CHAPTER 4

Antihypertensive Medication and Glycemic Control in Patients with Type 2 Diabetes Mellitus
Abstract

Aim - To investigate the association between antihypertensive medication and glycemic control in patients with type 2 diabetes, including the potential modification by glucose lowering therapy.

Methods - Type 2 diabetes mellitus patients were identified in general practices in a Dutch middle-sized town from 1994-2000. Comorbidity, laboratory tests, and blood pressure values and information on drug dispensings were obtained from general practitioners’ files, pharmacy records, and hospital admission data. Glucose lowering treatment was defined at the moment of the most recent measurement of the variable of interest. Differences in glycemic control (fasting blood glucose and HbA\textsubscript{1c} values) between users and non-users of antihypertensive medication were compared by analysis of variance.

Results - More than one third of the patients used any antihypertensive medication. Users of antihypertensive medication had significantly lower HbA\textsubscript{1c} values, increased weight and slightly, non-significant, lower fasting glucose values compared to non-users. When adjusting for category of diabetes treatment, duration of diabetes, blood pressure, and body weight, the HbA\textsubscript{1c} level was even more lower in patients using antihypertensive drugs (difference 0.5 percent-points, p< 0.05). The association with glycemic control was present in all categories of diabetes treatment.

Conclusion - Our study showed that patients with type 2 diabetes mellitus not using any antihypertensive medication have increased HbA\textsubscript{1c} levels and lower body weight. This may indicate a subgroup with predominantly beta-cell failure.
Introduction

In patients with type 2 diabetes mellitus antihypertensive drug treatment decreases both mortality and morbidity. A special consideration in diabetic patients is the effect of antihypertensive drugs on glycemic control. For instance, antihypertensive drugs, such as beta-blockers and diuretics, increase insulin sensitivity. In randomized intervention studies with different antihypertensive drugs among subjects without diabetes both an increased as well as decreased plasma glucose levels have been reported. Because these effects are not limited to one class of drugs, it may not be a specific drug effect that is independent of blood pressure lowering.

It is not well known if the effects of these drugs on glucose metabolism are also present in patients with type 2 diabetes. In the UKPDS hypertension study, patients treated with atenolol had higher HbA1c levels over the first four years of follow-up than those randomized to captopril (7.5% versus 7.0%, p=0.004), although during the second four years the levels were the same. The FACET trial compared the effects of fosinopril and amlodipine on serum lipids and diabetes control in hypertensive type 2 diabetes mellitus patients. After 3.5 years, HbA1c levels in both groups did not differ from the baseline values. The glucose values showed a small decrease, which was equal in both groups.

The effects probably differ between patients using different glucose lowering therapy (diet, oral agents, insulin), and may be dependent on the underlying pathophysiologic mechanism of diabetes. Because type 2 diabetes is a heterogeneous disease, the effects might vary considerably in daily clinical practice.

To investigate the associations between antihypertensive medication and glycemic control in patients with type 2 diabetes mellitus, including the potential modification by glucose lowering therapy, we performed an observational study in a population of type 2 diabetes patients treated by general practitioners.
Patients and Methods

Study setting
This study was performed among patients who received comprehensive primary care from 17 general practitioners (GPs) in a Dutch middle-sized town (n=50,574). All GPs used a single electronic medical record system (Medicom®), which was available for this study, as well as information on drug dispensings from the pharmacist database (Pharmacom®). Hospital admission and discharge data were available through the PHARMO Record Linkage System.\textsuperscript{12,13}

The following data were available for this study: demographic data, medical history, comorbidity (including International Classification of Primary Care (ICPC) codes), diabetic complications, drug dispensings, prescribing doctor (specialist, GP), referrals to specialists, and the medical journal (a database-file containing free text, as recorded by the GP).

