Antihypertensive Medication Postpones the Onset of Glaucoma
Evidence From a Nationwide Study

Anna Horwitz, Marc Klemp, Jørgen Jeppesen, James C. Tsai, Christian Torp-Pedersen, Miriam Kolko

Abstract—The aim was to investigate the impact of antihypertensive medication on the onset of glaucoma. Data from the complete Danish population between 40 and 95 years of age were used in the period from 1996 to 2012, covering >2.6 million individuals. The National Danish Registry of Medicinal Products Statistics was used to identify all claimed prescriptions for glaucoma medication and antihypertensive drugs. We first investigated basic correlations in the data and found that patients treated with antihypertensive medication, at any time during the study period, had a significantly higher overall relative risk (RR) of glaucoma, even when controlling for age and sex (with a RR of 1.31 and \( P<0.0001 \)). Furthermore, our data confirm the well-known positive association between age and glaucoma. To investigate the causal effect of antihypertensive treatment on the onset of treatment for glaucoma, we used a regression discontinuity study design. This analysis provides our main finding, namely that prescription of antihypertensive medication leads to a significant reduction in the risk of developing glaucoma. Therefore, although hypertension—as indicated by the use of antihypertensive medication—is positively correlated with glaucoma, our study indicates that antihypertensive medication itself may have a preventive effect on the development of glaucoma. (Hypertension. 2017;69:202-210. DOI: 10.1161/HYPERTENSIONAHA.116.08068.) ● Online Data Supplement

Key Words: epidemiology ■ glaucoma ■ hypertension ■ registries ■ risk

Glaucoma is the second most common irreversible cause of blindness worldwide.\(^1\) It is becoming increasingly important in the context of an aging world population.\(^1\)\(^,\)\(^2\) It possesses a considerable challenge to public health because blindness and visual impairment is costly and have a huge impact on life quality.\(^3\)

Raised intraocular pressure (IOP) remains the only successful treatable factor to reduce the progression of glaucoma. Yet, glaucoma is multifactorial, and the understanding of the pathology is incomplete. More than 2 decades ago, the first study to suggest that blood pressure (BP) should be considered in glaucoma treatment was published.\(^4\) Since then, the impact of BP on glaucoma has received greater attention as more evidence has mounted.\(^5\)\(^-\)\(^7\) Despite the increasing evidence of an association between BP and glaucoma, the exact relationship is complex. In this matter, epidemiological and case–control studies have shown diverse results, and some studies have presented evidence of a correlation between high BP and glaucoma,\(^5\)\(^-\)\(^11\) whereas other studies have linked glaucoma and low-tension glaucoma with low BP.\(^12\)\(^-\)\(^17\) The controversies have been discussed and related to the complexity of BP not only influencing IOP and ocular perfusion pressure, but also increasing the risk of compromised peripheral vascular capacity and a dysfunctional autoregulation.\(^5\)\(^,\)\(^7\)\(^-\)\(^9\) Recognized high BP is treated with many different antihypertensive medications, and growing evidence acknowledges that such treatment is associated with glaucoma.\(^20\)\(^-\)\(^22\) In this matter, antihypertensive medication may conflict with ocular perfusion and autoregulation.\(^20\)\(^,\)\(^23\) Although studies have shown a correlation between antihypertensive treatment and glaucoma, these studies have mostly been trials in small numbers of patients with minimal follow-up periods.\(^1\)\(^,\)\(^14\)\(^,\)\(^24\) Moreover, to the best of our knowledge, no previous study has benefited from a complete data sample from an entire population nor—importantly—estimated the causal effect of antihypertensive treatment on the risk of developing glaucoma.

The main outcome in our study is the treatment for glaucoma. We hypothesized, before embarking on the empirical analysis, that treatment with antihypertensive medication could have an ambiguous effect on the development...
of glaucoma. On the one hand, treatment with antihypertensive medication indicates inexcipient elevated systemic BP, which might affect the IOP and the ocular perfusion pressure, and thereby ultimately the development of glaucoma. On the other hand, treatment with antihypertensive medication could counteract this possible mechanism and, therefore, decrease the likelihood of developing glaucoma.

To estimate the causal effect of antihypertensive medications on the onset of glaucoma, we perform a regression discontinuity analysis. Regression discontinuity design was first introduced in the educational econometrics literature in the 1960s but has been underused in medicine, epidemiology, and public health.\textsuperscript{25} If the assumptions of the method are met, it can estimate the local average treatment effect.

Regression discontinuity analysis is a rigorous quasi-experimental method for estimating causal effects of treatments on outcomes, in cases where individuals are quasi-randomly treated.\textsuperscript{25} We argue that because antihypertensive treatment is not presently used against glaucoma, a set of individuals that are about to be treated with antihypertensive treatment and a set of individuals that have just started antihypertensive treatment provide useful comparison groups to estimate the causal effect of antihypertensive treatment on glaucoma. In particular, we assume that individuals who are just about to become treated with antihypertensive medication and individuals who have just initiated treatment do not differ substantially with respect to their likelihood of developing glaucoma except with respect to the effect of the antihypertensive treatment itself.

On the basis of regression discontinuity design, the purpose of this study was to investigate the causal effect of antihypertensive treatment on the development of glaucoma in the Danish population throughout a 16-year period. Furthermore, the aim was to explore the overall risk of glaucoma in patients treated with antihypertensive medication.

Methods

Population

The study population comprised all individuals living in Denmark in the period from 1996 to 2012, amounting to 7,585,176 individuals. Data from the National Danish Civil Registration System contain information of all individuals born in, or migrating to, Denmark.\textsuperscript{26} We restrict the sample to individuals aged 40 to 95 years in the period amounting to 2,689,434 individuals. The exclusion of individuals aged <40 years is designed to focus on age-dependent, rather than congenital, disorders.

