFS. However, statins might present a novel therapeutic avenue given their anti-inflammatory and antifibrotic properties as well as a low rate of drug related adverse effects. Based on published literature, we hypothesized that statin-treated patients might have more favourable long-term GFS outcomes compared to controls.

Materials and Methods

Objectives

The primary objective of this study was to determine whether systemic statin therapy impacts the long-term outcome after glaucoma filtration surgery (GFS) i.e., trabeculectomy (TRE), deep sclerectomy (DS) and glaucoma drainage device (GDD) by comparing reoperation rates after first registered procedure among statin users and non-users. The secondary objective was to address whether background variables, such as comorbidities, medications and demographics of the study population, affect outcomes of GFS, potentially mapping out risk factors for reoperation.

Study design and ethical considerations

This was a population-based, historic cohort study based on national health care register data. Data were retrieved from three registers: The Social Insurance Institution (SII/93/522/2017), the Finnish Institute for Health and Welfare (THL/2038/5.05.00/2017) and Statistics Finland (TK/SF-52-1785-18). Ethical approval was obtained from the Ethical Committee of the Faculty of Medicine, University of Helsinki (11/2017). All data were de-identified and handled under confidentiality agreements. The study design and execution adhered to the tenets of the Declaration of Helsinki.

Statistics Finland and THL hold institutional registers containing records of all medical centres performing glaucoma filtration surgery in Finland. The cost of GFS in Finland is covered by the public healthcare system amounting to reliable national statistics of all procedures charged by the performing medical units. Surgical procedures were classified by the following Nordic Medico-Statistical Committee (NOMESCO) codes ('NOMESCO Classification of Surgical Procedures (NCSP), version 1.16' 2011): DS (CHD60), DS with collagen implant (CHD65), TRE (CHD10), TRE with iridectomy (CHD15), GDD implantation (CHD50), trans-scleral cyclophotocoagulation (CPC; CHF05) and needling (CFW99) with or without antimetabolite application. Combined cataract and glaucoma surgeries were included whereas minimally invasive glaucoma surgeries (MIGS) were not. The validity of data was high due to systematic us of same NOMESCO codes throughout Finland.

Information about dispensed medication was collected through SII that monitors the medication reimbursement policies and prescriptions at a national level.

Cohort

The GFS cohort comprised of adult subjects undergoing incisional glaucoma surgery during the observation period from beginning of July 2009 to end of December 2016, covering 7.5 years. Glaucoma was classified using diagnostic International Classification of Diseases ICD-10 code H40.1 for open-angle glaucoma (OAG), consisting of five subtypes: H40.13 chronic primary open-angle glaucoma, H40.10 pseudoexfoliation glaucoma, H40.11 normal tension glaucoma, H40.12 pigmentary glaucoma, and H40.19 unspecified open-angle glaucoma. Glaucoma ICD-10 codes were linked to the surgical NOMESCO records obtained from hospital payment information. From the originally acquired surgical procedure data 68% were excluded due to missing laterality of the eye operated. Exclusion was handled at operation level, not patient level. Assuming that data of the laterality was missing completely at random and independent of patient characteristics or surgical outcome, we excluded only such surgeries that lacked information of the operated side. A minimum 6-month wash-in period from any previous glaucoma surgery with conjunctival incision was defined to lapse prior to inclusion.

Demographic factors including sex, age and educational status were recorded. Education was classified into three subgroups: (a) mandatory with no further education reported after compulsory education, (b) middle with up to 12 years and (c) higher education with additional years of education. Data on medication reimbursements and dispensed medications classified according to the Anatomical Therapeutic Chemical Classification system

(ATCC) were collected through SII. Individuals receiving reimbursement and being prescribed a drug were classified as users for any given medication category provided the drug was in use at least 6 months prior to the first documented surgery. Systemic medication classes were as follows: statins, anticoagulants/antithrombotic medication for coronary artery disease excluding acetylsalicylic acid, hypertensive medication, rheumatoid arthritis and connective tissue disease medication, antidepressants, diabetes medication, and insulin (Table 1).

