Winner, APEX Award of Excellence, 2017, APEX Awards forPublication Excellence

Winner, MarCom Platinum Award, 2017, Association of Marketing and Communication Professionals

IN CLINICAL STUDIES AND REAL-WORLD USE, TRESIBA® BOOSTS ITS STATUS AS BEST BASAL INSULIN

Saudi Endocrinologists Report Very Satisfying Results With Tresiba®

It has been more than two years since medical authorities in Saudi Arabia approved the marketing and use of Tresiba® (insulin degludec). That span of time has allowed Saudi endocrinologists to observe how Tresiba® performs and offer some conclusions.

Awad Alshahrani, MD, who attended the June 2018 Annual Scientific Sessions of the American Diabetes Association in Florida, USA, has formed some strong opinions about insulin degludec. Dr. Alshahrani is an endocrine and diabetes consultant, and KAMC assistant professor at King Saud Bin Abdulaziz University for Health Sciences in Riyadh.

Overall Impression

"I've had a very nice experience with Tresiba® with my patients in Saudi Arabia," says Dr. Alshahrani. "This relatively new insulin is a long-acting analog that probably has the longest half life of all the insulins we have. I use it with my heart patients who have difficulty controlling their blood glucose level. These patients require a very high dose of any other type of basal insulin.

(Continued on next page)

Long-Awaited CONFIRM Trials Results Are a Standout at ADA

The American Diabetes Association 78th Scientific Sessions brought more than 14,000 attendees, 900 speakers, and 2,100 poster presentations to Orlando, Florida, USA, June 22-26, 2018. The sessions are among the most important diabetes-related annual conferences in the world.

The conference highlighted new studies and offered key updates and treatment follow-up trial summaries. Several of its most notable papers focused on insulin degludec—Tresiba®—including the results of the CONFIRM study[1]. The CONFIRM study is a non-interventional, retrospective comparative effectiveness study of insulin degludec and insulin glargine U300 in 4,056 insulin-naïve adults in the USA with type 2 diabetes. Patients eligible for the study had no evidence of basal insulin use in the 365 days prior to the index date.

Among other things, the study found that insulin degludec is more effective at lowering rates of hypoglycemia—by 30%—than insulin glargine U300. Tresiba® displayed more flexible timing with regard to when diabetes patients can inject it.

(Continued on page 3)

changing diabetes®

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"When we compare insulin degludec with glargine U300 or any other basal insulin, the results are notable. Once we started using Tresiba®, we got excellent control with lower doses and better hemoglobin A1c levels, as well as lower incidences of hypoglycemia, especially nocturnal hypoglycemia."

Dr. Alshahrani adds that Tresiba® has had a specific beneficial effect for Muslims. "When we talk about Tresiba® and patients with type 2 diabetes, it is amazing to me, as a Muslim here in Saudi Arabia, or the Middle East, or any Muslim community, that it shows its effectiveness during Ramadan and even the hajj." The fact that its effectiveness extends well beyond one day, he says, is a great help to diabetics who are focused on events that can distract them from adhering to their insulin injection schedules.

> "When we talk about Tresiba® and patients with type 2 diabetes, it is amazing to me, as a Muslim, that it shows its effectiveness during Ramadan and even the hajj." – Awad Alshahrani, MD

Effects on Hypoglycemia and A1c

Dr. Alshahrani notes that because Tresiba® is long-acting and has an extended half life beyond 24 hours, he has found that Tresiba® is a better option for those patients who have early-morning hypoglycemia. "It has been a very good choice. It prevents nocturnal hypoglycemia."

Essa Al Dhafiri, MD, agrees that insulin degludec is particularly effective against hypoglycemia. "A hypoglycemia episode is a terrible experience and we've had some patients discontinue insulin because of it." Dr. Al Dhafiri is a consultant endocrinologist and medical director at Al Alam Medical Center in Riyadh. "It's a better option for those patients who have experienced hypoglycemia compared with other insulins. The CONFIRM study showed that a reduction in hemoglobin A1c level occurs more often with degludec than with glargine.[1] This means that degludec is a better choice for good or better control of diabetes."

Dr. Al Dhafiri says that because hypoglycemia in general and nocturnal hypoglycemia in particular is such a bad experience, "patients with frequent nocturnal hypoglycemia who wake up with all the symptoms of hypoglycemia are likely to discontinue insulin because of the risk its poses for inducing hypoglycemia. But with insulin degludec there is a lower risk of hypoglycemia compared with other insulins. Patients taking degludec will have less nocturnal hypoglycemia, and this will lead to better compliance and good sugar control."

Dr. Al Dhafiri refers to the SWITCH 1 and SWITCH 2 studies, which tracked the efficacy of Tresiba® in patients with type 1 diabetes (SWITCH 1)[2] and patients with type 2 diabetes (SWITCH 2).[3] Tresiba® showed non-inferior HbA1c control vs insulin glargine, he explains.

"But I think the most important study for degludec is the CONFIRM study, which was conducted to monitor the effectiveness of degludec versus glargine. It confirmed the likelihood that hemoglobin A1c levels are lower with degludec compared with glargine U300." Dr. Al Dhafiri adds that it's not necessary to discontinue insulin because of previous instances of hypoglycemia when there is an insulin—Tresiba®—that does not induce bouts of nocturnal hypoglycemia.

