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BRIEF REPORT

# Trends in the prescription of anti-diabetic medications in the United Kingdom: a population-based analysis†

Kristian B. Filion MSc[1,2,3], Lawrence Joseph PhD[1,2], Jean-François Boivin MD, ScD[1,3], Samy Suissa PhD[1,3] and James M. Brophy MD, PhD[1,2]*

[1]*Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada*
[2]*Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada*
[3]*Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, Montreal, Quebec, Canada*

## SUMMARY

**Purpose** Over the last decade, guidelines for the treatment of type 2 diabetes have increasingly favored tighter glycemic control, necessitating the use of more aggressive pharmacological therapy. The objective of this study was to describe trends in the prescription of anti-diabetic medications among patients with type 2 diabetes in the United Kingdom (UK).

**Methods** Using the General Practice Research Database, we constructed a cohort of patients with type 2 diabetes. Diabetes was defined as the presence of a diagnosis of diabetes, HbA1c $\geq 7\%$, or $\geq 2$ prescriptions for anti-diabetic medications. Analyses were conducted for the full cohort as well as a sub-cohort with incident diabetes.

**Results** Our full cohort involved 67 981 patients and a total of 320 089 patient-years, and our sub-cohort involved 30 234 patients with incident diabetes and 111 890 patient-years. From 2000 to 2006, there was a substantial increase in the prescription rate of anti-diabetic medications. Overall, there were 9.6 prescriptions/patient-year in 2000, and this had increased to 14.8 prescriptions/patient-year in 2006. The greatest relative increase occurred in the prescription of thiazolidinediones. The greatest absolute increase occurred in the prescription of metformin, which surpassed sulfonylureas as the most commonly prescribed anti-diabetic medication among patients with type 2 diabetes in 2002. Among those with incident diabetes, overall prescription rates were 4.6 prescriptions/patient-year in 2000 and 13.6 prescriptions/patient-year in 2006.

**Conclusions** There was a substantial increase between 2000 and 2006 in the UK in the prescription of anti-diabetic medications. This increasingly aggressive pharmacological management is consistent with recent practice guidelines. 

KEY WORDS — diabetes; medical therapy; prescribing patterns

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## INTRODUCTION

Over the last decade, guidelines for the treatment of type 2 diabetes have increasingly favored tighter glycemic control,[1–5] necessitating the use of more aggressive pharmacological therapy. However, the changes in prescribing patterns of anti-diabetic medications during this period remain poorly documented. Our objective was therefore to describe recent trends in the prescription of anti-diabetic medications among patients with type 2 diabetes in the United Kingdom (UK).

* Correspondence to: Dr J. M. Brophy, Division of Clinical Epidemiology, Ross Pavilion, Royal Victoria Hospital, 687 Pine Avenue West, R4.12, Montreal, Quebec, Canada H3A 1A1, Canada.
E-mail: james.brophy@mcgill.ca
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## METHODS

Using data from the General Practice Research Database (GPRD), we constructed a cohort of patients with type 2 diabetes from 1 January 2000 to 31 December 2006. The GPRD has been described in detail previously [6] and used extensively in pharmacoepidemiologic studies.[7,8] Briefly, this database links over 400 general practices and provides a representative sample of approximately 5% of the UK population.[6] Data include demographic information, clinical diagnoses, prescriptions issued, and laboratory data.

Diabetes was defined as the presence of a clinical diagnosis of type 2 diabetes, an HbA1c test $\geq 7\%$, or $\geq 2$ prescriptions for anti-diabetic medications. We excluded all patients with a diagnostic code of type 1

diabetes mellitus as well as those diagnosed with type 2 diabetes before the age of 30 years. Cohort entry was defined as the latest of the following four events: (1) date of registration at the GPRD practice; (2) date at which the GRPD practice became up-to-standard with respect to data validity; (3) date at which the patient met at least one component of our definition for type 2 diabetes; (4) 1 January 2000. If prescription data were used to define cohort entry, the date of cohort entry was defined by the date of the second prescription for an anti-diabetic medication. Cohort entry could occur between 1 January 2000 and 31 December 2005. Patients were followed until transfer to another practice, death, the date of the latest data upload from the practice to the GPRD, or 31 December 2006, whichever came first. We limited our study to patients with $\geq 1$ year of history in the GPRD prior to cohort entry.

We grouped prescriptions for anti-diabetic medications by medication class, including insulin, metformin, sulfonylureas, thiazolidinediones (TZDs), and other oral anti-diabetic agents. Prescription rates were calculated by year and are presented as prescriptions per patient-year. Prescription rates for the full cohort were calculated to describe population-level prescribing practices. In addition, we conducted analyses restricted to a sub-cohort of patients with incident diabetes to account for confounding by duration of disease and describe changes in prescribing patterns.

