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# Use of Insulin Therapy in VA for Treating Type 2 Diabetic Patients 2002-2013

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## Abstract

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By Shiyun Zhu

Objective: Early initiation of insulin can help diabetic 2 patients maintain target glycemic levels, and is associated with other additional benefits. It is informative to understand the current trend of A1c levels at which insulin is initiated and its association with glycemic response after 12 months, as well as the contribution of insulin to glycemic control.

Methods: Retrospective cohort study, using national VA data to examine 948,874 type 2 diabetic patients between 2002 and 2013, among which 210,183 started on insulin. All had 5-year continuity of care and ≥1 A1c measurements per year. All insulin patients initiated insulin in the 3rd year (termed index year) of the 5 year window. Trend analysis of A1c at insulin initiation and 12-month follow-up was performed for insulin patients by index year. Matched analysis was used to compare the 12 months follow-up and mean change in A1c between insulin and non-insulin group.

Results: Patients were predominately White males, with mean age 64.5 and mean BMI 32.1. Median A1c at insulin initiation decreased from 9.3% to 8.9% between 2002 and 2007, but increased from 8.9% to 9.3% between 2008 and 2013 ($P<0.001$). Glycemic response after 12 month showed an average 1.07% A1c reduction among insulin patients. Matched on baseline A1c and other covariates, mean follow-up A1c was 7.45% (95CI [7.43, 7.48]) for insulin group, compared to 7.53% (95CI [7.51 – 7.55]) for non-insulin group. At an elevated baseline A1c of 8% or more, insulin group showed nearly twice as much A1c reduction as non-insulin group.

Conclusions: The average A1c level at which insulin is initiated among patients with type 2 diabetes changed little between 2002 and 2013, and remain well above optimal A1c goals. Insulin therapy is an important contributor to glycemic control, particularly at an elevated A1c of ≥8%, in which oral agents or other non-insulin injectable medications cannot produce treatment results as effective as insulin.

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## Introduction

Insulin is effective in treating patients with type 2 diabetes, particularly after oral antidiabetic drugs (OADs) have failed or in the setting of severe hyperglycemia [1-3]. Early initiation of insulin therapy helps to maintain target glycemic levels, and is associated with additional benefits including reduction of risk for endothelial dysfunction and vascular disease [4]. Despite positive clinical outcomes, both primary care providers and patients often resist insulin therapy for reasons including fear of injections, concerns of side effects, stigma, and physician inertia among others [5]. These barriers frequently lead to delays in insulin initiation until well after glycemic targets have been surpassed or complications have already developed. A previous study using VA data found that insulin therapy started when patients' A1c levels were above the glycemic target of <7% [6].

According to the American Diabetes Association (ADA) guidelines on the treatment for type 2 diabetes, insulin is the recommended second or third line medication in patients who have not attained glycemic control with one or two non-insulin agents [2, 7]. Insulin should also be considered as an immediate treatment if a patient has a maintained level of A1c exceeding 8% [8]. Given the risks of diabetes-related complications with worsening glycemic control, and in light of the current treatment guidelines, it would be informative to understand the current trend of A1c levels at which insulin is initiated and its association with glycemic response after 12 months, and the contribution of insulin to glycemic control, using population-based data, in order to help guide the next steps necessary to improve diabetes management.

## Methods

*Source population and study sample*

Our source population included Veteran patients who visited any Veteran Health Administration (VHA) in the United States. Data were extracted from VA Corporate Database Warehouse (CDW), a relational database storing clinical and administrative information not for public access or use. The study was approved by Emory University's institutional review board (IRB), Atlanta VA R&D committee, and VA informatics and Computing Infrastructure (VINCI).

We included patients with the diagnosis of type 2 diabetes from January 1, 2000 to July 1, 2015. Diagnosis is determined if the patient met ≥1 of the following criteria: 1) ≥1 use of an ICD-9 code 250.xx in conjunction with a primary care attending visit; 2) any 2 uses of an ICD-9 code 250.xx.; or 3) prescription of two or more medications with VHA National Drug File Code HS500 (exenatide), HS501 (insulins), HS502 (noninsulin antihyperglycemic medications), or HS509 (GLP-1 agonists except exenatide).We further restricted our study population on criteria of sufficient A1c measurements and continuity of care. Sufficient A1c measurements is defined by ≥1 A1c measurement per year in the outpatient setting (not during hospitalization) for at least five consecutive calendar years. Continuity of care is satisfied if a patient has one or more outpatient primary care visits per year for five consecutive calendar years. This algorithm ensures that a patient will have at least one 5-year window of uninterrupted care.

*Insulin (Insulin patients)*

A patient who has ≥1 outpatient prescription for any basal or intermediate-acting insulin was considered as having insulin therapy. Among patients with insulin therapy, we only included those who satisfy the following requirements: 1) started on insulin in the third year of the 5-year continuous care window; and 2) started on at least one OAD

or other non-insulin injectable medications for at least one year before insulin initiation. The first insulin prescription date was assigned as index date and the prescription year was assigned as index year (Appendix A).