The data contain dates of redemption of antihypertensive or antiglaucomatous medication (if any) for each individual. For the regression discontinuity analysis, we transform the data to a yearly panel, generating dummies that indicate for each individual if he/she had an onset of either disease (as defined below) in a given or a previous year.

Our operating definitions of hypertension and glaucoma are based on redeemed prescriptions. This is important because it implies that we measure 2 things at once for either disease: whether individuals have the disease and whether they are being treated for the disease. This dual measurement is crucial for the interpretation of our statistical findings, and we pay special attention to this throughout the article.

All pharmacies in Denmark are required by the government-financed Danish healthcare system to register all redeemed prescriptions at the individual level by the Danish Personal Identification number (the so-called CPR-number). We identified individuals on antihypertensive therapy through the National Danish Registry of Medicinal Products Statistics. This registry records information about all prescribed drugs dispensed at all Danish pharmacies. Drugs administered during a hospital admission are not included, but immediately on discharge, patients purchase their own medication in Denmark. Our data contain the dates of all redeemed antihypertensive treatments and all antiglaucomatous treatments. All patients who redeemed prescribed antihypertensive or antiglaucomatous drugs before 1995 were excluded from the analysis.

Rationale for Definitions

Hypertension and glaucoma are most often managed and diagnosed by patients’ primary physicians and an out-hospital specialist in ophthalmology, respectively. Therefore, the in-hospital ICD-10 (International Classification of Diseases–10) diagnoses for essential hypertension and glaucoma are not relevant. Instead, we identify the population of hypertensive patients and glaucoma patients using the National Danish Registry of Medicinal Products Statistics. This means that we can precisely identify patients who were diagnosed with hypertension and glaucoma and who redeemed their prescription. Furthermore, it means that it is possible to identify the time of their diagnosis.

Hypertensive patients were identified using a validated algorithm based on the use of at least 2 classes of antihypertensive drugs. This algorithm has been shown to have a tremendous sensitivity of 94.7% and a positive predictive value of 80.0%,\textsuperscript{27} meaning that our validation algorithm precisely identifies individuals with hypertension.

Because we are interested in estimating the effect of treatment with antihypertensive medication in a regression discontinuity framework, it is important that the definition of our dependent variable enables a sensitive detection of short-run changes. Our glaucoma treatment variable is, therefore, chosen to be defined by the redemption of 1 class of medication only, thereby enabling us to capture the very onset of the use of antiglaucomatous drugs.

It should be noted that antiglaucomatous drugs can be used for other eye conditions that cause increased IOP. In this matter, the most apparent competing cause would be after cataract surgery. However, unless these other potential uses of antiglaucomatous drugs are not affected by antihypertensive medication, these alternative uses of antiglaucomatous drugs will not bias our estimate of the causal effect of antihypertensive treatment. We think that it is plausible to assume that the amount of antiglaucomatous drugs used to treat other eye conditions is not affected by starting treatment with antihypertensive medication, meaning that these other uses will not act as a confounding factor. For this reason, and in light of our interest in investigating the causal effect of antihypertensive drugs on the risk of need for treatment with antiglaucomatous drugs, we are convinced that the benefits of our glaucoma definition outweigh the downsides.

The Danish Civil Registration System contains information about dates of birth and death of all Danish citizens since 1972.\textsuperscript{26} The Danish Registry of Medicinal Products Statistics contains data on all prescriptions dispensed in Denmark since 1995, including information about size of doses, quantity dispensed, and dispensing date. Prescriptions are classified according to the Anatomical Therapeutic Chemical system.\textsuperscript{28} Because of the start phase of the nationwide registration, 1995 is thought to be a mixed year for which data on new and old prescriptions are combined. To be sure that the data only contain new prescriptions, we, therefore, exclude all prescriptions registered in the data for dates before January 1, 1996.

Tests of the assumptions of the regression discontinuity design and drug definitions can be found in the Appendix in the online-only Data Supplement.

Statistics

To describe the evolution of the incidence of hypertension and glaucoma, the incidence rates were calculated in 5-year age strata as a function of time. Furthermore, RRs estimates were based on the Poisson distribution with a log link function in investigating the associations between antihypertensive treatments and the risk of
development of glaucoma, controlling for a range of potentially confounding factors (Table 1).

Finally, the effect of the onset of hypertension on the risk of developing glaucoma was investigated with a regression discontinuity study design, accounting for individual fixed effects and potentially confounding factors. In particular, linear and logistic regression models were used to investigate the changing risk of developing glaucoma in the few years following the onset of treatment against hypertension. The validity of the data and study design was assessed by inspecting the distribution of the duration to the onset of hypertension and testing for an effect at an artificial treatment time preceding the actual one (a so-called placebo check).

All statistics were performed in SAS 9.4. Heteroscedasticity-robust SEs were used in the Poisson regression model, and cluster-robust SEs, clustered on the individual level, were used in the regression discontinuity models. A significance level of 0.05 was used, meaning that estimated coefficients with $P$ values <0.05 were considered statistically significant.

The assignment variable in our study measures time (ie, the year of onset of hypertension) and thereby represents a continuous variable. Furthermore, assuming that the time between redemption of a prescription and the onset of treatment is negligible, a sharp regression discontinuity was used.

