Hypotensive Medication, Statins, and the Risk of Glaucoma

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Purpose. To examine whether treatment with oral blood-pressure–lowering medication or statins influences the risk of glaucoma.

Methods. This study was a case–control investigation, nested within a computerized primary care database of 177 general practices across the United Kingdom; 8778 cases diagnosed and/or treated for glaucoma between 2000 and 2007, and 8778 glaucoma-free controls matched for age, sex, and practice. Odds ratios for treatment with oral antihypertensives (including selective β_1 and nonselective β-blockers) and statins in the 5 years before diagnosis were calculated by logistic regression, adjusted for a marker of socioeconomic position and number of drug types prescribed (as a measure of health service usage).

Results. Prevalence of oral β-blocker use in the 5 years before diagnosis was lower in the cases (22.5%) than in the controls (23.6%), adjusted odds ratio (OR) 0.87 (95% confidence interval [CI], 0.80–0.94). This effect was presence with treatment with β_1-selective medications (OR, 0.81; 95% CI, 0.74–0.88) but not with nonselective medications (OR, 1.08; 95% CI, 0.94–1.24). The prevalence of thiazide use was higher among the glaucoma cases than among the controls (OR, 1.13; 95% CI, 1.04–1.23). Neither statins nor other antihypertensive treatments were associated with the risk of glaucoma.

Conclusions. Oral β_1 β-blockers may protect against development of glaucoma. The current consensus on the relative importance of β_2 receptor blockade in treating glaucoma may have to be reviewed. Changes in prescribing oral β-blockers for cardiovascular disorders may affect the number of those who eventually have glaucoma. There is no evidence to suggest that statins have a preventive role in glaucoma. (*Invest Ophthalmol Vis Sci.* 2010;51:3524–3530) DOI:10.1167/iovs.09-4821

Primary open-angle glaucoma (POAG) is the most common type[1] and is a leading cause of incurable vision loss worldwide; as such, it represents a major challenge to public health.[2–4] Lowering levels of intraocular pressure (IOP), either medically or surgically, is used to control progression of the disease.[5] Since the late 1960s, when the intraocular hypotensive effect of systemic nonselective β-blockers (which block both β_1 and β_2 adrenoreceptors) was reported,[6,7] topical β-blockers have been extensively used in the medical management of glaucoma.[8] Although nonselective β-blockers are often used in topical medications for glaucoma (e.g., timolol), it is the antagonistic action, specifically on β_2 receptor cites, abundant in the ciliary body, that is thought to downregulate aqueous production and lower IOP.[9,10] However, possible adverse respiratory effects of β-receptor blockade (especially β_2 receptor blockade), even for topical treatment, have raised concern about their use.[11,12] More recently, topical drug therapies with alternative modes of action have increased in use, but β-blockers remain a popular form of treatment.[13]

Although calcium channel blockers, ACE inhibitors, or thiazide-type diuretic medication are now recommended as first-line treatment of hypertension,[14] oral β-blockers are still extensively used in the medical management of systemic hypertension and established cardiovascular disease.[14] In addition, other cardiovascular protective medications—statins in particular—are increasingly being used.[15] The escalating use of these oral medications for primary and secondary prevention of coronary heart disease may have wider implications for eye health. In the case of oral β-blockers, ocular hypotensive effects may be advantageous in decreasing the risk of POAG in later life. In addition, the potential antiapoptotic,[16,17] neuroprotective,[18,19] and ocular circulatory effects[20] of statins may modify the risk of POAG. However, few prospective studies have been conducted to examine whether treatment with these medications influences risk of later development of glaucoma. Prospective findings from the Rotterdam Eye Study have provided evidence that systemic use of β-blockers and calcium channel blockers may decrease and increase the risk of POAG, respectively.[21] However, with few incident cases of glaucoma ($n = 87$), further evidence is needed. Examining the effect of systemic treatments on the development of POAG is further complicated, in that the systemic condition being treated may be a risk factor for POAG in itself. Systemic hypertension, atherosclerosis, and vascular disease have all been proposed as risk factors for POAG.[22] However, associations with systemic hypertension are unclear, with both high and low blood pressure (BP) being implicated in the development of POAG.[22]

Primary care databases offer a source of longitudinal population-based clinical information on diagnoses recorded and medical treatments prescribed in primary care. We used data from a large-scale, primary care database in the United Kingdom (DIN-LINK) to perform a nested case–control study in which we examined the association of medical treatments for lowering levels of BP and blood cholesterol to subsequent diagnosis and treatments for glaucoma. We hypothesized that oral treatment with β-blockers, other BP-lowering medications, and statins may reduce the likelihood of diagnosis and/or the necessity for treatment of glaucoma. We also assessed whether any effects are independent of diagnoses of diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), asthma, or hypertension.

