

# Cardiovascular Drug Use and Hospitalizations Attributable to Type 2 Diabetes

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**OBJECTIVE** — To investigate cardiovascular drug use and hospitalizations attributable to type 2 diabetes from 1 year before until 6 years after the start of oral antidiabetic therapy.

**RESEARCH DESIGN AND METHODS** — In this cohort study, 2,584 patients with type 2 diabetes were selected from the PHARMO Record Linkage System, comprising pharmacy records and hospitalizations for all 320,000 residents of six Dutch cities. Patients with type 2 diabetes were identified as incident oral antidiabetic drug users between 1992 and 1997. Nondiabetic subjects were 1:1-matched for age, sex, pharmacy, and index date and received no insulin, oral antidiabetic drugs, or glucose-testing supplies.

**RESULTS** — Patients with type 2 diabetes were more likely to use cardiovascular drugs (RR 1.28 [95% CI 1.23–1.34]) and to be hospitalized because of cardiovascular diseases (1.54 [1.33–1.78]) after the start of oral antidiabetic therapy than nondiabetic subjects. Differences between patients with type 2 diabetes and nondiabetic subjects lessened from 1 year before until 6 years after the start of oral antidiabetic therapy, reflected by decreasing attributable risks for diuretics,  $\beta$ -blockers, calcium channel blockers, and cardiac and antithrombotic drugs. The difference in use of angiotensin-converting enzyme inhibitors and lipid-lowering drugs increased. Cardiovascular hospitalizations attributable to type 2 diabetes were ~50% in the years close to the start of oral antidiabetic treatment and decreased to ~33% in the following years.

**CONCLUSIONS** — Although cardiovascular drug use and hospitalizations remained increased in patients with type 2 diabetes after the start of oral antidiabetic therapy, cardiovascular drug use attributable to type 2 diabetes decreased after the start of oral antidiabetic therapy, especially  $\beta$ -blockers, whereas cardiovascular hospitalizations first decreased and then stabilized.

*Diabetes Care* 24:1428–1432, 2001

The introduction of new drugs and the more intensive treatment of cardiovascular risk factors (i.e., angiotensin-converting enzyme [ACE] inhibitors, lipid-lowering agents) in type 2 diabetes have influenced the prescribing behavior during the last decade.

Previous studies have indicated that patients with diabetes have high overall

drug use, particularly of cardiovascular drugs (1–6), have frequent cardiovascular diseases leading to hospital admissions (7,8), and consequently incur high costs for medical care (6,7,9). The timing of the excess of drug use and hospitalizations is not well documented in relation to the diagnosis of type 2 diabetes. This information may also be used for cost-effective-

ness studies and by health care policy makers in the allocation of healthcare resources. Specifically, it is not known how cardiovascular diseases attributable to type 2 diabetes vary from the time of diagnosis until many years after the diagnosis. Brown et al. (8,9) reported substantially higher costs in patients with type 2 diabetes compared with matched nondiabetic control subjects during the first 8 years after diagnosis. In addition to these findings, estimates of cardiovascular drug use and hospitalizations may be used to assess trends attributable to diagnosed type 2 diabetes and to calculate excess costs.

The aim of the study was to investigate cardiovascular drug use and hospitalizations attributable to type 2 diabetes from 1 year before until 6 years after the start of oral antidiabetic treatment.

## RESEARCH DESIGN AND METHODS

### Study setting

The data source for this study was the PHARMO Record Linkage System, comprising pharmacy dispensing records and hospital admission data of all community-dwelling residents of six Dutch cities and including more than 450,000 patient histories from 1985 to the present (10). Virtually complete data from this cohort covering a period from January 1991 to July 1999 and comprising 320,000 patients histories were available for each subject, including sex, date of birth, drug names with Anatomical Therapeutic Chemical codes, dispensing date, total supply, dosage regimen, prescriber, and hospital discharge diagnoses. Using data on supply and dosage regimen, a proxy duration of exposure could be estimated. Drugs were coded according to the Anatomical Therapeutic Chemical classification, and hospital diagnoses were coded according to the ICD-9-CM codes.

### Study subjects

Patients with incident type 2 diabetes were defined as subjects in whom oral an-

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Received for publication 5 December 2000 and accepted in revised form 12 April 2001.

