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Statin use and vitreoretinal surgery: Findings from a Finnish population-based cohort study

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ABSTRACT.

Purpose: **Vitreoretinal (VR) surgery is the third most common intraocular surgery after refractive and cataract surgery. The impact of statin therapy on VR surgery outcomes remains unclear, despite a potentially beneficial effect. We explored the association of preoperative statin therapy and the need for revitrectomy after primary vitrectomy.**

Methods: **Our historical, population-based, register-based, VR surgery cohort consisted of 5709 patients operated in a tertiary, academic referral hospital in Finland, during 2008–2014, covering 6.5 years.Subgroup analysis was performed as follows: eyes operated due to (i) rhegmatogenous retinal detachment (RRD), (ii) VR interface diseases (macular pucker/hole), (iii) diabetic maculopathy or proliferative retinopathy, (iv) vitreous haemorrhage, (v) lens subluxation, (vi) vitreous opacities or (vii) other VR indication.The primary end-point event was revitrectomy during a postoperative follow-up period of 1 year due to retinal redetachment, vitreous rehaemorrhage, postoperative endophthalmitis, recurrent pucker or unclosed macular hole.**

Results: **Rhegmatogenous retinal detachment (RRD) was the second most frequent indication of VR surgery, including 1916 patients, with 305 re-operations with rate 0.20 (95% CI 0.18–0.23) per person-year. Statin treatment in time of operation was associated with lower risk of re-operation according to relative scale (incidence rate ratio 0.72, 95% CI 0.53–0.97), but not in absolute scale (incidence rate difference −0.58, 95% CI −4.30 to 3.15 for 100 person-years). No association with statin therapy and vitrectomy outcome was observed in the other VR subgroups.**

Conclusion: **Use of statin treatment was associated with a 28% lower risk of revitrectomy in patients operated due to RRD. Further randomized clinical trials are highly warranted.**

Key words: cohort study – epidemiology – proliferative vitreoretinopathy – rhegmatogenous retinal detachment – statin therapy – vitreoretinal surgery

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Introduction

Many sight-threatening, posterior segment, eye diseases can only be treated with vitreoretinal (VR) surgery. It is the third most common intraocular surgery performed after refractive and cataract surgery in the United States and is required in 30 per 100 000 population in UK (El-Amir et al. 2009). Vitreoretinal (VR) surgery has a steeper learning curve and relatively high complication rate compared to cataract surgery (Wong et al. 2013). During the past two decades, great technological advances in pars plana vitrectomy (PPV) have been achieved, including the availability of new microincisional vitrectomy technology, wide-angle microscope viewing systems, perioperative optical coherence tomography imaging, pharmacologic chromovitrectomy and therapeutic agents (Gonzalez et al. 2015; Khan et al. 2016; Sharma et al. 2016). Novel 23, 25 and 27 small-gauge instrumentation with valved microcannulas, high-speed cutting rates (from 7500 up to 10 000 cuts per minute), use of preoperative applications of anti-angiogenic therapy and intraoperative chromo-assisted vitrectomy have (i) reduced surgical time, (ii) decreased surgical vitrectomy complications and (iii) increased surgical outcomes. Despite these advances, some VR patients nevertheless need to be re-operated, sometimes with poor functional and anatomical outcome. Of note, re-operation rates vary between different VR surgical indications.

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are one of the most commonly used drugs worldwide, with a generally favourable safety profile, representing evidence-based medication in primary and secondary prevention of coronary artery disease (Leung et al. 2012; Taylor et al.2013). Statins have well-known anti-inflammatory,

anti-oxidative, antifibroproliferative, microvasculo-protective and neuroprotective pleiotropic properties, rendering them as potential therapeutic adjuvants in controlling photoreceptor survival, the retinal wound-healing process and inflammation-related proliferative vitreoretinopathy (PVR) formation in eyes after VR surgery (Koh 2000; Takemoto & Liao 2001; Kawahara et al. 2008; Kita et al. 2008; Marcus et al. 2012).

Intraocular fibrosis formation, that is PVR, first reported in 1934 by Gonin, is a condition considered to be the worst-case scenario after VR surgery leading to need of re-operation (Sun et al. 2012; Soni et al. 2013; Claes & Lafetá 2014). Proliferative vitreoretinopathy (PVR) progression involves inflammatory and ischaemic processes, for which there is no known preventative pharmacotherapy (Chaudhary et al. 2016). Historically, many pharmacologic agents have been studied, including steroids, daunorubicin, anti-inflammatory, anti-VEGF agents and 5-fluorouracil (Pastor 1998; Moysidis et al. 2012; Pennock et al. 2013; Gagliano et al. 2015; Khan et al. 2015). Nonetheless, all of these compounds have failed to demonstrate a significant benefit in clinical VR trials. The use of statin in ophthalmic surgery has been shown to be beneficial, particularly after glaucoma filtration surgery in a rabbit model. Histologic analyses have revealed decreased inflammatory response and reduced fibrosis in the statin-treated group when compared with control group (Park et al. 2016). More recently, statin therapy was found to be beneficial also in VR surgery (Tuuminen et al. 2014, 2015, 2016).

Our aim was to examine whether systemic use of statin medication could prevent postoperative complications in a diverse range of vision-threatening posterior segment eye diseases and reduce the need for revitrectomies. Statins are currently widely used in many VR patients, but no population-based large-scale systematic studies of statin use and outcome of VR surgery have yet been published. Our main hypothesis was that use of statin medication might reduce the risk of re-operations based on the findings of our previous studies involving different VR pathologies (Tuuminen et al. 2014, 2015, 2016).

