Effect of treatment intensification on glycemic control in patients with subcontrolled type 2 diabetes who failed on two oral antidiabetic agents

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Title

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Title.

Effect of treatment intensification on glycemic control in patients with subcontrolled type 2 diabetes who failed on two oral antidiabetic agents

Short Running Title.

Intensification after two oral antidiabetic agents

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Author's Contribution.

The conceptual idea was proposed in collaboration by all authors. Malinda Tan, under the supervision of Kibum Kim and Diana Brixner, developed the research design and analysis plan. The research design and analysis plan were reviewed and modified by all co-authors. Cody Olsen contributed to data acquisition. Kibum Kim conducted the cohort extraction. Malinda Tan performed the statistical analysis. All authors reviewed the results and interpretation. Malinda Tan and Kibum Kim compiled the draft manuscript. All co-authors materially participated in this manuscript preparation. The overall research project was supervised by Kibum Kim, the co-primary and corresponding author of this manuscript.

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Declaration of Interests.

Malinda Tan and Cody Olsen have no conflicts of interest to declare. A part of Kibum Kim's previous research was supported by Sanofi. Inc. Diana Brixner served as an advisory board member and consultant for Sanofi. Inc.

Structured Abstract

Abstract

Aims:

Treatment intensification (TI) may help patients with type 2 diabetes mellitus (T2DM) achieve target hemoglobin A1c (A1c) < 7.0%. This study aimed to measure the influence of TI on A1c outcome in patients who insufficiently responded to two classes of oral antidiabetic drugs (2OADs).

Materials and Methods:

A retrospective observational study of patients with T2DM was performed using health plan claims and A1c records accrued between January 2010 and March 2017. The study population had an A1c ≥ 7.0% (baseline A1c) after treatment with 2OADs for one year. Patients who had TI with a third-class antidiabetic agent, including basal/biphasic insulin, glucagon-like peptide-1 receptor agonists (GLP-1RA), or OAD, within 365 days after baseline A1c were included. Patients who did not receive TI (NTI) within one year from the suboptimal A1c control were matched with TI patients using a propensity score approach. The odds ratio of achieving an A1c < 9.0% and < 7.0% for TI vs. NTI were calculated by logistic regressions.

Results

A1c values of 401 TI − NTI matched pairs were analyzed. TI patients achieved a significantly lower follow-up A1c than NTI patients (7.79% ± 1.45 vs. 8.02% ± 1.67, p = 0.03). The odds ratio [95% confidence interval] of achieving A1c < 9.0% and < 7.0% for TI was 1.50 [1.04−2.17] and 1.19 [0.87−1.63], respectively.

Conclusion

TI with a third-class agent further reduced A1c levels in patients whose A1c insufficiently responded with 2OADs; however, most patients failed to achieve an A1c < 7.0% on the intensified treatment.

Structured Abstract

Key Words: oral antidiabetic agents, treatment intensification, hemoglobin A1c, retrospective cohort study.

Main Text

Introduction:

Diabetes is a prevalent and costly chronic condition in the US population and imposes a significant burden on US healthcare. In the US, 30.3 million people (9.4% of the population) have diabetes, and 90-95% of the diagnoses are type 2 diabetes mellitus (T2DM).[1] The average medical cost of treating patients with diabetes is more than double that of those without diabetes.[2] Hemoglobin A1c (A1c) is the primary tool for the assessment of glycemic management and has strong predictive value for diabetes complications.[3] Previous studies showed that well-controlled A1c is a strong predictor of a decrease in the disease burden and complications of diabetes.[4]