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METHODS

The DIN-LINK Database

DIN-LINK is an anonymized database of individual primary care records in the United Kingdom, from general practices that use a health information systems software program (iSOFT, formerly Torex; iSOFT Group, plc, Manchester, UK). The database has been used to study trends in the prevalence of (1994–2003) and persistence with (1994–2005) treatment for glaucoma and ocular hypertension.[13,23] This report is based on 177 practices with a minimum of 5 years' continuous high-quality recording into 2007, with about half of these having such recording going back at least 15 years. We have outlined methods for identifying good-quality data in DIN-LINK, and this approach was repeated with the database updated to 2007.[24] Validations of the database have been published and show that the age–sex population structure of the DIN-LINK database is highly comparable to another large primary care database (the General Practice Research Database; GPRD) and other national data sources in the United Kingdom.[24,25] This study was approved by the National Heath Service Research Ethics Committee for Wandsworth (reference 05/Q0803/162).

Morbidity and prescription data are classified by "read codes." An important aspect of the database is the availability of a sociodemographic indicator linked to patient postal code, the ACORN (a classification of residential neighborhoods) index (CACI Ltd. London, UK), which uses data from the 2001 census to classify small areas.[26] The index provides many levels of detail, but at its most aggregated level categorizes residential neighborhoods into five groups, ranging from wealthy achievers to hard pressed. ACORN scores were available for 97% of patients in our study.

Case and Control Selection

The study design was a matched case–control study, nested within the DIN-LINK database, wherein cases of glaucoma were individually matched to control subjects. It complied with the Declaration of Helsinki in ensuring the privacy of all cases and controls. Such a design has the same strengths as a cohort analysis using the same database, whereas the case–control and matching process mean that controls for practice and period of diagnosis and treatment are more straightforward.[27]

Cases were patients first diagnosed with glaucoma or ocular hypertension between 2000 and 2007. We have shown that diagnostic codes for glaucoma are not consistently reported in primary care.[13] Hence, we based our definition on a combination of diagnostic codes for glaucoma or ocular hypertension and codes for prescriptions specific to the treatment of glaucoma (read codes starting with k8, listed in the Appendix).[13] The earliest date with any of these codes in a patients' record was defined as their date of diagnosis. We also required cases to be continuously registered for at least 1825 days (5 years) before their date of diagnosis, thus eliminating newly registered patients with existing glaucoma, aged between 40 and 90 years at diagnosis. This criterion identified 8796 cases from 177 practices.

We sought to match a single control to each case by practice, sex, and year of birth. Controls had to be currently registered at their respective case's diagnosis date and had to be similarly registered continuously for the five previous years. We excluded from the control group anyone who subsequently received a diagnosis of or was treated for glaucoma or possible glaucoma during follow-up. Our reasoning was that a diagnosis of glaucoma recorded by a general practitioner, although clearly identifying a subject as having glaucoma, does not give a good indication of the timing of disease incidence, which is likely to have been present before the diagnosis for a variable time. To include subjects as controls who are subsequently found to have glaucoma risks misclassifying patients and diluting the difference between cases and controls. Such an approach also has the advantage of increasing power. We also excluded any patients with codes for borderline glaucoma, to maximize the likelihood that the controls were glaucoma free. A total of 7506 (85.3%) controls were matched to the paired cases' exact years of birth. A further 1272 (14.5%) were matched within 1 year of birth. The remaining 18 cases (0.2%) were excluded. Sensitivity analyses showed no impact of including only those matched by exact year of birth, and so all analyses presented herein include the full set of 8778 controls.

