Time to Treatment Intensification After Monotherapy Failure and Its Association With Subsequent Glycemic Control Among 93,515 Patients With Type 2 Diabetes

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Diabetes Care 2018;41:2096–2104 | https://doi.org/10.2337/dc17-0662

OBJECTIVE

The goal of this study was to evaluate the association between the timing of treatment intensification and subsequent glycemic control among patients with type 2 diabetes in whom monotherapy fails.

RESEARCH DESIGN AND METHODS

This retrospective analysis of the U.K. Clinical Practice Research Datalink database focused on patients with type 2 diabetes and one or more HbA_{1c} measurements ≥7% (≥53 mmol/mol) after ≥3 months of metformin or sulfonylurea monotherapy (first measurement meeting these criteria was taken as the study index date). Baseline (6 months before the index date) characteristics were stratified by time from the index date to intensification (early: <12 months; intermediate: 12 to <24 months; late: 24 to <36 months). Intensification was defined as initiating after the index date one or more noninsulin antidiabetes medication in addition to metformin or a sulfonylurea. Association between time to intensification and subsequent glycemic control (first HbA_{1c} <7% [<53 mmol/mol] after intensification) was evaluated using Kaplan-Meier analyses and Cox proportional hazard models that accounted for baseline differences.

RESULTS

Of the 93,515 patients who met the study criteria (mean age 60 years; ∼59% male; 80% taking metformin), 23,761 (25%) intensified <12 months after the index date; 11,908 (13%) intensified after 12 to <24 months; and 7,146 (8%) intensified after 24 to <36 months. Patients who intensified treatment ≥36 months after the index date (n = 9,638 [10%]) and those with no evidence of treatment intensification during the observable follow-up period (n = 41,062 [44%]) were not included in further analyses. The median times from intensification to control were 20.0, 24.1, and 25.7 months, respectively, for the early, intermediate, and late intensification cohorts. After adjustment for baseline differences, the likelihood of attaining glycemic control was 22% and 28% lower for patients in the intermediate and late intensification groups, respectively, compared with those intensifying early (P < 0.0001).

CONCLUSIONS

Earlier treatment intensification is associated with shorter time to subsequent glycemic control, independent of whether patients initiate first-line treatment with metformin or a sulfonylurea.

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Received 3 April 2017 and accepted 13 July 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0662/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

Diabetes is a substantial and growing contributor to health services utilization, health care costs, and mortality worldwide (1). According to the World Health Organization, in 2014, 422 million people—or 8.5% of the adults across the world—had diabetes. In the U.K. in 2016, 4.5 million people (7% of the adult population) had diabetes, and of those 90% had type 2 diabetes (2). It is estimated that the National Health Service in the U.K. spends ~£10 billion—or 9% of its annual budget—on managing patients with diabetes.

The American Diabetes Association–European Association for the Study of Diabetes treatment guidelines recommend using a stepwise approach to managing glycemic control among people with type 2 diabetes, with a review of blood glucose targets within 3 months of treatment initiation (3,4). The usual first step is to initiate therapy with metformin or a sulfonylurea (monotherapy), followed by the addition of other oral antidiabetes medications, injectable therapies (including insulin), or both as needed to maintain lower blood glucose levels (determined on the basis of glycated hemoglobin [HbA_{1c}] levels). HbA_{1c} <7.0% (<53 mmol/mol) typically is considered "at goal." However, real-world evidence suggests that many patients with type 2 diabetes, including those in the U.K., do not receive intensified treatment for extended periods of time despite inadequate glycemic control when receiving monotherapy (5–9). For example, a recent study by Khunti et al. (5) found that despite elevated glucose levels, the median time until additional antidiabetes medications were initiated was over a year among those initially treated with monotherapy, suggesting that patients may be subject to prolonged periods of poor glycemic control.

Lack of adequate glycemic control is associated with development of cardiovascular complications, further increasing the burden of the disease (3,6,10,11). In addition, studies have shown that patients with prolonged periods of poor glycemic control before treatment is intensified have lower chances of attaining glycemic control after intensification. For example, in a study of ~1,100 patients receiving metformin therapy in the U.S., Nichols et al. (12) found that HbA_{1c} values before intensification with insulin accounted for nearly all of the variance in HbA_{1c} change after intensification: each percentage point of HbA_{1c} before intensification reduced the probability of attaining HbA_{1c} <7% (<53 mmol/mol) after intensification by 26%. In a separate study, Rajpathak et al. (13) reported that among those with HbA_{1c} ≥7.5% (≥58.5 mmol/mol) despite metformin monotherapy (the first date these criteria were met was considered the study index date), the likelihood of attaining the glycemic goal 18–24 months after the index date was 36% higher for those intensifying within 3 months after the index date than for those intensifying 10–15 months after the index date. A recent study used data from a large, integrated health system in the U.S. and found that among patients newly diagnosed with type 2 diabetes and in whom metformin monotherapy failed, early intensification (within 6 months) was associated with a significantly shorter time to subsequent HbA_{1c} control than the time until control in those who intensified after 6 months or who did not intensify at all (14). A different study by Watson et al. (15) found similar results among patients in the U.K.