Glycemic control in T2DM care is individualized. Depending on the age, concurrent conditions and treatment history, the A1c level may be set at a different target. For example, the American Diabetes Association (ADA) recommends a target A1c < 7.0% for most adults and a less stringent A1c goal (e.g., < 8.0%) for patients with comorbidities.[3] Moreover, the National Committee for Quality Assurance considers A1c > 9.0% poorly-controlled.[5] Poorly-controlled diabetes, if left untreated, can lead to cardiovascular complications and results in lower quality of life as well as increased disability and mortality.[5,6] Despite advances in diabetes care over the past decade, 36% of patients with diabetes receiving treatment still failed to achieve their individualized A1c target levels, ranging from 7.0% to 8.5%, between 2005 to2016.[7]

Because T2DM is a progressive chronic condition, patients generally require eventual treatment intensification (TI) to maintain adequate A1c control.[5,8] The ADA recommends a stepwise approach to TI starting with metformin monotherapy in patients with T2DM,[9-11] other therapies are then added on if intensification is required, and may ultimately be combined with or changed to injectable options, including insulin, if the A1c target is not achieved.[12,13] Despite ADA recommendations, studies demonstrate that clinical inertia, which is defined as a delay in TI or failure to initiate TI when indicated, is common in patients with uncontrolled A1c.[5,14,15] Ruiz-Negron et al. showed that about 35% of T2DM patients insured by a regional managed care organization experienced clinical inertia for 4 months.[16] Several studies have shown that factors contributing to clinical inertia may include health insurance

regulations and constraints that influence prescription practices and create formulary restrictions.[17,18] Furthermore, Fu et al. utilized data claims from more than 300 large self-insured US employers and more than 25 US health plans, and found more than 50% of patients who failed to achieve their A1c goal with metformin monotherapy or with another oral antidiabetic drug (OAD) experienced clinical inertia for longer than 12 months.[19]

Multiple studies have shown that for patients who were not responsive to the metformin-based treatment, the faster patients intensify their treatment to meet therapy goals, the bigger the impact it will be. For example, Fu et al. demonstrated that patients with an A1c ≥ 8% who received a TI within six months of therapy achieved a greater A1c reduction than those who did not intensify their treatment within six months.[10] Pantalone's retrospective observational research showed the superiority of TI within six months compared to clinical inertia for longer than six months.[20] Blonde et al. suggested that TI further reduced A1c levels in patients who failed to achieve A1c goals with an OAD monotherapy.[21] The outcomes of timely performed TI was recently confirmed from a global observational study.[22] A recent description of the A1c trajectory showed that TI following a suboptimally controlled A1c on the OADs in two different classes (2OADs) was associated with a significant improvement in glycemic control.[12,15] Nevertheless, the aforementioned studies provided an incomplete measurement of the effect of TI in patients who failed 2OADs within one year due to the lack of a proper control cohort. The purpose of this study was to quantitatively measure the influence of TI as compared to clinical inertia, on A1c outcomes in patients with T2DM, who did not sufficiently respond to 2OADs over one year.

Materials and Methods:

Data Source

This was a retrospective analysis of patients with T2DM. Health plan claims were obtained from SelectHealth, a managed care organization that covers approximately 800,000 members throughout the Intermountain West region with Commercial, Medicare, and Medicaid plans. SelectHealth offers a

diabetes incentive program for providers who file A1c results of their patients, which augmented the claims database with comprehensive A1c records. This research was exempt from the University of Utah's institutional review board (IRB) review (June 05, 2018) and was approved by the Intermountain Healthcare IRB (March 06, 2018).

