ADA®

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Conference Highlights & Insights for Managed Care Specialists

Toujeo®

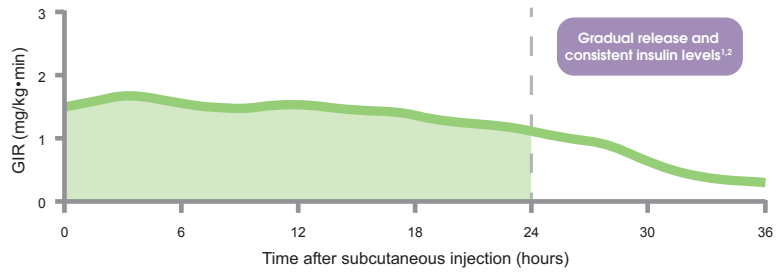
insulin glargine injection 300 Units/mL

An Insulin of Today

A stable activity profile[a] to last beyond 24 hours[1]

Once-daily Toujeo® should be injected at the same time each day.

A different distribution profile than an equivalent dose of Lantus® (insulin glargine injection) 100 Units/mL[1]



1/3 the injection volume of standard insulin (100 Units/mL)[1]

GIR=glucose infusion rate.

[a]The pharmacodynamics of Toujeo® at steady state after 8 days of daily injections was evaluated against Lantus® in a euglycemic clamp study of patients with type 1 diabetes mellitus (T1DM) (N=30). The dose on day 8 was followed by a 36-hour euglycemic clamp.[1,3]

- Toujeo® at steady state had a different activity profile than an equivalent dose of Lantus®, with a 27% lower GIR as measured by the 24-hour area under the curve[1]
- Steady-state levels are reached by at least 5 days of once-daily injections[1]
- Patients on Toujeo® may require a 10%-18% higher dose than patients on Lantus®[1]

Indications and Usage for Toujeo® (insulin glargine injection) 300 Units/mL

Toujeo® is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use: Toujeo® is not recommended for treating diabetic ketoacidosis.

Please see additional Important Safety Information for Toujeo® on the following pages.

Please see brief summary of full Prescribing Information for Toujeo® on the following pages.

Important Safety Information for Toujeo® (insulin glargine injection) 300 Units/mL

Contraindications

Toujeo® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to insulin glargine or any of its excipients.

Warnings and Precautions

Toujeo® contains the same active ingredient, insulin glargine, as Lantus®. The concentration of insulin glargine in Toujeo® is 300 units per mL.

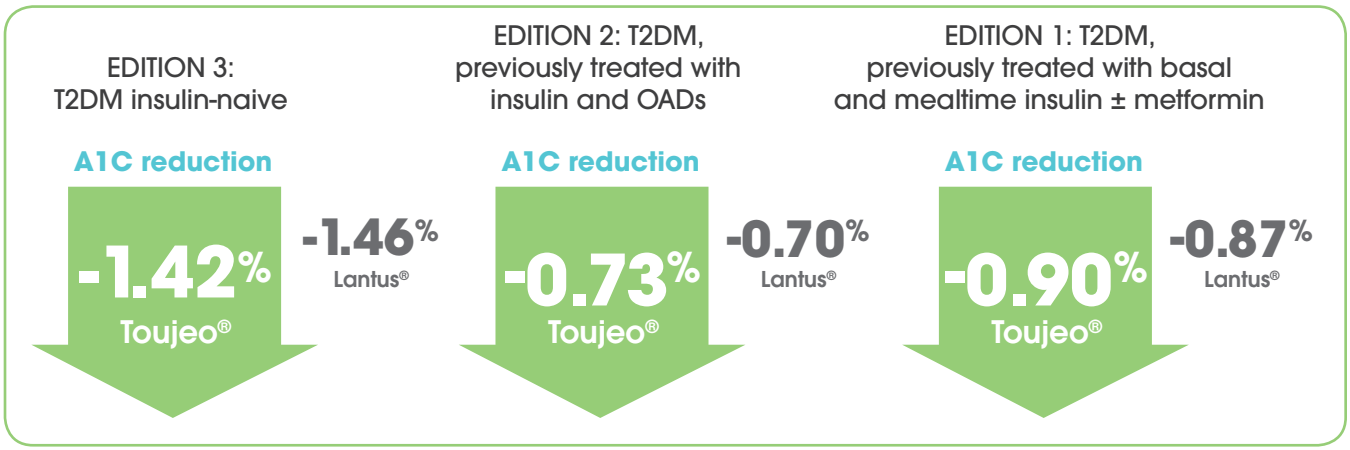
Insulin pens and needles must never be shared between patients. Do NOT reuse needles.

Toujeo® offers today's adult patients who require basal insulin:

- Small precipitate and gradual release[1,2]
- A1C: Reductions in a broad range of adult patients with diabetes[1,b]
- Proven safety profile[1]
- Redesigned pen
- Toujeo® COACH—tailored, integrated patient support

[b]Based on their previous anti-hyperglycemic therapy.

Toujeo® provides consistent and significant A1C reductions in a once-daily dose[1,c]



- In all studies Toujeo® met the primary endpoint (prespecified noninferiority margin of 0.4% and a 95% CI)[1,4]

[c]All studies were 26-week, open-label, controlled, titrate-to-target, noninferiority studies in adults with diabetes not at A1C goal (range: 7% to 10% or 11%), randomized to Toujeo® or Lantus® once daily. All patients were titrated to an FPG goal of 80-100 mg/dL. In EDITION 1, patients used Toujeo® with mealtime insulin analog ± metformin. In EDITION 2 and 3, patients used Toujeo® with OADs.

T2DM=type 2 diabetes mellitus; OAD=oral antidiabetes drugs; FPG=fasting plasma glucose.

Incidence of hypoglycemia in T2DM studies[1]	
Severe,[d] Toujeo® with OADs regimen	0.9% to 1.0%
Severe,[d] Toujeo® with mealtime insulin regimen	5%
Documented symptomatic hypoglycemia in multiple studies[e,f]	8% to 37%

- Most common adverse events with Toujeo® in T2DM patients: 7.1% nasopharyngitis, 5.7% upper respiratory infection

[d]Severe hypoglycemia: event requiring assistance of another person to actively administer a resuscitative action.

[e]Documented symptomatic hypoglycemia: an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value ≤54 mg/dL.

[f]Toujeo® with OADs or with mealtime insulin regimen with or without metformin.

Visit www.toujeopro.com for more information.

References

1. Toujeo® Prescribing Information. May 2015. **2.** Maiorino MI, et al. *Expert Opin Biol Ther.* 2014; 14(6):799-808. **3.** Becker RHA, Dahmen R, et al. *Diabetes Care.* 2015;38(4):637-643. **4.** Data on file, Sanofi US.

US.GLT.15.11.011

Toujeo®
insulin glargine injection 300 Units/mL

Important Safety Information for Toujeo® (insulin glargine injection) 300 Units/mL

Warnings and Precautions (cont'd)

Monitor blood glucose in all patients treated with insulin. Modify insulin regimens cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral antidiabetic treatment. Changes in insulin regimen may result in hyperglycemia or hypoglycemia.

Unit for unit, patients started on, or changed to, Toujeo® required a higher dose than patients controlled with Lantus®. When changing from another basal insulin to Toujeo®, patients experienced higher average fasting plasma glucose levels in the first few weeks of therapy until titrated to their individualized fasting plasma glucose targets. Higher doses were required in titrate-to-target studies to achieve glucose control similar to Lantus®.

Hypoglycemia is the most common adverse reaction of insulin therapy, including Toujeo®, and may be life-threatening.

Medication errors such as accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. Patients should be instructed to always verify the insulin label before each injection.

Do not dilute or mix Toujeo® with any other insulin or solution. If mixed or diluted, the solution may become cloudy, and the onset of action/time to peak effect may be altered in an unpredictable manner. Do not administer Toujeo® via an insulin pump or intravenously because severe hypoglycemia can occur.

Severe life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue Toujeo®, monitor and treat if indicated.

A reduction in the Toujeo® dose may be required in patients with renal or hepatic impairment.