Patients and Methods

Study design and cohort

This study was based on a nationally representative sample of 5796 VR patients aged 18 years or over, operated in a tertiary academic referral VR surgical unit, Helsinki University Hospital in Finland, covering 1.6 million of the total Finnish population of approximately 5.5 million inhabitants. The clinical and surgical data were collected from all vitrectomized VR-study patients between 12 May 2008 and 31 December 2014, covering altogether 6.5 years. After exclusions (Fig. 1), the final study population comprised 5707 patients. The exclusion criteria are given in Fig. 1.

Data sources and collection

Patient documentation was selected anonymously and included register data from three different registers including treating institution Helsinki University Hospital, Social Insurance Institution and Statistics Finland (SF), linked by means of the unique personal identification number assigned to all people living in Finland.

The baseline data collected from the hospital operating room management system (OPERA®; GE Healthcare, Helsinki, Finland) database consisted of the VR surgical procedure or patient-related variables, the mode of admission (day surgery/inpatient stay/emergency) and the main indications for VR surgery (International Classification of Diseases (ICD10) code [(http://urn.fi/URN:NBN:fi-fe201205085423), as follows: (i) eyes operated due to rhegmatogenous retinal detachment (RRD), H33.0, n = 1916)]; (ii) VR interface diseases (macular pucker or macular hole, H35.38/H35.37/H35.39, n = 2207; (iii) diabetic retinopathy (DR) (diabetic maculopathy and proliferative DR H36.01, H36.03, E10.3, E10.7, E10.9, E11.3; n = 184); (iv) vitreous haemorrhage (H43.1, n = 400); (v) lens subluxation (H27.1, n = 120); (vi) vitreous opacities (H43.2, H43.3, H43.9, H43.8; n = 52); and (vii) individuals who were operated due to other VR reasons such as retinal vein occlusion (H34.8 and H34.9), central serous retinopathy, exudative maculopathy (H35.31) or various unspecified reasons were included into the category 'other' (n = 830) in the final analysis.

The primary VR surgical procedure was recorded as follows http://urn.fi/URN:ISBN:978-952-245-858-2 (in Finnish and Swedish): vitrectomy through pars plana (CKD91; VIT); combined vitrectomy and retinal procedure (CKD92; VITRET); combined

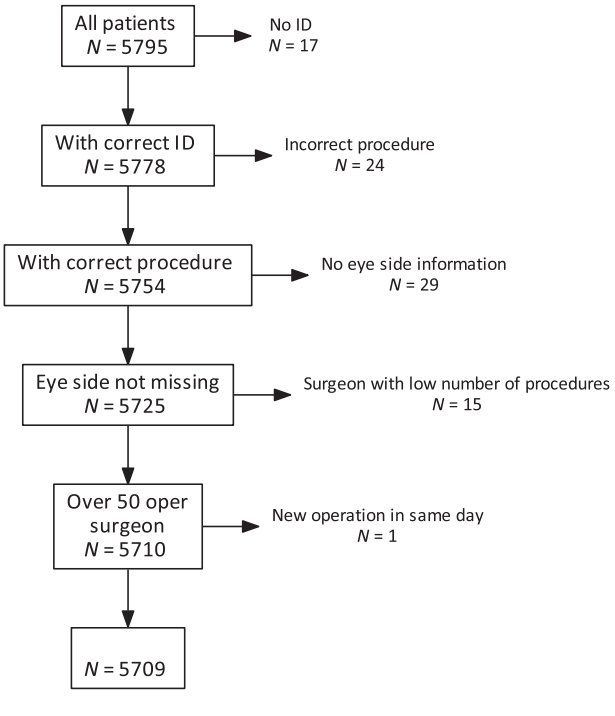

Fig. 1. Flow chart of the study population.

procedure on vitreous body and retina including encircling scleral buckle (SB) or band (CKD93; SBVIT); and combined phacoemulsification and intraocular lens (IOL) implantation together with PPV (CKD94; PHACOVIT). Accordingly, operation day and month, duration of anaesthesia and surgical procedure, as well as patient characteristics (age, gender, height, weight and body mass index [BMI], and the American Society of Anesthesiologists [ASA] Physical Status classification) were recorded.

Systemic diseases and concomitant medication were obtained from the Social Insurance Institution database. Information of the following systemic and ocular diseases was collected: diabetes (code 103), kidney disease with dialysis (137), hypothyreosis (104), transplantation (127), psychiatric and other mental illnesses (112), chronic heart disease (201), connective tissue disease, rheumatic diseases and other related conditions (202), chronic hypertension (205), coronary heart disease and hypercholesterolaemia (206), chronic arrhythmia (207), colitis ulcerosa and Crohn's disease (208), and Glaucoma (114).

Regarding concomitant medication, all purchased and reimbursed medications are recorded nationwide in the Finnish Prescription Register (FPR) and Finnish Registry for Reimbursed Medication (FRM), with generic name and World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) code (http://www.whocc.no/atc_ddd_index/). For each drug, reimbursement-related factors, including the dispensing date (date of purchase), the WHO ATC code and the quantity dispensed (amount in defined daily doses), were recorded as classified by WHO (WHOCC 2012) (WHOCC- ATC/DDD Index).

Details were obtained regarding the drugs prescribed in the year before and following the first operation, including statins (ATC code C10AA), insulins (A10A), other diabetes drugs (A10B), beta-blocking agents (C07) and antithrombotic drugs (B01A). Aspirin use could not be analysed, as this medication is not reimbursed in Finland. We assumed that the drug was used at time of the first surgery if the purchase before surgery would cover the operation date based on the information of the DDD purchased. We used only baseline usage of drugs as covariates.