**Regression Discontinuity Analysis**

The simplest and most transparent regression discontinuity design is implemented with regression models that allow for a jump at the cutoff and different slopes on either side a specified cutoff point:

$$\text{logit} \left( y_{i,t} \right) = \beta_0 + \beta_1 T_{i,t} + \beta_2 x_{i,t} + \beta_3 T_{i,t}x_{i,t},$$

where the variable $y_{i,t}$ is a dummy variable that indicates if individual $i$ has glaucoma at time $t$, the variable $T_{i,t}$ is a dummy variable (referred to as the assignment variable) that indicates if individual $i$ has hypertension at time $t$, the variable $x_{i,t}$ is a continuous variable (referred to as the assignment variable) capturing the time to the onset of hypertension of individual $i$ at time $t$. The coefficient $\beta_1$ captures a potential jump in glaucoma at the onset of hypertension. To check the robustness of our results, we will specify models that allow this potential jump to be nonzero and models that restrict this potential jump to be zero. The coefficient $\beta_3$ captures the relation between glaucoma and time, that is, the trend in glaucoma prevalence. The coefficient $\beta_0$, $\beta_1$, and $\beta_3$ are our main parameter of interest. It captures the potential change in the relation between glaucoma and time that may occur at the onset of hypertension. If our estimate of $\beta_0$ is different from zero, it indicates that the onset of hypertension (and the associated onset of antihypertensive treatment) has had an effect on the risk of developing glaucoma. In particular, if our estimate of $\beta_1$ is negative, it indicates that treatment with antihypertensive medication reduces the risk of developing glaucoma.

In the baseline analysis, we estimate the model with logistic regression, reflecting the binary nature of the outcome variable. Furthermore, we investigate the robustness of our conclusions with respect to alternative estimation techniques by estimating similar linear probability models with ordinary least squares. Finally, in the linear model, we are also able to account for between-individual heterogeneity by estimating fixed effects models accounting for individual fixed effects.

Definitions of the terms incidence and RR can be found in the Appendix.

**Ethics**

The Danish Data Protection Agency approved the study (2007-58-0015, int. ref: GEH-2010-001). Retrospective register-based studies do not require ethical approval in Denmark.

**Results**

Before turning to the regression analysis results, we present some descriptive statistics. Within the 16-year follow-up, a total of 739,494 patients were treated with antihypertensive drugs out of a total number of individuals of 7,585,176. The average age at onset for hypertension was 60.3 years (range: 0–109 years). A total of 133,982 incident glaucoma patients were identified in the same period of whom 115,617 patients were between 40 and 95 years old (Figure 1). In the group of individuals treated with antihypertensive medication, 5.8% initiated treatment with glaucoma medication throughout the study period. In comparison, 1.3% of patients without hypertension were prescribed with glaucoma medication within the period. Furthermore, 32.1% of patients with glaucoma were prescribed with antihypertensive medication within the period.

The incidence of glaucoma and hypertension in the Danish population during the period from 1996 to 2012 is depicted in Figure 2. There is a tendency to a decrease in new glaucoma cases per year for the older cohorts and a small increase for the younger cohorts, which forms a greater proportion of the total population. The incidence of hypertension seem to have increased from 1996 and until around the middle of the 2000s and to have decreased thereafter.

The rate of glaucoma is 0.81 cases per 100 person-years in the set of individuals treated with antihypertensive drugs, which is substantially larger than the corresponding rate of 0.19 cases per 100 persons-years in the set of individuals who were not treated with antihypertensive drugs.

These findings indicate an association between hypertension and glaucoma and, in particular, an over-representation of glaucoma among individuals with hypertension. However, a common association with age or other confounding factors may simply cause this association. In particular, the risks of developing either disease increase with age (Figure S1),

<table>
<thead>
<tr>
<th>Table 1. Poisson Regression Analysis</th>
<th>Relative Risk Estimates for Glaucoma (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Explanatory Variable</strong></td>
<td>(1)</td>
</tr>
<tr>
<td>Anti-HT drug, ref. no anti-HT drug</td>
<td>4.24* (4.19–4.29)</td>
</tr>
<tr>
<td>Female</td>
<td>0.82* (0.81–0.83)</td>
</tr>
<tr>
<td>5-year-age group dummies</td>
<td>No</td>
</tr>
<tr>
<td>Calendar-year dummies</td>
<td>No</td>
</tr>
</tbody>
</table>

Relative risk for developing glaucoma in patients treated with antihypertensive drugs in the Danish population (1996–2012). The model controls for age fixed effects (in columns 3 and 4), as well as calendar-year fixed effects (in column 5). The coefficients on these fixed factors are omitted. The numbers in parentheses at the top indicate the column numbers. CI indicates confidence interval; and HT, hypertensive.

*P < 0.0001.
which could potentially entirely explain their correlation. Furthermore, if one sex is more likely to develop both diseases, such a sex-related fixed effects may generate the correlation. In addition, there may be year-specific fixed factors, such as changes in public health policies or medical innovations that may affect the treatment of both diseases and that could, therefore, also act as confounding factors that generate a correlation between the diseases. Therefore, the next section further investigates the association while accounting for these potentially confounding factors.

**Poisson Regression**

To exclude the possibility that increased incidence of glaucoma among patients treated with antihypertensive medication is caused by a common association with age or other confounding factors, we implemented a multivariate Poisson regression model. Table 1 presents a series of Poisson regression models accounting for various sets of potential covariates, namely sex, age, and calendar-year fixed effects. We use the sample of individuals aged 40 to 95 years (Figure 1). The Poisson regression models estimate the RR for developing glaucoma in patients treated with antihypertensive drugs in the Danish population in the period from 1996 to 2012. Column 1 presents the unconditional association between hypertension and glaucoma. It establishes that patients treated with antihypertensive drugs had a significantly higher risk of glaucoma compared with individuals who never redeemed prescriptions of antihypertensive drugs (RR=4.24; *P*<0.0001). The model underlying column 2 accounts for the sex of the individuals and establishes that the RR of glaucoma in hypertensive individuals is still above unity when accounting for sex (RR=4.20; *P*<0.0001) and that there is a significantly lower risk of glaucoma in men (RR=0.82; *P*<0.0001). Column 3 establishes that treatment with antihypertensive drugs is still associated with an increased risk of glaucoma while accounting for age (as 5-year age group fixed effects) in addition to sex (RR=2.27; *P*<0.0001). The coefficient on sex becomes closer to unity, and its significance drops. Finally, column 4 establishes that antihypertensive drugs are still significantly associated with glaucoma while accounting for calendar-year fixed effects in addition to the other control variables (RR=1.31; *P*<0.0001). Furthermore, the coefficient on sex again indicates a significantly higher risk of glaucoma in women, indicating that this increased likelihood cannot be entirely attributed to the control variables.