A common attribute of the existing literature is that the study populations of interest have been limited to patients initiating metformin monotherapy. Studies have shown that as many as 45% of patients with type 2 diabetes initiate treatment with agents other than metformin after their initial diagnosis; the most common agent is a sulfonylurea (16). As such, it is important to assess the implications of monotherapy failure among the broader population with diabetes, including those using sulfonylureas as first-line treatment. The generalizability of findings from previous studies is limited further because they evaluated small populations and the outcomes were evaluated over short periods after intensification. In addition, little is known about the real-world implications of timely versus delayed intensification after monotherapy failure on subsequent glycemic outcomes in the U.K.

The primary objective of this study was to evaluate, through use of the U.K. Clinical Practice Research Datalink (CPRD), the association between timing of treatment intensification and subsequent glycemic control among patients with type 2 diabetes who did not attain adequate glycemic control after at least 3 months of monotherapy with metformin or a sulfonylurea. A secondary objective of the study was to describe the association between timing of intensification and duration of glycemic control after intensification among the same population.

RESEARCH DESIGN AND METHODS

Data Sources

A retrospective cohort study was conducted using CPRD data (2000–2014), which come from the four main electronic health record information technology systems used by general practitioners (GPs) in the U.K. The data contain information about patient registration and all care events that GPs choose to record, including but not limited to medical diagnoses (using Read codes), referrals to specialists and secondary care settings (e.g., hospitals), diagnostic testing, lifestyle information (e.g., BMI), and all other types of care provided by the GPs (e.g., surgeries, laboratory testing). In addition, the database contains information on all the drugs prescribed in the primary care setting, including formulation, strength, quantity, and the dates they were prescribed.

The data are well suited to answering the study question given that they also contain information about results from common laboratory tests, such as HbA_{1c}. Most patients included in this study (see SAMPLE SELECTION) had HbA_{1c} test results available. For the 1% of the records with missing information, the last test result was carried forward. The mean duration between a missing test result and the previous test result was 120 days; the median was 70 days.

Sample Selection

The analytic sample was limited to patients aged 18–79 years who had a diagnosis of type 2 diabetes (identified by Read codes and ICD-10 codes), who initiated treatment with only metformin or a sulfonylurea between 2000 and 2014 (the most recent year of available data), and who did not attain glycemic control (i.e., had HbA_{1c} ≥7% [≥53 mmol/mol]) after ≥3 months of monotherapy. The first indication of uncontrolled HbA_{1c} after ≥3 months of monotherapy was defined as the study index date. The

6 months before the index date constituted the baseline period. Patients were followed for up to 7 years after treatment intensification, defined as first indication of simultaneous use of metformin or a sulfonylurea and other noninsulin antidiabetes medications after the study index date. Specifically, two treatments were considered to be used concomitantly if the supplies of the medications overlapped by ≥28 days and there was one or more prescriptions for each of the component medications after the initial indication of simultaneous use.

Patients with type 1 diabetes (defined as one or more records with a diagnosis of type 1 diabetes and either no indication of oral antidiabetes medication other than metformin in their medical history, or one or more record of insulin use within 6 months of diagnosis [17]), secondary diabetes, gestational diabetes mellitus, or polycystic ovarian syndrome were excluded. In addition, we excluded patients aged ≥80 years and those with an indication of cancer at any time during the baseline or follow-up periods, as approaches to treatment intensification in these patients may differ from those for younger and cancer-free patients (18,19).

Patients who met the study selection criteria were stratified into three cohorts based on time from the index date to treatment intensification: *1*) early intensifiers (those intensifying within 12 months), *2*) intermediate intensifiers (those intensifying 12 to <24 months after the index date), and *3*) late intensifiers (those intensifying 24 to <36 months after the index date). Patients intensifying after 36 months and those with no evidence of treatment intensification during the observable follow-up period were excluded from further analyses.

Patient Characteristics

The following patient characteristics were described for the three cohorts: age, sex, type of antidiabetes medication used, duration of diabetes (years from type 2 diabetes diagnosis to the index date), duration of monotherapy (years from first indication of monotherapy to the index date), BMI measurement closest to the index date, HbA_{1c} level on the index date, Charlson comorbidity index (CCI) (20,21) during the baseline period, any referral to an endocrinologist during the baseline period, and rate of antihypertensive or statin use during the baseline period. Continuous measures are described using the mean and SD; numbers and proportions are reported for categorical variables. Statistical significance of difference was assessed using the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. The early intensification cohort (i.e., those intensifying within 12 months after the index date) was considered to be the reference group for all comparisons.

