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ORIGINAL REPORT

Antihypertensive drug therapy and the risk of lower extremity amputations in pharmacologically treated type 2 diabetes patients†

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SUMMARY

Purpose The objective of this study was to determine the association between different antihypertensive drug therapies and lower extremity amputations (LEAs) in type 2 diabetes patients.
Methods Data were obtained from the PHARMO Record Linkage System comprising pharmacy records and data on hospitalisations for all 450 000 residents of eight Dutch cities. In a nested case-control study among 12 140 type 2 diabetes patients who used antihypertensive drugs, 26 cases with a first LEA and 94 controls without a LEA matched on age, sex and calendar time were identified. Logistic regression was used to estimate the relative risk of LEA and to adjust for potential confounding factors.
Results Among type 2 diabetes patients who used antihypertensive drugs, subjects who used thiazide diuretics, alone or in combination, had a higher risk of LEA compared to subjects who used Angiotensin Converting Enzyme (ACE) inhibitor monotherapy (crude odds ratio (OR): 6.11 [95% confidence interval (CI): 1.32–28.27]). The use of thiazide diuretics was also associated with an increased risk of LEA when compared to the use of any non-thiazide antihypertensive drug (adjusted OR: 7.04 [1.10–45.30]). The increased risk of LEA associated with the use of thiazides compared to the use of non-thiazides depended on the duration of use (adjusted $OR_{\leq 365\ days}$, 4.82 [0.61–38.34] and adjusted $OR_{>365\ days}$, 26.16 [1.02–674.02], p-trend = 0.01).
Conclusions Treatment with thiazide diuretics compared to treatment with other antihypertensive drugs was associated with excess amputations in type 2 diabetes patients. Due to several limitations of this study, our findings do not preclude the use of thiazides in type 2 diabetes mellitus patients as yet. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — type 2 diabetes mellitus; amputation; antihypertensive drugs; thiazide

INTRODUCTION

Diabetes mellitus is the most common underlying cause of lower extremity amputations (LEAs). Compared to non-diabetic subjects, diabetes mellitus patients have a 20-fold increased risk of LEAs.[1] Previous studies among diabetes mellitus patients have established risk factors for LEA associated with diabetes mellitus, such as age, sex, race, BMI, smoking history, duration of diabetes, glycemic control, peripheral vascular disease, neuropathy and infections.[2–8] However, the role of blood pressure in the genesis of LEA is not clear. Some studies demonstrated that hypertension is a risk factor for LEAs,[9–12] while others

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did not find such association.[7,13,14] Whether pharmacological blood pressure treatment reduces the risk of LEA is uncertain. Randomized clinical trials of antihypertensive drug treatment have established the beneficial effects of these drugs on both major micro- and macro-vascular events,[11,15–22] but these studies have not specifically been designed to investigate LEA and will probably never be performed because of the low absolute risk of LEAs. Since antihypertensive drug treatment is often indicated in patients with type 2 diabetes due to the high prevalence of hypertension and cardiovascular comorbidity and because of the devastating consequences of a LEA, it would be useful to know whether specific antihypertensive drug classes differ in their risk of amputation. We had no *a priori* hypothesis about the risk of LEA associated with specific antihypertensive drug classes. Therefore, this study should be interpreted as a post-marketing surveillance study that compares the risk of LEA between different antihypertensive drug therapies in type 2 diabetes patients.

METHODS

Study setting

The PHARMO Record Linkage System (PHARMO RLS) was used as data source for this study. PHARMO RLS comprises pharmacy drug-dispensing records linked to hospital admission data of all community-dwelling residents of eight Dutch cities, counting for more than 450 000 patients' histories, from 1985 onwards.[23] Virtually complete data from this cohort, covering a period from 1985–1998, were available for each subject including sex, date of birth, drug names with Anatomical Therapeutic Chemical (ATC) codes, dispensing date, total supply, dosage regimen, prescriber and hospital discharge diagnoses. Using data on supply and dosage regimen, duration of exposure could be estimated. Drugs were coded according to the ATC classification. Hospital diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM codes).