The records for each case and control were electronically searched for oral prescriptions of antihypertensives (ACE inhibitors, β-blockers, calcium channel blockers, diuretics, and other antihypertensives) and statins in the preceding 5 years (also 730 days to 2 years) before the case diagnosis date. A list of medications is given in the Appendix. Days covered by a prescription were estimated by using the amount prescribed and dosage instructions coded into the database.

Statistical Analysis

Odds ratios (ORs) for oral treatment within the study period (5 years), comparing those who were subsequently treated for glaucoma with the controls who were not treated, were calculated by conditional logistic regression (PROC PHREG command; SAS version 9.1 for Solaris; SAS Institute, Cary, NC). Crude ORs were calculated, with cases and controls matched for age, sex, and practice. Additional adjustments were made for ACORN index (comparing those classified as wealthy achievers, urban prosperity, comfortably off, moderate means, and hard pressed), selected comorbidities before case diagnosis (diabetes, angina, myocardial infarction [MI] asthma, and COPD), and for number of drug types prescribed (excluding antihypertensives) in the calendar year before case diagnosis. The latter data were used as a measure of health care usage or of propensity to consult, a potentially important confounding variable.[27] We defined a drug type as the first three characters of the read code, as this approach identifies distinct drugs (excluding appliances and dressings), but does not count changes of dose or form as a different drug. Comparison of prescribing histories between cases and controls (yes versus no, days covered) were analyzed by the appropriate test (McNemar or Wilcoxon).

To examine whether there was a dose–response association between the prescribing of selected drugs and being treated for glaucoma, we further subdivided the data into three groups according to the number of days covered by a prescription in the 1825-day period (1–180, 181–730, and 731 or more days) and examined the ORs accordingly.

RESULTS

Analyses were based on 17,556 individuals in this study (8,778 cases and 8,778 controls; mean age, 70 years; 53% women). Table 1 summarizes the prescription histories (including medication type and number of days of drug coverage) in the 5 years preceding the diagnoses/treatment date for glaucoma in the cases and the matched study period in the controls. There was a higher prevalence of prescribing of all medication groups (ACE inhibitors, calcium channel blockers, diuretics, statins, and other antihypertensives) in the cases compared with the controls, except for β-blockers, for which the prevalence of use in cases was lower (22.5% of the cases, 23.6% of the controls). The difference appeared to be driven by β_1-selective blockers (18.2% of the cases, 20.0% of the controls), rather than nonselective β-blockers (5.6% of the cases, 5.1% of the controls). When the number of days of drug coverage was considered (Table 1), the cases had a lower mean number of days of treatment with β-blockers (again driven by β_1 blockers). Days of treatment with other BP-lowering drugs tended to be higher in the cases, although only for ACE inhibitors was the difference statistically significant. Trends were similar in the men and the women, and when the data were restricted to prescriptions in the 2-year period before diagnosis (data not shown).

Table 2 shows the results of conditional logistic regressions that examined the odds of a case being prescribed each of the

TABLE 1. Prescription Histories for Oral Medications in the Cohort in the 5 Years before Glaucoma Treatment/Diagnosis

Drug	Any Prescription Issued in Past 5 y (%)			Mean No. of Days (SE) with Drug Coverage in Past 5 y		
	Controls	Cases	*P**	Controls	Cases	*P*†
β-Blockers						
All	23.6	22.5	<0.001	210.2 (5.3)	182.0 (4.9)	<0.001
β1 only	20.0	18.2	<0.001	179.8 (4.9)	149.9 (4.5)	<0.001
β1 and β2	5.1	5.6	<0.001	30.6 (2.1)	32.3 (2.1)	0.44
Ace inhibitors	24.3	26.3	<0.001	213.7 (5.2)	235.3 (5.4)	0.002
Calcium channel blockers	20.4	21.8	<0.001	169.3 (4.7)	179.7 (4.9)	0.12
Diuretics	22.5	25.0	<0.001	181.1 (4.7)	190.8 (4.8)	0.08
Statins	18.7	19.6	<0.001	150.9 (4.3)	153.8 (4.3)	0.59
Other antihypertensives	6.1	7.0	<0.001	40.3 (2.3)	41.2 (2.3)	0.37

Cases and controls, $n = 8778$.
* McNemar's test.
† Wilcoxon signed rank test.

drug groups in the 2- and 5-year period before diagnosis and/or treatment for glaucoma compared with controls. The positive associations with ACE inhibitors, calcium channel blockers, other antihypertensives, and statins were attenuated and were no longer statistically significant after adjustment for ACORN index, comorbidities, and use of other drugs. However, the association with thiazides remained statistically significant, with the cases being more likely than the controls to have a prescription in the previous 2 and 5 years (OR, 1.16; 95% confidence interval [CI], 1.07–1.27; and 1.13, 1.04–1.23, respectively).

