Milliman

Real-world Insights & Economic Considerations in Type 2 Diabetes

The Challenge of Sustaining Glycemic Control & Medication Adherence Over Time

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HbA1c, hemoglobin A1c; PDC, proportion of days covered.

EXECUTIVE SUMMARY

For decades, clinical trials have shown that glycemic control is one of the most important goals for maintaining the health of people with diabetes. These trials have helped establish professional society recommendations for hemoglobin A1c (HbA1c) target levels and quality metrics for insurers. However, real-world population studies show poor results when it comes to glycemic control as measured by HbA1c, suggesting that the recommended actions available to patients—diet, exercise, and medications—are not being followed.

This paper presents patterns of HbA1c levels and diabetes medication adherence among people with type 2 diabetes mellitus (T2DM) based on real-world data from 2012 to 2014. We also present the results of 2 correlation analyses between HbA1c levels and diabetes medication adherence and HbA1c levels and medical costs. We combined large-scale administrative data from insurers with laboratory values of HbA1c to provide real-world insights that would be unavailable from each source individually.

In summary, we found that better adherence is associated with improved HbA1c control. Higher HbA1c is associated with higher expenses, but this is partly a result of higher spending on diabetes medications by people with higher HbA1c.

We constructed 3 cohorts of patients with T2DM to examine patterns in HbA1c laboratory values and diabetes medication adherence that could tie to findings reported in the literature.

- **Cohort 1: approximately 4,000 patients who had eligibility all months of 2012 to 2014 and at least 1 HbA1c laboratory test in each year**
    - ***Glycemic control was suboptimal and difficult to sustain***
        - The percentage of patients with glycemic control (HbA1c <7%) declined from 44% in 2012 to 38% in 2014
        - For patients with HbA1c levels <7% in 2012, only 70% and 64% sustained that level in 2013 and 2014, respectively
        - Only 24% of patients sustained HbA1c levels <7% for all 3 years
        - Patients with a higher HbA1c level in 2012 were less likely to achieve HbA1c control in 2013 and 2014
    - ***Diabetes medication adherence was suboptimal and difficult to sustain***
        - Diabetes medication adherence rates were measured by proportion of days covered (PDC). The percentage of patients with a PDC ≥80% increased from 40% to 42% between 2012 and 2014, but remained suboptimal
        - Adherence was challenging to maintain over time
            - Of the adherent patients in 2012 (PDC ≥80%), only 61% remained adherent in 2014
            - Of the nonadherent patients in 2012 (PDC <80%), 70% remained nonadherent in 2014
            - Only 18% of the patients were adherent in all 3 study years
- **Cohort 2: approximately 36,000 patients who had eligibility in all of 2013 and for at least 1 month of 2014, and at least 1 HbA1c laboratory test in 2014**
    - ***Patients with poor glycemic control had higher costs than those with glycemic control***
        - On a risk-adjusted basis, costs for patients with HbA1c levels ≥7% were 8.1% higher than for patients with HbA1c levels <7%
        - On a risk-adjusted basis, costs for patients with HbA1c levels ≥8% were 6.0% higher than for patients with HbA1c levels <8%
        - The cost difference was largely attributed to higher diabetes medication costs in patients with higher HbA1c levels

- **Cohort 3: approximately 80,000 patients generating approximately 190,000 "HbA1c 6-month episodes" (see definition on page 18) between 2012 and 2014**

    - ***Diabetes medication adherence was negatively correlated with HbA1c levels***
        - Higher HbA1c levels were associated with lower PDC rates; 54% of HbA1c episodes with HbA1c levels <7% demonstrated adherence compared to 36% of HbA1c episodes with HbA1c ≥9%
        - A greater proportion of HbA1c episodes exhibiting adherence had HbA1c <7% (44%) vs those not exhibiting adherence (36%)
        - Every 10% increase in PDC was associated with a 0.12% decrease in HbA1c levels

    - ***Complexity of diabetes treatment regimen may contribute to lower rates of diabetes medication adherence***
        - Adherence was exhibited in 53% of HbA1c episodes using oral-only drug therapy vs 43% with injectable-only therapy and 40% with combined oral and injectable therapy

Our results are consistent with findings in the literature that better diabetes medication adherence is correlated with better HbA1c control, and that HbA1c control and diabetes medication adherence among commercially insured patients is suboptimal. These findings highlight the need for evaluating medications and systems of care from the standpoint of real-world HbA1c control and health outcomes.

This report was commissioned by Intarcia Therapeutics, Inc. The findings reflect the research of the authors; Milliman does not endorse any product or organization. If this report is reproduced, we ask that it be reproduced in its entirety, as pieces taken out of context can be misleading. As with any economic or actuarial analysis, it is not possible to capture all factors that may be significant. Because we present national average data based on 2012 to 2014 Truven Health MarketScan® Research Database (MarketScan) data, the findings should be interpreted carefully before they are applied to any particular situation. Findings for particular populations and for different time periods will vary from these findings. Tyler Engel and Bruce Pyenson are Members of the American Academy of Actuaries and meet the Qualification Standards of the American Academy of Actuaries for their work on this report.

BACKGROUND

THE GROWING BURDEN OF DIABETES

Diabetes is a significant concern in the United States because of its high prevalence, morbidity, mortality, and medical costs.[1] The incidence of new diabetes cases each year is projected to increase from 8 per 1,000 people in 2008 to 15 per 1,000 in 2050, by which time 1 in 3 to 1 in 5 American adults is projected to have diabetes.[2] The total costs of diabetes in 2012 was estimated to be $245 billion, including medical costs and reduced productivity; direct medical costs for diabetes were estimated to be $176 billion.[3] The medical cost of people with diabetes is reported to be 2.3 times higher than for those without diabetes after adjusting for age and sex differences.[1] For the commercially insured population (the focus of our study), the prevalence of diabetes is significant and is projected to increase. The National Health and Nutrition Examination Survey (NHANES) 2009 to 2012 estimates applied to the US census data indicate that 4.1% of people aged 20 to 44 years and 16.2% of those aged 45 to 64 years have diagnosed or undiagnosed diabetes.[1]

THE IMPORTANCE OF GLYCEMIC CONTROL IN DIABETES

Glycemic control in diabetes, which typically is measured by HbA1c testing, is strongly correlated with macrovascular and microvascular disease, including coronary artery disease, stroke, peripheral vascular disease (associated with amputation), end-stage renal disease, and retinopathy (associated with blindness). Landmark studies consistently report that higher levels of HbA1c are associated with higher rates of these complications.[4-6] Nonetheless, the proportion of people with diabetes reaching the American Diabetes Association HbA1c goal of <7.0% was only 52.2% according to a 2007 to 2010 NHANES analysis.[7]

Although the NHANES analysis showed HbA1c control among adults with diabetes improved from an average HbA1c level of 7.6% between 1999 and 2002 to 7.2% between 2007 and 2010, the proportion reaching HbA1c goal remains suboptimal, as shown below.[7]

Table 1: Percentage of Age Group With and Without Diabetes Complications Achieving HbA1c Goal

Age Group, Years	Diabetes Complications	HbA1c Level	Percentage of Group Achieving Goal
18-44	No	≤6.5%	37.0%
	Yes	≤7.0%	39.4%
45-64	No	≤7.0%	52.0%
	Yes	≤8.0%	57.1%

Data Source: NHANES Analysis (2007 to 2010) from Ali MK et al. *N Engl J Med*. 2013;368(17):1613-1624.

The 2016 National Committee for Quality Assurance (NCQA) *State of Health Care Quality Report,* which reports performance on key quality metrics by individual health plans, indicates a decrease in glycemic control over the past 4 years for commercially insured people with diabetes in health maintenance organizations (HMOs) and preferred provider organizations (PPOs). In 2015, only 36.7% of people with diabetes in HMOs and 32.6% of people with diabetes in PPOs had an HbA1c level <7%, while 55.3% and 46.6%, respectively, had an HbA1c <8%. This compares with a 2012 rate of 43.2% and 36.0% with an HbA1c level <7% and 61.3% and 54.5% with an HbA1c level <8%, respectively.[8] The suboptimal HbA1c control rates appear to persist despite the availability of a broad selection of diabetes therapies, including the approval of 15 new diabetes therapies between 2013 and 2016.[9]

Poor glycemic control not only increases the risk of diabetes complications, but has been associated with higher healthcare costs. Gilmer and colleagues demonstrated that each HbA1c level increase >7% was associated with an increase in total medical care costs for populations with and without diabetes

complications. Specifically, patients with diabetes with hypertension and heart disease with levels of HbA1c of 7%, 8%, 9%, and 10% experienced charges that were 4%, 10%, 18%, and 28% higher than those with an HbA1c level of 6%, respectively. Patients with diabetes without hypertension and heart disease with levels of HbA1c of 7%, 8%, 9%, and 10% experienced charges that were 5%, 11%, 21%, and 36% higher than those with an HbA1c level of 6%, respectively.[10] A study that included 6,780 patients with diabetes showed that predicted annual diabetes-related costs for patients whose HbA1c level was >7% were 32% higher than for patients whose HbA1c level was ≤7%.[11] In a study of approximately 10,800 patients with T2DM from one large health plan, only 56% had HbA1c levels consistently ≤7%. Those with HbA1c levels ≤7% had annual direct diabetes-associated medical costs of $1,505, compared with $1,801 and $1,871 for patients with HbA1c levels >7% to ≤9% and >9%, respectively. Their annual prescription drug costs were $377, compared with $465 and $423 for patients with HbA1c levels >7% to ≤9% and >9%, respectively.[12]

Similarly, poor glycemic control has been associated with higher utilization of healthcare services in some real-world studies. In a managed care population of adults with diabetes (N=2,394), the average inpatient admission rate per 100 patients with long-term diabetes complications (average cost per admission) over 3 years was 30 ($2,610), 38 ($3,810) and 74 ($8,320) for patients with good glycemic control (HbA1c level <8%), fair glycemic control (HbA1c level 8%-10%), and poor glycemic control (HbA1c level >10%), respectively.[13] Another study in a similar population (N=4,744) showed that utilization of primary care and specialty visits was lower for patients with diabetes whose HbA1c levels improved over time.[14]