Study Population and Patient Selection

Figure 1 describes the analytic cohort, which was extracted from the claims for diabetes management between January 1, 2010, and March 31, 2017. Diagnosis of T2DM was defined by ICD-9 (250.x0 or 250.x2) and ICD-10 (E11.x) or by an A1c ≥ 6.5% on two different days within 12 months. The baseline A1c indicating a need of TI was determined by an A1c ≥ 7.0% despite being treated with 2OADs, either as two separate drug formulations or as a fixed-dose combination. Eligible subjects received the 2OADs over 365 days before the baseline A1c date. To allow time to respond to therapy escalation with a second class of OAD, baseline A1c had to be measured at least 60 days after the first prescription for the second class of OAD. Demographic information and clinical characteristics such as age, gender, type of insurance, diabetes complication severity index (DCSI) score,[23] Charlson's comorbidity index (CCI) score,[24] and 2OADs combinations were collected over the 365 days before the baseline A1c date. Patients were required to be continuously enrolled in the health plan or to have an enrollment gap no more than 90 days within the 12 months before and after the baseline A1c date. Patients with two or more claims for type 1 diabetes or gestational diabetes, and those who had a prescription claim for an injectable diabetes agent, such as insulin, glucagon-like peptide-1 receptor agonists (GLP-1RA), or pramlintide, before the baseline A1c date were excluded.

Patients with an A1c ≥ 7.0% on 2OADs were divided into two groups, TI and Non-Treatment Intensification (NTI) cohorts. The TI cohort included patients who received a third-class agent, including an OAD in a class different from the previous 2OADs, basal or biphasic insulin, or GLP-1RA, on or within 365 days after baseline A1c date. The TI-index date was the date of a prescription claim for the TI.

Main Text

The NTI were patients without prescription claims for antidiabetic agents in a third class for longer than 365 days after the baseline A1c date.

Propensity score matching was performed to account for potential confounders and minimize selection bias between the two cohorts. The coefficient predicting the assignment for the TI cohort was calculated from a logistic regression model where the variable selection was performed using a forward stepwise model selection process with a p-value of 0.1 for variable inclusion. Variables with differing distributions between the TI and NTI cohorts with a p-value < 0.1 were tested in the model selection process. Besides the propensity score, we addressed the time to TI from the baseline A1c date to address potential time-varying confounders. To match the time to index from baseline A1c and the time to A1c measure after TI, one-by-one Greedy-matching without a replacement was performed using the following algorithm:

(1) Randomly selected a TI patient if they had A1c results within 90 – 180 days from the index-TI date.
(2) Chose NTI patients within a range of 0.1 times the standard error of the logit of the propensity score from the propensity score of the selected TI patient.
(3) Each NTI patient meeting the matching criterion (2) had an assigned-index date. The assigned-index date was determined by adding the distance between the baseline A1c date and the TI-index date of the corresponding TI patient to the baseline A1c date of the NTI patient.
(4) Deleted subjects from the pool of the potentially eligible matched NTI patients if they did not have an A1c between 90 and 180 days from the assigned-TI date.
(5) Randomly selected one control if multiple NTI patients met criteria (2) – (4).
(6) Iterated (1) – (5) until there were no eligible subjects for matching.

Sample Size Calculation

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Based on the desired power of 80% and $\alpha = 0.05$, we estimated that 253 pairs of patients would be required to determine the difference in the A1c reductions from -1.0 ± 2.0% for the TI cohort and - 0.5 ± 2% for the NTI cohort.

Outcome

The outcomes of this study were A1c changes from the baseline A1c to 90 –180 days post index date, and the odds of achieving A1c < 7.0%, A1c < 8.0% and A1c < 9.0%.

Statistical Analysis:

We used descriptive statistics to summarize baseline characteristics and A1c outcomes for TI vs. NTI using both matched and non-matched cohorts. Means with standard deviations (SD) represented the central tendency of the continuous values, and frequencies with percentages summarize the categorical variables. Student t-test and Chi-square test were respectively used to compare the continuous and categorical data.

The matched cohort was used to assess the A1c outcomes. The average changes in the A1c level between the baseline and the 90 -180 days follow-up were compared between the TI and NTI groups using the student t-test. The odds ratio and 95% confidence interval for achieving A1c < 7.0%, A1c < 8.0%, and A1c < 9.0% for TI vs. NTI were calculated using a logistic regression model.