The inverse association between prescribing oral β-blockers and becoming a case was strengthened by adjustment (Table 2). The cases were 13% to 19% less likely than the controls to have been prescribed a β-blocker in the previous 2 and 5 years (OR, 0.81; 95% CI, 0.75–0.88; and 0.87, 0.80–0.94, respectively). Subdividing by type of β-blocker, the effect appeared to be due to the β_1 preparations only (OR, 0.81; 95% CI, 0.74–0.88 for 5 years), as there was no appreciable association with nonselective preparations (OR, 1.08, 0.94–1.24 for 5 years, findings similar to 2 years). The ORs presented in Table 2 were similar when restricted to those without a diagnosis of diabetes or MI (at least 90% of the sample) and in those without hypertension (data not presented).

For β-blockers only, we further calculated ORs by the number of days' coverage with these drugs during the 5 years before diagnosis. For β_1-specific blockers, there was no evidence of a protective effect for those with coverage of less than 180 days in the past 5 years: the OR (adjusted for ACORN, comorbidities, and number of drugs) were 1.10 (95% CI 0.95–1.27) for 1 to 180 days' coverage, 0.76 (0.66–0.89) for 181 to 730 days' coverage, and 0.78 (0.70–0.87) for 730 to 1825 days' coverage. For nonspecific β-blockers, the corresponding ORs were 1.22 (95% CI, 1.00–1.48) for 1 to 180 days' coverage, 0.87 (0.65–1.17) for 181 to 730 days' coverage, and 1.07 (0.85–1.33) for 730 to 1825 days' coverage.

DISCUSSION

This study has shown that patients with glaucoma who attend primary health care services are a fifth less likely to have a history of being treated with oral β_1-specific β-blockers than are those without a diagnosis for glaucoma. There was no evidence to suggest an association between being treated with oral statins and development of glaucoma, despite recent speculation on a protective effect.[28] Conversely, oral treatment with thiazides was associated with an increased risk of glau-

TABLE 2. Adjusted OR for Presence of Prescription in the Previous 2 and 5 Years

	2 Years ($n = 17,556$)			5 Years ($n = 17,556$)		
	No Adjustment	+Adj. for ACORN, Comorb, and No. Drugs*	+Adj. for Other Listed Antihypertensives†	No Adjustment	+Adj. for ACORN, Comorb, and No. Drugs*	+Adj for Other Listed Antihypertensives†
β-Blockers						
All	0.87 (0.81–0.95)	0.84 (0.78–0.92)	0.81 (0.75–0.88)	0.93 (0.87–1.00)	0.90 (0.83–0.97)	0.87 (0.80–0.94)
β1 only	0.83 (0.76–0.90)	0.80 (0.73–0.87)	0.76 (0.70–0.84)	0.89 (0.82–0.96)	0.85 (0.78–0.92)	0.81 (0.74–0.88)
β1 and β2	1.16 (0.99–1.36)	1.15 (0.97–1.35)	1.11 (0.94–1.31)	1.12 (0.98–1.28)	1.09 (0.95–1.25)	1.08 (0.94–1.24)
Ace inhibitors	1.14 (1.06–1.22)	1.03 (0.95–1.11)	1.01 (0.93–1.10)	1.12 (1.04–1.20)	1.01 (0.94–1.09)	0.99 (0.91–1.08)
Calcium channel blockers	1.11 (1.03–1.20)	1.05 (0.97–1.14)	1.04 (0.95–1.14)	1.09 (1.01–1.18)	1.03 (0.95–1.12)	1.03 (0.94–1.12)
Diuretics	1.19 (1.10–1.29)	1.14 (1.05–1.23)	1.16 (1.07–1.27)	1.15 (1.07–1.24)	1.10 (1.02–1.18)	1.13 (1.04–1.23)
Statins	1.07 (0.99–1.16)	0.97 (0.88–1.07)	0.98 (0.89–1.08)	1.06 (0.98–1.15)	0.96 (0.88–1.06)	0.97 (0.88–1.06)
Other antihypertensives	1.16 (1.01–1.33)	1.04 (0.90–1.19)	1.03 (0.89–1.18)	1.16 (1.03–1.31)	1.05 (0.92–1.18)	1.04 (0.91–1.18)