**Baseline Regression Discontinuity Analysis**

To motivate and introduce our regression discontinuity analysis, Figure 3 presents a nonparametric (LOESS [locally weighted scatterplot smoothing]) unconditional regression showing the association between time to the onset of antihypertensive medication and the development of glaucoma. The figure reveals a kink in the association at the onset of antihypertensive treatment. Our baseline regression discontinuity analysis is based on a logistic probability model with SE clustered on the individual level. The baseline specifications include data in the interval from 3 years before to 3 years after the onset of antihypertensive treatment.

The model includes a general time trend, which accounts for the fact that the risk of glaucoma is increasing with age (Figure S1; Figure 3) and in some specifications a dummy variable that captures a potential jump in the level of glaucoma development from the onset of antihypertensive treatment. The time trend variable is centered such that a value of zero represents the onset of antihypertensive treatment. Furthermore, the coefficient on sex again indicates a significantly higher risk of glaucoma in women, indicating that this increased likelihood cannot be entirely attributed to the control variables.
trend and the jump variable. The sign on the coefficient on this variable indicates the effect of the onset of antihypertensive treatment on the risk of the development of glaucoma. Table 2 establishes that there exists a negative causal effect of antihypertensive drugs on the risk of glaucoma, using data for the period 3 years before to 3 years after the onset of treatment with antihypertensive drugs (a total of 7 years of observation time). Before investigating the effect of antihypertensive treatment on the trend in glaucoma development, column 1 establishes that there is a positive trend in the development of glaucoma over time, reconfirming the insight from Figure S1 and Figure 3. Moving on to investigate how antihypertensive treatment affects this trend, column 2 establishes that the estimate of the coefficient of interest, the coefficient on the interaction term, is significantly negative, indicating that the trend in glaucoma development is significantly lowered by the onset of antihypertensive treatment. The size of the effect is substantial: the coefficient on the interaction term is, in absolute terms, 43% of the coefficient on the main trend variable, which can now be interpreted as the pretreatment trend. In other words, antihypertensive treatment reduces the risk of developing glaucoma by around 43% of the pretreatment trend. The change in the trend occurring at the onset of treatment with antihypertensive treatment correspond to the insight gained from Figure 3.

Column 3 investigates whether there is a jump in the level of glaucoma incidence appearing at the onset of antihypertensive medication. Although the interaction term remains significant, a significant jump is also observed. The models underlying columns 4 and 5 are similar to those in columns 2 and 3, respectively, except that they also adjust for sex. The estimates confirm the finding from Table 1, yielding a significantly negative partial association between glaucoma and being male (−0.17; *P* < 0.0001). Furthermore, the coefficient of interest—the interaction term—remains almost unchanged (especially when compared with the post-treatment trend) and highly significant in this specification. Furthermore, the models underlying columns 6 and 7 are similar to those of columns 4 and 5, except that they also account for age. The estimates establish that there is a positive effect of age at the beginning of the sample period (ie, year 1996) on the risk of developing glaucoma.

Table 2. Logistic Regression Models of Glaucoma Explained by the Number of Years Since the Onset of Hypertension With Clustered SEs on the Level of the Individual

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Coefficient Estimates for Glaucoma (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trend Break Break and Jump Break Break and Jump Break Break and Jump</td>
</tr>
<tr>
<td>Years since HT (ie, time trend)</td>
<td>0.11* (0.00) 0.14* (0.00) 0.14* (0.00) 0.14* (0.00) 0.14* (0.00) 0.10* (0.00) 0.10* (0.00)</td>
</tr>
<tr>
<td>Years since HT×HT (ie, break)</td>
<td>−0.06* (0.00) −0.07* (0.00) −0.06* (0.00) −0.07* (0.00) −0.05* (0.00) −0.05* (0.00)</td>
</tr>
<tr>
<td>HT (ie, jump)</td>
<td>0.01‡ (0.01)</td>
</tr>
<tr>
<td>Female</td>
<td>−0.17* (0.01)</td>
</tr>
<tr>
<td>Age</td>
<td>0.06* (0.00)</td>
</tr>
<tr>
<td>No. of observations</td>
<td>4179982 4179982 4179982 4179982 4179982 4179982 4179982</td>
</tr>
<tr>
<td>No. of individuals</td>
<td>700945 700945 700945 700945 700945 700945 700945</td>
</tr>
</tbody>
</table>

Data are shown for individuals aged 40 to 95 years in the 7-year period of 3 years before and after onset of treatment with antihypertensive medication (SEs are clustered on the individual level). The slope is smaller in the period after the onset of treatment with antihypertensive drugs. The numbers in parentheses at the top indicate the column numbers. HT indicates hypertensive.