Mohamed Abu Alhassan, MD, an endocrinologist at International Medical Center in Jeddah, has found that many patients experience fewer hypoglycemic attacks while using Tresiba®. "I have a small group of patients who use glargine U300. It frequently can cause hypoglycemia. But I don't have any patients, including those with type 1 diabetes, who suffer nocturnal hypoglycemic episodes when taking small doses of Tresiba® to control their fasting blood sugar level. So now 100% of the basal insulin I prescribe is degludec. Also, for my patients who do shift work, if they miss one dose of Tresiba® it is still working 36 hours later."

Dr. Abu Alhassan adds that he has had many patients with hemoglobin A1c levels of more than 10%. "Some of them were using glargine and short-acting insulin. When we shifted them to Tresiba® over a span of four weeks, they had a 2 and even a 3-percentage point reduction in their A1c levels. Their hypoglycemia disappeared. They were happy with their numbers for the first time. This was especially true for patients with type 1 diabetes, for whom control can be difficult. When they achieve control, it's a big achievement for them, as well as for us."

Cardiovascular and Renal Conditions

Can new basal insulins such as Tresiba® and glargine U300 pose a cardiovascular risk to diabetes patients? In the United States, the Food and Drug Administration (FDA) requires manufacturers of diabetes drugs to show whether their products increase the incidence of cardiovascular problems. This mandate covers GLP-1s and SGLT-2s as well as insulins.

(Continued from page 1)

CONFIRM reported that patients treated with Tresiba® had significantly lower A1c levels after 6 months compared with patients treated with insulin glargine U300. Findings also showed patients treated with Tresiba® had a higher treatment continuation rate compared with patients treated with insulin glargine U300.

Link to the CONFIRM Study

CONFIRM is clinical outcome assessment of the effectiveness of insulin degludec (Tresiba) in real-life medical practice (CONFIRM)–A comparative effectiveness study of degludec and insulin glargine 300U/mL (glargine U300) in insulin-naïve patients with type 2 diabetes (T2D).[1]

Other Tresiba®-related trials reported at the 2018 ADA Annual Scientific Sessions:

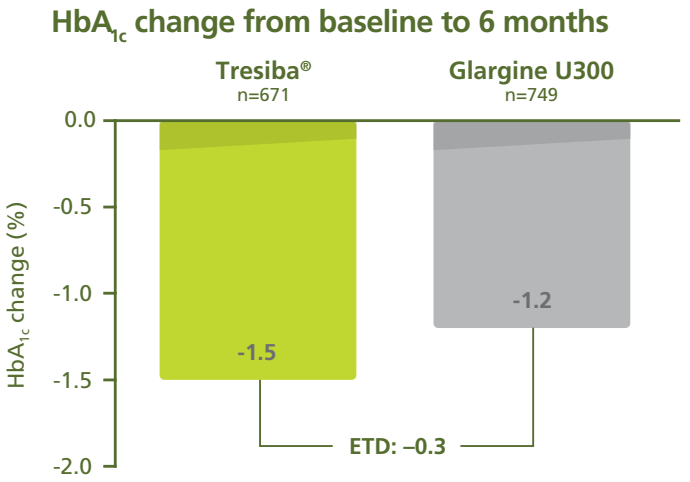
SWITCH Trials: Relationship between A1c and hypoglycemia risk comparing Tresiba® with insulin glargine U100 in type 1 and type 2 patients.[2,3]

The DEVOTE trial: In a randomized trial in patients with history of chronic kidney disease or cardiovascular disease, treatment with Tresiba® did not increase the patient risk of major adverse cardiovascular events, cardiovascular death, or all-cause mortality compared with glargine U100.[4]

European Tresiba Audit (EU-TREAT): This study evaluates the change in A1c level from switching to Tresiba® after at least 6 months of using another basal insulin.[5]

DELIVER D+ subgroup analysis: Switching to a 2nd generation basal insulin analog like Tresiba® or glargine U300 from glargine U100 or Insulin detemir is associated with comparable glycemic control and incidences and rates of hypoglycemia 6 months after switching.[6]

See "References" on the final page of this newsletter to view abstracts of the papers presented at the ADA Scientific Sessions.[7]



Results are presented as adjusted least square means with associated ETD. Robust standard errors were used to adjust for the potential dependence between repeated measures on individuals. *$p<0.01$ for change in HbA_{1c} over 180 days of treatment. CI, confidence interval; ETD, estimated treatment difference; glargine U300, insulin glargine 300 units/mL.

Source: CONFIRM study[1]

Both Dr. Alshahrani and Dr. Al Dhafiri vouch for the usefulness of Tresiba® in patients who have cardiovascular problems. "It's a good insulin even in type 2 patients who have or are worried about cardiovascular complications," says Dr. Alshahrani.

"The risk of cardiovascular problems with degludec are much less when compared with any other insulin," adds Dr. Al Dhafiri.

Dr. Alshahrani says insulin degludec is the best choice for use in diabetes patients who have renal problems and use insulin. "It can be used safely even in patients with chronic renal disease. We adjust the dose and use lower doses with Tresiba® than with other insulins."

"Renal insufficiency often is one of the effects of hypoglycemia," says Dr. Al Dhafiri. "Because use of degludec leads to much less hypoglycemia, I think it is a better choice than other insulins for patients who have renal disease or renal insufficiency."

