

Predictors and long-term patterns of medication adherence to glaucoma treatment in Denmark—an observational registry study of 30 100 Danish patients with glaucoma

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ABSTRACT

Background Self-treatment with glaucoma medication (eye drops) has been associated with adherence challenges. Poor adherence results in worse outcomes in terms of visual field loss.

Objective To investigate patterns in medication adherence among Danish patients with glaucoma in relation to selected predictors of adherence, long-term adherence patterns, and long-term societal economic consequences of poor adherence.

Methods and analysis This register-based study included 30 100 glaucoma patients followed for 10 years between 2000 and 2018. Glaucoma was identified from the Danish national registers by diagnosis of Open Angle Glaucoma and/or by redeemed prescriptions of glaucoma medication. Logistic regression models were applied to estimate patient characteristics related to medical adherence. Diagnosis-related group fees were applied to estimate healthcare costs.

Results High adherence in the first year(s) of treatment was less likely among men (OR_{first year}: 0.78, 95% CI: 0.75 to 0.82), younger individuals and among those with a positive Charlson Comorbidity Index (CCI) score (OR_{first year/CCI≥3}: 0.71, 95% CI: 0.63 to 0.80). Adherence in the first year and in the first two years was associated with adherence in the fifth (OR_{first year}: 4.55, 95% CI: 4.30 to 4.82/OR_{first two years}: 6.47, 95% CI: 6.10 to 6.86) as with adherence in the 10th year with slightly lower estimates. Being medical adherent was related to higher costs related to glaucoma medication after 5 and 10 years comparing with poor adherence, whereas poor adherence was associated with a marked increase in long-term costs for hospital contacts.

Conclusion Increasing age, female sex and low comorbidity score are correlated with better adherence to glaucoma treatment. Adherence in the first years of treatment may be a good predictor for future adherence. In the long term, patients with poor adherence are overall more expensive to society in terms of hospital contacts.

INTRODUCTION

Glaucoma is one of the leading causes of irreversible vision loss in the world.^{1,2} Worldwide, it

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A high proportion of patients with glaucoma have poor adherence to medical treatment.

WHAT THIS STUDY ADDS

⇒ This study addresses the importance of high adherence of glaucoma treatment in the first years of treatment. It showed statistically significant predictions of the two first years of adherence into future adherence patterns of glaucoma treatment. The study found a correlation between specific patient characteristics and adherence patterns and higher hospital cost for poorly adherent patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings may be of importance for physicians informing of the clinical value of adherence in the first years of treatment and may lead physicians to investigate other intraocular pressure-lowering options sooner in patients with poor adherence, particularly among those that are progressing at unsafe rates. Finally, in the long term, patients with poor adherence are overall more expensive to society in terms of hospital contacts.

has been estimated that more than 70 million people are affected by glaucoma, and of these approximately 10% are bilaterally blind.³ In Denmark, the prevalence has been reported to 3.7% of the population aged 50 years or older.⁴ The number of glaucoma patients is expected to increase in the future simultaneously with the growing and ageing population.⁵ Additionally, since glaucoma can remain asymptomatic until it is severe, it is highly likely that the number of affected individuals is much higher than what is known.^{6–8} Glaucoma comprises a group of eye conditions causing progressive degeneration of the



optic nerve leading to permanent visual impairment with blind spots, tunnel vision and in worst case blindness, if untreated. The most common type of glaucoma is open-angle glaucoma (POAG) with a normal appearing, open iridocorneal angle with restrictions in aqueous outflow and often accompanied by elevated intraocular pressure (IOP).^{9–11} Lowering IOP can prevent progression of both early and late stages of glaucoma by increasing aqueous outflow and/or reducing aqueous production^{12–16}. The treatment strategy for lowering the IOP includes primarily topical medication (eye drops), selective laser trabeculoplasty, and glaucoma surgery.¹⁷