Study subjects and design

Type 2 diabetes patients were identified in PHARMO RLS. Type 2 diabetes patients were defined as subjects in whom oral antidiabetic therapy was initiated between 1985 and 1998. Patients were eligible for inclusion in the cohort if they received no insulins during 180 days preceding the date of starting oral antidiabetic therapy, if they were dispensed at least two consecutive prescriptions of oral antidiabetic drugs and if the registration period in PHARMO RLS was larger than 180 days ($n = 12\,140$).

In this cohort, a nested case-control study was performed by selecting patients with a first LEA and with a PHARMO RLS registration of at least 3 years before the date of the LEA. The 3-year period was chosen to allow us to identify a minimum period of exposure. For each case, we identified up to five controls from the cohort of type 2 diabetes patients without a LEA who were matched on age (year of birth) and sex. An index date was assigned to each subject. For the cases, the index date was the date of the first amputation; for controls, the index date was identical to the index date of the case within the same case-control pair. Control subjects had to have at least 3 year of registration in PHARMO RLS before the index date. All subjects were required to have used antihypertensive drugs during the 3 years preceding the index date in order to reduce the influence of confounding by indication. If more than five controls were identified, we randomly selected five of them. LEAs were identified by using the classification of performances codes 5-845 through 5-848.[24] Subjects having an ICD-9-CM code for a traumatic amputation were excluded (ICD-9-CM: 895–897, 905.9, 928–929, 959).

From the type 2 diabetes cohort, 67 cases who met the inclusion criteria were identified in the period from 1985 to 1999; 23 cases were excluded because they did not use their first oral antidiabetic drug before the index date and 18 cases did not use antihypertensive drugs before the index date. Eventually, 26 cases and 94 controls were available for the analyses. Because cases and controls not using antihypertensive drugs were not eligible for this study, within a case-control pair it was possible that a case had used antihypertensive drugs, but that not all controls had and therefore the number of controls was sometimes less than five per case.

Antihypertensive drug use

Previous use of antihypertensive drugs among cases and controls was determined during 3 years preceding the index date. Antihypertensive drug use was classified into five major antihypertensive drug classes: thiazide diuretics, β-blockers, calcium-channel blockers, Angiotensin converting enzyme (ACE) inhibitors and a remaining category of miscellaneous antihypertensive drugs (mainly α-blockers).

To calculate the (cumulative) duration of antihypertensive drug use over the 3-year period, we constructed episodes of antihypertensive drug use. In case the time-span between two subsequent periods of

antihypertensive drug use was less than 60 days, the episode was considered uninterrupted.[25,26]

DATA ANALYSIS

Conditional logistic regression was performed to estimate matched OR and 95%CI using EGRET.[27] Potential confounders that could be assessed by using pharmacy and hospitalisation data included hospitalisations for macrovascular diseases (cerebrovascular disease (ICD-9-CM codes 430–438), congestive heart failure (ICD-9-CM codes 426–428), ischemic heart disease (ICD-9-CM codes 410–414), peripheral vascular disease (ICD-9-CM codes 441, 443.9, 785.4), hypertension (ICD-9-CM codes 401–405)), hospitalisations for microvascular diseases (retinopathy (ICD-9-CM codes 362, 250.5, 379.23), nephropathy (ICD-9-CM codes 581, 585, 586), neuropathy (ICD-9-CM codes 337, 357)), cardiovascular drug use (e.g. cardiac drugs, loop diuretics, lipid lowering agents, antithrombotic drugs), hormone replacement therapy, use of antiasthmatic drugs and comorbidity as measured by the chronic disease score (CDS). Cardiovascular disease was defined as any hospitalisation for macrovascular disease or the use of cardiacs and/or loop diuretics. All these variables were measured before the index date. The CDS was calculated by assigning scores (0–5) to classes of drugs according to the severity of the disease for which they were prescribed during the year before the index date.[28,29]