In addition, mean HbA_{1c} levels at 6-month intervals after the index date were described for the three cohorts. Where available, the most recent HbA_{1c} value prior to the end of each interval was used for the analysis. In the event that a patient did not have a test result during a 6-month interval, the last test result was used.

Outcomes and Analyses

The time from treatment intensification to attainment of glycemic control—defined as the first HbA_{1c} measurement <7% (<53 mmol/mol) after treatment intensification—was described for the three cohorts using Kaplan-Meier survival analyses. We used log-rank tests to assess the statistical significance of differences across cohorts. Patients were censored at whichever of the following occurred first: *1*) intensification without metformin or a sulfonylurea as a component of therapy, *2*) initiation of triple therapy, *3*) initiation of insulin, and *4*) the end of data visibility. In addition, the duration of glycemic control after treatment intensification was estimated as the number of months between the first indication of attainment of glycemic control and the first subsequent HbA_{1c} value ≥7% (≥53 mmol/mol). Cox proportional hazard models were used to estimate the likelihood of attaining glycemic control and of having at least one HbA_{1c} measurement ≥7% (≥53 mmol/mol) after attaining control. The key independent variable for both models was cohort assignment (reference group: those intensifying <12 months after the index date). Models adjusted for differences in age, sex, HbA_{1c} at the index date, BMI category at the index date, duration of monotherapy before the index date, endocrinologist visit before the index date, and use of antihypertensives and statins before the index date.

The study was approved by the Independent Scientific Advisory Committee, Medicines & Healthcare products Regulatory Agency, London, U.K. (protocol no. 15_171R). All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of the 93,515 patients who met the selection criteria (Supplementary Fig. 1), the majority (85%) used metformin as the first-line treatment for diabetes. Kaplan-Meier analyses indicated that the median time from the index date to intensification was 30.9 months. During the observable follow-up period, 42,815 of the patients (46%) meeting the selection criteria received intensified treatment within 3 years: 23,761 (25%), <12 months after the index date; 11,908 (13%), 12 to <24 months after the index date; and 7,146 (8%), 24 to <36 months after the index date. Patients who intensified treatment ≥36 months after the index date (*n* = 9,638 [10%]) and those with no evidence of treatment intensification during the observable follow-up period (*n* = 41,062 [44%]) were not included in further analyses.

Patient Characteristics

Early intensifiers were younger (mean age 58 years vs. 59 years for intermediate and 60 years for late intensifiers) and had significantly ($P < 0.05$) shorter durations of diabetes and monotherapy at the index date, but had a significantly higher mean CCI score than did intermediate and late intensifiers (Table 1). In addition, patients receiving early intensification had a higher mean HbA_{1c} level at the index date: 8.8% (73 mmol/mol); intermediate intensifiers had HbA_{1c} of 8.1% (65 mmol/mol) at the index date, and late intensifier, 7.9% (63 mmol/mol). The mean HbA_{1c} levels for patients intensifying within the first 12 months declined to 7.8% (62 mmol/mol) by the end of 18 months after the index date and remained stable thereafter (Fig. 1). For patients intensifying after 12 months, the mean HbA_{1c} levels decreased within the first 6 months after the index date (from 8.1% [65 mmol/mol] to 8.0% [64 mmol/mol] for the intermediate intensification cohort and from 7.9% [63 mmol/mol] to 7.7% [61 mmol/mol] for the late

Table 1—Patient characteristics during the 6 months before the index date, stratified by time from index date to intensification

	Time to treatment intensification (months)		
	<12 (*n* = 23,761)	12 to <24 (*n* = 11,908)	24 to <36 (*n* = 7,146)
Age at index (years)†, mean (SD)	58.1 (11.1)	59.0 (11.0)*	59.7 (10.7)*
Male sex, %	61.2	59.4*	60.6
HbA_{1c} on index date, mean (SD)			
% HbA_{1c}	8.8 (2.9)	8.1 (1.6)*	7.9 (1.4)*
mmol/mol	72.2 (31.6)	65.2 (17.9)*	63.1 (14.8)*
Antidiabetes medication used on index date, %			
Metformin	78.6	77.1*	78.4
Sulfonylurea	22.0	21.4	19.6*
BMI category‡, %			
Normal weight/underweight	7.7	7.8*	8.0*
Overweight	23.8	25.4*	25.9*
Obese	51.5	50.1*	48.3*
Unknown	16.9	16.7	17.9
Duration of diabetes (years)‖, mean (SD)	2.8 (3.6)	2.9 (3.5)*	3.1 (3.4)*
Duration of monotherapy (years)¶, mean (SD)	1.21 (1.33)	1.24 (1.29)*	1.28 (1.29)*
Duration of follow-up (years), mean (SD)	5.7 (3.5)	6.5 (3.3)*	7.2 (3.0)*
CCI, mean (SD)	0.51 (0.64)	0.46 (0.62)*	0.44 (0.60)*
Select prescription drug use, %			
Statins	63.2	62.6	61.7*
Antihypertensives	63.0	64.2*	65.3*
Any referral to an endocrinologist, %	0.5	0.5	0.3*