Mortality data were retrieved from SF, where the vital status is collected for all Finnish citizens into the Finnish Causes of Death Register (Gissler & Haukka 2004).

Vitreoretinal surgery

The surgical technique was the standard three-port 20-, 23- or 25-gauge transconjunctival PPV (Constellation Vision System, Alcon Laboratories, Inc., Fort Worth, TX, USA), using a valved microcannula (trocar) system and a noncontact EIBOS viewing system, with or without additional chandelier illumination. Our study population included VR patients with first-performed operations coded with frank vitrectomy (CKD91), vitrectomy with retinal procedure [including removal of membranes, use of perfluorocarbon if needed, endolaser, fluid-air exchange, with air, gas (SF6, C2F6, C3F8) or silicone oil tamponade] (CKD92), vitrectomy with encircling SB or band (CKD93) and phacovitrectomy (CKD94).

Follow-up time and end-points

The follow-up period commenced after the first operation. The primary end-point event was the revitrectomy during the postoperative follow-up period due to redetachment (H33.0), vitreous rehaemorrhage (H43.1), endophthalmitis (H44.0), secondary/recurrent pucker or unclosed macular hole (H35.38).

Revitrectomy was defined to be an operation with codes CKD91, CKD92, CKD93 or CKD94 of the same eye, and the follow-up time for revitrectomy was 1 year. Only the first revitrectomy was taken into account. If there was no revitrectomy in 1 year after start of follow-up, censoring took place. Death before 1 year after start of follow-up was accounted as a censoring event.

Ethical considerations

This is a register-based study without patient contact. The study protocol was approved by the Ethics Committees of the Hjelt Institute, University of Helsinki, and the Hospital District of Helsinki and Uusimaa, Helsinki, Finland.

Statistical analysis

We modelled incidence of resurgery using Poisson regression models. Incidence rate ratio (IRR) was calculated using log link function and incidence rate differences (IRD) with identity link function (Boshuizen & Feskens 2010). In both models, cumulated follow-up time was taken into account. All analyses were carried out separately for the seven above-mentioned diagnostic subgroups. Hazard of re-operation was modelled using Poisson regression with splines.

We controlled for confounding using background variables as model covariates and also applied inverse probability of treatment weighting (IPTW) method (Hernan et al. 2000). In IPTW, the propensity score (predicted probability of statin treatment given baseline characteristics) was used to generate patient-specific stabilized weights that control for covariate imbalances. The following variables were used in construction of weights: age, sex, BMI, year of surgery, type of surgery, baseline usage of insulin, other diabetes drug, antithrombotic drugs and beta-blocker. All data analyses were carried out using R language (R Core Team 2016. Available at https://www.R-project.org/).

Results

Baseline characteristics of our study cohort (n = 5709) are summarized in Table 1. Patients were operated as inpatient hospitalization (42%), day surgery (37.6%) and emergency cases (20.1%). The gender distribution was equal in our cohort. The mean duration of operation was 1.1 hr (SD 0.6 hr) in the whole cohort.

Systemic diseases in our study cohort

The most common systemic comorbidities of all VR patients (n = 5709) were hypertension (n = 1278, 22.4%), diabetes mellitus (n = 1014, 17.8%), coronary artery disease (n = 518, 9.1%), connective tissue disease such as rheumatoid arthritis (n = 203, 3.6%) and psychiatric disease (n = 91, 1.6%). Of the study patients, 8.1% (n = 465) had glaucoma.

Of the whole patient cohort, 8.8% (n = 504) received insulin therapy and 11.7% (n = 666) used oral antidiabetics ± insulin. Altogether 21% (n = 1198)

Table 1. Baseline characteristics of study population.

	All *n* = 5709			No statin *n* = 4266			Statin *n* = 1443		
Number	Mean	SD	NA	Mean	SD	NA	Mean	SD	NA
Age (y)	65.4	13.7	0	63.9	14.4	0	69.9	9.8	0
Height (cm)	170.1	10.5	199	170.3	10.7	144	169.5	9.7	55
Weight (kg)	77.2	16.6	216	76.3	16.6	154	79.8	16.5	62
BMI (kg/m2)	26.6	4.8	223	26.2	4.7	160	27.7	4.9	63
Duration of anaesthesia (h)	1.9	0.7	0	1.9	0.7	0	1.8	0.6	0
Duration of operation (h)	1.1	0.6	0	1.1	0.6	0	1.0	0.5	0
Gender									
Male	2915	51%		2151	50%		764	53%	
Female	2794	49%		2115	50%		679	47%	
Systemic diseases									
Diabetes mellitus									
No	4695	82%		3705	87%		990	69%	
Yes	1014	18%		561	13%		453	31%	
Severe psychotic and other severe mental disorders									
No	5618	98%		4194	98%		1424	99%	
Yes	91	2%		72	2%		19	1%	
Connective tissue diseases, rheumatoid arthritis and comparable diseases									
No	5506	96%		4112	96%		1394	97%	
Yes	203	4%		154	4%		49	3%	
Chronic hypertension									
No	4431	78%		3534	83%		897	62%	
Yes	1278	22%		732	17%		546	38%	
Chronic coronary heart disease									
No	5191	91%		4083	96%		1108	77%	
Yes	518	9%		183	4%		335	23%	
Ocular comorbidity									
Glaucoma									
No	5244	92%		3929	92%		1315	91%	
Yes	465	8%		337	8%		128	9%	
Systemic medication at baseline									
Insulin									
No	5205	91%		3999	94%		1206	84%	
Yes	504	9%		267	6%		237	16%	
Oral antidiabetics									
No	5043	88%		3957	93%		1086	75%	
Yes	666	12%		309	7%		357	25%	
Any beta-blocker									
No	4511	79%		3620	85%		891	62%	
Yes	1198	21%		646	15%		552	38%	
Metoprolol									
No	5477	96%		4149	97%		1328	92%	
Yes	232	4%		117	3%		115	8%	
Bisoprolol									
No	4988	87%		3883	91%		1105	77%	
Yes	721	13%		383	9%		338	23%	
Any antithrombotic									
No	5195	91%		4031	94%		1164	81%	
Yes	514	9%		235	6%		279	19%	
Warfarin									
No	5400	95%		4103	96%		1297	90%	
Yes	309	5%		163	4%		146	10%	
Clopidogrel									
No	5550	97%		4221	99%		1329	92%	
Yes	159	3%		45	1%		114	8%	
ASA Classification									
1	737	13%		723	17%		14	1%	
2	1732	30%		1480	35%		252	17%	
3	2401	42%		1443	34%		958	66%	
4	159	3%		88	2%		71	5%	
NA	680	12%		532	12%		148	10%	
Diagnosis group									
Retinal Detachment	1916	34%		1554	36%		362	25%	
Pucker/MH	2207	39%		1569	37%		638	44%	

