Treatment Patterns, Treatment Outcomes, and Health Care Costs Before and After Humulin R U-500 Initiation or Device Change among Patients with Type 2 Diabetes in the United States

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Content

Background

- Diabetes is a serious and growing public health concern, ~ 9.4% (30.3 million) of the US population had diabetes in 2015 and the prevalence of those who had diagnosed diabetes was estimated to be 7.2% (23.1 million).[1]
- The consistent rise in diabetes prevalence may be attributed to a corresponding rise in the prevalence of overweight and obesity diagnoses; epidemiological studies have shown strong positive associations between adiposity measures including body mass index (BMI), waist circumference, and diabetes.[2,3,4,5]
- National Health and Nutrition Examination Surveys (NHANES) data shows an increased prevalence of obesity over the period of 2007-2008 and 2015-2016.[6]
- The 2013-2014 NHANES survey results further confirmed the increased prevalence of obesity, along with a persistent rise in the type 2 diabetes mellitus (T2DM) since 1999-2000.[7]
- Despite major breakthrough in understanding the relationship between insulin resistance and both obesity and T2DM, the underlying mechanisms remain puzzled.[8]
- Together with an obesity epidemic, the process of reducing the national health care burden from diabetes is impeded, and such burden is more revealed among patients with poorly controlled blood glucose level.[9]
- It is often challenging to achieve desired blood glucose levels among T2DM patients with severe insulin resistance, using 100 units/mL (U-100) insulin,[10] and patients often require 4-8 daily injections to meet their high insulin requirements; these repeated injections may lead to a painful injection site reaction, which can adversely affect adherence to the insulin replacement therapy.[11]

Background

- Concentrated insulin products were designed to help meet the insulin requirements among patients with increased insulin resistance. However, the use of these products may be associated with an increased risk of severe hypoglycemia, which may be attributed to insulin stacking resulted from an unanticipated prolonged duration of effect from these products.[12]
- U-500 regular insulin (U-500R) is a five-fold concentrated form of insulin) indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day, and it has unique prandial/basal actions and thus can be used as insulin monotherapy.[13,14,15]
- Previous study showed a 10% reduction of recommended dose of U-500R insulin (>180 units) is justifiable to define the patient population that is compliant to FDA label for U-500R.[16]
- In the real-world setting, U-500R (vial) has been shown to improve glycated hemoglobin (HbA1c) levels among patients with T2DM.[15]
- Previous study also showed that U-500R is associated with lower health care costs and better adherence than U-100 users prescribed a similar dose.[17, 18]
- Currently, there was limited evidence regarding the real-world treatment patterns, compliance, outcomes, and economic burdens with U-500R among U-500R initiators and those who switched from U-500R syringe to Kwikpen.
- Additionally, given that physicians have hesitation in using U-500R with their elderly patients due to the highly concentrated nature of U-500R, exploring the outcomes among elderly population became significant to fully understand the use of U-500R.
- Furthermore, understanding of U-500R also needs to be developed within those who utilized U-500R in the manner that was consistent with FDA label (>180 units) vs. those who did not utilize U-500R consistent with the FDA label (<200 units).

Objectives

➢ Main study

- **Primary Objective 1:** Evaluate the treatment patterns including observed total daily dose [TDD] in claims, adherence, number of fills, claim gaps, persistence and concomitant medication use before and after U-500R initiation among T2DM patients.
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers. Similarly the analysis was repeated in the elderly any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators
- **Primary Objective 2**: Evaluate the HbA1c level before and after U-500R initiation among T2DM patients
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers. Similarly the analysis was repeated in the elderly any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators
- **Secondary Objective 2a**: Evaluate the hypoglycemia before and after U-500R initiation among T2DM patients
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers. Similarly the analysis was repeated in the elderly any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators
- **Primary Objective 3**: Evaluate out-of-pocket (OOP) pharmacy costs and total health care costs before and after U-500R initiation among non-elderly T2DM patients
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers.

Objectives

➢ **<u>High Dose U-500R initiators (TDD>180 units before and after U-500R initiation and on U-500R monotherapy Study)</u>**

- **Primary Objective 1:** Evaluate the treatment patterns including observed TDD in claims, adherence, number of fills, claim gaps, persistence and concomitant medication use among T2DM patients before and after high-dose U-500R initiation.
  - ❖ The analysis was performed separately in the high-dose any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers.
  - ❖ Similarly the analysis was repeated separately in the high-dose elderly U-500R initiators as well as in U-500R initiators with TDD 201-300 units/day in the post-index
- **Primary Objective 2**: Evaluate the HbA1c level before and after high-dose U-500R initiation among T2DM patients
  - ❖ The analysis was performed separately in the high-dose any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers.
  - ❖ Similarly the analysis was repeated separately in the high-dose elderly U-500R initiators as well as in U-500R initiators with TDD 201-300 units/day in the post-index
- **Secondary Objective 2a**: Evaluate the hypoglycemia before and after high dose U-500R initiation among T2DM patients
  - ❖ The analysis was performed separately in the high-dose any U-500R initiators, U-500R syringe initiators, U-500R Kwikpen initiators and U-500R device switchers.
  - ❖ Similarly the analysis was repeated separately in the high-dose elderly U-500R initiators as well as in U-500R initiators with TDD 201-300 units/day in the post-index
- **Exploratory Objective**: Evaluate out-of-pocket (OOP) pharmacy costs before and after high dose U-500R initiation among non-elderly T2DM patients
  - ❖ The analysis was performed separately in the high-dose any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators

Objectives

➢ **<u>Low Dose U-500R initiators (excluded patients with TDD>200 units before and after U-500R initiation)</u>**

- **Primary Objective 1:** Evaluate the treatment patterns including TDD in claims, adherence, number of fills, claim gaps, persistence and concomitant medication use among T2DM patients before and after low-dose U-500R initiation.
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators with TDD≤200 units/day before initiation and TDD>200 units/day after initiation
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators with TDD≤200 units/day before and after initiation
- **Primary Objective 2**: Evaluate the HbA1c level before and after low-dose U-500R initiation among T2DM patients
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators with TDD≤200 units/day before initiation and TDD>200 units/day after initiation
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators with TDD≤200 units/day before and after initiation
- **Secondary Objective 2a**: Evaluate the hypoglycemia before and after low-dose U-500R initiation among T2DM patients
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators with TDD≤200 units/day before initiation and TDD>200 units/day after initiation
  - ❖ The analysis was performed separately in the any U-500R initiators, U-500R syringe initiators, and U-500R Kwikpen initiators with TDD≤200 units/day before and after initiation

Data Source

- **Veterans Health Administration (VHA) Data**
  - National administrative database providing information on the services used by veterans across the country.
  - Largest integrated health care system in the United States providing care to >9 million veterans in various facilities including:
    - 153 medical centers,
    - 136 nursing homes, and
    - 882 ambulatory and community-based outpatient clinics
  - Allows for longitudinal tracking, capturing full episodes of care in the veteran population.
  - Important resource for understanding patterns of care and associated utilization as well as costs of inpatient, outpatient and pharmacy use by large, predominantly elderly male population.
  - The availability of clinical data including the weight, BMI and HbA1c was an added advantage which are essential to get a complete picture of the T2DM patients on U-500R initiators
  - Additionally, high VHA subsidization allowed for de facto cost-neutrality that helped remove cost as a confounder

Data Source

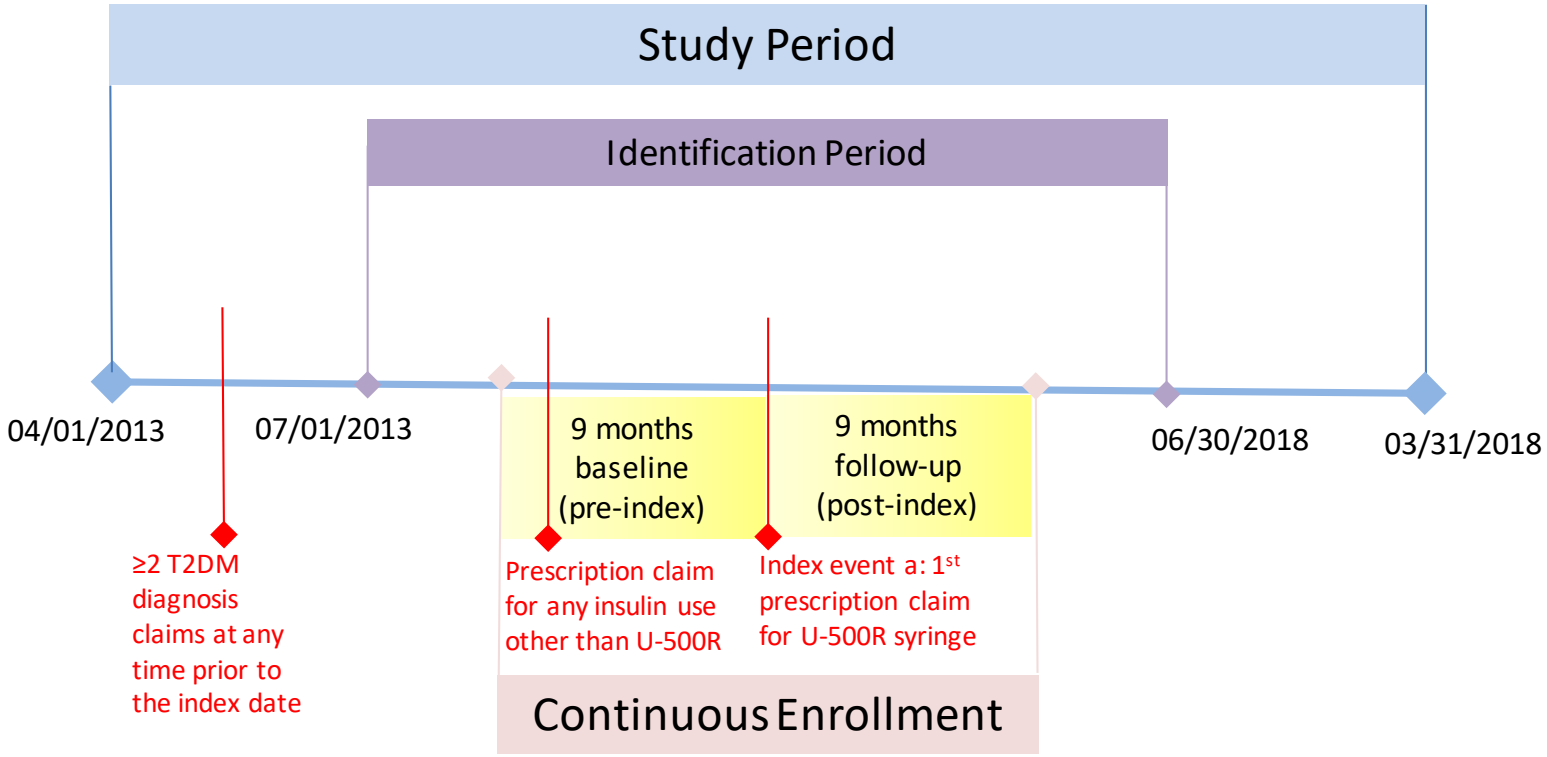
- **Truven MarketScan Claims Database**
  - The MarketScan® claims databases offer the largest convenience sample available in proprietary databases, with 69 million unique patients since 1996.
  - In the most recent data year, MarketScan® claims databases contain data on 29 million covered lives.
  - In the most recent 5 years of MarketScan® data, nearly 29 million patients (73%) have at least 12 months of continuous enrollment.
  - The MarketScan® claims databases contain complete information on outpatient prescriptions. These databases afford distinct advantages over others that track only prescription fills.
  - Because individual patients' prescription fills are recorded, therapies prescribed concurrently (and presumably used in combination) can also be identified.
  - This provides vital information about actual drug use patterns, as opposed to individual drug prescription trends.
  - The major disadvantage of this data was lack of complete clinical data. For example, there were very patients with A1c data available for meaningful analysis