Statistical analysis

The outcomes were modelled using the Poisson regression model, a standard method for time-to-event analyses. Two operated eyes from the same individuals were taken into account using General Estimation Equations (GEE) (Prentice & Zhao 1991; Halekoh, Højsgaard & Yan 2006). Two models were fitted, one with age and sex, and another with a large number of background variables (sex, age, any statin, education, chronic diseases, and cataract operation before start of follow-up). Results were presented as incidence rate ratios (IRR) indicating the number of incident cases divided by the person-time at risk. The reoperations used as endpoints in the model were: (1) needling of fibrotic bleb, (2) renewed GFS, (3) cyclophotocoagulation (CPC), and (4) implantation of glaucoma drainage device. In this study reoperations signify operations on the same eye after the first documented operation denoting start of follow-up. First documented surgery may be primary or renewed surgery as the coding system does not differentiate between these two. The analysis comparing the association of statin use was conducted using subgroups of different surgical procedures such that filtration surgeries without indwelling devices and shunt procedures were analysed both separately and together. Reoperation rates were analysed both with and without needling procedures as events. When analysed without needling, other glaucoma procedures were set as events. Subgroup analyses were incorporated as part of the sensitivity analysis and can be found in the online supplement. Calculations were carried out with R language (R Core Team 2019).

Table 1. Basic characteristics of study population at baseline

	Male	Female	Overall
Eyes operated (%)	964 (35.6)	1741 (64.4)	2705
Age			
Median (IQR)	71.26 (64.54, 78.12)	74.10 (66.95, 79.77)	73.15 (66.08, 79.20)
≤50 (%)	52 (5.4)	36 (2.1)	88 (3.3)
51–60 (%)	98 (10.2)	120 (6.9)	218 (8.1)
61–70 (%)	286 (29.7)	432 (24.8)	718 (26.5)
71–80 (%)	353 (36.6)	732 (42.0)	1085 (40.1)
>80 (%)	175 (18.2)	421 (24.2)	596 (22.0)
Surgical approach (%)			
TRE	12 (1.2)	36 (2.1)	48 (1.8)
TRE & Iridectomy	288 (29.9)	463 (26.6)	751 (27.8)
GDD	113 (11.7)	192 (11.0)	305 (11.3)
DS	4 (0.4)	10 (0.6)	14 (0.5)
DS & Collagen Implant	547 (56.7)	1040 (59.7)	1587 (58.7)
Diagnosis of glaucoma (%)			
PXG	369 (38.3)	695 (39.9)	1064 (39.3)
NTG	82 (8.5)	313 (18.0)	395 (14.6)
PG	32 (3.3)	35 (2.0)	67 (2.5)
POAG	479 (49.7)	694 (39.9)	1173 (43.4)
Unspecified	2 (0.2)	4 (0.2)	6 (0.2)
Education (%)			
Mandatory	393 (40.8)	755 (43.4)	1148 (42.4)
Middle	219 (22.7)	484 (27.8)	703 (26.0)
Higher	352 (36.5)	502 (28.8)	854 (31.6)
Cataract surgery			
Last 6 months (%)	26 (2.7)	44 (2.5)	70 (2.6)
Medication (%)			
OAD	133 (13.8)	142 (8.2)	275 (10.2)
Insulin	53 (5.5)	43 (2.5)	96 (3.5)
Statin	326 (33.8)	534 (30.7)	860 (31.8)
Simvastatin	185 (19.2)	302 (17.3)	487 (18.0)
Atorvastatin	90 (9.3)	159 (9.1)	249 (9.2)
Rosuvastatin	33 (3.4)	48 (2.8)	81 (3.0)
Other statin	20 (2.1)	30 (1.7)	50 (1.8)
Comorbidities (%)			
Diabetes	167 (17.3)	160 (9.2)	327 (12.1)
Thyroid insufficiency	15 (1.6)	108 (6.2)	123 (4.5)
Breast cancer	0 (0.0)	47 (2.7)	47 (1.7)
ACTD	26 (2.7)	85 (4.9)	111 (4.1)
Hypertension	247 (25.6)	401 (23.0)	648 (24.0)
CHD	108 (11.2)	157 (9.0)	265 (9.8)
Chronic arrhythmias	30 (3.1)	33 (1.9)	63 (2.3)

Number of different glaucoma surgeries set as start of follow-up. TRE = trabeculectomy; GDD = glaucoma drainage device implantation; DS = deep sclerectomy; PXG = exfoliation glaucoma; NTG = normal tension glaucoma; PG = pigmentary glaucoma; POAG = primary open-angle glaucoma; OAD = oral antidiabetic drug, ACTD = autoimmune connective tissue disorders, CHD = coronary heart disease.

