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► To cite this version:

Linong Ji, Fabrice Bonnet, Hungta Chen, Andrew Cooper, Niklas Hammar, et al.. Early versus late intensification of glucose-lowering therapy in patients with type 2 diabetes: Results from the DISCOVER study. Diabetes Research and Clinical Practice, 2021, 178, pp.108947. 10.1016/j.diabres.2021.108947 . hal-03476924

HAL Id: hal-03476924

<https://hal.science/hal-03476924v1>

Submitted on 14 Dec 2021

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Early versus late intensification of glucose-lowering therapy in patients with type 2 diabetes: results from the DISCOVER study

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Target journal: Diabetes Research and Clinical Practice

Word count: 4889 [max 5000, includes tables and figures with legends, does not include abstract and references]

Number of tables and figures: 1 table, 4 figures, 3 supplementary figures

Abstract [200/200 words]

Aims: To assess the effects of glycated haemoglobin (HbA_{1c}) levels at time of glucose-lowering treatment intensification in DISCOVER, a global observational study of patients with type 2 diabetes (T2D) initiating second-line therapy. Outcomes of interest were glycaemic control, hypoglycaemia, and need for further intensification during 3 years of follow-up.

Methods: We included patients who intensified treatment (add-on or insulin initiation) upon initiation of second-line therapy (baseline). Outcomes were assessed according to baseline HbA_{1c}: HbA_{1c} ≤7.5% (early intensification) or HbA_{1c} >7.5% (late intensification). Factors associated with early or late intensification were assessed using multivariate logistic regression.

Results: Of the 9575 patients included, 3275 (34.2%) intensified treatment early and 6300 (65.8%) intensified treatment late. During follow-up, mean (SD) HbA_{1c} was lower in the early- than in the late-intensification group (6.9% [0.95%] vs 7.5% [1.28%] at 36 months). More patients had HbA_{1c} <7.0% in the early- than in the late-intensification group (61.8% vs 37.9% at 36 months; $p<0.001$). The risk of further intensification was higher in the late-intensification group (hazard ratio 1.88 [95% confidence interval 1.68–2.09]). Occurrence of hypoglycaemia was similar in both groups.

Conclusions: Late intensification of glucose-lowering therapy after first-line treatment failure reduces the likelihood of reaching recommended treatment goals.

Keywords: glucose-lowering drug; glycaemic control; observational study; type 2 diabetes

Introduction

Therapeutic inertia, defined as the failure to initiate or intensify therapy in a timely and appropriate manner according to evidence-based guidelines, is a major reason for poor long-term glycaemic control in type 2 diabetes (T2D).[1] This delay in intensifying glucose-lowering therapy is often a complex interplay between patients and providers, and may be explained by several factors including providers' fear of overmedicating patients, suboptimal monitoring of glycaemic levels, and potential poor adherence to treatment.[2]

Diabetes guidelines recommend early and sustained glycaemic control to mitigate the risks of long-term complications and advocate a target glycated haemoglobin (HbA_{1c}) level of less than 7.0% (53 mmol/mol) for most patients; with timely intensification of glucose-lowering therapy if patients do not meet this target.[3] Despite these recommendations, many patients are initiated on second-line therapy with HbA_{1c} levels far exceeding this target, putting them at a heightened risk of complications.[4, 5] Indeed, delayed treatment intensification has been shown to be associated with a significantly increased risk of cardiovascular events, such as myocardial infarction, heart failure, and stroke.[6, 7]

DISCOVER is a global, prospective, observational 3-year study of patients with T2D moving from a first-line to a second-line glucose-lowering therapy. The research seeks to provide a comprehensive picture of T2D management patterns and clinical outcomes after first-line treatment failure. The present analysis of DISCOVER study data aims to explore the impact of early treatment intensification compared with late treatment intensification, i.e. at higher HbA_{1c} levels. This analysis includes DISCOVER patients who intensified treatment upon initiation of second-line therapy, divided into an early-intensification group (those who intensified with a baseline HbA_{1c} ≤7.5% [59 mmol/mol]) and a late-intensification group (those who intensified with a baseline HbA_{1c} >7.5% [59 mmol/mol]). Glycaemic control and need for further treatment intensification over the 3 years of follow-up were compared in these two groups. The factors associated with early and late treatment intensification, glycaemic control during follow-up, and risk of hypoglycaemia were also assessed.

Materials and Methods

The methods for the DISCOVER study programme have been reported in detail elsewhere,[8, 9] and are briefly summarised below.

Study design

The global DISCOVER study programme comprises two similar, 3-year, non-interventional, prospective studies conducted simultaneously in 38 countries; DISCOVER (NCT02322762) in 37 countries and J-DISCOVER (NCT02226822) in Japan. Included countries are categorised according to World Health Organization (WHO) regions: Africa (Algeria and South Africa); Americas (Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico, and Panama); South-East Asia (India and Indonesia); Europe (Austria, Czech Republic, Denmark, France, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, and Turkey); Eastern Mediterranean (Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Tunisia, and United Arab Emirates); and Western Pacific (Australia, China, Japan, Malaysia, South Korea, and Taiwan).

The study protocols were approved by the appropriate clinical research ethics committees in each participating country, and the relevant institutional review boards at each site. The protocols comply with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice, and the local clinical research regulations.

Site and investigator selection

Data relating to the management of T2D, including physician and site characteristics, the geographical and rural or urban distribution of practices, and the source of funding of practices, were assessed in each participating country before the start of the study. This was achieved by combining data from peer-reviewed articles, information from reports published by organisations such as the WHO, and insights from national coordinating investigators.[10, 11] A list of sites that would match these characteristics as closely as possible was then established for each country, and all sites were invited to participate in the study.[10, 11]

Patient recruitment

Adult patients with T2D who were initiating a second-line glucose-lowering therapy (addition of another glucose-lowering medication to their first-line therapy or switching to another therapy) after first-line oral treatment were invited to participate in DISCOVER from September 2014 to June 2016. Inclusion and exclusion criteria were kept to a minimum to reflect the diversity of patients treated in routine clinical practice (**supplemental table 1**). Exclusion criteria included being pregnant, undergoing dialysis, having a history of renal

transplant, and patients' first-line therapy being an injectable agent or herbal remedy/natural medicine alone.

Data collection

Data were collected at study baseline (initiation of second-line therapy) and 6, 12, 24, and 36 months using a standardised case report form, and transferred to a central database via a web-based data capture system. Some data were extracted from existing electronic health records in Canada, Denmark, France, Norway, and Sweden; an abbreviated electronic case report form was used in these countries to collect additional DISCOVER variables that would not be routinely entered in the electronic medical records.