To guarantee privacy, all analyses were performed using anonymous records. Regarding medication prescriptions and dispensings, all drugs were coded according to the Anatomical Therapeutic Chemical (ATC) Classification. Hospital diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Subjects
The study population consists of all cases with type 2 diabetes mellitus as seen by the network of collaborating GPs (n=17) during 1992-2000 (n=1,144). In the Netherlands, most patients with diabetes mellitus type 2 visit their GP for regular check-ups. They were identified from the registries by the use of oral glucose lowering agents or International Classification of Primary Care (ICPC-2) codes T90 or T90.2, and/or the description ‘diabetes mellitus type 2’ in their medical records.

Data from both primary care and the pharmacy based dispensing records were complete for the period of February 1994 to August 2000 and were available for the purpose of this study. Subjects in whom the correct diagnosis of type 2 diabetes remained uncertain, due to incomplete and missing data, were excluded.
(n=72), as well as patients with no glucose or HbA1c results in their medical files (n=257). Therefore, the study population consisted of 815 patients with fasting blood glucose (n=779) and/or HbA1c (n=572) measurements recorded. In patients with diagnosed type 2 diabetes but unknown date of diagnosis we relied on January 1990 as a reasonable estimate.

**Variables of interest**

In both cohorts of type 2 diabetic patients, patients with fasting blood glucose or HbA1c values recorded in their medical file, respectively, we ascertained differences in metabolic control between users and non-users of antihypertensive medication. We compared most recent (i.e. last available) measurements of blood glucose and HbA1c in both groups. Antihypertensive drug use was classified into the major antihypertensive classes: beta-blockers (C07), angiotensin converting enzyme (ACE) inhibitors (C09), thiazide diuretics (ATC codes C03A, C03B, C03EA), calcium channel blockers (C08), and a remaining category of miscellaneous blood pressure lowering drugs (C02, mainly alpha-blockers).

We defined users of antihypertensives as patients using any blood pressure lowering drugs in the half year preceding the last measurement of the glycemic parameter of interest. Blood pressure was defined at the date of measurement closest to the date of the most recent glycemic variable, but at least within the period from 3 months before until 3 months after this recording, otherwise blood pressure was coded as ‘missing’. We also compared glycemic control in users of lipid lowering drugs, defined as patients using any serum lipid lowering drug (ATC group C10) in the half year preceding the last measurement, with glycemic control in non-users. The diabetic treatment was defined at moment of the last available measurement of the variable of interest.

**Data analysis**

For categorical variables, numbers and percentages and for continuous data means and standard deviations were calculated. For comparison of the continuous variables between patients who did and did not use antihypertensive medication, we used the Students’ t-test. Analysis of covariance was used to adjust for potential
confounding factors, notably age, gender, duration of diabetes, body weight, and blood pressure. All analyses were performed by SPSS version 10 for Windows.

**Results**

The clinical characteristics of the study population are given in Table 4.1. Blood pressure and weight were recorded in a small proportion of the patient files, mainly in those patients using blood pressure lowering medication. More than one third of the patients used antihypertensive medication, half of them (52.1%) only one class of drugs (beta-blocker, ACE-inhibitor, Ca-antagonist, or thiazide diuretic). This did not result in optimal controlled blood pressure: the average blood pressure in antihypertensive drug users was 155/87 mmHg, compared to 148/83 mmHg in non-users (p< 0.01). Use of antihypertensive medication was not associated with diabetes treatment or recordings of glycemic control (data not shown).

Systolic blood pressure was not associated with glycemic control (p> 0.2). A higher diastolic blood pressure was associated with a slightly increased fasting glucose values (regression coefficient 0.035 mmHg/mmol/L, CI 95%: 0.008-0.061, p< 0.05). There was no association between diastolic blood pressure and HbA1c. Patients using antihypertensive medication had significant lower HbA1c values, increased weight and slightly, non-significant, lower fasting glucose values (Table 4.2). When adjusting for category of diabetes treatment (diet, sulfonylureas, metformin, insulin), duration of diabetes, blood pressure, and body weight, the HbA1c level was even more lower in patients using antihypertensive drugs (difference 0.5 percent-points, p< 0.05).
Table 4.1  Clinical characteristics at time of glycemic assessment