*P* < 0.001. †*P* < 0.05. ‡*P* < 0.1.
glaucoma. The partial association related to being male is now less pronounced (−0.03; P = 0.053), indicating that the higher likelihood of glaucoma in women can be partly attributed to their higher longevity and, thus, higher representation among elderly. Furthermore, the coefficient of interest remains almost unchanged when compared with the post-treatment trend and highly significant. Finally, the jump variable is insignificant (column 7) indicating that antihypertensive medication affects only the trend of glaucoma incidence but not the level, when accounting for age and the other variables. In other words, antihypertensive medication seems to reduce the rate at which the risk of developing glaucoma increases over time but not the immediate risk per se.

Robustness analyses can be found in the Appendix (Tables S1 through S4). These analyses establish that the results are robust to accounting for alternative bandwidths and statistical analyses. Furthermore, they show that there is no break found when offsetting the hypertension time by 3 years.

We furthermore investigated whether the preventive effect of antihypertensive medication varied with the number of concomitant antihypertensive drug classes used (a measure of treatment intensity) and the differential effects of the various antihypertensive medications used. The findings can be found in Table 3.

The Table 3 shows that individuals treated with a higher number of different antihypertensive drugs obtain a larger degree of protection. This result further strengthens the validity of our findings. We interpret the fact that both the extensive and intensive margins point in the same direction as corroborating evidence.

Furthermore, the Table 3 shows that the coefficients of interest in all types of antihypertensive medications, except for vasodilators (such as hydralazine)—which is insignificant—have the same sign. This concordance between qualitative conclusions further strengthens our analysis by providing a consistent picture of the effect of antihypertensive medication on glaucoma. Interestingly, the coefficients are not all significant to the same degree, and they are not all of the same size. In particular, the analysis shows that antiadrenergic drugs (β-blockers) and renin–angiotensin system inhibitors are those medications that have the strongest preventive effects on glaucoma.

In summary, we find a local causal effect of antihypertensive treatment on the risk of developing glaucoma.

### Discussion

Using data for the entire Danish population during a 16-year period, we find an overall significant increased risk of glaucoma among patients ever treated with antihypertensive drugs. This association remains evident when controlling for age, sex, and year-specific fixed effects. Furthermore, the risk of

### Table 3. Logistic Regression Models of Glaucoma Explained by the Number of Years Since the Onset of Hypertension, Interacted With the Number of Antihypertensive Medications Used (Column 1) and the Different Antihypertensive Medications (Columns 2 and 3)

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Coefficient Estimates for Glaucoma (SE)</th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since HT×HT×no. of HT medications</td>
<td>−0.02* (0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×antiadrenergic</td>
<td>−0.06† (0.02)</td>
<td>−0.06† (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×diuretics</td>
<td>−0.03§ (0.01)</td>
<td>−0.03§ (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×vasodilators</td>
<td>0.02 (0.01)</td>
<td>0.02 (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×β-blockers</td>
<td>−0.02‡ (0.01)</td>
<td>−0.02‡ (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×calcium antagonists</td>
<td>−0.02‡ (0.01)</td>
<td>−0.02‡ (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×angiotensin system inhibitors</td>
<td>−0.04‡ (0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×angiotensin-converting enzyme inhibitors</td>
<td>−0.03§ (0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×angiotensin II receptor blockers</td>
<td>−0.04‡ (0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HT×HT×renin inhibitor</td>
<td>−0.01 (0.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent effects</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No. of observations</td>
<td>4,179,982</td>
<td>4,179,982</td>
<td>4,179,982</td>
<td></td>
</tr>
<tr>
<td>No. of individuals</td>
<td>700,945</td>
<td>700,945</td>
<td>700,945</td>
<td></td>
</tr>
</tbody>
</table>

The SEs are clustered on the level of the individual. Data are shown for individuals aged 40 to 95 years in the 7-year period of 3 years before and after onset of treatment with antihypertensive drug (SEs are clustered on the individual level). All the specifications include controls for sex, age, and the separate variables forming the interaction terms shown (years since HT, HT number of HT medications, and medicine dummy variables). All 3 specifications, therefore, correspond to column 7 of Table 2, augmented with interactions with either the number of medications or each medication separately. The difference between columns 2 and 3 is that the renin–angiotensin system medications enter separately in column 3. The slope is smaller in the period after the onset of treatment with antihypertensive drugs. With antiadrenergic, we refer to β-blockers and with vasodilators we refer to, for example, hydralazine (ACT [anatomical therapeutic chemical] codes in the Appendix in the online-only Data Supplement). The numbers in parentheses at the top indicate the column numbers. HT indicates hypertensive.

*P < 0.05.
†P < 0.01.
‡P < 0.001.
developing glaucoma was found to be significantly higher in women and to increase with age.

The main novel finding of our analysis is the indication of a causal protective effect of antihypertensive medication on the development of glaucoma. Our analysis of separate antihypertension drugs showed that all drugs (except vasoconstrictors) have a protective effect. The relatively high effect of angiotensin-converting enzyme inhibitors is consistent with the literature that finds a higher concentration in glaucomatous eyes and that angiotensin-converting enzyme inhibitors reduce the IOP and have a protective effect against glaucoma. Furthermore, it has been found that low concentrations of angiotensin II might cause disturbance of retinal neuronal function. Nevertheless, according to our analysis, antihypertensive drugs seem to have the greatest protective effect.

Regression discontinuity designs are rarely used in medical research but have been described as an alternative to randomized experiments. It is especially potent when a treatment has already become the standard of care or in register studies, both of which are criteria that are relevant to this study. Previous studies have shown an association between antihypertensive medication and glaucoma (but the evidence is still scarce). However, no previous study has investigated the causal effect of antihypertensive medication on glaucoma.

Although the overall risk of treatment with antiglaucomatous drugs is increased in patients taking antihypertensive medication, we show that commenced treatment with antihypertensive drugs postpones the onset of glaucoma, or treatment with an antiglaucomatous drug, and leads to a reduction in the trend of glaucoma by around 43%.