As to other chronic diseases, self-treatment with glaucoma medication has been associated with adherence challenges with the therapeutic regimen given the asymptomatic nature of glaucoma and the self-effort needed for treatment.^{10 18–20} Although many studies have assessed patient adherence in relation to glaucoma medication, the measures of adherence vary greatly due to inconsistency in the assessment methods, period of interests, and criteria of adherence.¹⁹ This has resulted in the proportion of non-adherent patients to range from 5% to 80%.²¹ However, poor medication adherence in patients with glaucoma has been associated with factors such as difficulties with eye-drop administration, payment of medication, side effects, not being physically able to apply the eye drops themselves, and difficulties in remembering taking the medication at the right dose at the right time.^{18 22} Poor adherence has also been associated with sociodemographic factors such as younger age, lower socioeconomic status, as well as situational factors such as being away from home.^{10 18 23–25}

Poor adherence is not only a clinical problem related to faster progression of visual field loss²⁶ but may also represent an economic burden on the healthcare systems.^{27 28} The existing literature of the economic impact of poor adherence to glaucoma medication is limited.²⁷ However, there is an indication that healthcare costs for patients with glaucoma increase with disease severity, and therefore, adequate management of glaucoma treatment is needed to effectively delay disease progression and thus reduce the economic burden of glaucoma.^{18 28 29}

Therefore, the overall aim of this study was to investigate patterns in medication adherence in Danish patients with glaucoma. First, we aimed to explore selected predictors of medication adherence in Danish patients with glaucoma. Second, we aimed to investigate whether adherence in the early phase of the disease is associated with long-term adherence. Third, we aimed to investigate the consequences of poor adherence over time in terms of healthcare costs in relation to hospital contacts and reimbursement of medicines.

MATERIAL AND METHODS

Study population

The study population consisted of all Danish individuals (≥ 18 years) alive and residing in Denmark in the period from 2000 to 2009 identified with glaucoma. Patients

with glaucoma were identified as individuals who had minimum three redeemed prescriptions of glaucoma medication (ATC code: S01E group) in the Register of Pharmaceutical Sales or has been registered with a diagnosis of POAG (ICD-10 code: H40.1) in The Danish National Patient Register (DNPR) and had minimum one redeemed prescription of glaucoma medication. Patients were followed for 10 years from index date defined as first redeemed prescription or first registration of a POAG diagnosis, whatever came first, in the period between 2000 and 2009. Patients with a history of redeemed glaucoma prescriptions and/or POAG diagnosis registered in the period from 1995 to 1999 were excluded to ensure that the study was based on incident patients. In addition, individuals with missing data on date of birth or/and sex were excluded. Thus, the baseline study population consisted of 30 100 individuals.

Data were stored and processed in the data secure remote server environment at Statistics Denmark, and registers from The Danish Health Data Authority were linked through the unique personal identification number assigned to all persons with permanent residence in Denmark.^{30 31} According to Danish law and ethical guidelines, ethical approval of registry studies is not needed. This study was conducted in accordance with the Declaration of Helsinki. Patients or the public were not involved in the design, or conduct, or reporting of our research.

Medication adherence

Information on redeemed prescriptions on glaucoma medication was obtained from DNPR and was used to operationalise medication adherence to glaucoma treatment.³² Medication adherence was estimated by calculating proportion of days covered (PDC) using the redeemed defined daily dose (DDD) summarised for each year up to year 10 (defined by the index date) divided by 365 days assuming the patient taking one DDD of redeemed medication per day; thus, patients were allowed to shift from one adherence group to another across years. High adherence was defined as $PDC \geq 80\%$ and poor adherence as $PDC < 80\%$. This approach including the cut-off of 80% was adapted from previous studies in the field as was supported by clinical inputs.^{33–37} Adherence was variously expressed as (1) ‘First-year-adherence’ covering the first 365 days from index date, (2) ‘First-two-years-adherence’ covering the yearly mean of PDC estimates for the first 2 years from index date, (3) ‘Fifth-year-adherence’ covering PDC within the fifth year, and (4) ‘Tenth-year-adherence’ covering PDC within the tenth year from index date. Laser treatment is commonly used as an add-on to topical glaucoma medication within the first year of the disease and up to 74% become drop-free for a period after laser treatment, and thus, patients are not eligible for medication within this period.³⁸ Similarly, glaucoma surgery in terms of trabeculectomy is used if the effect of topical treatment or laser treatment is insufficient and may likewise be followed by a drop-free

period. Data on laser treatment and surgery were not available, therefore, to avoid misclassification of adherence in this regard, and thus to ensure that patients were consistently in medical treatment, patients were included in the respective analyses if they had minimum one glaucoma medication prescription redemption per year in the respective follow-up periods plus the following year.