Variables collected included: physician and site characteristics; patient socioeconomic demographics; physiological parameters; laboratory test results; change in glucose-lowering therapies and reason(s) for change; HbA_{1c} level at the time of treatment change; comorbidities including diabetes-related microvascular and macrovascular diseases; and co-mediations.

In line with the observational nature of the study, variables were measured and recorded according to routine clinical practice at each site. Patients were not obliged to attend study visits, data collection was not compulsory for any of the clinical variables, methods used to measure clinical variables were not specified, and the occurrence of complication events was not adjudicated.

Statistical analysis

Patients from China (n=1292) were not included, because data from these patients were unavailable at the time of the analysis owing to regulatory changes during study follow-up. Patients were included in the analysis if: they had an HbA_{1c} measurement available at baseline (initiation of second-line therapy); their first-line therapy consisted of one or two oral glucose-lowering drugs; and they intensified treatment upon initiation of second-line therapy. Treatment intensification was defined as adding a glucagon-like peptide 1 (GLP-1) receptor agonist or any oral drug to their first-line therapy, or insulin initiation (with or without other agents). Other treatment changes, such as switching between two different oral monotherapies, were not considered treatment intensifications.

Patients were divided into two groups according to their HbA_{1c} level at baseline: early treatment intensification (HbA_{1c} ≤ 7.5% [59 mmol/mol]) and late treatment intensification (HbA_{1c} > 7.5% [59 mmol/mol]). A hierarchical multivariate logistic regression model with country as a random factor, which adjusted for age, sex, time since T2D diagnosis, WHO region, first- and second-line glucose-lowering therapy, body mass index, history of major hypoglycaemia in the year before baseline, history of microvascular and macrovascular complications, education level, smoking status, health insurance status, and healthcare setting, was used to explore baseline patient characteristics associated with early or late initiation of second-line therapy. Differences in mean HbA_{1c} levels in the two groups at different time points were compared using Student's *t*-test. Differences in the proportions of patients with an HbA_{1c} level < 7.0% (53 mmol/mol) or > 9.0% (74 mmol/mol) at each time point were assessed using the chi-squared test.

Repeated-measures analysis via generalised estimating equations with country as a random factor, and adjusted for the covariates previously described, was used to assess the comparative effectiveness of early versus late treatment intensification to achieve HbA_{1c} < 7.0% (vs ≥ 7.0% [53 mmol/mol]) during the 3 years of follow-up. A Cox regression model, adjusted for the variables previously described, was used to assess the association between early versus late treatment intensification and the risk of need for additional treatment intensification (beyond second-line therapy, either via addition of another glucose-lowering drug or initiation of insulin) during the 3 years of follow-up. A Cox regression model, also adjusted for the variables previously described, was used to assess the association between early- versus late-intensification and risk of experiencing at least one hypoglycaemic event during the 3 years of follow-up. Hypoglycaemic events were reported by patients and included minor hypoglycaemic events which did not require third-party assistance in the 4 weeks prior to a study visit and major hypoglycaemic events that required an emergency room visit, a hospital admission, a visit to a physician or other healthcare professional, or third-party assistance in between study visits. In these multivariate models, missing or unreported data were accounted for using multiple imputation, which employed iterative sequential regression to sample missing values from the predictive distribution of each variable conditional to all other variables. Variables included in the imputation model were the dependent variables, all the independent variables (as previously described for the hierarchical multivariate logistic regression model), and country. The rate of missing data for individual variables ranged from 0.3% (history of macrovascular complications) to 9.7%

(level of education). Ten randomly imputed data sets were generated in this way. Analyses were replicated on each imputed data set, and the model estimates were pooled across imputations using Rubin's rule.[12]

Interval-censored survival analyses were used to estimate the incidence of hypoglycaemia and the cumulative incidence of additional treatment intensifications (beyond initiation of second-line therapy) in the early- and late-intensification groups, over 3 years of follow-up.

Results

Patient baseline demographics and clinical characteristics

Of the 14 691 DISCOVER patients assessed, 9575 (65.2%) had sufficient data for inclusion and intensified glucose-lowering therapy when initiating second-line treatment, either by the addition of another oral glucose-lowering drug or GLP-1 receptor agonist or the initiation of insulin (alone or in combination with other agents). Of these patients, 3275 (34.2%) intensified therapy with a baseline HbA_{1c} ≤ 7.5% (59 mmol/mol, early-intensification group) and 6300 (65.8%) intensified therapy with a baseline HbA_{1c} > 7.5% (59 mmol/mol, late-intensification group).

Baseline clinical and demographic characteristics of these patients, overall and stratified by their HbA_{1c} level at baseline, are summarised in **table 1**. Overall, 55.9% of patients were male, and the mean (standard deviation [SD]) age was 57.5 (12.0) years. The overall mean baseline HbA_{1c} level was 8.4% (68 mmol/mol). Mean (SD) age was 59.6 (12.1) years in the early-intensification group and 56.4 (11.8) years in the late-intensification group. In the late-intensification group, 42.2% of patients initiated second-line therapy with an HbA_{1c} level of at least 9.0% (75 mmol/mol). Mean (SD) time since T2D diagnosis was 5.7 (5.2) years in the early-intensification group and 5.6 (5.2) years in the late-intensification group. Overall, first-line therapy was most commonly metformin monotherapy (64.3% of patients). Upon initiation of second-line therapy, most patients (73.7%) received dual oral therapy and 8.7% of patients received insulin or GLP-1 receptor agonists (alone or in combination with other agents) (**table 1**). The percentage of patients intensifying early varied according to WHO region, and ranged from 22.3% in the Eastern Mediterranean region to 49.3% in the Western Pacific region (**supplemental table 2**). However, in the multivariable model, when other

regions were compared with Europe, the likelihood of early intensification was not statistically different, and 95% CIs were wide (**figure 1**).

First-line therapy with two oral glucose-lowering drugs was more common in the late-intensification group (18.7% of patients) than in the early-intensification group (7.5% of patients). Older age (per 5 years increase) was associated with a decreased likelihood of late treatment intensification (odds ratio 0.91 [95% CI 0.89–0.93]), as was secondary or higher education (vs primary or no formal education). First-line treatment with dual oral therapy (vs metformin monotherapy) and second-line treatment with three or more oral glucose-lowering drugs or an injectable agent (vs dual oral therapy) were associated with an increased likelihood of receiving late treatment intensification (**figure 1**).

Glycaemic control, hypoglycaemia, and further treatment intensification

At all time points during follow-up, the mean HbA_{1c} level was significantly lower in the early-intensification group than in the late-intensification group. Changes in mean HbA_{1c} levels between 6 and 36 months were small in both groups. Mean HbA_{1c} levels remained above 7.0% (53 mmol/mol) in the late-intensification group, whereas mean HbA_{1c} levels remained below 7.0% (53 mmol/mol) in the early-intensification group (**figure 2**).

