

Progression to severe visual impairment and blindness in POAG patients: pace and risk factors—a cohort study using German health claims data

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ABSTRACT

Objective Glaucoma is a leading cause of severe visual impairment and blindness (SVI/B) worldwide. Hence, it is of utmost importance to explore relevant risk factors and study the pace of progression to SVI/B.

Methods and analysis We used a random sample of 250 000 persons from administrative individual-level health records of the Allgemeine Ortskrankenkassen between 2004 and 2015. We identified 3535 primary open-angle glaucoma (POAG) patients aged 55 and older and followed them for up to 10 years. Monocular and binocular SVI/B were defined by the ICD-10 classifications H54.0 and H54.4. Ophthalmological and chronic disease risk factors were analysed by applying a multivariable Cox proportional hazard model.

Results The risk of SVI/B in POAG patients was significantly increased by the presence of specific additional eye diseases such as secondary glaucoma (HR: 3.08, $p<0.001$), retinal vascular occlusion (HR: 3.00, $p<0.001$) or age-related macular degeneration (AMD) (HR: 2.26, $p<0.001$). The risk was highest in the first 2 years after the POAG diagnosis and significantly decreased after the fifth year (HR: 0.36, $p=0.002$). Ocular injuries, other ocular diseases, non-ophthalmological comorbidities, and age and sex had no significant influence ($p>0.05$).

Conclusion Although progression to SVI/B is relatively rare in POAG patients in Germany, one must be aware of additional risk factors, such as secondary glaucoma, retinal vascular occlusion and AMD. Regular ophthalmological examinations help prevent the progression of SVI/B, especially in the first years after the POAG diagnosis. Specific, targeted, and timely treatments for the other eye diseases could help prevent or delay SVI/B.

BACKGROUND

Glaucoma is one of the leading causes of blindness worldwide. Primary open-angle glaucoma (POAG) is the most common type, accounting for 74% (58.9 million) of all glaucoma cases in 2020.¹ For the same year, Kapetanakis *et al* estimated that 65.5 million people worldwide, as well as 2.1% of the European population aged 40+ years, suffered from POAG.² Concerning visual impairment, the number of people of all ages is estimated

Key messages

What is already known about this subject?

- ▶ Glaucoma is one of the leading causes of irreversible blindness worldwide with primary open-angle glaucoma being the predominant subtype accounting for 74% of all glaucoma cases in 2020.

What are the new findings?

- ▶ A number of risk factors in primary open-angle glaucoma (POAG) patients, which increase the risk of severe visual impairment and blindness (SVI/B), were identified, such as additional eye diseases and disease duration.

How might these results change the focus of research or clinical practice?

- ▶ To know about risk factors and incident eye diseases of POAG patients might help to prevent the progression of SVI/B, especially in the first years after diagnosis. Adequate disease management is of immense importance to assess the need for medical care interventions and to further improve medical care.

to be 285 million, while those aged 50 years and older represent 65% of the visually impaired.³

POAG is not only one of the most common eye diseases worldwide, but also one of the major causes of blindness in Germany.^{4 5} In addition to age-related macular degeneration (AMD) and diabetic retinopathy, POAG continues to represent the second leading risk factor for becoming blind in Germany and in Western Europe.^{6 7} In 2006, glaucoma caused 15.4% of all cases of blindness in the German population.⁸ Despite a slight decrease in the incidence of vision loss in developed countries over the past decades, there is ample evidence of cataracts and diabetic retinopathy to still substantially increase its risk.^{4 9}

After a diagnosis of POAG, the aim is to slow or to prevent any further progression of the disease by lowering the intraocular

pressure (IOP). New IOP-lowering therapies, as well as new diagnostic and progression analysis methods, are continually developing and being improved.¹⁰ These enhancements in glaucoma treatment have helped many patients; nevertheless, lifelong regular follow-up examinations are necessary to ensure their effectiveness. The impact of POAG on the rate of severe visual impairment and blindness (SVI/B) in the general population is poorly understood, as POAG often shows no symptoms until advanced stages.¹¹ Due to the interaction of various risk factors, POAG patients still suffer from progression of visual function loss, which implies the need to provide further evidence on this topic.

