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ORIGINAL ARTICLE

Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy

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Aim: To evaluate the time to and factors associated with treatment intensification in patients with type 2 diabetes who failed metformin monotherapy.

Methods: In a retrospective analysis using a large US electronic medical record database, eligible patients included those with type 2 diabetes and an HbA_{1c} of ≥7.0% or at least two fasting blood glucose levels of ≥126 mg/dl while on metformin monotherapy for at least 6 months within the period of 1 January 1997 to 31 December 2008. Time to treatment intensification was calculated as the time between index date (date on which HbA_{1c} ≥ 7% after metformin monotherapy for at least 6 months) and first prescription for additional antihyperglycaemic agent during follow-up period. All patients were required to have data for at least 12 months prior to and following the index date. A Cox proportional hazards model was employed to determine patient baseline characteristics associated with time to treatment intensification.

Results: Of the 12 566 patients identified, mean age at index date was 63 years and 51% were female. Mean index HbA_{1c} was 8.0% overall, with 66, 19 and 15% of patients having an index HbA_{1c} of 7 to <8%, 8 to <9% and ≥9%, respectively. Median time to treatment intensification was 14.0 months overall and 19.0, 8.7 and 4.5 months for patients with index HbA_{1c} of 7 to <8%, 8 to <9% and ≥9%, respectively. Factors associated with treatment intensification included higher index HbA_{1c}, younger age, higher Charlson co-morbidity index, metformin daily dose ≥ 1500 mg and later index date (all $p < 0.05$).

Conclusions: In US clinical practice, median time to receive additional antihyperglycaemic medication is more than 1 year for patients with type 2 diabetes who failed metformin monotherapy.

Keywords: antihyperglycaemic agents, clinical inertia, type 2 diabetes

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Introduction

The prevalence of diabetes has increased from 1999 to 2006 in the USA. During this time, mean HbA_{1c} has decreased and the proportion of patients with diabetes achieving HbA_{1c} target of <7% has increased, with >80% of patients diagnosed with diabetes receiving antihyperglycaemic treatments [1]. Despite these improvements in diabetes care, >40% of US patients remain above the recommended HbA_{1c} target of <7% [1]. Following a 3–6-month period of lifestyle modification and metformin monotherapy [2], treatment intensification is recommended for patients with type 2 diabetes not meeting glycaemic treatment targets [2]. However, many patients do not receive treatment intensification in a timely manner [3–8], despite the additional glycaemic benefits [9]. This clinical inertia is a major barrier for optimal diabetes treatment and its associated clinical benefits [10].

Patients in the previous studies [3–9] were treated with various antihyperglycaemic therapies and regimens and thus time to treatment intensification cannot be described for a specific agent. Because metformin monotherapy is the recommended initial therapeutic intervention for patients with type 2 diabetes [2], it was of interest to identify the length of time for intensification of antihyperglycaemic treatment in those who failed metformin monotherapy in US clinical practice.

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Methods

Data Source

The study cohort was drawn from the General Electric (GE) Centricity electronic medical record database (www.gehealthcare.com/centricityenterprise). The database contains real-world ambulatory data collected at the point of care from over 9000 US providers. It is an anonymous Health Insurance Portability and Accountability Act-compliant clinical database in the USA covering over 12 million patient lives and includes demographic information, vital signs, laboratory orders and results, medication list entries, prescription orders, diagnoses and medical problems. Previous studies have shown that the GE electronic medical record population is generally

similar to the US population, except for a higher proportion of women in the GE electronic medical record population [11].

Study Design and Patient Selection

In this retrospective cohort study, patients with type 2 diabetes who were ≥18 years and on metformin monotherapy and had at least one HbA_{1c} measurement ≥7.0% or two fasting blood glucose measurements ≥126 mg/dl (7 mmol/l) were identified in the GE database from 1 January 1997 to 31 December 2008 (index period). The index date was the date of observing an HbA_{1c} of ≥7.0% after at least 6 months of metformin monotherapy. Patients were required to have continuous enrollment in the GE electronic medical record database for at least 12 months prior to and following the index date.