The proportion of patients achieving good glycaemic control (HbA_{1c} <7.0% [53 mmol/mol]) in the early-intensification group was significantly higher than that in the late-intensification group at all time points (**figure 3A**). The proportion of patients with HbA_{1c} levels less than 7.0% (53 mmol/mol) in the early-intensification group decreased from 72.8% at 6 months to 61.8% at 36 months. Conversely, the proportion of patients with HbA_{1c} less than 7.0% (53 mmol/mol) in the late-intensification group increased from 31.7% to 37.9% over the same period. Despite this gradual convergence, early intensification still significantly increased the odds of achieving good glycaemic control in comparison with late intensification (**supplemental figure 1**). The proportion of patients who had very poor glycaemic control (HbA_{1c} >9.0% [75 mmol/mol]) at each time point was substantially higher in the late-intensification group than in the early-intensification group (**figure 3B**). At 3 years of follow-up, the proportions of patients with an HbA_{1c} >9.0% (75 mmol/mol) were 3.0% and 10.5% in the early-intensification and late-intensification groups, respectively.

Although the incidence of patient-reported hypoglycaemia was numerically higher at all time points in the late-intensification group (**supplemental figure 2**), there was no significant

difference between the risk of experiencing at least one hypoglycaemic event during the 3 years of follow-up in the late-intensification group compared with the early-intensification group (hazard ratio 1.07 [95% CI 0.91–1.26]).

Cumulative proportions of patients intensifying to third-line therapy during follow-up in each treatment group are shown in **figure 4**. At 6, 12, 24, and 36 months, the cumulative proportion of patients receiving further treatment intensification was higher in the late-intensification group than in the early-intensification group. After adjusting for the same variables as the Cox regression analysis for likelihood of early or late intensification, patients in the late-intensification group had a significantly higher risk of requiring additional treatment intensification during the 3 years of follow-up than patients in the early-intensification group (hazard ratio 1.88 [95% CI 1.68–2.09]).

Discussion

To our knowledge, the DISCOVER study is the first global prospective study of patients with T2D initiating second-line therapy, and provides a comprehensive picture of the management of patients with T2D around the world. The present analysis of DISCOVER study data provides insights into glycaemic control and the need for further treatment intensification in a global population of patients with T2D who intensified glucose-lowering treatment upon initiation of second-line therapy. The findings demonstrate a clear association between late treatment intensification and long-term suboptimal glycaemic control.

Among the patients included in the present analysis of the study, nearly two-thirds had an HbA_{1c} level greater than 7.5% (59 mmol/mol) at initiation of second-line therapy. In addition, for 25.9% of patients, the baseline HbA_{1c} level was greater than 9.0% (75 mmol/mol), far above the target of 7.0% (53 mmol/mol) recommended by clinical guidelines for most patients.[3] These findings suggest a substantial delay in initiation of second-line therapy in a majority of patients. These results are in line with the delays in treatment intensification observed in other studies of patients with T2D, in which the median time from the first HbA_{1c} measurement of greater than 7.0% (53 mmol/mol) to treatment intensification ranged from approximately 1 to 3 years.[13-16] The high mean HbA_{1c} level (9.2% [77 mmol/mol]) at initiation of second-line therapy as well as the large proportion of patients with an HbA_{1c} level greater than 9.0% (75 mmol/mol) in the late-intensification group are of particular concern, because these patients are at an inherently higher risk of T2D

complications.[17, 18] Indeed, the large proportion of patients intensifying therapy with such poor glycaemic control is particularly concerning given that these patients are initiating second-line glucose-lowering therapy and are therefore likely to be early in the course of their disease.

Our multivariable models did not show statistically significant differences in likelihood of early versus late intensification between Europe and other WHO regions. However, we did observe differences of potential clinical importance in the proportions of patients who intensified early or late across regions, which can be potentially explained by differences in healthcare systems, access to glucose-lowering medications, or costs of treatment. Indeed, patients from Africa were less likely to receive further treatment intensification during follow-up than patients from Europe. Barriers to treatment, such as lack of routine HbA_{1c} measurements or limited access to relevant therapies in lower-income countries, may contribute to therapeutic inertia in some middle-income regions of the world.[19, 20] Additionally, previously observed shortcomings from middle-income countries in diabetes self-care behaviours such as diet, exercise and medication may have been partly responsible for the high degree of therapeutic inertia observed in the present analysis.[21] However, DISCOVER did not measure patient adherence to glucose-lowering medication or other metrics of self-care which have previously seen to be lacking in middle-income countries.

In the present analyses, patients with late treatment intensification were more likely to have received first-line dual oral therapy (vs metformin alone). This counterintuitive association between intensive first-line therapy with two oral agents and higher HbA_{1c} at initiation of second-line suggests that other factors not included in our analysis, such as genetics[22] and glycaemic control at initial diagnosis of T2D may have an impact on glycaemic control and selection of first line therapies. In addition, second-line therapy with three or more oral agents (vs dual oral therapy) was associated with a reduced likelihood of further treatment intensification during follow-up. This is in line with findings from a systematic review, which suggested that therapeutic inertia increased with the number of prescribed oral glucose-lowering drugs.[13]

After adjusting for potential confounders, late treatment intensification was associated with a decreased likelihood of having an HbA_{1c} level less than 7.0% (53 mmol/mol) during follow-up. These results are in line with those from a US retrospective study, which showed that, over 12 months of follow-up, glycaemic control was significantly better in patients who

intensified treatment early (in the 6 months after reaching an HbA_{1c} level of at least 7·0% [53 mmol/mol] or 8·0% [64 mmol/mol]) than in those who intensified late or did not intensify during the study period.[23] Similarly, a large-scale retrospective study from the UK found that early intensification of glucose-lowering therapy after an HbA_{1c} level of at least 7·0% (53 mmol/mol) was associated with an increased likelihood of, and a decreased time to, reaching an HbA_{1c} level less than 7·0% (53 mmol/mol), independent of first-line glucose-lowering medication.[16]

As may be expected on the basis of similar findings from prior studies carried out in the UK and Germany,[24, 25] patients who intensified therapy with a higher baseline HbA_{1c} achieved a greater absolute reduction in HbA_{1c} than those who intensified early. Despite this, mean HbA_{1c} levels were consistently lower in the early-intensification group, and the association of early intensification and increased likelihood of having an HbA_{1c} level less than 7·0% (53 mmol/mol) was observed at all time points. Among those who intensified therapy late, approximately two-thirds did not achieve HbA_{1c} levels less than 7·0% (53 mmol/mol) during the 3 years of follow-up, compared with only approximately one third of patients who intensified early, suggesting that early treatment intensification has long-term glycaemic benefits.