Covariates

Information on age at index date and sex were obtained from The Danish Civil Registration.³⁰ Number of comorbidities were obtained from DNPR and estimated from 5 years prior to index date and up to index date.³⁹ Comorbidities were further operationalised as a score according to the Charlson Comorbidity Index (CCI) by systematically quantifying and weighting ICD-10 codes.⁴⁰ Subsequently, CCI score was categorised into 0, 1–2 and ≥ 3 .

Healthcare costs

Services provided in the secondary sector (i, hospital sector) were defined in terms of costs in relation to hospital contacts registered for the study participants in the fifth and tenth year from index date. The cost estimates for all services provided in the secondary sector per year per patient were obtained from the diagnosis-related group (DRG)-grouped patient register available from 2002 to 2018.^{41 42} The DRG-grouped patient register includes information from the DRG system containing information on DRG-cost rates for all hospital contacts (ie, hospital admissions, scheduled procedures and ambulatory visits), including information on for example, diagnoses, surgeries, treatment procedures, hospitalisations, age of the patient and ways of discharge, which are used to calculate the annual resource use for each patient. In addition to this, we included costs of prescribed glaucoma medication purchased at Danish community pharmacies. These costs were estimated as public costs exclusively on prescriptions redeemed in the period 2000–2018, and thus, patient co-payments were not included.³² Since information on expenses was not available for the full study period, we performed the cost analyses in subpopulations corresponding the period with available data for each analysis (See online supplemental file 1 for details). All cost estimates were converted to 2021 prices using the net price index⁴³ and further converted from DKK to Euro using the exchange rate: 7.44 DKK=1.00 Euro.

Statistical analyses

All analyses were performed using SAS software, V.9.4 (SAS Institute Inc., Cary, NC, USA) and R (RCore Team, 2022), RStudio (Rstudio Team, 2022). Descriptive analyses were performed for patient characteristics and medication adherence to glaucoma treatment within the first year and the first two years from index date reported by frequency and tested for heterogeneity using chi-squared test. We applied crude and adjusted

multivariable logistic regression models to calculate OR and corresponding 95% CI for the association between patient characteristics and medical adherence, as well as to evaluate whether medical adherence in the first year and the first two years predisposed to medical adherence in the fifth and 10th year from index date. Cost analyses included calculations of average costs per patient within the fifth and within the 10th year of follow-up based on cost estimates for all patients with available data in the respective registers. Linear regression models were used to calculate beta estimates and 95% CI for associations between medical adherence and long-term public costs. The analyses were adjusted for age, sex, and CCI score. Finally, we examined the robustness of the results by conducting a sensitivity analysis in which we examined potential selection bias arising from selection into the study.

RESULTS

Within the first year from index date, 54.7% of the study participants were adherent to their glaucoma treatment, whereas 51.8% glaucoma patients were adherent in the first two years from index date (table 1). High adherence to medical treatment differed from poor adherence in terms of highly adherent patients often being of older age (>70% was above 60 years), being women (60.6%), and having lower CCI score. The same patterns were observed in the regression model applying both adherence in the first year and in the first two years as predictors of general adherence, also subsequently to simultaneously adjustment for the included covariates (table 2). We further observed that occurrence of specific comorbidities was negatively associated with high adherence. Specifically, glaucoma patients with diseases of the eye and adnexa, diseases of the musculoskeletal system and connective tissue, and ischaemic heart diseases were less likely to be adherent to glaucoma treatment compared with glaucoma patients without the presence of these comorbidities (table 3).

Both first year adherence and adherence in the first two years were strongly associated with being adherent within the fifth and 10th year from index date (table 4). Accordingly, we observed the most profound association estimates when applying adherence over the first two years, where the OR for fifth year adherence was 6.47 (95% CI: 6.10 to 6.86), and slightly lower for the 10th year adherence. These results underpinned that adherence in the first years of treatment, particularly consistent adherence over the first 2 years, was a strong predictor for general long-term adherence behaviour.