An advantage of studies focusing on the incidence of eye diseases concerns the potential to identify relevant risk factors which affect future visual outcomes. For the pathogenesis of SVI/B, relevant conditions include AMD, retinopathy, glaucoma and cataract as well as myopia, retinal vascular occlusions, injuries of the eye and optic nerve diseases.^{5 8 12–16} Based on the results of our previous study, which referred to the impact of incident eye diseases on the risk of SVI/B, in this study we analysed ten eye diseases as risk factors for the incidence of SVI/B in incident POAG patients.¹⁷

The epidemiology of SVI/B is also closely linked to demographic changes. Because the proportion of the elderly population will increase, there will be a further increase in both the prevalence of age-related eye diseases as well as in the proportion of individuals with SVI/B by 2030.^{5 7 18}

As POAG patients often have comorbid eye diseases, one hypothesis was that these additional eye diseases lead to a significant increase of the risk of SVI/B, although it is unclear which of these might pose the greatest risk factor when considered simultaneously. Therefore, our outcome measure included not only the transition to blindness but also to severe visual impairment. The second hypothesis dealt with the risk of SVI/B, which may be highest in the first few years after diagnosis, due to the fact that patients only consult an ophthalmologist when they first start to notice vision loss, even though the glaucoma is often at an advanced stage.

In Germany, severe visual impairment is defined by a visual acuity of 1/20 and less, regulated at the state level by the State Blindness Benefit Law. According to German law, legal blindness is a reduction of visual acuity to 1/50 (0.02). According to the WHO and the international classification system, blindness is defined by the threshold of visual acuity of 1/20 (0.05), which, according to ICD-10 coding, also includes severe visual impairment. This study uses the ICD-10 coding system as a basis, which combines SVI/B in one coding number.

Hence, the first aim of our study was to analyse the risk of severe monolateral or bilateral SVI/B in incident POAG patients. Second, we examined the pace of progression to SVI/B from the onset of POAG. Our third aim concerned the analysis of comorbid eye diseases as risk factors for SVI/B controlling for multimorbidity.

DATA AND METHODS

Data source

Data analysis is based on a random sample selection of 250 000 patients drawn from Germany's largest public health insurance company—the Allgemeine Ortskrankenkassen (AOK). The scientific institute of the AOK (WiDO) granted access to these data. The dataset included both persons from private households and from nursing homes. An observation period between 2004 and 2015 allowed for a 12-year follow-up of patient information on a quarterly basis. A change of the health insurance or death led to withdrawal from the sample. The routine data covered basic demographic characteristics such as sex, date of birth and death, as well as confirmed inpatient and outpatient diagnoses coded by the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM). It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Definition of SVI/B, POAG, and risk factors of SVI/B

We coded the outcome SVI/B using ICD H54.4 and H54.0. No information about the leading causes of SVI/B was available. Our main exposure variable POAG is based on ICD H40.1.

All patients with an incident POAG diagnosis (ICD: H40.1) were analysed. We defined the following selected eye diseases as risk factors: primary angle-closure glaucoma (ICD: H40.2), secondary glaucoma (ICD: H40.3–H40.6), myopia (ICD: H44.2, H52.1, H52.5), injuries of the eye (ICD: S05, T15, T26), AMD (ICD: H35.3), retinopathy (ICD: H35.0–H35.2) including diabetic retinopathy (ICD: H36.0), cataracts (ICD: H25–H26) including diabetic cataracts (ICD: H28.0), retinal vascular occlusion (ICD: H34) and disorders of optic nerves (ICD: H46–H48). As an independent risk factor of SVI/B, we considered type 2 diabetes mellitus (ICD: E11). In addition, we explored the effect of disease-duration of POAG by categorising patients into groups of 1st year, 2nd year, 3rd to 5th year and 6th to 10th year since their first valid diagnosis.

