Executive Highlights

We're back with our full coverage of the results from the DEVOTE cardiovascular outcomes trial for Novo Nordisk's next-generation basal insulin Tresiba (insulin degludec), which were presented to a packed auditorium at ADA 2017 on Monday (immediately before the CANVAS CVOT results). Read on below for our initial themes related to the results, followed by detailed coverage of the results and discussant presentations. For those looking for more, see our coverage of the topline results, initial breaking news report on the full results, and the full paper published in NEJM (which, by the way, has evidently become THE journal for diabetes CVOTs - the CANVAS publication can be found in the latest issue as well).

Table of Contents

Themes

- **The big headliner from DEVOTE is the demonstrated superior reduction in severe and nocturnal severe hypoglycemia with Tresiba vs. Lantus in long-term, randomized, double-blinded, large outcomes trial.** Tresiba was associated with a very significant 40% relative risk reduction in the overall rate of severe hypoglycemia compared to Lantus (HR=0.60, 95% CI 0.48-0.76, p<0.001 for superiority) and a whopping 53% reduced risk for nocturnal severe hypoglycemia (HR=0.47, 95% CI: 0.31-0.73, p<0.001). Overall, a participant taking Tresiba was 27% less likely to experience one or more episodes of severe hypoglycemia (HR=0.73, 95% CI:0.60-0.89, p<0.001). Very impressively, this reduction in hypoglycemia occurred in the context of non-inferior A1c and superior fasting plasma glucose reductions for Tresiba compared to Lantus. These results further substantiate the hypoglycemia reduction findings in the SWITCH 1 and SWITCH 2 trials - these trials also demonstrated impressive hypoglycemia risk reduction with Tresiba therapy compared to Lantus, though this was demonstrated in a much smaller and shorter blinded crossover study (in which participants served as their own controls). Data from multiple trials confirming risk reduction for hypoglycemia will likely prove convincing and compelling as patients, providers, and even payers consider the "validity" of benefit - we're curious if we might even see these findings discussed in future iterations of diabetes treatment guidelines.

    - **That said, there are several limitations to the findings from the current study.** For example, only information on severe hypoglycemia was collected and adjudicated, so it's difficult to assess the impact of Tresiba on "mild-to-moderate" hypoglycemia (though the SWITCH 2 trial showed a 30% reduction in overall symptomatic hypoglycemia). This does not affect "health outcomes" as much as severe hypoglycemia does, but this is still clearly an area of interest to clinicians and patients. As we understand it, there was no systematic collection of blood glucose levels or to insulin titration or mandated laboratory fasting blood glucose; as a result, Novo Nordisk says it could not have assessed incidence of blood glucose under 70 mg/dl because it didn't have the full dataset. It's unclear what data on this front would show - we certainly hope so as "less-severe" levels of hypoglycemia still have enormous quality of life and engagement and adherence and productivity implications for patients, that it will be considered going forward. Overall, we continue to believe that CGM studies would be enormously helpful in characterizing the benefit of next-generation insulin products especially (but other drugs as well) and we wish that CGM data could have been gathered for this large and long-term study. We recognize, of course, that this study initiated many years ago and CGM accuracy improved significantly with the advent of Dexcom's G4 approved in 2012, just before the 2013 study start date for DEVOTE and well after the DEVOTE clinical trial design was finalized.

- **With the DEVOTE results we can certainly rest assured that Tresiba is at the very least safe from a CV standpoint.** Tresiba demonstrated non-inferiority compared to standard of care insulin glargine (Sanofi's Lantus) for the primary 3-point MACE composite endpoint, as well as each of its individual components (non-fatal MI, non-fatal stroke, and CV death). Many of these hazard ratios trended in the "right direction" - more on this below - though we cannot draw any definitive conclusions about potential cardioprotective benefit. That said, non-inferiority in and of itself is reassuring given Tresiba's long and complicated regulatory history. As a reminder, the product's first regulatory submission in the US received a Complete Response Letter (CRL) from the FDA, requesting a CVOT to further investigate a signal for increase expanded MACE risk observed in the phase 3 trials. The FDA's eventual approval based on firewalled interim data was certainly reassuring on this front and we're pleased to get our hands on full CVOT data that suggests not even a whiff of increased risk for Tresiba.