Hypoglycaemia is often a major concern for clinicians when deciding to intensify glucose-lowering therapy, particularly in older patients.[26] As such, individualised target HbA_{1c} levels greater than 7·0% (53 mmol/mol) are typically recommended in individuals considered to be at a higher risk of hypoglycaemia.[27] However, in the present analysis, despite the higher mean age in the early-intensification group, there was no significant increase in the risk of patient-reported hypoglycaemic events. Coupled with the higher proportion of patients achieving HbA_{1c} levels less than 7·0% (53 mmol/mol) in the early-intensification group, these data reinforce the benefits of timely intensification.

Patients who intensified therapy late also had an increased likelihood of need for further treatment intensification during the 3 years of follow-up. This may be explained by the fact that HbA_{1c} levels remained high after second-line treatment initiation, thus requiring further treatment intensification during follow-up to control glucose levels. This observation echoes the results of the VERIFY clinical trial, in which patients treated early with combination therapy had a significantly lower rate of treatment failure than patients treated with monotherapy.[28] This underlines the need for early second-line treatment initiation to delay

further treatment intensification, particularly initiation of insulin, which is associated with poor adherence and an elevated risk of hypoglycaemia.[26, 29, 30].

Strengths and limitations

A key strength of DISCOVER is the global nature of the study, including many middle-income countries for which data on treatment intensification are lacking.[13] Thus, our findings complement results from previous studies mainly conducted in the USA and Europe. Another strength is the prospective nature of DISCOVER, which collected data for 3 years of follow-up from initiation of second-line therapy. The diversity of sites involved in the study resulted in a heterogeneous patient population from a range of clinical settings. However, as is the case for most observational studies, a truly representative patient sample was not possible. For example, participation of rural and primary care centres was lower than would be expected, owing in part to site limitations.[10] Time spent with an HbA_{1c} level above target before initiation of second-line therapy could not be assessed. Many patients included in the present analysis were prescribed dual oral therapy as a first-line treatment, suggesting a more advanced stage of diabetes in these patients. Hypoglycaemic events were reported by patients at each study visit; therefore, data on hypoglycaemia may be subject to recall bias and are most likely underreported, especially less severe events. In line with clinical practice at each site, follow-up visits and data collection were not mandated by the study protocol; 22.5% of patients had missing data for at least one of the examined variables, ranging from 0.3% (history of macrovascular complications) to 9.7% (level of education). Many DISCOVER patients (19.1%) lacked an HbA_{1c} measurement at baseline and therefore could not be included in this analysis, likely owing to HbA_{1c} not being monitored routinely – or not measured at all at the time of treatment initiation – in certain countries.[31]

Conclusion

In this large, global study of patients with T2D who intensified treatment upon initiation of second-line therapy, almost two-thirds intensified therapy late, with an HbA_{1c} level greater than 7.5% (59 mmol/mol). Early treatment intensification was associated with sustained improvements in glycaemic control without an elevated risk of hypoglycaemia, and a decreased likelihood of need for receiving further treatment intensification during the 3 years of follow-up. These results suggest that more efforts are needed globally to implement clinical guideline recommendations for timely treatment intensification. Regular healthcare

centre visits to quickly detect patients with poor glycaemic control, as well as policies recommending a low tolerance on the glycaemic level at which treatment is intensified after first-line treatment failure, would be beneficial for achieving optimal long-term glycaemic control. Such improvements in long-term glycaemic control could result in delayed onset and reduced severity of complications and a delayed need for further treatment intensification, thus improving patient's quality of life and reducing healthcare costs.

Contributors

The general content of the manuscript was agreed upon by all authors, and all authors contributed to manuscript development. All authors approved the final version of the manuscript before its submission. An AstraZeneca team reviewed the manuscript during its development and was allowed to make suggestions. However, the final content was determined by the authors. LJ is the guarantor of this work.

Declaration of interests

LJ, FB, AN, WR, MVS, and HW are members of the DISCOVER Scientific Committee, and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. HC, AC, PL, GLS, LR, JM, and FS are employees of AstraZeneca. NH is a former employee of AstraZeneca. In addition, LJ has received fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda, and research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, and Sanofi; FB has received fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, Novo Nordisk, Sanofi, and Takeda; AN has received fees from AstraZeneca, Eli Lilly, Medtronic, and Novo Nordisk, and research support from AlfaSigma, Artsana, Dexcom, Novo Nordisk, Pkdare, Sanofi, Shionogi, Sobi, and Theras; WR has received research support from Novo Nordisk; MVS has received fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Servier, and research support from Novo Nordisk and Sanofi; FT is an employee of the Mid America Heart Institute and has received research support from AstraZeneca; and HW has received fees from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Kissei Pharmaceutical, Kowa Pharmaceuticals America Inc., Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Novo Nordisk, Ono Pharmaceutical,

Sanofi, Sanwa Kagaku Kenkyusho, Sumitomo Dainippon Pharma, and Takeda, and research support from Abbott, Astellas Pharma, AstraZeneca, Bayer, Benefit One Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, Kissei Pharmaceutical, Kowa Pharmaceuticals America Inc., Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nitto Boseki, Novartis, Novo Nordisk, Ono Pharmaceutical, Pfizer, Sanofi, Sanwa Kagaku Kenkyusho, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceutical, Takeda, and Terumo Corp.

Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

Acknowledgments

The authors would like to thank all investigators and patients participating in the DISCOVER study programme. Medical writing support was provided by Oxford PharmaGenesis, Oxford, UK, and was funded by AstraZeneca.

Role of the funding source

The DISCOVER study programme is funded by AstraZeneca. DISCOVER is a non-interventional study, and no drugs were supplied or funded.

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Tables and figures

Table 1: Patient baseline characteristics, overall and according to early or late treatment intensification