As with all insulins, Toujeo® use can lead to life-threatening hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Closely monitor potassium levels in patients at risk of hypokalemia and treat if indicated.

Fluid retention, which may lead to or exacerbate heart failure, can occur with concomitant use of thiazolidinediones (TZDs) with insulin. These patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of TZD must be considered.

Drug Interactions

Certain drugs may affect glucose metabolism, requiring insulin dose adjustment and close monitoring of blood glucose. The signs of hypoglycemia may be reduced in patients taking anti-adrenergic drugs (eg, beta-blockers, clonidine, guanethidine, and reserpine).

Adverse Reactions

Adverse reactions commonly associated with Toujeo® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain.

Important Safety Information for Toujeo® SoloStar®

Toujeo® SoloStar® is a disposable prefilled insulin pen. To help ensure an accurate dose each time, patients should follow all steps in the Instruction Leaflet accompanying the pen; otherwise they may not get the correct amount of insulin, which may affect their blood glucose levels.

Do not withdraw Toujeo® from the SoloStar® disposable prefilled pen with a syringe.

Please see Brief Summary of Prescribing Information on the following pages.

Brief Summary

TOUJEO® **Rx Only**
(insulin glargine injection) U-300, for subcutaneous use

Brief Summary of Prescribing Information

1. INDICATIONS AND USAGE

TOUJEO is indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use

TOUJEO is not recommended for the treatment of diabetic ketoacidosis.

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

- Inject TOUJEO subcutaneously once a day into the abdominal area, thigh, or deltoid at the same time each day.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[See Adverse Reactions (6.1)]*.
- Individualize and titrate the dosage of TOUJEO based on the individual's metabolic needs, blood glucose monitoring results, and glycemic control goal. The dosage of TOUJEO ranges from 1 to 80 units per one injection.
- To minimize the risk of hypoglycemia titrate the dose of TOUJEO no more frequently than every 3 to 4 days.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.2), and Use in Specific Populations (8.5, 8.6)]*.
- To minimize the risk of hypoglycemia, do not administer TOUJEO intravenously, intramuscularly or in an insulin pump.
- To minimize the risk of hypoglycemia, do not dilute or mix TOUJEO with any other insulin products or solutions.

2.2 Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes:

- The recommended starting dose of TOUJEO in insulin naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.
- The maximum glucose lowering effect of a dose of TOUJEO may take five days to fully manifest and the first TOUJEO dose may be insufficient to cover metabolic needs in the first 24 hours of use [*See Clinical Pharmacology (12.2) in the full prescribing information*]. To minimize risks associated with insufficient insulinization when initiating TOUJEO, monitor glucose daily, titrate TOUJEO per instructions, and adjust co-administered glucose lowering therapies per standard of care.

Type 2 Diabetes:

- The recommended starting dose of TOUJEO in insulin naïve patients with type 2 diabetes is 0.2 units per kilogram of body weight once daily. The dosage of other anti-diabetic drugs may need to be adjusted when starting TOUJEO to minimize the risk of hypoglycemia *[See Warnings and Precautions (5.3)]*.

2.3 Starting Dose in Patients with either Type 1 or Type 2 Diabetes Already on Insulin Therapy

- To minimize the risk of hypoglycemia when changing patients from a once daily long-acting or intermediate acting insulin product to TOUJEO, the starting dose of TOUJEO can be the same as the once daily long-acting dose. For patients controlled on LANTUS (insulin glargine, 100 units/mL) expect that a higher daily dose of TOUJEO will be needed to maintain the same level of glycemic control *[see Clinical Pharmacology (12.2) in the full prescribing information and Clinical Studies (14.1) in the full prescribing information]*.
- To minimize the risk of hypoglycemia when changing patients from twice-daily NPH insulin to once-daily TOUJEO, the recommended starting TOUJEO dose is 80% of the total daily NPH dosage.
- To minimize the risk of hyperglycemia when changing patients to TOUJEO, monitor glucose frequently in the first weeks of therapy titrate the dose of TOUJEO per instructions and the dose of other glucose lowering therapies per standard of care. *[See Warning and Precautions (5.2) and Clinical Pharmacology Section (12.2) in the full prescribing information]*.

2.4 Important Administration Instructions

- Prior to initiation of TOUJEO, patients should be trained by their healthcare professional on proper use and injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Patient should follow the *Instructions for Use* to correctly use the pen device and administer TOUJEO.

Please see Brief Summary of full Prescribing Information for Toujeo® on the following pages.

- Patients should be informed that the dose counter of the TOUJEO SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected. The TOUJEO SoloStar prefilled pen has been specifically designed for TOUJEO, therefore no dose conversion is required *[Patient counseling information (17) in the full prescribing information].*
- Patients should be instructed to visually inspect the TOUJEO solution for particulate matter and discoloration prior to administration and only use if the solution is clear and colorless with no visible particles.
- For single patient use only *[see Warnings and Precautions (5.1)].*
- Refrigerate unused (unopened) TOUJEO SoloStar prefilled pens.

4. CONTRAINDICATIONS

TOUJEO is contraindicated:

- During episodes of hypoglycemia *[See Warnings and Precautions (5.3)].*
- In patients with hypersensitivity to insulin glargine or one of its excipients *[See Warnings and Precautions (5.5)].*

5. WARNINGS AND PRECAUTIONS

5.1 Never Share a TOUJEO SoloStar pen Between Patients

TOUJEO SoloStar disposable prefilled pens must never be shared between patients, even if the needle is changed. Pen sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant oral anti-diabetic products may be needed.

On a unit to unit basis, TOUJEO has a lower glucose lowering effect than LANTUS *[See Clinical Pharmacology (12.2) in the full prescribing information].* In clinical trials, patients who changed to TOUJEO from other basal insulins experienced higher average fasting plasma glucose levels in the first weeks of therapy compared to patients who were changed to LANTUS. To minimize the risk of hyperglycemia when initiating TOUJEO monitor glucose daily, titrate TOUJEO according to labeling instructions, and adjust co-administered glucose lowering therapies per standard of care *[See Dosage and Administration (2.2, 2.3)].* Higher doses of TOUJEO were required to achieve similar levels of glucose control compared to LANTUS in clinical trials *[*see *Clinical Studies (14.1) in the full prescribing information].*

The onset of action of TOUJEO develops over 6 hours following an injection. In type 1 diabetes patients treated with IV insulin, consider the longer onset of action of TOUJEO before stopping IV insulin. The full glucose lowering effect may not be apparent for at least 5 days *[See Dosage and Administration (2.2) and Clinical Pharmacology (12.2) in the full prescribing information].*

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulin, including TOUJEO. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving, or operating other machinery). Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[See Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of TOUJEO may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature *[*see *Clinical Pharmacology (12.2) in the full prescribing information].* Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[*see *Drug Interactions (7)].* Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.5, 8.6)].*

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. To minimize the risk of hypoglycemia do not administer TOUJEO intravenously, intramuscularly or in an insulin pump or dilute or mix TOUJEO with any other insulin products or solutions.

5.4 Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TOUJEO and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including TOUJEO. If hypersensitivity reactions occur, discontinue TOUJEO; treat per standard of care and monitor until symptoms and signs resolve *[See Adverse Reactions (6)].* TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or other of the excipients *[See Contraindications (4)].*

5.6 Hypokalemia

All insulin products, including TOUJEO, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including TOUJEO, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[See Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[See Warnings and Precautions (5.5)]*
- Hypokalemia *[See Warnings and Precautions (5.6)]*

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates actually observed in clinical practice.

The data in Table 1 reflect the exposure of 304 patients with type 1 diabetes to TOUJEO with mean exposure duration of 23 weeks. The type 1 diabetes population had the following characteristics: Mean age was 46 years and mean duration of diabetes was 21 years. Fifty five percent were male, 86% were Caucasian, 5 % were Black or African American and 5 % were Hispanic. At baseline, the mean eGFR was 82 mL/min/1.73m^2 and 35% of patients had eGFR≥90 mL/min/1.73m^2. The mean BMI was 28 kg/m^2. HbA1c at baseline was greater or equal to 8% in 58% of patients.