Results:

The unmatched analytic cohort consisted of a total of 3,739 patients. Of the selected patients, 1,403 had a TI within 365 days after the baseline A1c date. Before matching, TI differed significantly from NTI in several baseline characteristics. For instance, TI patients had a greater average baseline A1c (8.77 ± 1.62) compared to NTI (8.01 ± 1.29; $p < 0.01$). The proportion of patients with baseline A1c ≥ 9.0% was more than double in TI (34.6%) compared to the proportion out of the NTI (15.4%). Within one

year before the baseline A1c date, the majority of TI (54.9%) and NTI (68.8%, $p < 0.01$) patients were treated with metformin and sulfonylureas; and a smaller proportion of TI (28.2%) and NTI (19.3%; $p < 0.01$) were treated with metformin and dipeptidyl peptidase-4 inhibitor (DPP4I). The TI cohort was younger (54.6 ± 10.3 years) compared to the NTI cohort (57.0 ± 10.9 years, $p < 0.01$). Table 1 describes the baseline characteristics of TI and NTI cohorts before and after matching.

Independent variables for the propensity score calculation included grouped baseline A1c (7.00 – 7.99, 8.00 – 8.99, and 9.00 or above), grouped year age (< 55 vs. ≥ 55), gender, baseline treatment classes, and types of insurance. A total of 401 matched pairs of patients had A1c outcomes measured within 90 – 180 days post-index date. Matching created an analytic cohort with a well-balanced average baseline A1c between TI and NTI (8.53 ± 1.45% and 8.45 ± 1.67%; $p = 0.46$) with a similar proportion of patients with an A1c ≥ 9.0% (27.4% and 26.4%; $p = 0.70$). The other demographics and clinical characteristics were also similar between the TI and NTI after matching. The mean ± SD ages for TI and NTI were 54.9 ± 10.5 and 55.8 ± 10.5 ($p = 0.23$), respectively, and the respective proportions of males were 56.9% and 58.9% ($p = 0.62$). The proportion of patients receiving each possible combination of 2OADs was also similar ($p = 0.65$), as described in Table 1. The overall study cohort had a mean DSCI score of 0.8 ± 1.4 for the TI cohort vs. 0.9 ± 1.4 for the NTI cohort ($p = 0.36$), which indicated that the study cohort had a mild diabetic complication profile. About 60% of patients of both TI and NTI cohorts had a DCSI score of zero. Of the TI patients, 240 (60%) intensified their treatment with a third-class OAD, 98 (24%) with basal or biphasic insulin, and 63 (16%) with GLP-1RA. TI with insulin was associated with the largest A1c reduction of -1.1% (9.24 ± 1.91% at baseline vs. 8.14 ± 1.68% at follow-up), OAD reduced A1c by 0.65% (8.34 ± 1.24% vs. 7.69 ± 1.25%), and GLP1-RA reduced A1c by 0.43% (8.07 ± 0.92% vs. 7.64 ± 1.51%). The average time from the index to follow-up A1c was slightly shorter in the TI (129 ± 28 days) compared to the NTI (133 ± 27 days; $p = 0.045$), which is not considered as a clinically significant difference.

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Table 2 describes the A1c outcome for TI vs. NTI. Average of the follow-up A1c in the TI and NTI cohorts were 7.79 ± 1.43% and 8.02 ± 1.62% (p = 0.03), which were equivalent to the A1c reduction of 0.74 ± 1.62% and 0.43 ± 2.26% (p = 0.03), respectively. The proportion of patients achieving an A1c < 9.0% at the 90-180 day follow-up was significantly higher in the TI cohort (84.3%) compared to NTI (78.6%; p = 0.046). The number of patients having follow-up A1c < 8.0% and < 7.0% were also larger in the TI vs. NTI cohort with the respective proportions of 64.8% vs. 61.4% and 29.0% vs. 25.7%, but the differences as a measure of TI effect were not statistically significant. The respective odds ratios (95% confidence interval) of achieving follow-up A1c < 7.0%, A1c < 8.0%, and A1c < 9.0% for TI vs. NTI were 1.19 (0.87 – 1.63), 1.18 (0.88 – 1.58), and 1.50 (1.04 – 2.17) respectively. Compared to the NTI cohort, TI cohort was significantly less likely to have worsening A1c (28.4% vs. 38.2%; p < 0.01), which was defined as the follow-up A1c measurement higher than the baseline A1c.