Study Design

- **Study Design:** This was a retrospective study using the VHA and Truven databases.
- **Study period:**
  - VHA: 01APR2013-31MAR2018
  - Truven: 01JUL2013-30JUN2018
- **Identification period:**
  - VHA: 01JAN2014-30JUN2017
  - Truven: 01JUL2014-30JUN2017
- **Index date:**
  - U-500R initiation: 1st prescription claim date for U-500R administration
  - U-500R device switch: The date for U-500R device switch from syringe to Kwikpen.
- **Pre-Index period:** 9 months (VHA) and 12 months pre-index date (Truven)
- **Post-Index period:** 9 months (VHA) and12 months post-index date (Truven)

Study Design

Figure 1. Study Design for U-500R Syringe Initiators (VHA)



Note: This figure depicts a schematic representation of the study design for U-500R syringe initiators in VHA. Similar study design was followed for identifying U-500R KP initiators, any U-500R initiators and U-500R device switchers.
For analysis conducted in the Truven database, a 12-month pre-and post-index period was used.

Study Population

Inclusion criteria:

U-500R Initiators

Patients were included if they:

- had ≥1 prescription claim for U-500R syringe/Kwikpen during the identification period (VHA: 01JAN2014-30JUN2017; Truven:01JUL2014-30JUN2017) - the first prescription claim for U-500R was designated as the index date;
- had ≥2 claims with an ICD-9/10-CM code for T2DM in any position (primary/secondary) at any time prior to the index date;
- were aged ≥18 years on the index date;
- had continuous health plan enrolment with medical and pharmacy benefits for ≥9 (VHA) or ≥12 (Truven) months pre- and post-index event;
- had ≥1 prescription claim for any insulin other than U-500R in the pre-index period;
- had ≥1 HbA1c measurement within 90-day pre-index or 30-day post-index event; and
- had ≥1 HbA1c measurement after the 30-day post-index period at any time in the post-index period.

Study Population

Exclusion criteria:

U-500R Initiators

Patients were excluded if they:

- had both T1DM and T2DM, had no oral anti-diabetic drug (OADs) other than metformin, and the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA: 01APR2013-31MAR2018; Truven: 01JUL2013-30JUN2018);
- had ≥1 prescription claim for U-500R use in the pre-index period;
- had ≥1 claim with an ICD-9/10-CM code for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, or puerperium, or non-clinical diabetes at any time in the pre-index period;
- had claims indicating pump use in the post-index period; or
- had claims indicating TDD above 2000 units/day at any time in the pre-index or post-index periods.

Note: Similar criteria were used to identify the U-500R syringe/U-500R Kwikpen initiators separately. However, the index date was the first prescription claim for U-500R syringe or U-500R Kwikpen respectively.

Additionally, T2DM patients with evidence of U-500R syringe use in the pre-index and with U-500R Kwikpen use in the identification period were identified as U-500R device switchers

Cohort Assignment

After applying the inclusion and exclusion criteria, eligible patients were assigned to the following main cohorts:

- **Any U-500R Initiators Cohort:** Patients who initiated U-500R (syringe or Kwikpen) on their index date.
- **U-500R Syringe Initiators Cohort:** Patients who initiated U-500R syringe on their index date.
- **U-500R Kwikpen Initiators Cohort:** Patients who initiated U-500R Kwikpen on their index date.
- **U-500R Device Switchers Cohort:** Patients who switched from U-500R syringe to Kwikpen on their index date.
    - Further subgroup analysis was performed among patients aged ≥65 years (elderly) in each of the above 3 initiator cohorts (U-500R syringe initiators, U-500R Kwikpen initiators, U-500R Any initiators).

High-Dose U-500R Initiators: Subgroup analysis was performed among patients who had their TDD>180 units in the pre- and post-index periods and had no evidence of other insulins at any time in the post-index period in each of the initiator cohorts.

- Additionally subgroup analysis was also performed in the elderly (aged ≥65 years) high-dose as well as the high-dose patients with TDD ≤ 300 units in the post-index

U-500R low-dose cohort: Subgroup analysis was performed among patients after excluding those with TDD>200 units in the pre- and post-index periods in each of the initiator cohorts. Analysis was performed separately among:

- U-500R patients with TDD≤200 units in the pre-index and TDD>200 in the post-index
- U-500R patients with TDD≤200 units in the pre-index and TDD ≤ 200 in the post-index

Patient Characteristics

- **Demographic characteristics: Evaluated on index date**
  - Age
  - Sex
  - Race (VHA database only)
  - US region (Truven database only)
  - Medicare eligibility (Truven database only)

- **Clinical characteristics: Evaluated during pre-index period**
  - Body mass index (BMI: VHA database only)
  - Quan-Charlson comorbidity index (CCI) score
  - Individual comorbidities
    - ❖ Retinopathy
    - ❖ Nephropathy
    - ❖ Neuropathy
    - ❖ Coronary artery disease
    - ❖ Peripheral vascular disease
    - ❖ Congestive heart failure
    - ❖ Hypertension
    - ❖ Depression
    - ❖ Obesity
    - ❖ Malignant tumor

Variables and Definitions

<u>Treatment Patterns</u>: Evaluated in both pre-index and post-index periods

- **Observed TDD in claims:** total number of insulin units/total unique days of supply as recorded in claims and was reported as both a continuous and categorical variable. Additionally, TDD in units/kg was reported
- **Change in observed TDD:** difference in the pre-index observed TDD and post-index observed TDD.
- **Observed average daily dose (ADD) in claims:** total number of insulin units divided by the total number of days in the pre- or post-index period, respectively.
- **Adherence (proportion of days covered [PDC]):** number of days covered by the prescription claims of insulin (any insulin) divided by the total days in the pre- or post-index period, respectively.
- **Number of fills:** average number of insulin prescription fills
- **Claim gaps:** average gap between prescription fills of insulin.
- **Concomitant medications**: thiazolidinediones, sulfonylureas, biguanides, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT-2 inhibitors, bile acid sequestrants, fixed-dose combinations, GLP-1 receptor agonists, and amylin agonists
- **Persistence/time to discontinuation (only in post-index):** Patients were considered to have discontinued if there was no refill of the index medication within 60 days of the run-out date (date of last prescription + days of supply). Time to discontinuation was defined as the total number of days from the index date to the discontinuation date during the post-index period.

Variables and Definitions

<u>Treatment Outcomes</u>: Evaluated in both pre- and post-index periods

- **HbA1c (only in VHA):**
  - Pre-index HbA1c (pre-index HbA1c) was the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date was reported as the pre-index HbA1c value.
  - The follow-up HbA1c value was the HbA1c measurement taken farthest in the time period after the 30 day-post index event date.
  - Change in HbA1c was defined as the difference in the pre-index HbA1c and the post-index HbA1c values.
- **Hypoglycemic events (only in VHA):**
  - Hypoglycemia events in the pre-index and post-index period was evaluated using the ICD-9 codes from the Ginde algorithm [19] or the presence of a cutoff of blood glucose ≤70 mg/dL, or any evidence of intramuscular glucagon administration.
  - Hypoglycemia events that occurred on or after the index date were considered the follow-up hypoglycemia event. Hypoglycemia events that occurred on or prior to -1 day after the index date (i.e., any time before the index date) were considered the pre-index hypoglycemia event.
  - The number of hypoglycemia events per patient per year (PPPY) was reported in both the pre-index and post-index periods.
- **Body weight in kg (only in VHA):** Body weight in the pre-index and post-index period was evaluated.

Variables and Definitions

Health Care Costs (only in Truven)

- **OOP pharmacy costs:**
  - Diabetes-related OOP pharmacy costs (i.e., the costs associated with any insulins and antihyperglycemic agents)
  - Insulin-related OOP pharmacy costs
  - All-cause OOP pharmacy costs
- **Total medical costs:**
  - Diabetes-related inpatient costs
  - Diabetes-related outpatient costs
  - Non-diabetes-related inpatient costs
  - Non-diabetes-related outpatient costs
- **Total pharmacy costs:**
  - Diabetes-related total pharmacy costs
  - Insulin-related total pharmacy costs
  - All-cause pharmacy costs

Note: Costs were adjusted to 2018 US dollars using the annual medical care and drug costs components of the Consumer Price Index to reflect inflation.

Descriptive Analysis

- Numbers and percentages were provided for dichotomous and polychotomous variables.
- Means and standard deviations (SDs) were provided for continuous variables; Additional descriptive statistics including medians and percentiles were provided for costs.
- McNemar's test was used to determine statistical significance of before and after values for categorical variables, and the paired t-test/Wilcoxon rank sum test was used to assess the statistical significance of before and after values in continuous variables.
- A p-value of <0.05 was considered statistically significant.
- SAS for Windows Version 9.4 was used for all statistical analyses.

Multivariable Analysis

Mixed Models

- Mixed models were used evaluate the effect of both time-varying and time-independent variables on adherence, HbA1c, and hypoglycemia while controlling for correlation due to multiple assessments from the same individual.
  - Mixed linear model (MLM) for adherence
    - PDC measured at two time intervals (before and after the index event), was considered the dependent variable. The independent variables included, age, gender, race, pre-index BMI, pre-index CCI, TDD (time varying), time (pre/post).
    - However, in the model for any high-dose U-500R initiators, index device was included as a covariate, while in the MLM for any low-dose U-500R initiators, index device, interaction effect of TDD with time and BMI with index device were included.
  - MLM for HbA1c
    - HbA1c measured at two time intervals (before and after the index event), was considered the dependent variable. The independent variables included, age, gender, race, pre-index BMI, pre-index CCI, TDD (time varying), time (pre/post).
    - However, in the model for any high-dose U-500R initiators, index device and the interaction effect of BMI with index device was included as a covariate, while in the model for any low-dose U-500R initiators, index device, interaction effect of index device with race were included.
  - Zero-inflated negative binomial mixed model (ZINBMM) for hypoglycemia:
    - Number of hypoglycemia events measured at two time intervals (before and after the index event), was considered the dependent variable. The independent variables included, age, gender, race, pre-index BMI, pre-index CCI, pre-index HbA1c, TDD (time varying), time (pre/post).
    - However, in the model for any high-dose U-500R initiators, index device and the interaction effect of age and race with index device were included as covariates, while in the model for any low-dose U-500R initiators, index device, interaction effect of index device with TDD were included.
  - Generalized Linear mixed model (GLMM) for costs:
    - Insulin-related OOP costs measured at two time intervals (before and after the index event), was considered as the dependent variable. The independent variables included, age, gender, region, health plan type, pre-index CCI, TDD (time varying), number of fills (time varying), time (pre/post), interaction effect of fills with time, and TDD with time.