Control variables

The demographic control variables were age at the first POAG-diagnosis (55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90+), as well as sex. For analysis, the multimorbidity status of patients was categorised into none, 1–2, 3–4 or 5 or more severe comorbidities and consisted of the following non-ophthalmic diagnoses: acute myocardial infarction (ICD: I21–I22, I25.2), cerebrovascular diseases (ICD: G45–G46, H34.0, I6), ischaemic (ICD: I20–I25) and other heart diseases (ICD: I43, I50, I09.9, I11.0, I13.0–2, I25.5, I42.0–9, P29.0), cancer (ICD: C00–C97), kidney (ICD: N11–N19, I12.0, I13.1–2, N03.2–7, N05.2–7, N25–N29, Z49.0–2, Z94.0, Z99.2), liver (ICD: B18, K70, K71.1,3,4,5,7, K72.1,9, K76.0,2–9, Z94.4) and lung diseases (ICD: J44), nervous diseases (ICD: G0–1, G4–9, G20–22, G23.0,2,8,9, G24–26, G31.2,9, G31.81,88,

G32.35–37), dementia (ICD: F00.0–9, F01.0–9, F02.0–8, F03, F05.1, G23.1, G30.0–9, G31.0 G31.82) and injuries of hips and legs (ICD: S7–S9).

Validation strategy of the eye diseases

As an internal validation strategy, all selected eye diseases matched the M2Q-criterion (minimum two quarters criterion) to reduce the problem of false-positive diagnoses.¹⁹ To ensure the validity of a first diagnosis, a second diagnosis in another quarter during the observation period was necessary. All covariates, with the exception of sex and age at incident POAG-diagnosis, were considered to be time-varying variables with the value of '1' since first valid diagnosis and '0' otherwise.

Sample selection procedure

The data set comprised 249 742 persons in the first quarter of 2004, with plausible information on the date of birth and death. We excluded 230 896 persons who had no valid POAG-diagnosis throughout the entire observation period. To explore the pace of the transition to SVI/B for incident POAG patients, we defined the 2 years 2004 and 2005 as wash-out periods, and excluded all patients who had a diagnosis of POAG (n=344) or SVI/B (n=30) in these 2 years. To assure that the duration of POAG was not confounded by the duration of the other eye diseases, we also excluded patients who had at least one of the listed eye diseases during the wash-out period (n=11 990). We studied the incidence of POAG from the first quarter of 2006 onwards. An additional 2862 patients were dropped due to death or change of health insurance. Another 85 persons with a simultaneous diagnosis of POAG and SVI/B were excluded, as well as patients under the age of 55 years at the time of the valid glaucoma-diagnosis. The final study sample consisted of 3535 patients with

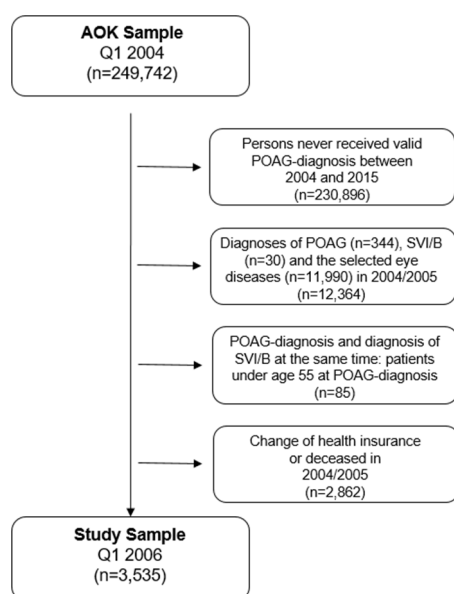


Figure 1 Flowchart of sample selection procedure. AOK, Allgemeine Ortskrankenkassen; POAG, primary open-angle glaucoma; SVI/B, severe visual impairment and blindness.

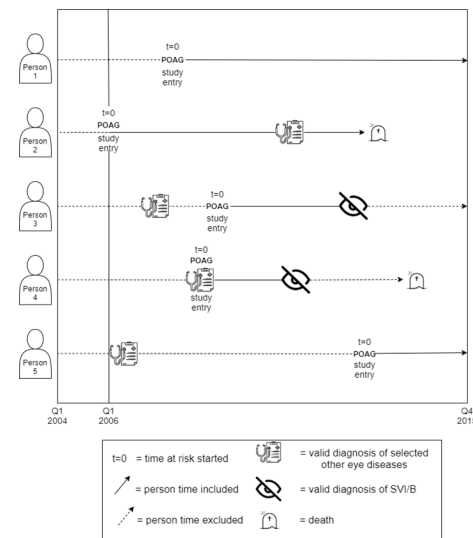


Figure 2 Time at risk in multivariable analysis. POAG, primary open-angle glaucoma; SVI/B, severe visual impairment and blindness.

incident POAG diagnosed between 2006 and 2015 with a maximum follow-up of 10 years (figure 1).