In the first analysis, the use of ACE inhibitor monotherapy served as reference category. The use of thiazide diuretics, betablockers, calcium channel blockers and miscellaneous antihypertensive drugs alone or in combination were compared with the use of ACE inhibitor monotherapy. A dichotomous variable was created that indicated whether a subject was using the antihypertensive drug alone or in combination and included this variable in the model to investigate how the use of multiple drug therapies for hypertension affected the findings. In a second analysis, we compared the use of specific antihypertensive drug classes versus all other antihypertensive drug classes combined. Confounding was addressed by adding confounding factors one at a time to the univariate logistic regression model with LEA as dependent variable and antihypertensive drug regimen as independent variable. A change in the association between antihypertensive drug and LEA of more than 10% (relative change of OR) was considered as an important confounder. Due to the limited number of cases, we were not allowed to make adjustments for all significant variables simultaneously.[30] Therefore, we could only adjust for the three most important variables simultaneously.

RESULTS

The incidence of amputations in type 2 diabetes patients was estimated as 3.9 per 10 000 person years (44/114099.2 person years). General characteristics of cases and controls using antihypertensive drugs are given in Table 1. Due to the matching, the mean age (72.9 ± 1.7 years and 72.7 ± 0.9 years respectively)

Table 1. General characteristics of the study population using antihypertensive drugs

Variable	Cases	Controls
Number	26	94
Mean age (years ± S.E.M)	72.9 ± 1.7	72.7 ± 0.9
Male	15 (58)	57 (61)
Mean duration in PHARMO RLS (years ± S.E.M.)	9.4 ± 0.5	6.2 ± 0.3[a]
Mean duration of DM type 2 (years ± S.E.M.)	4.1 ± 0.5	2.0 ± 0.2[a]
Insulin use	7 (27)	10 (11)
Number of amputations		
1	18 (69)	
2	5 (19)	
3	3 (12)	
Comedication		
Antiasthmatic drugs	9 (35)	23 (25)
Hormone replacement therapy	2 (8)	3 (3)
Cardiacs[b]	17 (65)	43 (46)
Nitrates	9 (35)	33 (35)
Loop diuretics	13 (50)	34 (36)
Lipid lowering drugs	2 (8)	10 (11)
Antithrombotic drugs	22 (85)	51 (54)[a]
Antibiotic drugs	24 (92)	67 (71)[a]
Antigout drugs	2 (8)	5 (5)
Chronic Disease Score		
0	0 (0)	3 (3)
1–5	13 (50)	51 (54)
>5	13 (50)	40 (43)
Hospitalisations		
Cerebrovascular disease	5 (19)	2 (2)[a]
Congestive heart failure	12 (46)	3 (3)[a]
Ischemic heart disease	7 (27)	4 (4)[a]
Peripheral vascular disease	9 (35)	2 (2)[a]
Hypertension	3 (12)	1 (1)[a]
Retinopathy	1 (4)	0 (0)
Neuropathy	0 (0)	0 (0)
Nephropathy	3 (12)	2 (2)
Percutaneous transluminal angioplasty	3 (12)	0 (0)[a]

Data are means ± S.E.M. or number (%).
DM type 2: type 2 diabetes.
[a] $p < 0.05$.
[b] Includes mainly heart glycosides, antiarrythmics and nitrates (ATC code C01).

and sex distribution (men 58% and women 61% respectively) were similar in cases and controls. Cases had a longer duration of treatment for type 2 diabetes (4.1 ± 0.5 and 2.0 ± 0.2 years respectively) and a longer mean registration period in PHARMO RLS (9.4 ± 0.5 and 6.2 ± 0.3 years respectively) than controls. Insulin use at the index date was more common in cases than controls (27% and 11% respectively). With respect to drug use, antithrombotics and antibiotic drugs were prescribed more frequently in cases than controls. Hospitalisations for cerebrovascular diseases, congestive heart failure, ischemic heart diseases, peripheral vascular diseases, hypertension and percutaneous transluminal angioplasty were more common in cases than controls (Table 1). The use of combinations of antihypertensive drugs was similar for those who use thiazides (51%), β-blockers (66%), ACE inhibitors (49%), calcium-channel blockers (63%) and miscellaneous antihypertensive drugs (45%).