Fewer Patients Abandoning Insulin

Saudi endocrinologists also say that the flat-line behavior of Tresiba® offers the possibility of fewer patients abandoning the use of insulin to manage their diabetes. "In the past, for the patient who experiences hypoglycemia, we either discontinued using insulin or decreased insulin doses to the degree that it would not cause hypoglycemia," says Dr. Al Dhafiri. "The problem with that is while we are controlling hypoglycemia, we are not controlling blood sugar levels. Because degludec causes less hypoglycemia compared with other basal insulins, the number of patients who may eventually discontinue using it will be fewer than the number of patients who stop using other insulins."

"Tresiba® is long-acting, the longest-acting insulin available," says Dr. Alshahrani. "It produces less weight gain than any other insulin, and because of its lack of peaks, we can prevent a hypoglycemic event. We can use it safely."'

Effects on Type 1s and the Elderly

Tresiba® has also greatly benefited patients with type 1 diabetes. "This is a story I don't mind telling about type 1s and Tresiba®," says Dr. Alshahrani. " Type Is usually are very tough, very special patients. We have to be very careful with them. Why? Because changes in the units of insulin they are injecting might change their ability to control their diabetes. From my practice, from clinical experience, and from the experience of other experts who manage patients with type 1 diabetes, we conclude that Tresiba® is an excellent choice as evidenced by less nocturnal hypoglycemia, less weight gain, better A1c control, and less of an accumulative dose compared with other insulins."

In dealing with elderly patients, Dr. Al Dhafiri says degludec is the better option for them. "Degludec allows for better control of sugar levels and fewer hypoglycemic episodes. Hypoglycemic events occurred about 33% less often with degludec compared with glargine. Elderly patients are often afraid of having a hypoglycemia episode. With degludec, they have less risk of hypoglycemia, so it's the better choice for them."

Establishing Doses and Titration

Although shifting patients to Tresiba® is becoming commonplace, Dr. Alshahrani says the switch requires caution. "When we switch patients from another insulin and replace it with insulin degludec, we have to be careful. Patients might need a lower dose initially than with other basal insulins. We have to observe patients for a few weeks to see what is the best dose for them. In my practice, many patients require high doses of different types of insulin.

CONFIRM: Retrospective real-world data in insulin-naïve patients with type 2 diabetes

REAL-WORLD DATA MAY GIVE YOU AND YOUR PATIENTS CONFIDENCE

PRIMARY ENDPOINT	Change in mean HbA_{1c} from initiation to 6 months of follow-up
OTHER ENDPOINTS*	Change in rates of hypoglycaemic episodes from initiation to 6 months of follow-up
	Change in proportion of patients with ≥1 episode of hypoglycaemia from initiation to 6 months of follow-up

Hypoglycaemia was recorded by the treating clinician and defined according to International Classification of Diseases codes 9 and 10.†

Limitation: Real-world data is generated outside a controlled clinical trial setting, the main methodological difference from RCTs being it does not randomise patients to treatment groups.

RCT (randomised controlled trial).

* Rate of hypoglycaemic episodes and proportion of patients with hypoglycaemia were estimated over a period of 180 days (pre- or post-initiation of basal insulin) using negative binomial and logistic regression, respectively and a generalised estimating equation approach.

† This definition differs from key Novo Nordisk RCTs with Tresiba®, e.g. SWITCH and DEVOTE.

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insulin degludec [rDNA origin] injection

"When they begin using degludec they usually require less insulin. As a consequence, patients don't gain much weight." Tresiba® trials showed comparable weight gain vs comparator insulins.

Dr. Al Dhafiri says it is now a year since he began prescribing degludec, and he has been pleased with the results. "A lot of patients whose blood glucose level was uncontrolled now are achieving control once we shift them to degludec. Their A1c levels have decreased and they are approaching their targets. Patients all have their own titration schedules, and may try to titrate by increasing their doses 1 to 2 units daily to achieve their targets. For those patients who are already using other basal insulins, we may start with the same dose of degludec that they've been using with other basal insulins, and give them two-thirds of the dose in the morning and one-third in the evening."

> "A lot of patients who have been uncontrolled now are achieving control once we shift them to degludec. Their A1c levels have decreased and they are approaching their targets."
> -- Essa Al Dhafiri, MD

Dr. Abu Alhassan usually starts with 10 units of Tresiba® when shifting patients from other basal insulins to Tresiba®. "By starting with small doses, my patients avoid hypoglycemia." He adds that hypoglycemia is more likely to occur in patients who are using other diabetes medications in addition to Tresiba®. He says that in his experience Tresiba®'s effectiveness ranges from a slight lowering of A1c level to "a 4% decrease that simply amazed me. None of my patients ever matched that number with another insulin."

"We are using fewer doses of Tresiba®, injecting it only once daily, knowing that it will more than cover 24 hours," says Dr. Alshahrani. "Because we are using it only once daily, we can predict its action. Glargine is effective for only about 20 hours. After that, patients' blood sugar levels can go sky high. And when we give a patient taking glargine another dose, the previous dose is still active. This can lead to hypoglycemia. This is why Tresiba®, from all clinical trials that have been done, is such a good choice for hypoglycemia, as well as lowered A1c levels, and less weight gain because of smaller doses."