Ethical approval was obtained by the McGill University Health Centre (MUHC) Research Ethics Board and by the Scientific and Ethical Advisory Group (SEAG) of the GPRD.

## RESULTS

Our full cohort involved 67 981 patients with type 2 diabetes, contributing a total of 320 089 patient-years, and our sub-cohort included 30 234 patients with incident type 2 diabetes and a total of 111 890 patient-years. Among all patients, the mean age at cohort entry was 64.0 years (standard deviation = 12.7), and 55% were male. In addition, 8% had a previous myocardial infarction and 46% had hypertension. The mean HbA1c in the year before cohort entry was 8.3% (standard deviation = 1.9%).

Between 2000 and 2006, prescription rates of anti-diabetic medications increased with time (Figure 1a). Overall, there were 9.6 prescriptions/patient-year in 2000. By 2006, the overall prescription rate of anti-diabetic medications had increased to 14.8 prescriptions/patient-year. The greatest relative increase occurred in the prescription of TZDs. The greatest absolute increase occurred in the prescription of metformin, which surpassed sulfonlyureas as the most commonly prescribed anti-diabetic medication among patients with type 2 diabetes in 2002. Prescription of sulfonylureas and other oral anti-diabetic agents decreased modestly over time. During this period, there was also a small but important increase in the prescription of insulin, which increased by approximately 10%.

Among patients with incident diabetes, there was a substantial increase in prescription rates between 2000 and 2006 (Figure 1b). During this time, the overall prescription rate increased from 4.6 to 13.6 prescriptions/patient-year. Prescription rates for TZDs and metformin increased dramatically during the study period. In addition, important increases in the prescription of insulin in patients with incident diabetes were observed.

## DISCUSSION

We found sharp increases in the overall prescription of anti-diabetic medications between 2000 and 2006. The greatest increase were observed in metformin and TZDs. TZDs entered the market place early in the study period and were characterized by rapid uptake. There was also an increase in the prescription of insulin during this period, particularly among patients with incident type 2 diabetes. Prescription patterns among patients with incident disease suggest that physicians are being increasingly aggressive in the pharmacological treatment of type 2 diabetes.

This pattern of increasingly aggressive prescription of anti-diabetic medications is consistent with most treatment guidelines.[1-5] Although most guidelines recommend an HbA1c $< 7\%$, many now recommend lower HbA1c targets and suggest tailoring treatment targets based on individuals' risk of microvascular and macrovascular complications.[1] In addition, the American Diabetes Association now recommends targeting as close to normal HbA1c as possible without inducing hypoglycemia.[2]

The effect of aggressive management of type 2 diabetes on clinical outcomes remains unclear. Recently, the effect of intensive therapy to target normal HbA1c was examined in the ACCORD trial.[9] In this trial, over 10 000 patients with established cardiovascular disease or additional cardiovascular risk factors were randomized to intensive therapy to target an HbA1c $< 6\%$ or usual care. The investigators found that patients randomized to intensive therapy had higher mortality compared with those randomized to usual care. In contrast, the ADVANCE trial,[10]