Detailed Discussion and Commentary

Symposium: Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) Trial Results

INTRODUCTION AND TRIAL DESIGN

Steven Marso, MD (University of Missouri, Kansas City, MO)

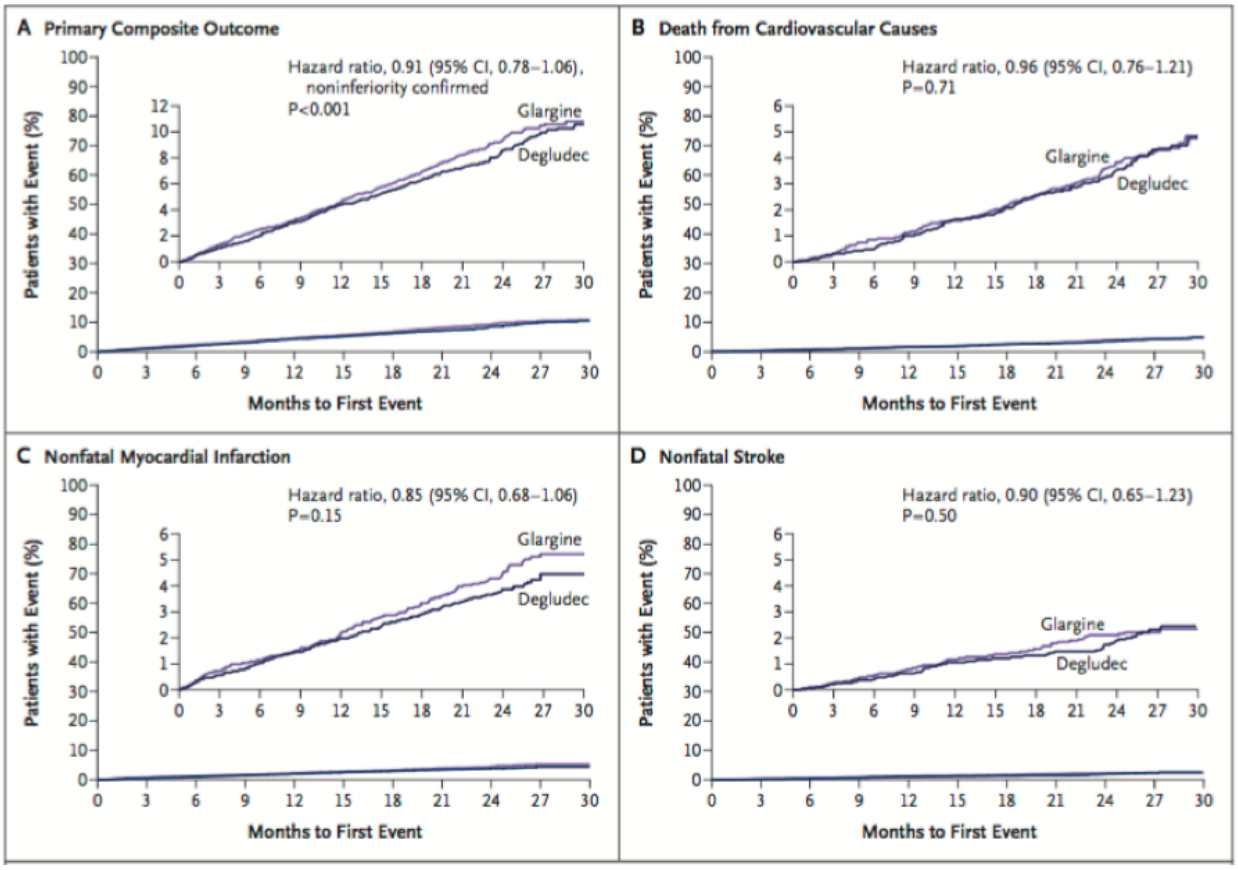
Dr. Steven Marso set the stage by presenting the trial design for DEVOTE. This randomized, double-blind, treat-to-target trial (n=7,637) enrolled people with type 2 diabetes on at least one diabetes therapy and an A1c >7% or <7% with basal insulin treatment at least 20 units/day. The study population had a high-risk cardiovascular profile; enrollment criteria included cardiovascular or chronic kidney disease for people over the age of 50 and the presence of cardiovascular risk factors for people over the age of 60. This global population included participants from five continents, 20 countries, and 438 trial sites. As is typical for CVOTs, the primary endpoint was time from randomization to first occurrence of a three-point MACE (non-fatal MI, non-fatal stroke, or CV death). Secondary endpoints included rate and incidence of severe hypoglycemia episodes.