Discussion: Timely performed optimal TI is important in that T2DM is a progressive disease. β-cell dysfunction and insulin resistance lead to deterioration of glycemic control over time.[25] With respect to the glycemia trajectory, A1c level increases by approximately 1% every two years despite effective and potent antidiabetic agents have advanced.[25] Clinical inertia may worsen the trajectory of A1c and contribute to suboptimal management of diabetes, which eventually increases the risks of diabetic complications.[5] Thus, patients with T2DM consistently need to intensify antidiabetic agents to maintain adequate glycemic control and delay the onset of complications.[5] The ADA guideline and previous studies recommend reassessing and modifying treatment regimen regularly, every 3-6 months if needed, to avoid clinical inertia.[10,12,20] Guidelines have recommended to shorten the clinical inertia and perform TI less than six months when A1c management does not respond to a current antidiabetic regimen.[10,16,19] Nevertheless, real-world practice is not adherent to the guideline recommendations with the average clinical inertia of 14.0 months.[20]

Our study demonstrated that TI with a third class of antidiabetic agent within one year provided a better A1c control compared to NTI among patients with T2DM who failed to achieve an A1c < 7.0%

with 2OADs. Patients who received TI in this study were also less likely to experience worsening A1c at follow-up compared to NTI. Though intensification of therapy within 6 months of treatment failure is ideal, this study suggested that the benefits of TI would be superior to NTI up to one-year after a suboptimally controlled A1c on 2OADs.

According to the ADA guideline, choice of pharmacologic agents should be individualized based on comorbidities, hypoglycemia risk, and other various factors.[13] From our study, baseline A1c is the primary factor to determine the needs of treatment intensification with the proportion of patients with TI vs. NTI was 34.6% vs. 15.4%, respectively. The superior TI impact in higher baseline A1c is supported by the odds ratio of achieving an A1c < 9.0% that significantly preferred TI to NTI. Our study also showed that the TI with insulin provided the largest A1c reduction compared to other agents (data not provided), which probably happened in patients with higher baseline HbA1c.[12] If risks of hypoglycemia are minimized, clinicians may consider the use of aggressive therapy options such as insulin, in patients with poor glycemic control (A1c > 9.0%).

The odds ratios of achieving A1c < 8.0% and A1c < 7.0% consistently favored TI over NTI, but were not statistically significant. At least three factors could contribute to the lack of statistical significance. First, this study could be underpowered due to the small sample size, specifically when the cohort was stratified for the subgroup analysis. Second, the cut-off A1c ≥ 7.0% was relatively aggressive, and therefore there may not be enough room to improve the A1c level specifically in the patients with a lower baseline A1c between 7.0% to 7.9%, which represents approximately 40% of the study population and results in the diminished effect size. Third, the study population was limited to those who failed to achieve an optimal glycemic control on 2OADs within one year before the confirmed suboptimal response. Because the medication history earlier than one year before the baseline A1c was not available, patients who had failed three or more classes of antidiabetic agents could not be determined. Thus, the study cohort might include patients with a rapidly progressed T2DM that may not be controlled by the usual diabetes management approach in general.