*Oral agents and non-insulin injectable medications (Non-insulin patients)*

Among type 2 diabetic patients who were not on insulin therapy, we included those who had one or more OADs or insulin alternatives which were dispense at least two separate times. Index year was assigned as the third year of their first 5-year continuous care window (Appendix B).

*Hemoglobin A1c*

For insulin patients, A1c at insulin initiation (termed baseline A1c) is identified by using lab test date of A1c and index date. Patients were included if their test date is no more than three months prior to index date. We selected the test date that is the closest to the index date and its corresponding A1c value. Similarly, follow-up A1c was selected if the test date is within 9 to 15 months subsequent to the index date. We chose the date and value that is the closest to "12 months follow-up". For non-insulin patients, A1c values were identified using A1c lab test date and index year. Baseline and follow-up A1c were the median A1c measured in the index year and the subsequent year, respectively.

*Covariates*

Covariates included age in the index year, gender, self-reported race/ethnicity, BMI, distinct number of medications used prior to index date for insulin patients and index year for non-insulin patients, and Charlson Comorbidity Index (CCI) one year prior to index year. We regrouped age as <50, 50-59, 60-69, and ≥70; BMI as <25, 25-29.9, 30-34.9, 35-39.9, and ≥40; CCI as 1, 2-3, and ≥4; number of medications as 1, 2, 3, and

≥4. Age and BMI were categorized based on mean and standard deviation later obtained, while CCI and number of medications were regrouped to ensure that each category has similar proportion of patients. Self-reported race/ethnicity was categorized based on *VHA Practice Guide* [9] as White, Black or African American, and Other.

*Statistical Approach*

Analyses were performed using SAS Enterprise Guide 7.1 (Cary, N.C., USA) within the VINCI processing environment. Descriptive statistics comparing baseline characteristics by index year were performed for insulin patients. F-tests were used for continuous variables (age and BMI) and chi-square tests were used for categorical variables.

Trend analysis of baseline A1c among insulin patients was performed using univariate linear regression to obtain crude mean A1c and P-value. Crude median baseline A1c by index year was obtained and Kruksal Wallis test was used. Index year 2008 – mid-point during the study period – was used as a cut-off point to observe separate trends from 2002 – 2007 and 2008 – 2013. We then performed overall trend analyses stratified by age group and race. Glycemic response after 12-month by index year was analyzed by fitting multivariate linear regression to obtain mean follow-up A1c, mean reduction of A1c from follow-up to baseline and 95% confidence interval (95 CIs). This analysis was adjusted for all covariates.

To address the question to what extent insulin contributes to 12-month glycemic response, compared to oral agents and other non-insulin injectable medications, we first used univariate linear regression with change in A1c as dependent variable. We examined prescription of insulin (yes or no) and all above-specified covariates one at a time (i.e.,

unadjusted models), and then fit an adjusted model by including insulin as independent variable and control for covariates that are significantly associated with A1c change in the unadjusted models. Parameter estimates (with 95 CIs) and p-values were calculated. We then performed a matched analysis by selecting a subgroup of non-insulin patients who had the same baseline A1c levels as those who started on insulin, and compare their 12-month follow-up A1c measurements. Matching was done by Greedy matching technique. The validity and effectiveness of this method to reduce bias and approximate an observational study to a randomized control trial (RCT) has been well documented [10]. In addition to baseline A1c, we also matched on all covariates. Follow-up and change in A1c were compared between insulin versus non-insulin groups by fitting a univariate linear regression model and stratified on baseline A1c by levels of 4 – 6.9%, 7 – 7.9%, 8 – 8.9%, 9 – 9.9%, 10 – 10.9%, and ≥11%.

**Results**

Our final sample consisted of 210,183 (22.15%) type 2 diabetic patients initiated insulin therapy and 738,691 (77.85%) non-insulin patients from 2000 – 2015 after inclusion and exclusion criteria (Figure1). Patients were predominately White males, with mean age 64.5 (±10.03) and mean BMI 32.1 (±6.17). Number of patients started insulin therapy increased from 2002 –2008 by an average rate of 11.28% per year, followed by some decreases from 2008 –2009 by 8.44%, from 2009 – 2010 by 12.19%, and from 2011 – 2012 by 7.47% (Table 1). Overall, all baseline characteristics fluctuated by index year with some exhibited a certain form of trend than others (all P-value <0.001). For example, patients were more likely to be older at insulin initiation from 2002 to 2012; beginning in 2007, the proportion of people started insulin with four or more CCI

decreased (Table 1).

Between 2002 and 2013, the mean A1c at insulin initiation ranges from 9.18 – 9.66% and the median A1c from 8.9 – 9.3% (both P<0.001). Median A1c at insulin initiation decreased slightly from 2005 – 2007 by an average of 0.1% per year (P<0.001). Between 2008 and 2013, however, mean A1c at insulin showed significant increase from 8.99% – 9.61%, and median A1c from 8.9% – 9.3% (Figure 2A). Stratified by age group and race, median baseline A1c was highest among African Americans or patients aged below 50 years regardless of index year (Figure 2B). Glycemic response after 12 month of insulin initiation showed an average 1.07% A1c reduction between 2002 – 2013 (Table 2), with the highest reduction of 1.2% (95 CI [0.85, 1.56]) and the lowest reduction 0.92% (95 CI [0.57, 1.27]).

