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# Evaluating glycaemic control in patients poorly controlled on oral antidiabetic drugs in real-world setting: Results from assessing the Appropriate Timing of Type 2 diAbetes INtensification (ATTAIN)

Edward B. Jude[1] | Caroline O'Leary[2] | Melissa Myland[2] | Mark Nixon[2] | Nick Gooch[3] | Alka Shaunik[4] | Elisheva Lew[5]

[1]Diabetes Centre, Tameside General Hospital, Ashton-under-Lyne, UK

[2]IQVIA, London, UK

[3]Sanofi, Guildford, UK

[4]Sanofi, Bridgewater, NJ, USA

[5]Sanofi, Chilly-Mazarin, France

**Correspondence**
Edward B. Jude, Diabetes Centre, Tameside General Hospital, Ashton-under-Lyne, UK.
Email: Edward.Jude@tgh.nhs.uk

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## Abstract

**Introduction:** Many patients with type 2 diabetes mellitus (DM) fail to achieve glycaemic control despite recommended treatment strategies to reduce glycated haemoglobin (HbA1c). This real-world retrospective cohort study compared HbA1c change and treatment patterns between those intensifying and not intensifying therapy with oral antidiabetic drugs (OADs).

**Materials and methods:** Patients suboptimally controlled on OADs (>58 mmol/mol [>7.5%] or >64 mmol/mol [>8.0%] for high risk, index 1) were included from IQVIA Medical Research Data. Intensifiers within 12 months of index 1 were matched (1:1) to nonintensifiers. Primary outcomes were HbA1c change and proportion of participants achieving HbA1c targets 6 and 12 months post-index 2 (date of intensification [intensifiers] or pseudodate [nonintensifiers]). Therapy adherence was also assessed.

**Results:** A total of 10 832 participants (5539 intensifiers and 5293 nonintensifiers) were included. Mean HbA1c decrease from baseline to 6 months was −1.13% (intensifiers) vs −0.75% (nonintensifiers), with no substantial further change at 12 months. Cox proportional hazards (PH) analysis suggested a nearly 20% greater chance of target achievement at 6 months for intensifiers vs nonintensifiers (hazard ratio [HR]: 0.79 [95% confidence interval [CI]: 0.73-0.86]), which was similar at 12 months (HR: 0.80 [95% CI: 0.74-0.86]). Intensifiers tended towards greater adherence to baseline therapy (90% [standard deviation (SD): 14.9] vs nonintensifiers 87% [SD: 16.0]), which decreased following intensification.

**Conclusions:** Significant reductions in HbA1c were evident at 6 months and were greater in intensifiers vs nonintensifiers. Little additional clinical benefit was seen 12 months postintensification. Despite good treatment adherence, many participants failed to achieve target HbA1c; actions beyond improved adherence are needed to improve suboptimal HbA1c.

**KEYWORDS**
adherence, electronic medical records, glycaemic control, oral antidiabetic drugs, real-world study, treatment intensification, type 2 diabetes melitus

## 1 | INTRODUCTION

An estimated 422 million people worldwide have been diagnosed with diabetes, and the number of patients with type 2 diabetes mellitus (DM) has been increasing steadily worldwide.[1,2] In 2014, diabetes contributed to nearly 5 million deaths globally.[1] Diabetes is associated with a range of serious complications that affect quality of life and may lead to premature mortality, through heart disease, stroke, visual impairment, chronic kidney disease and peripheral vascular disease associated with poor glycaemic control.[3]

The National Institute for Health and Care Excellence (NICE) guidelines recommend that patients with type 2 DM who do not achieve glycaemic control through lifestyle interventions alone are first offered metformin.[4] If metformin is contraindicated or not tolerated, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone or sulfonylureas will be offered.[4] Clinicians may intensify or 'escalate' treatment to promote better blood glucose control through the use of additional blood glucose–lowering interventions such as pioglitazone, sulfonylureas or sodium-glucose cotransporter-2 (SGLT-2) inhibitors.[5] NICE guidelines recommend an HbA1c target of <6.5% (48 mmol/mol) or <7.0% (53 mmol/mol), according to hypoglycaemia risk.[4] Furthermore, the guidelines recommend treatment intensification for patients with HbA1c measurements of >58 mmol/mol (>7.5%) and advise that HbA1c should be measured every 3-6 months until controlled.[4] If control is still not achieved, a second intensification step can be implemented with either three oral antidiabetic drugs (OADs) (triple therapy), or any combination of OADs with insulin.[4] The NICE guidelines are generally aligned with those of the American Diabetes Association (ADA), which recommend an HbA1c target of <7.0% (53 mmol/mol) for most nonpregnant adults with type 2 DM, including HbA1c measurements at 3-6 monthly intervals, and intensification strategies dependent on individual patient factors.[6]