Multivariable Analysis

- **Linear regression model**
  - Linear regression model was used to evaluate factors associated with post-index HbA1c. Post-index HbA1c was the dependent variable while age, gender, race, BMI, CCI, change in TDD and pre-index HbA1c were included as independent variables.
- **Zero-inflated Negative Binomial Model**
  - Zero-inflated negative binomial model was used to evaluate the factors associated with post-index hypoglycemic events. The number of hypoglycemia events in the post-index period was considered as dependent variable while age, gender, race, BMI, CCI, changed in observed TDD, change in HbA1c, and pre-index hypoglycemia were included as covariates.

Exploratory Analysis

Mediation Analysis in U-500R KP Initiators

- Mediation Analysis on HbA1c
  - Mediation analysis following the below modeling steps was considered to understand the impact of index event (time: pre-index indicates use of other non-U-500R insulins and post-index indicates exposure to U-500R use) on HbA1c through potential mediators.
  - Adherence (PDC) and observed TDD were considered as potential mediators between HbA1c and treatment period (i.e. exposure).
  - The key steps in mediation analysis included a model of the outcome (HbA1c) as a function of both the mediators (PDC, and TDD) and the predictor (treatment period) and a model of the mediators (PDC and TDD) as functions of the predictor (treatment period). Confounders were included in the models.
  - More details can be found in attached technical appendix

Adobe Acrobat Document

RESULTS

Links to Results Tables

The results tables for the analysis in the overall U-500R initiators including the results for any U-500R initiators, U-500R syringe initiators, U-500R KP initiators, U-500R Device switchers and the corresponding elderly subgroup can be found in the attached excel file below

Key Findings of Any U-500R Initiators

- A total of 2,391 people initiated U-500R via syringe or Kwikpen.

Patient Characteristics

- Mean age was 63 years and majority of patients were men (96.5%) and white (82.0%)
- Mean Quan CCI score was 3.6 and mean BMI was 40.0 kg/m2
- Hypertension (89.9%) was the most common comorbidity followed by obesity (59.6%), and neuropathy (49.1%)

Treatment Patterns

- 58.1% patients were on TDD ≤200 units prior to any U-500R initiation, while 10.6% remained on TDD ≤200 units after initiation
- Observed TDD significantly increased from 195.2 units in pre-index to 347.0 units in post-index ($p<0.0001$). Additionally, the mean TDD at initiation (on the index date) was 358 units
- Also, insulin dosage (TDD in units/kg) increased significantly (1.58 units/kg to 2.76 units/kg; $p<0.0001$)
- PDC significantly increased after U-500R initiation (0.7 vs 0.8, $p<0.0001$) and the results were confirmed form MLM analysis ($p<0.0001$)
- The number of fills significantly decreased from 8.7 vin pre-index to 6.8 in post-index ($p<0.0001$)
- Proportion of patients with evidence of sulfonylureas (10.2% vs 2.8%, $p<0.0001$) and biguanides significantly decreased (60.4% vs 55.3%, $p<0.0001$); however the use of SGLT2 (1.7% vs 3.6%, $p<0.0001$) and GLP-1 receptor agonists (7.8% vs 12.5%, $p<0.0001$) had significantly increased after U-500R initiation

Key Findings of Any U-500R Initiators

Treatment Outcomes

- HbA1c significantly dropped from 9.5% in pre-index to 8.6% in post-index ($p<0.0001$) and this was further confirmed in the MLM ($p<0.0001$)
- Additionally, after U-500R initiation it was observed that the proportion of patients with HbA1c >9% (58.2% vs 32.7%, $p<0.0001$) and those with HbA1c >7.5% (91.6% vs 74.9%, $p<0.0001$) significantly decreased
- The number of hypoglycemia events PPPY significantly increased after U-500R initiation (2.2 vs 3.5, $p<0.0001$) which was further confirmed by the ZINBMM results ($p<0.0001$)
- Among patients who had body weight in the pre- and post-index periods (97.8%), body weight significantly increased (127.1 vs 128.8 kg; $p<0.0001$)

Elderly sub-cohort of U-500R initiators

- The analysis was repeated in the 1,239 elderly any U-500R initiators and the results remained very consistent with the total sample of any U-500R initiators.

Conclusion

- After U-500R initiation via syringe/Kwikpen, TDD as reflected in claims as well as the insulin dosage in units/kg increased, with a significant decrease in HbA1c by 0.9%, accompanied by a comparatively modest increase in hypoglycemia

Key Findings of U-500R Syringe and Kwikpen Initiators

- A total of 1,766 patients initiated U-500R via syringe while 647 patients initiated U-500R via Kwikpen (KP).
- It is important to note that both of these subgroups were not mutually exclusive due to a study period substantially longer than the pre- and post-index periods, during which patients may have switched between U-500R devices
- The results were mostly consistent with the any U-500R initiators, however some of the notable differences are described below

<u>Patient Characteristics</u>

- Syringe initiators were slightly younger with mean age of 63 years, while KP initiators mean age was 64 years
- The proportion of patients with neuropathy was only 38% in syringe initiators but 82% in KP initiators.

<u>Treatment Patterns and Outcomes</u>

- Treatment patterns and outcomes remained mostly similar with the any initiators, with few notable differences.
- Syringe initiators had considerably higher TDD both in the pre- and post-index periods (syringe 197.7 to 373.9 [p<0.0001]; KP: 188.2 to 270.0 [p<0.0001]).
- The mean HbA1c dropped by 0.9% (9.5% vs 8.6%, p<0.0001) after syringe initiation, while the drop was 0.8% (9.5% vs 8.7%, p<0.0001) after KP initiation
- Syringe initiators had notably fewer hypoglycemia events both in the pre- and post-index periods (syringe: 1.5 to 2.9 [p<0.0001]; KP: 4.3 to 5.3 [p<0.0001])

Key Findings of U-500R Syringe and Kwikpen Initiators

Exploratory results from mediation analysis among U-500R KP Initiators:

- U-500R KP initiation directly resulted in a significant drop in HbA1c of 0.4%, while the indirect effect of U-500R syringe initiation as mediated by PDC and TDD resulted in a drop of HbA1c 0.12%.
- The indirect effect was not significant and only 24% of the total effect of U-500R KP

Elderly sub-cohort of U-500R syringe and KP initiators

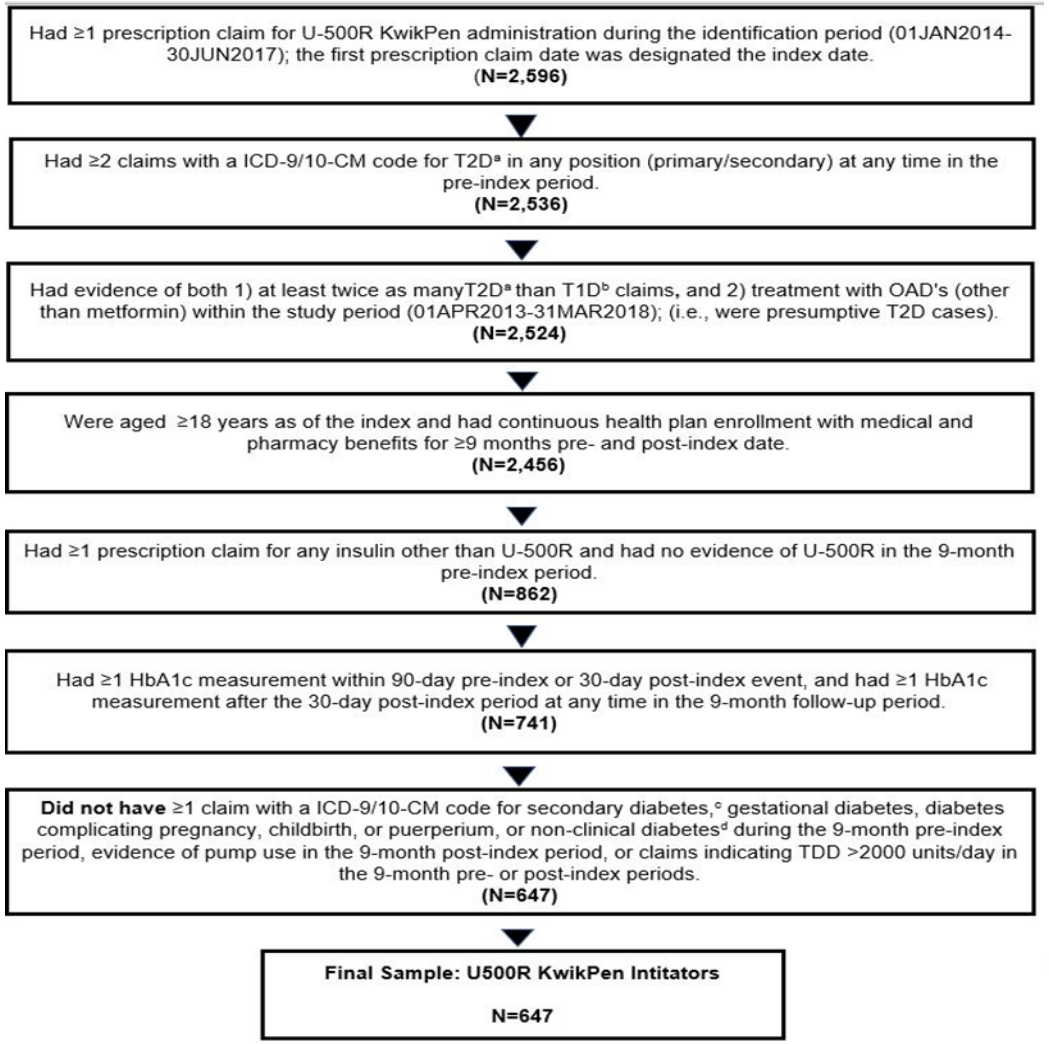
- The analysis was repeated in the 833 elderly U-500R syringe initiators and 370 elderly U-500R KP initiators and the results remained very consistent with the corresponding total sample.