Healthcare expenses

Poor adherence in the first years of glaucoma treatment was associated with increased healthcare costs in relation to hospital contacts after both 5 and 10 years from index date. We observed that patients having poor adherence in the first two years had an average increase in costs in relation to hospital contacts of 190.77 Euro per patient

Table 1 Patient characteristics according to adherence in the first year and the first two years of treatment

	First year adherence (n=30 100)			First two years adherence (n=28 615)		
	Poorly adherent, n(%)	Highly adherent, n(%)	P (chi ² test)	Poorly adherent, n(%)	Highly adherent, n(%)	P (chi ² test)
Total	13 633 (45.3)	16 467 (54.7)		13 792 (48.2)	14 823 (51.8)	
Sex			<0.001			<0.001
Women	7268 (53.3)	9983 (60.6)		7394 (53.6)	9051 (61.1)	
Men	6365 (46.7)	6484 (39.4)		6398 (46.4)	5772 (38.9)	
Age			<0.001			<0.001
<40 years	880 (5.8)	487 (2.6)		875 (5.7)	342 (2.0)	
40–49 years	1411 (9.7)	1190 (6.5)		1447 (9.8)	968 (5.8)	
50–59 years	2861 (19.3)	3165 (17.6)		2918 (19.7)	2760 (16.9)	
60–69 years	4102 (29.8)	5392 (32.1)		4169 (29.8)	4972 (32.8)	
70–79 years	3347 (25.8)	4931 (31.1)		3366 (25.7)	4588 (32.2)	
≥80 years	1032 (9.5)	1302 (10.1)		1017 (9.3)	1193 (10.3)	
CCI score			<0.001			<0.001
CCI=0	10 768 (79.0)	13 323 (80.9)		10 917 (79.2)	12 019 (81.1)	
CCI=1–2	2304 (16.9)	2650 (16.1)		2320 (16.8)	2362 (16.0)	
CCI≥3	561 (4.1)	494 (3.0)		555 (4.0)	442 (3.0)	

CCI, Charlson Comorbidity Index.

within the fifth year and of 205.16 Euro per patient within the 10th year from index date relative to patients with high adherence (table 5, online supplemental file 2a and 2b). This association was statistically significant,

also after adjustment for age, sex, and CCI score. Societal costs in relation to glaucoma-related medicines were higher for the patients with high adherence; however, the cost difference between the group of poor adherence

Table 2 Multiple logistic regression model of the association between sex, age, and CCI score, respectively, and early adherence in the first year and in the first two years of treatment

Characteristics	First year adherence (n=30 100)		First two years adherence (n=28 615)	
	Crude* (OR 95% CI)	Adjusted*† (OR 95% CI)	Crude* (OR 95% CI)	Adjusted*† (OR 95% CI)
Sex				
Women	Ref.	Ref.	Ref.	Ref.
Men	0.74 (0.71–0.78)	0.77 (0.73–0.81)	0.74 (0.70–0.77)	0.77 (0.73–0.81)
Age				
<40 years	Ref.	Ref.	Ref.	Ref.
40–49 years	1.50 (1.30–1.73)	1.50 (1.30–1.73)	1.70 (1.45–1.99)	1.70 (1.45–2.00)
50–59 years	2.05 (1.81–2.34)	2.03 (1.79–2.31)	2.47 (2.14–2.86)	2.45 (2.12–2.83)
60–69 years	2.42 (2.14–2.74)	2.40 (2.12–2.72)	3.16 (2.75–3.64)	3.14 (2.74–3.62)
70–79 years	2.71 (2.39–3.07)	2.64 (2.33–2.99)	3.59 (3.12–4.13)	3.50 (3.05–4.04)
≥80 years	2.39 (2.09–2.75)	2.27 (1.98–2.61)	3.18 (2.73–3.70)	3.02 (2.59–3.52)
CCI score				
CCI=0	Ref.	Ref.	Ref.	Ref.
CCI=1–2	0.93 (0.87–0.99)	0.90 (0.84–0.95)	0.93 (0.87–0.99)	0.88 (0.83–0.94)
CCI≥3	0.71 (0.63–0.81)	0.71 (0.63–0.80)	0.72 (0.64–0.82)	0.72 (0.63–0.82)

*In all analyses, poor adherence was considered the reference group.

†Simultaneously adjusted for the remaining variables in the model.

CCI, Charlson Comorbidity Index.