Overall, we found that starting insulin therapy and all covariates were significantly associated with A1c change between follow-up and baseline, but variations existed among different groups in terms of glycemic control. For example, compared to non-insulin group which had an average 0.03% (95 CI [0.001, 0.058]) reduction in A1c 12 months subsequent to the index year, patients who started insulin showed an average 1.47% (95 CI [1.42, 1.52]) A1c reduction (Figure 3). Compared to Whites, African Americans responded to both insulin and non-insulin treatments better with an additional 0.2% (95 CI [0.15, 0.17]) A1c reduction, adjusting for other covariates. It is worth noticing that when patients were on four or more medications, the 12-month glycemic response decreased among insulin patients by 1.18% (95 CI [1.33, 1.47]), while increased among non-insulin patients by 0.26% (95 CI [0.21, 0.31]).

We identified 17,481 pairs from the study sample with similar baseline A1c and

other covariates. The mean baseline A1c was 7.80% (95CI [7.79, 7.81]). The mean follow-up A1c was 7.45% (95CI [7.43, 7.48]) for insulin group, compared to 7.53% (95CI [7.51 – 7.55]) for non-insulin group (Table 3). Stratified on baseline A1c, insulin group showed substantive lower mean follow-up A1c than that of non-insulin group when the baseline A1c level was at 8% or more. Differences of A1c changes from follow-up to baseline between two groups became larger with increased baseline A1c. For example, at baseline A1c from 8 – 8.9%, the mean A1c change was –0.73 % (95 CI [–0.77, –0.69]) for insulin group and –0.45% (95 CI [–0.49, –0.41]) for non-insulin group, resulting a difference of –0.30 (95 CI [-0.36, 0.25]). At baseline A1c from 10 – 10.9%, however, the mean A1c change was – 2.15% (95 CI [–2.27, –2.03]) for insulin group and –1.35% (95 CI [–1.47, –1.24]) for non-insulin group, resulting a difference of –0.74 (95 CI [-0.91, -0.58]) (Table 3, Appendix C).

**Discussion**

*Trend in A1c at insulin initiation*

A previous study using VA data found that insulin therapy started when patients' A1c levels were well above the glycemic target of <7% [6]. We were interested in whether there was any improvement of insulin use among primary care providers on a national scale between 2002 and 2013. Our results showed that between 2002 and 2008, the A1c at insulin initiation decreased slightly by 0.1% per year. After 2008, however, the A1c at insulin initiation increased again, and the highest A1c value of 9.61% occurred in 2013. These levels were well above glycemic control. We postulated that medical practice on insulin prescription among primary care providers may be related to VA facility. For example, a VA facility that is associated with an academic and research

entity is likely to have better practice, as more updated information and resources are easily available. In contrast, facilities located at relatively small cities and without any tie to a research entity may take long time getting the latest medical practices implemented. Alternatively, the late initiation of insulin is possibly related to new OADs available in the market. For instance, Saxagliptin has been widely used in VA starting 2008. More research is needed to disentangle factors that may explain the increasing trend of A1c at insulin initiation.

We found that A1c at insulin initiation differed by age and race systematically. It is consistently higher among African Americans or patients who aged less than 50, compared to their counterparts, regardless of index year. Moreover, the older the patient, the lower the A1c at insulin initiation. We tested if race and age interaction is present in which African Americans were also the younger population, and we failed to find this is the case. These results suggest that both primary care providers and patients may take into account factors other than A1c level and OADs used when started on insulin. For example, patients who are relatively young may resist insulin therapy than the elderly, as type 2 diabetes was traditionally perceived as an aging disease [5]. Consequently, young patients who started on insulin are likely to be those who are in severely ill conditions. Moreover, it is well documented that diabetes and its related comorbidities differ by race/ethnicity [11]. Adding to this knowledge, our results indicate that there is also likely to be race/ethnicity difference in diabetes management.

*12-month follow-up A1c reduction*

We evaluated the contribution of insulin to glycemic control firstly by looking at the 12-month follow-up A1c only among insulin patients. On average, A1c fell by 1.04%.

This change was smaller than the results from a prospective study conducted in Europe, which showed an average 1.6% reduction 6 months following insulin initiation [12]. Possible reasons include failure of treatment adherence or discontinuing lifestyle change such as diet restriction and reduced physical activity. On the other hand, insulin is the biggest contributor to glycemic control, especially when patients were on two or more medications or in the situation of hyperglycemia. We noticed that 12-month follow-up A1c is likely to increase among patients who were on third or fourth OADs or non-insulin injectable drugs, but were not on insulin therapy. Moreover, with an elevated A1c $\geq$ 8%, OADs or non-insulin drugs could not produce treatment results as effective as insulin therapy, and insulin therapy contributes to additional A1c reduction, compared to using OADs or non-insulin injectable drugs only.