THE IMPORTANCE OF DIABETES MEDICATION ADHERENCE FOR GLYCEMIC CONTROL

A key factor impacting HbA1c control in diabetes is patient adherence to an appropriate plan of care, including prescribed medications. Several retrospective database analyses have shown an inverse correlation between adherence with oral diabetes medications and HbA1c levels; however, studies report that medication adherence in diabetes is suboptimal.[15-18]

A 2012 meta-analysis that included 34 studies of oral hypoglycemic drugs in patients with T2DM found that the mean medication possession ratio (MPR) was 75.3% and that 67.9% of patients were adherent (MPR ≥80%).[19] In a meta-analysis of papers from 2004 to 2013 that examined 27 studies of adherence to diabetes medication in patients with T2DM, the percentage of patients who were considered adherent (MPR ≥80%) varied from 38.5% to 93.1%, based on different samples and methodologies.[20] Kirkman and colleagues analyzed a pharmacy claims database with >200,000 patients with diabetes treated with noninsulin drugs. Defining adherence as MPR ≥80%, Kirkman and colleagues found that 69% of patients were adherent. Factors that were positively associated with adherence included lower out-of-pocket costs, primary care vs non-endocrinology specialist prescriber, use of mail-order vs retail pharmacies, and a higher number of pills per day. Demographic factors positively associated with adherence included older age, male sex, higher educational attainment, and higher income.[21]

In a study that compared real-world HbA1c control in patients with T2DM with that of the clinical trial environment for 2 different classes of diabetes drugs, a greater reduction of HbA1c levels was found in clinical trials compared with the real-world setting. Moreover, 75% of the difference between clinical trial and real-world results was reported to result from medication adherence as measured by PDC methodology.[22]

The level of adherence to diabetes medications is also associated with utilization and economic outcomes. Defining nonadherence as PDC <80%, a study of approximately 11,500 patients with diabetes in a managed care organization found that 20.3% were nonadherent to oral hypoglycemics; both their all-cause mortality and all-cause hospitalization rates (adjusted for comorbidities and baseline clinical characteristics) were approximately 1.4 times those of adherent patients.[23] A study of 900 patients with diabetes in one managed care plan found that adherence measured by MPR was negatively correlated with the rate of subsequent hospitalization for diabetes or cardiovascular disease. Enrollees who were nonadherent to oral antihyperglycemic medications in 1 year were more likely to have an inpatient hospitalization the following year.[24] A review of 12 US studies of the impact of medication adherence or persistence on costs in T2DM

found that MPR was negatively associated with total healthcare costs in 7 studies, was negatively associated with hospitalization costs in 4 studies, and was not associated with changes in health costs in 1 study.[25] Jha and colleagues used a multivariable analysis to examine the impact of diabetes medication nonadherence on the risk of hospitalizations and emergency department (ED) visits in a commercially insured patient population and found that when patients switched from being adherent to nonadherent (MPR <80%), their odds of subsequent hospitalizations or ED visits in a given year increased by 13%; for patients who switched to being adherent, the odds of those outcomes decreased by 15%.[26]

WHY HEALTH PLANS TARGET HbA1c CONTROL AND DIABETES MEDICATION ADHERENCE AS KEY QUALITY OUTCOME MEASURES

In addition to the health consequences and costs associated with poor glycemic control, glycemic control rates affect health plans' standings on key quality outcome measures. Both HbA1c control and diabetes medication adherence are key quality outcome measures reported by commercial health plans, Medicare Advantage plans, and accountable care organizations (ACOs); performance on these measures can influence revenue. NCQA Health Plan Employer Data and Information Set (HEDIS), the gold standard for health plan quality outcome measures, includes the following comprehensive diabetes care indicators: HbA1C poor control (>9.0%), HbA1c control (<8.0%), and HbA1c control (<7.0%) for selected populations (commercial and Medicaid).[8] NCQA publishes performance reports by individual health plans on these measures, and health plan performance can be used by payers to influence reimbursement rates, plan selection by employer groups, and pay-for-performance arrangements. ACO quality metrics include HbA1c control, which can influence the proportion of savings an ACO can retain.[27]

Finally, the 47 Medicare Advantage Star program measures include the HEDIS measure of HbA1c poor control (>9.0%) and the National Quality Forum measure, "Taking Diabetes Medication as Directed."[28] This measure uses PDC methodology to assess adherence to noninsulin diabetes medication for those patients with diabetes with at least 2 fills of medications across any of the drug classes during the measurement period.[28] For the performance year 2015, 30% of plans had a 5-star rating in measure C15 "Diabetes Care – Blood Sugar Controlled," and 22% of plans had a 5-star rating in D12 "Medication Adherence for Diabetes Medications."[28,29]

ABOUT THIS ANALYSIS

The objective of this report is to provide insights into glycemic control and diabetes medication adherence using commercial claims data and linked HbA1c laboratory data. We defined 3 population cohorts to analyze health insurance claims and HbA1c laboratory data:

1. **Three-year longitudinal analysis:** follows a sample of >4,600 patients with T2DM to identify trends in HbA1c levels and diabetes medication adherence
2. **One-year snapshot analysis:** analyzes a sample of 36,233 patients to assess the correlation between HbA1c levels and costs
3. **Six-month HbA1c episode analysis:** analyzes >191,000 HbA1c episodes for 79,933 members to assess the correlation between HbA1c and medication adherence with consideration of diabetes medication treatment characteristics (see page 18 for HbA1c episode definition)

These analyses offer real-world insights that may supplement currently available evidence regarding the state of glycemic control and diabetes medication adherence among commercially insured members with T2DM.

THREE-YEAR LONGITUDINAL ANALYSIS

SAMPLE SIZE OVERVIEW

The longitudinal analysis followed patients with T2DM from 2012 to 2014 to assess dynamics in HbA1c levels and diabetes medication adherence. Table 2 provides sample sizes. Please see Appendices A, B, and C for detailed descriptions of the data sources, methodology, and diabetes identification codes. In addition, Appendix D includes supplemental data with patient characteristics.

Table 2: Patient Identification and Sample Size for the Longitudinal Analysis

Eligibility Criteria	Members, n
Total number of members with 48 months of eligibility in 2011-2014	8,535,173
Members aged ≥18 years in 2012 and <64 years in 2014	6,164,139
Adult patients with diabetes coded in each year of 2011-2014	213,598
Adult patients with T2DM coded in each year of 2011-2014	186,647
Adult patients with T2DM having an HbA1c test in ≥1 of the years of 2012-2014	12,476
HbA1c CONTROL ANALYSIS	
Adult patients with T2DM having ≥1 HbA1c test in each year of 2012-2014	**4,620**
DIABETES MEDICATION ADHERENCE ANALYSIS	
Adult patients with T2DM having ≥1 HbA1c test and ≥1 diabetes medication prescription claim in each year of 2012-2014	**4,179**

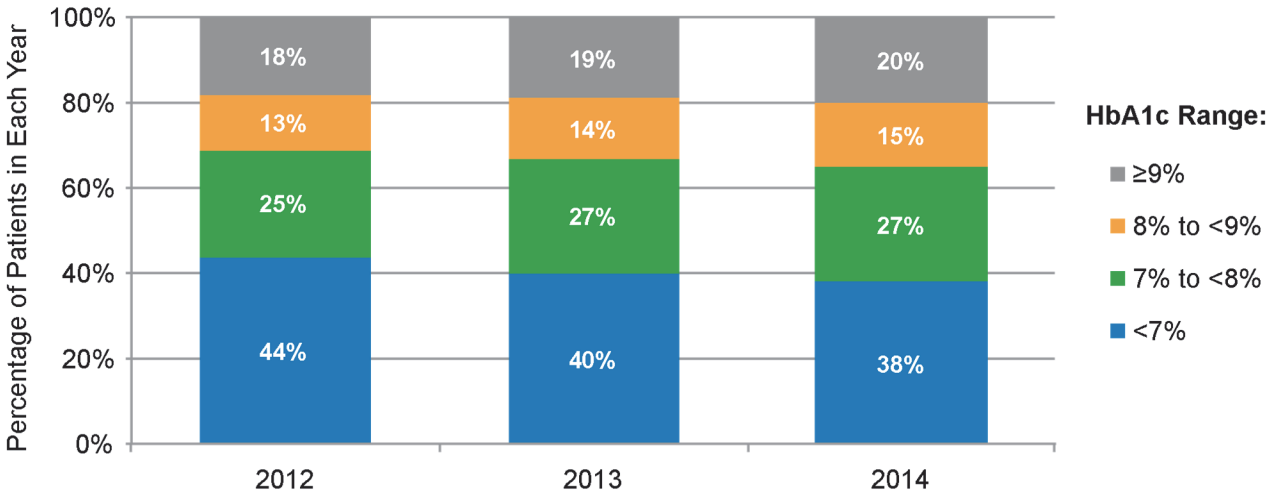
Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

HbA1c CONTROL

TRENDS IN HbA1c LEVELS

Studies describe the progressive nature of T2DM resulting in glucose levels increasing over time that are likely due to declining beta-cell function.[30] This progression typically requires an escalation of drug doses and use of combination diabetes drug therapies or addition of insulin.[31,32] We analyzed the longitudinal population for the trend in HbA1c levels from 2012 to 2014 and identified that the average HbA1c levels increased by 0.16% (from 7.61% in 2012 to 7.76% in 2014, $P<0.001$). We used the last HbA1c level reported in each calendar year, which follows HEDIS annual HbA1c measurement. Figure 1 shows that the proportion of patients with T2DM with HbA1c levels <7% decreased from 44% in 2012 to 38% in 2014 ($P<0.001$), and the proportion of patients with T2DM with HbA1c levels ≥7% increased from 56% in 2012 to 62% in 2014 ($P<0.001$). These findings support the previous findings regarding the increase in HbA1c levels over time and the increasing difficulty of controlling and sustaining HbA1c levels.[31] These findings also support the suboptimal levels of glycemic control reported in the 1999-2010 NHANES analysis.[7]