Data are the mean (SD) or %. *$P < 0.05$; calculated using the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. †The index date corresponds to the first record of an HbA_{1c} measurement ≥7.0% (≥53 mmol/mol) in the ≥3 months after the first prescription for metformin or a sulfonylurea. ‡BMI (kg/m^2) was calculated with the use of height from the record closest to the index date at any point in the patient's history and weight from the closest record to the index date during the 12 months before the index date. We used the World Health Organization's International Classification to define BMI categories (underweight <18.5, normal weight 18.5 to <25 kg/m^2, overweight 25 to <30 kg/m^2, obese ≥30 kg/m^2). ‖Defined as time from the first type 2 diabetes diagnosis to the index date. ¶Defined as time from the patient's first prescription for metformin or a sulfonylurea to the index date.

intensification cohort), but increased again leading up to the time of intensification. This trend was reversed shortly after intensification, and a modest decrease was observed in mean HbA_{1c} levels over time. Beginning at 42 months after the index date, the mean HbA_{1c} levels for the three cohorts were very similar.

Attainment and Duration of Glycemic Control After Treatment Intensification

Overall, 65% (*n* = 27,670) of the patients who intensified within 3 years after initial indications of monotherapy failure attained glycemic control during the follow-up period: 66% among early intensifiers, 63% among intermediate intensifiers, and 62% among late intensifiers. Kaplan-Meier analyses found that patients intensifying within 12 months of the index date had a significantly shorter median time from intensification to attaining glycemic control. Specifically, the median times from intensification to control were 20.0 months for the early intensification cohort, 24.1 months for the intermediate intensification cohort, and 25.7 months for the late intensification cohort ($P < 0.0001$) (Fig. 2*A*). After accounting for differences across groups, the likelihood of attaining glycemic control was 22% and 28% lower for the intermediate and late intensification cohorts, respectively, than for the early intensification cohort ($P < 0.0001$) (Table 2).

The median durations of glycemic control after attaining control were 16.2, 15.7, and 15.9 months for early, intermediate, and late intensifiers, respectively ($P = 0.055$) (Fig. 2*B*). After adjustment for baseline differences, the likelihood of having an HbA_{1c} measurement ≥7% (≥53 mmol/mol) after attaining control was 6% higher among patients intensifying within 12 to <24 months than in those intensifying <12 months after the index date ($P = 0.002$) (Table 2). The likelihood of having a subsequent HbA_{1c} measurement ≥7% (≥53 mmol/mol) among patients intensifying later (after 24 to <36 months) was similar to that in the early intensification cohort.

CONCLUSIONS

The study findings indicate that a majority (75%) of patients with type 2 diabetes in the U.K. do not receive intensified treatment for more than 12 months after initial indications of monotherapy failure. In fact, 44% of the patients who met the selection criteria did not have any indication of treatment intensification during the mean observable follow-up period (>5 years)—findings that are consistent with those of prior studies (5,6). Among those receiving intensified treatment within 3 years after the index date, patients who intensified treatment earlier (within the first 12 months) were younger and had a higher comorbidity burden than those who intensified after 12 months. In addition, early intensifiers had higher mean HbA_{1c} levels at the index date, suggesting that the timing of treatment intensification may in part be associated with disease severity. Previous studies have reported similar findings (8,13,22). For example, in a smaller study by Rajpathak et al. (13) that used U.S. data, among patients taking metformin who