When Dr. Abu Alhassan switches uncontrolled type 2 patients who use glargine to degludec, he usually prescribes the same dose. "For patients with type I diabetes, I'll usually decrease dosage by 2 or 3 units. With Tresiba® I usually only need to titrate doses 1 or 2 times. But when I'm using glargine, I'm titrating maybe every day or every 2 days. Often at the end of 2 weeks, some glargine users complain about hypoglycemia. With degludec this isn't an issue."

Treatment Costs

Tresiba® therapy over the long run, says Dr. Alshahrani, ends up costing less than treatment with other basal insulins. "It will cost less because it will require smaller doses to be effective. If we track the accumulative effects and cost, we'll be able to calculate that Tresiba® is more cost effective than glargine U300."

A Better Choice for Control

Dr. Alshahrani reports that his patients who have shifted to degludec, "mention that there's something different about it. The point they stress the most is less hypoglycemia, especially with type 1 diabetes patients. It plays a major role in preventing nocturnal hypoglycemia, especially in type 1 diabetes. It makes life easier for type 1 patients."

"My patients are telling me that this is the first time they were able to control their fasting blood sugar level," says Dr. Abu Alhassan. "It's easier to dilute than other insulins. The Important thing is the speed with which we achieve control. With other insulins it can take 4 weeks to 2 months to achieve control. But when we switch to Tresiba®, we often don't need more than 1 week to control a patient's blood glucose level with small doses."

Real World Performance

"I agree totally with the conclusions of the CONFIRM trial. And we see it in our practice," says Dr. Alshahrani. "When we compare Tresiba® with glargine U300, it's clear that those patients taking glargine U300 require high doses, which makes them more likely to experience nocturnal hypoglycemia. Patients are very happy with Tresiba®. A lower-dose insulin leads to fewer incidence of nocturnal hypoglycemia, and even their A1c levels are better controlled. So our real-world experiences certainly match the conclusions of clinical studies. We may need

more clinical trials but what's mentioned and confirmed so far is accurate."

> "With other insulins it can take 4 weeks to 2 months to achieve control. But when we switch to Tresiba®, we often don't need more than 1 week to control a patient's blood glucose level with small doses." – Mohamed Abu Alhassan, MD

Dr. Abu Alhassan appreciates Tresiba®'s lack of peaks. "Because Tresiba® is a steady worker, with no peaks, when a patient injects the insulin at night, for example 10 p.m., it works steadily through the night without peaking. This may be the most important feature of Tresiba®. With glargine, for example, it works for 6 hours and then reaches a high peak, which at this time of night can lead to hypoglycemia. That's why we haven't found instances of morning hypoglycemia in our patients who use Tresiba®."

Summing Up Tresiba®'s Appeal

What emerges from discussions with Saudi endocrinologists is a set of observations that are common to them all. Maiasa Mohammad Alqurashy, MD, endocrinology consultant and program director of the Endocrine Fellowship at Security Forces Hospital in Riyadh, says she agrees with the findings of the CONFIRM study and other reports presented at the American Diabetes Association annual meeting on the performance and effectiveness of Tresiba®. She offers a succinct list of Tresiba®'s strengths when contrasted with glargine U300.

Advantages of Tresiba®

- Fewer incidences of hypoglycemia
- Greater reduction in hemoglobin A1c levels
- Better patient compliance because of flexible injection times
- Easier, faster titration leading to quicker blood glucose control
- Significantly lower requirements for insulin needed to control blood glucose levels
- Fewer incidences of hypoglycemia means patients can be started on a lower dose of Tresiba®
- Fewer incidences of patients discontinuing insulin use
- Less hypoglycemia in labile or brittle diabetes

Novo Nordisk Response to CONFIRM

The CONFIRM trial was highlighted at the 78th American Diabetes Association Scientific Sessions held in Orlando, Florida, USA in June.[1] Those results included reports from Tresiba®-prescribing practitioners that, overall, they prescribed 9% lower doses of degludec compared with glargine U300. Also, they noted that with glargine U300, there was a 37% higher incidence of users discontinuing insulin therapy—perhaps because of an increased risk of hypoglycemia with glargine U300—compared with Tresiba® patients.

Amy Hess Fischl, MS, RDN, LDN, BC-ADM, CDE, a certified diabetes educator from the University of Chicago, USA, comments on these exciting results.

Based on the evidence presented, it is clear that the CONFIRM trial is validation of what is already known from data generated in the development Tresiba®. It also solidifies the results seen in the degludec versus glargine U100 trials and highlights the advantages of degludec versus glargine U300 in a real-world dataset.

> Lower hemoglobin A1c levels and fewer incidences of hypoglycemia are two compelling characteristics of Tresiba®.

As in clinical practice, we may not always be able to ascertain the exact reasons why patients discontinue therapy from a real-world database, it is reassuring that more patients on Tresiba® choose to continue taking insulin compared with glargine U300.

Lower hemoglobin A1c levels and fewer incidences of hypoglycemia are two compelling characteristics of Tresiba®.