Figure 1: Patient Distribution by HbA1c Range in 2012, 2013, and 2014 (n=4,620)



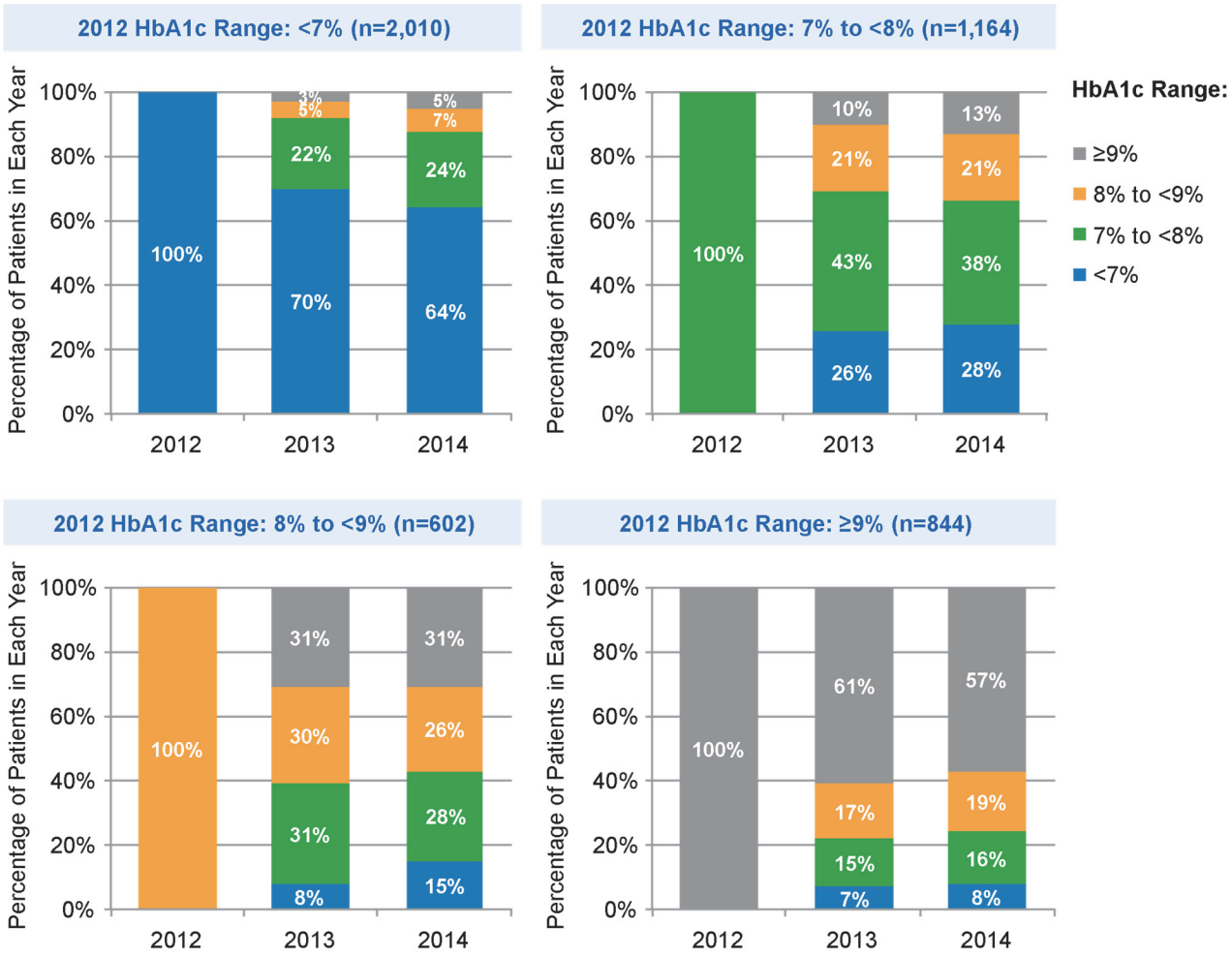
Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

BETWEEN 2012 AND 2014, THE PERCENTAGE OF PATIENTS WITH HbA1c LEVELS <7% DROPPED FROM 44% TO 38%.

To identify further evidence of a decline in glycemic control and the challenge of glycemic control attainment over time, the longitudinal sample was divided into 4 cohorts based on the HbA1c level in 2012 (<7%, 7% to <8%, 8% to <9%, and ≥9%) and followed during 2013 and 2014. Several findings were identified:

- Glycemic control was difficult to attain for patients who started out with suboptimal HbA1c levels
  - For patients with HbA1c levels ≥7% in 2012, less than one-third were able to reach glycemic control by 2014
- The higher the HbA1c level in 2012, the lower the chance of achieving HbA1c control in 2013 and 2014
- For those who achieved glycemic control in 2012, it was difficult to sustain glycemic control in 2013 and 2014
  - For patients with HbA1c levels <7% in 2012, only 64% sustained that level for the subsequent 2 years
  - For patients who started with HbA1c levels between 7% to <8% in 2012, only 66% sustained HbA1c levels of <8%

Figure 2: Annual Changes in Patient Distribution According to the 2012 HbA1c Range



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

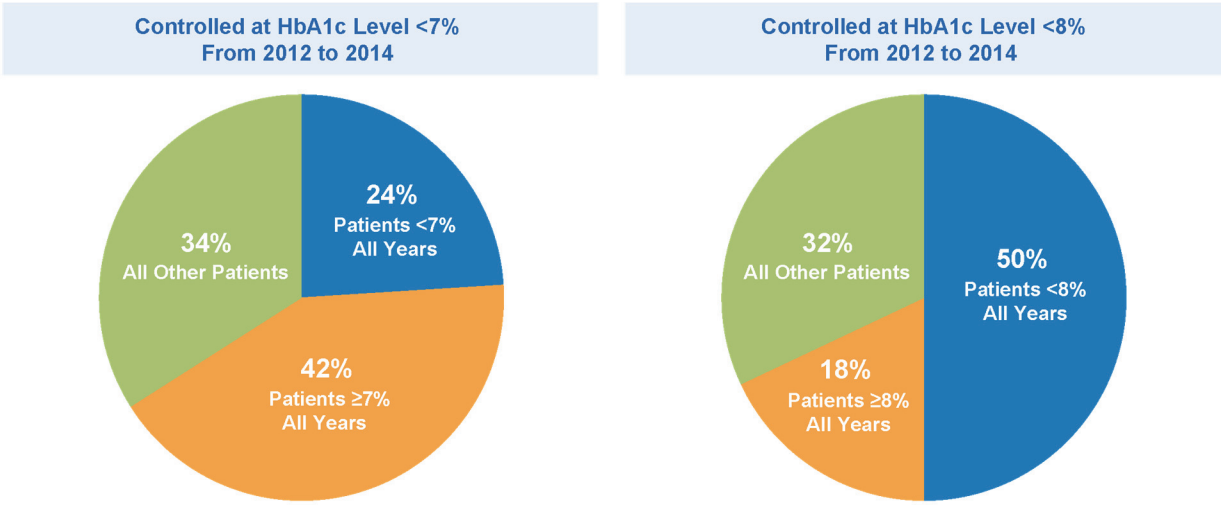
ACHIEVING GLYCEMIC CONTROL AND SUSTAINING IT OVER THE 3 STUDY YEARS WAS A SIGNIFICANT CHALLENGE.

We also identified patients with HbA1c levels <7% and <8% in all 3 study years, which are the HbA1c levels that NCQA's Comprehensive Diabetes Care analyzes as part of the HEDIS measures.[8]

Figure 3 shows only 24% of patients sustained glycemic control <7% in each study year. We also identified that 42% of the patients had HbA1c levels ≥7% in every study year, while the remaining 34% had HbA1c levels <7% only one or two of the study years.

Figure 3 shows only 50% of patients sustained glycemic control <8% in each study year. We also identified that 18% of the patients had HbA1c levels ≥8% in every study year, while the remaining 32% had HbA1c levels <8% in only one or two of the study years.

Figure 3: Proportion of Patients With HbA1c Control From 2012 to 2014 (N=4,620)



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

**OVER THE 3-YEAR PERIOD FROM 2012 TO 2014,
ONLY 24% OF PATIENTS
WERE ABLE TO REACH AND SUSTAIN HbA1c LEVEL <7%.**

HEALTHCARE COSTS AND HbA1c CONTROL

In order to analyze healthcare costs by HbA1c level, we performed a 2014 snapshot analysis of patients with T2DM. We required that patients have ≥1 month of eligibility and ≥1 HbA1c test in 2014 as well as 12 months of eligibility in 2013 to calculate US Department of Health and Human Services-Hierarchical Condition Categories (HHS-HCC) risk scores. We calculated healthcare costs, including pharmacy and medical costs, for a sample of 36,233 patients (see Table 3 below for sample size details).