Despite the presence of clear recommendations, in real-world clinical practice, up to 50% of patients with type 2 DM remain in suboptimal glycaemic control for years before treatment intensification is considered.[7-9] Previous investigations of treatment intensification patterns show delays in escalating intensification despite recommendations and guidelines on the importance of early glucose control, with many patients failing to achieve therapeutic goals for glycaemic control.[10,11] This 'clinical inertia' can lead to increased healthcare resource utilization and the associated costs,[12-14] and may lead to detrimental outcomes for those with diabetes. Successful glycaemic control can have a significant effect on reducing the risk of type 2 DM-related complications, including mortality, myocardial infarction and microvascular complications,[15] suggesting that delays in (or absence of) intensification could lead to harmful outcomes.

**What is already known?**

- Many patients with type 2 diabetes mellitus fail to achieve glycaemic control despite recommended treatment strategies to manage glycated haemoglobin (HbA1c).

**What has this study found?**

- In this study, participants who intensified therapy experienced clinically and statistically significant greater improvements in HbA1c control compared with non-intensifiers; most of this improvement occurred in the first 6 months postintensification. No further clinically significant reductions in HbA1c were achieved at 12 months.

**What are the clinical implications of the study?**

- Despite good adherence to treatment, there remained a large proportion of participants who did not achieve their target HbA1c levels. For those patients who do not achieve their target levels after 6 months of intensification, another change in therapy should be considered.

While the effects of reducing HbA1c levels and achieving targeted control have been extensively studied, to our knowledge, little research has been conducted to assess the appropriate timing for therapy changes to achieve optimal clinical benefit. The aim of this study was to evaluate the effect of treatment intensification on change in HbA1c at 6 and 12 months postintensification for patients with type 2 DM suboptimally controlled on OADs. The findings intend to guide healthcare providers (HCPs) in their daily practice on optimal timing for next steps of treatment intensification.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and data source

Data extracted from IQVIA Medical Research Data incorporating data from The Health Improvement Network (THIN), a Cegedim database, were used to conduct the analyses. THIN is a primary care database containing pseudonymized electronic medical records (EMRs) from over 16 million patients in the UK, 3.1 million of whom are actively registered in a THIN-contributing general practice. The prevalence of type 2 DM in THIN is comparable to national UK estimates.[16] THIN comprises a range of data, including clinical coding, laboratory markers and all primary care prescribing data.

This study was approved by THIN's Scientific Review Committee on 15 August 2017 (THIN068).

## 2.2 | Study cohort

Participants were included in the study cohort if they met inclusion criteria between 1 January 2005 and 16 May 2017. The aim of the inclusion criteria was to define patients for whom treatment intensification should be clinically considered, based on poor diabetes control on OADs: (a) a diagnosis of type 2 DM; (b) currently prescribed ≥2 OADs (metformin, sulphonylurea, a DPP-4 inhibitor, a sodium-glucose cotransporter-2 [SGLT-2] inhibitor, or pioglitazone); and (c) uncontrolled HbA1c during the study time period (Fig. S1). Uncontrolled HbA1c was defined as a recorded HbA1c of >58 mmol/mol (>7.5%) in participants not at high risk of hypoglycaemia; or >64 mmol/mol (>8.0%) in those with a high risk of hypoglycaemia (documented history of hypoglycaemia or age >65 years with a diagnosis of heart disease or renal dysfunction defined by diagnosis Read codes).[17] Index 1 was the date of the first uncontrolled HbA1c record and index 2 was the date of treatment intensification, defined as the addition of a new injected diabetes treatment class (glucagon-like peptide-1 receptor agonist [GLP-1 RA], basal insulin [BI], rapid-acting insulin [RAI], premixed insulin), or the addition of a nonindex/new OAD to their baseline regimen. Participants with evidence of treatment intensification within 12 months of index 1 were classified as 'intensifiers'. Participants who did not intensify (nonintensifiers) were assigned a pseudo-index 2 date. Pseudotreatment intensification index dates were randomly assigned according to the distribution of time to intensification in the intensification cohort. Patients were included in the study cohort if they had ≥6 months of data prior to index 1, ≥12 months of data following index 2 and ≥1 HbA1c results ≥60 days after the index 2 date. Patients were excluded if they had gestational diabetes during the study period, were <18 years of age at index 1, had a pregnancy diagnosis during the study period or had received the agent they intensified to during the pre-index 1 period.

## 2.3 | Outcomes of interest

Primary outcomes of interest were the change in HbA1c from baseline measurement at 6 and 12 months post-index 2, as well as the proportion of participants achieving HbA1c target at 6 and 12 months. Secondary outcomes of interest included treatment adherence, persistence of treatment between pre-index 1 and post-index 2, and the assessment of delay in initiation of intensification. Persistence was defined as the number of days without any gaps in therapy exceeding 60 days.