Analysis strategy and statistical methods

Parametric proportional-hazards models were performed including sex, age, selected eye diseases which are associated with an elevated risk of SVI/B, multimorbidity and the duration since the onset of POAG. Analysis time was measured in quarters and started at the first valid POAG-diagnosis and ended with death or change of health insurance (figure 2, person 1), valid diagnosis of SVI/B (figure 2, persons 3 and 4), or due to right censoring in Q4 2015 (figure 2, persons 1 and 5). The censoring time was set to the middle of the last observed quarter of SVI/B-diagnosis and for deaths in the month of death. We assumed analysis time to follow an exponential distribution with a constant baseline hazard over time. All statistical analysis was performed using Stata (V.16.1).

RESULTS

Characteristics of study population

The final study population comprised 3535 incident POAG patients of whom 109 received an additional diagnosis of SVI/B between 2006 and 2015 (table 1). The number of POAG and SVI/B patients increased with age: the majority received their first diagnosis of POAG at the ages of 70 to 74 (n=762, 21.56%) and 75 to 79 (n=784, 22.18%), while 25.69% (n=28) suffered from SVI/B between 80 and 84 years. Approximately two-thirds of POAG patients were female (n=2265, 64.07%), which was also true for SVI/B (n=74, 67.89% females vs n=35, 32.11% males).

At study entry, 84.64% (n=2992) of all patients suffered from cataract, about one-third from disorders of optic nerve (n=1171, 33.13%), retinopathy (n=1142, 32.31%) or myopia (n=1122, 31.74%). 28.29% (n=1000) of POAG patients showed AMD, and angle-closure glaucoma

Table 1 Descriptive overview of patients' characteristics at the time of SVI/B and study entry, 2006–2015

Covariates	At time of SVI/B 2006–2015		At time of study entry 2006–2015	
Age at POAG-diagnosis				
55–59	3	2.75%	152	4.30%
60–64	4	3.67%	251	7.10%
65–69	12	11.01%	456	12.90%
70–74	17	15.60%	762	21.56%
75–79	25	22.94%	784	22.18%
80–84	28	25.69%	658	18.61%
85–89	18	16.51%	366	10.35%
90+	2	1.83%	106	3.00%
Sex				
Male	35	32.11%	1270	35.93%
Female	74	67.89%	2265	64.07%
Eye diseases (ever diagnosed after 2005)				
Cataract				
No	6	5.50%	543	15.36%
Yes	103	94.50%	2992	84.64%
Age-related macular degeneration				
No	46	42.20%	2535	71.71%
Yes	63	57.80%	1000	28.29%
Disorders of optic nerve				
No	56	51.38%	2364	66.87%
Yes	53	48.62%	1171	33.13%
Myopia				
No	66	60.55%	2413	68.26%
Yes	43	39.45%	1122	31.74%
Retinopathy				
No	67	61.47%	2393	67.69%
Yes	42	38.53%	1142	32.31%
Secondary glaucoma				
No	88	80.73%	3347	94.68%
Yes	21	19.27%	188	5.32%
Retinal vascular occlusions				
No	88	80.73%	3371	95.36%
Yes	21	19.27%	164	4.64%
Angle-closure glaucoma				
No	92	84.40%	3301	93.38%
Yes	17	15.60%	234	6.62%
Injuries of the eye				
No	104	95.41%	3440	97.31%
Yes	5	4.59%	95	2.69%
Ever diagnosed type 2 diabetes mellitus				
No	63	57.80%	2047	57.91%
Yes	46	42.20%	1488	42.09%
Comorbidities				
None	3	2.75%	347	9.82%