Conclusion

- After U-500R syringe initiation , TDD as reflected in claims increased by 176 units, with a significant decrease in HbA1c by 0.9%, accompanied by a comparatively modest increase in hypoglycemia
- Similarly, after U-500R KP initiation, TDD as reflected in claims increased by 82 units, with a significant decrease in HbA1c by 0.8%, accompanied by a comparatively modest increase in hypoglycemia

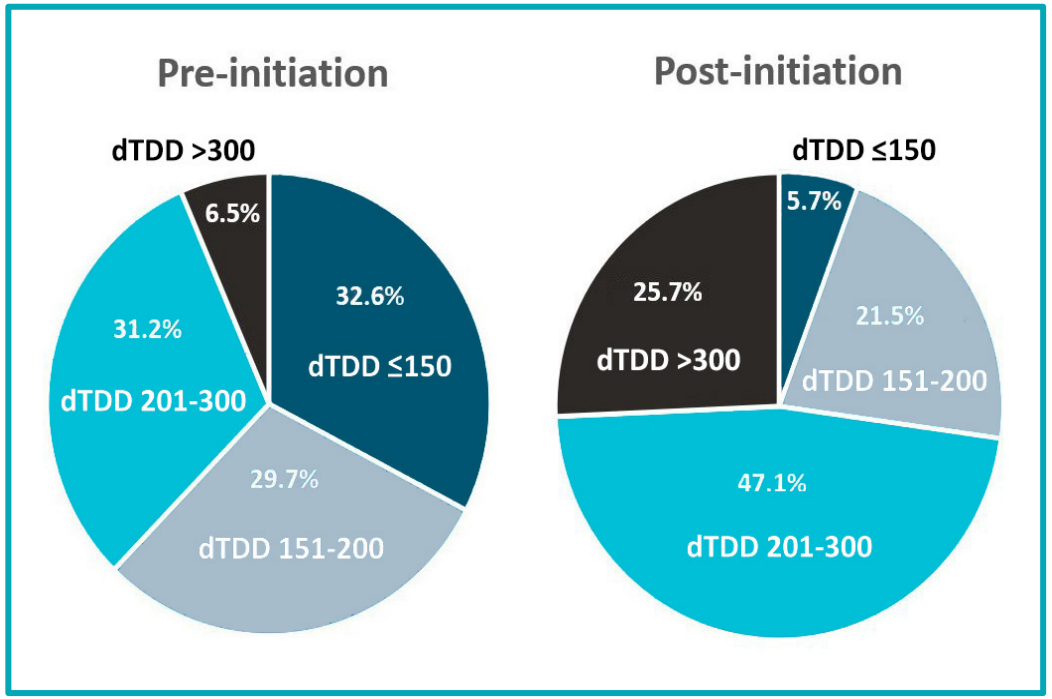
Figures from Posters/Manuscripts Corresponding to the Analysis in the U-500R Kwikpen Initiators

Figure 2. Patient Selection for KP Initiators



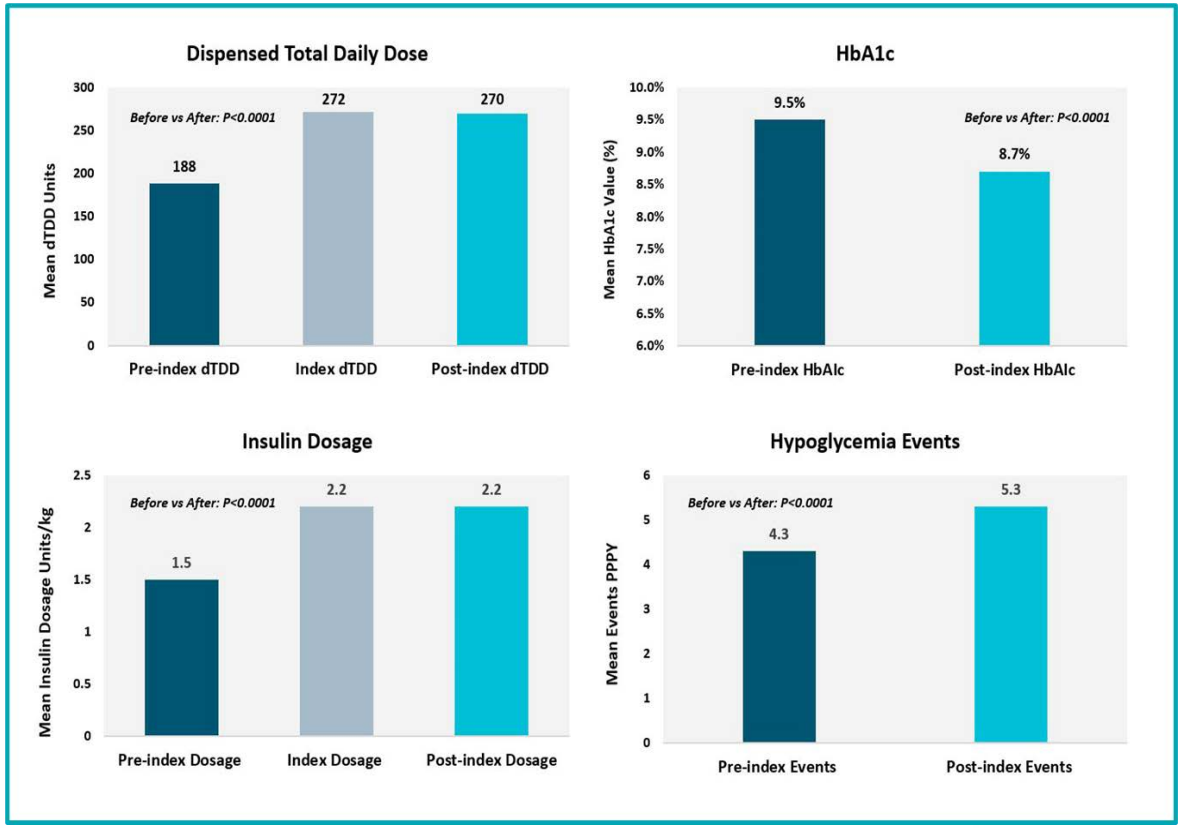
Figures from Posters/Manuscripts Corresponding to the Analysis in the U-500R Kwikpen Initiatros

Figure 3. Dispensed Total Daily Dose Before and After U-500R Initiation via KwikPen



dTDD: Dispensed total daily dose

Figure 4. Key Treatment Patterns and Outcomes Before and After U-500R Initiation via KwikPen



Key Findings of U-500R Device Switchers (syringe to KP)

- A total of 1,094 patients who switched from U-500R syringe to U-500R KP were included.

Patient Characteristics

- Patient characteristics remained consistent with the U-500R KP initiators

Treatment Patterns

- Only 0.37% patients were on TDD ≤200 units while on U-500R syringe, while 21.6% remained on TDD ≤200 units after switching to U-500R KP
- Observed TDD significantly decreased from 427.5 units in pre-index to 339.4 units in post-index ($p<0.0001$). Additionally, the mean TDD at initiation (on the index date) was 335 units
- PDC significantly increased after switching to U-500R KP (0.6 vs 0.7, $p<0.0001$) and the results were confirmed form MLM analysis ($p<0.0001$)
- The number of fills significantly increased from 4.0 in pre-index to 5.9 in post-index ($p<0.0001$)
- Proportion of patients with evidence of sulfonylureas (2.5% vs 1.5%, $p=0.0218$) significantly decreased (60.4% vs 55.3%, $p<0.0001$); however the use of SGLT2 (4.0% vs 9.4%, $p<0.0001$) and GLP-1 receptor agonists (17.9% vs 25.6%, $p<0.0001$) had significantly increased after switching to U-500R KP

Key Findings of U-500R Device Switchers (syringe to KP)

Treatment Outcomes

- HbA1c significantly dropped from 8.6% in pre-index to 8.5% in post-index ($p=0.0014$) and this was further confirmed in the MLM ($p=0.082$)
- The number of hypoglycemia events PPPY remained the same after switching to U-500R KP (4.5 vs 4.6, $p=0.7297$) which was further confirmed by the ZINBMM results ($p<0.8500$)

Conclusion

- After switching from U-500R syringe to U-500R KP, TDD as reflected in claims significantly decreased, with only 0.1% decrease in HbA1c, and no significant difference in hypoglycemic events.

Links to Results Tables for Analysis in High-Dose Initiators

The results tables for the analysis in the high-dose U-500R initiators including the results for any U-500R initiators, U-500R syringe initiators, U-500R KP initiators, and the corresponding elderlyand TDD 201-300 units subgroups can be found in the attached excel file below

Key Findings of High-dose Any U-500R Initiators

- Among the 2,391 any U-500R initiators, 951 patients were identified as high-dose (TDD>180 units in pre- and post-index and on U-500R monotherapy)

Patient characteristics, Treatment patterns and outcomes:

- Patient characteristics remained consistent with the main cohort of any U-500R initiators
- Observed TDD significantly increased after initiation, from 249 units pre-index to 392 units post-index (p<.0001). Notably, the mean TDD of the index (first) U-500R claim was 375 (±138) units.
- The proportion of patients with PDC >80% significantly increased (44.7% vs 50.0%, p=0.0122), which was confirmed by the results from MLM (p<0.0001)
- The number of fills significantly reduced (8.7 vs 6.4, p<0.0001)

- HbA1c significantly dropped from 9.3% in pre-index to 8.5% in post-index (p<0.0001) and this was further confirmed in the MLM (p<0.0001)
- The number of hypoglycemia events PPPY significantly increased after high dose U-500R initiation (2.1 vs 3.1, p<0.0001) which was further confirmed by the ZINBMM results (p<0.0001)

Conclusion

- U-500R initiation via syringe or KwikPen among severely insulin-resistant T2DM patients was associated with considerable improvements in treatment patterns and glycemic control.
- TDD and insulin dosage (units/kg) captured in claims increased dramatically. Together with improved adherence as measured by PDC, this suggests U-500R addresses unmet patient insulin needs.
- The decrease in HbA1c was clinically meaningful (0.8%), with modest increases in hypoglycemic events.

Key Findings of High-Dose U-500R Syringe and Kwikpen Initiators

- Among a total of 1,766 syringe initiators, 714 patients were identified as high-dose U-500R syringe initiators

Patient Characteristics, Treatment Patterns and Outcomes

- Patient characteristics were mostly similar to high-dose any initiators, except that a higher proportion of KP initiators were elderly.
- Treatment patterns also remained consistent with the overall group, except that the TDD (syringe 249.4 to 415.2, $p<0.0001$; KP: 246.0 to 320.8; $p<0.0001$) and insulin dosage (syringe: 2.00 to 3.22, $p<0.001$; KP: 1.93 TO 2.46, $P<0.0001$) were generally lower in the KP initiators
- The mean HbA1c dropped by 0.9% (9.5% vs 8.6%, $p<0.0001$) after syringe initiation, while the drop was 0.8% (9.5% vs 8.7%, $p<0.0001$) after KP initiation
- Syringe initiators had notably fewer hypoglycemia events both in the pre- and post-index periods (syringe: 1.6 to 2.7, $p<0.0001$; KP: 3.5 to 4.2, $p<0.0001$)

Conclusion

- U-500R syringe initiation among severely insulin-resistant T2DM patients was associated with dramatic increase in TDD by 176 units, with a significant decrease in HbA1c by 0.9%, accompanied by a comparatively modest increase in hypoglycemia
- Similarly, U-500R KP initiation in these patients, was associated with a dramatic increase in TDD by 82 units, with a significant decrease in HbA1c by 0.8%, accompanied by a comparatively modest increase in hypoglycemia

Key Findings of Elderly High-dose U-500R Initiators

Elderly high-dose any U-500R initiators:

- A total of 492 (51.7%) elderly high-dose any U-500R initiators were included. Elderly subgroup results were consistent with the overall group.
- TDD significantly increased by 132 units ($p<0.0001$), with a significant increase in the mean PDC (0.75 to 0.78, $p<0.0001$) and decrease in the number of fills (8.8 to 6.5, $p<0.0001$). The increase in PDC was further confirmed by MLM ($p<0.0001$)
- Similar to the overall group, HbA1c significantly decreased by 0.8% (9.1% to 8.4%, $p<0.0001$), which was further confirmed by MLM.
- Hypoglycemia events significantly increased from 1.9 to 3.3 events PPPY ($p<0.0001$), which was further confirmed by ZINBMM.