It is also important to stress the value of real-world studies that parallel clinical studies. It shows that Novo Nordisk wanted to prove the benefits of its products in the real world, which is why real-world studies tend to be conducted along with clinical trials. When a clinical trial program is almost over, having reached Phase 3A, and those products are in the marketplace and being used, then it's time for evidence that shows the benefits of products in the general population. Based on the information provided, it appears this is how Novo Nordisk developed CONFIRM.

It was started last summer (2017) once they knew they had enough US patients to conduct a real-world study.

The findings of Tresiba®'s superiority in several areas—A1c levels, lower doses, and fewer insulin dropouts—are consistent with what Novo Nordisk saw in clinical trials. When companies are designing clinical trials, they use what is called 'Treat to Target,' meaning that all patients receive insulin treatments that will aid in reducing their blood glucose to the same level. When that happens the main measure —the key endpoint and outcome in a clinical trial—is hypoglycemia.

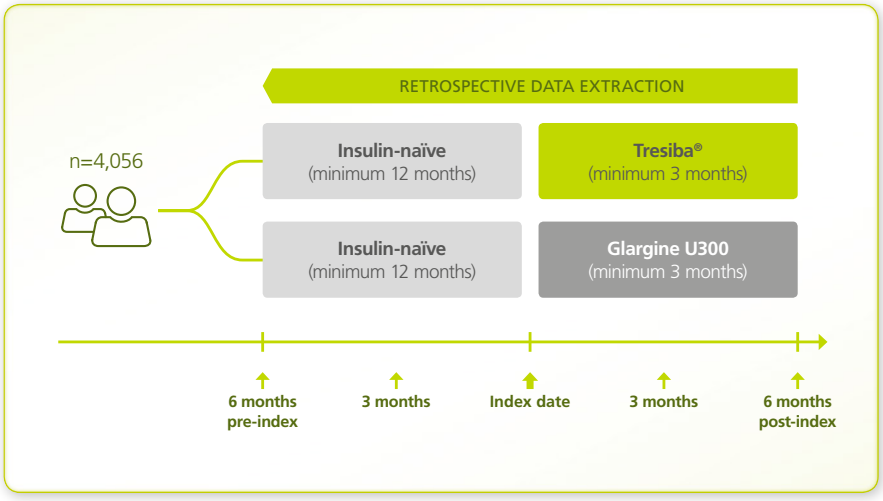
But in the real world, Treat to Target is not typically the measure. It depends upon patients and their doctors to decide their course of insulin treatment. In this format, they can measure an insulin's effectiveness in controlling blood sugar levels. What they found was improved glycemic control and a reduced rate of hypoglycemia, things that are not typically measured in a clinical trial but can be highlighted in the real world.

Effect on Hypoglycemia and A1c

It is clear to health care practitioners that the number 1 limiting factor to getting A1c levels down successfully is hypoglycemia. There is always a trade-off between lower blood sugar levels to reduce risk of long-term complications and hypoglycemia. As pharmaceuticals have advanced from human insulin, NPH, to analog insulin, there have been improvements in rates of hypoglycemia. Enter Tresiba®, which has the lowest rate of hypoglycemia among all insulins, based on its pharmacodynamics and pharmacokinetics. It has a very desirable profile in regards to the risk of hypoglycemia, which makes it a more desirable basal insulin.

CONFIRM: Retrospective real-world data in insulin-naïve patients with type 2 diabetes

CONFIRM IS A LARGE, LONGITUDINAL, RETROSPECTIVE, REAL-WORLD STUDY[1]



CONFIRM results were taken from electronic medical record data within the Explorys (IBM Watson Health™) US database.

The Explorys database included records from **over 50 million patients**, sourced from multiple health systems and integrated delivery networks representing patients across the continuum of care.

4,056 insulin-naïve patients were propensity-score-matched for baseline characteristics, which helped to **limit confounding factors** and achieve comparability of the two treatment groups.

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insulin degludec [rDNA origin] injection

The time of day that basal insulin typically affects the risk of hypoglycemia is mostly overnight, because patients take it with dinner or at bedtime. We know that bolus insulin will increase risk of hypoglycemia several hours after if the dose is too high. If the basal insulin has been dosed appropriately, diabetes patients should not have hypoglycemic events. Patients at risk for nighttime hypoglycemia would want to choose an insulin that has the lowest risk. It has been shown that Tresiba® has a lower risk of nocturnal hypoglycemia compared with other basal insulins."

Type 1 patients experience more hypoglycemic episodes than type 2 patients. Type 1 diabetes patients tend to take 3 or more insulin doses per day; the mere increase in insulin will increase their risk. The head-to-head studies show that Tresiba® does much better than glargine in reducing not only nocturnal hypoglycemia risk but hypoglycemia risk in general. This trend is seen with both type 1 and type 2 diabetes patients.

Cardiac Safety

It does not appear that there are specific cardiovascular benefits of any insulin product over another. However, patients who are at risk for cardiovascular events need to be careful to avoid hypoglycemia, which stresses the circulatory system and can precipitate a cardiac event.

Recently the label for Tresiba® included the DEVOTE study data from a randomized, controlled trial that patients who are at high risk for cardiovascular events and who are older, had a significant reduction in hypoglycemia episodes versus glargine U100.