Table 3 Distribution of comorbidities prior to index date according to adherence status in the first year and in the first two years of treatment

Comorbidities	First year adherence (n=30 100)			First two years adherence ^a (n=28 615)		
	Poorly adherent, n(%)	Highly adherent, n(%)	P (chi ² test)	Poorly adherent, n(%)	Highly adherent, n(%)	P (chi ² test)
Diseases of the eye and adnexa*			<0.001			<0.001
No	9594 (70.4)	13 485 (81.9)	...	9898 (71.8)	12 313 (83.1)	...
Yes	4039 (29.6)	2982 (18.1)	...	3894 (28.2)	2510 (16.9)	...
Visual disturbances and blindness†			<0.001			<0.001
No	13 436 (98.6)	16 303 (99.0)	...	13 594 (98.6)	14 685 (99.1)	...
Yes	197 (1.4)	164 (1.0)	...	198 (1.4)	138 (0.9)	...
Diseases of musculoskeletal system and connective tissue‡			<0.05			<0.001
No	10 601 (77.8)	13 040 (79.2)	...	10 710 (77.7)	11 792 (79.6)	...
Yes	3032 (22.2)	3427 (20.8)	...	3082 (22.3)	3031 (20.4)	...
Diabetes§			<0.05			<0.001
No	12 980 (95.2)	15 806 (96.0)	...	13 119 (95.1)	14 251 (96.1)	...
Yes	653 (4.8)	661 (4.0)	...	673 (4.9)	572 (3.9)	...
Metabolic diseases¶			0.685			0.088
No	13 255 (97.2)	16 023 (97.3)	...	13 399 (97.2)	14 449 (97.5)	...
Yes	378 (2.8)	444 (2.7)	...	393 (2.8)	374 (2.5)	...
Hypertension**			0.637			0.754
No	12 641 (92.7)	15 292 (92.9)	...	12 785 (92.7)	13 755 (92.8)	...
Yes	992 (7.3)	1175 (7.1)	...	1007 (7.3)	1068 (7.2)	...
Ischaemic heart diseases††			<0.05			<0.001
No	12 657 (92.8)	15 443 (93.8)	...	12 799 (92.8)	13 916 (93.9)	...
Yes	976 (7.2)	1024 (6.2)	...	993 (7.2)	907 (6.1)	...
Diseases of the nervous system‡‡			<0.05			<0.001
No	12 729 (93.4)	15 502 (94.1)	...	12 785 (92.7)	13 755 (92.8)	...
Yes	904 (6.6)	965 (5.9)	...	1007 (7.3)	1068 (7.2)	...
Other§§			<0.001			<0.001
No	4901 (35.9)	6499 (39.5)	...	5001 (36.3)	5918 (39.9)	...
Yes	8732 (64.1)	9968 (60.5)	...	8791 (63.7)	8905 (60.1)	...

ICD-10: H00-H59*, excl. H40.1 and H53*-H54*
 †ICD-10: H53*-H54*
 ‡ICD-10: M00*-M99*
 §ICD-10: E10*-E14*
 ¶ICD-10: E00*-E07* and E15*-E16*
 **ICD-10: I10*-I15*
 ††ICD-10: I20-I25
 ‡‡ICD-10: G00-G99
 §§All other ICD-10 codes

Table 4 Association between early adherence and adherence after 5 and 10 years of treatment

Adherence	No. of cases§	Fifth year adherence (n=23472)		No. of cases¶	Tenth year adherence (n=19968)	
		Crude† (OR 95% CI)	Adjusted† (OR 95% CI)		Crude† (OR 95% CI)	Adjusted†† (OR 95% CI)
First year adherence*						
Poorly adherent	3382	Ref.	Ref.	3573	Ref.	Ref.
Highly adherent	11 003	4.66 (4.40–4.93)	4.55 (4.30–4.82)	9744	2.86 (2.69–3.04)	2.81 (2.64–2.99)
First two years adherence†						
Poorly adherent	3009	Ref.	Ref.	3729	Ref.	Ref.
Highly adherent	10 152	6.67 (6.29–7.07)	6.47 (6.10–6.86)	9588	3.43 (3.27–3.65)	3.36 (3.16–3.57)

*First year adherence and adherence in the first two years were tested separately.
†In all analyses, poor adherence was considered the reference group.
‡The analyses were adjusted for age, sex, and CCI score.
§Cases were defined as individuals who were adherent in the fifth year.
¶Cases were defined as individuals who were adherent in the 10th year.

and good adherence decreased by half from the fifth to the 10th year.