The data in Table 2 reflect the exposure of 1242 patients with type 2 diabetes to TOUJEO with mean exposure duration of 25 weeks. The type 2 diabetes population had the following characteristics: Mean age was 59 years and mean duration of diabetes was 13 years. Fifty three percent were male, 88% were Caucasian, 7% were Black or African American and 17% were Hispanic. At baseline, mean eGFR was 79 mL/min/1.73m^2 and 27% of patients had an eGFR≥90 mL/min/1.73m^2. The mean BMI was 35 kg/m^2. HbA1c at baseline was greater or equal to 8% in 66% of patients.

Common adverse reactions were defined as reactions occurring in ≥5% of the population studied.

Common adverse reactions occurring for TOUJEO-treated subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Hypoglycemia is discussed in a dedicated subsection below.

Table 1: Adverse reactions in two pooled clinical trials of 26 weeks and 16 weeks duration in adults with type 1 diabetes (with incidence ≥5%)

	TOUJEO + mealtime insulin*, % (n=304)
Nasopharyngitis	12.8
Upper respiratory tract infection	9.5

*"mealtime insulin" refers to insulin glulisine, insulin lispro, or insulin aspart

Table 2: Adverse reactions in three pooled clinical trials of 26 weeks duration in adults with type 2 diabetes (with incidence ≥5%)

	TOUJEO*, % (n=1,242)
Nasopharyngitis	7.1
Upper respiratory tract infection	5.7

*one of the trials in type 2 diabetes included mealtime insulin

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TOUJEO *[See Warnings and Precautions (5.3)].* In the TOUJEO program, severe hypoglycemia was defined as an event requiring assistance of another person to administer a resuscitative action and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored or plasma glucose value equal to or less than 54 mg/dL.

The incidence of severe hypoglycemia in patients with type 1 diabetes receiving TOUJEO as part of a multiple daily injection regimen was 6.6% at 26 weeks. The incidence of documented symptomatic hypoglycemia was 69% at 26 weeks. There were no clinically important differences in hypoglycemia between TOUJEO and LANTUS among type 1 diabetes patients.

The incidence of severe hypoglycemia in patients with type 2 diabetes was 5% at 26 weeks in patients receiving TOUJEO as part of a multiple daily injection regimen, and 1.0% and 0.9% respectively at 26 weeks in the two studies where patients received TOUJEO as part of a basal-insulin only regimen. The incidence of documented symptomatic hypoglycemia in patients with type 2 diabetes receiving TOUJEO ranged from 8% to 37% at 26 weeks and the highest risk was again seen in patients receiving TOUJEO as part of a multiple daily injection regimen.

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

Insulin, including TOUJEO, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy

Long-term use of insulin, including TOUJEO, can cause lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients and may affect insulin absorption *[see Dosage and Administration (2.1)].*

Weight gain

Weight gain has occurred with some insulin therapies including TOUJEO and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Allergic Reactions

Some patients taking insulin therapy, including TOUJEO have experienced erythema, local edema, and pruritus at the site of injection. These conditions were usually self-limiting. Severe cases of generalized allergy (anaphylaxis) have been reported *[See Warnings and Precautions (5.5)]*.

Cardiovascular Safety

No clinical studies to establish the cardiovascular safety of TOUJEO have been conducted. A cardiovascular outcomes trial, ORIGIN, has been conducted with LANTUS. It is unknown whether the results of ORIGIN can be applied to TOUJEO.

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The incidence of MACE was similar between LANTUS and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE; 1.02 (0.94, 1.11)].

In the ORIGIN trial, the overall incidence of cancer (all types combined) [Hazard Ratio (95% CI); 0.99 (0.88, 1.11)] or death from cancer [Hazard Ratio (95% CI); 0.94 (0.77, 1.15)] was also similar between treatment groups.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

In a 6-month study of type 1 diabetes patients, 79% of patients who received TOUJEO once daily were positive for anti-insulin antibodies (AIA) at least once during the study, including 62% that were positive at baseline and 44% of patients who developed anti-drug antibody [i.e., anti-insulin glargine antibody (ADA)] during the study. Eighty percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

In two 6-month studies in type 2 diabetes patients, 25% of patients who received TOUJEO once daily were positive for AIA at least once during the study, including 42% who were positive at baseline and 20% of patients who developed ADA during the study. Ninety percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TOUJEO with the incidence of antibodies in other studies or to other products, may be misleading.

7. DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with TOUJEO use may be increased with antidiabetic agents, (ACE) inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be decreased when co-administered with atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isonazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline) and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be increased or decreased when co-administered with alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.4 Drugs That May Affect Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)]* may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with TOUJEO.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking TOUJEO.

Human data

There are no clinical studies of the use of TOUJEO in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal data

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 50 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.3 Nursing Mothers

Endogenous insulin is present in human milk; it is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when TOUJEO is administered to a nursing woman. Use of TOUJEO is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of TOUJEO have not been established in pediatric patients.

8.5 Geriatric Use

In controlled clinical studies, 30 of 304 (9.8%) TOUJEO treated patients with type 1 diabetes and 327 of 1242 (26.3%) TOUJEO treated patients with type 2 diabetes were ≥65 years of age, among them 2.0 % of the patients with type 1 and 3.0% of the patients with type 2 diabetes were ≥75 years of age. No overall differences in effectiveness and safety were observed in the subgroup analyses across the age groups.

Nevertheless, caution should be exercised when TOUJEO is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia *[See Warnings and Precautions (5.3), Adverse reactions (6) and Clinical Studies (14) in the full prescribing information]*.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of TOUJEO has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with hepatic impairment *[See Warnings and Precautions (5.3)]*.

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of TOUJEO has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with renal impairment *[See Warnings and Precautions (5.3)]*.

8.8 Obesity

No overall differences in effectiveness and safety were observed in subgroup analyses based on BMI.

10. OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*. Mild episodes of hypoglycemia can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity level may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

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TABLE OF CONTENTS

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Financial Impacts of Care Models and Complications in Diabetes

The financial strain of diabetes on the health care industry and those individuals with diabetes is staggering. The *Economic Costs of Diabetes in the U.S. in 2012* study commissioned by the American Diabetes Association® estimated a diabetes-associated cost of $245 billion in the U.S., the figure having risen in the 4 years that have followed the study.

Hospital inpatient care, prescription medications to treat associated complications, anti-diabetic agents and supplies, physician office visits, and nursing/residential facility stays accounted for the largest percentage of the expenditure costs. Indirect costs such as missing work, lowered productivity or ability to work also contributed to the economic burden of diabetes, according to the study. The Sessions featured a number of insights into these pressing issues.

American Diabetes Association®
Scientific Sessions

Increases in Expenditures on Glycemic Control Drugs Among U.S. Adults with Diabetes, 1987–2013

In the United States, expenditures for prescription medications for glycemic control are proving to be one of the greatest causes of financial burden on diabetic patients. Even so, "little is known about the pattern of the increase over time," said **Xilin Zhou, MD,** study presenter.

Using nationally representative data from the 1987 National Medical Expenditure Survey and the 1996–2013 Medical Expenditure Panel Survey, study authors analyzed trends in per capita expenditures (in 2013 dollar-value) on glycemic-control drugs, specifically focusing on over 36,000 patients, at least 18 years of age, with self-reported diabetes.

Their analysis showed:

- The glycemic-control drug expenditure per person with diabetes quintupled from $243 in 1987 to $1,152 in 2013.
- The percentage of patients who took glycemic medications increased from 55% to 83% from 1987 to 2013.
- Annual spending on insulins increased by $11 from 1987 to 2006, and by $81 from 2007 to 2013.

However, the pattern of annual spending on non-insulin glucose-lowering agents was more irregular with up-and-down inflections (FIGURE).