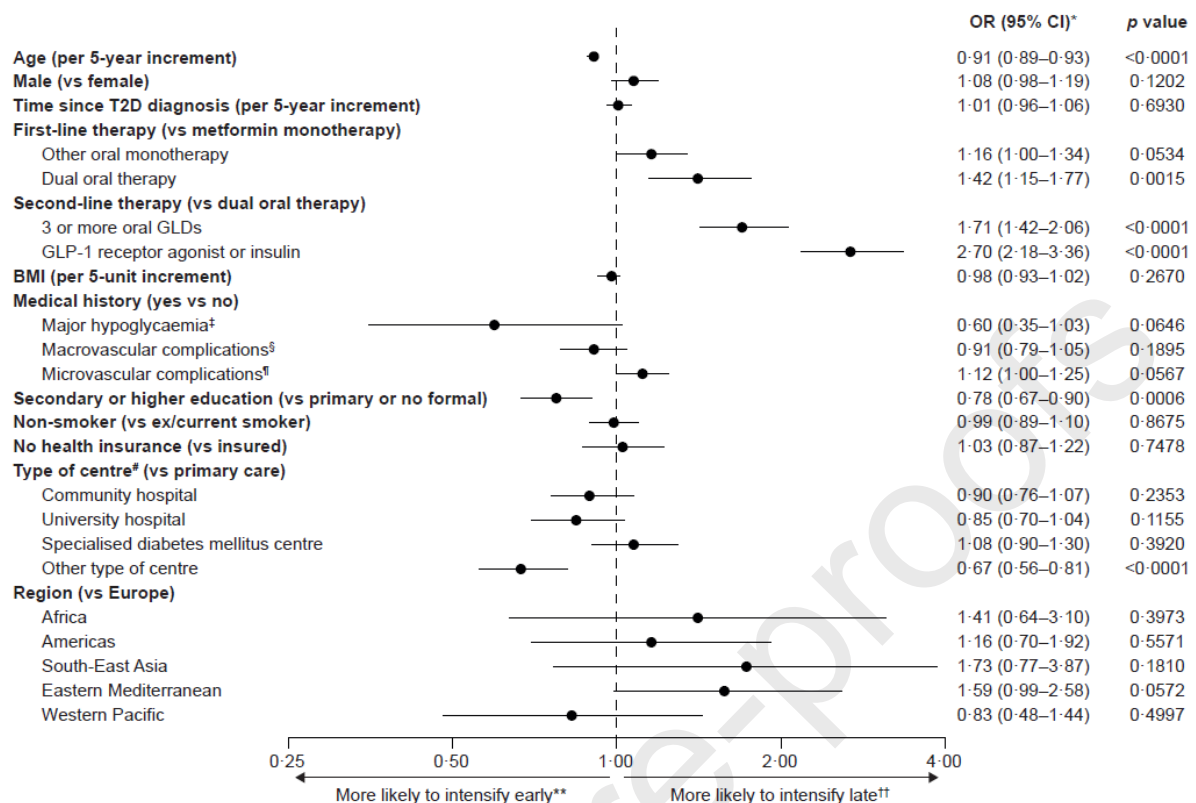
..	Overall (n=9575)	HbA _{1c} at baseline	
		≤7.5% (n=3275; 34.2%)	>7.5% (n=6300; 65.8%)
Age, years, mean (SD)	57.5 (12.0)	59.6 (12.1)	56.4 (11.8)
Male, n (%)	5351 (55.9)	1804 (55.1)	3547 (56.3)
Region, n (%)	..	..	..
Africa	416 (4.3)	128 (3.9)	288 (4.6)
Americas	1345 (14.0)	429 (13.1)	916 (14.5)
South-East Asia	1396 (14.6)	349 (10.7)	1047 (16.6)
Europe	2384 (24.9)	844 (25.8)	1540 (24.4)
Eastern Mediterranean	1712 (17.9)	381 (11.6)	1331 (21.1)
Western Pacific	2322 (24.3)	1144 (34.9)	1178 (18.7)
HbA _{1c} , %, mean (SD)	8.4 (1.7)	6.9 (0.5)	9.2 (1.5)
≤7.0%	1717 (17.9)	1717 (52.4)	0 (0)
>7.0% to ≤7.5%	1558 (16.3)	1558 (47.6)	0 (0)
>7.5% to ≤8.0%	1653 (17.3)	0 (0)	1653 (26.2)
>8.0% to ≤9.0%	2168 (22.6)	0 (0)	2168 (34.4)
>9.0%	2479 (25.9)	0 (0)	2479 (39.3)
BMI, kg/m ² , mean (SD)	29.4 (5.9)	29.0 (6.0)	29.6 (5.9)
Missing, n	649	198	451
FPG, mg/dL, mean (SD)	173.4 (57.2)	138.8 (31.9)	190.6 (59.2)
Missing, n	2632	965	1667
Time since T2D diagnosis, years, mean (SD)	5.6 (5.2)	5.7 (5.2)	5.6 (5.2)
Missing, n	295	133	162
First-line therapy, n (%)	..	..	..
Metformin monotherapy	6161 (64.3)	2179 (66.5)	3982 (63.2)
Other monotherapy	1990 (20.8)	851 (26.0)	1139 (18.1)
Dual therapy	1424 (14.9)	245 (7.5)	1179 (18.7)
Second-line therapy, n (%)	..	..	..
Dual oral therapy	7059 (73.7)	2790 (85.2)	4269 (67.8)
Three or more oral therapies	1683 (17.6)	344 (10.5)	1339 (21.3)
Insulin* or GLP-1 receptor agonist	833 (8.7)	141 (4.3)	692 (11.0)
Medical history, n (%)	..	..	..
Major hypoglycaemia†	76 (0.8)	31 (1.0)	45 (0.8)
Missing, n	607	202	405
Macrovascular complications‡	1358 (14.2)	528 (16.2)	830 (13.2)
Missing, n	32	15	17
Microvascular complications§	2037 (21.3)	671 (20.5)	1366 (21.7)

..	Overall (n=9575)	HbA _{1c} at baseline	
		≤7.5% (n=3275; 34.2%)	>7.5% (n=6300; 65.8%)
Missing, n	10	5	5
Health insurance, n (%)	..	..	..
Insured	7555 (83.9)	2707 (87.6)	4848 (82.0)
No insurance	1450 (16.1)	384 (12.4)	1066 (18.0)
Missing, n	570	184	386
Tobacco smoking status, n (%)	..	..	..
Non-smoker	6166 (66.1)	2013 (63.2)	4153 (67.6)
Ex/current smoker	3165 (33.9)	1173 (36.8)	1992 (32.4)
Missing, n	244	89	155
Education level, n (%)	..	..	..
No formal education	259 (3.0)	59 (2.0)	200 (3.5)
Primary (1–6 years)	1308 (15.1)	381 (13.1)	927 (16.1)
Secondary (7–13 years)	4346 (50.2)	1512 (52.0)	2834 (49.4)
University/higher (>13 years)	2736 (31.6)	955 (32.9)	1781 (31.0)
Missing, n	926	368	558
Type of centre, n (%)	..	..	..
Primary care centre	3541 (38.1)	1351 (42.6)	2190 (35.7)
General/community hospital	1231 (13.2)	436 (13.8)	795 (13.0)
University/teaching hospital	1477 (15.9)	505 (15.9)	972 (15.9)
Specialised diabetes centre	1595 (17.2)	390 (12.3)	1205 (19.7)
Other	1454 (15.6)	488 (15.4)	966 (15.8)
Missing	277	105	172

Percentages are reported for all patients with data available; missing data are excluded. BMI=body mass index.