At the ADA, some discussion centered on whether degludec or glargine U100 and U300 led to the most weight gain. Insulin-naive patients who start taking insulin will all gain some weight. We cannot avoid that. With higher blood glucose levels, the patient is urinating the glucose out, essentially eliminating calories. By improving blood glucose levels, the body starts using the glucose better and retaining those calories, leading to some weight gain. There was no difference in the amount gained between Tresiba® and glargine U300.

Tresiba® and Elderly Patients

Tresiba®'s lower rate of hypoglycemia can serve older patients well. The elderly are at higher risk of hypoglycemia as they age and as they become more susceptible to cardiovascular risk factors. This event can be even more dangerous for elderly diabetes patients who live alone, or fall, or have trouble driving. These situations possibly can precipitate changes in blood pressure and heart rate, creating responses that can lead to cardiac stress. There is a clear benefit for all age groups who use Tresiba®, but for older individuals who have additional risk factors, it is particularly important to avoid hypoglycemia—and Tresiba® helps with that.

An added bonus to Tresiba® is its flexible dosing option. A patient does not need to take it at the exact same time every day. There are instances where people forget to take their basal dose. With other basal insulins, it can greatly affect blood glucose levels if it is not taken around the same time every day.

Patients Who Abandon Insulin

Why do some patients abandon insulin therapy? There are many reasons patients stop therapy and risk of hypoglycemia is a common reason. Over the course of the studies Tresiba® users experienced 37% fewer episodes of hypoglycemia than glargine U100 users. Being able to avoid hypoglycemia certainly can lead some patients to stay on insulin therapy longer and experience more success with it.

CONFIRM also showed that practitioners prescribing degludec prescribed 9% lower doses of Tresiba® compared with glargine U300. Clinical trials have found a reduction in basal dose by 20% when switching to Tresiba®.

When considering product cost, it's important to take into account all the benefits an insulin provides. With Tresiba® these benefits include: lower doses, lower A1c levels, and less risk of hypoglycemia.

3 Novo Nordisk Drugs Join Tresiba® in the Saudi Market

Recent approval by medical authorities in Saudi Arabia of three Novo Nordisk diabetes drugs has vastly expanded the ability of Saudi endocrinologists to effectively treat patients with diabetes in conjunction with insulin degludec.

The three drugs are Ryzodeg®, a 70/30 combination of insulin degludec and insulin aspart; Saxenda® (liraglutide), used to treat obese or overweight patients; and Victoza®, a less potent form of liraglutide used to treat type 2 diabetes patients.

Three Saudi endocrinologists shared their observations about the use and effectiveness of the 3 diabetes medications.

Ryzodeg®

"Although many patients inject Tresiba® once per day, others use Tresiba® along with short-acting aspart analog insulin at 2 meals per day to cover mealtime hyperglycemia," says Awad Alshahrani, MD. "We can now use Tresiba® with other agents, such as aspart, which is Ryzodeg®. This is an excellent and very promising combination. I use it now for many patients who report very good control of their blood glucose levels. They are very comfortable with that."

Mohamed Abu Alhassan, MD, says he prescribes Ryzodeg® to elderly patients (70 years and older) who prefer 1 or 2 injections daily. "Some patients just don't like to use multiple-insulin doses spread over 4 injections per day. They prefer two.

That's where Ryzodeg® comes in. Dr. Abu Alhassan notes that 95% of elderly diabetes patients in Saudi Arabia use premixed drugs other than Ryzodeg® that require multiple daily injections. "When we shift them to Ryzodeg®, they find they don't need 4 injections. Instead they adhere to a 2 dose daily regimen, and note how quickly they reach their targets, sometimes with A1c levels that have dropped 2 or even 3 percentage points.

"Unlike other premixed insulins, Ryzodeg® is a mixture of long-acting plus short-acting insulin. Other premixes usually have no long-acting insulin in them. So the benefit of Ryzodeg® benefit is that there is a long-acting, basal insulin in the pen."

Dr. Abu Alhassan adds that in his experience Ryzodeg® users suffer fewer episodes of hypoglycemia. "With Ryzodeg®, there is less hypoglycemia linked to it than with other premixed drugs."

Dr. Abu Alhassan has also used Ryzodeg® in some type 1 diabetes patients. "I've had good results controlling pre- and postprandial sugar. Also, many of these patients are young, and they're tired of having to give themselves injections over many years. They're looking for something that will improve their situation. They want something that can help them avoid injecting at their school or work. I have prescribed twice-daily Ryzodeg® injections and the results have been gratifying: better control of postprandial sugar and less hypoglycemia."

Dr. Alshahrani appreciates the pharmacokinetics of Ryzodeg®. "It works even if you inject it just twice daily. So we give it before breakfast and before dinner. It controls postprandial hyperglycemia. Regarding lunch-time, hyperglycemia is neutralized by the degludec as well. For most all of the day, a patient's glycemic control will be excellent."

He has already introduced Ryzodeg® to many patients. "These patients showed excellent control after suffering for years from postprandial sugar spikes. Ryzodeg® is also an excellent choice for type 2 diabetes patients who require 2 daily doses of insulin, one a.m. and the other p.m. doses. It's a predictable insulin; you know how it should be acting. The actions of other pre-mixed formulas are more difficult to predict. So this is an excellent solution to hypoglycemia as well as causing less weight gain," says Dr. Alshahrani.