<table>
<thead>
<tr>
<th></th>
<th>n=779*</th>
<th>n=572†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.9 (13.1)</td>
<td>65.3 (12.2)</td>
</tr>
<tr>
<td>Male</td>
<td>44.3</td>
<td>45.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.2 (17.6) (n=195)</td>
<td>83.4 (18.6) (n=127)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>5.0 (5.0)</td>
<td>5.2 (4.8)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td>8.5 (3.1)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td>7.8 (1.6)</td>
</tr>
</tbody>
</table>

Glucose lowering treatment

- Diet                      | 18.0   | 15.4   |
- Sulphonylureas            | 43.8   | 49.8   |
- Metformin                 | 20.8   | 19.2   |
- Insulin                   | 17.5   | 15.6   |

Switchers to insulin therapy | 20.3   | 20.6   |

Lipid lowering medication   | 14.6   | 14.3   |

Systolic blood pressure (mmHg)   | 152.0 (23.0) (n=343) | 152.1 (23.2) (n=224) |
Diastolic blood pressure (mmHg)  | 85.1 (11.1) (n=343) | 85.5 (11.4) (n=224) |

Antihypertensive medications  | 39.7   | 34.8   |
- Beta-blockers              | 18.5   | 15.4   |
- ACE-inhibitors             | 23.5   | 20.5   |
- Thiazide diuretics         | 10.9   | 9.1    |
- Ca-blockers                | 10.0   | 9.4    |
- Miscellaneous drugs        | 0.9    | 1.4    |

* Patients with fasting blood glucose values recorded  
†† Patients with HbA1c values recorded  
Values are means with standard deviation between parentheses, or percentages
If the analyses were restricted to patients with hypertension based on blood pressure values (>= 160/95 mmHg), the same associations were found. This was also when the analyses were performed for each general practice separately. The association with glycemic control was present in all categories of diabetes treatment (Figure 4.1). The use of lipid lowering medication (93.9% statins) was not associated with glycemic control (Table 4.2).

**Figure 4.1**  HbA₁c by antihypertensive medication use

* p< 0.05, ** p< 0.01
### Table 4.2 Glycemic control by current medication use

<table>
<thead>
<tr>
<th>Currently using antihypertensive medication</th>
<th>HbA1c (%)</th>
<th>Fasting glucose (mmol/l)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- no</td>
<td>8.0 (1.7)</td>
<td>8.6 (3.2)</td>
<td>78.7 (17.0)</td>
</tr>
<tr>
<td>- yes</td>
<td>7.6 (1.4)**</td>
<td>8.5 (3.0)</td>
<td>85.0 (18.0)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Currently using lipid lowering medication</th>
<th>HbA1c (%)</th>
<th>Fasting glucose (mmol/l)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- no</td>
<td>7.8 (1.6)</td>
<td>8.5 (3.2)</td>
<td>80.8 (17.4)</td>
</tr>
<tr>
<td>- yes</td>
<td>7.9 (1.6)</td>
<td>8.4 (2.6)</td>
<td>83.2 (18.9)</td>
</tr>
</tbody>
</table>

Values are means with standard deviation between parentheses.
* p< 0.05, ** p< 0.01

### Table 4.3 HbA1c and blood pressure by class of antihypertensive medication

<table>
<thead>
<tr>
<th>Class of antihypertensive medication</th>
<th>HbA1c (%)</th>
<th>Glucose (mmol/l)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antihypertensive</td>
<td>8.0 (0.1)</td>
<td>8.6 (0.1)</td>
<td>148/83 (2/1)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7.5 (0.3)</td>
<td>8.0 (0.4)</td>
<td>150/86 (4/2)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>7.7 (0.2)</td>
<td>8.5 (0.3)</td>
<td>155/88 (3/2)*</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>8.4 (0.5)</td>
<td>9.3 (0.9)</td>
<td>142/80 (7/3)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>7.8 (0.4)</td>
<td>7.4 (0.5)</td>
<td>156/85 (8/2)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6.9 (0.5)</td>
<td>- †</td>
<td>- †</td>
</tr>
<tr>
<td>Combinations</td>
<td>7.5 (0.1)*</td>
<td>8.5 (0.3)</td>
<td>158/87 (2/1)**</td>
</tr>
</tbody>
</table>