Table 3: Patient Identification and Sample Size for 2014 Study of HbA1c Association With Cost

Eligibility Criteria	Members, n	Percentage of Total Study Population	Percentage of T2DM
Total number of members with 12 months of eligibility in 2013	22,359,228	100.0%	
Members meeting diabetes criteria in 2013	872,292	3.9%	
Members with T2DM in 2013	804,072	3.6%	100.00%
Members with T2DM and at least 1 month of eligibility in 2014	536,736	2.4%	66.75%
Members aged 18-64 years in 2014	531,528	2.4%	66.10%
Members with at least one HbA1c test in 2014 (study population)	36,233	0.2%	4.51%

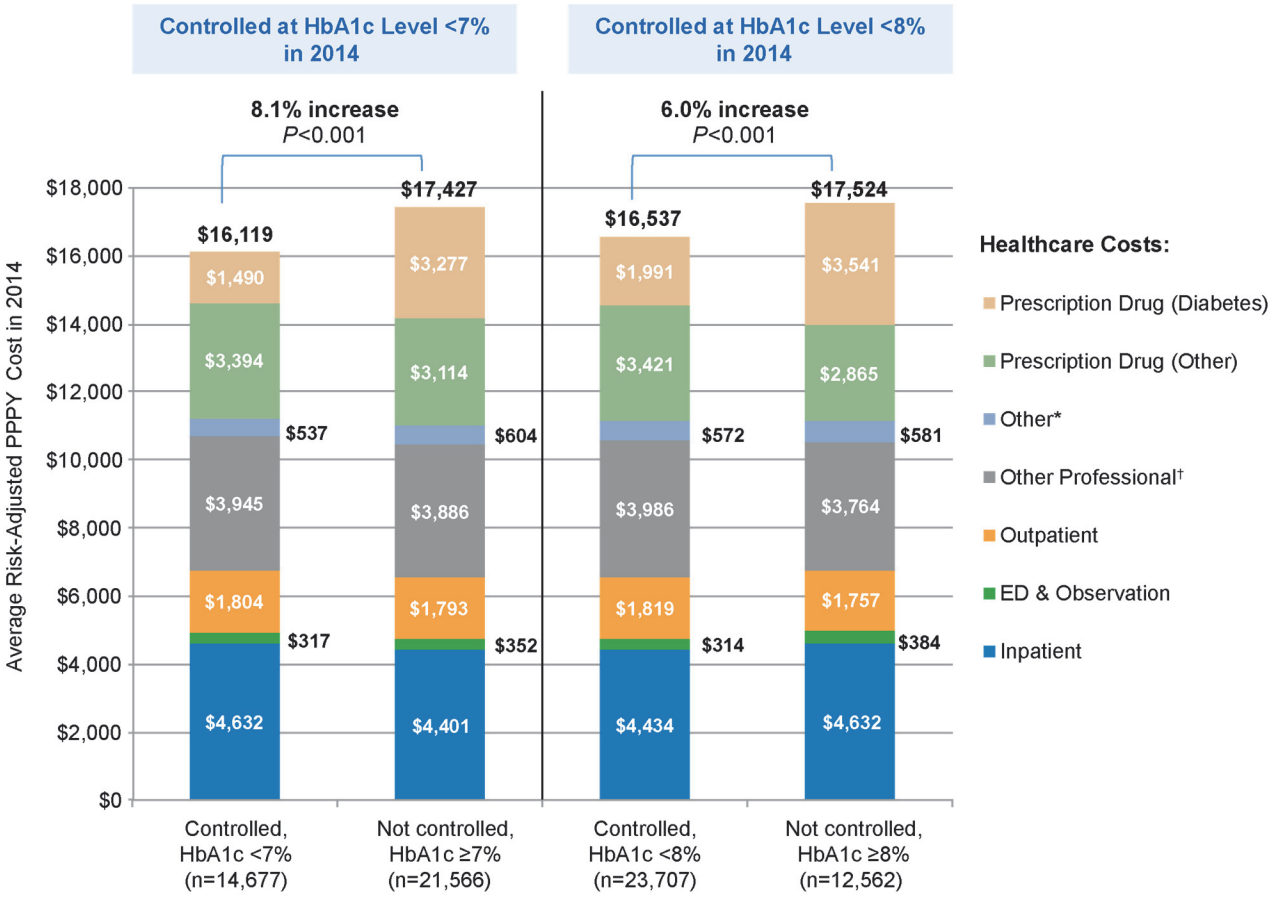
Data Source: Milliman analysis of MarketScan medical and pharmacy data (2013-2014) and HbA1c laboratory data (2014).

To measure the relationship between HbA1c levels and costs among the study population, we normalized costs to account for the variability in reimbursement rates in the MarketScan data. All claims were repriced to a standard Medicare fee schedule. Costs were then adjusted back to the commercial cost level using the ratio between the total estimated Medicare spending and the total observed commercial spend by major service category. Costs reflect allowed costs, which represent the amount paid by the health plan plus patient cost sharing. Costs were reported on a per-patient-per-year (PPPY) basis. To compare the average PPPY costs for individuals in each HbA1c cohort, we risk-adjusted the cohorts using the HHS-HCC scores, which adjusts for differences in age, sex, and comorbidity. Details of the repricing methodology and the HHS-HCC methodology are provided in Appendix B.

We segmented the population by HbA1c levels (<7% vs ≥7% and <8% vs ≥8%) and compared healthcare costs in total as well as by major categories of medical and pharmacy services. We identified statistically significantly lower costs when comparing both HbA1c levels <7% and <8% to HbA1c levels ≥7% and ≥8% on a risk-adjusted basis. Specifically, 2014 healthcare costs for patients with HbA1c levels <7% were 8.1% lower than costs for patients with HbA1c levels ≥7% ($16,119 vs $17,428, respectively; $P<0.001$). There was also a 6% lower cost for patients with HbA1c levels <8% compared with those with HbA1c levels ≥8% ($16,536 vs $17,524, respectively; $P<0.001$).

The cost differences between patients with and without glycemic control were largely attributed to diabetes drug therapy prescription costs, as shown in Figure 4. Ogelsby and colleagues also reported increases in diabetes-related pharmacy costs for patients with inadequate glycemic control.[12] They noted that patients with more progressed disease may require more intensified treatment, which may result in higher pharmacy costs.[12] The findings highlight the challenge of achieving expected value for higher drug spend.

Figure 4: HHS-HCC Risk-Adjusted PPPY Cost by HbA1c Control in 2014 (n=36,233)



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).
*Other cost category includes home care, ambulance, and skilled nursing home.
†Other professional cost category includes all professional claims other than those associated with an inpatient stay, ED or observation unit, or outpatient procedure.

IN 2014, TOTAL HEALTHCARE COSTS FOR PATIENTS WITH HbA1c LEVELS <7% WERE 8.1% LOWER THAN FOR PATIENTS WITH HbA1c LEVELS ≥7%; FOR PATIENTS WITH HbA1c LEVELS <8%, TOTAL HEALTHCARE COSTS WERE 6% LOWER THAN FOR PATIENTS WITH HbA1c LEVELS ≥8%.

DIABETES MEDICATION ADHERENCE

As noted previously, the progressive nature of T2DM and the need for intensification of diabetes medication therapies over time increase the challenge of maintaining glycemic control.[31,32] In addition, adherence to diabetes medication therapies is a significant contributor to maintaining glycemic control. Studies have shown an inverse correlation between adherence with oral diabetes medications and HbA1c levels; however, studies report that medication adherence in diabetes is suboptimal.[15-18]

Using the longitudinal sample of patients with T2DM from our HbA1c trend analysis, we investigated patterns in diabetes medication adherence and identified that diabetes medication adherence was suboptimal and difficult to sustain, similar to what is reported in the literature.

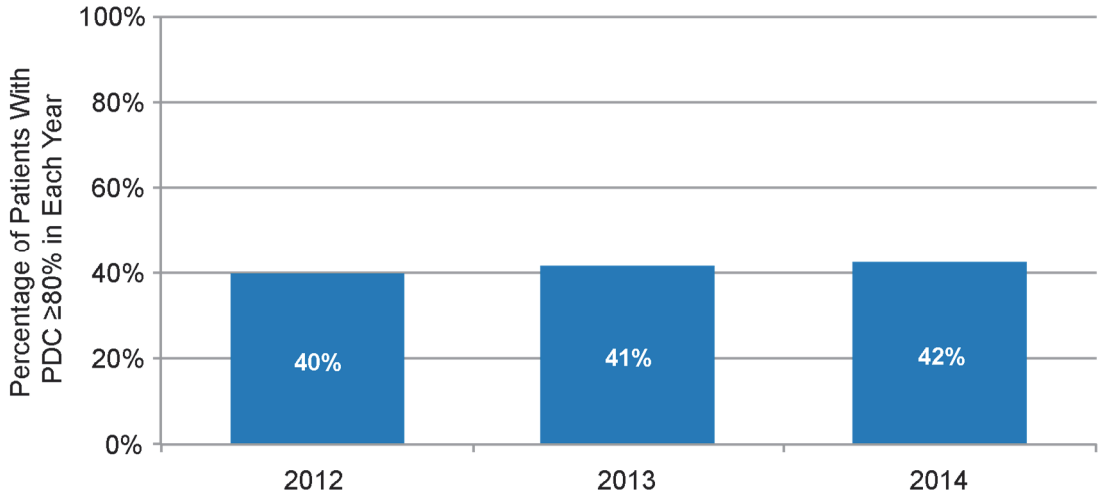
TRENDS IN DIABETES MEDICATION ADHERENCE

Diabetes medication adherence rates for 2012 to 2014 were estimated for the sample of 4,179 patients in the longitudinal analysis with diabetes drug claims. We assigned each diabetes drug claim, by National Drug Code (NDC), to one of 7 diabetes drug classes, including metformin, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, sulfonylurea and meglitinide, glucagon-like peptide 1 (GLP-1) receptor agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, thiazolidinedione, and insulin. Based on the Pharmacy Quality Alliance (PQA) endorsement of the use of PDC rather than MPR as a more accurate and consistent method for measuring adherence from claims data, we used PDC for measuring diabetes drug therapy adherence.[33]

For each patient, PDC was calculated across the 12 months of the designated year by diabetes drug class and then averaged across the drug classes. The 3 months prior to the 12-month PDC measurement period was used to identify prior use of a drug class. If a drug class script was identified within the 3-month prior period, the entire 12 months was considered the denominator for that drug class PDC calculation. If a drug class script was not identified within the 3-month prior period, the first month of the drug class claim in the 2014 12-month PDC calculation period initiated the denominator months for that drug class PDC calculation. A PDC of <80% is considered to be nonadherent. See Appendix B for a detailed description of PDC calculations.