Results

Basic characteristics

The cohort consisted of 2263 subjects, 823 men and 1440 women. GFS was performed on 2705 eyes, of which 1741 (64%) were eyes of female and 964 of male subjects. The median age (IQR) at start of follow-up was 73 (66–79) years (Table 1).

The most commonly performed glaucoma operation in our cohort was DS (n = 1601) followed by TRE (n = 799) and GDD (n = 305). The total number of subsequent secondary operations was 438 (Table S1) over the observation period of 7.5 years with the median follow-up time being 2.25 years. The proportions of secondary operations after DS, TRE, and GDD were 19%, 12%, and 13%, respectively.

One third of the surgical procedures were performed on eyes of statin users (n = 860, 32 %) at the time of inclusion. The most commonly used statin was simvastatin with 487 (18%) subjects on that medication. Chronic hypertension was the most common

Table 2. Secondary Glaucoma Surgery Rates for Open-Angle Glaucoma

Variable	Person years (1/1000)	Events	Rate (1/1000)	IRR (univariate)	IRR (adjusted)
Sex					
Male	6.73	164	24.39 (20.80–28.42)	reference	reference
Female	13.56	274	20.20 (17.88–22.74)	0.83 (0.68–1.01)	0.87 (0.68–1.11)
Age					
≤50	0.78	16	20.64 (11.79–33.51)	reference	reference
51–60	1.62	45	27.79 (20.27–37.19)	1.35 (0.76–2.38)	1.56 (0.78–3.14)
61–70	5.38	125	23.25 (19.35–27.70)	1.13 (0.67–1.90)	1.27 (0.66–2.47)
71–80	8.25	166	20.12 (17.17–23.42)	0.97 (0.58–1.63)	1.06 (0.55–2.05)
>80	4.27	86	20.16 (16.13–24.90)	0.98 (0.57–1.67)	1.09 (0.55–2.19)
Education					
Mandatory	8.98	169	18.83 (16.10–21.89)	reference	reference
Middle	5.2	107	20.56 (16.85–24.84)	1.09 (0.86–1.39)	0.91 (0.66–1.24)
Higher	6.11	162	26.53 (22.60–30.94)	1.41 (1.14–1.75)	1.27 (0.97–1.65)
Statin					
No	14.18	296	20.87 (18.56–23.39)	reference	reference
Yes	6.1	142	23.26 (19.59–27.42)	1.11 (0.91–1.36)	1.06 (0.82–1.37)
Comorbidities					
ACTD					
No	19.48	429	22.02 (19.98–24.21)	reference	reference
Yes	0.81	9	11.18 (5.11–21.21)	0.51 (0.26–0.98)	0.63 (0.32–1.25)
Hypertension					
No	15.61	333	21.34 (19.11–23.76)	reference	reference
Yes	4.68	105	22.43 (18.35–27.16)	1.05 (0.84–1.31)	1.05 (0.80–1.38)
CHD					
No	18.27	400	21.89 (19.80–24.15)	reference	reference
Yes	2.02	38	18.84 (13.33–25.86)	0.86 (0.62–1.20)	0.75 (0.48–1.16)
Diabetes					
No	18.1	377	20.83 (18.78–23.05)	reference	reference
Yes	2.19	61	27.83 (21.29–35.75)	1.34 (1.02–1.75)	1.24 (0.86–1.77)
Cataract surgery					
Last 6 months (%)					
No	19.83	427	21.53 (19.54–23.68)	reference	reference
Yes	0.46	11	23.96 (11.96–42.86)	1.11 (0.61–2.02)	1.45 (0.79–2.66)

Number of secondary surgeries after surgical treatment for open-angle glaucoma presented with person years cumulated (1/1000), incidence rates (95% confidence interval), and incidence rate ratios (IRR) (95% CI) adjusted with age, sex, education, statin usage, comorbidities at baseline, and cataract surgery in preceding 6 months. ACTD = autoimmune connective tissue disorders, CHD = coronary heart disease.

comorbidity with 24% of the study population receiving medication for high blood pressure. Seventy (3%) eyes underwent cataract surgery less than 6 months prior to the first documented glaucoma surgery (Table 1).

Secondary operations following filtration surgery

DS and TRE procedures were analysed as one subgroup to assess the outcomes of filtration surgery adjusted with statin use. DS and TRE were set as the starting point for follow-up and subsequent procedures including renewed GFS, needling of fibrotic bleb, and CPC were documented as events.