CARDIOVASCULAR OUTCOMES

Darren McGuire, MD (University of Texas Southwestern Medical Center, Dallas, TX)

Dr. Darren McGuire took the stage to discuss the primary cardiovascular outcomes from DEVOTE. Novo Nordisk's next-generation basal insulin Tresiba (insulin degludec) met its primary endpoint by

demonstrating non-inferiority compared to standard of care insulin glargine (Sanofi's Lantus) for three-point MACE (non-fatal MI, non-fatal stroke, and CV death). The hazard ratio (HR) point estimate was in the "right direction" at 0.91, but did not achieve statistical significant for superiority (95% CI:0.78-1.06, p<0.001 for non-inferiority, p=0.21 for superiority). Expanded MACE (including hospitalization for unstable angina) was non-inferior as well (HR=0.91, 95% CI:0.80-1.05, p=0.22), and Tresiba additionally demonstrated non-inferiority for each component of the MACE endpoint, with point estimates to the "left of unity" (meaning <1.0) in each case, including non-fatal MI (HR=0.85, 95% CI: 0.68-1.06, p=0.15), non-fatal stroke (HR=0.90, 95% CI: 0.65-1.23, p=0.50), and hospitalization for unstable angina (HR=0.95, 95% CI:0.68-1.31, p=0.74). Similarly, point estimates for all reported mortality endpoints were in the "right direction," though not statistically significant for superiority, including CV death (HR=0.96, 95% CI: 0.0.76-1.21), all-cause mortality (HR=0.91, 95%CI:0.76-1.11), CV death excluding undetermined cause of death (HR=0.91, 95% CI: 0.69-1.20), and non-CV death (HR=0.84, 95% CI: 0.60- 1.16).