"Further research is needed to understand the underlying reasons associated with the substantial increase in total medi-

FIGURE. Per capita expenditures on glycemic-control drugs among adults with diabetes, 1987–2013

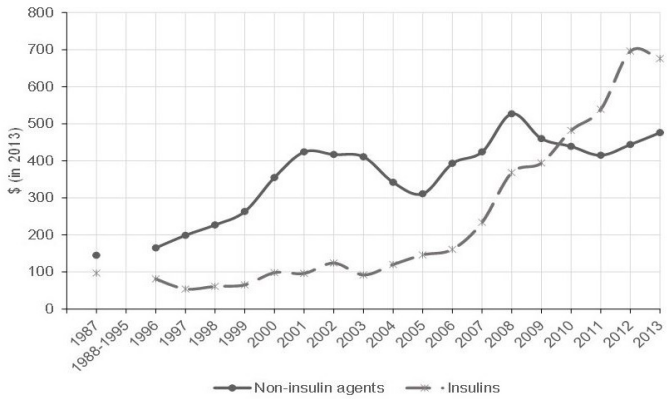


Photo: © ADA 2016

cation expenditure on glycemic-control drugs, as well as different expenditure patterns exhibited by insulin and non-insulin glucose-lowering agents," said Zhou.

110-OR

Chronic Care Model in an Integrated Primary Care Clinic Improves Financial Outcomes

Interventional strategies to prevent diabetes mellitus (DM) are growing as a key focus in endocrinology as diabetes is a chronic illness that represents one of the highest health care cost factors attributed to hospital admissions.

Athena Philis-Tsimikas, MD, and colleagues recruited 236 patients with type 1 and 2 DM (mean age = 61.94 ± 11.44 years; 51% male) from a San Diego, CA, clinic that included diverse payors and an integrated primary care physician (PCP) group. Patients were then risk-stratified by HbA1c, blood pressure, and low-density lipoprotein cholesterol, and subsequently enrolled in a 1-year care management program comprised of standardized decision-support tools, team-based care from an RN, health coach, and PCP, as well as a depression-care manger.

Study authors recruited patients for comparison from a separate San Diego clinic with the same health system of treating diabetic patients. The comparison group of 239 patients were matched by gender, age, and clinical risk.

Results showed that 18.4% of patients from the comparison clinic had an emergency department (ED) or inpatient admission during the follow-up period—more often than those treated at the care management clinic (5.1%). There were also significant differences in the mean number of ED and inpatient admissions per clinic patient in the comparison group versus the care management clinic. The direct variable costs per clinic were also much higher in the control group (M = $1,852; SD = $8,194) than in the care managed group ($932; SD = $7,845).

"Previously presented data showed significant improvements in HbA1c, lipids and patient satisfaction," for the care managed group, said Philis-Tsimikas. "The results of this population-based, chronic care management program within a PCP site of a large urban health system indicate that hospital and ED cost reductions of 50% can be achieved within the first year of implementing the program. This is in line with the broader general mandate of achieving the triple aim of improved health, cost and satisfaction."

115-OR

The Slipping Slipper Sign—A Poor Man's Test for Severe Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy—damage to peripheral nerves, often causing weakness, numbness and pain, usually in hands and feet—has thought to be detectable using the slipping slipper sign (SSS) screening method. The method is simple: patients are asked, "Have you ever lost a slipper (footwear unstrapped at the ankles) while walking without being aware that you have done so?" An affirmative response confirms the presence of SSS.

Surujpal Teelucksingh, MD, and colleagues sought to examine what it could mean for patients and screenings to have a positive SSS compared to traditional neuropathy scores, nerve conduction studies, and ultrasounds of the right sural nerve.

Study authors looked at 74 patients with diabetes who underwent ultrasonographic and nerve conduction studies of the right sural nerve by an examiner unaware of each participant's SSS status. Findings were assessed against demography, clinical history, anthropometry, as well as traditional clinical and autonomic neuropathic scores.

The analysis revealed a number of differences between the patients who had SSS as compared with those who did not:

- The duration of diabetes in SSS differed significantly from patients without the SSS.
- Those with SSS were more likely to have reported a higher frequency of retinopathy (36.8%) and cerebrovascular accidents (18.4%) compared with those without, (2.8% and 13.9%, respectively).
- There was notable diminished nerve conduction as evidenced by both latency and amplitude.
- There was a reduction of the maximal thickness of the right sural nerve measured by utrasonography at the ankle (3.0 vs. 3.5) and leg (3.4 vs. 3.9).

Overall, "The SSS, when positive, identifies individuals with severe diabetic peripheral neuropathy and highly abnormal nerve conduction and ultrasonographic characteristics," said Teelucksingh.

22-LB

Impact of a Patient Engagement Program on Patients with Type 2 Diabetes from a Patient-centered Medical Home Model

Helping patients with type 2 diabetes mellitus (T2DM) manage their care is essential for better outcomes, lower treatment costs, and overall patient quality of life. The Patient-centered Medical Home (PCMH) care-delivery model, in which care is coordinated through a patient's primary care physician, "has had great impact on improving quality of care through better care coordination and clinician alignment," said **Mazi Rasulnia, MD,** study presenter.

While the usefulness of PCMH is known, Rasulnia and colleagues further examined the incorporation and impact of external coaching and engagement services into the PCMH care delivery.

To do so, study authors analyzed participants in a remote behavioral counseling interventional program for management of T2DM, dividing the patients into two groups. One cohort, numbering 64 patients, was enrolled in the intervention through the New Jersey Academy of Family Physicians, and the non-PCMH group of patients, numbering 102 patients, either self-enrolled in the intervention or were enrolled by their clinician. Participants were selected based on HbA1c levels of 6.5% or higher at enrollment.

Results showed that there were no statistically significant difference between the two study groups in HbA1c at baseline ($p = 0.531$) or graduation ($p = 0.341$) or weight at baseline ($p = 0.821$) or graduation ($p = 0.777$) between the PCMH group and non-PCMH group, meaning participation in PCMH did not affect these levels. (See TABLE.)

"However," Rasulnia said, "both groups saw a statistically significant reduction of HbA1c and weight through the intervention. Results suggest that, no matter the setting, a high-touch, patient centered engagement intervention is an effective solution for the management of type 2 diabetes."

144-LB

TABLE. Differences in Patient-centered Medical Home Care-delivery Study Groups

	PCMH Group n = 64	Non-PCMH Group n = 102	p-value
HbA1c Baseline	8.33%	8.49%	0.531
HbA1 Graduation	7.30%	7.14%	0.341
Weight (lbs.) Baseline	219	220	0.821
Weight (lbs.) Graduation	213	215	0.777

Comparing Medical and Prescription Costs in Disease-specific and Standard Benefit Plans Over Time

Results from the Natural Experiments for Translation in Diabetes Study show that disease-specific insurance benefit design may, over time, improve health care costs.

Tannaz W. Moin, MD, and colleagues analyzed the Diabetes Health Plan (DHP), a disease-specific health plan for individuals with diabetes and prediabetes. DHP increases access to medications, primary care, chronic disease management, and patient clinical care reminders.

In comparing eight employer groups offering the DHP and 37–45 concurrent control employers that offered standard benefits, study authors looked at comparative changes in total, out-of-pocket (OOP) and plan, medical, and prescription costs between 2009 and 2013; specifically, they conducted an interrupted time series (ITS) analysis of mean employer-level costs per member per month (PMPM). Over 2,400 employees and dependents (aged 19–62) who were continuously enrolled over 4 years were included.

Employer-level propensity matches identified comparable control employers offering standard benefit plans. Distinct ITS models were estimated for total, OOP, and plan prescription costs and for total, OOP, and plan medical costs, all reported on a PMPM basis.

Follow-up, averaged over 3 years, showed significantly lower monthly changes in prescription costs and significantly lower monthly changes in medical costs.

"We found that DHP employer groups had lower monthly changes in PMPM total, OOP and plan prescription and medical costs over 3 years of follow-up, compared with concurrent controls offering standard benefit plans," said Moin. "These findings suggest that disease-specific insurance benefit designs that enhance access to care may play an important role in decreasing prescription and medical costs over time."