Analyses

The primary outcome variable was the time to treatment intensification, which was calculated as the time between the index date and the first prescription for an additional oral or injectable antihyperglycaemic agent during the follow-up period. Time to treatment intensification was evaluated for the overall cohort and by index HbA_{1c} subgroups (7 to <8%, 8 to <9% and ≥9%). To account for the potential confounding of metformin titration, an additional analysis compared treatment intensification in patients who had a metformin daily dose that was either always below 1500 or ≥1500 mg. Data were censored at the end of the follow-up period. Kaplan–Meier estimation was used to calculate time to treatment intensification. A Cox proportional hazards model was employed to determine baseline characteristics associated with treatment intensification controlling for other factors with the measure of associations reported as hazards ratios and 95% confidence intervals.

Patient baseline characteristics were assessed based on medical records during the 12 months preceding the index date. Demographic characteristics included age on the index date and gender. Clinical and laboratory measurements included index HbA_{1c}, blood pressure, body mass index (BMI), lipids and smoking status. Using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9 CM) and Current Procedural Terminology codes, co-morbid disease conditions that could impact prescribing behaviour were indentified and included hypoglycaemia, neoplasms, nephropathy and cardiovascular diseases. To adjust for the potential confounding effect from the residual co-morbidities, a modified Charlson co-morbidity index was calculated excluding diabetes and the aforementioned disease conditions. Additional variables included number of office visits, metformin daily dose and polypharmacy use (antihypertensive or lipid-lowering agents). The baseline characteristics of the overall patients and by the index HbA_{1c} subgroups were tabulated using mean and standard deviation for continuous variables and proportions for categorical variables.

Results

Of the 12 566 patients identified, mean age at index date was 63 years, BMI was 34 kg/m^2 and 51% were female (Table 1). Mean index HbA_{1c} was 8.0% overall, with 66, 19 and 15% of patients having an index HbA_{1c} of 7 to <8%, 8 to <9% and ≥9%, respectively. Metformin daily dosage was ≥1500 mg in 46% of patients. The proportion of patients with selected pre-existing co-morbid conditions are listed in Table 1. The proportion of patients using antihypertensive and lipid-lowering agents was 67 and 50% overall, respectively, with greater use of these agents observed in patients with lower index HbA_{1c} (Table 1).

The median follow-up time was 2.2 years (mean = 2.9 years). Overall, 63.9% of all patients had treatment intensification, among which 35.4% received therapy intensification within 3 months, 49.7% within 6 months, 66.1% within 1 year and 84.5% within 2 years. Median time to treatment intensification was 14.0 months overall (figure 1A), and 19.0, 8.7 and 4.5 months for patients with an index HbA_{1c} of 7 to <8%, 8 to <9% and ≥9%, respectively (figure 1B). As the physicians may be less likely to intensify treatment in patients near HbA_{1c} treatment targets, a sensitivity analysis was performed that excluded patients with an index HbA_{1c} of ≤7.2% (n = 3016). After excluding these patients, the time to treatment intensification was 11.7 months. For those who had metformin daily dosage ≥1500 mg, median time to treatment intensification was 8.9 months compared with 20.0 months for those with a metformin daily dosage always >1500 mg (figure 1C).

Factors associated with treatment intensification are shown in Table 2. Compared with patients with an index HbA_{1c} of 7 to <8%, patients with an index HbA_{1c} of 8 to >9% and ≥9% had significantly shorter time to treatment intensification with hazard ratios of 1.51 and 1.93, respectively. Use of lipid-lowering agents and lower low-density lipoprotein (LDL)-cholesterol levels were associated with treatment intensification. Younger age, male gender and patients from Midwest providers were associated with treatment intensification.

Patients with earlier index dates had a longer time to treatment intensification relative to those with an index date within the most recent period evaluated (i.e. 2007–2008; Table 2). The index period results may have been confounded by the shorter follow-up period in patients with a later index date. A sensitivity analysis was performed to evaluate treatment intensification within a fixed follow-up time period for the patients within each index period grouping. Consistent with the modelled results, the proportion of patients receiving treatment within 1 year after the index date was higher for those within the index period of 2007–2008 (86.5%) relative to the other index periods (1997–1998: 52.6%; 1999–2000: 50.8%; 2001–2002: 55.9%; 2003–2004: 52.8%; 2005–2006: 61.5%). In an analysis assessing the influence of index period by baseline HbA_{1c} categories on treatment intensification, results were generally consistent with the findings for the individual variables, index period or baseline HbA_{1c} (data not shown).