Source: NEJM

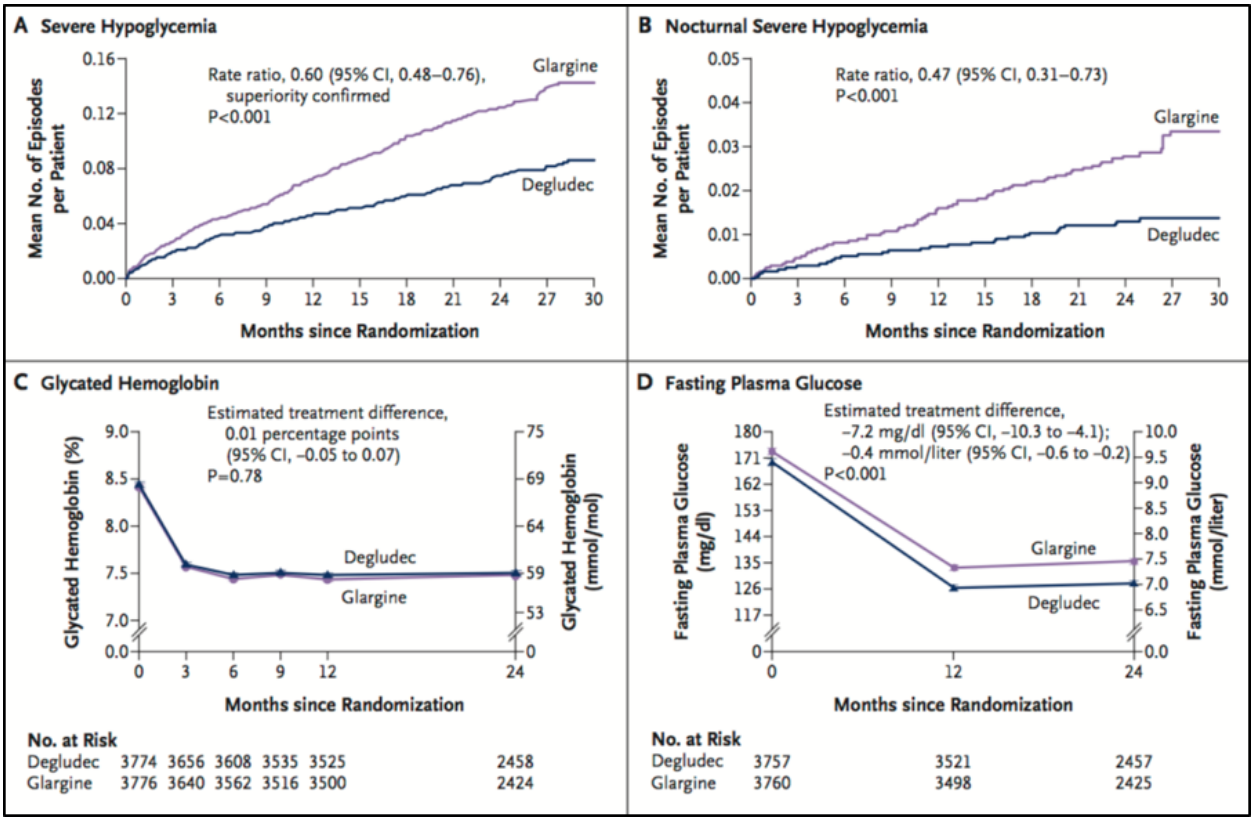
- **All in all, we can certainly rest assured that Tresiba is at the very least safe from a CV standpoint (though we cannot draw any definitive conclusions about potential benefit).** That said, non-inferiority in and of itself is reassuring given Tresiba's long and complicated regulatory history. As a reminder, the product's first regulatory submission in the US received a Complete Response Letter (CRL) from the FDA, requesting a CVOT to further investigate a signal for increase expanded MACE risk observed in the phase 3 trials. The FDA's eventual approval based on firewalled interim data was certainly reassuring on this front and we're pleased to get our hands on full CVOT data that suggests not even a whiff of increased risk for Tresiba.
- **The robustness of these results are underscored by the fact that the DEVOTE study population was selected to reflect the global population of people with type 2 diabetes.** Between the Tresiba (n=3,818) and insulin glargine (n=3,819) arms, participants aged 65 years, an average diabetes duration of 16 years, a BMI of 33.6 kg/m3, and an A1c of 8.4%. Respectively, 86%

and 85% of participants had established cardiovascular disease or chronic kidney disease and the remaining 14% and 15% had cardiovascular risk factors.

GLYCEMIC EFFICACY AND HYPOGLYCEMIA

Bernard Zinman, MD (University of Toronto, Canada)

The great Dr. Bernard Zinman presented the very impressive hypoglycemia and glycemic efficacy findings from the DEVOTE trial. In many ways, while these were all secondary endpoints, these findings were the real headliners of the study - indeed, the independent commentary from hypoglycemia expert Dr. Elizabeth Seaquist focused almost entirely on the hypoglycemia results. The results are a big win to be sure: Tresiba was associated with a very significant 40% relative risk reduction in the overall rate of severe hypoglycemia compared to Lantus (HR=0.60, 95% CI 0.48-0.76, p<0.001 for superiority) and a whopping 53% reduced risk for nocturnal severe hypoglycemia (HR=0.47, 95% CI: 0.31-0.73, p<0.001). (Amazing confidence intervals.) Severe hypoglycemia was adjudicated in the study and defined as low blood glucose requiring the assistance of another person - in total, 1,005 events were sent for adjudication and the independent confirmed 752 events as severe hypoglycemia for the analysis. 4.9% of participants in the Tresiba group experienced one or more episodes of severe hypoglycemia, compared to 6.6% of participants in the Lantus group (odds ratio: 0.73; 95% CI: 0.60-0.89; p<0.001 for superiority). Overall, a participant taking Tresiba was 27% less likely to experience one or more episodes of severe hypoglycemia (HR=0.73, 95% CI:0.60-0.89, p<0.001).