111-OR

Effect of High-deductible Insurance on Acute Diabetes Complications

How high-deductible health plans (HDHP) affect diabetes mellitus (DM) outcomes is unclear, despite the known prevalence of HDHP, which represent 46% of all plans, according to study presenter **James Frank Wharam, MD.**

Wharam and colleagues looked at a national sample of over 12,000 HDHP members, aged 12–64, with DM who had been enrolled for 1 year in a low-deductible plan ($500 or less a year), and who were then enrolled for 2 years in a HDHP ($1,000 or more a year) after an employer had mandated the change in plan. Study authors propensity-score matched (1:1) HDHP patients to concurrent controls whose employers offered only low-deductible plans. Outcomes were time to first acute DM complication and the total expenditure of the first complication.

> "Disease-specific insurance benefit designs that enhance access to care may play an important role in decreasing prescription and medical costs over time."
>
> *—Tannaz W. Moin, MD*

Results showed that "HDHP members with DM, especially high morbidity patients, experienced highly concerning delays in acute complication visits and increases in costs per complication episode," said Wharam.

Specifically:

- HDHP members delayed first acute complication visits during follow-up and cumulative mean costs per episode were $12,935.40—higher than for controls after 2 years.
- High morbidity HDHP members delayed acute complication visits and experienced a $19,605.20 absolute increase in cumulative costs per complication episode after 2 years.
- Corresponding values among low income HDHP members were 0.914 and $8,217.70.

114-OR

Frequency of Hypoglycmia in Hospitalized Patients Treated with Insulin Increases Overall Costs Associated with Hospitalization

While hospital-associated hypoglycemia is often correlated to inpatient-associated complications—and therefore cost of care—**Joseph Aloi, MD,** study presenter, explained that the financial implications of inpatient hypoglycemia have been unclear.

"The aim for this study was to examine the association of incidence and severity of hypoglycemia for patients prescribed insulin during a hospitalization with length of stay and overall cost of the inpatient stay," said Aloi.

For 1 year, study authors evaluated approximately 44,400 admitted patients with diabetes who were prescribed insulin during hospitalization at an academic medical center. Researchers compared the 387 patients who had been treated with insulin and who had experienced a significant hypoglycemic event to the 44,000 patients who did not experience a significant hypoglycemia during their admission, specifically comparing length of stay and overall cost of the inpatient stay.

The patients who experienced a severe hypoglycemic event had longer lengths of stay than those who did not, being admitted, on average, 8 days more (4.3 days vs. 12.3 days). The costs were also higher in the patients who experienced these events and who had been treated with insulin: $83,000 vs. $29,700.

The frequency of the hypoglycemic events also impacted length of stay and costs; more than three events translated to an additional 4 days of hospitalization and an increase of associated costs of $27,000.

"These data support an association between inpatient hypoglycemia and increased costs of care mostly attributable to increasing length of stay," said Aloi. "Further prospective studies are needed to further clarify the association and identify strategies to prevent hypoglycemia and possibly lower costs."

152-LB

INTERVIEW

Insulin Glargine Injection, a Once-daily Basal Insulin

An interview with Deborah A. Hinnen, APN, BC-ADM, CDE, FAAN

What is the insulin glargine U300 injection and what is it indicated for?

Glargine U300 is trade named Toujeo® and it is a long-lasting basal insulin pen. It lasts 24 hours and up to 36 hours, and it is indicated for adult patients with type 1 or type 2 diabetes who are taking insulin.

How does it differ from other insulin injections?

Because Toujeo® lasts up to 36 hours, it is truly a once-a-day basal insulin. This makes it so much more convenient for our patients. In fact, I tell patients it's fine to take it in the morning. I have patients worry and say, "Gosh, Debbie, my blood sugar's good. It's 98 at bedtime and I don't wanna take a shot. I might get low in the middle of the night." So I say, "Fine. Take it in the morning." That lifts a worry, a burden off of them. So I think our compliance improves. Moreover, glargine U300 is what I would call an ultra-long basal; it lasts longer than other insulin glargine or insulin detemir options, such as Lantus® or Levemir®. It also has a flatter pharmacodynamic profile and there's less nocturnal hypoglycemia, as well as less weight gain than these other options.

Does the longer-lasting feature of insulin glarine U300 affect prescribers or payers?

Prescribing is a little bit different because each pen has 1.5 ml. It's three times more concentrated. So there are 450 units in each pen, three pens per box. So it took me a while to get accustomed to this. When you're writing the prescription, it goes up by 45's. So if a patient is new to Toujeo®, they might be on a minimal dose and you might write up to 46 units per day, one box of three pens per month. But as their dose increases, or if it is a patient you're transitioning over, it's a unit-for-unit transition, but it would be up to 90 units, so two boxes of three pens per month; 135 units, three boxes of three pens; 180 units, four boxes of three pens

And we've also found that the pen is covered incredibly well by payers, both commercial and Part D, so it is an easy opportunity for clinicians. If people have commercial insurance and they can use the co-pay card, they can get the product for $15.00. It's once-a-day and affordable; that's the bottom line. ●

Estimating the Cost of Incident Diabetes Complications

While it is clear that diabetes comprises a substantial proportion of health care expenditures, knowing how to best plan financially and assess quality across the United States health care system could be improved with cost models based on updated complication rates and the associated costs of these incidences.

Zhu and colleagues sought to develop such a cost model by gathering published data to gauge the direct medical costs of diabetes-related complications for adults in the U.S. Researchers conducted a systematic search for literature that provided the incidence and/or cost of diabetes-related complications, such as cardiovascular disease, neuropathy, nephropathy, retinopathy, and acute metabolic complications; 54 studies met eligibility criteria.

The cost models estimated complication-related incident and follow-up costs for 10,000 adults with diabetes over 1-, 3-, and 5-year time horizons. Estimates for costs at 1, 3, and 5 years respectively showed:

Congestive Heart Failure
- $7,320,287
- $26,791,067
- $50,697,865

Gangrene:
- $2,844,381
- $9,426,696
- $17,200,417

End-stage Renal Disease:
- $4,225,384
- *Not Available*
- $13,211,204

Blindness:
- $320,460
- $1,922,758
- $4,806,896

"This model provides a benchmark for health systems to prospectively model interventions to reduce diabetes-related medical expenditures and estimate cost-effectiveness and potential leakage within a care delivery network," said **Kia Zhu, MD**, study presenter. ●

1239-P

"We've also found that [Toujeo®] is covered incredibly well by payers, both commercial and Part D, so it is an easy opportunity for clinicians."

—Deborah A. Hinnen, APN, BC-ADM, CDE, FAAN

Technology and the Diabetic Patient

Advances in technology have been a key component of diabetes management and treatment since the discovery of the disease in the early 20th century. From methods of testing blood glucose to insulin injections to artificial to pancreases to advanced monitoring systems that deliver needed medication, the devices used by clinicians and patients with diabetes must advance as quickly as other widely used technologies. In some cases, using technologies already available can be as useful as developing new ones, especially since so many clinicians and patients have access to tools like mobile phones or computers.

American Diabetes Association® SVP of medical innovation **Jane Chiang, MD,** and IBM Watson Health chief health officer **Kyu Rhee, MD,** met at the 76th Scientific Sessions where the two organizations announced their co-effort to reimagine how diabetes is managed.

Photo: © A.J. Sisco/Feature Photo Service for IBM 2016

Skype-based Intervention for Teens with Poorly Controlled Diabetes: A Family Affair

Managing the care for adolescents with type 1 diabetes can be difficult for both adolescents and caregivers as issues such as miscarried helping, family conflict, and acceptance of illness can act as barriers to quality care.

Study authors questioned if long-distance live-video intervention could assist in resolving some of these issues. Researchers randomized 90 adolescent participants with type 1 diabetes with poor glycemic control with HbA1c levels 9.0% or greater to receive Behavioral Family Systems Therapy for Diabetes (BFST-D) via Skype or via Clinic conditions.

Participant characteristics:

- Mean HbA1c at time of enrollment was 11.01%;
- Mean duration of diabetes was 6.7 years;
- Mean participant age was 15.0;
- 45% were female; and
- 88% were Caucasian.

At 3 months, adolescents and a caregiver completed the Helping for Health Inventory (HHI), Conflict Behavior Questionnaire (CBQ), and the Acceptance of Illness Scale (AIS) at baseline, post, and at follow-up.