Following the first registered glaucoma surgeries (DS or TRE $n = 2400$), altogether 400 secondary procedures were documented. After DS ($n = 1601$), further 307 (19%) procedures ensued with needling ($n = 252$) as the most common secondary procedure, followed by renewed DS ($n = 30$), CPC ($n = 19$), and TRE ($n = 4$). After first registered TRE ($n = 799$), there were 93 (12%) secondary procedures: 70 needling procedures, 14 renewed TREs, 4 GDD implantations, 4 CPCs, and one DS (Table S1).

Secondary operations following glaucoma drainage device

Implantation of a GDD was performed on 305 (13%) eyes as the first registered glaucoma surgery. In this subgroup, secondary operations were performed in 38 eyes (12%), including 23 renewed GDD implantations, 11 needling procedures, 1 CPC and 3 DS.

Role of statins in glaucoma surgery

We detected no difference in rates of secondary glaucoma surgeries related to statin use (IRR 1.06, 95 % confidence interval 0.82–1.37; Table 2). This observation holds for the GFS subgroup (IRR 1.06, CI 0.80–1.40) regardless of omitting needling as event (IRR 1.24, CI 0.73–2.11; Table S2 & S3). Similarly, statin use did not affect secondary operation rates after GDD implantation (IRR 0.57, CI 0.20–1.63).

Sensitivity analysis

In secondary analyses, there was no difference in secondary operation rates between genders when adjusted for comorbidities, medication and sociodemographic variables in the cohort (IRR 0.87, CI 0.68–1.11) or the GFS (IRR 0.84, CI 0.65–1.08) and GDD (IRR 2.22, CI 0.38−13.17) subgroups. Higher education was not linked to increased number of secondary surgeries when adjusted for other background variables (1.27, CI 0.97–1.65). When examined in the GFS (IRR 1.26, CI 0.95–1.67) and GDD (IRR 0.62, CI 0.06–6.03) subgroups, education status did not correlate with reoperation rates. However, secondary surgeries other than needling were less frequent among subjects with higher education in the GFS subgroup (IRR 0.44, CI 0.23–0.84; Table S3).

Systemic medication for diabetes, severe psychiatric disorders, rheumatoid arthritis and related connective tissue diseases, coronary artery disease and hypertension were not associated with the longevity of filtration surgery in the cohort or its subgroups. Nor did previous cataract surgery, performed less than 6 months prior to the first documented glaucoma surgery, influence the reoperation rate (IRR 1.45, CI 0.79–2.66) in a small subset.

Discussion

In our national population-based register study, systemic statin use was not associated with secondary operation rates after GFS, counter to our study hypothesis. Although there is ample research covering the interactions of statins with incident glaucoma (McGwin et al. 2004; Marcus et al. 2012; Stein et al. 2012; Talwar, Musch & Stein 2017), IOP (Khawaja et al.

2014; Ho et al. 2017), and glaucoma progression (De Castro et al. 2007; Leung et al. 2010; Stein et al. 2012; Pappelis et al. 2019), little research has focused on the association between glaucoma filtration surgery and systemic medications to date, let alone statins specifically.

In a rabbit model investigating the antifibrotic properties of subconjunctival lovastatin injection in conjunction with filtration surgery Park et al. reported promising short-term results for bleb morphology (Park, Yoo & Kim 2016). Although the antifibrotic and IOP-lowering effects of lovastatin were not superior to MMC, histologic analysis demonstrated fewer avascular blebs along with lower inflammation and myofibroblast transdifferentiation. Thus, the authors suggested that lovastatin might serve as a local adjuvant for MMC to control inflammation and subsequent fibrosis while lowering the risk of avascular blebs.

While there is some evidence of morphological benefits of locally administered lovastatin for GFS, no benefit has been reported with systemic statin use. One cohort study by Stein et al. on statin use among open-angle glaucoma patients showed no association with the number of glaucoma surgeries needed (Stein et al. 2012). However, statin appeared protective against both incident glaucoma and need for glaucoma medication, suggesting that the benefit of statin use might play out early in the course of glaucoma. Another case-control study on the association of commonly used systemic medications in OAG requiring laser therapy or surgery showed no relationship between systemic statin use and incident glaucoma (Zheng et al. 2018). The ideal administration route, dosage and timing for harnessing the optimal anti-inflammatory and antifibrotic effect of statins in GFS remains a topic for further research.