## 2.4 | Statistical analysis

Participants with uncontrolled HbA1c who did not intensify within 12 months (nonintensifiers) were matched 1:1 with intensifiers using exact matching according to age-band, sex, baseline HbA1c, number of unique OADs at index 1 and duration of diabetes. The treatment effect was a change in HbA1c at 6 and 12 months post-index 2. This difference in effect between intensifiers and nonintensifiers was described using summary statistics and estimated with unadjusted and adjusted mixed model repeated measures (MMRM). All available data were included in the MMRM, and no participants were excluded because of incomplete records. Variables for adjustment included age, sex, body mass index (BMI), HbA1c, duration of diabetes and number of unique molecules, all at index 1. To minimize confounding by indication, whereby those with more severe disease may have been more likely to receive certain regimens or intensification than others,[18] exact matching as well as multivariable modelling was used. Measurements at milestones were captured up to 3 months after the timepoint of interest (ie up to 9 and 15 months for the 6- and 12-month end-points, respectively) to account for the real-world frequency of HbA1c measurements; only participants with measurements within these windows were included in change in HbA1c and MMRM analyses. Achievement of HbA1c targets set at baseline (58 mmol/mol [7.5%] or 64 mmol/mol [8.0%] depending on the participant's risk of hypoglycaemia) was also described at 6 and 12 months according to the proportion of participants achieving the target, and visualized using Kaplan-Meier survival curves. Cox proportional hazards (PH) models were fitted to estimate the association between intensification and achievement of target HbA1c levels up to 12 months, and were adjusted for age, sex, BMI, HbA1c, duration of diabetes and number of unique molecules, all at index 1. As a Bonferroni adjustment was applied to $P$ values based on 100 conducted tests, significance was defined as $P < .0005$.

Adherence was calculated using proportion of days covered (PDC), defined as the days supplied divided by the total follow-up days, removing any overlapping days supplied.[19] Days supplied was taken either directly from the participant's record or calculated, based on quantity supplied and daily dose. PDC is commonly used to measure adherence to OADs in database studies.[20,21] Pharmacy claims data were not available; therefore, persistence with the intensification regimen was assessed post-index 2 until the earliest end of study time period, switch/discontinuation of intensification regimen, transfer out of practice, or death. Treatment persistence was defined as a period free of any gaps in therapy greater than 60 days post-index 2 (gaps of ≤60 days were allowed). Gaps in treatment were calculated, based on the time between the calculated end date for a prescription (based on start date and recorded or derived duration) and the start date of the next prescription. Persistence was compared between intensification regimens using summary statistics and Cox PH models (adjusted for age, gender, BMI, HbA1c, duration of diabetes and number of unique molecules, all at index 1) to estimate the probability of discontinuation or switching to an alternative therapy.

# 3 | RESULTS

A total of 10 832 participants (5539 intensifiers and 5293 nonintensifiers) uncontrolled on ≥2 OADs met the study inclusion criteria. Amongst intensifiers, 34.1%, 25.5%, 24.6% and 15.9% had BI, GLP-1