Figure 5 shows that from 2012 to 2014, the proportion of the sample considered adherent increased slightly from 40% to 42% (1.7%, *P*<0.001).

Figure 5: Proportion of Adherent Patients (PDC ≥80%) in 2012, 2013, and 2014 (n=4,179)



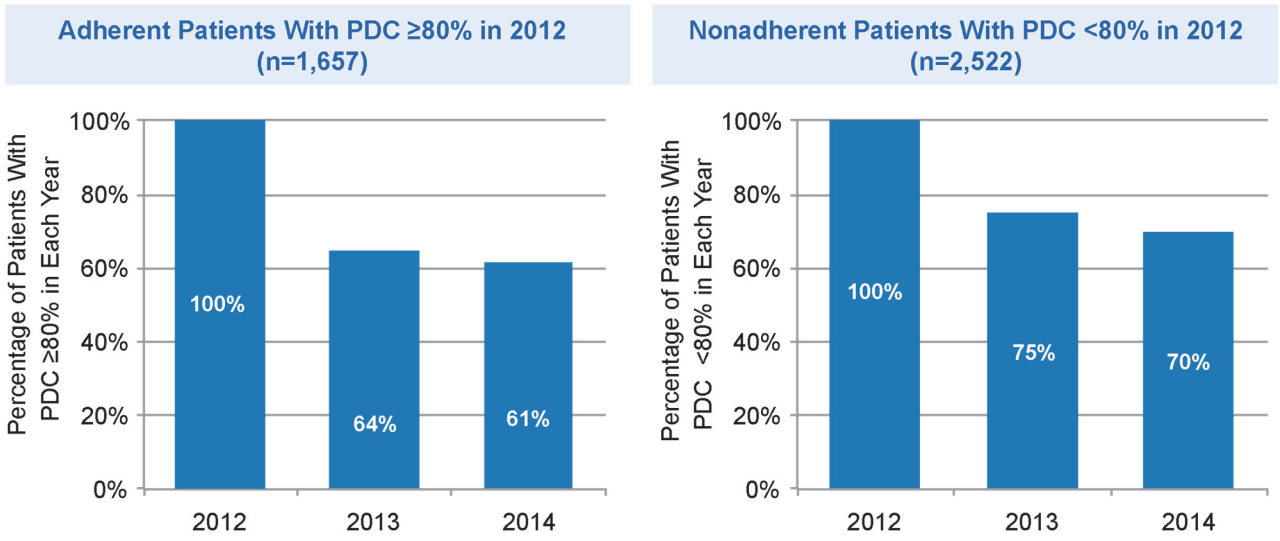
Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

BETWEEN 2012 AND 2014, THE PERCENTAGE OF PATIENTS WHO WERE ADHERENT TO THEIR DIABETES MEDICATION THERAPY (PDC ≥80%) INCREASED SLIGHTLY FROM 40% TO 42%.

Analogous to the HbA1c analysis, the patient sample was divided into 2 cohorts based on the status of diabetes medication adherence in 2012, the first year of analysis.

Figure 6 highlights 2 important findings. First, adherence is challenging to maintain. Among adherent patients in 2012 (PDC ≥80%), only 61% were adherent by 2014. Second, once patients were nonadherent, they were less likely to become adherent. Specifically, among nonadherent patients in 2012 (PDC <80%), 70% were nonadherent in 2014. These findings support previous findings that medication adherence fluctuates and often declines over time.[20]

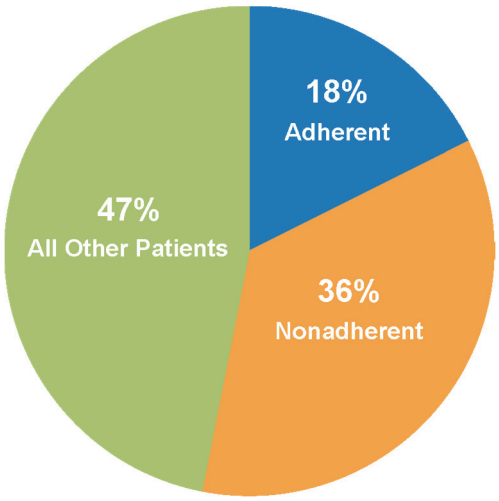
Figure 6: Annual Changes in the Proportion of Adherence in Patients According to the 2012 Adherence Level



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

AMONG PATIENTS WHO WERE NONADHERENT (PDC <80%) IN 2012, 70% OF PATIENTS CONTINUED TO BE NONADHERENT TO THEIR DIABETES MEDICATION THERAPY IN 2014.

Figure 7: Proportion of Adherent Patients in All Years 2012 to 2014 (n=4,179)



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).
Numbers may not add to 100% due to rounding.

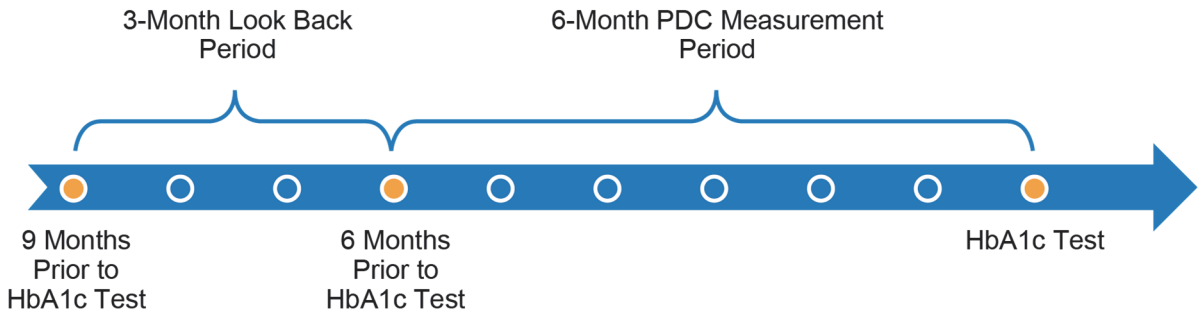
OVER THE 3-YEAR PERIOD FROM 2012 AND 2014, ONLY 18% OF PATIENTS WERE ABLE TO REMAIN ADHERENT TO THEIR DIABETES MEDICATION THERAPY ALL 3 YEARS.

SIX-MONTH HbA1c EPISODE ANALYSIS

To analyze the association between diabetes medication adherence and HbA1c levels, we created "HbA1c episodes" using the 2012 to 2014 MarketScan laboratory value and claims data. HbA1c episodes were triggered by a unique HbA1c testing claim and included the 6 months of claims experience prior to the HbA1c claim, which was the period during which PDC was calculated.

Similar to our longitudinal sample adherence analysis, we assigned each diabetes drug claim, by NDC, to one of 7 diabetes drug classes, including metformin, SGLT-2 inhibitor, sulfonylurea and meglitinide, GLP-1 receptor agonist, DPP-4 inhibitor, thiazolidinedione, and insulin. The 3 months prior to the 6-month PDC measurement period was used as a look-back period to identify prior use of a drug class. If a drug class script was identified in the 3-month prior period, the entire 6 months was considered as the denominator for that drug class PDC calculation. If a drug class script was not identified in the 3-month prior period, the first month of the drug class claim in the 6-month PDC calculation period initiated the denominator for that drug class PDC calculation. Figure 8 provides a schematic of the HbA1c episode designation timeline.

Figure 8: HbA1c Episode Designation



Because HbA1c levels reflect the state of glycemic control during the 3 months preceding the test, we chose the 6-month period to reflect a relevant medication adherence period prior to the HbA1c test.[16] A number of studies have evaluated the correlation between medication adherence and glycemic control in a given year, without consideration of the timing of the drug therapy adherence period and the HbA1c test, which may not adequately reflect the direct impact of medication adherence on HbA1c level.[15-17,34-36]

We identified 191,331 episodes generated by 79,933 patients. Table 4 provides the sample size and HbA1c episode counts. See Appendices A, B, and C for detailed descriptions of the data sources, methodology, and codes. In addition, Appendix D includes supplemental data with patient characteristics.

Table 4: HbA1c Episode Identification and Sample Size

Eligibility Criteria	Patients, n	HbA1c Tests, n
Patients with diabetes in the calendar year of the HbA1c test (2012-2014)	130,657	375,936
Patients with T2DM in the calendar year of the HbA1c test (2012-2014)	125,475	360,487
Patients aged 18-64 years at the time of the HbA1c test	121,314	302,762
Adult patients with T2DM with 9 months of eligibility prior to the HbA1c test	97,079	231,808
HbA1c EPISODE SAMPLE		
Adult patients with T2DM and ≥1 claim for a diabetes medication in the 6-month period prior to the HbA1c test	**79,933**	**191,331**

Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

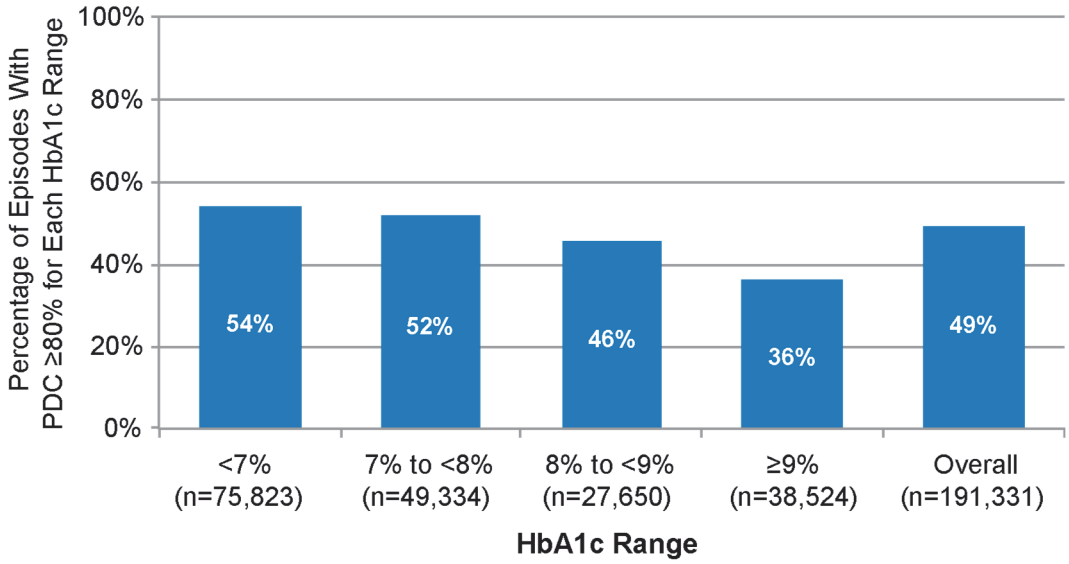
ASSOCIATIONS BETWEEN HbA1c LEVELS AND DIABETES MEDICATION ADHERENCE

DISTRIBUTION OF HbA1c EPISODES BY HbA1c LEVELS

We split episodes by HbA1c ranges and identified that approximately 40% of all episodes had HbA1c levels <7% (n=75,823) and 66% of episodes had HbA1c levels <8% (n=125,157), while 20% of episodes had HbA1c levels ≥9% (n=38,524).