Continued

Table 1 Continued

Covariates	At time of SVI/B 2006–2015		At time of study entry 2006–2015	
1–2	26	23.85%	1341	37.93%
3–4	35	32.11%	1020	28.85%
5+	45	41.28%	827	23.39%
Year since POAG diagnosis				
1st year	22	20.18%	3535	100.00%
2nd year	26	23.85%	0	0.00%
3rd–5th year	46	42.20%	0	0.00%
6th–10th year	15	13.76%	0	0.00%
Total	109	100%	3535	100%

POAG, primary open-angle glaucoma; SVI/B, severe visual impairment and blindness.

affected 6.62% (n=234). 5.32% (n=188) of persons had an additional diagnosis of secondary glaucoma. The proportion of patients with retinal vascular occlusions amounted to 4.64% (n=164), whereas injuries of the eye concerned a minority of the sample (n=95, 2.69%).

Compared with study entry, at the time of SVI/B the prevalence of eye diseases had increased for AMD (n=63, 57.80%), retinal vascular occlusions (n=21, 19.27%), secondary glaucoma (n=21, 19.27%) and angle-closure glaucoma (n=17, 15.60%). A large majority of patients suffered from cataract (n=103, 94.50%), whereas the prevalence of injuries of the eye (n=5, 4.59%), myopia (n=43, 39.45%), retinopathy (n=42, 38.53%) and disorders of optic nerve (n=53, 40.37%) was marginally higher at the time of SVI/B than at first POAG-diagnosis.

At study entry, 42.09% (n=1488) suffered from type 2 diabetes mellitus which also affected 42.20% (n=46) of patients at the time of SVI/B. At the time of SVI/B, 2.75% (n=3) of the patients did not have any severe comorbidities but 41.28% (n=45) had five or more comorbid diagnoses. Conversely, at study-entry, the number of comorbidities decreased from two onwards. In 42.20% (n=46) SVI/B occurred between 3 and 5 years after the first POAG-diagnosis, decreasing to 13.76% (n=15) after 6–10 years from POAG diagnosis.

Multivariable regression analysis of risk factors

POAG patients with angle-closure glaucoma, AMD, retinal vascular occlusions and secondary glaucoma had a two to three times significantly higher risk of SVI/B compared with persons without these eye diseases (table 2). In detail, the risk of SVI/B was the highest for secondary glaucoma (HR: 3.08, 95% CI 1.89 to 5.02, $p<0.001$) and retinal vascular occlusions (HR: 3.00, 95% CI 1.83 to 4.90, $p<0.001$), followed by angle-closure glaucoma (HR: 1.98, 95% CI 1.17 to 3.35, $p=0.011$) and AMD (HR: 2.26, 95% CI 1.52 to 3.37, $p<0.001$). Patients with injuries of the eye, myopia, retinopathy, cataract or disorders of optic nerve also showed an enhanced risk of SVI/B, but this was not confirmed by the conventional significance levels ($p<0.05$).

Diabetes mellitus type 2 did not affect the risk of SVI/B (HR: 0.81, 95% CI 0.63 to 1.04, $p=0.100$). With an increasing number of non-ophthalmic comorbidities, the risk increased nearly twofold, but not significantly. A longer disease duration up to 10 years of POAG was associated with a lower risk of SVI/B. Compared with patients in the second year since the onset of POAG, persons with a valid POAG-diagnosis from 6 years and more had a 64% (HR: 0.36, 95% CI 0.19 to 0.68, $p=0.002$) lower risk of SVI/B. No significant differences existed up to 5 years. Age and sex of POAG patients had no significant effect on the risk of SVI/B.

DISCUSSION

Glaucoma incidence and SVI/B

POAG is one of the major eye diseases in Germany and also a leading cause of blindness worldwide.¹ Our study revealed a low risk of SVI/B among POAG patients, as 109 of 3535 POAG patients (3%) suffered from monocular or binocular SVI/B within 10 years of the onset of POAG. Previous studies have already demonstrated that patients who received their first POAG diagnosis after 1980 had a decreased risk of SVI/B, which is attributable to the development of appropriate medical treatment as well as optimal surgical strategies.^{10 20} The risk of experiencing SVI/B in our study was concentrated in the first years after the POAG-diagnosis and became significantly lower after 6–10 years compared with disease onset. In the study of Yonekawa and colleagues, 1.2% of participants developed incident visual impairment, 2.9% developed monocular VI with a 4-year incidence and 1.2% developed monocular blindness.²¹ These numbers are similar to those we found, where 3% of patients developed incident SVI/B, with the difference that we also included patients developing incident binocular blindness. In our study, we not only benefitted from the long-term follow-up and the number of patients included, but also from information about the time at which POAG-patients received incident diagnoses of additional eye diseases. Thus, our study is better suited to differentiate between the effect of POAG and the effects of other eye diseases on the transition