Discussion

Clinical inertia is defined as the absence of treatment intensification despite suboptimal medical management of a disease state [12] and may be due to patient-, system- and physician-related factors [5,6,9]. Metformin monotherapy

Table 1. Baseline characteristics for all patients and by index HbA_{1c} subgroups.

Variables	HbA_{1c} level			Overall
	7 to <8%	8 to <9%	≥9%	
	n = 8291	n = 2412	n = 1863	n = 12 566
Age	64	62	58	63 ± 12
Female (%)	51.5	50.6	48.4	50.9
Smoking (%)	7.3	8.4	10.3	7.9
Latest laboratory results before index date				
HbA_{1c}, % (at index date)	7.4	8.4	10.3	8.0 ± 1.2
Systolic BP, mmHg	132	134	134	133 ± 17
Diastolic BP, mmHg	77	78	80	78 ± 10
BMI, kg/m^2	33.5	34.5	35.2	34.0 ± 7.5
Total cholesterol, mmol/l	4.6	4.7	5.1	4.7 ± 1.1
HDL-cholesterol, mmol/l	1.2	1.1	1.1	1.1 ± 0.3
LDL-cholesterol, mmol/l	2.5	2.6	2.8	2.6 ± 0.9
Triglycerides, mmol/l	2.2	2.5	3.0	2.3 ± 2.0
Had daily metformin dose ≥1500 mg in baseline (%)	42.8	49.5	54.8	45.9
Number of office visits in 12 months prior to index date	4.7	4.5	4.3	4.6 ± 3.8
Co-morbid disease conditions				
Hypoglycaemia diagnosis (%)	0.2	0.2	0.2	0.2
Neoplasm diagnosis (%)	3.9	4.0	3.2	3.8
Nephropathy (%)	1.1	1.2	1.5	1.2
Cardiovascular disease (%)	4.5	4.6	4.2	4.5
Cerebrovascular disease (%)	1.4	0.9	0.8	1.2
Myocardial infarction (%)	0.3	0.4	0.5	0.4
Ischaemic heart disease (%)	1.9	2.6	2.2	2.0
Peripheral vascular disease (%)	1.3	1.1	1.1	1.2
Charlson co-morbidity index*	0.13	0.15	0.16	0.14 ± 0.51
Baseline polypharmacy use				
Use of antihypertensive agents (%)	68.5	64.9	63.0	67.0
Use of lipid-lowering agents (%)	52.7	46.9	42.8	50.1
Geographic region				
Midwest (%)	25.2	24.3	23.9	24.8
Northeast (%)	34.4	32.0	33.0	33.7
South (%)	29.7	32.9	32.9	30.8
West (%)	10.7	10.7	10.3	10.6

Data are mean, mean ± s.d. or proportion of patients. BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Calculation of Charlson co-morbidity index excludes the above-specified conditions and diabetes, but diabetes with chronic complications is included.

is typically recommended as the initial pharmacologic intervention in addition to lifestyle modifications, followed by therapy modification or intensification for those not adequately controlled with initial therapies [2]. The present study was performed to estimate the time for antihyperglycaemic treatment intensification specifically in patients with type 2 diabetes who failed metformin monotherapy in US clinical practice. Only 64% of patients who failed metformin monotherapy (i.e. $HbA_{1c} \geq 7\%$ after at least 6 months of treatment) had their antihyperglycaemic therapy intensified in the present study. Furthermore, the median time to intensification was 14 months for those who received additional antihyperglycaemic therapy. Given that physicians may be less inclined to initiate or intensify therapy in patients near HbA_{1c} treatment targets, an analysis excluding patients with an index HbA_{1c} of 7.2% or less showed that the time to treatment intensification was still approximately 1 year.