**TABLE 1** Baseline characteristics for the study population at index 1

| | OAD baseline regimen | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Intensified | | | | | Nonintensified |
| | Total OAD (intensified and nonintensified) (n = 10 832) | Third OAD (n = 879) | BI (n = 1887) | GLP-1 RA (n = 1412) | Premixed insulin (n = 1361) | Total OAD intensified (n = 5539) | OAD (n = 5293) |
| Mean age at baseline, years (SD) | 59.3 (12.4) | 57.9 (12.0) | 63.0 (12.7) | 53.6 (10.0) | 60.7 (11.9) | 59.2 (12.3) | 59.3 (12.6) |
| Male, n (%) | 6062 (56.0) | 533 (60.6) | 1019 (54.0) | 753 (53.3) | 786 (57.8) | 3091 (55.8) | 2971 (56.1) |
| HbA1c at baseline | | | | | | | |
| Mean, % (SD) | 9.40 (1.57) | 9.05 (1.37) | 9.38 (1.50) | 9.17 (1.38) | 9.89 (1.83) | 9.40 (1.57) | 9.41 (1.57) |
| HbA1c category n (%) | | | | | | | |
| 58-75 mmol/mol (7.5%-9.0%) | 5134 (47.4) | 495 (56.3) | 882 (46.7) | 763 (54.0) | 520 (38.2) | 2660 (48.0) | 2474 (46.7) |
| 75-86 mmol/mol (9.0%-10.0%) | 2359 (21.8) | 182 (20.7) | 450 (23.8) | 295 (20.9) | 268 (19.7) | 1195 (21.6) | 1164 (22.0) |
| >86 mmol/mol (>10.0%) | 3339 (30.8) | 202 (23.0) | 555 (29.4) | 354 (25.1) | 573 (42.1) | 1684 (30.4) | 1655 (31.3) |
| Diabetes diagnosis duration to baseline (category) n (%) | | | | | | | |
| <5 y | 1010 (9) | 82 (9) | 152 (8) | 136 (10) | 172 (13) | 542 (10) | 468 (9) |
| 5-10 y | 4988 (46) | 471 (54) | 798 (42) | 705 (50) | 562 (41) | 2536 (46) | 2452 (46) |
| >10 y | 4834 (45) | 326 (37) | 937 (50) | 571 (40) | 627 (46) | 2461 (44) | 2373 (45) |
| Mean (SD) BMI, kg/m$^2$ | 32.9 (7.4) | 32.7 (6.6) | 31.1 (6.4) | 39.0 (7.0) | 31.1 (7.0) | 33.4 (7.5) | 32.4 (7.1) |
| Comorbidities n (%) | | | | | | | |
| Hypertension | 1149 (10.6) | 103 (11.7) | 195 (10.3) | 130 (9.2) | 157 (11.5) | 585 (10.6) | 564 (10.7) |
| Dyslipidaemia | 157 (1.4) | 10 (1.1) | 28 (1.5) | 21 (1.5) | 20 (1.5) | 79 (1.4) | 78 (1.5) |
| Obesity (including baseline BMI >30 kg/m$^2$) | 4523 (41.8) | 369 (42.0) | 652 (34.6) | 942 (66.7) | 511 (37.5) | 2474 (44.7) | 2049 (38.7) |
| Delay in treatment intensification for participants intensifying treatment at any point | | | | | | | |
| N | - | 3652 | 2078 | 1635 | 1481 | 8846 | - |
| Mean (SD) | - | 15.1 (16.46) | 8.4 (10.67) | 9.4 (11.79) | 8.0 (10.03) | 11.3 (13.84) | - |
| Median (IQR) | - | 9 (5-19) | 6 (2-10) | 6 (3-11) | 5 (2-10) | 7 (3-12) | - |

Abbreviations: BI, basal insulin; BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IQR, interquartile range; OAD, oral antidiabetic drug; RAI, rapid-acting insulin; SD, standard deviation.

**TABLE 2** Participant persistence on intensification therapy during intensification period, by intensification regimen

| | OAD baseline regimen | | | | |
|---|---|---|---|---|---|
| | Intensified | | | | |
| Characteristic | Third OAD (n = 879) | BI (n = 1887) | GLP-1 RA (n = 1412) | Premixed insulin (n = 1361) | Total OAD intensified (n = 5539) |
| Participant level persistence (days following intensification) | | | | | |
| Mean (SD) | 870.0 (1119.8) | 998.04 (1136.8) | 817.26 (649.7) | 1383.55 (1327.1) | 1026.36 (1107.1) |
| Median (IQR) | 504 (190-1118) | 541 (212-1341) | 625 (323-1117) | 900 (411-1953) | 634 (275-1376) |
| Participant level persistence category (intensification) (%) | | | | | |
| <1 y | 357 (40.6) | 705 (37.4) | 407 (28.8) | 306 (22.5) | 1775 (32.0) |
| 1-5 y | 416 (47.3) | 860 (45.6) | 879 (62.3) | 681 (50.0) | 2836 (51.2) |
| >5 y | 106 (12.1) | 322 (17.1) | 126 (8.9) | 374 (27.5) | 928 (16.8) |

Abbreviations: BI, basal insulin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; OAD, oral antidiabetic drug; SD, standard deviation.

RA, premixed insulin or a third OAD, respectively, added to their regimen. Mean age at baseline was 59.3 years (SD 12.4) overall and was similar between intensifiers and nonintensifiers. Of the intensifier subgroups, those intensified with BI were the oldest (63.0 years, SD 12.7). Mean BMI was similar across intensifiers and nonintensifiers (32.9 kg/m$^2$, SD 7.4) overall but was greatest in participants intensified with GLP-1 RA (39.0 kg/m$^2$, SD 7.0) (Table 1). Overall, 52.6% of participants had an HbA1c level ≥75 mmol/mol (≥9.0%), with a mean of 79 mmol/mol (9.4%) (SD 1.6%). Of those intensified with premixed insulin, 61.8% had an HbA1c ≥75 mmol/mol (≥9.0%), averaging 85 mmol/mol (9.91%) (SD 1.8%), while those intensifying on a third OAD had the lowest proportion with an HbA1c ≥75 mmol/mol (≥9.0%) at baseline, averaging 75 mmol/mol (9.12%) (SD 1.46%). Over 90% of the cohort had a diabetes duration greater than 5 years and tended to intensify treatment an average of 11.3 (SD 13.8) months following uncontrolled HbA1c.