Table 1. (Continued)

	All $n = 5709$			No statin $n = 4266$			Statin $n = 1443$		
Number	Mean	SD	NA	Mean	SD	NA	Mean	SD	NA
Vitreous haemorrhage	400	7%		263	6%		137	9%	
Lens subluxation	120	2%		91	2%		29	2%	
DR(PDR/DME)	184	3%		119	3%		65	5%	
Vitreous opacities	52	1%		39	1%		13	1%	
Other	830	15%		631	15%		199	14%	
Operation type									
CKD91	2255	39%		1625	38%		630	44%	
CKD92	2017	35%		1591	37%		426	30%	
CKD93	211	4%		172	4%		39	3%	
CKD94	1226	21%		878	21%		348	24%	
Operation mode									
1. Inpatient	2399	42%		1794	42%		605	42%	
2. Day surgery	2146	38%		1544	36%		602	42%	
3. Emergency	1147	20%		912	21%		235	16%	
5. Day surgery/Inpatient	14	0%		13	0%		1	0%	
6. Policlinic	3	0%		3	0%		0	0%	

BMI = body mass index, DME = diabetic macular oedema, DR = diabetic retinopathy, MH = macular hole, NA = not available, PDR = proliferative DR.
Extended vitrectomy through pars plana (CKD91), combined vitrectomy and retinal procedure (CKD92), extended combined procedure on vitreous body and retina including encircling scleral band (CKD93) and combined phacoemulsification and intraocular lens implantation together with pars plana vitrectomy (CKD94).

used beta-blockers (bisoprolol 12.6% ($n = 721$) and metoprolol 4.1% ($n = 232$)), and 9.1% ($n = 514$) had antithrombotics (warfarin 5.4% ($n = 309$) and clopidogrel 2.8% ($n = 159$)).

Statin medication in our study cohort

Among the whole cohort, the most common medication used was statin therapy ($n = 1443$, 25.3%), simvastatin being the most commonly used statin (n = 904, 15.8%), following atorvastatin ($n = 313$, 5.5%) and rosuvastatin ($n = 130$, 2.3%). The majority of statin users ($n = 1257$, 87.1%) had been using statin therapy longer than 6 months before VR operation.

Statin was used in 362 of 1916 RRD patients (18.9%), in 638 of 2207 macular hole or pucker patients (29%), in 137 of 400 vitreous haemorrhage patients (34%) and in 29 of 120 lens subluxation patients (24.2%).

Type of primary VR surgical procedure

Interestingly, frank vitrectomy was the most common type of VR surgery performed in our cohort ($n = 2255$; 39.4%). The vitrectomy with retinal procedure comprised the second largest group with 2017 cases (35.5%). Phacovitrectomy was performed in 1226 operations (21.5%). Only a minority of patients underwent vitrectomy with an encircling element (SB or encircling band) ($n = 211$, 3.7%).

Of the vitrectomized (CKD91 operated) patients, 630 (27.9%) used statin compared with 426 (20.1%) of patients that underwent vitrectomy with retinal procedure (CKD92 operation), 39 (18.5%) of patients with vitrectomy and encircling SB or band (CKD93 operated) and 348 (28.4%) of patients with phacovitrectomy (CKD94 operated).

Re-operation rate in the whole cohort

Altogether, re-operation was performed in 10% of our cohort study eyes ($n = 5709$). We observed 569 re-operations in 4556 person-years of follow-up with 0.80 years mean follow-up time. Females had lower re-operation rate (10.6 per 100 person-years; 95% CI 9.3–12.1) than males (14.3; 12.8–16.0), with IRR 0.74 (0.63–0.88).

Of the 569 re-operated patients, 453 had no statin therapy as compared with 116 cases with statin therapy (70 patients with simvastatin, 22 atorvastatin, 14 rosuvastatin and 10 other statin). Median age at re-operation was 67 years (IQR 59–74). Simvastatin and atorvastatin were evidently more beneficial than rosuvastatin regarding the re-operation rate in our cohort (Fig. 2).

Incidence of revitrectomy was 5% in eyes originally operated with frank vitrectomy ($n = 119$), 13% in eyes operated with vitrectomy and retinal procedure ($n = 262$), 40.3% in eyes with vitrectomy and encircling SB or band ($n = 85$) and 8.4% in eyes with phacovitrectomy ($n = 103$), respectively.

Hazard of re-operation modelled with Poisson regression in the whole cohort ($n = 5709$) was highest approximately 1 month postoperatively (Fig. 3).