Higher index HbA_{1c} positively influenced time to treatment intensification, with those having an HbA_{1c} of ≥9% or 8 to <9% receiving additional treatments within 4.5 or 8.7 months compared with 19 months for those with an HbA_{1c} of 7 to <8%. Cheung et al. [1] reported that 66% of patients with poorly controlled type 2 diabetes (i.e. $HbA_{1c} \geq 8\%$) received therapy modification within 6 months. Moreover, Brown and Nichols [13] found that an $HbA_{1c} \geq 9\%$ influenced the addition of metformin therapy to ongoing sulphonylurea therapy. Although the time to treatment intensification was shorter in these higher risk patients relative to those with lower HbA_{1c}, there is still an apparent treatment gap. To account for the potential confounding of metformin titration, an analysis compared treatment intensification in patients who had a metformin daily dose of less than or ≥1500 mg. Patients who never exceeded a metformin dose of 1500 mg had a median time to treatment intensification of 20.0 months, which was more than double the median time (8.9 months) of those who had a metformin daily dosage ≥1500 mg. These data suggest that patients in the lower dose metformin group are being undertreated with regard to therapy intensification with either

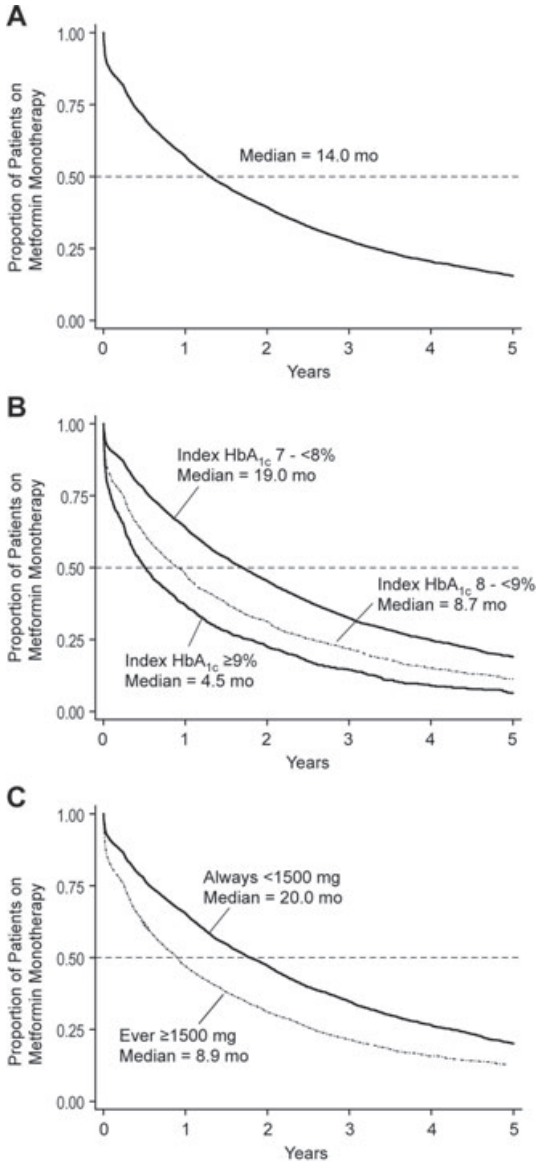

Figure 1. Time to treatment intensification for all patients (A), by index HbA_{1c} level (B), by metformin daily dose (C).

metformin titration and/or use of another antihyperglycaemic agent.

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) treatment algorithm was first introduced in 2006 and updated in late 2008 [2,14]. The algorithm recommends that HbA_{1c} be checked every 3 months until <7%. If HbA_{1c} is above target, additional treatments should be added to metformin and lifestyle interventions should be re-inforced. The impact of time period on treatment intensification was assessed in 2-year intervals relative to 2007–2008 (i.e. the period after algorithm was published). Patients with an index date within the recent index period of 2007–2008 were more likely to receive treatment intensification relative to earlier periods, suggesting greater action and awareness among US physicians following publication of the algorithm. Furthermore, the results are consistent with the temporal trends in improved diabetes care observed using the National Health and Nutrition Examination Survey (NHANES) database [1,15].