Elderly high-dose U-500R syringe initiators and U-500R KP initiators:

- A total of 350 elderly high-dose U-500R syringe initiators and 145 high-dose U-500R KP initiators were included.
- Results were consistent with the above subgroup of any U-500R initiators. More specifically, the trend was very similar to the overall U-500R syringe and KP initiators discussed in previous slides.

Conclusion

- U-500R initiation among elderly severely insulin-resistant T2DM patients was associated with considerable improvements in treatment patterns and glycemic control similar to the overall group.
- TDD and insulin dosage (units/kg) captured in claims increased dramatically, with a decrease in HbA1c which was clinically meaningful and with modest increases in hypoglycemic events.

Key Findings of High-dose U-500R Initiators with TDD 201-300 units in Post-Index

Any U-500R initiators with TDD 201-300 units in post-index:

- Among high-dose any U-500R initiators, 148 (15.6%) patients had TDD 201—300 units in the post-index.
- After initiation, TDD significantly increased by 40 units from 227 to 266 units ($p<0.0001$), with a significant increase in the mean PDC (0.71 to 0.78, $p<0.0001$) and decrease in the number of fills (7.9 to 6.7, $p<0.0001$). The increase in PDC was further confirmed by MLM ($p<0.0001$)
- Similar to the overall group, HbA1c significantly decreased by 0.9% (9.3% to 8.4%, $p<0.0001$), which was further confirmed by MLM.
- However, this subgroup did not have significant increase in hypoglycemia events after initiation (3.4 to 4.0, $p=0.1556$), which was further confirmed by ZINBMM ($p=0.2958$).

U-500R syringe and KP initiators with TDD 201-300 units in post-index:

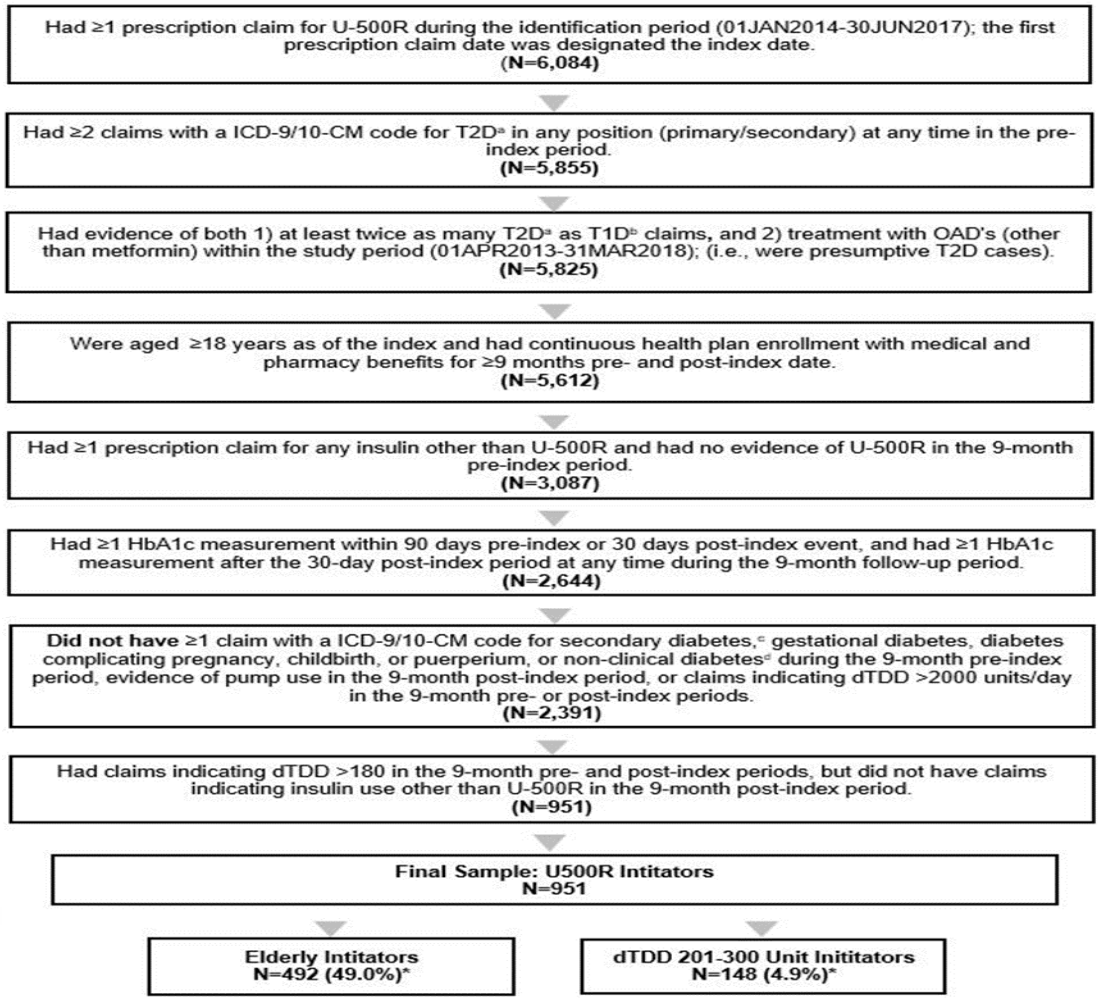
- 35 (4.9%) and 118 (48.4%) patients among high-dose U-500R syringe initiators and U-500R KP initiators respectively, had TDD 201—300 units in the post-index.
- The results in these two subgroups were consistent with the above subgroup of any U-500R initiators.

Conclusion

- U-500R initiation among severely insulin-resistant T2DM patients with TDD 201-300 units was associated with considerable improvements in treatment patterns and glycemic control similar to the overall group.
- TDD and insulin dosage (units/kg) captured in claims increased by ~40 units, with a decrease in HbA1c of ~0.9% which was clinically meaningful and no increase in hypoglycemic events.

Figures from Posters/Manuscripts Corresponding to the Analysis in the High-Dose U-500R Initiators

Figure 5. Patient Selection for High-Dose Any U-500R Initiators



Figures from Posters/Manuscripts Corresponding to the Analysis in the High-Dose U-500R Initiators

Figure 6. Insulin Dosage Distribution Before and After High-Dose Any U-500R Initiation

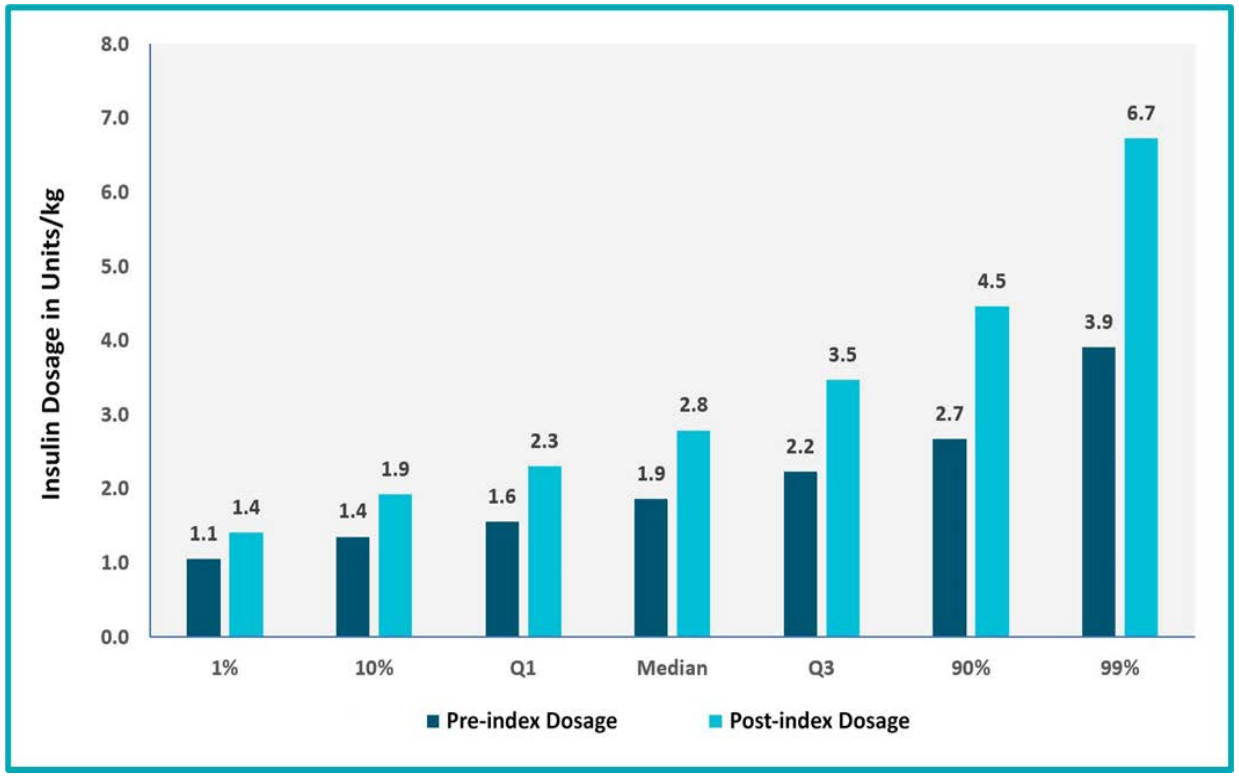
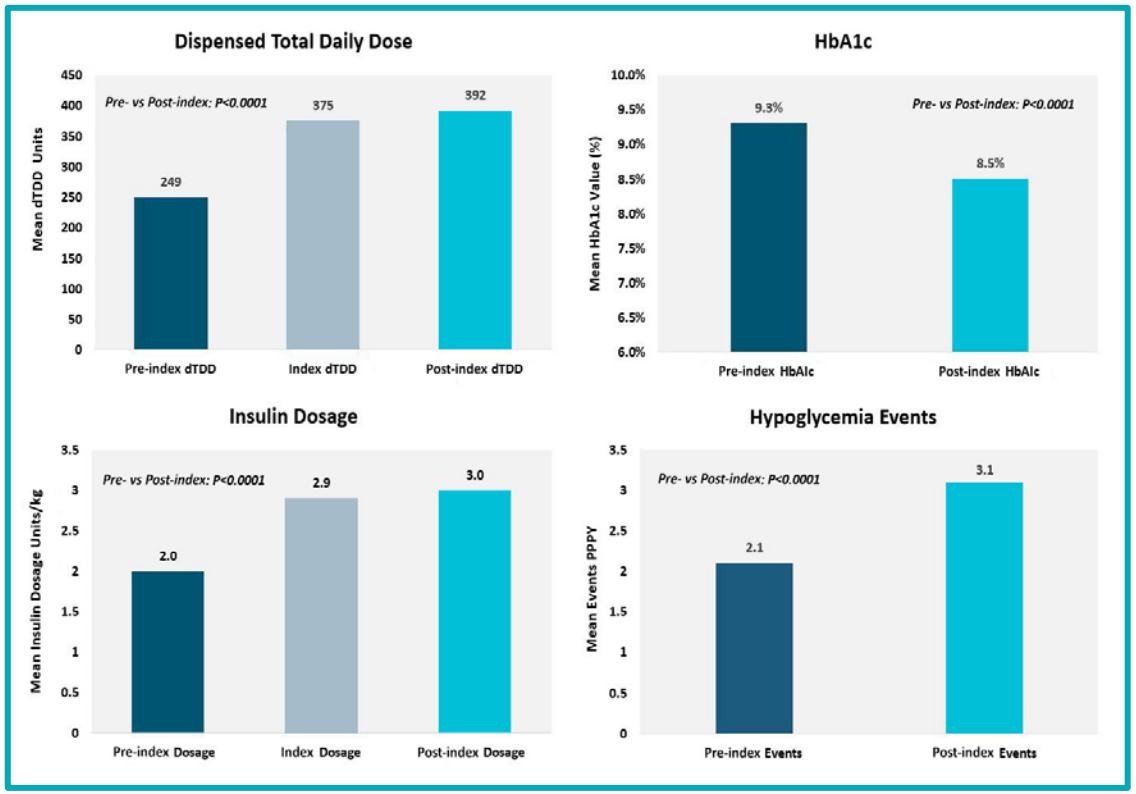