Upon review, responses showed no significant variances in outcomes across Skype and Clinic conditions, so researchers collapsed the cohorts for further examination. In doing so, repeated measure of analysis of variation showed great improvements occurring from pre- to follow-up in parent- and youth-reported HHI scores, as well as in parent- and youth-reported CBQ scores. What's more, parent AIS scores were greatly improved from pre- to follow-up; youth AIS scores did not.

"Interestingly," said **Danny C. Duke, MD,** study author, "post hoc analysis identified that, for parents, the relationship between miscarried helping and acceptance of illness was mediated by overall reductions in family conflict."

"Findings provide further support for the equivalence of BFST-D delivered via videoconferencing when compared to traditional in-person delivery," said Duke. "Additional support was also provided for BFST-D as a means of reducing miscarried helping and family conflict, and for improving parental adjustment to illness. Results suggest parent acceptance of illness is associated with family conflict such that reductions in family conflict improve parental acceptance of illness, and that youth acceptance of illness is not related to family conflict."

284-OR

Technology-assisted Case Management in Low-income, Rural Adults with Type 2 Diabetes

Research shows that adults with diabetes of a lower income in rural regions have poorer access to treatment and, consequently, worse outcomes. To help address these disparities, "case management with home telemonitoring is a viable strategy for care," said **Leonard E. Egede, MD**. "We evaluated the efficacy of nurse case management with home telemonitoring and supervised medication titration in low-income rural adults with poorly controlled diabetes."

In their evaluation, study authors focused on rural federally qualified health centers in South Carolina, looking at 113 adults with baseline hemoglobin A1c (HbA1c) of 8% or greater, randomizing them to either technology assisted case management (TACM) or usual care (UC).

> "A combined technology-assisted and nurse-case managed intervention in low-income patients with poorly controlled T2DM is effective compared to usual care."
>
> *—Leonard E. Egede, MD*

The patients in the TACM group were given a 2-in-1 blood pressure and blood glucose device that uploads readings to a secure server; this cohort was asked to test daily. Using an American Diabetes Association® and Joint National Committee guided algorithm approved by primary care providers at the study clinics, nurses then reviewed the readings, titrating medications every 2 weeks based on average readings. Nurses were supervised by an internist and an endocrinologist.

The UC cohort received usual care.

Researchers evaluated patients at baseline, 3 months, and 6 months. The primary outcome was HbA1c at 6 months post-randomization.

At 3 months, 77% of patients had completed measurements. Seventy-five percent of patients had completed measurements at 6 months. Ultimately, at 6 months, HbA1c for the TACM cohort was "significantly lower at -.99 compared to usual care." Moreover, results also suggested that the rate of decline in HbA1c (-0.16) over time for TACM was significantly faster compared to usual care.

"A combined technology-assisted and nurse-case management intervention in low-income patients with poorly controlled T2DM is effective compared to usual care," said Egede. "This finding suggests that TACM provides a novel approach to diabetes care in under-resourced, primary care settings for patients with limited income and resources."

46-LB

Diabetes Alert Dogs vs. Technology

Patient Experiences and Perceived Accuracy

While not yet common, Diabetes Alert Dogs (DADs) are increasingly being used as a method of monitoring blood glucose. What isn't clear, said **Jaclyn A. Shepard, MD,** study presenter, are "the reasons patients with type 1 diabetes (T1D) decide to use alternatives to current blood glucose monitoring technology in their self-management."

Shepard and colleagues conducted a preliminary investigation of nine patients (age 22–43 years; seven female; median A1c = 7.2%) who had experiences with and views about DAD-use and continuous glucose monitoring. Study authors also gleaned insight from eight parents of youth with T1D (youth age 8–17 years; four female; median A1c = 8.0%) who owned DADs. Study participants responded via questionnaires that evaluated prior experience with continuous glucose monitoring, as well as their views on DAD performance. Advocates claim that DADs can detect changes in blood chemistry that occur during rapid changes in blood sugar levels.

Nearly all participants, with the exception of two parents, said that they had previously used but discontinued continuous glucose monitoring. Respondents reported that they had discontinued continuous glucose monitoring because of issues such as "inaccuracy, burden of use, and financial reasons." Specifically, parents said that burden of use for their child, as well as inaccuracy, lead to discontinuation.

Researchers also identified a prevalent theme regarding why participants obtained a DAD: problems associated with severe hypoglycemia and hypoglycemia unawareness. What's more, "parents reported obtaining a DAD to provide them with a sense of security, especially overnight, regarding their child's

blood glucose fluctuations and to promote increased autonomy for their child," said Shepard.

Respondents overwhelmingly, with the exception one parent, believed that their DAD was "more accurate than current diabetes technology, reporting that DADs could detect BGs outside a median target range of 4.4 mmol/L –9.7 mmol/L and 4.7 mmol/L–11.1 mmol/L, respectively," Shepard said.

This preliminary study suggests that those who obtain a DAD had previously used but discontinued continuous glucose monitoring. "Overall, DAD owners tend to believe that their DADs are more accurate than current diabetes technology," said Shepard, and DADs "offer perceived benefits related to low blood glucose detection and peace of mind."

Presenters stressed that larger trials with a focus on objective accuracy measurements are needed, however.

75-LB

Comparative Effectiveness of Telemedicine Strategies

A recent systematic review and network analysis reveals that telemedicine may assist in the management of type 2 diabetes mellitus (T2DM).

"Telemedicine has been introduced as a tool to support health care delivery and management of type 2 diabetes," said **Shaun W. Lee, MD**, study presenter. "However, the effectiveness of different telemedicine strategies on diabetes care remains unclear, as head-to-head comparisons are sparse. We performed a systematic review of randomized, controlled clinical trials which investigated the effect of telemedicine on type 2 diabetes," he said.

Looking at data up to June 2015, Lee and colleagues examined information from over 6,500 patients across 38 studies. The analysis revealed a number of findings that supported telemedicine as a promising strategy.

In the pairwise random-effects meta-analysis, telemedicine was found to reduce reduced HbA1c by a weighted mean difference of -0.77% and fasting plasma glucose by 0.78mmol/L. Moreover, network meta-analysis revealed that tele-education and telemonitoring were connected with a significantly better HbA1c control compared to usual care at -0.71% and -0.38%, respectively.

The findings showed, however, that changes in HbA1c were similar for other telemedicine strategies compared to usual care: telemanagement (-0.06%); teleconsultation (-0.30%); tele-education and telemonitoring (-0.41%), telemanagement and telemonitoring (-0.36%); and tele-education and telemanagement (-0.30%). There were no significant differences in the various telemedicine strategies.

"The results suggest that most telemedicine [strategies] were associated with small but modest improvements in glycemic control," said Lee, "especially those targeting patient education and monitoring."

289-OR

Mobile Apps

Facilitating Diabetes Problem Solving

Mobile applications may help with critical problem solving that teenaged type 1 diabetics face in managing their own diabetes, according to new research.

"Teens with type 1 diabetes (T1D)

INTERVIEW

Inhaled Human Insulin: A More Rapid Onset of Action

An interview with Robert A. Baughman, PharmD, PhD

Tell us about this inhaled human insulin, specifically the insulin inhalation system Technosphere®.

Technosphere® insulin is a dry powder insulin. It's administered with what we call the Gen2 Inhaler and it is used to control hyperglycemia in individuals with type 1 or type 2 diabetes. It is a rapidly absorbed insulin. Of all the insulins that are administered, it is the one that most closely resembles the endogenous insulin released by the pancreas following a meal. The powder is administered with a Gen2 inhaler—about the size of a whistle—immediately before the first bite of food; patients can administer a second dose if necessary if they find that they've eaten too much or it didn't correlate their meal to their projected insulin dose.

You performed a meta-analysis of clamp data from three clinical studies. What was the purpose of your analysis and how was it conducted?

The study was a meta-analysis of the pharmacokinetics and pharmacodynamics of Technosphere® insulin; the data was obtained from both type I diabetics and healthy, normal volunteers. When the Afrezza®, insulin human, was first launched, the prescribing information had indicated that, although the insulin concentrations were more rapidly absorbed with Technosphere®, that it wasn't translating to a faster onset of action. Our experience was just the opposite in almost all of our trials. So we've gone back and looked at 59 subjects in a single, large analysis to evaluate the onset of action.