Mean HbA1c decrease from baseline to 6 months was −1.13% (SD 2.1%) for intensifiers vs −0.75% (SD 2.1%) for nonintensifiers, with no substantial further change seen at 12 months for intensifiers (–1.26%, SD 2.4%) vs nonintensifiers (–0.77%, SD 2.4%) (Figure 1A). For specific intensification regimens, HbA1c reduction at 6 months was largest at −1.64% (SD 2.4%) with the addition of premixed insulin, −1.17% (SD 2.0%) with GLP-1 RA, −0.97% (SD 2.0%) with BI, and −0.61% (SD 2.0%) with a third OAD; similar results were seen at 12 months post-index 2 (Figure 1B).

When considering results obtained from the unadjusted/adjusted MMRM for HbA1c change, participants intensifying therapy also experienced larger reductions in HbA1c, with estimates broadly similar between unadjusted and adjusted models. The largest numerical reduction in HbA1c in adjusted estimates was seen for intensifiers at 12 months (−0.468, 95% CI −0.557-0.379; $P < .0001$); however, it was not substantially larger than the 6-month change (−0.438, 95% CI −0.527-0.349; $P < .0001$).

Analyses of target achievement at 6 months indicated that, on average, 38% of intensifiers achieved the HbA1c target set at baseline compared with 28% of nonintensifiers ($P < .0001$ for both logistic regressions); GLP-1 RA users accounted for the greatest proportion achieving target amongst intensification regimens (45%), while the lowest proportion achieved target by intensifying with a third OAD (34%). Kaplan-Meier analysis of target achievement also indicated a greater probability for intensifiers compared with nonintensifiers. As shown in Figure 2A, the curves diverged at 3 months where intensifiers began having a greater probability of achieving target. This change became most pronounced at 6 months and was sustained at 12 months, but with no further significant clinical improvement. At 12 months, there was a 48% chance of intensifiers achieving target compared with a 38% chance for nonintensifiers ($P < .0001$ for both logistic regressions) (Figure 2B). The probability of achieving HbA1c target was earlier for the intensified compared with the nonintensified cohort, with intensifiers having the same chance of achieving target at 5 months as nonintensifiers at 9 months. Intensifiers continued to have a greater proportion achieving glycaemic target than nonintensifiers up to the 12 months of observation for this study, and the difference remained constant and sustained.

Cox PH models further examined the likelihood of target achievement, with adjusted analyses suggesting a nearly 20% greater chance of achievement at 6 months for intensifiers compared with nonintensifiers (HR 0.79, 95% CI 0.73-0.86; $P < .0001$). The difference in the likelihood of achievement was slightly lower at 12 months (HR 0.80, 95% CI 0.74-0.86; $P < .0001$) (Table S1).

The results of participant persistence on intensification therapy during intensification period were shown in Table 2. In regards to adherence to therapy, intensifiers tended to have greater baseline adherence at index 1 compared with nonintensifiers (90%, SD 14.9) for intensifiers vs 87% (SD 16.0) for nonintensifiers; $P < .0001$). Adherence following index 2 tended to be slightly lower (80% overall, SD 19.9) across treatments, with GLP-1 RA users having the greatest adherence to therapy (86%, SD 16.2).