Higher HbA1c levels were associated with lower PDC rates. Specifically, while 54% of episodes with HbA1c levels <7% were considered to be adherent (PDC <80%), for episodes with HbA1c levels ≥9%, only 36% of episodes were considered to be adherent (Figure 9).

Figure 9: Proportion of Adherent Episodes (PDC ≥80%) Across the HbA1c Range

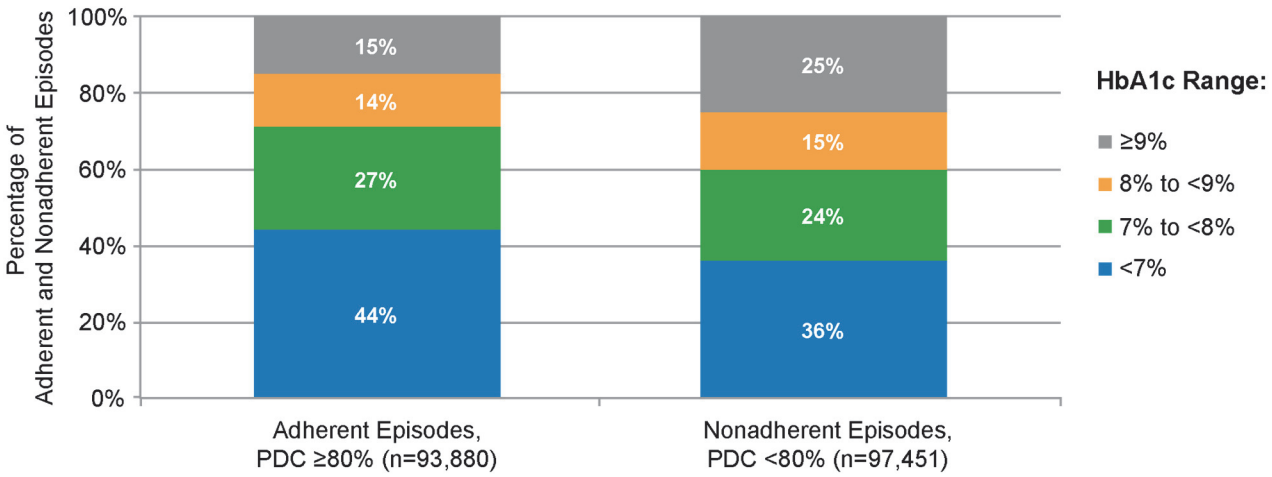


Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

ADHERENT VS NONADHERENT EPISODES

We split episodes into those exhibiting adherence (PDC ≥80%) and those not exhibiting adherence (PDC <80%). For episodes exhibiting adherence, a larger proportion of episodes had HbA1c levels <7% (44%) and <8% (71%) compared with episodes without adherence (36% and 60%, respectively; $P<0.001$). In addition, a smaller proportion of episodes exhibiting adherence had HbA1c levels >9% (15%) compared with episodes without adherence (25%; $P<0.001$).

Figure 10: Comparison of HbA1c Levels Between Adherent and Nonadherent Episodes



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

GREATER PROPORTION OF ADHERENT EPISODES (PDC ≥80%) THAN NONADHERENT EPISODES WERE ASSOCIATED WITH GLYCEMIC CONTROL (44% VS 36% HAD HbA1c LEVELS <7%; 71% VS 60% HAD HbA1c LEVELS <8%).

ROLE OF DIABETES MEDICATION THERAPY CHARACTERISTICS

MODE OF ADMINISTRATION

For each episode, we assigned each diabetes drug claim by NDC to a diabetes drug class, including metformin, SGLT-2 inhibitor, sulfonylurea and meglitinide, GLP-1 receptor agonist, DPP-4 inhibitor, thiazolidinedione, and insulin. Most episodes (79%) had utilization of metformin therapy, 40% had utilization of sulfonylurea and meglitinide therapy, and 29% had utilization of insulin.

We further classified the episodes by the mode of administration:

- Oral-only episodes, during which the medication was any of the above drug classes except for GLP-1 receptor agonist and insulin
- Injectable-only episodes with GLP-1 receptor agonist and/or insulin
- Oral + injectable episodes, during which patients were taking a combination of both oral and injectable diabetes medications

Nearly two-thirds of episodes utilized oral diabetes medications only, 10% utilized injectable therapy only, and 25% of episodes utilized a combination of oral and injectable therapies (Table 5).

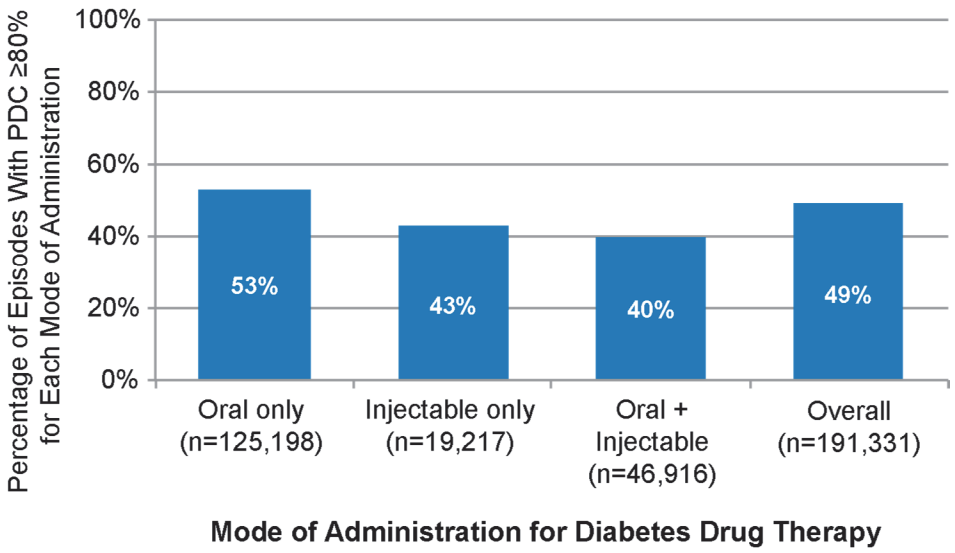
Table 5: Distribution of HbA1c Episodes by the Mode of Administration for Diabetes Treatment (N=191,331 among 79,933 patients)

Mode of Administration for Diabetes Treatment	Number of Episodes, n	Percentage of Episodes
Oral only	125,198	65%
Injectable only	19,217	10%
Oral + injectable	46,916	25%

Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

As noted in prior studies, our analysis illustrated that adherence was lower for injectable-only episodes as well as episodes during which both orals and injectables were used. For oral-only modes of administration, 53% of episodes exhibited adherence vs 43% (*P*<0.001) of injectable only and 40% (*P*<0.001) of oral and injectable (Figure 11). Studies have reported adherence to be lower when the treatment itself is perceived to be more difficult or inconvenient.[37] This is particularly true for insulin, which has been found to be a significant predictor of nonadherence.[38] A review of studies on diabetes medication adherence found monotherapy regimens had higher adherence than polytherapy regimens, once-daily regimens had higher adherence than twice-daily regimens, and adherence rates were lower for insulin than oral diabetes drugs.[39]

Figure 11: Percent of Episodes Exhibiting Adherence (PDC ≥80%) by Mode of Administration for Diabetes Drug Therapy



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

FOR EPISODES WITH MORE COMPLEX DIABETES MEDICATION REGIMENS, A HIGHER PERCENTAGE OF EPISODES EXHIBITED NONADHERENCE (PDC <80%).

IMPACT OF DIABETES MEDICATION ADHERENCE ON HbA1c LEVELS

EFFECT OF A 10% INCREASE IN PDC

Using the HbA1c and PDC data for each episode, we performed a multiple linear regression analysis to calculate the effect of a 10% increase in PDC on a patient's HbA1c laboratory test result. We analyzed this relationship for the 3 different modes of administration categories (oral only, injectable only, and oral + injectable). For each regression, we included age and sex in our models to account for any potential confounding effects. We found that for every 10% increase in PDC, HbA1c level decreased by approximately 0.12% across diabetes therapies, as shown in Table 6. Similar impact was observed for episodes using oral or injectable therapy; the negative correlation was greatest for episodes using a complex regimen of oral and injectable therapy (10% increase in PDC was associated with a 0.17% decrease in HbA1c, significant with $P<0.001$).

Table 6: Change in HbA1c Level With Every 10% Increase in PDC

Diabetes Treatment Characteristics	HbA1c Change
Any diabetes therapy	-0.115
By Mode of Administration	
Oral only	-0.089
Injectable only	-0.087
Oral + injectable	-0.174

Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

EVERY 10% INCREASE IN PDC WAS ASSOCIATED WITH A 0.12% DECREASE IN HbA1c LEVEL.