Table 2 Results of multivariable regression model, 2006–2015

Covariates	HR	P value	95% CI
Cataract			
No	1.00		
Yes	1.76	0.188	(0.76 to 4.09)
Age-related macular degeneration			
No	1.00		
Yes	2.26	<0.001	(1.52 to 3.37)
Disorders of optic nerve			
No	1.00		
Yes	1.37	0.109	(0.93 to 2.00)
Myopia			
No	1.00		
Yes	1.21	0.339	(0.82 to 1.78)
Eye diseases (ever diagnosed after 2005)			
Retinopathy			
No	1.00		
Yes	1.02	0.921	(0.67 to 1.55)
Secondary glaucoma			
No	1.00		
Yes	3.08	<0.001	(1.89 to 5.02)
Retinal vascular occlusions			
No	1.00		
Yes	3.00	<0.001	(1.83 to 4.90)
Angle-closure glaucoma			
No	1.00		
Yes	1.98	0.011	(1.17 to 3.35)
Injuries of the eye			
No	1.00		
Yes	1.37	0.500	(0.55 to 3.39)
Ever type 2 diabetes mellitus			
No	1.00		
Yes	0.81	0.100	(0.63 to 1.40)
Comorbidities			
None	1.00		
1–2	1.70	0.386	(0.51 to 5.67)
3–4	2.32	0.172	(0.69 to 7.74)
5+	2.57	0.131	(0.76 to 8.72)
Year since POAG diagnosis			
1st year	0.93	0.800	(0.53 to 1.64)
2nd year	1.00		
3rd–5th year	0.72	0.183	(0.44 to 1.17)
6th–10th year	0.36	0.002	(0.19 to 0.68)
Age at POAG-diagnosis			
55–59	1.00		
60–64	0.79	0.757	(0.18 to 3.54)
65–69	1.05	0.945	(0.29 to 3.76)

Continued

Table 2 Continued

Covariates	HR	P value	95% CI
70–74	0.80	0.731	(0.23 to 2.81)
75–79	1.03	0.962	(0.30 to 3.54)
80–84	1.30	0.676	(0.38 to 4.49)
85–89	1.79	0.372	(0.50 to 6.39)
90+	0.68	0.679	(0.11 to 4.26)
Sex			
Males	1.00		
Females	1.14	0.538	(0.75 to 1.73)

POAG, primary open-angle glaucoma.

to SVI/B than earlier studies. Furthermore, the total number of 3% may be attributable to the German health-care system, which entails a regular 3-month follow-up after the first glaucoma diagnosis. In addition, Germany has a Disease Management Programme (DMP), which aims to increase the cooperation between general practitioners and ophthalmologists, thereby improving the coordination of therapies after the onset of the disease. However, with the exclusion of prevalent eye diseases at study entry, our sample may represent a healthier selection of POAG patients, which may account for the lower number of persons with SVI/B. The health selection into the study group also concerned the age of the incident POAG patients, as the majority received their first diagnosis later in life (75–79 years). The number of 3% incident glaucoma patients seems to be low compared with other studies, where a late presentation was the main cause for 23% of patients eligible for blindness registration, reducing to 12% in a study conducted a decade later.^{22–23} These results still seem low compared with other studies, in which 30%–35% of the patients presented bilaterally blind to the clinic or were blind at the end of follow-up.^{24–26} In contrast to these high numbers, prevalence of bilateral blindness was 0.02% when combinations of glaucoma and other causes were included.²⁷