Figure 7. Key Treatment Patterns and Outcomes Before and After High-Dose Any U-500R Initiation



Pre-index: averaged over 9-months before initiation (first claim); post index: averaged over 9-months after initiation (first U-500R claim)

Links to Results Tables for Analysis in Low-Dose Initiators

The results tables for the analysis in the low-dose U-500R initiators including the results for any U-500R initiators, U-500R syringe initiators, U-500R KP initiators, can be found in the attached excel file below

Key Findings of Low-dose Any U-500R Initiators

- Of the total 2,391 U-500R initiators who switched from U-100 to U-500R, 42% (N=1,002) with pre-index dTDD >200 units/day were excluded. Of the remaining 58% (N=1,398) who had pre-index dTDD ≤200 units/day, 14% (N=198) with post-index dTDD remaining at ≤200 units/day were further excluded. The remaining 86% **(N=1,191)** of U-500R initiators who transitioned from ≤200 to >200 units/day dTDD after initiation were included as low-dose U-500R initiators.

Patient characteristics, Treatment patterns and outcomes:

- Patient characteristics remained consistent with the main cohort of any U-500R initiators
- Observed TDD significantly increased after initiation, from 147 units pre-index to 346 units post-index (p<.0001). Notably, the mean TDD of the index (first) U-500R claim was 354 units.
- Mean insulin dosage increased considerably after initiation (from 1.2 units/kg to 2.8 units/kg, p<.0001)
- Although, the proportion of patients with PDC >80% did not increase significantly after initiation in univariate analysis, however after adjusting for potential covariates, MLM analysis revealed a significant increase in PDC after initiation (p<.0001)
- The number of fills significantly reduced (8.5 vs 6.5, p<0.0001)
- HbA1c significantly dropped from 9.6% in pre-index to 8.6% in post-index (p<0.0001) and this was further confirmed in the MLM (p<0.0001)
- The number of hypoglycemia events PPPY significantly increased after low-dose U-500R initiation (2.0 vs 3.3, p<0.0001) which was further confirmed by the ZINBMM results (p<0.0001)

Conclusion

- A significant portion of U-500R initiators were found to have lower than 200 units/day insulin dose in their insulin claims and poor glycemic control while previously prescribed U-100 insulin
- U-500R initiation was associated with large increases in purchased insulin dosage (199 units) as well as clinically important improvement in glycemic control (HbA1c 1%), together with relatively modest increases in hypoglycemic events.
- This suggests U-500R addresses unmet patient insulin needs, in particular among the most markedly underdosed.

Key Findings of Low-Dose U-500R Syringe and Kwikpen Initiators

- Among patients initiating U-500R via syringe (N=1,766), 56.5% (N=998) had pre-index dTDD ≤200 units/day, of which 93.5% (N=933; included as the syringe cohort) had dTDD >200 in the post-index period.
- Among patients initiating U-500R via KP (N=647), 62.3% (N=403) had pre-index dTDD ≤200 units/day, of which 65.3% (N=263; included as the KP cohort) had dTDD >200 units/day in the post-index period.

<u>Patient Characteristics, Treatment Patterns and Outcomes</u>

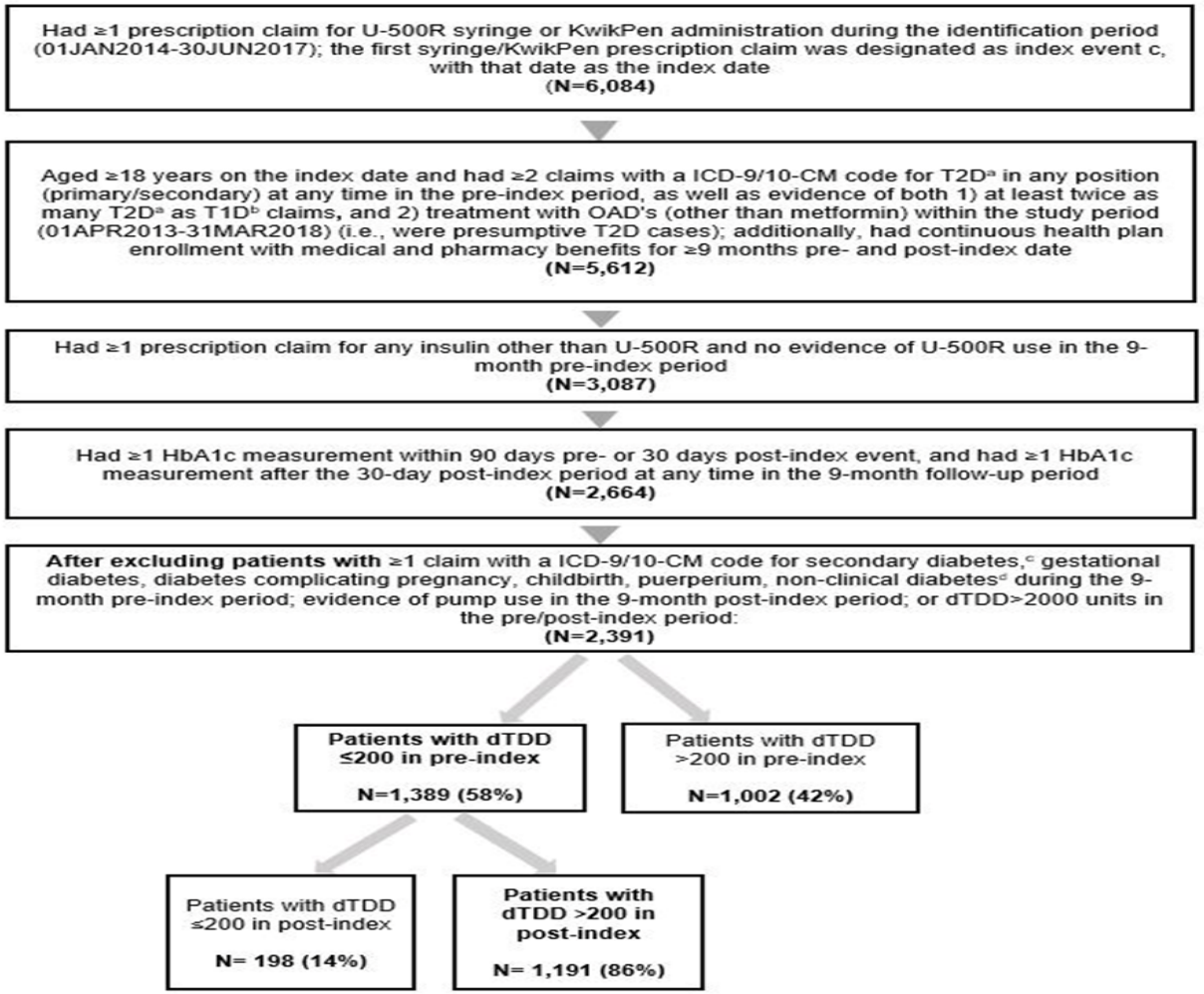
- Patient characteristics were mostly similar to low-dose any initiators, except that a higher proportion of KP initiators were elderly.
- Treatment patterns also remained consistent with the overall group, except that the TDD (syringe 147 to 363, p<0.0001; KP: 149 to 284; p<0.0001) and insulin dosage (syringe: 1.20 to 2.92, p<0.001; KP: 1.23 to 2.33, p<0.0001) were generally lower in the KP initiators
- While the HbA1c change was mostly similar among the syringe and KPen initiators, the number of hypoglycemia events is important to note
- Syringe initiators had notably fewer hypoglycemia events PPPY both in the pre- and post-index periods (syringe: 1.3 to 2.8, p<0.0001; KP: 4.5 to 5.1, p<0.0001)

<u>Conclusion</u>

- In low-dose patients, U-500R initiation via syringe was associated with large increases in purchased insulin dosage (217 units) as well as clinically important improvement in glycemic control (HbA1c 1%), together with relatively modest increases in hypoglycemic events.
- Similarly U-500R initiation via KP in these patients was associated with large increases in purchased insulin dosage (136 units) as well as clinically important improvement in glycemic control (HbA1c 0.8%), together with relatively modest increases in hypoglycemic events.

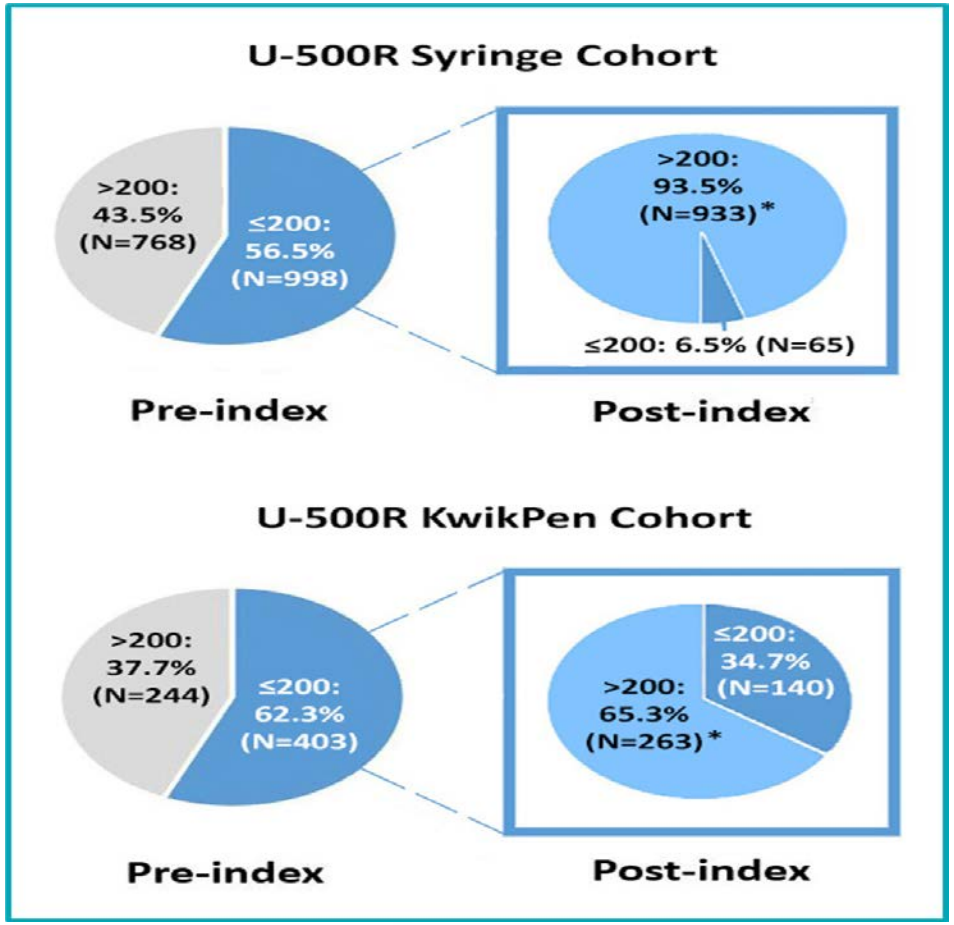
Figures from Posters/Manuscripts Corresponding to the Analysis in the Low-Dose U-500R Initiators