**Abbreviations:** ACE, angiotensin-converting enzyme; AR, attributable risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—Annual cardiovascular drug use and hospitalizations from 1 year before until 6 years after the initiation of oral antidiabetic therapy comparing patients with type 2 diabetes (DM) and nondiabetic subjects (Non-DM)**

Years	n	Cardiovascular drug use			Cardiovascular hospitalizations		
		DM (%)	Non-DM (%)	AR [95% CI]	DM (%)	Non-DM (%)	AR [95% CI]
*	2,584	56.1	41.2	26.6 (22.2–30.7)	5.0	2.3	53.1 (37.8–66.0)
1	2,584	60.3	44.9	25.5 (21.5–29.4)	4.7	2.5	47.5 (28.4–60.5)
2	2,088	63.2	47.4	25.0 (20.7–29.1)	5.4	3.5	35.4 (13.6–51.4)
3	1,526	63.1	47.1	25.4 (20.3–30.1)	4.3	2.9	32.2 (1.9–53.6)
4	980	64.2	48.6	24.3 (18.0–30.1)	4.6	3.1	33.3 (–5.8 to 57.1)
5	579	61.1	48.7	20.3 (11.4–28.3)	3.6	2.4	33.3 (–25.0 to 65.9)
6	249	58.2	48.6	16.5 (1.5–29.2)	3.2	4.0	–25.0 (–212.1 to 49.9)
1–6†	2,584	73.8	57.5	22.1 (18.9–25.2)	15.4	10.0	35.1 (24.8–43.9)

\*The first year before the start of oral antidiabetic therapy; †average prevalence of years 1–6 calculated per subject.

tid diabetic therapy was initiated between 1992 and 1997. Patients with type 2 diabetes were included in the cohort if they received at least two consecutive prescriptions of antidiabetic drugs and no insulin and analogs before the date of starting oral antidiabetic therapy. The index date was defined as the date of the first dispensed oral antidiabetic drug.

For each patient with type 2 diabetes, one nondiabetic subject was matched for age (year of birth), sex, pharmacy, and index date and randomly selected from eligible nondiabetic subjects in the PHARMO area. All patients with diabetes and nondiabetic subjects had at least 1 year of drug-dispensing records available before and after the index date. Only full years of follow-up were used for the analysis.

Nondiabetic subjects received no antidiabetic treatment, i.e., insulin, oral antidiabetic drugs, or glucose-testing supplies. The index date and the duration of the pharmacy record history were matched for the patients with diabetes and nondiabetic subjects. We also excluded patients with diabetes with hospital admissions related to diabetes (ICD-9-CM: 250–251), polyneuropathy in diabetes (ICD-9-CM: 357.2), diabetic retinopathy (ICD-9-CM: 362.0), diabetic cataract (ICD-9-CM: 366.4), diabetes during pregnancy (ICD-9-CM: 648), or insulin intoxication (ICD-9-CM: 962.3) in the year before the start of the index date. Subsequently, nondiabetic subjects who were admitted to the hospital because of any of these diabetes-related disorders during the study period were excluded.

## Outcomes

Drug-dispensing records of cardiac drugs (mainly cardiac glycosides, antiarrhythmics, and nitrates), diuretics (mainly thiazides, loop diuretics, and combination therapy of potassium-sparing agents and diuretics),  $\beta$ -blockers, calcium-channel blockers, ACE inhibitors, lipid-lowering agents, or antithrombotic and miscellaneous antihypertensives (mainly  $\alpha$ -blockers) were identified for patients with type 2 diabetes and nondiabetic subjects. Antithrombotic drugs mainly consisted of platelet aggregation inhibitors (e.g., acetylsalicylic acid) and vitamin K antagonists (e.g., acenocoumarol). Cardiovascular hospitalizations were defined by the following discharge diagnoses: ischemic heart disease (ICD-9-CM: 410–414), congestive heart failure (ICD-9-CM: 428), arrhythmia (ICD-9-CM: 426–427), peripheral vascular disease (ICD-9-CM: 441, 443.9, 785.4), cerebrovascular disease (ICD-9-CM: 430–438), and hypertension (ICD-9-CM: 401–405).

## Data analysis

Annual period prevalences of cardiovascular drug use and hospitalizations were determined for the study population by assessing the number of subjects who received at least one prescription of the specific drug category or had at least one hospitalization for the specific indication, respectively. Prevalence ratios (type 2 diabetic versus nondiabetic subjects) and 95% CIs were expressed as RRs.