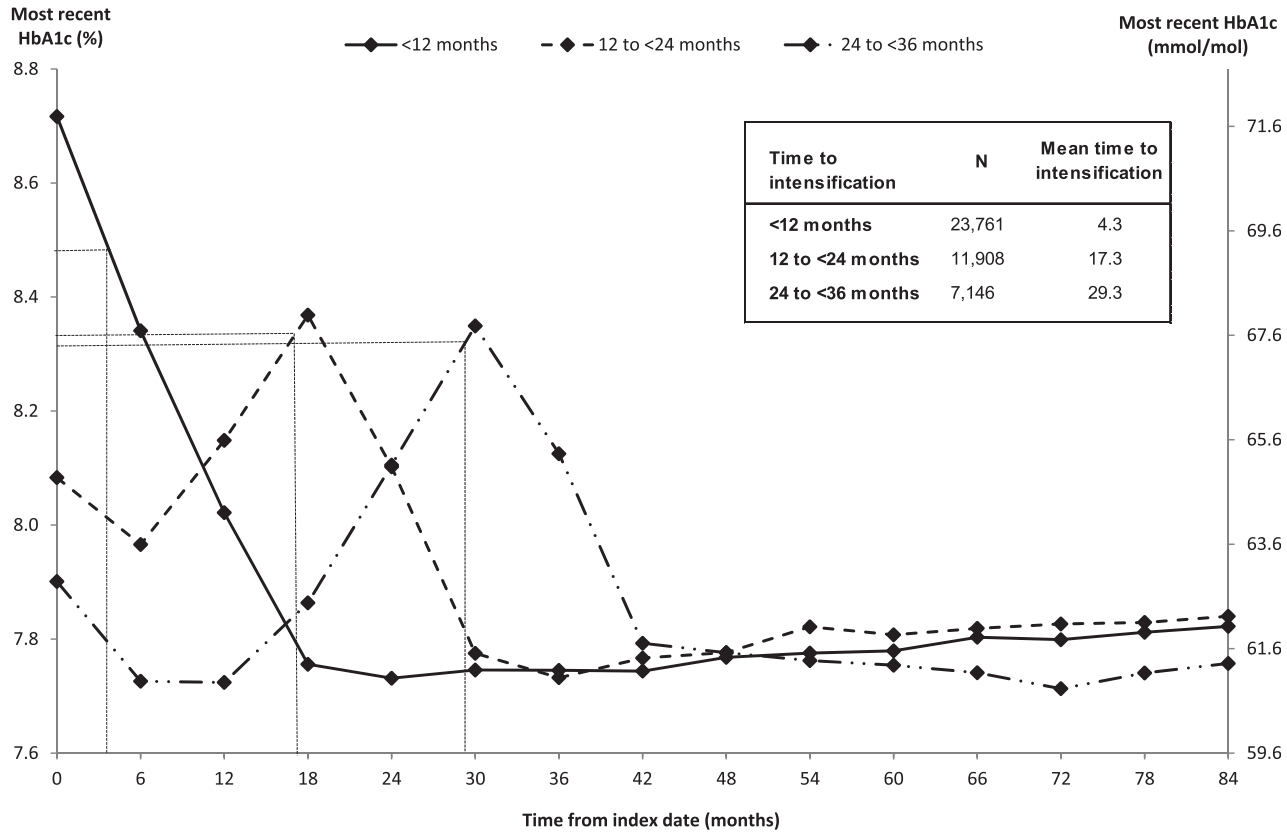

Figure 1—HbA_{1c} value trajectory from the index date to the end of follow-up, stratified by time to intensification. The index date corresponds to the first record of an HbA_{1c} measurement ≥7.0% (≥53 mmol/mol) in the ≥3 months after the first prescription for metformin or a sulfonylurea. When available, we used the most recent HbA_{1c} value before the end of each interval for the analysis. In the event that a patient did not have a test result during a 6-month interval, the last test result was used.

intensified within 3, 4 through 9, and 10 through 15 months of monotherapy failure, the mean HbA_{1c} levels were 8.5% (69.4 mmol/mol), 8.2% (66.6 mmol/mol), and 8.2% (66.3 mmol/mol), respectively. Similarly, in a retrospective analysis of patients with type 2 diabetes enrolled in a large electronic medical records database in the U.S., Fu et al. (8) found that the median time to intensification was shorter among those with higher HbA_{1c} levels at baseline: 19 months for those with index HbA_{1c} of 7% to <8% (53 to <63.9 mmol/mol) and 4.5 months among those with index HbA_{1c} ≥9% (≥74.9 mmol/mol). Over time, the early intensifiers in our study achieved a greater decline in mean HbA_{1c} level, especially within the first 18 months, than did those in the other cohorts—a finding similar to that reported by Paul et al. (6).

During the period after intensification, approximately two-thirds of all intensifiers attained glycemic control, and the proportions were greater for those intensifying within 12 months (66%) than among intermediate (63%) and late (62%) intensifiers. In addition, the median time from intensification to attainment of control was ~6 months shorter among early intensifiers than among late intensifiers. Using a Cox proportional hazards model to account for differences in baseline patient characteristics, the likelihood of attaining control was 22% and 28% lower among those intensifying 12 to <24 and 24 to <36 months after the index date than among those intensifying within the first 12 months. These findings are similar to results from the U.S. study by Rajpathak et al. (13), who found earlier intensification to be associated with 36% greater likelihood of attaining control than late intensification, and by Pantalone et al. (14), who found earlier intensification to be associated with a 43% lower likelihood of not attaining subsequent glycemic control than later or no intensification. The previous literature also documents that despite attaining control after intensified treatment, many patients have difficulty sustaining HbA_{1c} levels <7% (<53 mmol/mol) over extended periods of time (6,7,23). In our study, patients who intensified within 12 months after the index date had a marginally but statistically significantly lower likelihood of having an HbA_{1c} measurement ≥7% (≥53 mmol/mol) after first attaining glycemic control than did those who intensified within 12 to <24 months. In addition, the lower HbA_{1c} levels were generally maintained over the observable follow-up period—a finding consistent with those of several major prospective trials that evaluated the effects of intensive glucose-lowering strategies on glycemic control and risk of microvascular and macrovascular complications in patients with diabetes (24–27). Analyses of data from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) trial further revealed that the observed reduction in risk of diabetes complications during the trial duration among patients who received intensive treatment was largely explained by the sustained