In Table 2, the associations between antihypertensive drug therapies and the risk of amputation in type 2 diabetes patients are shown. Subjects who used thiazide diuretics had a higher risk of LEA (OR: 6.11 [95%CI: 1.32–28.27]) compared to those who used ACE inhibitor monotherapy. The use of β-blockers was associated with a non-significantly lower risk of LEA (OR: 0.29 [95%CI: 0.07–1.22]). The use of calcium channel blockers and miscellaneous antihypertensive drugs were associated with a non-significantly increased risk of LEA (OR: 2.96 [95%CI: 0.83–10.58] and 2.93 [95%CI: 0.31–27.80] respectively). When compared to the use of other non-thiazide antihypertensive drugs, the use of thiazide diuretics was associated with an increased risk of LEA (OR: 3.33 [95% CI: 1.00–11.06]. This increased risk of LEA remained after adjustment for several factors (Table 3).

We also compared the risk of LEA among thiazide users compared to non-thiazide users after exclusion of all subjects who used β-blockers because of the possibility of confounding by contraindication to the use of β-blockers in subjects with peripheral vascular disease. When excluding those who used β-blockers, the risk of LEA remained increased, although not statistically significant, for use of thiazides compared to use of ACE inhibitor monotherapy (OR unadjusted, 2.41 [95%CI: 0.24–24.01]) and compared to the use of non-thiazide antihypertensive drugs (OR unadjusted, 1.83 [95%CI: 0.41–8.09], OR (adjusted for insulin use and duration of DM), 5.15 [0.46–57.11]).

Table 3. Effect of adjustment on the association of thiazide use and the risk of LEA in type 2 diabetes patients compared to other antihypertensive drug use

Adjustment	OR [95%CI]
No adjustment	3.33 [1.00–11.06]
Duration of type 2 diabetes (1)	6.70 [1.21–37.08]
Congestive heart failure (2)	3.53 [1.00–12.45]
Other vascular diseases (3)	2.53 [0.64–10.08]
Cardiovascular disease (4)	3.36 [0.95–11.84]
Combination of antihypertensives (5)	3.36 [1.00–11.30]
Chronic Disease Score > 5 (6)	3.83 [1.10–13.29]
Use of insulin (7)	4.87 [1.19–20.01]
Use of lipid lowering drugs (8)	3.62 [1.06–12.35]
Use of antithrombotics (9)	3.72 [1.03–13.47]
Use of antibiotics (10)	3.58 [0.99–13.02]
1, 4 and 7	7.04 [1.10–45.30]

The association between thiazide use and the risk of LEA was similar in subgroups defined by age, sex and duration of type 2 diabetes.

When cumulative thiazide use was stratified into $\leq$365 and >365 days during the 3-year period before the index date, we found a duration-dependent increased risk of amputation among thiazide users (adjusted $OR_{\leq 365\ days}$, 4.82 [0.61–38.34] and adjusted $OR_{>365\ days}$, 26.16 [1.02–674.02]) compared with subjects who used other antihypertensive drugs (p-trend = 0.01, Table 4).

DISCUSSION

In this nested case-control study among incident type 2 diabetes patients, the use of thiazide diuretics was associated with an increased risk of LEA compared to the use of non-thiazide antihypertensive drugs.