We estimated attributable risks (ARs) with the following formula:  $AR = (RR - 1)/RR \times 100\%$ . The 95% CIs of AR were calculated by substitution of RR with the lower or upper confidence limits of the RR

into the equation (11). Linear regression was used to determine trends in cardiovascular drug use and hospitalizations after the start of oral antidiabetic therapy.

**RESULTS** — A total of 2,584 patients with incident type 2 diabetes and 2,584 matched nondiabetic subjects were identified in the period from 1992 to 1997. At the index date, the mean age was 62.6 years, and 45.1% of the subjects were older than 65 years of age. Female subjects represented 52.4% ( $n = 1,354$ ) of the study population and were older ( $67.5 \pm 14.2$  years) than the male subjects ( $64.0 \pm 13.0$  years).

The sample size of the study population changed over time as the follow-up period differed per matched pair, decreasing from 2,584 pairs in the first year to 249 pairs in the sixth year after the index date.

Cardiovascular drug use after the start of oral antidiabetic therapy was significantly increased in patients with type 2 diabetes compared with nondiabetic subjects (RR 1.28 [95% CI 1.23–1.34]) and was increased consistently for all individual cardiovascular drug categories (Table 1). Comparison of 1 year before with 1–6 years after the start of oral antidiabetic therapy showed that the differences between patients with type 2 diabetes and nondiabetic subjects in the use of diuretics,  $\beta$ -blockers, calcium channel blockers, and cardiac and antithrombotic drugs lessened, reflected by decreasing ARs (Table 2 and Fig. 1). The use of ACE inhibitors and lipid-lowering drugs increased in patients with type 2 diabetes and nondiabetic subjects, more so for patients with type 2 diabetes, reflected by increasing

**Table 2—Cardiovascular drug use attributable to type 2 diabetes from 1 year before ( $AR_{before}$ ) and the first until sixth years after ( $AR_{after}$ ) the initiation of oral antidiabetic therapy**

Cardiovascular drug	$AR_{before}$ (95% CI)	$AR_{after}$ (95% CI)
Cardiac drugs*	37.4 (28.0–45.6)	29.9 (22.7–36.4)
Diuretics	39.9 (33.3–45.9)	30.5 (24.7–35.8)
$\beta$ -blockers	31.2 (23.4–38.2)	17.3 (9.8–24.1)
Calcium channel blockers	42.9 (32.8–51.4)	35.1 (27.0–42.4)
ACE inhibitors	44.2 (35.0–52.2)	49.1 (43.6–54.0)
Lipid-lowering drugs	16.1 (–6.2 to 33.6)	50.7 (43.4–57.2)
Antithrombotics	29.0 (20.0–37.0)	23.4 (16.9–29.5)
Miscellaneous antihypertensive drugs†	40.0 (6.7–61.4)	42.5 (21.3–58.0)
Total cardiovascular drugs	26.6 (22.2–30.7)	22.1 (18.9–25.2)

\*Includes mainly heart glycosides, antiarrhythmics, and nitrates (Anatomical Therapeutic Chemical code C01); †includes mainly  $\alpha$ -blockers (Anatomical Therapeutic Chemical code C02).

ARs. The largest contributions of drug use attributable to type 2 diabetes after the start of oral antidiabetic therapy were lipid-lowering drugs (AR 50.7% [95% CI 43.4–57.2]) and ACE inhibitors (AR 49.1% [43.6–54.0]), whereas  $\beta$ -blockers contributed less (AR 17.3% [9.8–24.1]). An increasing trend in use of ACE inhibitors attributable to type 2 diabetes was observed in the years following the initiation of oral antidiabetic therapy ( $\beta = 1.64$ ,  $P = 0.04$ ), with significant decreasing trends for  $\beta$ -blockers ( $\beta = -5.75$ ,  $P = 0.002$ ), calcium channel blockers ( $\beta = -2.61$ ,  $P = 0.048$ ), antithrombotic drugs ( $\beta = -4.23$ ,  $P = 0.04$ ), and all cardiovascular drugs ( $\beta = -1.72$ ,  $P = 0.02$ ). The AR of the other drug categories remained almost equal throughout the 6 years after the initiation of oral antidiabetic therapy. Until the fifth year after the start of oral antidiabetic therapy, patients with type 2 diabetes were more likely to use  $\beta$ -blockers than nondiabetic subjects, whereas after the fourth year, use of  $\beta$ -blockers was equal in both groups.