† No observations

Values are means with standard error between parentheses
* p< 0.05, ** p< 0.01, compared to no antihypertensive use
The difference in HbA₁c was present for all classes, except for calcium-antagonists, of antihypertensive medication, but only reached statistical significance in the largest subgroup of patients using drugs from more than one class (Table 4.3). The same associations were found in the four categories of diabetes treatment, but due to small numbers these associations were not statistically significant (data not shown). The fasting glucose levels were slightly lower for all classes of blood pressure lowering drugs, again as well in each stratum of glucose lowering treatment.

Patients using antihypertensive medication started more often with insulin treatment during the follow-up period (23.9% versus 17.9%, p< 0.05). However, when adjusting for duration of diabetes the association was no longer present.

**Discussion**

In this study we showed that patients using antihypertensive medication had better glycemic control, notably lower HbA₁c levels, and increased body weight. This was not explained by differences in diabetes treatment, duration of diabetes, or achieved blood pressure level.

In this observational study, a potential explanation for our findings is that antihypertensive treatment is driven by glycemic control and vice versa (confounding by indication). However, if anything, patients with worse glycemic control are likely to receive more antihypertensive medication, because they are at an increased risk for vascular complications, and are likely to visit the GP more often.

We found an opposite association, so confounding by indication can not explain our results. A more probable explanation might be that both use of antihypertensive medication and better glycemic control are the result of appropriate treatment of patients with diabetes. However, the absence of an association between lipid lowering medication and HbA₁c level does not support this explanation.
Beta-blockers and diuretics increase insulin sensitivity\(^4, \, 6\), whereas ACE-inhibitors have a potential protective effect on diabetic nephropathy.\(^{16}\) As a consequence, patients with type 2 diabetes are more likely to switch to ACE-inhibitors, and start more frequently with ACE-inhibitors.\(^{17}\) In the hypertension sub-study of the UKPDS patients were randomized to captopril or atenolol. Patients given atenolol gained more weight and had higher HbA\(_{1c}\) levels in the first half of the study. However, both treatments reduced blood pressure to the same extent and were similarly effective in reducing the risk of macrovascular and microvascular complications of diabetes.\(^{10}\)

Several studies have shown a positive association between blood pressure and insulin sensitivity.\(^{18, \, 19}\) Indeed, the 'metabolic syndrome' includes both insulin resistance and hypertension.\(^{20}\) A few studies have reported lower glucose or HbA\(_{1c}\) levels in type 2 diabetes patients with hypertension (or antihypertensive medication) compared to normotensive diabetes patients, as found in the present study.\(^{21, \, 22}\) In the ABCD trial the HbA\(_{1c}\) values continuously decreased in all treated diabetes patients during the study.\(^{23}\) These results are compatible with the hypothesis that type 2 diabetes patients without hypertension are a subgroup of patients with predominant beta-cell failure. Indeed, we found an increased weight in patients using antihypertensive medication.

The strength of our study is the use of routinely collected primary care data, which reflect usual clinical practice. General practice networks provide databases that may fruitfully be used for research.\(^{24}\) A limitation of this approach is the incompleteness of the data, notably of body weight, which is consistent with other studies performed in general practice.\(^{25}\)

In conclusion, this study shows that patients with type 2 diabetes mellitus who do not use any antihypertensive medication have increased HbA\(_{1c}\) levels. This may indicate that this subgroup has predominantly beta-cell failure.
References