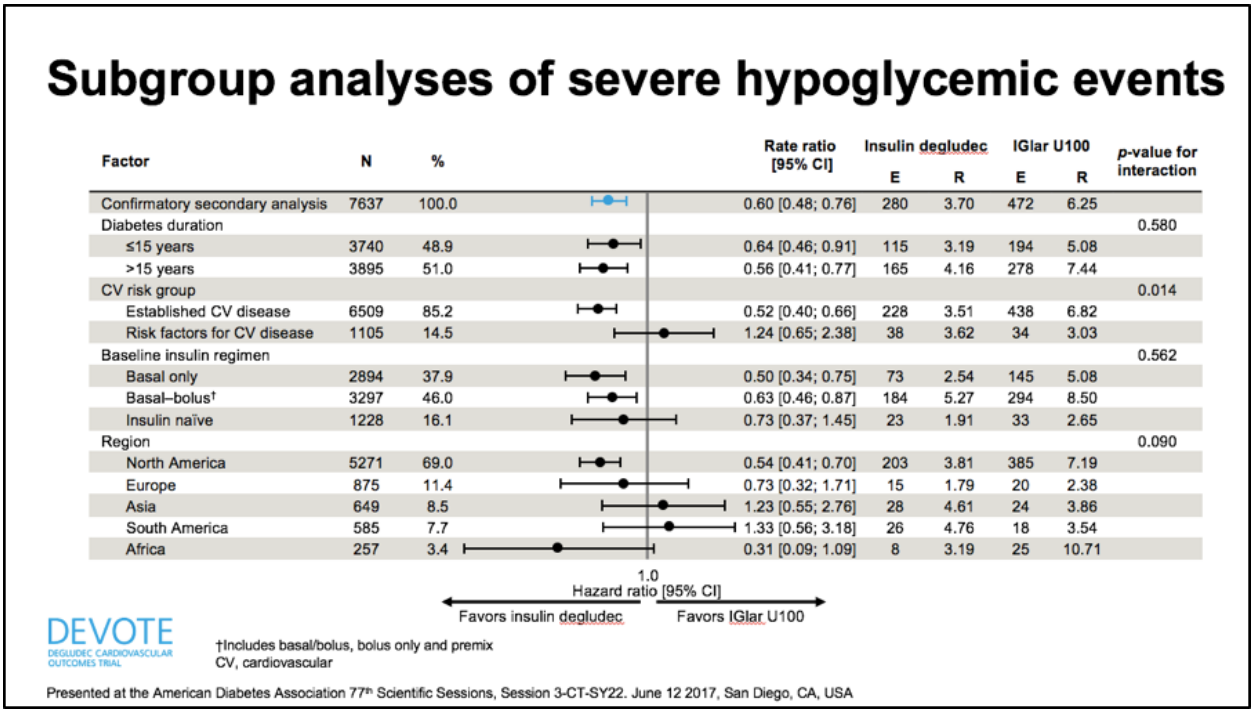


Source: NEJM

- **Notably, these reductions in hypoglycemia occurred in the context of virtually identical low mean A1cs at the end of the trial and lower fasting plasma glucose.** Mean A1c was 7.55% in the Tresiba group and 7.5% in the Lantus group (baseline A1c=8.4%). The end-of-trial A1c difference between the two arms was estimated at 0.01% (p=0.78). On the other hand, mean fasting plasma glucose (FPG) was 7.2 mg/dl lower in the Tresiba group compared to the Lantus group at the end of the trial (128 mg/dl vs. 136 mg/dl, p<0.001). This was driven by a larger

reduction in FPG in the Tresiba group - 40 mg/dl vs. 35 mg/dl. The end-of-trial average basal insulin dose was slightly but significantly higher in the Tresiba group (2 units higher than average in Lantus group, p=0.04).