Figure 8. Patient Selection for Low-Dose U-500R Initiators



Figures from Posters/Manuscripts Corresponding to the Analysis in the Low-Dose U-500R Initiators

Figure 9. dTDD Distribution Before and After U-500R Initiation



Figures from Posters/Manuscripts Corresponding to the Analysis in the Low-Dose U-500R Initiators

Figure 10. Insulin Dosage Distribution Before and After Low-Dose Any U-500R Initiation

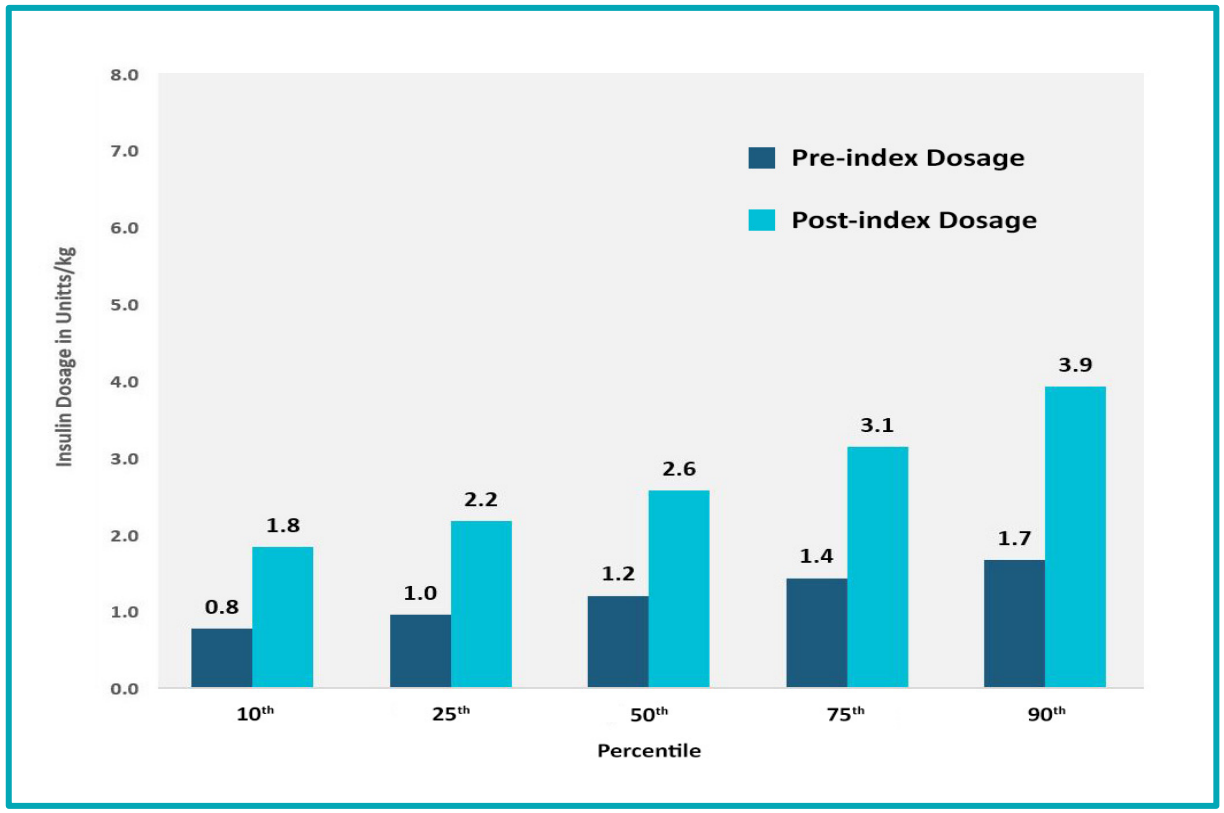
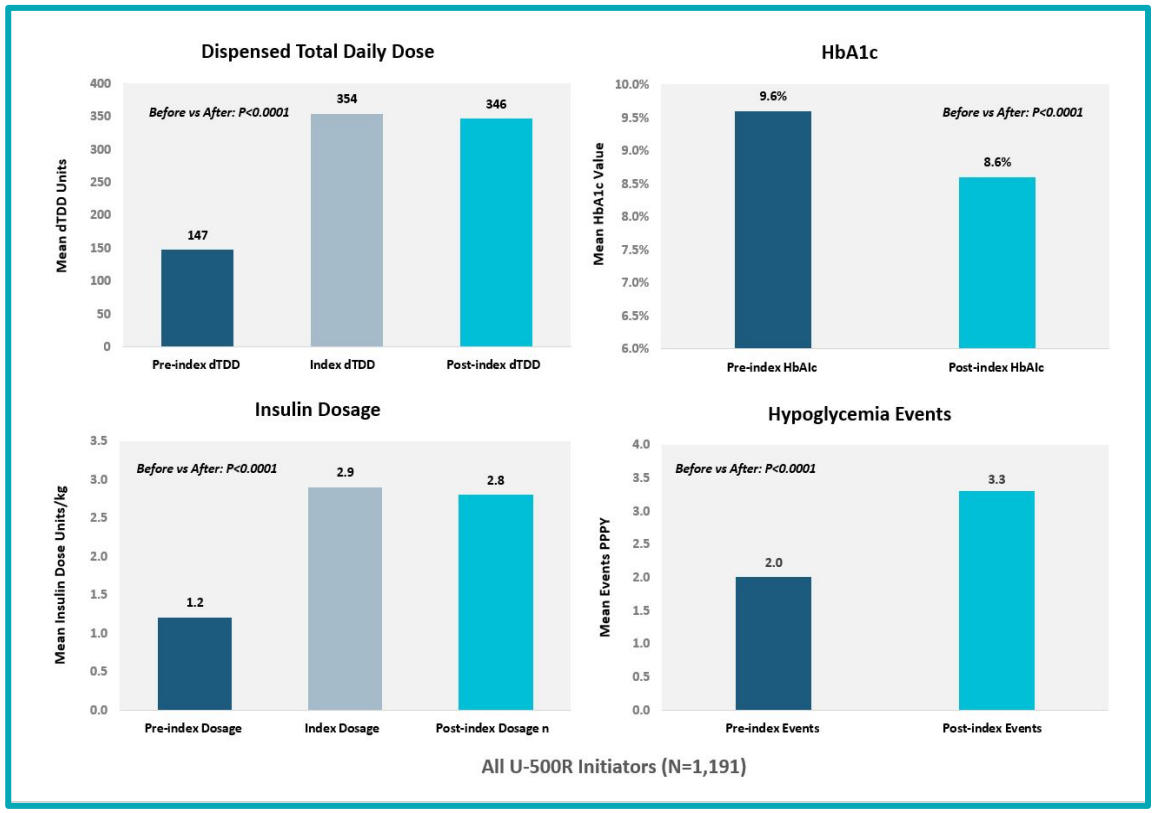


Figure 11. Key Treatment Patterns and Outcomes Before and After High-Dose Any U-500R Initiation



Pre-index: averaged over 9-months before initiation (first claim); post index: averaged over 9-months after initiation (first U-500R claim)

Links to Results Tables for Cost Analysis in Truven

The results tables for the analysis in the U-500R initiators including the results for any U-500R initiators, U-500R syringe initiators, U-500R KP initiators, and U-500R device switchers can be found in the attached excel file below (Tables 18-32)

Key Findings of Any U-500R Initiators

- A total of 1,337 commercial and Medicare people initiated U-500R via syringe or Kwikpen. The results were mostly consistent with the VHA analysis

<u>Patient Characteristics, Treatment Patterns and OOP Costs</u>

- Mean age was 57 years and majority of patients were men (57.7%) and from Southern region (45.8%)

<u>Treatment Patterns</u>

- 76% patients were on TDD ≤200 units prior to any U-500R initiation, while 24.5% remained on TDD ≤200 units after initiation
- Observed TDD significantly increased from 164 units in pre-index to 293.9 units in post-index ($p<0.0001$). Additionally, the mean TDD at initiation (on the index date) was 314 units
- PDC significantly increased after U-500R initiation (0.70 vs 0.72, $p=0.0204$) and the results were confirmed form MLM analysis ($p<0.0001$)
- The number of fills significantly decreased from 9.6 in pre-index to 7.8 in post-index ($p<0.0001$)
- Proportion of patients with evidence of sulfonylureas (18.5% vs 8.8%, $p<0.0001$) and biguanides significantly decreased (57.6% vs 53.1%, $p<0.0001$) after U-500R initiation

Key Findings of Any U-500R Initiators

Out of pocket (OOP) pharmacy costs

After initiation of U-500R,

- Median Insulin related (IR) OOP pharmacy costs significantly decreased, while mean showed no difference [(mean: $1,209 vs $1,214, p=0.9715) (median $379 vs $314; p<0.0001)]. This was further confirmed from the results of GLMM (p=0.6046)
- Median diabetes related OOP pharmacy costs significantly decreased [(mean: $1,388 vs $1,388, p=0.9975) (median $379 vs $314; p<0.0001)]
- Median all-cause OOP pharmacy costs significantly decreased [(mean: $2,644 vs $2727, p=0.8632) (median $1,140 vs $1,065; p<0.0001)]

Non-Elderly sub-cohort of any U-500R initiators

- The analysis was repeated in the 1,001 non-elderly any U-500R initiators (mean age 53 years) and the results remained very consistent with the commercial and Medicare sample of any U-500R initiators.
- After U-500R initiation, TDD significantly increased (163.0 to 292.5, p<0.0001) and the mean IR-OOP costs remained the same while median showed a significant decrease ([(mean: $559 vs $523, p=0.4027) (median $369 vs $287; p<0.0001)]

Conclusion

- After U-500R initiation via syringe/Kwikpen, despite the significant increase in TDD the mean annual IR-OOP costs did not increase.

Key Findings of U-500R Syringe and KP Initiators

- A total of 799 commercial and Medicare people initiated U-500R via syringe, and 530 initiated U-500 via KP.

<u>Patient Characteristics, Treatment Patterns and OOP Costs</u>

- Patient characteristics were mostly similar to any initiators
- Treatment patterns also remained consistent with the any initiators, except that the TDD (syringe 172 to 326, $p<0.0001$; KP: 153 to 245; $p<0.0001$) was generally lower in the KP initiators
- The magnitude of costs were generally higher in the KP initiators. Median Insulin related (IR) OOP pharmacy costs significantly decreased (Syringe: \$356 vs \$280, $p<0.001$; KP: \$405 VS \$380, $p=0.0146$) while mean showed no difference (Syringe: \$726 vs \$865, $p=0.2188$; KP: \$1,953 VS \$1,781, $p=0.5834$). This was further confirmed from the results of GLMM.