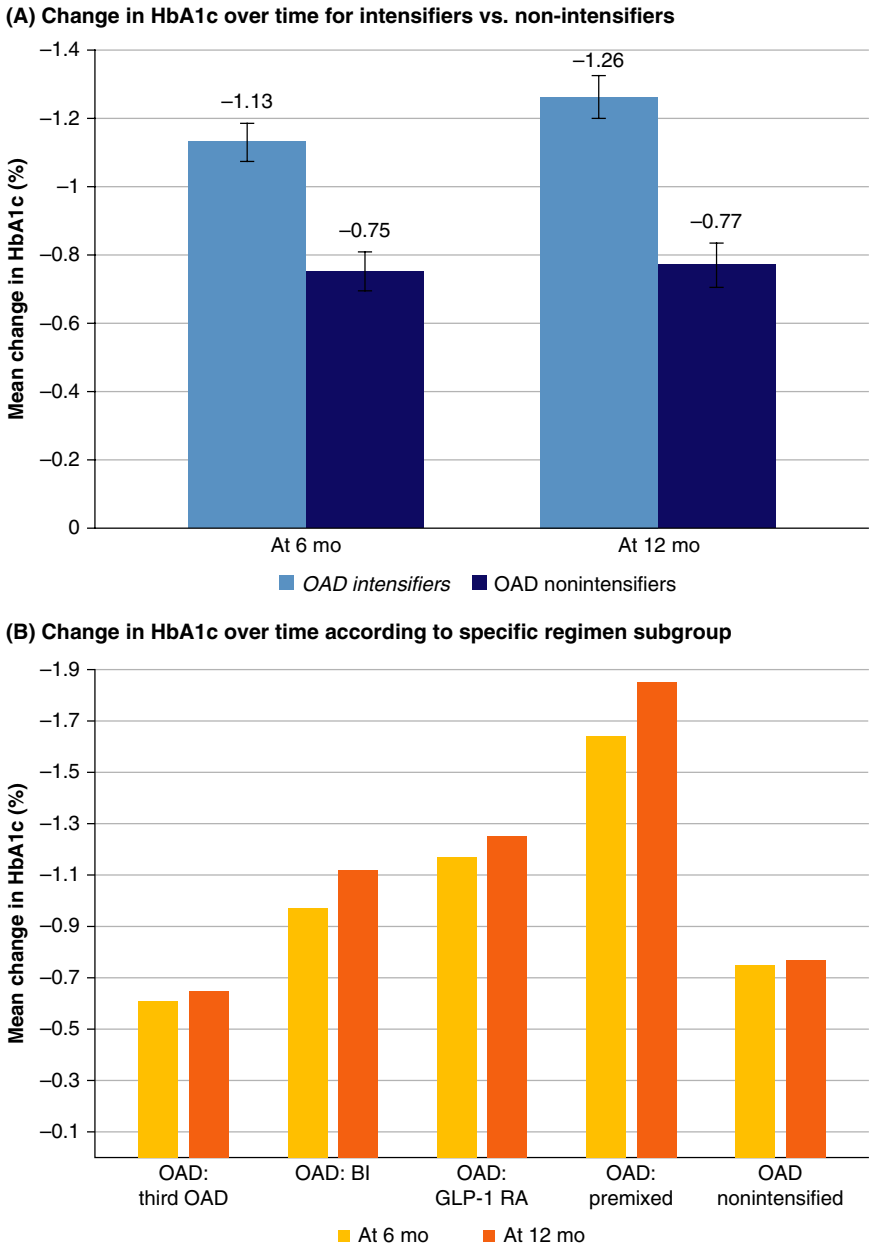


**FIGURE 1** A, Change in HbA1c over time for intensifiers vs nonintensifiers. B, Change in HbA1c over time according to specific regimen subgroup. BI, basal insulin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug

BI, basal insulin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antidiabetes drug.

## 4 | DISCUSSION

In this study, participants intensifying therapy experienced clinically and statistically significant larger improvements in HbA1c control compared with nonintensifiers, with most of this improvement occurring in the first 6 months postintensification. No further clinically significant reductions in HbA1c were achieved at 12 months, indicating that the majority of clinical benefit occurred during the first 6 months postintensification. Further clinical action is therefore needed to achieve control amongst the large proportion of patients with type 2 DM who fail to achieve their target HbA1c goal. Review of previously conducted studies shows similar results, and these results are aligned with other real-world studies which concluded that the probability of achieving glycaemic control decreased rapidly within the first year of treatment intensification and remained low in the subsequent year.[22] However, this study looked at achievement as milestones rather than sustained control over time. This is especially relevant because HCPs prescribe periodic HbA1c investigation to determine if a patient's HbA1c is in control, as this is recommended by ADA/EASD, NICE and other guidelines.

We observed significant delays in treatment intensification, despite most participants having a high baseline HbA1c (mean baseline HbA1c at intensification of 79 mmol/mol [9.4%], nearly 2% higher than recommendations by NICE[10]) and a history of diabetes exceeding 5 years. Our findings of delay in intensification are consistent with previous UK-based analyses which found that the initiation of