ORs are for any prescription versus none.
* Comorbidities adjusted for were history of diabetes, angina (only), MI (with or without angina), asthma, and COPD before case diagnosis date. No. drugs is number of drug types (excluding antihypertensives) prescribed in calendar year before the case diagnosis year.
† Adjusted for all variables in the ACORN column plus the antihypertensives listed in the Table.

coma, but ACE inhibitors, calcium channel blockers, and other BP-lowering medications had no effect.

Strengths of the Study

Primary care databases offer clinical and therapeutic information on a large number of individuals who are representative of the population as a whole. They provide a rapid and inexpensive method of examining prevalence and management of diagnosed disorders. We have previously used the DIN-LINK database, with nearly half a million patients aged 40 years or more registered annually, to examine trends and persistence with treatments for glaucoma in the United Kingdom over nearly a decade (1994–2005).[13,23] Although the potential to use health care databases for surveillance of diagnosed disorders and their treatment has been realized with other conditions,[15,29,30] the possibility of using these databases to examine determinants of glaucoma (especially medical treatments) has been largely untapped. Although in one earlier study, researchers examined whether current or prior use of cardiovascular medications and current hypertension are associated with glaucoma, they did not differentiate between types of β-blockers and excluded more recently developed medications such as statins.[31]

Limitations

A limitation in using primary care databases for etiologic studies is that only diagnosed cases will be identified. Moreover, identified cases will include all types of glaucoma (as diagnostic codes for glaucoma type were not routinely recorded), although most within the age group will be those with open-angle glaucoma.[1] We have considered these problems with respect to diagnoses of glaucoma in the DIN-LINK database.[13] In the context of the current case–control study, the presence of undiagnosed glaucoma in the controls cannot be excluded, as no clinical examination of study subjects was undertaken. However, although the presence of undiagnosed glaucoma among the controls and ocular hypertension among the cases may explain the lack of association observed with statins, these possibilities would attenuate any true inverse association with β-blockers and thus cannot explain our strong inverse association. Moreover, the association observed with β-blockers was present in both males and females, robust to different definitions of cases (based on diagnostic or drug codes only, or both; data not shown) and periods of follow-up (2 or 5 years). That the lower risk of glaucoma was specific to patients who were prescribed β1-specific preparations for at least 6 months of the 5-year period is further evidence in favor of a causal interpretation.

In interpreting our observational results, we must ensure that our finding on β-blockers cannot be explained by response or information bias or confounding. Given that our study is based on entire practice populations, response bias cannot be an explanation. Nor is it likely to be a false-positive chance finding. Two possible explanations are that the disease/condition for which the β_1-blockers are prescribed themselves protect against glaucoma and that glaucoma is less likely to be diagnosed in those prescribed β_1-blockers. Again, neither explanation seems plausible, given the lack of association with other antihypertensives, including nonselective blockers. Moreover the association appears independent of having a history of diabetes, MI, angina, COPD, and asthma and was present in nonhypertensives. Our practice-matched analysis also takes account of potential geographic differences in access to diagnosis of glaucoma. Similarly, control for ACORN takes account of socioeconomic differences in case identification.