Re-operation rate differs between types of surgical procedure performed and according to main VR surgical indication

The rate of re-operations varied among the main VR surgical study groups, which displayed various incidence for eyes re-operated: 15.9% in the RRD group, 3.5% in the macular pucker/hole group, 9.75% in the VH group, 8.3% in the lens subluxation group and 13% in the diabetic group. Generally, survival from re-operation was best in frank vitrectomy-operated eyes, followed by phacovitrectomized eyes, eyes operated with vitrectomy and retinal procedure, and it was worst in eyes with vitrectomy and encircling SB or band (Fig. 4).

RRD subgroup

Overall, RRD was the second most frequent indication of VR surgery,

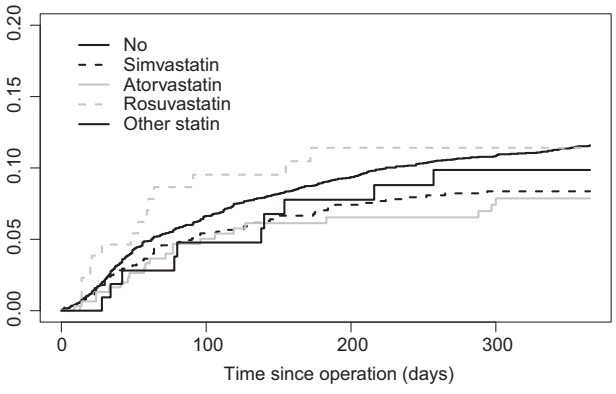

Fig. 2. Incidence of re-operation modelled with Poisson regression in the whole cohort (n = 5709) differed according to statin compound.

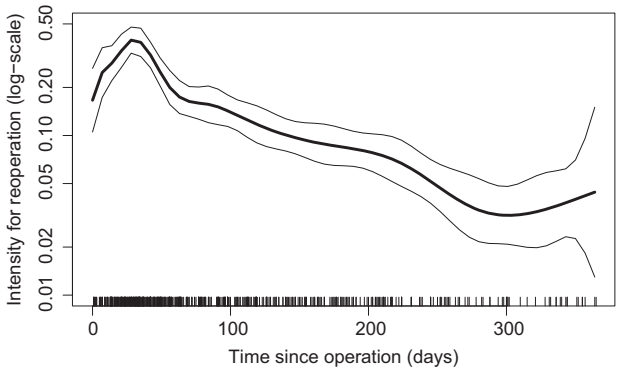

Fig. 3. Hazard of re-operation in retinal detachment and pucker/MH subgroups (N = 569) (95% CI). Rug plot indicates timing of re-operations. Hazard curve and confidence interval estimated using Poisson regression model with splines.

performed in 1916 (34%) patients, with 305 re-operations with a rate of 0.20 (95% CI 0.18–0.23) per person-year. Almost half of our RRD patients were operated as emergency patients (48.7%) and 81.6% of all RRD patients underwent vitrectomy and retinal procedure surgery, with vitrectomy and encircling SB or band performed in 8.8%, phacovitrectomy in 6.6% and frank vitrectomy in 3%.

The majority of patients operated due to RRD were male (n = 1242, 64.8%), 17.3% had hypertension, 9.0% diabetes, 6.7% coronary artery disease, 2.9% connective tissue disease (rheumatoid arthritis) and 1.6% psychiatric disease. The most common concomitant ocular disease of RRD patients was glaucoma (5.7%).

In the RRD group, 18.9% (n = 362) used statin therapy (11.1% simvastatin, 4.3% atorvastatin, 2.1% rosuvastatin). In general, RRD was the second most common diagnosis (25%) among all statin-treated patients (n = 1443). Noteworthy, only 3.1% of RRD patients were on insulin therapy, while 15.6% used beta-blocker and 6.2% antithrombotic (3.4% warfarin, 2.1% clopidogrel).

Re-operation rate was lower in statin-treated RRD eyes (n = 49) compared with nonstatin-treated RRD eyes (n = 256; Table 2) during our 6.5-year study, with a rate of 16.8 per 100 person-years (95% CI 12.4–22.2).

After adjustment for baseline characteristics, patients with RRD experience a greater benefit from statin therapy compared with RRD patients without statin therapy (Table 3). Statin treatment at the time of operation was associated with lower risk of re-operation in patients with RRD according to relative scale (IRR 0.72, 95% CI 0.53–0.97), but not in absolute scale (IRD −0.01, −0.04 to 0.03). Furthermore, according to cumulative incidence of re-operation (Fig. 5), statin treatment at the time of operation was associated with lower risk of re-operation in patients with RRD.

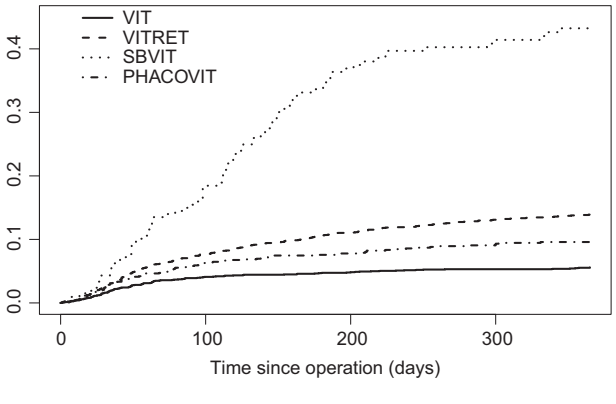

Fig. 4. Survival from re-operation according to vitreoretinal surgery procedure. Vitrectomy through pars plana (CKD91, VIT), combined vitrectomy and retinal procedure (CKD92, VITRET), combined procedure on vitreous body and retina including encircling scleral band (CKD93; SBVIT) and combined phacoemulsification and intraocular lens implantation together with pars plana vitrectomy (CKD94; PhacoVIT).