Glaucoma pace and worsening of SVI/B

The analysis of the pace showed that almost half of all individuals with SVI/B received their diagnosis between 3 and 5 years after POAG onset, whereas after 5 years since the first POAG diagnosis the risk for SVI/B decreased significantly. In context of the worsening of SVI/B, incident additional eye diseases with an onset prior to first POAG diagnosis need to be considered, while the contribution of the history of additional eye diseases as a risk factor for VI has been described earlier. Yonekawa and colleagues demonstrated that persons with a history of eye diseases are predisposed to develop vision loss either due to the presence of a progressive ocular or systemic condition or due to increased environmental exposure to factors that may contribute to progressive vision loss.²¹ Another study investigating the rate of change in patients

with POAG showed a median time of worsening at 7.5 years, after which the progression slowed. Also, deterioration was higher among patients with more advanced glaucoma at the time of initial presentation.²⁸ Several reasons may be responsible for progression within the first 5 years of POAG onset: delayed consultation of an ophthalmologist or, as described by Eid and colleagues, the progression of glaucoma was rapid. Another possibility concerned an ineffective therapy to lower IOP, which failed to attenuate the progression of the disease.

Eye disease-related risk factors and SVI/B

We identified several eye diseases as additional risk factors of SVI/B, such as secondary glaucoma and retinal vascular occlusions. We also confirmed additional adverse effects of AMD and angle-closure glaucoma. These eye diseases generally increase the risk of SVI/B, however, among POAG patients it is even more necessary to closely monitor whether these additional eye diseases develop.²⁹ Ocular morbidities contributing to sight loss in addition to glaucoma have also been described by others. In the study of Kotecha *et al* 29 patients of 100 had a secondary comorbidity contributing to sight loss, with some of the same ocular diseases investigated in our study, such as retinal vascular occlusion, macular detachment including AMD, traumatic ocular injury and high myopia. Nevertheless, glaucoma was listed as the primary cause of visual impairment.¹¹ As early as 1980 Luntz and Schenker confirmed the correlation between the incidence of glaucoma and retinal vascular occlusion.³⁰ Chen evaluated patterns of blindness in POAG patients, whereby a significant risk factor for developing blindness over time was visual field loss at POAG diagnosis.²⁰ Late detection and a higher IOP constituted significant risk factors in the study of Kooner and colleagues.³¹ Blomdahl and colleagues investigated risk factors for bilateral blindness and also the extent to which other eye diseases contributed in 210 patients, who represented 11% of the total cohort. Macular degeneration was the most common disease contributing to visual impairment in this group, with 52.9%, followed by cataract with 17.1% and retinal vein occlusion with 10%. In addition, some patients had more than one contributing eye disease,

similar to our study.²⁷ The authors concluded that blindness in glaucoma patients is primarily due to other eye diseases. Therefore, our study leads to the conclusion that comorbid other eye diseases represented one of the most significantly found risk factors for SVI/B in POAG patients.

Sociodemographic-related risk factors (age and gender)

In our study, POAG patients of different age groups as well as both sexes showed the same risk for SVI/B. Paula *et al* investigated possible risk factors for blindness and revealed similar results: age and gender were not associated with unilateral and bilateral blindness, with 24.5% of investigated POAG patients presented unilateral and 34.0% presented bilateral blindness from glaucoma. Paula and colleagues examined risk factors of blindness in patients with open-angle glaucoma within a follow-up time of at least 15 years and also showed that sex was not associated with an enhanced risk of blindness.²⁶ The Reykjavik Eye Study, the Melbourne Visual Impairment Project and the Priverno Eye Study also demonstrated no sex-related differences, similar to our results.^{32–34} In agreement with Kwon *et al*, who evaluated the long-term visual field outcome in POAG, no differences in the risk of SVI/B in POAG patients among the sexes were detected.³⁵ In Germany, gender-specific and age-specific differences can be found in the non-cause-specific incidence of blindness, but these do not apply to the risk of SVI/B among POAG patients.⁴ On the contrary, older age was a risk factor for incident VI, monocular VI and worsening vision in the Los Angeles Latino Eye Study (LALES) and for the progression of visual field loss of POAG patients.^{21 36 37} Also, a number of population-based studies investigating different ethnicities, within a follow-up period of 3–7 years and a sample size larger than 500, such as the Beaver Dam Study, the Blue Mountain Study, the Barbados Eye Study and others, identified older age as a risk factor for incident VI.^{32–34 38–41}