*Limitation*

Our study has several limitations. First, for non-insulin patients, our assigned index year is arbitrary. We chose the third year of the first 5-year continuity care window and only counted each patient once. In our non-insulin patient pool, however, many patients have more than 5 year of continuity care and had changes in BMI, CCI and number of medications used throughout their follow-up period. We failed to capture such information and can only use their partial data according to our criteria. For example, if a patient was followed up for ten years, we assigned the third year as the index year and only used his/her A1c, BMI, age and other information according to this index year, while in fact, we could assign the fourth or fifth year as the index year. This may lead to an underestimation of A1c levels among non-insulin patients, as type 2 diabetes is progressive by nature and A1c tends to getting worse. Second, we did not have

information on patients' diet, physical exercise, smoking, or other lifestyle factors, which are critical to glycemic control and diabetes management, and are contributors to A1c changes. Third, our study sample of insulin patient is large. Thus, small changes are easily detectable on a statistical level. For example, the proportion of male patients did not change drastically between 2002 and 2013 by looking at the data, yet the calculated p-value indicates significance. We must be cautious to interpret the study results on a clinical standpoint rather than on a statistical standpoint.

**Conclusion**

We conducted a trend analysis on A1c at insulin initiation using national VA data and evidence suggested that A1c at insulin initiation in VA had little change between 2002 and 2013. Other factors such as age and race may also play a role in insulin prescription or patients' willingness to start on insulin therapy. Despite all these, insulin is an important contributor to glycemic control. Particularly at an elevated A1c, oral agents or other non-insulin injectable medications cannot produce treatment results as effective as insulin. Given the benefits of insulin therapy and current medical practice on insulin prescription, some form of policy may be needed to prompt insulin therapy at an early stage.