Similar correlations between diabetes medication adherence and glycemic control have been reported in other studies.[15,34] In 2002, Schectman and colleagues reported that for each 10% increment in diabetes medication adherence, HbA1c level decreased by 0.16%.[34] Rozenfeld and colleagues identified very similar results reporting that each 10% increase in diabetes medication adherence was associated with a 0.1% decrease in HbA1c level.[15] As noted in the background section, landmark studies report a higher risk of diabetes complications with poor glycemic control.

LIMITATIONS

There are several limitations associated with retrospective administrative data to be considered in the review of this analysis:

- HbA1c laboratory data were available for approximately 7% of the T2DM population in our claims database, and the population with HbA1c laboratory values may not be representative of all T2DM commercially insured patients
- A small proportion of the HbA1c laboratory values (<5%) were removed from our analysis; we excluded all tests with an HbA1c value from the analysis that were <4% or >20% or appeared to be invalid
- When comparing costs, although we risk-adjusted using the HHS-HCC risk scores cohorts with HbA1c levels <7% and <8% compared with those with HbA1c levels ≥7% and ≥8%, we cannot adjust for the length of time the individual has had T2DM, which is an important influence on cost
- We used standard metrics to measure adherence, but these metrics measure prescription dispensing, not whether the patient actually takes the medication. This is an inherent limitation with claim-based adherence studies
- Measuring adherence with insulin is limited by intermittent dose titration, which may lead to dose adjustment. Therefore, the insulin adherence figures are likely subject to less certainty than the figures for oral medications
- Adherence is affected by socio-economic circumstances, which cannot be identified in claims data. Therefore, our findings should be seen as averages for the commercially insured population and subpopulations are likely to have different results
- Many factors beyond HbA1c strongly influence diabetes outcomes, including diet, exercise, cholesterol levels and blood pressure. We could not account for these factors

Despite these limitations that are inherent in claims-based analyses, our findings are consistent with findings reported in the literature regarding suboptimal HbA1c control and diabetes medication adherence among patients with T2DM.

KEY FINDINGS RELEVANT TO PAYERS

Our analysis supports prior studies that note glycemic control and diabetes medication adherence in patients with T2DM is suboptimal. The following table links relatively uncontroversial statements about diabetes management to the findings in our real-world data analysis using MarketScan laboratory and medical and pharmacy claims data (2012-2014).

Potential Unmet Need	Relevant Findings

Sustaining diabetes medication adherence and glycemic control is a significant challenge	• Few patients were able to maintain adherence to their diabetes medications and sustain glycemic control in every study year between 2012 and 2014
	  ○ Only 18% of patients maintained adherence (PDC ≥80%) for all 3 years
	  ○ Only 24% of patients had HbA1c levels <7% and 50% of patients had HbA1c levels <8% for all 3 years
	• Past diabetes medication adherence and level of glycemic control served as good indicators of future medication adherence and glycemic control rates
	  ○ Only 30% of nonadherent patients in 2012 became adherent by 2014
	  ○ Less than 28% of patients with HbA1c levels ≥7% and less than 8% of patients with HbA1c levels ≥9% in 2012 lowered their HbA1c level to <7% by 2014

Poor diabetes medication adherence has a strong association with higher HbA1c levels and higher HbA1c levels are associated with higher costs	• Adherent behavior was more likely correlated with glycemic control
	  ○ 44% of adherent episodes vs 36% of nonadherent episodes had HbA1c levels <7%
	  ○ 71% of adherent episodes vs 60% of nonadherent episodes had HbA1c levels <8%
	• Adherence was inversely correlated with HbA1c levels
	  ○ For the study population, every 10% increase in PDC was associated with a 0.12% decrease in HbA1c level
	• Inadequate glycemic control in 2014 was associated with significantly higher risk-adjusted per-patient total healthcare costs in 2014
	  ○ 8% higher total cost for HbA1c levels ≥7% vs <7% ($17,428 vs $16,119)
	  ○ 6% higher total cost for HbA1c levels ≥8% vs <8% ($17,524 vs $16,536)
	• Diabetes prescription drug spending was the primary driver of the cost difference between the cohorts with and without glycemic control, highlighting the challenge of achieving expected value for higher drug spend
	  ○ 120% higher diabetes-related pharmacy cost for HbA1c levels ≥7% vs <7% ($3,277 vs $1,490)
	  ○ 78% higher diabetes-related pharmacy cost for HbA1c levels ≥8% vs <8% ($3,541 vs $1,991)

These findings highlight the need for evaluating the financial and population health outcomes of diabetes medications and delivery systems that can improve adherence and HbA1c control.

APPENDIX A: DATA SOURCES

Truven Health MarketScan Research Database (MarketScan): MarketScan contains all paid claims generated by 15 million to 50 million commercially insured lives annually (depending on the year of data). The MarketScan database represents the inpatient and outpatient healthcare service use of individuals nationwide who are covered by the benefit plans of large employers, health plans, the government, and public organizations. The data include diagnosis codes, procedure codes, diagnosis-related group (DRG) codes, and NDC codes, along with site-of-service information and the amounts paid by commercial insurers. The MarketScan database links paid claims and encounter data to detailed patient information across sites and to types of providers. Patient identifiers are consistent over time, allowing for longitudinal studies. The annual medical database includes private sector health data from approximately 100 payers. MarketScan data from 2011 to 2014 were used for the analyses in this paper.

Truven Health MarketScan laboratory value database from 2012 to 2014: The HbA1c laboratory data values from the MarketScan laboratory database were used. The members represented in the laboratory database have linked IDs with the MarketScan medical and pharmacy data set. The members with laboratory data are a subset of the total MarketScan database.

Medi-Span Database: The Medi-Span database from 2011 to 2014 was used to identify diabetes drug NDCs. Medi-Span provides prescription and over-the-counter drug product data, including drug name, therapeutic class, dosage form, NDC, and Generic Product Identifier.

APPENDIX B: METHODOLOGY

PATIENT IDENTIFICATION

For each of the study years, our MarketScan denominator population met the following standard inclusion criteria:

- Not enrolled in a capitated plan in all months of eligibility
- Prescription drug coverage for all months of medical benefit eligibility
- Both employees and dependents

Members with diabetes were identified using standard HEDIS criteria, which require that the member meet any of the following criteria:

- At least 2 outpatient visits, observation visits, or nonacute inpatient encounters on different dates of service with a diagnosis of diabetes. Visit type need not be the same for the 2 visits
- At least 1 acute inpatient encounter with a diagnosis of diabetes
- At least 1 ED visit with a diagnosis of diabetes
- 1 or more diabetes drug claims
  - We used the HEDIS diabetes drug list for NDC codes that identify diabetes, available at: https://www.ncqa.org/HEDISQualityMeasurement/HEDISMeasures/HEDIS2015/HEDIS2015NDCLicense/HEDIS2015FinalNDCLists.aspx

Members with T2DM were identified using the following criteria:

- Meets HEDIS diabetes definition
- Does not meet the following type 1 diabetes definition:
  - Having a fifth digit for 250.xx coded at least 1 time, and the fifth digit is always coded with 1 or 3, or
  - Having a fifth digit for 250.xx coded at least 1 time, and the fifth digit is 1 or 3 most of the time

HbA1c DATA

HbA1c laboratory values were excluded if

- Test results were outside of acceptable ranges of HbA1c levels 4% to 20% of total hemoglobin
- There were duplicate tests, defined as same day and result for the same patient
- Tests were performed within 30 days of each other for the same patient

For an HbA1c episode (see page 18 for HbA1c episode definition) to be included in our analysis, we required

- A credible HbA1c value (between 4% and 20%)
- The member with the HbA1c level to be aged between 18 and 64 years at the time of the HbA1c test
- 9 months of eligibility for the member prior to the HbA1c test
  - 6-month period prior to the HbA1c test date for PDC calculation
  - 3 months prior to the 6-month adherence period to identify prior use of diabetes drug classes that impacted the characterization of drug class initiation in the adherence period
- HbA1c tests that were more than 30 days apart for an individual initiated a unique HbA1c episode
  - HbA1c tests for an individual that were within 30 days of each other resulted in only the last of the HbA1c tests being considered a unique HbA1c episode
  - The other tests did not qualify as an HbA1c episode
- ≥1 claim for a diabetes drug in the 6 months prior to the HbA1c test
- Members could contribute multiple HbA1c episodes over the 3-year study period

DIABETES MEDICATION ADHERENCE

Diabetes medications were categorized into metformin, sulfonylureas and meglitinides, thiazolidinediones, DPP-4s, SGLT-2s, GLP-1s, and insulin using the Medi-Span 2012 to 2014 NDC lists with drug descriptions. The NDC lists are available on request.