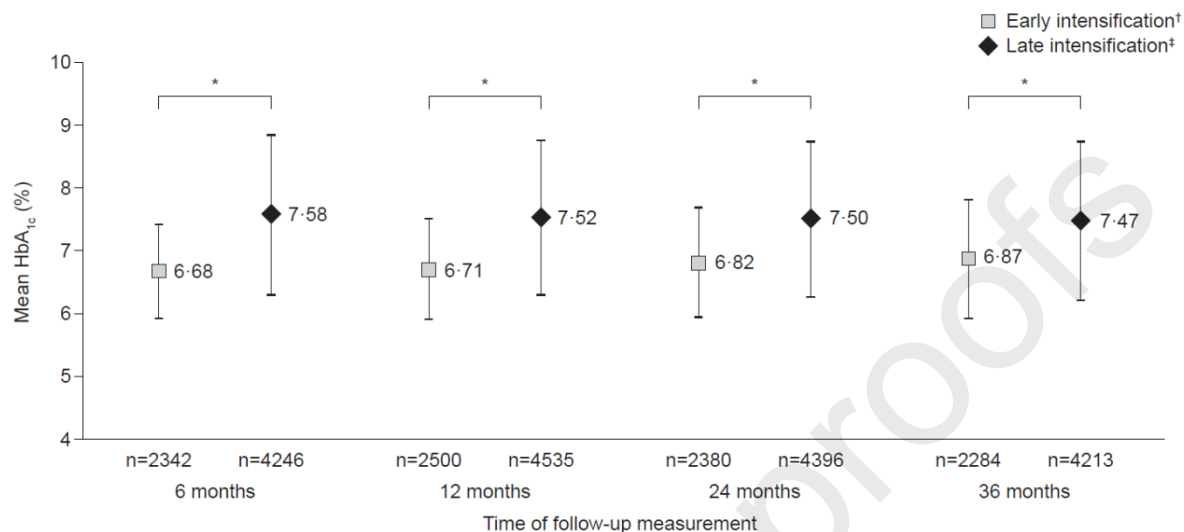
FPG=fasting plasma glucose. GLP-1=glucagon-like peptide 1. HbA_{1c}=glycated haemoglobin. SD=standard deviation. T2D=type 2 diabetes. *Includes insulin monotherapy, insulin + GLP-1 agonist, and insulin + oral glucose-lowering drugs. †Hypoglycaemic events that required an emergency room visit, a hospital admission, a visit to a physician or other healthcare professional, or third-party assistance, in the year before baseline.

‡Includes coronary artery disease, cerebrovascular disease, peripheral artery disease (including diabetic foot disease and amputation), heart failure, and implantable cardioverter defibrillator use. §Includes nephropathy, retinopathy, and neuropathy (peripheral and autonomic neuropathy and erectile dysfunction).

Figure 1: Factors associated with early or late treatment intensification

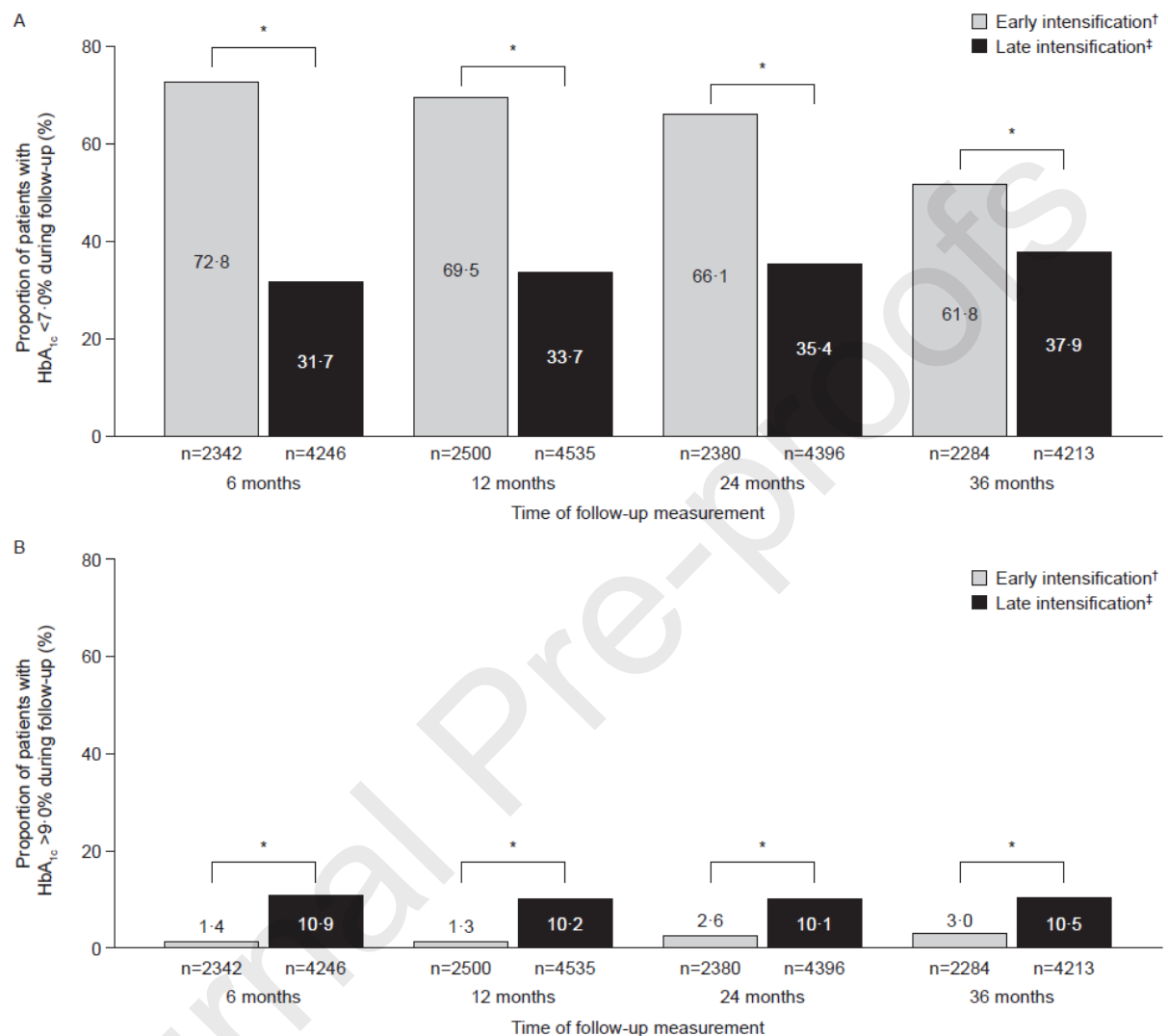
BMI=body mass index. CI=confidence interval. GLD=glucose-lowering drug. GLP-1=glucagon-like peptide 1. HbA_{1c}=glycated haemoglobin. OR=odds ratio. T2D=type 2 diabetes. *ORs and 95% CIs calculated using a hierarchical logistic regression model adjusted for all variables in the figure. †Alone or in combination with other agents. ‡Hypoglycaemic events that required an emergency room visit, a hospital admission, a visit to a physician or other healthcare professional, or third-party assistance, in the year before baseline. §Includes coronary artery disease, cerebrovascular disease, peripheral artery disease (including diabetic foot disease and amputation), heart failure, and implantable cardioverter defibrillator use. ¶Includes nephropathy, retinopathy, and neuropathy (peripheral and autonomic neuropathy and erectile dysfunction). #The healthcare setting in which glucose-lowering therapy was intensified. **Treatment intensification at a baseline HbA_{1c} ≤7.5% (59 mmol/mol). ††Treatment intensification at a baseline HbA_{1c} >7.5% (59 mmol/mol).