Main reasons for re-operation in the RRD group

Of 305 re-operated RRD eyes, 236 were operated due to redetachment and 34 due to secondary epiretinal membrane, that is macular pucker or macular hole. Five RRD-operated patients developed postoperative endophthalmitis and were re-operated. The other 30 eyes with RRD were re-operated due to removal of silicon oil that was not counted as a re-operation. None of the patients who developed endophthalmitis were diabetic or had preoperative antiplatelet therapy. Interestingly, three of them had glaucoma with topical therapy and two used simvastatin therapy.

Other subgroups in our cohort

In our cohort, the largest VR group (31%) consisted of eyes operated due to

Table 2. Number and rate of (per 100 person-years) re-operation for each vitreoretinal surgical diagnosis subgroup. 95% confidence interval (CI) based on Poisson distribution.

Vitreoretinal surgery indication	No statin					Statin				
	p-years (1/100)	Events	Rate	95% CI		p-years (1/100)	Events	Rate	95% CI	
Retinal Detachment	12.18	256	21.0	18.5	23.8	2.92	49	16.8	12.4	22.2
Pucker/MH	12.83	61	4.8	3.6	6.1	5.28	17	3.2	1.9	5.2
Vitreous haemorrhage	2.13	24	11.3	7.2	16.8	1.09	15	13.8	7.7	22.8
Lens subluxation	0.69	7	10.1	4.1	20.9	0.25	3	12.2	2.5	35.6
DR (PDR/DME)	0.86	18	21.0	12.4	33.1	0.50	6	12.0	4.4	26.2
Vitreous opacities	0.33	3	9.0	1.9	26.3	0.10	0	0.0	0.0	35.4
Other	4.91	84	17.1	13.6	21.2	1.48	26	17.6	11.5	25.7

DME = diabetic macular oedema, DR = diabetic retinopathy, MH = macular hole, PDR = proliferative DR.

Table 3. Comparing statin to no statin group. Multivariate models adjusted with sex, age, duration of operation, type of procedure, insulin usage, oral antidiabetic drug usage, antihrombotic drug usage and beta-blocker usage, and diagnosis subgroup as covariates, and IPWT weighted.

Vitreoretinal surgery indication	No statin						Statin					
	IRR, univariate			IRD, univariate			IRR, IPWT model			IRD, IPWT model		
	IRR	95% CI		IRD	95% CI		IRR	95% CI		IRD	95% CI	
Retinal Detachment	0.80	0.59	1.08	−4.25	−9.60	1.11	0.72	0.53	0.97	−0.58	−4.30	3.15
Pucker/MH	0.68	0.34	1.16	−1.54	−3.48	0.40	0.86	0.52	1.44	−0.05	−2.04	2.14
Vitreous haemorrhage	1.23	0.64	2.34	2.54	−5.78	10.86	1.84	0.99	3.42	7.54	−2.11	17.19
Lens subluxation	1.20	0.31	4.64	2.04	−13.67	17.75	0.15	0.02	1.47	0.16	−3.89	4.21
DR (PDR/DME)	0.57	0.23	1.45	−8.92	−22.57	4.72	0.33	0.08	1.28	−6.52	−19.41	6.37
Vitreous opacities	NA	NA	NA	−8.99	−19.16	1.18	NA	NA	NA	0.71	−12.50	13.92
Other	1.03	0.66	1.59	0.44	−7.24	8.11	1.38	0.88	2.15	6.72	−1.15	14.58
All combined	0.75	0.61	0.92	−3.37	−5.56	−1.18	0.94	0.76	1.15	−0.22	−1.81	1.36

DME = diabetic macular oedema, DR = diabetic retinopathy, IRD = Incidence rate difference for 100 person-years, IRR = incidence rate ratio, MH = macular hole, NA = not available, PDR = proliferative DR.

age-related VR eye diseases, macular hole or pucker (n = 2207). Of those eyes, 81.4% (n = 1796) were operated as day surgery cases (elective surgery). Of these cases, 67.4% (n = 1487) underwent frank vitrectomy surgery and 28.5% (n = 629) combined phacovitrectomy.

Based on our analysis, the overall re-operation rate was lowest in this group (3.5%). Operation duration was also shortest in this group, being comparable with cases operated due to vitreous opacities.

Altogether 638 patients (28.9%) with macular hole or pucker were on statin therapy. However, in this subgroup, no beneficial effect of statin use was observed regarding re-operation rate (Table 2, Fig. 5).

Patients operated due to DR (n = 184), vitreous haemorrhage (n = 400), lens subluxation (n = 120), vitreous opacities (n = 52) or other VR reasons (n = 830) were analysed accordingly, but in these subgroups, no beneficial effect of statin use was found in regard to re-operation rate (Table 2).

Discussion

Our cohort study demonstrated that statin treatment was associated with a relatively lower incidence of revitrectomy by 28% in the group of patients operated due to retinal detachment. Currently, there is no evidence-based data supporting our findings for statin use in RRD surgery, with no randomized controlled study, systematic reviews, or Cochrane database data related to this clinically important topic (PubMed search). Interestingly, no association between statin therapy and lower re-operation rate was found in other studied VR indication groups in our epidemiologic study.