Three main phases define the cellular process of wound healing in the anterior segment of the eye: inflammatory, proliferative and remodelling. During haemostasis a fibrin clot and platelet plaque form to restore the integrity of vasculature at the site of tissue injury. Activated platelets release cytokines and growth factors initiating the inflammatory response (Knorr et al. 1997). The inflammatory phase is characterized by infiltration of neutrophils and monocytes guided to the site of injury by cytokines. Monocytes differentiate into macrophages that modulate the repair process through release of cytokines and growth factors, phagocytosis and multiple cellular interactions including fibroblast activation. T-lymphocytes have a stimulatory function in the early phase and a regulatory function in the later phase of wound healing (Chang et al. 2000). In the proliferative phase epithelial cells seal the tissue surface whereas beneath it a granulation tissue forms exhibiting angiogenesis and fibroplasia. This immature fibrovascular tissue matures into a scar through the remodelling phase displaying extra-cellular matrix degradation and collagen deposition and cross-linking. Aberrant fibrosis of the anterior segment, especially in the regions of aqueous outflow, is postulated as a major driver in the pathophysiology of glaucoma (Ferrer 2006).

Our earlier population-based study demonstrated that statin use was associated with 28 % lower vitreoretinal surgery reoperation rates after rhegmatogenous retinal detachment (RRD) (Loukovaara et al. 2018). We postulate that the difference in reoperation rates among statin users after RRD surgery, as opposed to glaucoma filtration surgery, may be related to the dissimilar response to injury in the anterior and posterior segments of the eye. While wound healing of the anterior segment is characterized by cellular reactions and stages defined as fibrosis analogous to the scarring of the skin, the posterior segment has a unique response to wounds corresponding to the tissue repair process in central nervous system described as gliosis (Friedlander 2007; Zada, Pattamatta & White 2018). Furthermore, the overpowering effect of adjunct MCC at the surgical site may mask presumably more subdued modulating effects of systemic statin use. The dissimilar responses to systemic statin therapy after vitreoretinal and glaucoma surgery may lie in the patient characteristics and pathophysiology. Compared to RRD patients, glaucoma patients are generally older, have a long history of varying topical anti-glaucoma medications often exposing the eye to preservatives, with prolonged chronic local side effects, and are generally operated only after other treatment modalities have shown unsuccessful.

Study strengths and limitations

Our study represented real-world scenarios in a large cohort with strict inclusion criteria. The cohort captured all GFSs performed during the follow-up period in Finland. Such representative nationwide data on GFS in the Nordics has not been published before. We used comprehensive administrative registers held by the Finnish Social Insurance Institute to identify OAG subjects and systemic medication use based on long-term medication reimbursements. For the NOMESCO coded surgical glaucoma procedures we employed Statistics Finland registers gathered from hospital billing records of performing medical centres. The selected surgeries represent the armamentarium of glaucoma surgeries in Finland during study period.

We used Poisson regression because it requires less assumptions on the proportionality of hazards as opposed to Cox's proportional hazards regression. We modelled separately different types of initial surgeries, instead of adding them as covariates into one model, in order to check if risk factors vary between initial type of surgery. This approach allowed a more detailed analysis of outcomes for each surgical technique due to their unique character. Separate modelling requires less assumptions on the effects of covariates on the outcome variables.

However, our study setting carries certain limitations. Since the national registries use the same billing code for primary and secondary surgeries, it was not possible to capture only primary surgeries as the start of follow-up. Hence, the study focused on the total number of surgeries performed on any study eye during the observation period. Statin use was documented at the time of inclusion and continuous use could not be monitored at other points of the follow-up period. Alteration of statin therapy or dose dependent effects could not be taken into account.

Severity of glaucoma is difficult to control for. Clinical decision of reoperation may depend on systemic comorbidities and fitness for surgery, glaucoma severity, target pressure, and progression of unstable disease despite functioning filtration. Since the patients receive the decision of a lifelong reimbursement for glaucoma medication upon diagnosis, medically