Main Text

Overall, the findings from this study supports previous observational studies that TI improved A1c outcomes.[10,16,20,21,26] Besides this similarity, some key differences expand interpretations of the effect of TI. For example, prior studies selected patients based on a liberal and generous A1c criteria of ≥ 8.0% to identify patients with a subcontrolled or uncontrolled glycemia.[10,16] To have the eligible subjects matched with the guideline-recommended criteria and quality of care matric, we defined an insufficiently controlled A1c by stringent criteria of ≥ 7.0%.[12,27] Second, the timeline to capture the HbA1c changes applied in this study corresponds with the guideline recommendation, which were not applied for the recent outcome assessment using a similar cohort from the regional managed care.[12,15,16] For example, Ruiz-Negron et al. showed that TI within 4 months of the confirmed A1c > 8.0% led to a significantly higher proportion of patients attaining an A1c < 7.0%.[16] Also, Kim et al. predicted A1c to be the lowest at 6 - 12 months post intensification,[12] and that the proportion of patients meeting A1c goal of < 7.0% to < 9.0% increased after the third treatment intensification.[15] While, the three previous studies measured A1c outcome within one-year post TI, this study measured the A1c outcome within 3 - 6 months, which is adherent to the A1c monitoring frequency recommended by the ADA.[3] This period provided a better-reflection of the real-world practice given that many patients receive TI approximately14 months.[20]

Our study found that about 35% of patients with T2DM who were treated between 2010 and 2017 failed to achieve their A1c < 8.0%. The study results were similar to the findings in Kazemian et al.,[7] which is concerning given the high prevalence of diabetes and its associated complications. Kazemian et al. also suggested people with health insurance were more likely to achieve glycemic control compared to those without health insurance.[7] From our assessment, patients who were commercially insured were more likely to intensify their treatment compared to the patients covered by Medicaid (2.1% vs. 12.7%), which generally would be considered a primary reason for less likelihood of achieving glycemic control in the underserved population.[7,28] All things considered, despite advances in diabetes care treatment, such as newer effective medications, patient outcomes have not improved much over the past decade.

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A causal-inference frame applied for the assessment of TI effect was another strength of this study. We used a propensity score matching to control for the differences in variables, including baseline A1c, baseline treatment, gender, and age, as these variables might influence outcomes. By incorporating multiple factors of the clinical decision into the analytic cohort creation, the TI and NTI cohorts in this study were more balanced in patient characteristics and demographics. This minimized confounders in the measurement of the TI effect on A1c outcomes. There were slight differences in the average days from TI to follow-up A1c measurements between TI (129 days) and NTI (133 days; $p = 0.045$); however, the four days difference would not be considered as a source of bias or confounder in the exposure-outcome association. Moreover, incorporating the time to TI and time to A1c outcome measure in the matching process, the late treatment intensification that negatively influence the measure of TI effect or a delayed measurement that presumably leads to a better TI effectiveness measure were generally controlled. To better explain the time-varying TI and outcome effect on A1c control, future studies may use a nested matching, which allows patients to be included in a risk set until they received TI.

There are some limitations to this study that should be noted. To begin with, the TI cohort was defined as T2DM patients with a third-class agent within 365 days after the A1c ≥ 7.0% date. Although the assessment on TI in our study is closer to real-world practice,[20] further specific investigation into the timeline performed TI is needed.[29] In addition, TI was determined by claims for a new class of diabetes medication, we did not distinguish if the newly prescribed class was an add-on or a switch in therapy. Given a larger database access, analysis stratified by specific patterns of treatment regimen will offer better insights into the outcomes of TI. Health plan coverage and provider specialty were not sufficiently addressed in our study, which was another limitation. [9,30] Therefore, future studies in the outcomes of TI and clinical inertia influenced by the diverse access to the resources are warranted. Lastly, the study findings may suffer from limited generalizability due to the nature of a retrospective observational study using a regional health plan database. Future studies using administrative records from multiple states will generalizable insight into the outcomes of TI.

Conclusion:

Main Text

Overall, our study provides real-world evidence that for patients whose A1c was not sufficiently controlled on 2 OADs, the benefit of initiation of TI with a third class of medication within one-year outweighed NTI by further reduced A1c levels and decreased likelihood of experiencing an elevation of A1c. However, TI with a third class of medication alone might not be able to help the majority of patients to achieve A1c < 7.0%, and some might still experience deteriorated A1c despite receiving TI.