Previously, statin therapy has been shown to reduce the rate of major coronary heart disease events by 25% [Cholesterol Treatment Trialists' (CTT) Collaborators 2008]. In Finland, statins are available by prescription only, and adherence to statin therapy is known to be better in patients with a history of cardiovascular disease or diabetes, and among middle-aged and older patients (Halava et al. 2016). Simvastatin was introduced to the Finnish market in 1992, atorvastatin in 1998 and rosuvastatin in 2003. Simvastatin has also been the most commonly used statin in Finland since 1997, being chosen for 39% of new statin users in 1998 as compared with 18% with atorvastatin (Halava et al. 2009). However, 12% of statin initiators are known to discontinue therapy due to side-effects (Halava et al. 2016).

Among all VR surgical indications, RRD is the most feared, potentially sight-threatening VR disease and ophthalmic emergency (Feltgen & Walter 2014). In our study, the re-operation rate of all RRD patients was 15.9%, being in accordance with previous studies. Observational studies have reported the re-operation rate to be 13.3% for PPV, 12.3% for SB, 14.5% for combined PPV and SB surgery, and around 12–13% for emergency and routine patients (Koch et al. 2012; Jackson et al. 2014).

Fibrosis formation is associated with various posterior segment eye diseases

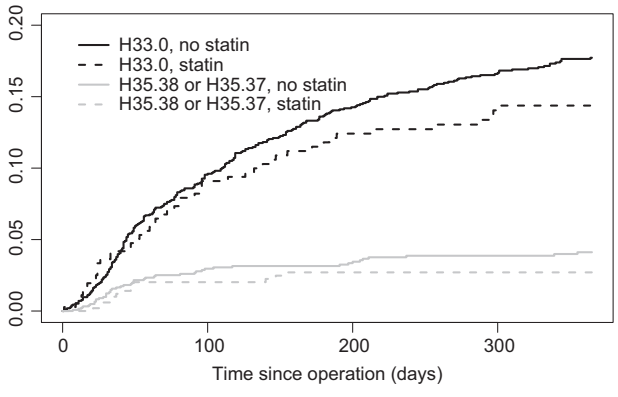

Fig. 5. Cumulative incidence of re-operations among the two most frequent vitreoretinal surgery diagnosis groups (H33.0 = retinal detachment and H35.38/H35.37/H35.39 = macular pucker and hole) according to baseline statin usage. Third edition of the Finnish version of the International Statistical Classification of Diseases and Related Health Problems (http://urn.fi/URN:NBN:fi-fe201205085423) was used after February 2011. In this updated version of the ICD coding classification, macular hole (H35.37) and macular pucker (H35.38) got their own ICD codes in Finland instead of both being recorded as H35.39.

including vascular (DR), nonvascular (RRD) and neurodegenerative (macular pucker/hole) eye diseases. Even after initial successful primary RRD surgery, fibrosis or PVR is the most frequent and severe complication and a major cause of failure after RRD surgery, with an incidence occurring in 4–34% of operated RRD eyes in prospective studies (Heimann et al. 2007; Kawahara et al. 2008; Pastor et al. 2016). Ischaemia, hypoxia and (neuro)inflammation are considered to be the major components of PVR formation after RRD surgery, amplified by a genetic pro-inflammatory profile (Garweg et al. 2013; Rojas et al. 2013). To improve the surgical outcome of eyes with RRD, modification of the inflammatory, cell proliferation, tissue remodelling and scar tissue-related processes involved in PVR is of great importance (Kawahara et al. 2008; Garweg et al. 2013; Pennock et al. 2013; Li et al. 2014). According to our cohort study, statin treatment could be associated with a decreased risk of PVR fibrosis in our RRD eyes and therefore reduce the risk of re-operation.

Herein, we analysed all eyes that underwent vitrectomy procedure in our hospital during 2008–2014. In our study, the RRD eyes operated with conventional SB surgery without vitrectomy were not included or analysed. Rates of RRD patients undergoing vitrectomy have shown a more than 10-fold increase from 1985 to 2004 in UK (El-Amir et al. 2009), and in our centre, vitrectomy has become the preferred surgical technique for primary RRD (Sahanne et al. 2017), being in line with other latest studies (Poulsen et al. 2016; Haugstad et al. 2017).

In a recent paper, the most common systemic comorbidities of VR surgical patients were hypertension (53%), diabetes mellitus (37%) and coronary artery disease (18%) (Shalwala et al. 2015). In our study, however, these systemic diseases were less common among the patients. Shalwala et al. (2015) also reported significantly increased incidence of postoperative systemic adverse events after VR surgery in patients with coronary artery disease, asthma, chronic renal disease or in patients operated under general anaesthesia. Unfortunately, in our study, the documented register data did not allow us to analyse systemic adverse events among the cohort.

As regards the other VR surgical groups studied in our cohort, we found no beneficial effect associated with statin use. One reason might be that in the majority of other VR groups, less than 10% of operated patients received statin therapy. The only exception was patients operated due to MH/pucker ($n = 2207$), of which one-third were prescribed statin therapy well before surgery, without statistically significant beneficial effect of statin being found in the re-operation rate. The majority of these MH/pucker patients underwent elective day surgery, either frank vitrectomy or combined phacovitrectomy, that also are generally considered relatively safe surgical procedures with lower rate of adverse outcome compared with eyes with more complex VR pathology. Perhaps the additional benefit of statin was too small to be found in the statistical analysis. Of note, in our previous paper, we found that systemic statin therapy might have a favourable effect on intravitreal factors involved in fibroproliferation in ageing human pucker eyes (Tuuminen & Loukovaara 2016).