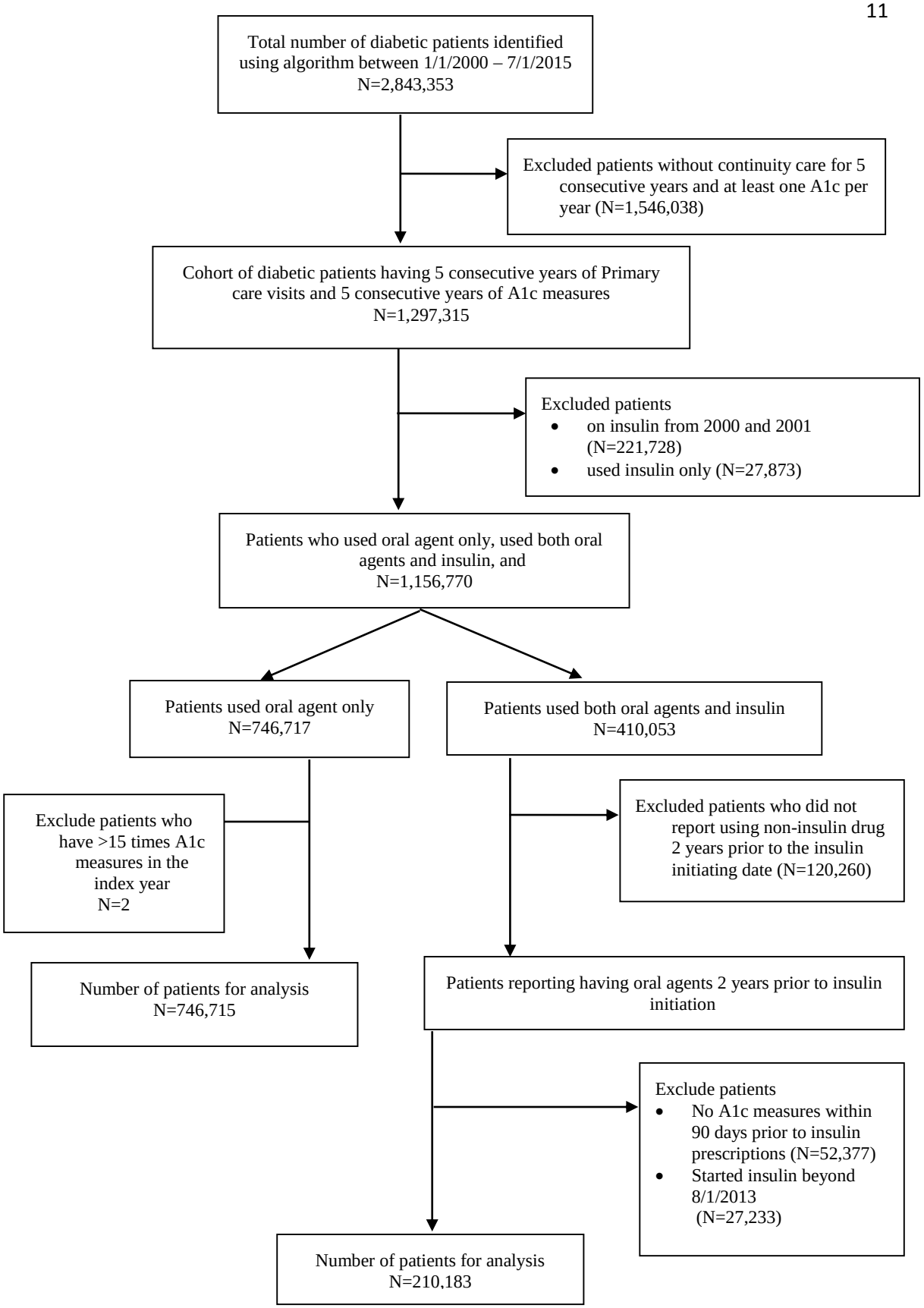


Figure 1: Selection process of insulin and non-insulin patents

| | Index year | | | | | | | | | | | | P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2002** | **2003** | **2004** | **2005** | **2006** | **2007** | **2008** | **2009** | **2010** | **2011** | **2012** | **2013** | |
| **Total, n** | 8,389 | 10,868 | 13,657 | 16,166 | 17,926 | 21,295 | 25,064 | 23,114 | 20,603 | 21,227 | 19,752 | 12,122 | |
| **Mean Age (SD), year** | 61.8 (10.3) | 62.8 (10.5) | 63.7 (10.4) | 64.1 (10.3) | 64.2 (10.2) | 64.4 (10.0) | 64.8 (9.9) | 64.7 (10.0) | 64.9 (9.9) | 65.0 (9.9) | 65.2 (9.8) | 65.6 (9.5) | **<.001** |
| **Mean BMI (SD), kg/m$^2$** | 31.7 (6.2) | 31.7 (6.2) | 31.6 (6.1) | 31.8 (6.2) | 31.9 (6.2) | 32.3 (6.2) | 32.3 (6.2) | 32.4 (6.2) | 32.3 (6.1) | 32.4 (6.3) | 32.4 (6.1) | 32.4 (6.1) | **<.001** |
| **Gender, %** | | | | | | | | | | | | | |
| Males | 97.8 | 97.9 | 97.9 | 97.8 | 97.6 | 97.7 | 97.7 | 97.5 | 97.3 | 97.1 | 97.1 | 97.2 | |
| **Race, %** | | | | | | | | | | | | | **<.001** |
| White | 79.2 | 80.3 | 80.8 | 81.7 | 81.5 | 81.2 | 82.3 | 81.5 | 81.5 | 81.0 | 81.2 | 81.2 | |
| Black | 19.0 | 17.9 | 17.2 | 16.6 | 16.5 | 17.0 | 15.9 | 16.6 | 16.3 | 16.9 | 16.8 | 16.7 | |
| Other | 1.8 | 1.8 | 2.0 | 1.7 | 2.0 | 1.8 | 1.7 | 1.9 | 2.3 | 2.1 | 2.0 | 2.1 | |
| **Charlson Comorbidity Index (CCI), %** | | | | | | | | | | | | | **<.001** |
| 1 | 35.7 | 36.3 | 36.2 | 37.7 | 39.9 | 40.7 | 41.5 | 42.5 | 42.1 | 43.1 | 44.0 | 44.6 | |
| 2-3 | 39.47 | 39.6 | 39.6 | 39.3 | 39.7 | 39.5 | 39.7 | 39.7 | 39.8 | 39.3 | 39.2 | 38.5 | |
| ≥4 | 24.8 | 24.2 | 24.2 | 23.0 | 20.4 | 19.8 | 18.9 | 17.9 | 18.1 | 17.7 | 16.8 | 16.9 | |
| **Number of medications used prior to insulin prescription, %** | | | | | | | | | | | | | **<.001** |
| 1 | | | | | | -- | | | | | | | |
| 2 | 12.7 | 13.1 | 13.1 | 12.7 | 11.9 | 10.8 | 12.2 | 14.1 | 15.2 | 15.3 | 16.4 | 16.7 | |
| 3 | 49.5 | 48.0 | 46.3 | 45.9 | 46.1 | 45.4 | 47.1 | 49.7 | 53.1 | 53.6 | 55.5 | 56.5 | |
| ≥4 | 37.8 | 39.0 | 40.7 | 41.4 | 42.0 | 43.8 | 40.7 | 36.3 | 31.8 | 31.1 | 28.1 | 26.8 | |

Table2: Demographic information of patients from 2002 – 2015. Index year indicates the year they started on insulin. All patients have 5-year continuity of care – 2 years before and after insulin initiation, and ≥1 A1c measurements per year.