"I have prescribed twice-daily Ryzodeg® injections and the results have been gratifying: better control of postprandial sugar and less hypoglycemia." – Mohamed Abu Alhassan, MD

"Ryzodeg® is well suited for diabetes patients whose blood glucose is not well controlled. The combination of degludec and aspart is beneficial because patients' sugar levels don't increase sharply after meals. A combination of those two is more convenient for patients than other formulations. It leads to a good control because patients don't have to take 2 shots twice or thrice a day. I have been prescribing this combination for the past 6 months and have observed that most of my patients are achieving very reasonable blood sugar levels because of it."

Saxenda®

The addition of Saxenda® (the GLP-1 receptor liraglutide) has earned a positive response.

"What really supports Saxenda® from a clinical scientific point of view," says Essa Al Dhafiri, MD, "is that when we combine it with degludec, we see a decrease in all-cause mortality and major adverse cardiovascular events. That's because its use leads to significant weight loss, which lessens cardiovascular risk. Saxenda® is very popular here in Saudi Arabia. Some of my patients lost 5 kilograms per week with it. In some patients 6 months of use has led to a 10% reduction in their BMI. I've also seen even more dramatic results. Some of my patients have shed 25 kilograms in only 3 months. These positive results are helped by an emphasis on a healthy diet and exercise."

Dr. Alshahrani has also seen distinct weight reductions in patients who use Saxenda®. "It's safe to use as a treatment for obesity, so it is an excellent addition to the range of diabetes drugs we now have available."

Victoza®

Dr. Abu Alhassan has been impressed by results from adding Victoza®, a less potent version of liraglutide, to degludec. He has witnessed dramatic weight loss in type 2 patients taking the combination. "I've seen a weight reduction of 10 to 15 kg in the 3 to 6 months after prescribing Victoza®," he says.

He only prescribes the degludec/liraglutide combination for type 2 diabetes patients and suggests that adding a short-acting insulin to the combination would sharpen its good effects even more.

"I've seen weight reduction and have noted that patients who lose weight with Victoza® have a decreasing need for blood pressure medications," says Dr. Abu Alhassan. "Some patients who were taking 3 to 4 medications to treat their hypertension, would lose 15 kg or 20 kg. Now they need only 1 or 2 medications to treat their hypertension."

Dr. Alshahrani thinks that more clinical trials should focus on possible use of Victoza® for treating obese and overweight type 1 diabetes patients. "Type 1 diabetes is a very special disease because most of those patients in my practice are either children or teenagers, so we are dealing with very critical ages. They might not be that compliant with their medication and many of them are obese. They often require high doses of insulin, which adds to the tendency to gain weight. I would like to see clinical trials for Victoza® to treat obesity in type 1 diabetes patients."

Dr. Al Dhafiri will prescribe Victoza® for type 1 patients if they are obese and have a body mass index (BMI) of 35 or more. "There is often little decrease in weight. But the important thing is that they are not gaining weight. If a patient is verging on obesity, say, with a BMI of 32 or34, he is a good candidate for a GLP-1, specifically liraglutide.

"Also, cardiac safety is increased if we combine liraglutide with degludec. While there is a benefit in using Victoza® to help control blood pressure, its effectiveness in that control increases if a patient loses weight."

US Expert Adds Details to Results From the DEVOTE and SWITCH Trials

Along with the CONFIRM trial the DEVOTE and SWITCH clinical trials received considerable attention at the ADA Scientific Sessions. A main presenter of conclusions from those two trials was Helena Rodbard, MD, endocrinologist at Endocrine & Metabolic Consultants, Rockville, MD, USA, and a contributor to CONFIRM.

Dr. Rodbard is also past president of the American College of Endocrinology and past president of the American Association of Clinical Endocrinologists.

"DEVOTE was the cardiovascular outcome trial that was the response to the 2008 FDA mandate that every new drug approved, or waiting to be approved for the management of diabetes had to show cardiovascular safety," explains Dr. Rodbard. "The study involved more than 7,600 patients, about two-thirds of them in the United States. Patients were randomized to receive either Tresiba® U100 or insulin glargine U100.

"Patients received insulin from vials, not pens. That was the only way to keep the study masked. The study went on for more than 3 years and by the end confirmed the safety of degludec. It did not show superiority and that wasn't really its purpose."

Dr. Rodbard also talked about the different early stage trials, clinical trials that preceded DEVOTE. "I talked about type 2 and type 1 patients, then shifted to talking about the SWITCH 1 trial. The SWITCH trial involved looking for rates of hypoglycemia among Tresiba® users. Patients taking Tresiba® and patients taking glargine U100 spent 32 weeks on their respective insulins. There was a 16-week of titration then 16 weeks of maintenance. After the 32 weeks, the patients who had been taking Tresiba® were switched to insulin glargine. The ones who had been taking insulin glargine were switched to Tresiba®.