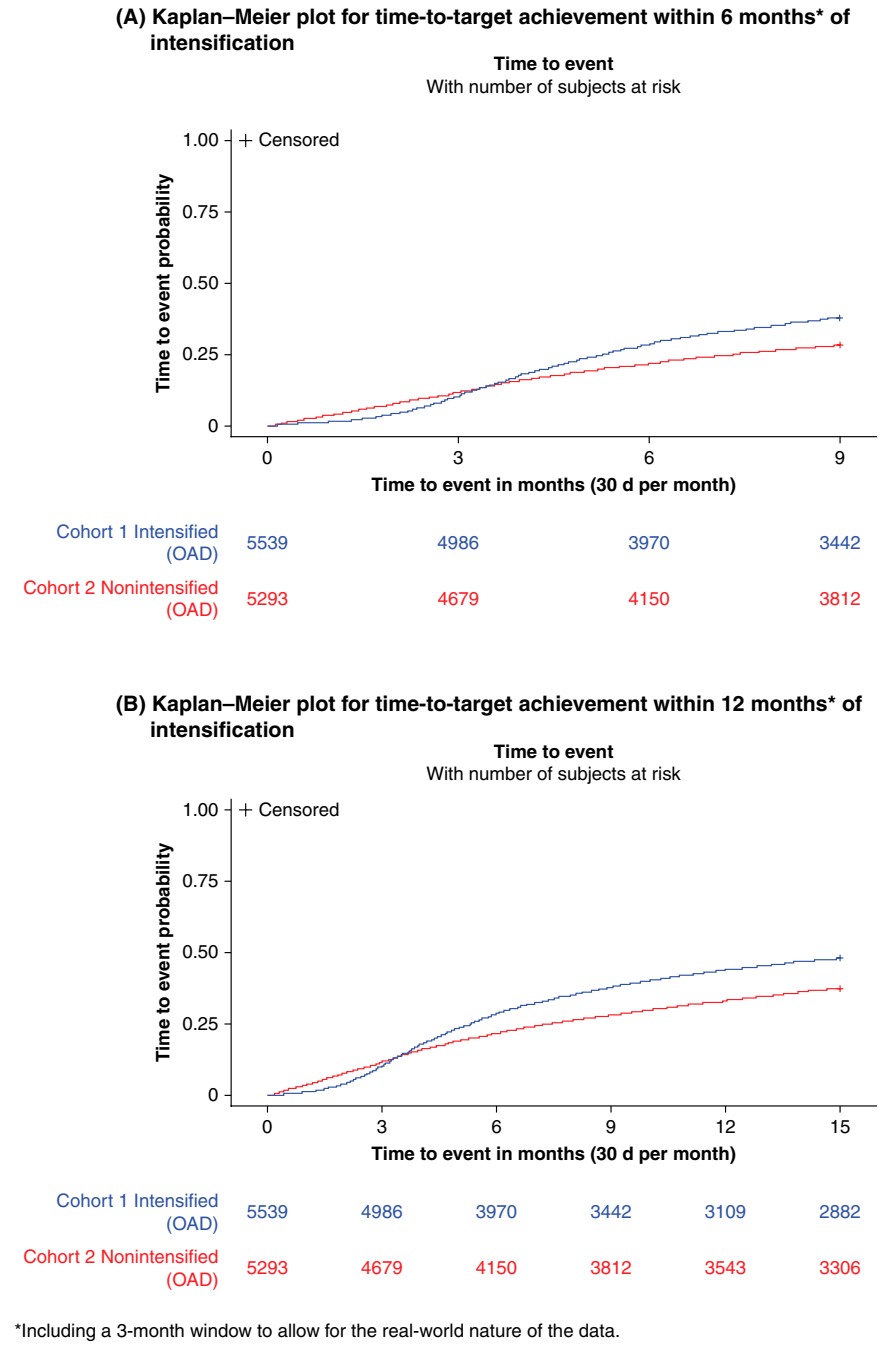


**FIGURE 2** A, Kaplan-Meier plot for time-to-target achievement within 6 mo* of intensification. B, Kaplan-Meier plot for time-to-target achievement within 12 mo* of intensification. *Including a 3-month window to allow for the real-world nature of the data. It should be noted that the crossing of the curves at approximately 3 mo is an artefact of the data due to intensifiers being 'anchored' by the intensification event, meaning they are unlikely to be retested within the next 3 mo (ie the earliest point that a change is likely to be seen is at 3 mo when they are retested). Nonintensifiers are assigned a 'pseudo' date with no anchoring event, which means they may be tested sooner than 3 mo. Consequently, some nonintensifiers seemingly improve faster, but following 3 mo of intensifiers, consistently do better. OAD, oral antidiabetic drug

insulin following OADs can take nearly 8 years.[7,23] Our study, in addition to others, confirms the presence of clinical inertia—the failure to establish appropriate targets and escalate treatment in order to meet treatment goals.[24] These data suggest that in routine care, many patients are not receiving treatment intensification according to NICE recommendations, which state that physicians should consider a second intensification for patients if their blood glucose is not controlled on dual therapy and HbA1c levels are ≥58 mmol/mol (7.5%), and that patients should have HbA1c measured every 3-6 months until they have reached appropriate glycaemic targets.[4] The need for timely intensification has been demonstrated in a UK-based study using the Clinical Practice Research Datalink (CPRD), which indicates that delay in treatment intensification and prolonged hyperglycaemia can lead to significantly increased risk of cardiovascular complications.[25]

Importantly, the improvements in HbA1c observed in the intensifiers were clinically meaningful when contextualized with previous studies showing the benefit of blood glucose control in diabetes: each 1% reduction in HbA1c was shown to correspond to a 21% risk reduction in diabetes-related deaths, a 14% risk reduction for myocardial infarctions and a 37% risk reduction for microvascular complications.[26] Although premixed intensifiers experienced the largest reduction in HbA1c, a greater proportion of GLP-1 RA intensifiers reached HbA1c targets over time. Participants intensified with premixed insulin also had the highest baseline HbA1c, which may have inherently made it more likely to see a reduction in HbA1c

(a regression to the mean); however, this was controlled for in the mixed models by adjusting for the baseline HbA1c.