Declaration of Interests.

Malinda Tan and Cody Olsen have no conflicts of interest to declare. A part of Kibum Kim's previous research was supported by Sanofi. Inc. Diana Brixner served as an advisory board member and consultant for Sanofi. Inc.

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Tables and Figures

Table 1: Baseline Characteristics

	Before Matching			After Propensity Score Matching		
Mean ± SD or % of patients	TI n = 1,403	NTI n = 2,336	P-value	TI n = 401	NTI n = 401	P-value
Age (year)	54.6 ± 10.3	57.0 ± 10.9	< 0.01	54.9 ± 10.5	55.8 ± 10.5	0.23
≥ 65	12.8%	19.5%	< 0.01	12.2%	14.2%	0.47
≥ 55	53.0%	60.1%	< 0.01	87.8%	85.8%	0.72
Male-Gender	57.2%	60.7.0%	0.04	56.9%	58.9%	0.62
Geographic region			0.08			0.31
Utah	94.8%	93.5%		95.3%	96.0%	
Idaho	3.6%	5.1%		3%	3.7.0%	
Others	1.6%	1.4%		1.70%	0.3%	
DCSI	0.79 ± 1.35	0.80 ± 1.35	0.84	0.79 ± 1.35	0.88 ± 1.41	0.36
DCSI 0	61.6%	61.9%	0.70	61.6%	60.6%	0.21
DCSI 1	18.2%	17.0%		19.2%	15.2%	
DCSI 2	10.5%	11.3%		9.0%	12.5%	
DCSI ≥ 3	9.7.0%	9.8%		10.2%	11.7.0%	
CCI	1.65 ± 0.96	1.66 ± 1.00	0.73	1.72 ± 0.85	1.70 ± 0.82	
CCI 1	58.1%	57.4%	0.79	55.1%	55.4%	0.91
CCI 2	26.4%	27.7.0%		27.7.0%	28.4%	
CCI 3	10.5%	9.8%		10.2%	10.5%	
CCI ≥ 4	5.1%	5.1%		7.0%	5.7.0%	
Baseline Treatment			< 0.01			0.65
Met + SU	54.9%	68.8%		56.4%	57.4%	
Met + DPP4I	28.2%	19.3%		30.4%	28.2%	
Met + TZD	4.3%	2.4%		6.2%	5.0%	
SU + DPP4I	8.0%	6.3%		3.5%	4.7.0%	
Other	4.6%	3.1%		3.5%	4.7.0%	
Baseline A1c (%)	8.77 ± 1.62	8.01 ± 1.29	< 0.01	8.53 ± 1.45	8.45 ± 1.67	0.46
7.00 – 7.99 %	39.8%	65.1%	< 0.01	43.6%	41.9%	0.70
8.00 – 8.99%	25.5%	19.5%		28.9%	31.7.0%	
9.00% or above	34.6%	15.4%		27.4%	26.4%	
Days from baseline to intensification	111 ± 111	N/A	N/A	110 ± 110	110 ± 110	N/A
Type of Health plan						0.16
Commercial	89.0%	84.5%		90.5%	87.5%	
Medicare	8.8%	2.8%		8.0%	9.0%	
Medicaid	2.1%	12.7%		1.5%	3.5%	

TI: treatment intensification; NTI: non-treatment intensification
SD: standard deviation; DCSI: Diabetes Comorbidity Severity Index; OAD: oral antidiabetic drugs, CCI: Charlson Comorbidity Index; Met: metformin; SU: sulfonylurea, DDP4I: dipeptidyl peptidase 4 inhibitor; TZD: thiazolidinedione. N/A: non-applicable

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Table 2: A1c outcome for treatment intensification (TI) vs. non-intensification (NTI)