Table 2. Antihypertensive drug use and the risk of LEA in type 2 diabetes patients

Antihypertensive drug	Cases	Controls	OR crude [95%CI]
	$n = 26$	$n = 94$	
ACE inhibitor monotherapy	5	23	1.00 [reference]
Thiazide[a]	11	20	6.11 [1.32–28.27]
β-blocker[a]	7	34	0.29 [0.07–1.22]
Calcium-channel blocker[a]	10	30	2.96 [0.83–10.58]
Miscellaneous antihypertensive drugs[a]	2	9	2.93 [0.31–27.80]
ACE inhibitor combination therapy	7	21	1.68 [0.37–7.55]

[a]Alone or in combination (not including an ACE inhibitor).

Table 4. Cumulative duration of thiazide use and the risk of LEA in type 2 diabetes patients compared to other antihypertensive drug use

Antihypertensive drug	Case	Control	OR crude [95%CI]	OR adjusted [95%CI][a]
Other antihypertensive drugs	15	74	1.00 [reference]	1.00 [reference]
Thiazides	11	20	3.33 [1.00–11.06]	7.04 [1.10–45.30]
Other antihypertensive drugs	15	74	1.00 [reference]	1.00 [reference]
Thiazides $\leq$365 days	6	15	2.00 [0.48–8.33]	4.82 [0.61–38.34]
Thiazides $>$ 365 days	5	5	11.52 [1.16–114.11]	26.16 [1.02–674.02]

[a]Adjustment: duration of type 2 diabetes, cardiovascular disease, use of insulin.

Several possible mechanisms may explain the increased risk of LEA associated with the use of thiazides. First, due to the supposed diabetogenic effects of diuretics on the glucose metabolism and insulin sensitivity[31] and their ability to alter the lipid profile,[32] risk of development of vascular diseases via atherosclerosis, which may lead to amputations in a later stadium, may be increased in subjects using these drugs. This also may explain the observed duration-dependent effect of thiazides on the risk of amputations among diabetes mellitus patients. Second, decreased serum potassium and magnesium depletion may occur with thiazides contributing to insulin release, insulin resistance, vasoconstriction and thrombosis.[33–36] This may worsen or cause peripheral vascular complications leading to amputations. Although these metabolic disturbances may not appear clinically large enough to cause a worsening of peripheral vascular disease in diabetes mellitus patients, risk table analysis suggests that they can offset or even reverse the benefits of reducing blood pressure.[37] Another potential explanation may be that ACE inhibitors had a beneficial effect over the other therapeutic classes and that diuretics actually have a null effect.[38] Since we compared different antihypertensive drugs and did not include an untreated reference group we cannot tell whether diuretics have a negative effect or that ACE inhibitors have a beneficial effect.

Only few studies have reported results of antihypertensive drug use and the risk of amputations. In the United Kingdom prospective diabetes study (UKPDS), a similar effect of captopril and atenolol on the risk of amputations was shown (RR 1.48 [99% CI: 0.23–9.71]).[16] However, due to the small number of events, it is difficult to draw a strong conclusion from these results. Other randomized controlled trials of antihypertensive drug treatment included peripheral vascular disease, which may be an intermediate step leading to an amputation,[39] as an endpoint. For instance, the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) including 33% diabetes mellitus patients[40,41] found that subjects randomized to treatment with doxazosin, amlodipine or lisinopril compared to subjects randomized to chlorthalidone had a similar risk of peripheral arterial disease (RR 95%CI: 1.07 [0.88–1.30], 0.87 [0.75–1.01] and 1.04 [0.90–1.19] respectively). In the intervention as a goal in hypertension treatment (INSIGHT) trial comprising 20.6% diabetes mellitus patients, subjects using co-amilozide had more peripheral vascular disorders as adverse event than nifedipine users (5.3% and 3.0%, respectively; $p < 0.0001$).[42]