Broad support for our findings comes from an earlier nested case–control study based on the GPRD, an entirely independent primary care database.[31] This study was more limited than ours, in that the investigators did not control for practice, prescribing propensity, or socioeconomic factors and did not differentiate between different types of β-blocker. However, they did find that, unadjusted for prescribing of other drugs, all antihypertensives except for β-blockers were positively associated with glaucoma diagnoses, while β-blockers appeared protective. They also found that these findings were independent of the established link between hypertension and glaucoma. The prospective Rotterdam Eye Study also showed that systemic use of β-blockers was associated with a reduction in incident cases of open-angle glaucoma, though there were insufficient cases for the findings to be statistically significant.[21]

Implications

Oral β-blockers have been used extensively in the management of cardiovascular disorders (such as hypertension, coronary heart disease, and cardiac arrhythmias) for some time and their main therapeutic action is mediated through cardiac β_1 adrenoreceptor blockade. However, the specific drugs used vary in their selectivity for β_1 receptors, with few being highly selective to β_1 receptor sites and many acting nonselectively on both on β_1 and β_2 adrenoreceptors.[32] Conventionally, nonselective β-blockers, primarily timolol, have been used topically to lower intraocular pressure; β_1-selective β-blockers, such as topical betaxolol, have been less commonly used and are viewed as less effective. Established pharmacologic theory suggests that topical β-blockers that target β_2 receptor sites, abundant in the ciliary body,[9] are the primary mechanism by which IOP is lowered.[10,33] However, it is known that β_1-selective β-blockers, such as betaxolol, also lower IOP, but the mechanism by which topical β_1-blockers exert an ocular hypotensive effect is poorly understood[34] and may be explained by a partial unselective action. However, our finding that systemic use of β_1-selective β-blockers (mostly atenolol), instead of nonselective β-blockers, was associated with lower risk of glaucoma was not expected and raises the possibility that more complex pharmacologic actions of these medications may be at work,[35,36] in addition to a direct effect on IOP. Exploring this notion may include consideration of other properties of oral β-blockers such as ocular penetration and influences on ocular hemodynamics (including different effects on ocular blood flow and perfusion pressure).[37,38] A neuroprotective effect from β_1-selective antagonists has also been observed recently in animal models.[39]

The higher risk of glaucoma associated with thiazides in the present study was a surprise finding. Although it is consistent with the higher risk associated with diuretics in the earlier GPRD study,[31] there was no adjustment in that study for propensity to consult. Although thiazides have been implicated in closed-angle glaucoma, due to acute allergenic swelling of the ciliary body and lens thickening,[40] the mechanism by which these effects might increase the risk of development of POAG remains unclear. Hence, this finding needs further replication before speculation on potential explanations and mechanisms. The evidence in an earlier prospective study that use of calcium channel blockers is associated with glaucoma[21] was not replicated in this study.

Despite the proposed antiapoptotic,[16,17] neuroprotective,[18,19] and ocular circulatory effects[20] of statins and the suggestion (from initial findings from another health care database) that long-term use may reduce the risk of glaucoma,[28] there was no association between prescription of statins and treatment or diagnosis of glaucoma. This finding cannot rule out that statins may have a role in managing patients with glaucoma[41] (especially as statins have been shown to have

neuroprotective effects among those with other degenerative neurologic conditions),[42] but provides no evidence to suggest that it prevents development of the disease.

There have been changes in the use of medications for hypertension and cardiovascular disorders, with current guidelines recommending alternatives to β-blockers for initial treatment of hypertension.[14] Hence, the use of β-blockers for hypertension and established cardiovascular disease is likely to decline. However, there are still a large number of patients being treated with β-blockers (14% of those aged 40 years or more, and 22% of those aged 60 years in the DIN-LINK database). We have resisted the temptation of calculating the population-attributable impact of reductions in prescribing of β-blockers, but consequences of recommendations to avoid their use may impact on the number developing glaucoma. With an estimated 0.5 million patients with POAG in the United Kingdom,[3] the potential number could well be substantial. Clarification of the role of β_1-selective and nonselective β-blockade is needed before the population impact can be inferred.

New studies of the pharmacotherapeutic action of β-blockers with different adrenoreceptor selectivity is warranted and may offer new strategies for the prevention and treatment of glaucoma.