We cannot know if the estimates could be affected by an increased avoidance of glaucomatous diagnostics after the onset of antihypertensive treatment. Furthermore, the present analysis assumes that there is no algorithm in the medical care system that leads to patients who start antihypertensive medication being more or less likely to be examined for glaucoma. To our knowledge, there are no similar mechanisms at play. In any case, our assessment of the data and study design indicated that the model assumptions are well satisfied.

There is one possible confounding effect, which could affect the interpretation of our estimates, namely a possible effect of detection of hypertension on the likelihood of detection of glaucoma. However, this possible effect will tend to bias against (if at all) finding the effect that we observe, meaning that the effect that we observe presents a lower bound of the causal effect of treatment with antihypertensive medication on the development of glaucoma. In particular, if patients who start antihypertensive medication are more likely to be examined for glaucoma—for example, if the detection of hypertension lead to a frequency of medical check-ups for hypertensive retinopathy—such an effect would tend to increase the trend of glaucoma after the onset of antihypertensive treatment. To the extent that such an effect is present, our estimates of the negative effect of antihypertensive treatment on the prescription of antiglaucomatous medicine will present a lower bound of the causal effect of treatment with antihypertensive medication on the development of glaucoma.

It is worth considering the possible consequences of the fact that our operating definition of hypertension is given by the redemption of at least 2 different types of antihypertensive medications. How might our estimates be affected by the use of this definition, rather than the usual definition of BP exceeding 140/90 mm Hg? In particular, how would we presume that our estimates would differ if we had identified, and treated, hypertensive individuals by BP measurements in a screening study. We think that the main consequence of this would be a higher number of individuals diagnosed with and treated for hypertension because some individuals in our data probably went undiagnosed. If antihypertensive medication has a different effect on the risk of glaucoma in these otherwise undiagnosed individuals, the estimated effect would change with the inclusion of these individuals. It is difficult to make predictions about whether individuals not defined as having hypertension could differ with respect to the effect of antihypertensive medication on their risk of developing glaucoma. We do not see any particular reason for why such individuals should be expected to differ substantially in this respect, and our best guess is, therefore, that the estimates and conclusions would not change much by the inclusion of such individuals. However, we must await future research to shed light on this question.

Furthermore, it is also worth considering the possible consequences of untreated glaucoma. By the same logic as above, if we could have identified all individuals with untreated glaucoma in the data (and corrected for the average time from the onset of glaucoma to the onset of treatment for glaucoma), we would expect that our estimates would only differ if these individuals were affected differently by antihypertensive treatment. As in the case of undiagnosed individuals with hypertension, we see no special reason for why the inclusion of individuals who were undiagnosed with glaucoma should react differently on average than the individuals in our existing sample. Again, future research could shed light on this question.

The main strength of our study was the use of comprehensive data resources covering a large sample, namely the entire Danish population during 16 years.

This study could not differentiate between particular agents because of our strict definition of patients with hypertension. Thus, hypertension was defined as a patient receiving ≥2 antihypertensive compounds. Because previous studies have shown a decreased risk of glaucoma in patients treated with systemic β-blockers or calcium channel inhibitors, it seems reasonable to interpret the present observed reduction of the risk of developing glaucoma in patients treated with antihypertensive as a causal effect of particular antihypertensive drugs.

Limitations

A theoretical limitation of the study concerns the availability and completeness of the information from the National Danish registries; however, the National Danish Registry of Medicinal Products Statistics records 100% of all dispensed prescriptions of antihypertensive medication in all pharmacies in Denmark, and the National Danish Civil Registration System captures 100% of all births, deaths, emigrations, and immigrations in Denmark.
However, as also discussed above, because our outcome variable identifies individuals receiving ≥1 antiglaucoma drugs, which may include some individuals, who received antiglaucomatous medication for other reasons than glaucoma, we cannot necessarily infer that our estimates reveal the effect of antihypertensive treatment on glaucoma itself, only on prescription for antiglaucomatous drugs. In other words, a limitation of the study is that we do not have information on why a specific treatment was selected. Nevertheless, as argued above, although the use of antiglaucomatous drugs for reasons other than glaucoma may bias the estimates if they are interpreted as estimates of the effect of antihypertensive treatment on the development of glaucoma (rather than antiglaucomatous treatment per se), they will bias the estimates against finding a negative effect. Because we do find a negative effect, we can, therefore, infer that our estimates represent a lower bound of the true effect of antihypertensive treatment on the development of glaucoma.

Other limitations of the study are not having information on actual BP control or whether the administered dose resulted in the target BP systemically or in the eyes. Future research could investigate the found associations, focusing on the effect of the BP. Furthermore, we do not know the origin or type of glaucoma.

Likewise, while we account for individual-specific fixed effects that could potentially affect the risk of glaucoma,38 future research could also include time-varying covariates.

Another potential limitation of the present approach is the question of whether all participants took their medication. Such exposure misclassification is, however, usually similar in cases and controls and should, therefore, not significantly affect the qualitative conclusions. Our study is inherently limited by the observational nature of data, and we acknowledge the possibility of bias, including confounding by indication.

Because considerable attention has been given to an association between dips in nocturnal BP, after commenced treatment with antihypertensive drugs,12,16,39 and worsening and onset of low-tension glaucoma, it is possible that this particular subtype of glaucoma differs from the found delayed onset of glaucoma in newly diagnosed hypertensive patients. However, the study is not able to distinguish between glaucoma subtypes.

The study does not shed light on the underlying biological mechanism or the type of glaucoma (if not all) for which it is relevant. Furthermore, because of the strict definition of the variable indicating hypertension, we lose information about the different antihypertensive treatment groups separately, which could be interesting to investigate in future research.