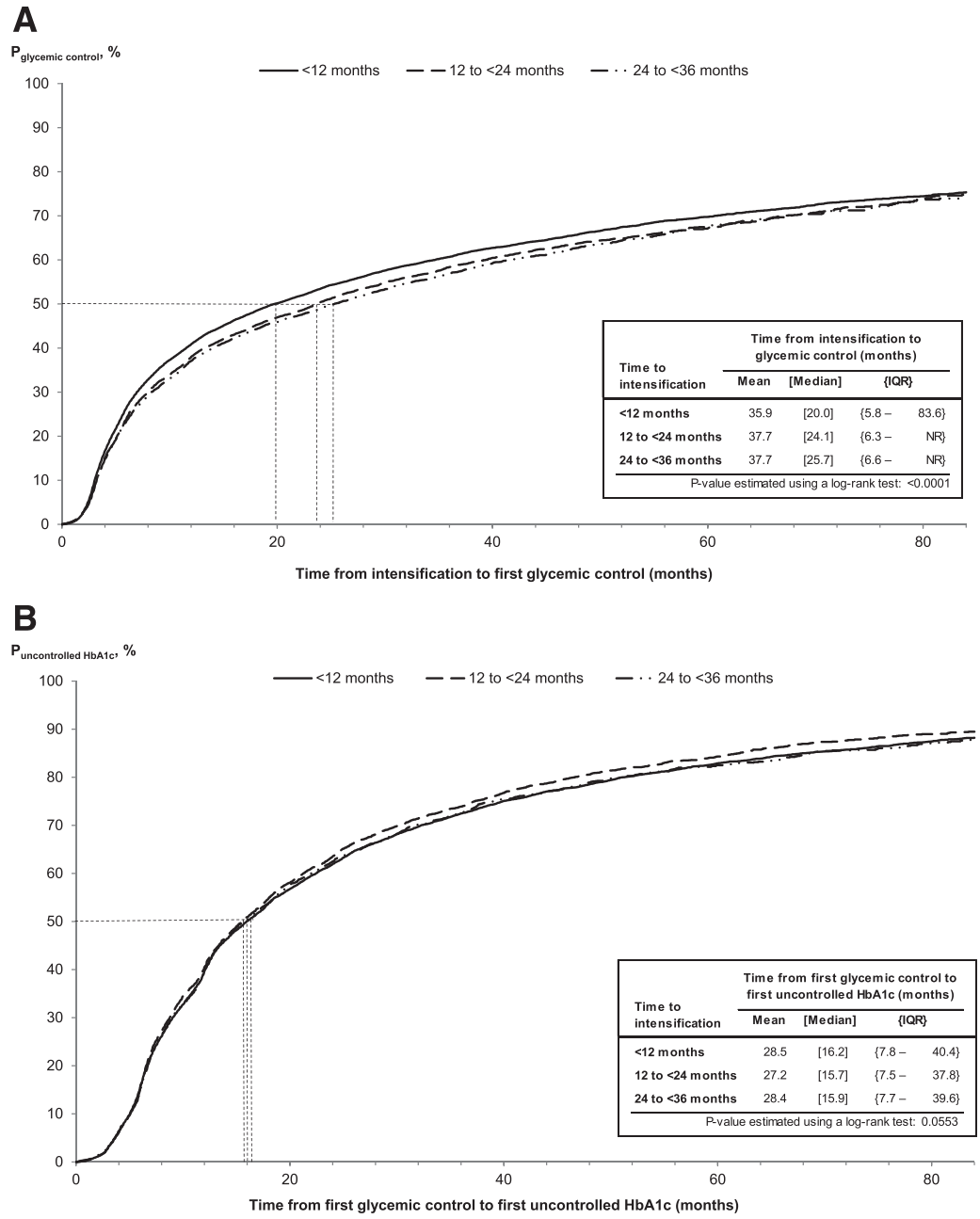

Figure 2—*A*: Time to first glycemic control within 7 years after intensification, stratified by time to intensification. The index date corresponds to the first record of an HbA_{1c} measurement ≥7.0% (≥53 mmol/mol) in the ≥3 months after the first prescription for metformin or a sulfonylurea. Glycemic control was defined as the first indication of HbA_{1c} <7.0% (≥53 mmol/mol) after the index date. Patients were censored at whichever of the following occurred first: *1*) intensification without metformin or a sulfonylurea as a component of therapy, *2*) initiation of triple therapy, *3*) initiation of insulin, or *4*) the end of data visibility. Nearly half (49%) of the patients were censored in this analysis. Pairwise comparisons of time to glycemic control were conducted using log-rank tests among those who required intensified therapy: <12 vs. 12 to <24 months, $P < 0.0001$; <12 vs. 24 to <36 months, $P < 0.0001$; 12 to <24 vs. 24 to <36 months, $P = 0.2199$. *B*: Time from first glycemic control to first instance of uncontrolled HbA_{1c}, stratified by time to intensification. First glycemic control was defined as the first indication of HbA_{1c} <7.0% (≥53 mmol/mol) after intensification. First uncontrolled HbA_{1c} was defined as the first indication of HbA_{1c} ≥7.0% (≥53 mmol/mol) after the date of first glycemic control. Patients were censored at whichever of the following occurred first: *1*) intensification without metformin or a sulfonylurea as a component of therapy, *2*) initiation of triple therapy, *3*) initiation of insulin, or *4*) the end of data visibility. Nearly 30% of the patients were censored in this analysis. Pairwise comparisons of time to glycemic control were conducted using log-rank tests among those who required intensified therapy: <12 vs. 12 to <24 months, $P = 0.0191$; <12 vs. 24 to <36 months, $P = 0.9511$; 12 to <24 vs. 24 to <36 months, $P = 0.1004$. IQR, interquartile range; NR, not reached.

reduction in HbA_{1c} levels observed during the DCCT (27). A recent study using the same data source as the current study (i.e., the U.K. CPRD) also found that compared with patients newly diagnosed with type 2 diabetes who had HbA_{1c} <7% (<53 mmol/mol) in the year after diagnosis, a 1-year delay in initiating additional antidiabetes medications among

Table 2—Determinants of attaining glycemic control after intensification and of having HbA_{1c} ≥7% (≥53 mmol/mol) after attaining control*

	Attaining glycemic control (HbA_{1c} <7% [53 mmol/mol]) after intensification			HbA_{1c} ≥7% (53 mmol/mol) after attaining control		