What did your analysis find?

We were able to show that, regardless of how you choose to determine the onset of action—and we looked at five different methods of determining that—Technosphere® insulin showed a more rapid onset. Now that's significant because, if patients have an elevated value that needs to be lowered quickly, then they have, at their disposal, a product that will be able to do so and assist them in controlling their hyperglycemia. The good news is that it can be done with simple finger sticks—or what they call self-monitored blood glucose—and can also be used with continuous glucose monitoring. So we look forward to better controlling a diabetic's glucose levels. ●

struggle to identify and resolve barriers to self-care," said **Sarah E. Vaala, MD**, study presenter. As many teenagers today have ease of access to and familiarity with smart phones, mobile applications seem to be an obvious choice for helping this demographic manage diabetes.

A mobile application called MyDay utilizes real-time blood glucose with data of key psychosocial factors that influence teens, such as mood and social context. This information is graphed via tracking, and supplies real-time feedback, showing how behavior influences high, low, or missing blood glucose levels.

To better understand the effectiveness of the app, Vaala and colleagues conducted a pilot 2-week randomized clinical trial with 28 teens, aged 13–19, with T1D. The teens used the app and a Bluetooth meter for 2 weeks. The teens then entered daily data at meals and bedtime. This data was further studied as participants were asked to execute a structured problem-solving interview regarding their data patterns and self-care goals.

At 54%, "most teens reported that they were surprised by app feedback," said Vaala. "All [participants] independently identified at least one relevant pattern from the feedback graphs—such as times of day associated with high blood glucose." Other findings included:

- 86% of teens reported identifying a new self-care insight;
- 79% of teens identified viable reasons for data patterns; and
- 9% of teens generated a self-care goal related to their feedback.

"Results suggest graphical feedback that combines momentary cognitive-behavioral and contextual data with blood glucose facilitates critical steps in teens' diabetes problem solving," said Vaala, including "pattern recognition, problem awareness and barrier identification." ●

283-OR

INTERVIEW

Trends in Medication Use in Patients with T2DM: A Long-term View of Real-world Treatment Between 2000 and 2015

An Interview with Victoria Higgins

What was the purpose of this analysis and why did you focus on the real-world clinical practice?

A lot of current data looks at clinical trial data, which is very important to review, but clinical trial data has quite strict inclusion/exclusion criteria; diabetics with cardiovascular-related issues, older patients, or females might be excluded, for example.

In looking at real-world data, we looked at physician consulting practices, and there's no exclusion criteria. These are everyday type 2 diabetics coming to their doctors. We wanted the doctors' opinions and assessment of how they're treating patients, as well as the patient opinions. We also wanted to see how the newer classes of drugs that have been introduced have changed and impacted that treatment over time.

How did you conduct your analysis?

The analysis covered five key European Union markets; France, Germany, Italy, Spain, the United Kingdom, as well as the United States. We collected the research from 2000 to 2015. There were separate data points; the analysis wasn't longitudinal in that we didn't track the same patient. We also, over time, looked at the newer therapy classes being introduced in place of some of the older therapies. We went to primary care practitioners and diabetes specialists—endocrinologists in the U.S. and diabetologists in the European countries. We asked the physicians to complete very comprehensive case report forms on patients. It included a lot of clinical data, including their A1C measurements and current treatment plans.

We conducted an interview with the physicians to gather the perceptions of how they think they're treating the disease as well. For example, when we asked them, "At what AIC level would you introduce insulin at which A1C level?", we saw a disconnect between the clinical data and real-world data.

What did your analysis reveal?

To start, we are starting to see higher prevalence of more poly pharmacy with more drugs being used in patients, as well as a slightly higher increase in insulin usage, especially amongst the specialist population. Moreover, when we asked at what A1C level physicians would introduce insulin, it was lower in 2000. Then, more doctors were saying between less than 8% or between 8% to 8.99%. But in 2015, more doctors were saying they would wait until a higher A1C at about 9% before they'd start introducing insulin. And, interestingly, you've got all these new classes coming along, which are being used. More poly pharmacies are being used, but we're not seeing that translate to a more positive outcome in more patients in terms of an A1C level of control.

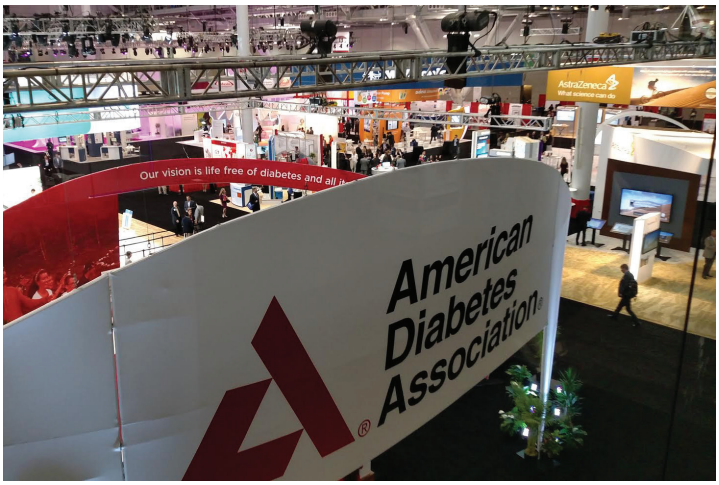
What are the implications of these insights of the real-world practices on those patients with type 2 diabetes?

I think the data we've collected shows that there needs to be a clearer pathway of how these newer classes are being used and introduced in real-world settings. There could be more real-world analysis on, say, adherence. Perhaps the more drugs patients are using, the more confused they are, especially older patients who might have more comorbidities and have a higher drug burden; that might be one area to explore further to see if that's why, ultimately, the A1C levels aren't being achieved.

A lot of doctors are used to clinical trial data. So this is new way of looking at things. Ninety percent of type 2 diabetics would not qualify for a clinical trial and 49% of newly diagnosed diabetics also would not qualify. So real-world data is more representative. ●

Diabetes in the Real World

As diabetes affects a great number of people in the United States—1.4 million Americans are estimated to be diagnosed with diabetes every year, according to the ADA®—a key research focus has been how diabetes affects patients in the real world. This real-world data is necessary because much of the research used for treating diabetes and developing therapies comes from clinical trials, which can often have strict inclusion criteria. This practice may cause "every day" diabetics to be excluded from the benefits of the findings. Moreover, as the Sessions showed, the clinical trial data and real-world data often do not correlate. Using data that accurately represents the reality of diabetes complications, managed care trends, medication efficacy, and other critical issues is more important now than ever.



American Diabetes Assocation
76th Scientific Sessions

Real-world Use of Open Source Artificial Pancreas Systems

Artificial Pancreas Systems (APS) with off-label use of existing insulin pumps, continuous glucose monitors (CGM), and open source software (OpenAPS) have been developed by over 40 diabetes patients over a 6-month period. Measuring safety by evaluating the duration of hypoglycemia and hyperglycemia, researchers have thought that OpenAPS is much safer than typical pump/CGM therapy; there have been no reports of severe hypo or hyperglycemic events.

"[OpenAPS] has allowed patients and caregivers remarkable improvements in quality of life due to increased time in range, uninterrupted sleep, and peace of mind," said **Dana M. Lewis, MD,** study presenter.

To gain further insight into the efficacy and user experience of OpenAPS, researchers, using both qualitative and quantitative measures, surveyed 18 respondents on their experience using self-built APS. Respondent characteristics:

- 67% male / 33% female;
- 61% adults / 39% children;
- median age 27 years old;
- 15 years with diabetes;
- 10 years on pump therapy; and
- 3 years on CGM.

Respondents self-reported that, while using OpenAPS, outcome measures showed median HbA1c levels fell from 7.1% to 6.2%, and median percent time in range (80–180 mg/dL) increased from 58% to 81%. All but one of the respondents reported some improvement in sleep quality, and 56% reported a significant improvement.