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APPENDIX

TABLE A1. List by Drug Type of k8 Read Codes Used in the DIN-LINK Database for Treatment of Glaucoma

Drug Group	Read Codes
β-Blockers only	**k83** (Betaxolol hydrochloride), **k85** (cartelol hydrochloride), **k8b** (Metipranolol), **k8f** (timolol maleate), **k8g** (levobunolol hydrochloride)
Prostaglandin only	**k8i** (Latanoprost), **k8n** (travoprost), **k8o** (bimatoprost)
Cholinergic agent	**k84** (Carbachol), **k86** (demecarium bromide), **k89** (ecothiopate iodide), **k8c** (physostigmine sulphate), **k8d** (pilocarpine hydrochloride), **k8e** (pilocarpine nitrate)
Sympathomimetic	**k82** (Adrenaline), **k88** (dipverfine hydrochloride), **k8a** (guanethidine monosulph), **k8j** ((brimonidine tartrate)
Sympathomimetic and β-blocker	**k8p** (Brimonidine+timolo)
Carbonic anhydrase inhibitor only	**k81** (Acetazolamide), **k87** (dichlophenamide), **k8h** (dorzolamide), **k8l** (brinzolamide)
Carbonic anhydrase inhibitor and β-blocker	**k8k** (Dorzolamide+timolol)
Prostaglandin and β-blocker	**k8m** (Latanoprost+timolol), **k8q** (travoprost+timolol), **k8r** (bimatoprost+timolol)

TABLE A2. Blood-Pressure–Lowering Medications and Statins Used in the DIN-LINK Database

β-Blockers	
bd1	Propranolol hydrochloride
bd2	Acebutolol
bd3	Atenolol
bd4	Betaxolol hcl (β-Blocker)
bd5	Labetalol hydrochloride
bd6	Metoprolol tartrate
bd7	Nadolol
bd8	Oxprenolol hydrochloride
bd9	Penbutolol sulph (ingredient)
bda	Pindolol
bdb	Practolol [β-Blocker]
bdc	Sotalol hydrochloride
bdd	Timolol maleate [β-blocker]
bde	Compound β-blockers
bdf	Bisoprolol fumarate
bdg	Xamoterol fumarate
bdh	Metoprolol fumarate
bdi	Carteolol hydrochloride
bdj	Celiprolol hydrochloride
bdk	Esmolol hydrochloride
bdl	Carvedilol
bdm	Nebivolol
bdn	Propranolol hydrochloride [2]
ACE inhibiters (and ARB)	
bi1	Captopril
bi2	Enalapril maleate
bi3	Lisinopril
bi4	Quinapril
bi5	Perindopril erbumine
bi6	Ramipril
bi7	Sodium fosinopril
bi8	Cilazapril
bi9	Trandolapril
biA	Moexipril
biB	Imidapril hydrochloride
bk3	Losartan
bk4	Valsartan
bk5	Irbesartan
bk6	Trandolapril+verapamil Hcl
bk7	Candesartan cilexetil
bk8	Telmisartan
bk9	Eprosartan
bkA	Bosentan
bkB	Olmesartan
Calcium channel blockers	
bl5	Diltiazem hydrochloride
bl6	Lidoflazine
bl7	Nicardipine hydrochloride
bl8	Nifedipine
blb	Amlodipine
blc	Felodipine
ble	Lacidipine
blg	Nisoldipine
blh	Lercanidipine hydrochloride
bli	Mibefradil
blj	Diltiazem hydrochloride 2
bli	Nifedipine [2]
bb3	Verapamil hydrochloride
Diuretics	
b21	Bendroflumethiazide
b22	Chlorothiazide
b23	Chlortalidone
b24	Clopamide [ingred See Bdek]
b25	Cyclopenthiazide
b26	Hydrochlorothiazide
b27	Hydroflumethiazide
b28	Indapamide
b29	Mcfruside
b2a	Methyclothiazide
b2b	Metolazone
b2c	Polythiazide
b2d	Xipamide
Other antihypertensives	
bh1	Indoramin
bh2	Phenoxybenzamine hcl (cvs)
bh3	Phentolamine Mesylate
bh4	Prazosin hydrochloride
bh5	Terazosin hydrochloride
bh6	Doxazosin
bf1	Clonidine hcl (Antihypertens)
bf2	Methyldopa
bf3	Reserpine/Rauwolfia Alkaloids
bf4	Moxonidine Statins
Bxd	Simvastatin
Bxe	Pravastatin Sodium
Bxg	Fluvastatin Sodium
Bxi	Atorvastatin
Bxj	Cerivastatin
Bxk	Rosuvastatin