Parameters	HR	95% CI	*P* value†	HR	95% CI	*P* value†
Time to intensification (months)‡						
<12		Reference			Reference	
12 to <24	0.78	0.76–0.81	<0.0001	1.06	1.02–1.10	0.0023
24 to <36	0.72	0.70–0.75	<0.0001	1.01	0.97–1.06	0.5394
HbA_{1c} on index date, %	0.77	0.76–0.78	<0.0001	1.01	1.00–1.03	0.0153
Age at index date, years	1.02	1.01–1.02	<0.0001	0.99	0.99–1.00	<0.0001
Male sex	1.08	1.06–1.12	<0.0001	1.05	1.02–1.08	0.0044
BMI category‖						
Normal weight/underweight		Reference			Reference	
Overweight	1.00	0.95–1.05	0.9497	0.97	0.91–1.04	0.3999
Obese	0.99	0.94–1.05	0.8172	0.91	0.86–0.97	0.0026
Unknown	0.86	0.81–0.91	<0.0001	0.89	0.83–0.96	0.0014
Duration of monotherapy (years)¶	1.06	1.05–1.07	<0.0001	0.98	0.96–0.99	0.0002
Any referral to an endocrinologist	1.05	0.86–1.28	0.6283	1.16	0.92–1.46	0.1994
Prescription drug use						
Statins	1.18	1.15–1.22	<0.0001	0.97	0.94–1.01	0.1192
Antihypertensives	1.13	1.09–1.16	<0.0001	0.90	0.87–0.93	<0.0001

HR, hazard ratio.*Data were estimated using a Cox proportional hazard model and were adjusted for differences at baseline. †Statistical significance defined as $P < 0.05$. ‡Time to intensification from the index date. The index date corresponds to the first record of an HbA_{1c} measurement ≥7.0% (≥53 mmol/mol) in the ≥3 months after the first prescription for metformin or a sulfonylurea. ‖BMI (kg/m^2) was calculated using height from the record closest to the index date at any point in the patient's history and weight from the closest record to the index date during the 12 months before the index date. We used the World Health Organization's International Classification to define BMI categories (underweight <18.5 kg/m^2, normal weight 18.5 to <25 kg/m^2, overweight 25 to <30 kg/m^2, obese ≥30 kg/m^2). ¶Defined as time from the patient's first prescription for metformin or a sulfonylurea to the index date.

those who consistently had HbA_{1c} ≥7% (≥53 mmol/mol) was associated with a 62% increase in the risk of fatal and nonfatal cardiovascular events (myocardial infarction, stroke, heart failure) during the 5-year median follow-up period (6). In another study, Folse et al. (28) used a patient simulation method (based on the Archimedes model) and found that patients without a delay in intensification had lower HbA_{1c} levels after 1 year than did patients with delayed intensification (6.8% vs. 8.2%) and had ~20% lower risk for major adverse cardiac events and amputations at 5 years. Additional research is warranted to understand whether such effects persist among patients with type 2 diabetes more broadly (i.e., independent of disease duration).