Cardiovascular hospitalizations attributable to type 2 diabetes were ~50% in the years before initiation of oral antidiabetic therapy and decreased to ~33% in the following years (Table 1).

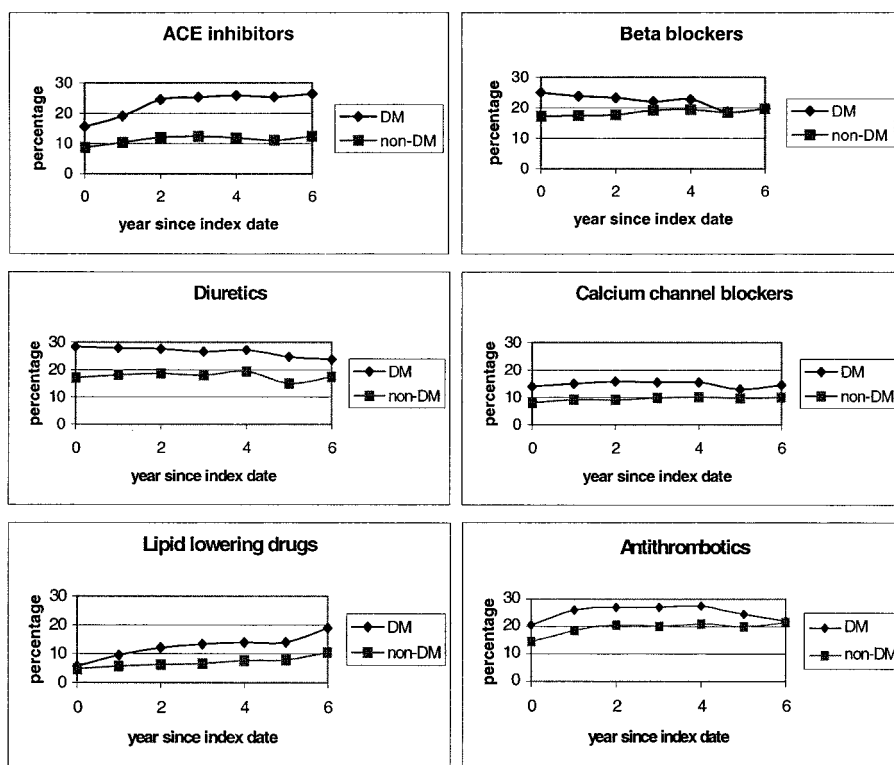
Although the numbers of specific cardiovascular hospitalizations were low, hospitalizations attributable to type 2 diabetes decreased from 1 year before to 6 years after the initiation of oral antidiabetic therapy for ischemic heart disease ( $AR_{before}$  47.1 [12.7–67.9] vs.  $AR_{after}$  34.4 [8.0–53.2]), congestive heart failure or arrhythmia ( $AR_{before}$  69.6 [48.6–82.0] vs.  $AR_{after}$  36.0 [20.4–48.6]), and cerebrovascular disease ( $AR_{before}$  55.6 [7.7–78.6] vs.  $AR_{after}$  37.5 [–25.0–68.7]).

**CONCLUSIONS**— These data suggest an increased risk for cardiovascular drug use and hospitalizations before and after the initiation of oral antidiabetic therapy in patients with type 2 diabetes compared with nondiabetic subjects, which agreed with earlier findings (1–5). However, the excess risk in type 2 diabetes decreased for cardiovascular drug use, especially for  $\beta$ -blockers, and decreased, but stabilized, for cardiovascular hospi-

talizations in the years following the start of oral antidiabetic therapy.

After the initiation of oral antidiabetic therapy, use of ACE inhibitors and lipid-lowering drugs increased among patients with type 2 diabetes compared with nondiabetic subjects. More intensive treatment with lipid-lowering and antihypertensive drugs in patients with diabetes has been propagated since the results of the Scandinavian Simvastatin Survival Study (12) and the U.K. Prospective Diabetes Study (13). Awareness of these beneficial effects may have influenced the prescription practices of physicians (14,15).