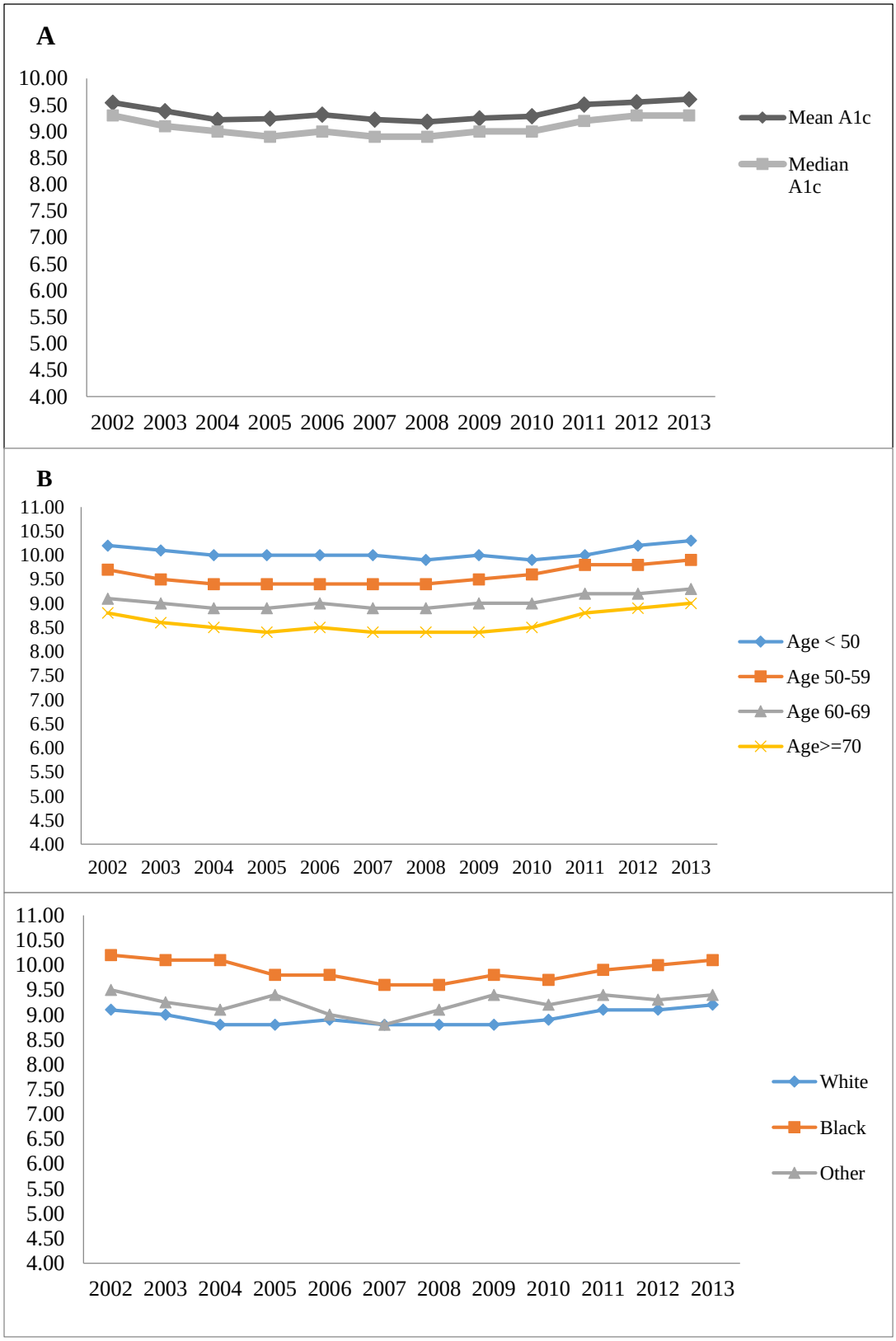


Figure 2: Crude baseline A1c by index year. [A] Overall median and mean A1c. [B] Median A1c stratified by age (above) and Race (below)

| Index year | Mean A1c (95%CI) | | | P-value[#] |
|---|---|---|---|---|
| | **Baseline** | **Follow-up** | **Reduction** | |
| **2002** | 9.13 (8.80, 9.45) | 8.00 (7.72, 8.28) | 1.13 (0.77, 1.48)* | **<0.001** |
| **2003** | 9.08 (8.76, 9.41) | 7.97 (7.69, 8.25) | 1.11 (0.76, 1.47)* | |
| **2004** | 8.91 (8.59, 9.23) | 7.99 (7.71, 8.27) | 0.92 (0.57, 1.27)* | |
| **2005** | 8.97 (8.65, 9.29) | 7.98 (7.71, 8.26) | 0.99 (0.63, 1.34)* | |
| **2006** | 9.03 (8.71, 9.35) | 7.92 (7.65, 8.20) | 1.10 (0.75, 1.46)* | |
| **2007** | 8.91 (8.59, 9.23) | 7.89 (7.61, 8.16) | 1.03 (0.67, 1.38)* | |
| **2008** | 8.92 (8.60, 9.24) | 7.85 (7.58, 8.13) | 1.07 (0.72, 1.42)* | |
| **2009** | 8.98 (8.66, 9.30) | 7.89 (7.62, 8.17) | 1.09 (0.74, 1.44)* | |
| **2010** | 9.01 (8.69, 9.33) | 8.06 (7.78, 8.33) | 0.95 (0.59, 1.30)* | |
| **2011** | 9.24 (8.92, 9.57) | 8.10 (7.82, 8.37) | 1.15 (0.80, 1.50)* | |
| **2012** | 9.29 (8.97, 9.61) | 8.14 (7.86, 8.41) | 1.15 (0.80, 1.50)* | |
| **2013** | 9.37 (9.05, 9.69) | 8.17 (7.89, 8.45) | 1.20 (0.85, 1.56)* | |

Table 2: Mean baseline and 12 months follow-up A1c, and change in A1c from follow-up to baseline by index year. Model adjusted for age, BMI, gender, race, CCI, and number of medications used prior to index date. All covariates were in their original scale (e.g., not in regrouped categories)

*Indicates significant reductions between follow-up and baseline A1c at each index year
[#]Indicates between-group difference.