Table 2. Factors associated with treatment intensification in patients with type 2 diabetes who failed metformin monotherapy.

Variables	Hazard ratio	95% CI	p value
Age	0.995	0.992–0.997	<0.001
Female	0.89	0.85–0.93	0.001
BMI	1.006	1.003–1.009	<0.001
Index HbA_{1c} level			
7 to <8% (reference)	1		
8 to <9%	1.51	1.43–1.60	<0.001
≥9%	1.93	1.81–2.06	<0.001
Metformin daily dose ≥1500 mg at baseline	1.55	1.48–1.62	<0.001
Baseline number of office visits	1.010	1.004–1.016	0.001
LDL-cholesterol	0.9992	0.9985–0.9999	0.031
Use of lipid-lowering agents	1.10	1.05–1.16	<0.001
Charlson co-morbidity index	1.06	1.01–1.11	0.023
Year of index date			
1997–1998	0.75	0.56–1.00	0.048
1999–2000	0.65	0.59–0.72	<0.001
2001–2002	0.72	0.66–0.78	<0.001
2003–2004	0.75	0.70–0.81	<0.001
2005–2006	0.79	0.74–0.84	<0.001
2007–2008 (reference)	1		
Geographic region			
Northeast (reference)	1		
Midwest	1.13	1.06–1.20	<0.001
South	0.97	0.92–1.03	0.35
West	1.00	0.92–1.08	0.98

Non-significant factors included current smoker, systolic blood pressure, baseline use of antihypertensive agents, neoplasm diagnosis and presence of cardiovascular disease. BMI, body mass index; CI, confidence interval; LDL, low-density lipoprotein.

Additional baseline factors associated with treatment intensification included younger age, higher number of office visits, higher BMI, higher Charlson co-morbidity index, male gender, lower LDL-cholesterol level, use of lipid-lowering agents and Midwest region relative to Northeast region. The present findings are in agreement with previous studies which have reported that higher HbA_{1c} and younger age were associated with treatment intensification or appropriate care in patients with type 2 diabetes and suboptimal glycaemic control [6,8,16]. The relationship between the use of lipid-lowering agents and antihyperglycaemic treatment intensification may be reflective of better overall patient care and management of the diabetic condition and associated co-morbid conditions.

Several strengths and limitation need to be acknowledged. With regard to strengths, the study included a large sample of >12 500 patients with at least 1 year of follow-up data (median follow-up time was 2.2 years). Additionally, as the GE electronic medical record database is physician-based and not insurance claim- or employer-based, patients are retained in

the database as long as no switch in physicians has occurred, regardless of whether there is a change in insurance or employer. With regard to limitations, the use of the electronic medical records is more common for primary care physicians in larger practices, younger physicians and those in Western region of the USA [11]. Thus, the results may not be generalizable to other patient populations. Additionally, the prescription records in the electronic medical records may not reflect the actual medication use. In addition, race, fasting blood glucose and insurance status were not included in the analyses because of large proportions of missing values. The GE electronic medical record database does not include information on socioeconomic or education status; thus the effect of these variables on outcome cannot be assessed.

In summary, in US clinical practices from 1997 to 2008, median time to receive treatment intensification with additional antihyperglycaemic agents is more than 1 year among patients with type 2 diabetes who failed metformin monotherapy. Interestingly, patients with an index date in the latest period analysed in this study (i.e. 2007–2008) were more likely to receive treatment intensification, suggesting temporal improvements in diabetes care. Factors associated with treatment intensification can be assessed to improve clinical care of these patients.

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Conflict of Interest

Y. Q., M. J. D., L. R. and S. S. E. are employees of Merck Sharp & Dohme, Corp. A. Z. F. received research grant support from Merck Sharp & Dohme, Corp. for this study.

A. Z. F., Y. Q. and L. R. were involved in the concept and design of the study and in the data collection and/or analysis. All authors were involved in interpretation of the results. M. J. D. and A. Z. F. drafted the article and all authors were involved in the critical revisions, discussions and approval of the article.

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