To appreciate our results, some limitations of this study need to be addressed. Confounding may have occurred in this observational study, as physicians prescribe antihypertensive drugs not randomly. The increased risk of LEA among thiazide users may be partly explained by confounding by contraindication. Thiazides could have been prescribed more often in patients with peripheral vascular disease, as this is a contraindication for β-blockers, because of their perceived vasoconstrictive effect.[43,44] Although subjects who used thiazide diuretics were less often hospitalized for peripheral vascular disease compared to users of non-thiazide antihypertensive drugs, we could not fully investigate this hypothesis because we had no information on the presence of peripheral vascular disorders that did not require hospitalisation. We further explored the possibility of confounding by contraindication by excluding subjects who used β-blockers. In this analysis, the risk of LEA among thiazide users decreased, suggesting that confounding by contraindication to the use of β-blockers lead to overestimation of the risk of LEA among users of thiazide diuretics. However, the association remained increased. Confounding by indication was less likely to have influenced our results because both thiazides and β-blockers are currently first choices for the treatment in type 2 diabetes patients and may therefore be prescribed more often to lower risk patients than other antihypertensive drugs such as ACE inhibitors and calcium antagonists.

This was in agreement with the observation that thiazide users were less often hospitalised for congestive heart failure, peripheral vascular disease and

other (cardiovascular) comorbidity. A history of cardiovascular complications and a longer duration of type 2 diabetes was more often present among cases compared to controls. However, adjustment for these factors did increase the risk of LEA among thiazide users compared to users of non-thiazide antihypertensive drugs. Thus, these factors did probably not explain our findings.

Another limitation includes the lack of information on certain prognostic factors, such as body mass index, smoking history, lipids, HbA_{1c} and blood pressure. However, since these factors may not all influence the choice of antihypertensive drug, they would not confound our results. Nonetheless, residual confounding due to unmeasured or inadequately measured confounders cannot be excluded.

Finally, we cannot exclude the possibility of a chance finding due to the small numbers in this study. For the analysis of thiazides versus ACE inhibitor therapy and also for the second analysis of thiazides-versus non-thiazides the power was 66% ($\alpha = 0.05$).

Reducing the occurrence of amputations by treating risk factors in an earlier stage of the etiological chain of LEAs may have large effects later on the occurrence of amputations among diabetes mellitus patients. Coexistence of several risk factors for LEAs, such as hyperglycemia, peripheral vascular disease, neuropathy implicates that decreasing the risk of LEAs should deal with treatment of several risk factors.[4] Furthermore, the implementation of patient education and foot care programmes is important in reducing the need for LEAs.[45–47] While it is clear that many diabetes mellitus patients require antihypertensive drug treatment to reduce their risk of cardiovascular complications, it is less certain which antihypertensive drug should be chosen as a first choice.[48] Recent evidence from ALLHAT suggests that chlortalidone is superior to lisinopril and amlodipine in the reduction of one or more major cardiovascular disease events in diabetics and non-diabetics.[41] The choice of initial antihypertensive agent depends not only on the risk reduction of cardiovascular disease but also on potential adverse effects of antihypertensive agents. An assessment of the overall benefits and risks of antihypertensive drugs should also include the effect of these drugs on the risk of LEA.

In conclusion, our data suggest that treatment with thiazide diuretics compared to treatment with antihypertensive drug regimens not including a thiazide diuretic may be associated with an increased risk of LEA in type 2 diabetes patients. However, due to several limitations of our study, an overall benefit/risk assessment including the risk of LEA is not yet feasible. Future studies, with larger sample sizes may address this question more adequately.

KEY POINTS

- Amputations are severe complications in type 2 diabetes mellitus patients.
- Antihypertensive drug treatment may influence the risk of amputations.
- Thiazide diuretics may increase the risk of amputations in comparison to other antihypertensive drug therapies.
- Confounding and chance remain alternative explanations for the increased risk of amputations among thiazide users compared to users of other antihypertensive drugs.

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