However, despite good adherence to treatment, there remained a large proportion of participants who did not achieve their target HbA1c. Clinically significant reductions in HbA1c, therefore, are unlikely to be delivered through therapy dose changes or improving patients' therapy adherence, as these are already approaching optimal rates of about 80%.[27] The study data demonstrate that if a person does not reach glycaemic goals 6 months postintensification, physicians should consider treatment change or new therapeutic intervention. The study demonstrates the impact on clinical outcomes such as HbA1c for a >1 year study period, and thus, the results from this real-world study demonstrate the clear benefits and are an impetus for HCPs for timely intensification for early and continued glycaemic control.

### 4.1 | Limitations

Some limitations with regard to the study are presented. Due to the study design, nonintensifiers were able to obtain changes in HbA1c results before 3 months, while intensifiers, due to clinical practice,[4] were more likely to have their results >3 months after index 1. These circumstances meant the proportional hazards assumption was not met; however, the findings of the Cox models supported the other study findings. Dose changes (within the same therapy) could have led to decreases in HbA1c in the nonintensifier cohort, but this was not assessed. In addition, treatment duration was estimated based on days' supply of therapy, which could have led to over- or underestimations of adherence. Although adherence was high in the present study, a recently conducted systematic literature review of adherence studies found that 22% of papers reported adherence ≥80%.[28] In addition, adherence was calculated using PDC, which is commonly used in retrospective studies and is more conservative than other methods such as medication possession ratio.[29] An inherent limitation in the use of PDC to evaluate adherence is the assumption that a patient who fills a prescription also takes their medication as prescribed. Furthermore, immortal time bias could have been introduced by the requirement of 12 months of data post-index 2; participants may have died within this time period and would therefore have been unable to take part, which could have led to overestimation of treatment effectiveness.[30] Finally, the HbA1c targets that were used in this study were guideline targets and may not have reflected the individual targets of each person.

## 5 | CONCLUSIONS

In real-world clinical practice, treatment intensification is associated with clinically significant improvements in HbA1c and an increased likelihood of achieving HbA1c targets once initiated, but is often delayed for patients with poorly controlled type 2 DM. Patients experienced a mean delay in intensification of 11.3 months. In this population suboptimally controlled on 2 OADs, significant reductions in HbA1c were rapidly evident at 6 months postintensification in 38% of intensifiers, but with little additional clinical benefit at 12 months postintensification. Importantly, the probability of target achievement was greater for intensifiers compared with nonintensifiers, with the change being most pronounced at 6 months, and this remained constant and sustained at 12 months. There was high adherence to therapy in this population, and this adherence tended to decrease with intensification. It is important to note that despite good adherence to treatment, there remained a large proportion of participants who did not achieve their target HbA1c levels. Clinically significant reductions in HbA1c, therefore, are unlikely to be delivered through improving patients' adherence to therapy, as they are already approaching optimal rates[27] near 80%. Thus, for those patients who do not achieve their target after 6 months of intensification, there should be a clinical impetus considered for timely change or therapeutic intensification to achieve and maintain glycaemic control and the risk of associated micro- and macrovascular complications and outcomes.

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### CONFLICTS OF INTEREST

EBJ has received advisory board honoraria and grant/research support from Sanofi, and has received speaker honoraria from Bayer AG, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Takeda. CO, MM and MN are employees of IQVIA, UK, which was contracted by Sanofi to conduct the analyses. NG, AS and EL are employees of Sanofi.

### AUTHOR CONTRIBUTIONS

All authors participated in the study design. MN, CO and MM acquired and analysed the data. All authors interpreted the data, contributed to the drafting, critical review and revision of the manuscript.

### ETHICAL APPROVAL

This study was conducted in compliance with the ethics guidelines for research in humans as recorded in the Helsinki Declaration of 1964. Given the observational retrospective nature of this study, individual consent was not required after ensuring for anonymization of data.

## DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed during the current study are not publicly available due to patient privacy, but are available from the corresponding author on reasonable request.

## ORCID

*Edward B. Jude* https://orcid.org/0000-0002-4096-3376
*Caroline O'Leary* https://orcid.org/0000-0002-0001-4010
*Elisheva Lew* https://orcid.org/0000-0001-5097-0169

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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