Selection of study participants

Study participants were a selected sample (29.9%) of the background population (ie, all patients with glaucoma in the respective period) due to the inclusion criteria of being alive for 10 years from index date. The study participants were younger, more likely to be women, and had lower CCI score compared with the excluded population (online supplemental file 3). Furthermore, they were less likely to be adherent in the first year of treatment.

DISCUSSION

This register-based study following around 30 000 glaucoma patients over a period of 10 years between 2000 and 2018 demonstrated that increasing age, being a woman, and low

CCI-score predisposed to being medical adherent to glaucoma treatment. Being adherent in the first and the first two years, respectively, increased the probability of being adherent after 5 and 10 years from index date, with the most profound association identified for those being adherent over the first two years. Finally, poor adherence was associated with increased healthcare costs in relation to hospital contacts, whereas high adherence was associated with higher costs to glaucoma-related medical treatment.

Around 60% of the highly adherent glaucoma patients were women and women in general were more likely to be adherent than men. These findings were in line with previous findings indicating a slight predominance of women.^{44 45} We further demonstrated that the vast majority of glaucoma patients were more than 60 years old (approx. 65%), which

Table 5 Long-term public healthcare costs in Euro in the fifth and 10th year from index date according to medication adherence to glaucoma treatment in the first year and in the first 2 years

Healthcare costs*	Adherence†	5 years follow-up		10 years follow-up	
		Estimate (95% CI)†‡	P	Estimate (95% CI)†‡	P
Hospital contacts	First year adherence				
	Poorly adherent	Ref.		Ref.	
	Highly adherent	-106.57 (-160.25; -52.89)	<0.001	-117.76 (-171.46; -64.06)	<0.001
Glaucoma-related medicines	Poorly adherent	Ref.		Ref.	
	Highly adherent	140.50 (135.61; 145.40)	<0.001	77.59 (73.25; 81.94)	<0.001
	First two years adherence				
Hospital contacts	Poorly adherent	Ref.		Ref.	
	Highly adherent	-190.77 (-245.95; -135.59)	<0.001	-205.16 (-260.36; -149.96)	<0.001
	Glaucoma-related medicines				
Hospital contacts	Poorly adherent	Ref.		Ref.	
	Highly adherent	164.26 (159.30; 169.22)	<0.001	92.67 (88.19; 97.15)	<0.001

*The analyses of hospital contacts and glaucoma-related medicines were tested separately, and adjusted for age, sex, and CCI.

†In all analyses, poor adherence was considered the reference group.

‡Beta estimates denoting differences between average costs in the sample (poor adherence vs adherence).

likewise corresponds to previous findings.^{44,45} Despite similar age distributions across the studies, an Italian study found a significantly higher average CCI score in their sample compared with the CCI score identified in this study.⁴⁴ This discrepancy may be due to heterogeneity in the study designs but may also be due to national differences in disease occurrence and registration practices. Our findings further suggested that early adherence patterns were closely associated with adherence patterns in the longer term, and thus, early adherence behaviour may be a predictor for future adherence behaviour. This was supported by findings from a cohort study from the USA in which adherence patterns in the first year of treatment persisted in the subsequent three years of treatment.²⁰

In general, poor adherence was related to younger age, men, and higher CCI score compared with the highly adherent patients. Glaucoma is often asymptomatic until advanced stages of the disease, and therefore, the consequences of not treating glaucoma may feel intangible.^{10 18–20} When looking at the patients who have poor adherence to medical treatment, one may wonder if the patients who have poor adherence are the less severe glaucoma cases, if they have been diagnosed at an earlier stage of the disease, or if their glaucoma disease is less progressive when initiating treatment compared with the highly adherent patients. In contrast, patients with more advanced glaucoma may be more motivated to be adherent since they may have already experienced negative visual symptoms from glaucoma. These speculations were supported in a cohort study demonstrating that patients with highest disease severity had the highest medication adherence, and that patients with greater adherence to glaucoma medication seem to have a slower deterioration in visual function over time compared with those with poor adherence.³⁴ In accordance with this, we observed a reduction over time in the differences in costs to glaucoma-related medication between the patients with poor and high adherence. This may be explained by the poorly adherent group over time starting to experience an increase in disease severity (negative visual symptoms) and then may need more glaucoma medication or become more compliant which will increase their yearly cost for glaucoma-related medicines over time. However, it may also be explained by decreasing medication prices over time resulting in a lower absolute cost differences.