Figure 2: Overall mean HbA_{1c} during 3-year follow-up in patients who received early treatment intensification (n=3275) and those who received late treatment intensification (n=6300)



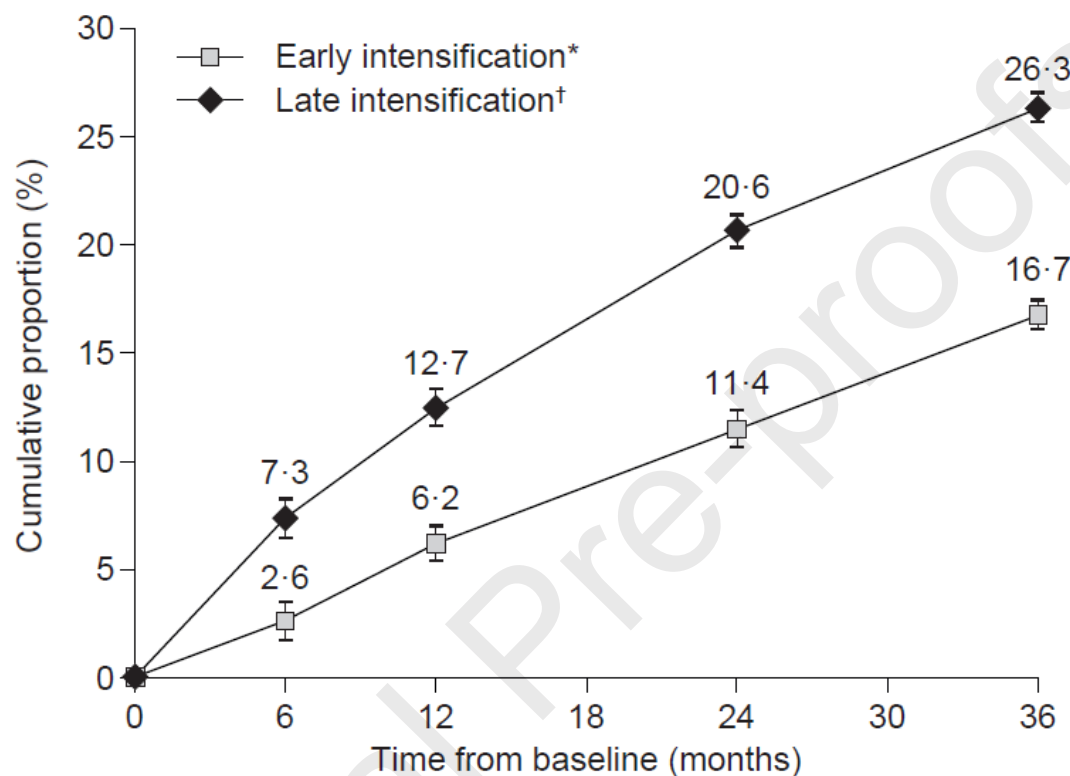
HbA_{1c}=glycated haemoglobin. *p<0.001. p values for differences between early and late treatment intensification groups were calculated using Student's *t*-test. Whiskers represent standard deviation. Numbers on the x-axis represent the number of available measurements from each group at that time point. †Early intensification defined as treatment intensification with a baseline HbA_{1c} ≤7.5% (59 mmol/mol). ‡Late intensification defined as treatment intensification with a baseline HbA_{1c} >7.5% (59 mmol/mol).

Figure 3: Proportions of patients with (A) HbA_{1c} <7.0% (53 mmol/mol) and (B) HbA_{1c} >9.0% (75 mmol/mol) during 3-year follow-up, in those who intensified treatment early (n=3275) and those who intensified treatment late (n=6300)



HbA_{1c}=glycated haemoglobin. *p<0.001. p values for differences between proportions of patients achieving HbA_{1c} <7.0% (53 mmol/mol) (A) and HbA_{1c} >9.0% (75 mmol/mol) (B) at each time point during follow-up were calculated using the χ^2 test. †Early intensification defined as treatment intensification with a baseline HbA_{1c} measurement $\leq 7.5\%$ (59 mmol/mol). ‡Late intensification defined as treatment intensification with a baseline HbA_{1c} measurement >7.5% (59 mmol/mol). Numbers on the x-axis represent the number of available measurements from each group at that time point.

Figure 4: Cumulative proportion of patients receiving additional treatment intensification (either via addition of another glucose-lowering drug or initiation of insulin [alone or in combination with other agents]) in patients who intensified treatment early (n=3275) versus those who intensified treatment late (n=6300)



Whiskers represent 95% confidence intervals. HbA_{1c}=glycated haemoglobin. *Early intensification defined as treatment intensification with a baseline HbA_{1c} measurement of $\leq 7.5\%$ (59 mmol/mol). †Late intensification defined as treatment intensification with a baseline HbA_{1c} measurement of $> 7.5\%$.

Supplemental Table 1: Inclusion and exclusion criteria

Inclusion criteria
• Diagnosis of type 2 diabetes • Age ≥ 18 years* • Initiating a second-line therapy (add-on or switching) after a first-line oral treatment with monotherapy, dual therapy, or triple therapy† • Provision of written informed consent
Exclusion criteria
• Type 1 diabetes • Pregnancy • Initiation of dual therapy after having previously received two different lines of monotherapy (eg, initiation of a combination of a sulphonylurea and a DPP-4 inhibitor after successive metformin monotherapy and sulphonylurea monotherapy) • Current treatment with chemotherapy or oral or intravenous steroids • Undergoing dialysis or has had a renal transplant • First-line treatment was insulin or an injectable agent‡ • First-line treatment was herbal remedies/natural medicines alone • Participation in an interventional trial • Condition/circumstance which, in the opinion of the investigator, could significantly compromise the 3-year follow-up (eg, life-threatening comorbidities, tourist, non-native speaker or does not understand the local language where interpreter services are not reliably available, psychiatric disturbances, dementia, alcohol, or drug abuse)