Mean ± SD or % of patients	TI (n = 401)	NTI (n = 401)	P-value
Follow-up A1c (%)	7.79 ± 1.43	8.02 ± 1.62	0.03
Follow-up A1c < 9 %	84.3%	78.6%	0.046
Follow-up A1c < 8 %	64.8%	61.4%	0.34
Follow-up A1c < 7 %	29.0%	25.7%	0.34
A1c change from Baseline	-0.74 ± 1.62%	-0.43 ± 2.26%	0.03
Follow-up A1c > baseline A1c, Deteriorating A1c level	28.4%	38.2%	< 0.01
Days from treatment intensification to follow-up A1c	128.76 ± 27.98	132.70 ± 27.47	0.045

TI: treatment intensification; NTI: non-treatment intensification
SD: standard deviation

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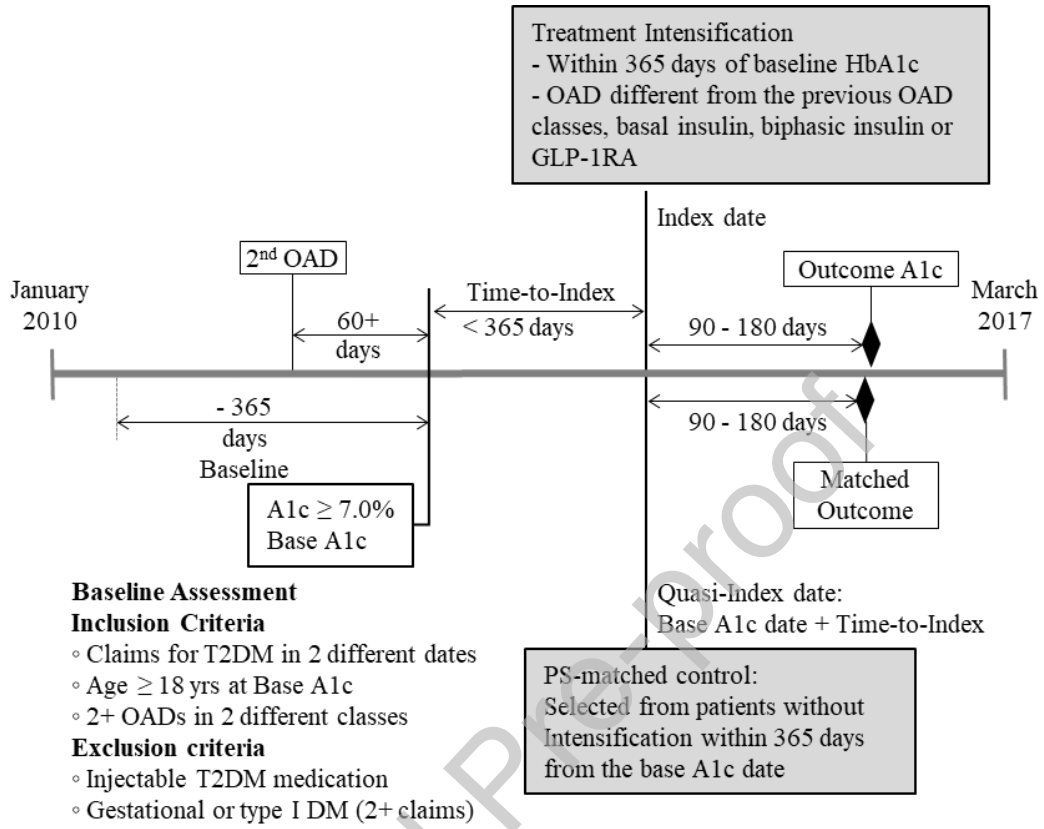
Figure 1. Cohort Selection



Abbreviations: DM, Diabetes Mellitus; GLP-1RA, Glucagon-like peptitde-1 receptor agonist; OAD, Oral Anti-diabetic agents; PS, Propensity score

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Figure 2: Odds ratio of achieving A1c < 9.0%, A1c < 8.0% and A1c < 7.0% for TI