Finally, since some patients progress faster than others, the annual resource use would not only depend on disease severity but also on the progression rate.¹⁸ A Danish study of glaucoma costs demonstrated that glaucoma-related healthcare costs increased with the number of treatment changes indicating that the more intense treatment, the higher healthcare costs.⁴⁶ Our findings suggested that patients with poor adherence in general were more costly in the longer perspective for the society in relation to overall

healthcare services in the secondary sector compared with patients with high adherence, also after conditioning on age, sex, and comorbidities. This may reflect increased costs in relation to hospital contacts directly associated with glaucoma but also arising from glaucoma for example accidents, fractures, and concussions due to the increased risk of falling and unsafe driving among glaucoma patients, particularly among those with severe visual loss.⁴⁷

Strengths and limitations

A strength of this study is that the applied data were based on national registers covering the full Danish population in which all Danish patients registered with at least one relevant ICD-10 diagnosis code of glaucoma or having at least three redemptions of glaucoma medicines in the period 2000–2009 were identified. Further, it is general practice in Denmark to record activities of healthcare services in the central administrative databases, why the registers have high validity and completeness.⁴⁶ Another strength is that Danish data are available historically which ensured that all study participants were incident glaucoma patients, which we followed in relation to adherence patterns of the glaucoma patients and public costs over a period of 10 years.

There are, however, limitations to this study that need awareness in the interpretation of results. There is a risk of misclassification, as calculation of adherence was based on data of redeemed prescriptions, and we assumed that each patient was recommended to take one DDD of redeemed medication per day. However, the recommended dose may vary for each patient as may patients who received laser treatment or surgery not have needed eye drops for a certain period within a year, which may impact the classification of adherence. Furthermore, it is well-known that many glaucoma patients are struggling with instilling the eye drops properly,²⁰ and for the calculations of adherence based on registry data, it is not possible to identify whether the patients were using the medication and whether the patient instilled the medication correctly. We do believe, however, that this potential misclassification is non-differential, and had no essential impact on the direction of effects. Furthermore, socioeconomic status is assumed to influence the likelihood of high adherence.²⁵ For some of the analyses in this study, socioeconomic status may work as a confounder, and thus the estimates may be slightly overestimated since information on socioeconomic status was not available in the data at hand for this study. The same applies for other sociodemographic variables for example, civil status and residence. Finally, the study design forced all included patients to be followed for 10 years. In the selection process, we excluded individuals that were not alive in a period of 10 years from the time of glaucoma diagnosis, and thereby, we excluded the oldest people in the population, mostly men, and those with a high CCI score. Thus, women and individuals of younger age (ie, those being most likely to be adherent) were overrepresented in our



sample. This selection may have introduced immortal time bias. Even though this might have impacted the results and that the proportion of poor adherent patients can be both overestimated and underestimated, we expect that the impact may profoundly be an issue in the oldest part of the population with the highest CCI score. Despite the age distribution in our study population is corresponding to findings from previous studies on glaucoma patients,^{44 45} this selection may thus have diluted the estimates against the null. Overall, balancing the advantages of using national patient data to estimate predictors, investigating adherence in a long-term perspective, and estimating the public economic burden of medical adherence among glaucoma patients over time, we believe the strengths of being able to include data on the entire Danish population and follow over 30 000 glaucoma patients for 10 years overseed the limitations of this work.