Despite the clear beneficial effects of diuretics and  $\beta$ -blockers in the reduction of cardiovascular events in patients with diabetes (16,17), the use of  $\beta$ -blockers, and to a lesser extent of diuretics, decreased in patients with type 2 diabetes compared with nondiabetic controls after the initiation of the oral antidiabetic therapy. The presumed negative effects of diuretics and  $\beta$ -blockers on insulin sensitivity may have triggered physicians to discontinue prescription of these drugs in patients with diabetes (18–20). The de-



**Figure 1—Annual cardiovascular drug use stratified by drug class in patients with diabetes (DM) compared with nondiabetic controls (non-DM) 1 year before (time = 0) until 6 years after the initiation of oral antidiabetic therapy (index date).**



creased use of  $\beta$ -blockers in patients with type 2 diabetes may also be explained by a higher case-fatality rate of patients with diabetes and angina compared with nondiabetic subjects with angina (21). Unfortunately, we could not evaluate this with the current data. However, among individuals who received  $\beta$ -blockers during the first year, the mean duration of follow-up was comparable for patients with type 2 diabetes (2.93 years) and nondiabetic control subjects (2.96 years).

Differences between patients with type 2 diabetes and nondiabetic subjects became less for the use of calcium channel blockers, cardiac drugs, and antithrombotic drugs in the years following the initiation of oral antidiabetic therapy. Over time, nondiabetic subjects may have visited physicians more often with their increasing age and subsequently had higher morbidity and, therefore, were more often diagnosed with cardiovascular diseases. As a result, the difference in cardiovascular drug use between the groups may have lessened in the consecutive years.

Although we observed that cardiovascular hospitalizations attributable to type 2 diabetes were  $\sim$ 50% in the years around the initiation of oral antidiabetic therapy and that there was a decrease, but stabilization, in the following years, patients with type 2 diabetes still had an excess risk of cardiovascular hospitalizations during the first 6 years compared with nondiabetic control subjects. Intensive control of cardiovascular risk factors and the higher case-fatality rates in patients with diabetes may have contributed to the stabilization of cardiovascular hospitalizations. Patients who were first diagnosed with type 2 diabetes while hospitalized for a cardiovascular disease may partially account for the high number of hospitalizations during the first year.

Limitations of this study include the lack of information on prognostic factors, such as BMI, smoking history, lipids, albumin, HbA<sub>1c</sub>, and blood pressure. Bias may have occurred in selecting the patients with diabetes and the nondiabetic subjects. The clinical diagnosis of type 2 diabetes was probably determined before the pharmacological treatment of type 2 diabetes. We excluded admissions during which diabetes was diagnosed. However, patients who had been diagnosed with type 2 diabetes and who were being

treated with diet only were not identified in the database, and nondiabetic subjects may have been selected while being treated with diet for type 2 diabetes. However, in the Netherlands, only  $\sim$ 7% of patients with clinically diagnosed type 2 diabetes are treated with diet only (22). Furthermore, patients with undiagnosed type 2 diabetes may have been included in the nondiabetic control group (23,24). These biases would, however, probably underestimate the associations.

Patients with diabetes may receive more drug because their condition brings them into frequent contact with the health care system, increasing both the likelihood of detecting and treating previously undiagnosed diseases and the continuation of medication for known chronic disorders.

In conclusion, cardiovascular drug use and hospitalizations remained higher for patients with type 2 diabetes compared with nondiabetic subjects during the 6-year time period. This emphasizes the need for intensive treatment of cardiovascular diseases and risk factors in patients with type 2 diabetes. However, our findings reflect diminishing cardiovascular drug use and hospitalizations since the initiation of oral antidiabetic therapy in patients with type 2 diabetes compared with nondiabetic subjects. Moreover, a decreasing trend in cardiovascular drug use attributable to type 2 diabetes, especially of  $\beta$ -blockers, was found in the years following the initiation of oral antidiabetic therapy, whereas cardiovascular hospitalizations attributable to type 2 diabetes decreased after the first year and stabilized during the following years. This decreasing trend in the use of  $\beta$ -blockers is not in agreement with current evidence suggesting that these drugs are beneficial in patients with diabetes.

**Acknowledgments**—This study was supported by an unrestricted grant from Novo Nordisk, Alphen aan den Rijn, the Netherlands.

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