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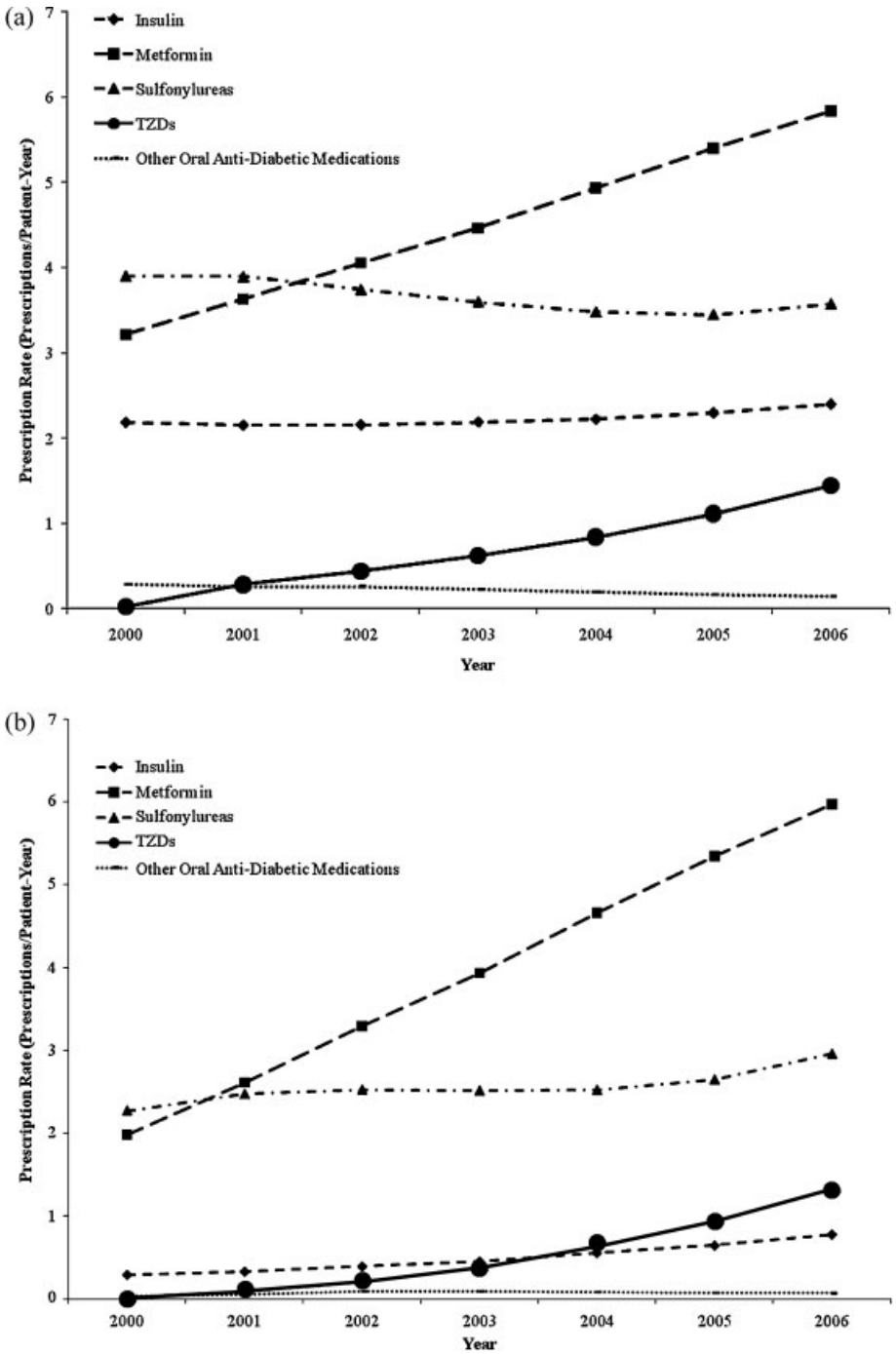


Figure 1. Trends in the prescription of anti-diabetic medications among patients with type 2 diabetes in the United Kingdom between 2000 and 2006. (a) Full cohort; (b) sub-cohort of patients with incident type 2 diabetes. Prescription rates are presented as prescriptions per patient-year

which randomized more than 11 000 patients with type 2 diabetes, found that intensive glucose control targeting an HbA1c $< 6.5\%$ was associated with a decrease in their primary endpoint, a composite of incident macro- and microvascular events, but had no effect on mortality or major macrovascular events. In light of these conflicting results, there is a need to examine the effect of the observed shift toward more aggressive anti-diabetic therapy on outcomes in actual practice.

Our study has a number of strengths. First, the GPRD data provide a representative sample of the UK



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KEY POINTS

- There was a substantial increase between 2000 and 2006 in the UK in the prescription rate of anti-diabetic medications among patients with type 2 diabetes.
- The greatest increase was observed in metformin and TZDs.
- Future studies need to examine the effect of these prescription trends on population-level clinical outcomes.

population. These data are well validated and have been the source of over 600 peer-reviewed publications.[11] Second, the GPRD records prescriptions issued rather than prescriptions filled.[6] Consequently, it is an ideal data source for studies examining physician prescription patterns at the population level.

Our study also has potential limitations. First, we have not accounted for the duration of prescriptions, which typically vary from 28 to 90 days in the GPRD. However, it is unlikely that these durations differ systematically over time. Second, our cohort was somewhat heterogeneous, consisting of patients with a clinical diagnosis of type 2 diabetes, an abnormal HbA1c test result, or treated for type 2 diabetes. However, greater than 90% of patients met all three criteria and greater than 98% met at least two of these criteria while in the GPRD. Third, medication data in the GPRD represent prescriptions issued rather than prescriptions filled or taken. Thus, although these data are ideal for measuring prescription patterns, there is likely imperfect patient adherence to these prescriptions. Finally, it is possible that the observed increase in prescriptions was the result of temporal changes in patient population, including changes in the mix of patients in the cohort and increasing diabetes duration. However, to assess the impact of duration of diabetes, we repeated analyses among a sub-cohort of patients with incident type 2 diabetes. These analyses suggest that increasing duration of diabetes and changes in the mix of patients are unlikely explanations for the observed changes in prescriptions and that physicians are utilizing more aggressive pharmacological management during the study period.

## CONCLUSION

There was a substantial increase between 2000 and 2006 in the UK in the prescription rate of anti-diabetic medications among patients with type 2 diabetes. This increasingly aggressive pharmacological management is consistent with recent practice guidelines. However, the effect of these prescription trends on clinical outcomes at the population level remains unknown.

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