-
- Not willing to sign the informed consent form
-

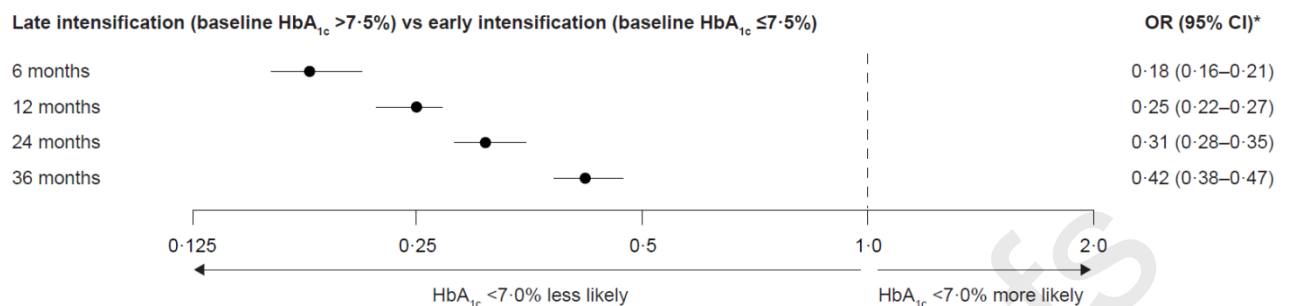
DDP-4=dipeptidyl peptidase-4. *Age ≥ 20 years in Japan. †In Japan, only patients using an oral monotherapy as first-line treatment were included. ‡Patients who received short-term initial treatment with insulin followed by oral therapy were eligible if the treatment with insulin lasted no more than 2 weeks and occurred at least 6 months before initiation of second-line therapy. In such patients, insulin was considered not as a first-line treatment, but as a short-term treatment to lower glycaemic levels quickly before starting regular treatment.

Supplemental Table 2: HbA_{1c} at baseline, by WHO region

..	WHO region					
	Africa	Americas	South-East Asia	Europe	Eastern Mediterranean	Western Pacific
	(n=416)	(n=1345)	(n=1396)	(n=2384)	(n=1712)	(n=2322)
HbA _{1c} at baseline, n (%)	..	..	..	..	..	..
≤7·5%	128 (30·8)	429 (31·9)	349 (25·0)	844 (35·4)	381 (22·3)	1144 (49·3)
>7·5%	288 (69·2)	916 (68·1)	1047 (75·0)	1540 (64·6)	1331 (77·7)	1178 (50·7)

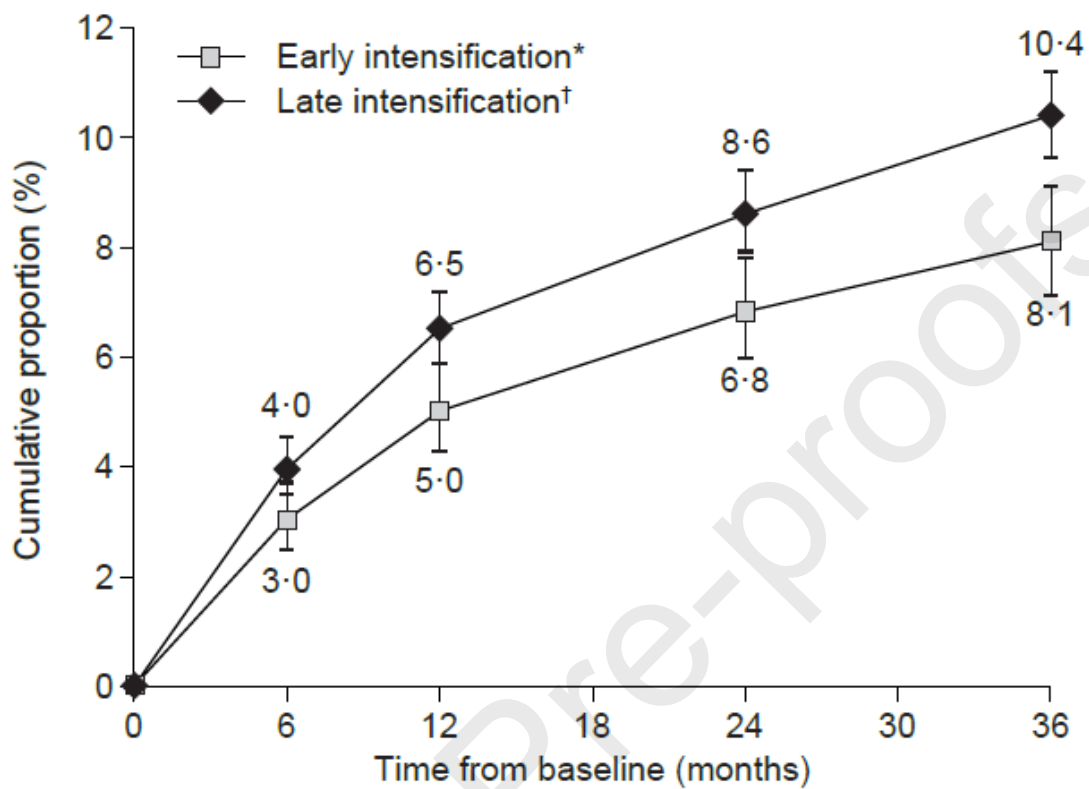
HbA_{1c}=glycated haemoglobin. WHO=World Health Organization.

Supplemental Figure 1: Likelihood of having HbA_{1c} <7.0% (53 mmol/mol) during follow-up in the late-intensification group (vs the early-intensification group)



CI=confidence interval. HbA_{1c}=glycated haemoglobin. OR=odds ratio. T2D=type 2 diabetes. *ORs and 95% CIs calculated using a repeated-measures model with country as a random factor, and adjusted for age, sex, time since T2D diagnosis, first-line therapy, second-line therapy, body mass index, history of hypoglycaemia requiring third-party assistance in the year before baseline, history of macrovascular complications (includes coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, and implantable cardioverter defibrillator use), history of microvascular complications (includes nephropathy, retinopathy, and neuropathy), education level, smoking status, health insurance, type of centre, and World Health Organization region.

Supplemental Figure 2: Cumulative proportion of patients reporting at least one hypoglycaemic event during follow-up in patients who intensified treatment early (n=3275) versus those who intensified treatment late (n=6300)



Whiskers represent 95% confidence intervals. HbA_{1c} =glycated haemoglobin. *Early intensification defined as treatment intensification with baseline $HbA_{1c} \leq 7.5\%$ (59 mmol/mol). †Late intensification defined as treatment intensification with baseline $HbA_{1c} > 7.5\%$ (59 mmol/mol).