Overall, we think that this study identifies a causal effect of antihypertensive treatment on antiglaucomatous treatment, and considering the arguments above, therefore, also a lower bound on the causal effect of antihypertensive treatment on the development of glaucoma.

Conclusions and Perspectives

In conclusion, we found a significantly increased risk of developing glaucoma among patients ever treated with antihypertensive drugs. However, antihypertensive drugs seem to reduce the risk of developing glaucoma. Thus, our study presents the first evidence of antihypertensive medication having a preventive effect against the development of glaucoma. Overall, our results highlight a causal relationship between systemic BP and glaucoma.

Acknowledgments

We thank Henrik Horwitz for valuable comments to our article and good statistical support. A. Horwitz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

None.

References


Online Supplement

Anti-hypertensive Medication Postpones the Onset of Glaucoma: Evidence from a Nationwide Study

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Further Methods Information

Medication

The ATC codes for anti-hypertensive drugs used in the analyses are listed here by classes of origin: β-blockers (BB) are C07AA01-03, C07AA05-07, C07AA16, C07AB02-05, C07AB07, and C07AB12; diuretics (DD) are C03AA01, C03AB01, C03BA11, C03CA01-02, C03CB02, C03DA01, C03DA04, and C03EA01; vasodilators are C02DB, C02DD, C02DG; anti-adrenergic drugs, C02A, C02B, C02C; calcium antagonists (Ccb) are C08DA01, C08CA01-06, C08CA08-10, C08CA13, and C08DB01; angiotensin II receptor blockers (ARB) are C09CA01-04 and C09CA6-08; and angiotensin converting enzyme inhibitors (ACEI) are C09AA01-07, C09AA09-10, and C09AA13. Patients were defined as having hypertension if they received at least 2 classes of antihypertensive drugs.

The ACT codes for glaucoma medication used in the analyses are: β-blockers, S01ED01-05; prostaglandin analogs, S01EE; 2-adrenergic agonists, S01EA; parasympathomimetic drugs, S01EB; carbon anhydrase inhibitors, S01EC; fixed combination drugs, S01EA51, S01EB51, and S01ED51. Patients were defined as having glaucoma if they received at least one kind of anti-glaucomatous medication.

Patients were classified as incident with glaucoma (i.e., having their onset of glaucoma) at their first redemption of a glaucoma medication, and they were classified as incident with hypertension (i.e., having their onset of hypertension) at their first redemption of a second anti-hypertensive drug.

Regression Discontinuity: Tests of Assumptions

The main underlying explanatory variable in the regression discontinuity analysis, also denoted the assignment variable, measures the number of years to the treatment with anti-hypertensive medication. The regression discontinuity model investigates how the risk of developing glaucoma is affected when an individual passes the point in time when he starts anti-hypertensive treatment. Evidence of a sudden change in the level and/or the trend of glaucoma development occurring just following the point in time at which an individual starts anti-hypertensive treatment is indicative of a causal effect of anti-hypertensive treatment of glaucoma.

An underlying assumption of the regression discontinuity analysis is that the treatment status (here: anti-hypertensive treatment) is not affected by considerations related to glaucoma. A typical assessment of the existence of treatment manipulation is achieved by investigating the distribution of the assignment variable, i.e., the number of years to treatment against hypertension.

Given an approximately uniform distribution of the onset of hypertension over the 16-year period for any individual, we would expect to find that the distribution of the assignment variable is hump-shaped. To see this, consider the fact that there is only one kind of individual-year observations for which there is 16 years to treatment in the sample. In particular, this is the case only for the year 1996 and for individuals who have their onset of hypertension in 2012. Meanwhile, there are two types of of individual-years for which there are observations with 15 years to treatment, namely the year 1996 for individuals with an onset of hypertension in 2011 or the year 1997 for individuals with an onset in 2012. Following this logic, the distribution of observations tend to be concentrated around the middle of the distribution of the assignment variable.

To assess treatment status manipulation, we looked for signs of “bunching” of the histogram around the onset of treatment, which would indicate treatment status manipulation. The hump-shaped distribution of the treatment variable is depicted in Fig. S2. It does not indicate bunching of observations around the treatment, suggesting that the treatment status manipulation is not a concern.

Further Statistics Information

Terms

The incidence in a given year is defined as the number of new cases in that year divided by the number of individuals living in that year. The incidence rate is the number of new cases over the 16-year study period per population at
risk (measured in 100 person-years). The relative risk (RR) of developing glaucoma is the probability of developing glaucoma for a certain group (e.g. males or individuals with hypertension) divided by the probability of developing glaucoma for the converse group. The estimates of the duration analysis are converted to relative risk estimates by calculating their antilogarithm.

**Further Results Information**

**Robustness Checks**

**Alternative Bandwidths**

To establish robustness of the effect size estimate, we modify the regression sample restrictions, changing the bandwidths to investigate the effect of including observations with different distances from the cut-off and the effects of this on the parameter estimates. Ranges of bandwidths (or “windows” of data) around the threshold are investigated.

Table S1 investigates the effect of changing the time interval from the baseline ±2 years to ±10 years. The coefficient of interest remains statistically significant and of a similar magnitude compared to the pre-treatment trend. The robustness checks to alternative regression sample restrictions therefore indicate that the main finding is not specific to the baseline regression sample.

**Alternative Statistical Analysis**

In Table S2 we use the same specifications as in Table 2, except that we use a linear regression model. The table establishes that the qualitative findings of Table 2 are robust to the use of linear regression. In particular column 2 establishes that the coefficient of interest is significantly negative. Column 4 establishes that the coefficient of interest remains significantly negative when controlling for sex and age.