With ageing population, the number of patients using anticoagulant/antiplatelet treatment has increased in recent years worldwide (Grzybowski et al. 2015; Kong & Khan 2015). Concomitant use of novel oral anticoagulants (clopidogrel) or old warfarin and statin is common in the secondary prevention of cardiovascular events, representing 4.9% of study eyes in our VR surgical cohort. According to our analysis, VR surgery of eyes of patients who were under warfarin or clopidogrel therapy was not associated with increased risk of re-operations after primary surgery. Therefore, our findings are in agreement with previous studies, suggesting that patients with anticoagulant may enter VR surgery safely while maintaining their anticoagulant therapy (Ryan et al. 2013), as long as their INR values are within the therapeutic range 2–3. Actually, revitrectomy rate in our study setting was lower in patients undergoing VR surgery using clopidogrel than without. However, patient population undergoing VR surgery using clopidogrel was small in our study.

Of the three statins used by our cohort (simvastatin, atorvastatin, rosuvastatin), only simvastatin seemed to be associated with the incidence of lower revitrectomy rate. Statin compounds have distinct pharmacokinetic and pharmacodynamic properties that affect their overall efficacy, safety and potential non-LDL-cholesterol action (Mason et al. 2005). Atorvastatin and simvastatin are both lipophilic agents, whereas rosuvastatin is not. Lipophilicity may influence the efficacy of the statin compound and has an effect on the pleiotropic effects of statins such as cell function, coagulation and inflammation. Atorvastatin/simvastatin may have a greater effect on inflammatory pathways compared with rosuvastatin and explain our results (Mason et al.

2005). Interpreting the study results, we should, however, bear in mind that the reasons for prescribing different types of statins to patients are related to systemic diseases, and therefore, we may not draw strong conclusions regarding the type of statin compound. Statin therapy was initiated well before, for the majority of statin users (87.1%) longer than 6 months before, the index VR operation was performed, most probably exerting the full pleiotropic effect on the operated eye (Barakat et al. 2016). More thorough analysis of this pharmacologic aspect cannot be performed based on our register-based study setting.

A clear increase in VR surgical activity in our VR unit took place between 2008 and 2014, which was the period when operations were carried out. The total volume of operated VR cases was higher during 2011–2014 than during 2008–2010. This trend probably reflects the development of surgical instrumentation, technique and shorter operational times. The major limitation of our study was its register-based design with somewhat robust data collection and a limited 1-year postoperative follow-up. Therefore, baseline ophthalmic data (such as degree of PVR fibrosis), intra-operative complications arising from surgery, and surgical procedure-related characteristics (intravitreal dyes, type of gas/silicone oil) could not be taken into account in the analysis. This kind of very accurate eye-related analysis is beyond the scope of an epidemiological register-based study without pre-planned structural databases. By improving the present structural databases at a national level, however, Finland and the other Nordic countries could form a proper environment for top-level internationally competitive medical research in the future. Prospective clinical surgical studies are thus warranted to address these features in the future. Another major limitation was that the operations were not performed by the same VR surgeon. It is also commonly known that choice of the VR surgical method varies between VR surgeons and centres. However, it is not probable that there is an association between surgeon and the effect of statin. Thus, potential differences between surgeons probably did not cause any bias on statin effect. In observational studies, it is possible that there are confounding factors connected to statin use. We controlled for this confounding using background variables as model covariates and also applied IPTW method. Despite these attempts, it is possible that some bias remains.

The remaining important issues that are not addressed in our cohort observational study are as follows. To whom and what age groups should statin therapy be given and how is statin therapy best used as an adjuvant agent in prevention of re-operations after RRD surgery? Should we perhaps start all diagnosed RRD patients with statin? And if so, what would be the optimal dose of statin therapy, timing of medication and form of delivery (oral, nanomicelles, simvastatin-coated implant, intravitreal single dose statin injection)? Based on animal studies, use of statin should not hinder retinal function, but surely, further ultrastructural human eye studies are also warranted (ILM, nerve fibre layer, ganglion cell) to address this issue more properly. Future studies of ligustrazine implant (Zhang et al. 2015) and resveratrol (Ishikawa et al. 2015) might also address whether these novel agents could be beneficial in prevention of PVR. As a whole, an assessment of pathogenesis of PVR is needed to help development of novel effective therapeutic approaches, especially treatment targeting epithelial to mesenchymal transition of retinal pigment epithelial cells in the pathogenesis of PVR (Ishikawa et al. 2015; Pastor et al. 2016). In Finland, our population is homogenous and our study results might not reflect the re-operation rate in RRD eyes operated in genetically more heterogenous study populations and backgrounds.

To conclude, use of statin treatment was associated with 28% lower risk of revitrectomy in the group of patients operated due to RRD in our real-world cohort setting. Therefore, our study highlights the idea of prescribing statin, especially simvastatin, treatment in the future, for surgical RRD patients. However, before we actually can recommend the prescription of any statin therapy to RRD patients that are to be operated, our intriguing preliminary findings based on an epidemiologic single-centre study merit confirmation by other more in-depth studies. At the population level, a clear benefit has been observed in favour of statins in general, and currently statin therapy is considered safe, with few side-effects. In fact, in USA, statins are the most commonly prescribed medication class and it has been estimated that half of the population aged 40–75 would benefit from statin therapy, as statins are known to decrease incidence of coronary heart disease (Taylor et al. 2013; Kantor et al. 2015). In practice, one major limitation is the compliance and adherence to statin therapy. It is generally known that some patients are afraid of potential side-effects (rhabdomyolysis), and unwilling to use statins. Currently, there is very limited data available regarding the efficacy of statin treatment in reducing adverse postoperative VR surgical outcomes, and therefore, further observational studies and randomized clinical trials studies are highly warranted. Noteworthy, early perioperative exposure to statin was very recently shown to be associated with a significant reduction in several surgical complications, including neurosurgery and orthopaedic (London et al. 2016). As VR surgery was not covered and analysed in that study, our preliminary data are needed to cover the full spectrum of different procedures more thoroughly.

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