While improvements were relayed, the OpenAPS users also warned that these "do it yourself" artificial pancreas implementations necessitate a major effort to build and maintain, and users also stressed that "these systems cannot be considered a 'technological cure,' but [they] were extremely satisfied with the 'life-changing' improvements associated with using an APS." In terms of health care providers, many users said that their providers were supportive, while some showed a lack of interest, to the disappointment of respondents.

"These experiences are instructive for what patients can expect from commercial APS when they become available," said Dr. Lewis, and "can help health care providers be prepared to set patients' expectations properly when discussing or recommending an APS."

104-LB

Improvement in Quality of Life After Initiation of Basal Insulin: Trials vs. Real-world

Poor medication adherence by patients with type 2 diabetes mellitus (T2DM) in real-world settings impacts therapy outcomes, particularly when compared with trial outcomes.

Edward Tuttle, MD, study author, and colleagues sought to evaluate the change of HbA1c levels in real-world settings

for patients initiating second-line diabetes medications. They also sought to assess the gap between randomized control trial and real-world efficacy, as well as what factors might account for these differences.

Using the U.S. EMR-administrative claims database, study authors initiated a retrospective cohort study to identify adult T2DM patients who had initiated a glucagon-like peptide-1 receptor agonist (GLP1) or a dipeptidyl peptidase-4 inhibitor (DPP-4). Researchers calculated the HbA1c level changes for patients with an HbA1c at drug initiation (-90, + 14 days) and a second HbA1c 1 year (± 90 days) after drug initiation.

Tuttle and colleagues looked at data that investigated the use of GLP1 or DPP-4 as a second-line treatment from 11 randomized control trials of products taken by more than 5% of real-world patients. Selected real-world patients had similar baseline HbA1c levels (7–10%) to the randomized clinical trial patients. Real-world patients were also drug-treated, but did not take insulin at baseline.

In calculating changes in HbA1c levels, study authors used a multivariate regression, controlling for baseline patient factors such as age, significant diabetes complications prior to a T2DM drug regimen, medication adherence (in this case, if patients adhered 80% or more of days covered by GLP1 or DPP-4), as well as the addition of other T2DM drugs.

In real-world settings, patients with T2DM who opt to change their medication regimen from other basal insulins to Gla-300 have improved glycemic control.

The 221 patients treated with GLP1 were younger than DPP-4 patients (57 vs. 63 years) had higher baseline HbA1c (8.34% vs. 8.15%) and were less adherent (29% vs. 37%). In comparing real-world GLP1-treated patients to those treated with DPP-4, researchers found that both had similar changes in HbA1c levels. In contrast, randomized clinical trials typically described a larger reduction in HbA1c than real-world study results. From the regression model, Tuttle and colleagues estimated that poor adherence accounted for 75% of the gap between the real-world and predicted trial results in both drug classes.

"Second-line treatments such as GLP1s and DPP-4s suffer from poorer outcomes in real-world settings, primarily due to poor adherence," said Tuttle, "indicating an urgent need for strategies to improve real-world adherence and realize the full benefit of therapy."

117-LB

Real-world Assessment of Patient Characteristics and Clinical Outcomes of Early Users of the New Insulin Glargine 300 U/mL (Gla-300)

In real-world settings, patients with type 2 diabetes mellitus (T2DM) who opt to change their medication regimen from other basal insulins to Gla-300 have improved glycemic control, and show a trend towards less hypoglycemia.

The new basal insulin glargine 300 U/mL (Gla-300), introduced to the United States market in 2015 based on data from the EDITION clinical trial program, is a formulation of insulin glargine that has a more constant pharmacokinetic profile with a prolonged duration of action, compared with insulin glargine 100 U/mL. To better evaluate the efficacy of Gla-300 in the management of T2DM, researchers assessed the use of Gla-300 in real-world settings.

Study author **Paulos Berhanu, MD,** and colleagues consulted the Predictive Health Intelligence Environment database, which is comprised of 24 integrated delivery networks in the United States. Researchers isolated patient-level data from 881 T2D patients—mainly male (53%), Caucasian (59.4%), nearly 60 years of age—who had used other basal insulins within 6 months prior to Gla-300 initiation; these patients were identified as having ≥ 1 prescription order of Gla-300 between March 2015, and Dec. 2015. Hypoglycemic events were identified based on ICD-9-CM diagnosis codes or blood glucose ≤ 70 mg/dL. Study authors looked at data for up to 6 months prior to and 6 months following the initiation of Gla-300.

Dr. Berhanu noted other prevalent medical conditions present in the cohort: Comorbid hypertension (86%); Dyslipidemia (88%), and diabetes-related complications (neuropathy [35%], nephropathy [17%], and retinopathy [11%]).

For patients who switched to Gla-300—specifically the subset of 267 patients whose A1c levels were measured at baseline and during follow-up—the mean A1c levels

decreased from 8.97% at baseline to 8.33% at follow-up, with a mean estimated reduction of 0.64%. Hypoglycemia also decreased for 449 patients who had switched to Gla-300 from other basal insulins: 6.0% vs. 5.1%, baseline vs. follow-up.

> "Second-line treatments such as GLP1s and DPP-4s suffer from poorer outcomes in real-world settings, primarily due to poor adherence, indicating an urgent need for strategies to improve real-world adherence and realize the full benefit of therapy."
>
> *—Edward Tuttle, MD*

The improved glycemic control and lessened hypoglycemia for patients with T2DM in real-world setting suggests that switching to Gla-300 from other basal insulins shows promise as a better method of T2DM management.

943-P

A Real-world Comparison of Longitudinal HbA1c and Health Care Costs in Patients Receiving Two Oral Antidiabetic Therapies, GLP-1RAs, or Basal Insulin

When treating type 2 diabetes mellitus (T2DM), clinicians usually adhere to a stepwise approach, based on many treatment guideline recommendations, but this may not be optimal as patients can experience uncontrolled HbA1c between steps.

"Timely and durable glycemic control is a key goal of T2DM treatment," said **Lawrence Blonde, MD**, Director of the Ochsner Diabetes Clinical Research Unit in the Department of Endocrinology, Diabetes and Metabolism, and an Associate Internal Medicine Residency Program Director at the Ochsner Medical Center in New Orleans, LA, and study author. Toward this end, researchers sought to understand this possible complication in the real world.

"[Our] study compare[d] treatment patterns and health care costs in patients with uncontrolled T2DM receiving two oral antidiabetic (OAD) therapies versus GLP-1RAs or basal insulin (BI) in a real-world setting using an administrative claims database," he said.

Using the MarketScan claims database, researchers looked at patients with T2DM from the start of Jan. 2007 to the end of Dec. of 2014. Those patients who were being treated with two OAD's, GLP-1RAs, or BI were selected (date of initiation of two OAD's, GLP-1RAs, or BI termed index), and were then required to have 6 months pre- and 1 year post-index plan enrollment and pre-index HbA1c greater than 7%. In total, the study included 4,375 patients treated with OAD's, 358 with GLP-1RAs, and 1,203 with BI patients.

Study authors then compared HbA1c from 6 months pre- to 1 year post-index, while also reporting all-cause costs for 1 year post-index. Moreover, a logistic regression evaluated demographic and clinical influences associated with being in the top 20% of the cost distribution.

Pre- to post-index, the study showed that BI patients had the largest HbA1c decrease—a mean decline of 10.0% to 8.0%. Patients treated with two OAD's showed a mean decline of 9.1% to 7.7%, followed by GLP-1RAs patients, whose mean HbA1c decrease of 8.8% to 7.6%.

Mean costs were:

- BI: $18,851
- GLP-1RAs: $14,099
- 2 OADs: $9,999.

Patients with higher comorbidity burden or receiving BI were at greatest risk of incurring high costs.

"Despite robust lowering in HbA1c, many patients did not achieve HbA1c < 7%," said Dr. Blonde. "While BI was associated with a large decrease in HbA1c, it was prescribed to patients with high baseline HbA1c and was associated with higher costs. Timely and intensive initiation of pharmacotherapy would likely have clinical and economic benefits." ●

355-OR

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