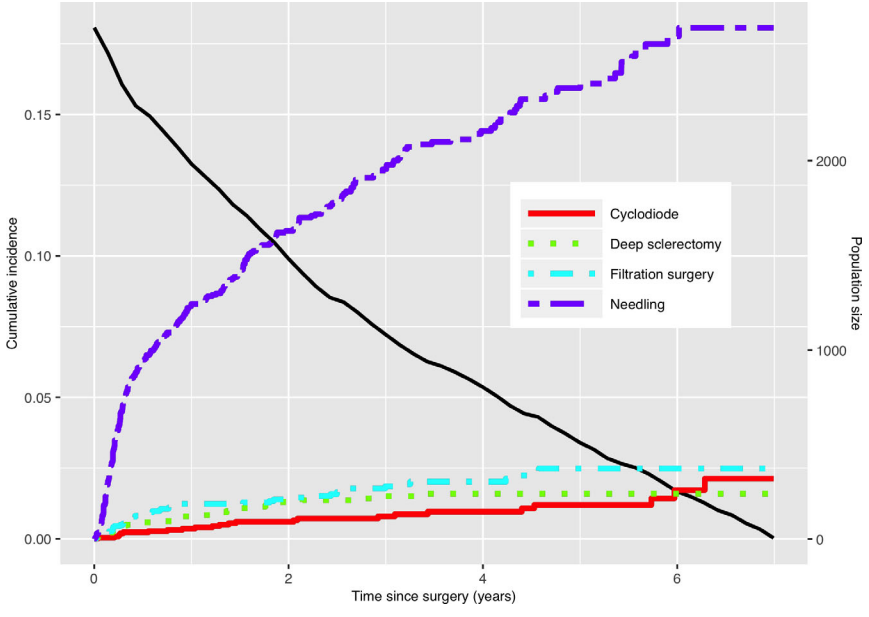

Figure 1. Cumulative incidences for various reoperations after surgical treatment of open-angle glaucoma are illustrated in coloured lines. The population size in follow-up is shown as the decreasing curve (black line)

treated surgical failures that did not lead to reoperation remained undetected. Careful patient selection for glaucoma surgery may explain why background variables showed no association with the likelihood of reoperation.

A small number of the documented surgeries deviated from the standard procedures. The filtration surgery subgroup covered 1587 deep sclerectomies with collagen implant and 14 without implant, as well as 751 trabeculectomies and additionally 48 procedures registered as trabeculectomies without iridectomy. As collagen implant is considered a standard step in deep sclerectomy as well as iridectomy is ubiquitous in trabeculectomy the latter numbers may represent erroneous classification. Antimetabolites are assumed customary to GFS in Finnish glaucoma surgery and data on their use were deemed unreliable. Therefore, we did not seek to analyse this individually. Revisions other than needle revision i.e., needling, are infrequent in Finnish clinical practice and could not be accounted for due to inconsistent coding. Our data do not include information on whether needling was performed in operation theatre or outpatient clinic. All CPCs were trans-scleral.

Real-world register studies cannot take into account the tissue level preoperative ocular characteristics of conjunctival inflammation, hyperaemia, and pre-existing fibrosis that could affect the surgical success after GFS. Nor could the rate of intraoperative complications associated with surgical procedures be analysed due to the register nature of the study. Varying operation criteria across different hospitals and possible advances in surgical techniques over the course of the 7.5-year follow-up period could not be accounted for. Limitations of the cohort may mask more subtle effects potentially detectable in a more rigorously selected subset of glaucoma patients or a controlled trial.

In conclusion, this study was conducted to explore the general reoperation rate after glaucoma surgery in Finland, aiming to clarify the potential therapeutic value of statins in GFS. Using Poisson regression model, in this population-based historic cohort of 2705 operated eyes no difference in reoperation rates between statin users and non-users was detected following DS, TRE or GDD implantation. There were most probably some uncontrolled confounders and modifiers that could play a role in the final outcome. This study could not replicate, in a real-world setting, the antifibrotic pleiotropic effect of statins previously reported in cellular and animal models. The optimal dosage and administration route as well as the stage of glaucoma ideal for adjuvant use of statins in GFS remains to be explored in further studies and in other settings.

Authors' Contributions

Concept and design: Virtanen, Haukka, Loukovaara, Harju. Acquisition, analysis, or interpretation of data: Virtanen, Haukka, Loukovaara. Drafting of the manuscript: Virtanen. Critical revision of the manuscript for important intellectual content: Loukovaara, Harju. Statistical analysis: Haukka. Supervision: Haukka, Loukovaara, Harju.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Number of combinations of first operation and next event.
Table S2. Incidence rate ratios (IRR) with 95% confidence intervals comparing statin users to non-users in filtration surgery subgroup (1) including deep sclerectomies and trabeculectomies and glaucoma drainage device subgroup (4). Different endpoints are presented in the key table.
Table S3. Incidence rate ratios (IRR) with 95% confidence intervals comparing statin users to non-users in filtration surgery subgroup (1) including deep sclerectomies and trabeculectomies and glaucoma drainage device subgroup (4).