To the best of our knowledge, this is the first study to comprehensively assess both the timing of treatment intensification and the implications of differential times of treatment intensification on subsequent glycemic control among patients with type 2 diabetes in whom monotherapy fails with either metformin or sulfonylureas—two of the classes of medications most commonly used for first-line treatment of diabetes (16). In addition, the study included a large number of patients from contemporary clinical practices in the U.K. and assessed outcomes over a long follow-up period (>5 years). Furthermore, the study used robust statistical methods to estimate the likelihood of multiple cohorts experiencing an outcome relative to a common reference group while also accounting for observable differences in patient characteristics to minimize the effects of selection bias and confounding.

The study does, however, have a number of limitations. First, the analysis relies on accuracy and completeness of coding of diagnoses and laboratory test results (for HbA_{1c} assessment). Relatedly, the effect of incomplete medical and pharmacy records, especially for patients who switched practices, on assessment of treatment intensification and outcomes is unknown. Second, the study relied on the date, type, and days' supply of medications prescribed to the patients in a primary care setting in order to assess treatment intensification and may not reflect the actual treatment regimens used by patients. In addition, because medication doses are not readily identifiable from the data, we did not account for dose titration of existing regimens when we assessed treatment intensification. Third, the study was limited to patients with diabetes in the U.K. who showed evidence of uncontrolled glycemic levels despite receiving prescriptions for metformin or a sulfonylurea (representing approximately two-thirds of all patients initiating metformin or a sulfonylurea; see Supplementary Fig. 1), and findings may not generalize to the overall population with diabetes. Fourth, the study used an observational design, and although the statistical methods control for observable differences across patient cohorts where appropriate, they cannot account for unobserved heterogeneity (e.g., in diet and exercise, provider preferences).

While the regression-based approach used in this study increases statistical power and generalizability by retaining all patients in the analyses, we acknowledge that the average baseline patient characteristics varied somewhat across cohorts. Alternative statistical techniques such as matching could increase the overlap in patient characteristics across cohorts and potentially increase

the internal validity of the comparison, although this would occur at the expense of excluding patients outside the common support and threatening external validity. Moreover, such techniques may necessitate modifying the multicohort comparison by considering multiple two-way comparisons, each consisting of slightly different patient populations. We believe the approach used in this study is preferable, but future studies should evaluate the robustness of our findings against those obtained with alternative approaches.

In conclusion, the study findings suggest that despite higher HbA_{1c} levels, several patients do not receive intensified treatment for extended periods of time. However, among those who received intensified treatment, earlier intensification may provide an opportunity not only to improve the likelihood of attaining desired HbA_{1c} levels but also to sustain these levels for somewhat longer periods of time than those achieved with delayed intensification, independent of the drug used as first-line therapy. This in turn can potentially reduce the risk of developing diabetes-related complications, as evidenced by the findings of several major clinical trials that evaluated the effects of intensive glucose control on diabetes complications, as well as those of other studies using observational data similar to the data used in the current study. Additional research is required to understand better the factors related to delay in treatment intensification and subsequent outcomes (e.g., patient and provider attitudes), and the implications of timing of treatment intensification on incidence of diabetes-related complications among patients in whom monotherapy with oral antidiabetes agents fails in the real world.

Funding and Duality of Interest. Funding for this research was provided by Bristol-Myers Squibb and AstraZeneca to Analysis Group, Inc. U.D. and N.Y.K. are employees of Analysis Group, Inc. J.K. is an employee of AstraZeneca. K.K. has received funds for research from, acted as consultant to, or received honoraria from Boehringer Ingelheim, Janssen Pharmaceuticals, Eli Lilly and Company, Merck Sharpe & Dohme, Novartis, Novo Nordisk, F. Hoffmann-La Roche, Sanofi, Takeda Pharmaceutical Co., Bristol-Myers Squibb, and Unilever. K.K. also acknowledges support from a National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care–East Midlands and the NIHR Leicester–Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit. S.K., E.T., and M.H. were employees of Analysis Group, Inc., at the time of this research. P.R.H is an employee of Evidera and serves as a consultant to AstraZeneca. J.M. is an employee of and owns stock in Bristol-Myers Squibb.

Author Contributions. U.D. and N.Y.K. conceptually designed the study, reviewed and discussed the study results, and wrote the manuscript. J.K. and P.R.H. reviewed and discussed the study results and reviewed and edited the manuscript. K.K. and J.M. conceptually designed the study, reviewed and discussed the study results, and reviewed and edited the manuscript. S.K., E.T., and M.H. conceptually designed the study, analyzed data, and reviewed and edited the manuscript. N.Y.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. An abstract containing results from this analysis was presented at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

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