Conclusion

Increasing age, female sex, and low comorbidity score are correlated with high adherence to medical treatment for glaucoma. High adherence in the first years of glaucoma treatment, particularly over the first two years, may be a good predictor for persistent adherence in a five-year and 10-year perspective. This finding may be of importance for physicians informing of the clinical value of adherence in the first and the first two years of treatment and may lead physicians to investigate other IOP-lowering options sooner in patients with poor adherence, particularly among those that are progressing at unsafe rates. Finally, in the long term, patients with poor adherence are overall more expensive to society in terms of hospital contacts. Future studies exploring the direction of the association between severity and progression of glaucoma disease and poor adherence seem essential for enriching the interpretation of the findings from this study. The understanding of the interplay is likewise highly relevant for enhancing the glaucoma treatment, and thus, seeking to prevent the negative consequences of poor medical adherence to glaucoma treatment.

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Competing interests 'Yes, there are competing interests for one or more authors and I have provided a Competing Interests statement in my manuscript and in the box below'

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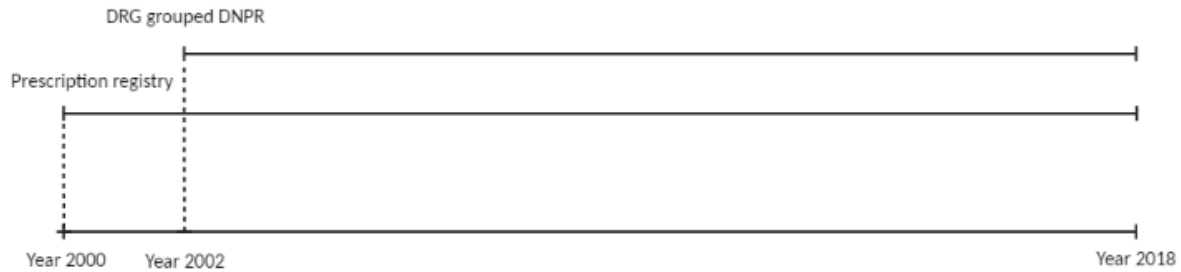
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Title: Predictors and long-term patterns of medication adherence to glaucoma treatment in Denmark – A observational register study of 30,100 Danish patients with glaucoma

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Supplementary File 1. Timeline for subpopulations in analysis of healthcare expenses

Supplementary File 2a. Mean annual healthcare costs at year 5 and 10 from index date applying first year adherence		
	Hospital contacts	Redeemed glaucoma- related medicines
Fifth year from index date		
Poorly adherent	EUR 3,195.80	EUR 111.29
Highly adherent	EUR 3,042.11	EUR 262.92
Tenth year from index date		
Poorly adherent	EUR 3,037.87	EUR 80.01
Highly adherent	EUR 3,198.89	EUR 164.70

Supplementary File 2b. Mean annual healthcare costs at year 5 and 10 from index date applying first-two years adherence		
	Hospital contacts	Redeemed glaucoma- related medicines
Fifth year from index date		
Poorly adherent	EUR 3,223.17	EUR 103.93
Highly adherent	EUR 2,994.80	EUR 288.05
Tenth year from index date		
Poorly adherent	EUR 3,226.90	EUR 75.32
Highly adherent	EUR 2,989.04	EUR 179.37

Supplementary File 3. Loss-to-follow-up analysis (N=100,536)			
	Included population (Alive 10 years from index date) N (%)	Excluded population (Not alive 10 years from index date) N (%)	P (chi ² -test)
Total	30,100 (29.9)	70,436 (70.1)	
Age at index			< 0.001
<40 yrs.	1,367 (4.7)	2,172 (3.0)	
40-49 yrs.	2,601 (8.7)	3,501 (4.9)	
50-59 yrs.	6,026 (20.1)	8,235 (11.5)	
60-69 yrs.	9,494 (31.4)	18,372 (26.1)	
70-79 yrs.	8,278 (27.4)	23,182 (33.1)	
≥80 yrs.	2,334 (7.7)	14,974 (21.5)	
Sex			< 0.001
Female	17,251 (57.3)	37,425 (53.1)	
Male	12,849 (42.7)	33,011 (46.9)	
CCI-score			< 0.001
CCI = 0	24,091 (79.9)	48,010 (68.0)	
CCI = 1-2	4,954 (16.5)	16,785 (23.9)	
CCI ≥3	1,055 (3.6)	5,641 (8.1)	
Adherence (first-year)			< 0.001
Poorly adherent	13,633 (47.0)	30,767 (42.9)	
Highly adherent	16,467 (53.0)	39,669 (57.1)	