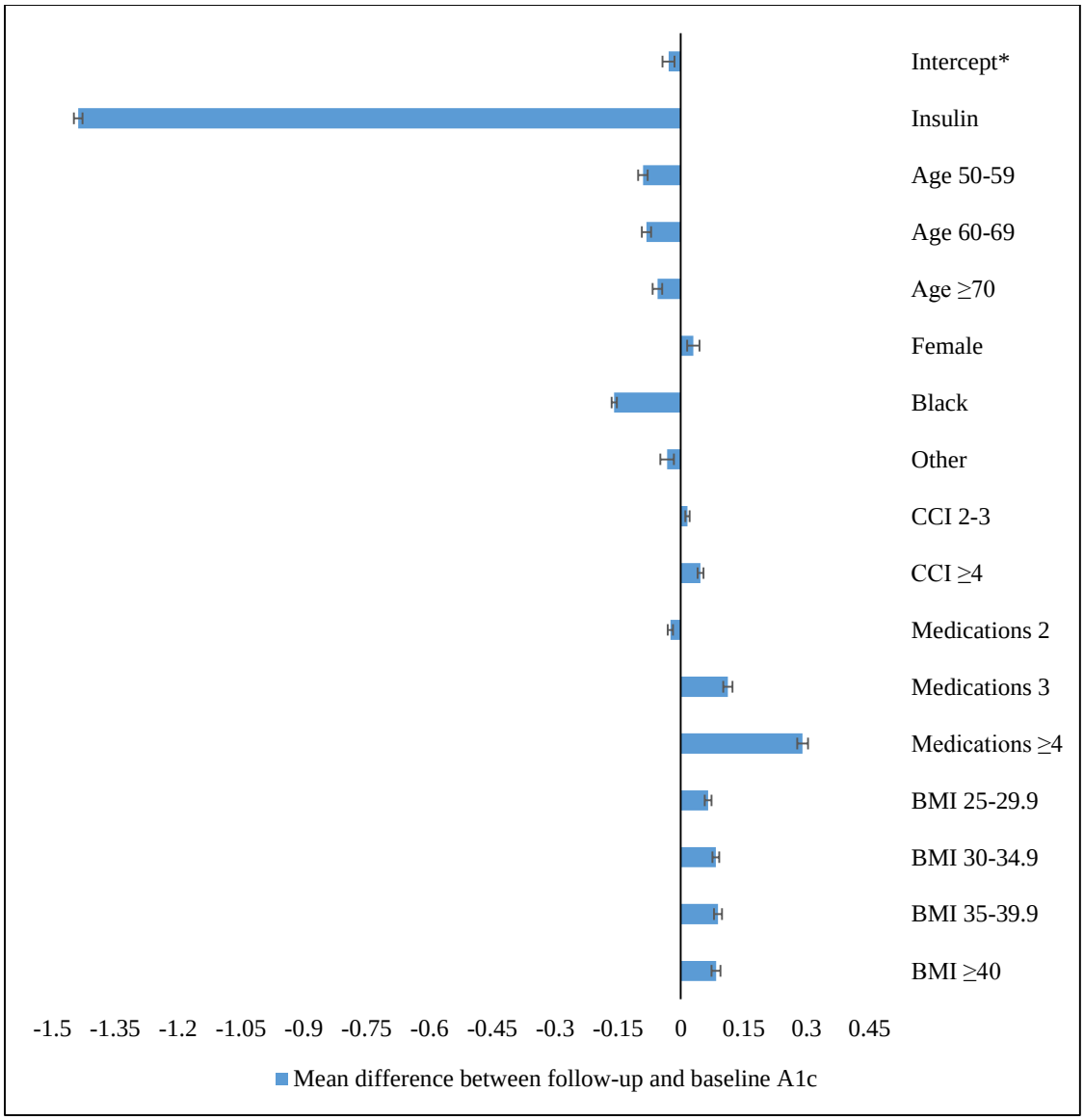


Figure 3b: Contributors of A1c change. Model used all insulin and non-insulin patients identified in our study. Model used insulin as independent variable and controlled for all covariates.

*Intercept indicates the reference group –White male non-insulin patients with age<50, BMI <25, 1 CCI, and 1 medications used prior to index year, and whose index year is 2002