Furthermore, since it is possible to account for individual-specific fixed effects in a linear regression model with the data at hand. Column 5 and 6 account for individual-level fixed effects to estimate the causal effect of treatment with anti-hypertensive drugs on the risk of glaucoma. Notably, the coefficient of interest is highly significantly negative in the specification in column 6. Interestingly, the coefficient of interest is insignificant in column 5, in which we do not allow for a jump while accounting for individual-fixed effects (please see the discussion of Table S3 below). Overall, Table S2 establishes that the finding of a negative effect of the onset of anti-hypertensive treatment on the development of glaucoma is robust to the use of logistic regression.

In Table S3, we further investigated the robustness to accounting for individual-specific fixed effects. The table includes specifications that are similar to those of Column 5–6 of Table S2, while focusing on alternative bandwidths. The table establishes that the main conclusions are robust to accounting for potentially confounding factors that are constant for each individual, for alternative bandwidths. Furthermore, the table establishes that the main coefficient of interest remains significant when excluding the hypertension dummy (i.e., the jump variable) for these alternative samples.

**Placebo Break**

Finding breaks at points different from the onset of anti-hypertensive treatment could raise the likelihood that the main finding is spurious. Therefore, we investigate the existence of breaks at an earlier point in time. In particular, we create a variable that measures the number of years to the onset of anti-hypertensive treatment minus three. We run a regression, which investigate for breaks at this earlier point in time, restricting the sample to a period before the actual onset of hypertension. Table S4 shows the results from this regression. The results indicate that there is no evidence of a break at the earlier point in time.
<table>
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<th>Explanatory variable</th>
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<th>±4 Years</th>
<th>±6 Years</th>
<th>±8 Years</th>
<th>±10 Years</th>
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<td>0.11*</td>
<td>0.10*</td>
<td>0.10*</td>
<td>0.10*</td>
</tr>
<tr>
<td></td>
<td>(0.00)</td>
<td>(0.00)</td>
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<td>(0.00)</td>
<td>(0.00)</td>
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<tr>
<td>Years Since HT × HT</td>
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<td>0.06*</td>
<td>0.06*</td>
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</table>

Number of Observations | 1,918,418 | 1,918,418 | 4,179,982 | 4,179,982 | 6,035,726 | 6,035,726 | 7,482,416 | 7,482,416 | 8,532,848 | 8,532,848 |
Number of Individuals  | 687,905   | 687,905   | 700,945   | 700,945   | 708,457   | 708,457   | 712,664   | 712,664   | 714,733   | 714,733   |

Table S1: Logistic Regression models of glaucoma explained by the number of years since the onset of hypertension with clustered standard error within individuals. Individuals aged 40–95 years. The numbers in parentheses at the top part of the table indicate the column numbers. Abbreviations: HT, Hypertensive.

* p < 0.001. † p < 0.05. ‡ p < 0.01.
<table>
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<th>Explanatory variable</th>
<th>(1)</th>
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<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
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<td>0.0031*</td>
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<td>(0.0001)</td>
<td>(0.0001)</td>
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<tr>
<td>Years Since HT × HT</td>
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<th>No</th>
<th>No</th>
<th>No</th>
<th>Yes</th>
<th>Yes</th>
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</table>

Table S2: Linear Regression models of glaucoma explained by the number of years since the onset of hypertension. The regressions include individuals aged 40–95 years in the 7-year period of 3 years before and after onset of treatment with anti-hypertensive drugs (standard errors are clustered on the individual level). Columns 1–5 does not account for individual-fixed effects. Columns 5–6 account for individual-fixed effects. The numbers in parentheses at the top part of the table indicate the column numbers. Abbreviations: HT, Hypertensive.

* $p < 0.001$. † $p < 0.01$. 
<table>
<thead>
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<th>Explanatory variable</th>
<th>±2 Years</th>
<th>±5 Years</th>
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<td>Break &amp; Jump</td>
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<td></td>
<td>(1)</td>
<td>(2)</td>
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<tr>
<td>Years Since HT (i.e., Time Trend)</td>
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<td>0.0048* (0.0001)</td>
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<td>Years Since HT × HT (i.e., Break)</td>
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<td>-0.0010* (0.0001)</td>
</tr>
<tr>
<td>HT (i.e., Jump)</td>
<td>-0.0000 (0.0002)</td>
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</tbody>
</table>

Accounting for Individual Fixed Effects | Yes | Yes | Yes | Yes

Table S3: Linear Regression models of glaucoma explained by the number of years since the onset of hypertension with person fixed effects. The different models investigate the range of bandwidths (or “windows” of data) around the threshold. The numbers in parentheses at the top part of the table indicate the column numbers. Abbreviations: HT, Hypertensive.

* $p < 0.001$. † $p < 0.01$. 
<table>
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Table S4: Logistic regression when using a placebo break at -3 years (column 1). The table establishes reassuringly that the use of a hypothetical break point three years before the onset of hypertension results in an insignificant break estimate that is virtually zero. For convenience, the comparable estimates from column 1 of Table 2 are presented in column 2. The numbers in parentheses at the top part of the table indicate the column numbers. Abbreviations: HT, Hypertensive.

* $p < 0.001$. 
Figure S1: Age-specific incidence rates for glaucoma divided into groups of patients treated, and not treated, with anti-hypertensive drugs in the period 1996–2012. The y-axis represents rates per 100 individual-years. The x-axis represents age (divided into 5-year age groups). The dashed red line represents individuals treated with anti-hypertensive drugs. The solid blue line represents individuals not treated with anti-hypertensive drugs.
Figure S2: Histogram of time to onset of hypertension across all individual-years. The histogram shows a hump-shaped uniform distribution of the onset of hypertension, and does not indicate bunching of observations around the treatment time, suggesting that treatment status manipulation is not a concern.