PDC was calculated by drug class using the standard PDC calculation as defined by Nau:

- "The PDC calculation is based on the fill dates and days supply for each fill of a prescription; however, it differs from the MPR in that the PDC is not a simple summation of the days supply. The denominator for the PDC (at the patient-level) is the number of days between the first fill of the medication during the measurement period and the end of the measurement period. For example, if the measurement period is a calendar year (365 days), and if the patient's first fill of the medication is on day 10 of the year, then the denominator period is 355 days (365 – 10 = 355). This means that a patient who discontinues the medication during the measurement period will still be tracked through the end of the year, and thus the non-persistence is accounted for in the PDC
- The patient-level numerator for the PDC is the number of days covered by the prescription fills during the denominator period. Rather than summing the days supply, the analyst should create time arrays (or vectors) to reflect the dates that were encompassed by each fill. So, a 30-day supply of medication obtained on March 1st would create an array that covers March 1-30. Once the arrays are created for each fill during the denominator period, the analyst can then determine how many of the days in the denominator period were covered by at least 1 array. This method is described in detail, along with SAS program codes, by Leslie (2007). PQA also recommends the method described by Leslie for adjusting the start date of each array when the patient has overlapping arrays for an identical (e.g., generically equivalent) medication. This adjustment is based on the premise that when a patient refills a prescription before the preceding medication supply was exhausted (i.e., early refill), that the patient finishes the supply for the preceding fill before starting the new supply. However, when patients are taking multiple concurrent medications within a broad class (e.g., a class defined as all oral diabetes drugs), then the arrays would not be adjusted since the patient was taking the medications concurrently. Therefore, the PDC would reflect whether the patient had at least one of those drugs available on a particular day (i.e., if they are taking metformin and glipizide on the same day, the day is only counted once as a covered day). This approach is similar to the 'at least 1' method for PDC suggested by Choudhry and colleagues (2009)."[33]

COST ANALYSIS

HHS-HCC scoring:
To adjust for differences in age, sex, and comorbidity in our cost comparison analysis of individuals below and above HbA1c levels, we used a federally certified risk-adjustment methodology developed by the HHS. The methodology uses an HCC method to categorize diagnosis codes by severity for calculating metallic tier risk scores (ie, platinum, gold, silver, bronze, and catastrophic). The risk scores are intended to predict cost in the subsequent year—a higher risk score is associated with higher costs. Based on the HHS-HCC gold metallic tier risk score differences, we adjusted the comparison cohorts.

Medicare repricing of claims:
Because of regional and payer-specific variation in reimbursement rates in the commercial population, we standardized the costs found in the MarketScan claims data. The cost standardization is intended to remove the influence of regional and provider variation in contracted rates for the same service. Using the Milliman Medicare Repricer software, we calculated the nationwide average Medicare-allowed amount for each service. The Milliman Medicare Repricer uses a combination of Medicare Severity Diagnosis-Related Group (MSDRG) weights, Medicare's physician resource-based relative value scale (RBRVS), and many other publicly available fee schedules to assign the allowed costs of each claim. Costs were then adjusted back to commercial levels using the ratio between Medicare and commercial reimbursement by major service category.

APPENDIX C: CODING DETAILS

Qualifying claims for identification of diabetes included acute inpatient, observation, nonacute inpatient, ED, or outpatient site of service noted in the table below.

Claim Type	*CPT* Code	Revenue Codes
Outpatient	99201-99205, 99211-99215, 99241-99245, 99341-99345, 99347-99350, 99381-99387, 99391-99397, 99401-99404, 99411, 99412, 99420, 99429, 99455, 99456, G0402, G0438, G0439, G0463, T1015	0510-0517, 0519-0523, 0526-0529, 0982, 0983
Nonacute inpatient	99304-99310, 99315, 99316, 99318, 99324-99328, 99334-99337	0118, 0128, 0138, 0148, 0158, 0190-0194, 0199, 0524, 0525, 0550-0552, 0559, 0660-0663,0669
Acute inpatient	99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291, 99468, 99469, 99471, 99472, 99475-99480	010x, 0110-0115, 0117, 0119-0125, 0127, 0129-0135, 0137, 0139-0145, 0147, 0149-0155, 0157, 0159-0162, 0164, 0166-0175, 0179, 0200-0204, 0206-0214, 0219, 0720-0724, 0729, 0987
Observation	99217-99220	
ED	99281-99285	0450-0452, 0456, 0459, 0981

Diabetes *International Classification of Diseases, Ninth Revision* (*ICD-9*) Diagnosis Codes

Code	Code Description
250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
250.01	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
250.03	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
250.10	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
250.21	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled
250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled
250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.31	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
250.32	Diabetes with other coma, type II or unspecified type, uncontrolled
250.33	Diabetes with other coma, type I [juvenile type], uncontrolled
250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
250.41	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
250.43	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
250.51	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
250.53	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled

Code	Code Description
250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
250.61	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
250.63	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled
250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
250.71	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled
250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
250.73	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
250.80	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
250.81	Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled
250.82	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
250.83	Diabetes with other specified manifestations, type I [juvenile type], uncontrolled
250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
250.91	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
250.92	Diabetes with unspecified complication, type II or unspecified type, uncontrolled
250.93	Diabetes with unspecified complication, type I [juvenile type], uncontrolled
357.2x	Polyneuropathy in diabetes
366.41	Diabetic cataract
362.0x	Diabetic retinopathy

APPENDIX D: SUPPLEMENTAL DATA

THREE-YEAR LONGITUDINAL ANALYSIS

Table D1: Patient Characteristics in the 3-year Longitudinal Analysis

Characteristics	Proportion of the Population in 2012				
	All (n=4,620)	HbA1c <7% (n=2,010)	HbA1c 7% to <8% (n=1,164)	HbA1c 8% to <9% (n=602)	HbA1c ≥9% (n=844)
Total Population	100.0%	43.5%	25.2%	13.0%	18.3%
By Sex					
Male	57.4%	55.8%	58.7%	60.1%	57.7%
Female	42.6%	44.2%	41.3%	39.9%	42.3%
By Age, years					
18-24	0.2%	0.1%	0.0%	0.2%	0.4%
25-34	1.6%	1.7%	0.9%	1.7%	2.5%
35-44	10.3%	8.8%	9.3%	11.5%	14.6%
45-54	41.3%	39.7%	39.3%	46.0%	44.4%
55-64	46.6%	49.7%	50.5%	40.7%	38.2%
By Average HHS-HCC Risk Score Range*					
Average HCC Risk Score	4.0	4.1	3.9	4.0	4.0
By Comorbidity					
Hypertension	68.4%	68.9%	68.6%	66.4%	68.1%
Hyperlipidemia	64.2%	65.2%	62.8%	65.1%	63.2%
Hypoglycemia	1.5%	1.0%	1.8%	1.3%	2.6%

Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).
***Note:** Average risk score for commercial population with 3 years of enrollment is 1.35.

SIX-MONTH EPISODE ANALYSIS

Table D2: Distribution of Patients in the 6-month Episode Analysis

Attributes	Number of Patients, n	Percentage of Patients
Total patient population (191,331 episodes)	79,933	100%
By Contribution Year		
From 2012 (61,798 episodes)	35,772	45%
From 2013 (64,591 episodes)	38,500	48%
From 2014 (64,942 episodes)	36,842	46%
By Number of Episodes		
1 episode	33,972	43%
2 episodes	18,332	23%
3 episodes	11,597	15%
4 episodes	6710	8%
≥5 episodes	9322	12%

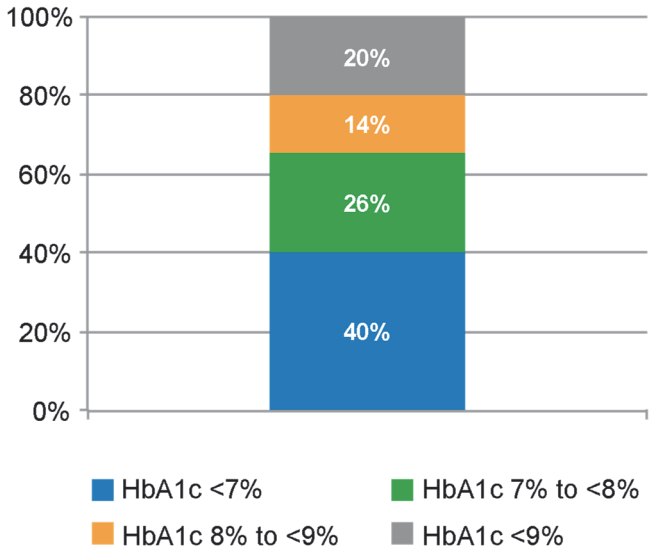
Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014).

Table D3: Patient Characteristics in the 6-month Episode Analysis

Characteristics	Proportion of the Population Based on the First HbA1c Result				
	All (n=79,933)	HbA1c <7% (n=32,132)	HbA1c 7% to <8% (n=18,862)	HbA1c 8% to <9% (n=10,964)	HbA1c ≥9% (n=17,975)
Total Population	100.0%	40.2%	23.6%	13.7%	22.5%
By Sex					
Male	54.4%	51.0%	55.7%	60.1%	57.1%
Female	45.6%	49.0%	44.3%	39.9%	42.9%
By Age, years					
18-24	0.6%	0.5%	0.3%	57.8%	1.0%
25-34	2.9%	3.1%	2.0%	42.2%	3.6%
35-44	12.9%	11.9%	10.9%	57.8%	16.9%
45-54	36.1%	34.1%	35.2%	42.2%	39.6%
55-64	47.6%	50.5%	51.7%	57.8%	38.9%
By Eligibility Months					
30-36	38.0%	39.4%	37.2%	36.4%	37.4%
24-29	38.9%	37.5%	39.4%	39.8%	40.5%
18-23	6.5%	6.3%	6.6%	6.7%	6.8%
12-17	13.9%	14.3%	14.2%	14.5%	12.6%
7-11	1.8%	1.7%	1.7%	1.8%	1.9%
1-6	0.8%	0.8%	0.9%	0.8%	0.8%

Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014).

Figure D1: Distribution of Episodes by HbA1c Level



Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014) and HbA1c laboratory data (2012-2014).

Table D4: Distribution of HbA1c Episodes by the Mode of Administration for Diabetes Treatment

Diabetes Medication Class	Oral Only (n=125,198)	Injectable Only (n=19,217)	Oral + Injectable (n=46,916)	Total (n=191,331)
Metformin	88.1%	N/A	85.8%	78.7%
GLP-1 receptor agonist	0.0%	13.8%	31.1%	9.0%
SGLT-2 inhibitor	1.6%	N/A	4.0%	2.0%
DPP-4 inhibitor	26.7%	N/A	23.6%	23.2%
Sulfonylurea & meglitinide	43.9%	N/A	44.8%	39.7%
Thiazolidinedione	10.5%	N/A	12.8%	10.0%
Insulin	N/A	92.6%	80.1%	28.9%

Data Source: Milliman analysis of MarketScan medical and pharmacy data (2011-2014).

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