Non-eye disease-related risk factors and SVI/B

In our SVI/B cohort, 23.8% of patients had 1–2 comorbidities, 32.1% had 3–4 comorbidities and 41.2% had more than five comorbidities, other than eye diseases. Our descriptive analysis showed that a higher number of non-eye-related diseases increased the risk of SVI/B, however, this gradient was not significant in multivariable analysis. This number was very similar to the number (41%) of patients who had two or more comorbidities in the LALES, which investigated risk factors for incident visual impairment and monocular blindness.²¹

Population-based studies showed that persons with diabetes are predisposed to developing multiple ophthalmic conditions, including diabetic retinopathy, cataract, optic nerve damages, as well as glaucoma and central vein occlusion.^{21 29 42} Although 42% of patients included in our study had diabetes mellitus type 2, it was not a risk factor for SVI/B. The absence of an increased risk for SVI/B in prevalent diabetic patients is attributable

to our study design: because we controlled for the risk of SVI/B in incident additional eye diseases potentially caused by diabetes in our study, the effect of diabetes mellitus as such was absent. Furthermore, cataract surgery constitutes a routine intervention in developed countries and the risk for SVI/B decreased significantly, which is also true for POAG patients.⁴³ Another major factor for diabetes not being identified as a risk factor might be Germany's DMP. This potentially increased utilisation of ophthalmic services, leading to a more frequent diagnosis of POAG of diabetic patients.

Limitations and strengths

By using health claims data we benefitted from a large sample size as well as from a high number of POAG-diagnoses confirmed by inpatient and outpatient ophthalmologists. We attained improvement of validity and minimised false-negative diagnosis by the use of 'M2Q-criterion'. The cohort study design offered a long-term follow-up of patients' health progression; however, false negative POAG-diagnoses due to right censoring were possible if patients received their second POAG-diagnosis after Q4 2015. Despite the adjustment of control variables in multivariable analysis, the data provided no information about cause-specific SVI/B. We investigated monocular and binocular SVI/B, which consisted of incident POAG patients as well as of patients with incident other eye diseases. Hence, the strict inclusion criteria may account for the small number of cases of SVI/B. One limitation to be aware of is the increasing selection bias due to mortality and change of health insurers with increasing duration of the observation period. Also, as the ICD-10 coding includes SVI/B, no conclusion about blindness itself and the reasons for blindness were possible from these data. However, it may also be seen as a strength of the study that it is not confined to blindness alone. An advantage of health claims data is the composition of the sample, including persons from both private households and nursing homes. There was no mortality selection into as well as out of the AOK sample. There is no bias due to survey sample-selection or non-response. The AOK covers almost one third of the German population but it covers roughly half of the population aged 70 and older. There is an insurance selection bias, implying a worse health profile of the insured compared with the average population. Thus, while our sample may not be representative of the total German population in terms of incidence and prevalence of diseases, the mechanisms leading to SVI/B certainly are.

Due to differences in age selection criteria, ethnicity, follow-up time, definitions of risk factor and end-points, Yonekawa and colleagues discuss the importance of general considerations of risk associations rather than directly compare studies.²¹ The authors address exactly these points we also consider to be of immense importance. In addition to the criteria mentioned above, there is the additional issue of different definitions of visual impairment, blindness and glaucoma in different regions

of the world. These points should always be kept in mind when discussing results from different countries.

CONCLUSION

The risk of SVI/B of incident glaucoma patients in Germany is generally low. Our results revealed that if SVI/B develops, it occurs within 2 years after the first glaucoma diagnosis. In addition, some incident eye diseases were analysed to be risk factors for SVI/B of incident glaucoma patients. These findings emphasised the importance of early detection of glaucoma onset, regular ophthalmological examinations to medicate higher IOP, and to prevent the progression to SVI/B. Also, the general importance of eye care management in addition to a solid working patient–doctor relationship will improve disease management. But prevention also depends on the early detection of non-ophthalmic conditions. Knowledge of the factors that may be responsible for increased risk of SVI/B is important for all those involved in healthcare management to assess the need for medical care interventions and to further improve medical care.

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