| | | Insulin A1c (95 CI) | | | Non-insulin A1c (95 CI) | | | Difference in A1c change (95 CI)[#] |
|---|---|---|---|---|---|---|---|---|
| | N | Baseline | Follow-up | Change | Baseline | Follow-up | Change | |
| | 34,962 | 7.80 (7.79, 7.81) | 7.45 (7.43, 7.48) | -0.40 (-0.42, -0.38) | 7.80 (7.79, 7.81) | 7.53 (7.51, 7.55) | -0.27 (-0.29.-0.25) | -0.13 (-0.16, -0.10)* |
| **A1c categorization** | | | | | | | | |
| **4-6.9** | 10,728 | 6.27 (6.27, 6.28) | 6.83 (6.80, 6.86) | 0.52 (0.49,0.55) | 6.33 (6.32, 6.33) | 6.57 (6.55, 6.60) | 0.24 (0.22, 0.27) | 0.27 (0.23, 0.30)* |
| **7-7.9** | 10,172 | 7.43 (7.42, 7.43) | 7.40 (7.37, 7.43) | -0.03 (-0.06, 0.00) | 7.43 (7.42, 7.43) | 7.38 (7.35, 7.40) | -0.05 (-0.08, -0.02) | 0.02 (-0.02, 0.06) |
| **8-8.9** | 7,014 | 8.42 (8.41, 8.42) | 7.69 (7.64, 7.73) | -0.73 (-0.77, -0.69) | 8.41 (8.40, 8.41) | 7.96 (7.92, 8.00) | -0.45 (-0.49, -0.41) | -0.30 (-0.36, -0.25)* |
| **9-9.9** | 4,248 | 9.38 (9.38, 9.39) | 8.04 (7.97, 8.10) | -1.34 (-1.41, -1.28) | 9.39 (9.39, 9.40) | 8.52 (8.46, 8.59) | -0.87 (-0.93, -0.80) | -0.49 (-0.57, -0.40)* |
| **10-10.9** | 1,762 | 10.34 (10.34, 10.35) | 8.19 (8.07, 8.31) | -2.15 (-2.27, -2.03) | 10.37 (10.36, 10.38) | 9.02 (8.90, 9.13) | -1.35 (-1.47, -1.24) | -0.74 (-0.91, -0.58)* |
| **≥11** | 1,038 | 11.87 (11.85, 11.90) | 8.53 (8.33, 8.73) | -3.37 (-3.58, -3.16) | 12.02 (11.99, 12.05) | 9.66 (9.50, 9.82) | -2.36 (-2.53, -2.18) | -0.98 (-1.26, -0.70)* |

Table 3: Matched analysis compare 12 months follow-up A1c between insulin and non-insulin groups. Matched factors include baseline A1c, age, BMI, gender, race, CCI, number of medications used prior to index date or year. All variables were used on the redefined scale (e.g., recategorization of age and BMI)

[#]Indicates differences in A1c change comparing insulin to non-insulin group.

*Differences are significant

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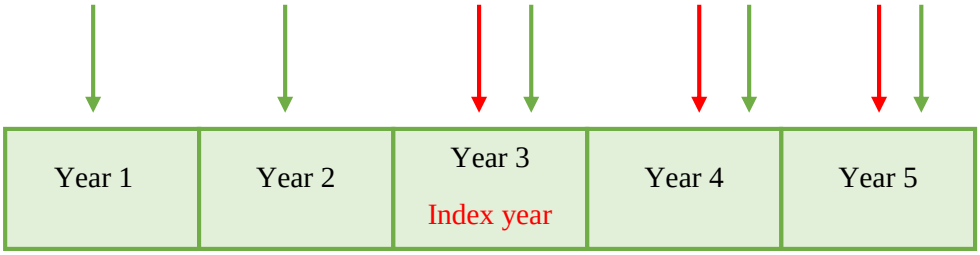
Appendix A: Design of database query for insulin patients

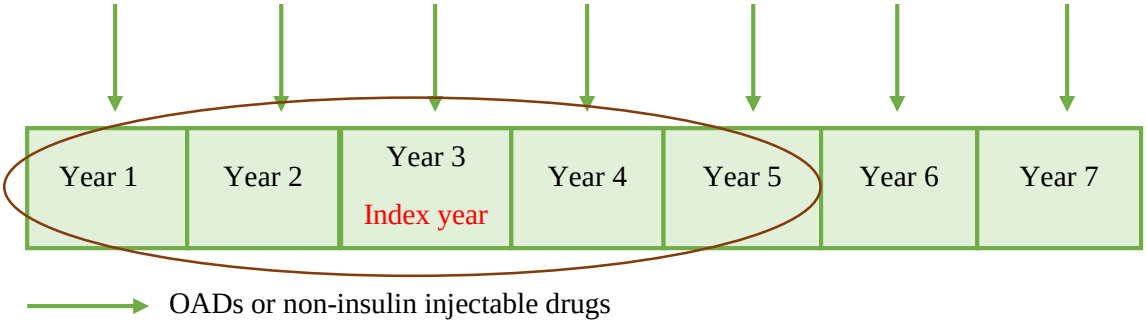



OADs or non-insulin injectable drugs

Insulin therapy

| Insulin patient eligibility:<br>• Had at least one primary outpatient visit and A1c measurement during each year of the cohort period;<br>• Did not start on insulin therapy until the index year | Cohort period | Index year* |
|---|---|---|
| | 2000 – 2004 | 2002 |
| | 2001 – 2005 | 2003 |
| | 2002 – 2006 | 2004 |
| | 2003 – 2007 | 2005 |
| | 2004 – 2008 | 2006 |
| | 2005 – 2009 | 2007 |
| | 2006 – 2010 | 2008 |
| | 2007 – 2011 | 2009 |
| | 2008 – 2012 | 2010 |
| | 2009 – 2013 | 2011 |
| | 2010 – 2014 | 2012 |
| | 2011 – 2015 | 2013 |

Appendix B: Design of database query for non-insulin patients




Non-insulin patient eligibility:

- Had at least one primary outpatient visit and A1c measurement each year for at least 5 consecutive calendar years;
- Had one or more OADs or insulin alternatives which were dispense at least two separate times.
- Only used the first 5 continues care window.
- Index year was the third year.

Appendix C: Figure generated from Table 3