MACE and all-cause mortality by liraglutide use in DEVOTE

	Degludec/ glargine U100 with concomitant liraglutide use		Degludec/ glargine U100 with no concomitant liraglutide use		Liraglutide use vs no liraglutide use (HR [95% CI])	Two-sided *p*-value
	Number of events	Events per 100 patient-years of observation	Number of events	Events per 100 patient-years of observation		
MACE	25	2.91	656	4.74	0.62 [0.41; 0.92]	0.02
CV death	8	0.91	270	1.90	0.47 [0.23; 0.96]	0.04
Non-fatal MI	15	1.73	298	2.13	0.82 [0.49; 1.37]	0.45
Non-fatal stroke	5	0.57	145	1.03	0.56 [0.23; 1.37]	0.20
All-cause mortality	13	1.48	410	2.88	0.50 [0.29; 0.88]	0.02

HRs presented are for the time to the first confirmed event (in days).
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; glargine U100, insulin glargine 100 units/mL; MACE, major adverse cardiovascular events (CV death, non-fatal MI, or non-fatal stroke); MI, myocardial infarction.

Source: DEVOTE study subanalysis[8]

"At the end of the SWITCH trial, it showed that the patients that had been on Tresiba® had less hypoglycemia. That is true as well for t]he DEVOTE trial which showed a 53% reduction in severe nocturnal hypoglycemia episodes."

> "Degludec is an excellent basal insulin. The new basal insulins are clearly superior to the old NTH and insulin glargine U100." – Helena Rodbard, MD

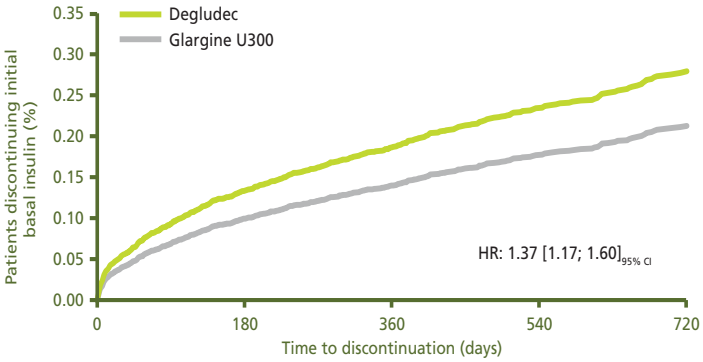
Dr. Rodbard stresses the difference between CONFIRM and DEVOTE. CONFIRM is the comparative effectiveness study of degludec and insulin glargine U300 in insulin-naïve type 2 patients—totally different from the DEVOTE trial. In DEVOTE insulin glargine U100 was tested against Tresiba®.

CONFIRM was a real-world study as opposed to a randomized controlled clinical trial. There were 6,375 patients in CONFIRM. At the end of the trial, patients had hemoglobin A1c levels of minus 1.5% reduction with degludec and minus 1.2% with insulin glargine U300. There also was a decrease in hypoglycemia in the patients who had been taking degludec. These patients experienced 30% fewer episodes of hypoglycemia compared with insulin glargine U300.

Dr. Rodbard says it is important to understand the differences between the trials. With CONFIRM, she says, researchers were trying to build a database based on physicians' and clinicians' reports about real-world patient experiences with Tresiba® and glargine U100. "This wasn't a randomized controlled clinical trial, with patients being randomly selected to try one or the other drug. It was all just commerce. Also there was a lower rate of insulin discontinuation in patients who had been on degludec compared with patients taking insulin glargine U300.

"Degludec is an excellent basal insulin. The new basal insulins are superior to NTH and insulin glargine U100. Glargine U300 is a different formulation. They're both superior to insulin detemir, which will eventually be replaced by insulin degludec and insulin glargine U300."

Likelihood of discontinuation of basal insulin in patients initiated with degludec or glargine U300



CI, confidence interval; HR, hazard ratio; glargine U300, insulin glargine 300 units/mL.

Source: CONFIRM study[1]

Regarding Tresiba®'s effect on cardiovascular health, Dr. Rodbard says no insulin has been shown to be cardioprotective. "Degludec did not show cardiovascular superiority. It doesn't prevent heart attacks or strokes. But it did show cardiovascular safety, which was the aim of the study."

Dr. Rodbard uses Tresiba® extensively in her practice. "I have experience with degludec both in clinical trials and in my own clinical practice. When I'm ready to start a patient on insulin, I remind them that diabetes is a progressive disease. As time goes by, even an injectable GLP-1 receptor agonist is no longer sufficient to keep the blood glucose levels under control. At that point, we need to add something. Basal insulin is the next step, and Tresiba® happens to be an excellent choice.".

Dr. Rodbard says it depends on the patient whether she will prescribe Ryzodeg® as a combination therapy or insulin or a GLP-1 separately. When it comes to glycemic variability, she thinks there is not that much of a difference among basal insulins. "In general, glycemic variability is not affected by basal insulin. What is needed is a medication that can cover postprandial spikes as basal insulin does not provide good coverage after meals. Basal insulin provides a baseline and long-acting effect.

"Glycemic variability is typically what you see after meals. A GLP-1 receptor agonist provides good postprandial coverage as well as rapid-acting insulins. These are the best agents to control postprandial hyperglycemia."

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Tresiba® is supported by a substantial clinical development programme

The **efficacy** and **safety** of Tresiba® were tested in a clinical developmentprogramme that included[3]:

- **40** countries
- **>11,000** patients
- **1,000** clinical sites

9 head-to-head randomised controlled trials(RCTs) were conducted in phase 3a:

- T1DM on basal-bolus regimen: **3 trials**[2,6,7]
- T2DM on basal-oral regimen: **5 trials**[1,4,8,9,10]
- T2DM on basal-bolus regimen: **1 trial**[5]

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