<u>Non-Elderly sub-cohort of any U-500R initiators</u>

- The analysis was repeated in the 577 non-elderly U-500R syringe initiators and 415 U-500R KP initiators and the results remained very consistent with the commercial and Medicare sample of any U-500R initiators.
- After U-500R initiation, median Insulin related (IR) OOP pharmacy costs significantly decreased (syringe: \$353 vs \$251, $p<0.001$; KP: \$376 VS \$353, $p=0.0340$) while mean showed no difference (Syringe: \$493 vs \$445, $p=0.3268$; KP: \$644 vs \$650, $p=0.95$)

<u>Conclusion</u>

- Despite the significant increase in TDD the mean annual IR-OOP costs did not increase in both the U-500R syringe initiators and KP initiators

Figures from Posters/Manuscripts Corresponding to the Analysis in the U-500R Initiators from Truven Data

Figure 12. Number of prescription fills significantly decreased after U-500KP initiation

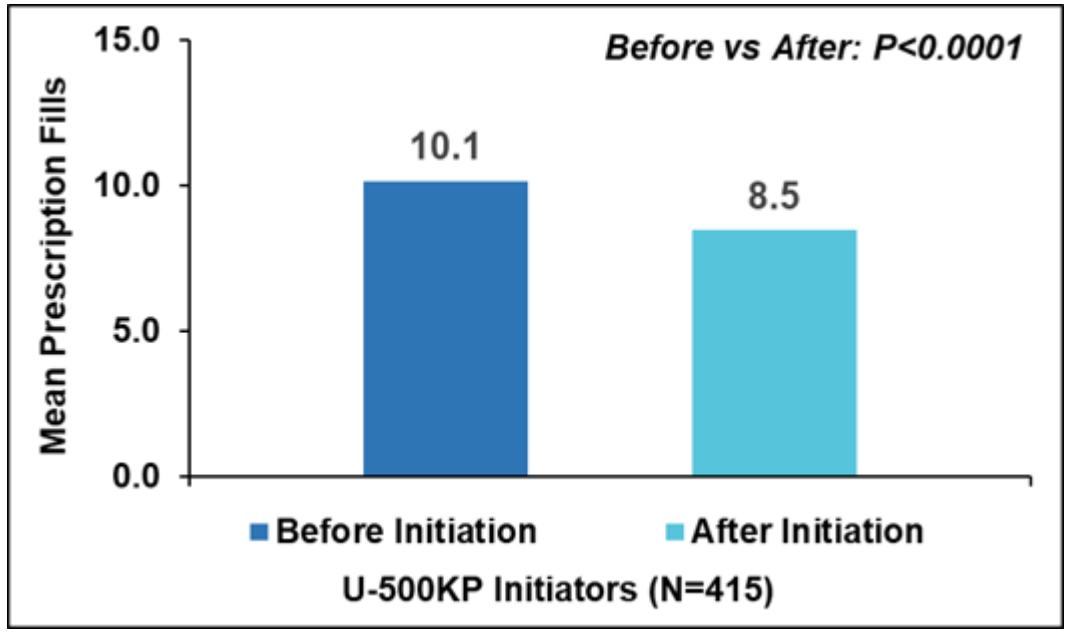
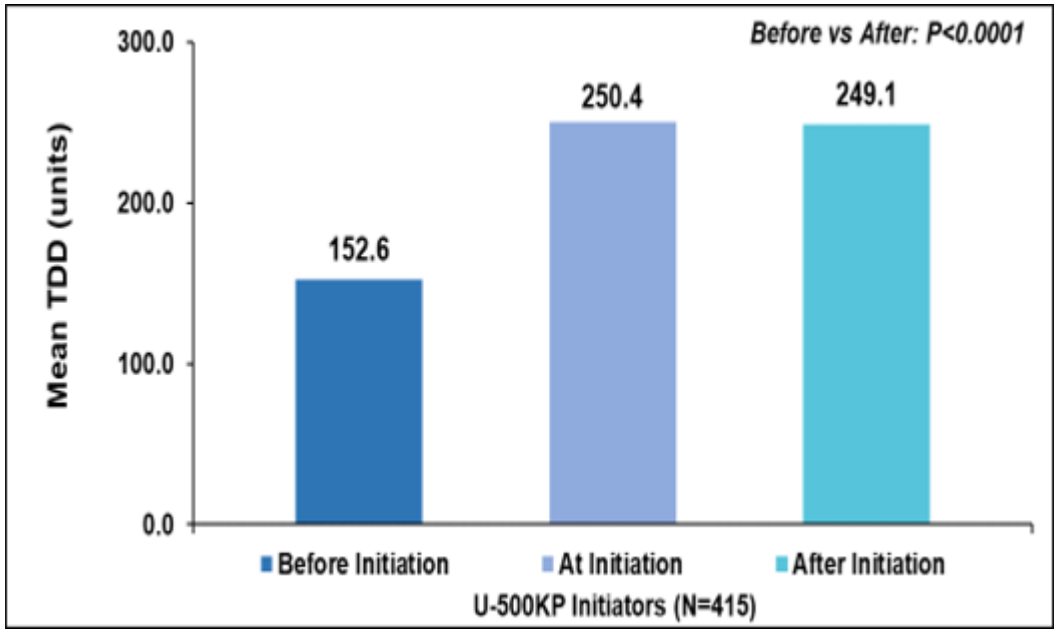


Figure 13. TDD significantly increased after U-500KP initiation



Links to Exploratory Results and Abstract/Posters

Exploratory Results

Low Dose any U-500 Initiators ADA 2020 poster

Adobe Acrobat Document

ISPOR 2020 OOP in KP Initiators poster

Adobe Acrobat Document

KP Initiators ADA 2019 poster

Adobe Acrobat Document

Limitations

- The study had inherent limitations of all retrospective administrative database analyses, and interpretation is limited to association rather than causal inference.
- While claims data are extremely valuable for the efficient and effective examination of health care outcomes, they are collected for administration and not research.
- Therefore, the use of claims data has certain limitations. For example, the presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed.
- Continued titration needs after U-500R initiation could also not be evaluated.
- Medications filled over-the-counter or provided as samples by the physician cannot be observed in the claims data. Because physician prescriptions were not capturable in the database, noncompliance could not be confirmed by comparing dTDD with prescribed TDD.
- The presence of a diagnosis code on a medical claim does not necessarily indicate a positive presence of disease, as the diagnosis code may be incorrect or included as rule-out criteria rather than actual disease.
- Also, certain information that is not readily available in claims could influence study outcomes, such as clinical and disease-specific parameters.
- The algorithm for hypoglycemia events likely captured only severe events, possibly underestimating hypoglycemia of other severities.

Conclusions

- This retrospective analysis of a large VHA database among T2DM patients showed that U-500R initiation was associated considerable improvements in treatment patterns and glycemic control.
- Dispensed total daily dose (dTDD) and insulin dosage (units/kg) captured in claims increased dramatically. Together with improved adherence as measured by PDC, this suggests U-500R addresses unmet patient insulin needs. The decrease in HbA1c was clinically meaningful, with modest but statistically significant increases in hypoglycemic events.
- The discovery of significantly lower insulin usage before U-500R initiation warrants future research on the prevalence of unmet medical needs and suboptimal dosing among this patient population. Such research can help clinicians identify patients with compliance issues and thereby formulate more effective T2D management strategies.
- Additionally, analysis in the commercial and Medicare MarktScan data showed that U-500R, can be used as monotherapy to reduce patient financial burden.
- Despite the significant increase in TDD, which likely helped to address the less-than-optimal dosing with standard concentration insulin, mean annual IR-OOP pharmacy costs did not increase after U-500KP initiation.
- The results suggest that a decreased number of copays over the 12-month study period reduced IR-OOP pharmacy costs for a majority of patients.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
2. Nguyen NT, Nguyen XM, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: Findings from the National Health and Nutrition Examination Survey, 1999–2006. Obes Surg. 2011;21(3):351-5.
3. Qiao Q, Nyamdorj R. Is the association of type II diabetes with waist circumference or waist-to-hip ratio stronger than that with body mass index? Eur J Clin Nutrition. 2010;64(1):30-4.
4. Biggs ML, Mukamal KJ, Luchsinger JA, et al. Association between adiposity in midlife and older age and risk of diabetes in older adults. JAMA. 2010;303(24):2504-12.
5. Berentzen TL, Jakobsen MU, Halkjaer J, Tjønneland A, Sørensen TI, Overvad K. Changes in waist circumference and the incidence of diabetes in middle-aged men and women. PloS One. 2011;6(8):e23104.
6. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. Jama. 2018 Apr 24;319(16):1723-5.
7. Caspard H, Jabbour S, Hammar N, Fenici P, Sheehan JJ, Kosiborod M. Recent trends in the prevalence of type 2 diabetes and the association with abdominal obesity lead to growing health disparities in the USA: an analysis of the NHANES surveys from 1999 to 2014. Diabetes, Obesity and Metabolism. 2018 Mar;20(3):667-71.
8. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and Type 2 diabetes. Nature. 2006 Dec;444(7121):840.
9. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. World journal of diabetes. 2017 Apr 15;8(4):120.
10. Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: Review and meta-analysis. J Diabetes Science Technol. 2012;6(2):412-20.
11. Lane WS, Weinrib SL, Rappaport JM, Hale CB, Farmer LK, Lane RS. The effect of long-term use of U-500 insulin via continuous subcutaneous infusion on durability of glycemic control and weight in obese, insulin-resistant patients with type 2 diabetes. Endocr Pract. 2012;19(2):196-201.
12. Painter NA, Sisson E. An overview of Concentrated Insulin Products. Diabetes Spectr. 2016;29(3):136-40.
13. Eby EL, Curtis BH, Gelwicks SC, et al. Initiation of human regular U-500 insulin use is associated with improved glycemic control: A real-world US cohort study. BMJ Open Diabetes Res Care. 2015;3(1):e000074.
14. United States Food and Drug Administration. Humulin R U-500 Label. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018780s153lbl.pdf. Accessed July 7, 2018.
15. Hood RC, Arakaki RF, Wysham C, Li YG, Settles JA, Jackson JA. Two treatment approaches for human regular U-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose U-100 insulin therapy with or without oral agents: a randomized, titration-to-target clinical trial. Endocrine Practice. 2015 Mar 26;21(7):782-93.
16. Grunberger G, Bhargava A, Ly TT, et al. Human regular U-500 insulin via continuous subcutaneous insulin infusion vs. multiple daily injections in adults with T2D—The VIVID study—all randomized population [abstract]. Diabetes. 2018;67(suppl 1). https://dx.doi.org/10.2337/db18-351-OR
17. Eby EL, Zagar AJ, Wang P, et al. Healthcare costs and adherence associated with human regular U-500 versus high-dose U-100 insulin in patients with diabetes. Endocr Pract. 2014;20(7):663-70.
18. Eby EL, Wang P, Curtis BH, et al. Cost, healthcare resource utilization, and adherence of individuals with diabetes using U-500 or U-100 insulin: A retrospective database analysis. J Med Econ. 2013;16(4):529-38.
19. Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. BMC Edocr Disord. 2008;8(1):4.