- **Based on a subgroup analysis, it appears that the severe hypoglycemia benefit of Tresiba is more pronounced in those with established CV disease than in those without.** There is a very clear 48% rate reduction for severe hypoglycemia in those with established CV disease at baseline (HR=0.52, 95% CI: 0.40-0.66). On the other hand, the point estimate among those with risk factors for CV disease - but no established CV disease - actually trended slightly toward increased risk at 1.24, though the confidence intervals were very wide and crossed the line of unity (95% CI: 0.65-2.38). Very notably, the p-value for interaction was 0.014. We've seen some previous analyses (based on the very large TECOS dataset) suggesting that those with a history of a previous CV event are more likely to experience subsequent severe hypoglycemia - suggesting that those with established CV disease at baseline are more vulnerable to hypoglycemia. While of course this subgroup analysis is only exploratory and hypothesis-generating, we're intrigued by the implication that Tresiba therapy could perhaps offer hypoglycemia benefit to those who are most vulnerable and most at risk. We've increasingly heard some suggest that older patients, more frail patients (many of whom have had a previously hypoglycemic event) should be treated to higher A1c targets due to concerns about hypoglycemia. At the same time, some of these same thought leaders advocate for the use of human insulins in patients who are unable to afford newer analogs (including older patients in the Medicare Part D "donut hole") and argue that insulin analogs - including next-generation analogs like Tresiba - offer only "incremental benefits". We hope that long-term, compelling data like these findings from DEVOTE can help improve reimbursement and access to these drugs and allow older patients achieve lower A1c targets safely. We also hope that providers and others in the community who are concerned about both hypoglycemia and cost do more to advocate for the inclusion of these next-generation agents on formularies, etc.
    - **There was no heterogeneity in effect for differences in sex, age, BMI, renal function, diabetes duration, baseline insulin regimen, or region.**



- **The full results offered a very exciting and impressive - but limited - look into the impact of Tresiba on outcomes beyond A1c.** The data released thus far does not mention impact on weight - we hope to see this and other outcomes beyond A1c in future analyses. "Mild-to-

moderate" blood glucose-confirmed hypoglycemia was not adjudicated in this trial and it's unclear if any data on this front was collected - we certainly hope so as "less-severe" levels of hypoglycemia still have enormous quality of life and productivity implications for patients. We continue to believe that CGM studies would be enormously helpful in characterizing the benefit of next-generation insulin products especially (but other drugs as well) and we wish that CGM data could have been gathered for this large and long-term study (though, of course, we recognize that this study initiated many years ago and CGM accuracy has only relatively recently tremendously improved).

SAFETY

Richard Pratley, MD (Florida Hospital Diabetes Institute, Orlando, FL)

Dr. Richard Pratley reviewed safety outcomes from DEVOTE, which were largely similar between Tresiba- and Lantus-treated participants, indicating that insulin degludec is safe and well-tolerated. There were 1,473 serious adverse events in the Tresiba arm of the trial, affecting 39% of patients vs. 1,517 serious adverse events in the Lantus arm, affecting 40% of patients. Severe adverse events occurred in 25% of both the Tresiba and Lantus groups (945 and 962 events, respectively). Adverse events leading to treatment discontinuation occurred in 5% of the Tresiba group vs. 6% of the Lantus group (200 and 222 events, respectively) - 24 of these events were reported by investigators as probably/possibly related to insulin degludec, while 31 were probably/possibly related to insulin glargine. He called special attention to neoplasms, likely because of age-old concerns that insulin, as a growth factor, heightens cancer risk (though these worries have dissipated with additional studies, including ORIGIN). In DEVOTE, neoplasms were classified by one chairman and two independent oncologists, who sorted events into categories for malignant, benign, and unclassifiable. The hazard ratio for benign neoplasm was 1.37 in favor of Lantus, though this did not reach statistical significance (95% CI: 0.76-2.47). The hazard ratio for malignant neoplasm was 0.94 in favor of Tresiba, but there was no statistically significant signal for risk reduction (95% CI: 0.71-1.24). All in all, there were 45 benign neoplasms observed during the course of the trial (26 in the degludec group and 19 in the glargine group) and 192 malignant neoplasms (93 in the degludec group and 99 in the glargine group). These safety findings underscore Tresiba's non-inferior profile vs. Lantus, which holds true not only for CV effects, but for all adverse events as well.

- **Dr. Pratley listed 16 adverse events occurring at a frequency ≥1% in DEVOTE, but emphasized that they were all equally likely to happen whether a patient was randomized to insulin degludec or insulin glargine.** Hypoglycemia reported as an SAE was more common with Tresiba then glargine (see table), but adjudicated events (actually numerically higher in number as they were captured on a special form) were lower. This likely an effect of the reporting structure. The adjudicated events are the most accurate representation of the difference in hypoglycemia risk. Other adverse events included atrial fibrillation, acute MI, angina pectoris, angina unstable, coronary artery disease, MI, congestive cardiac failure, non-cardiac chest pain, cellulitis, pneumonia, fall, hypoglycemia, ischemic stroke, transient ischemic attack, acute kidney injury, and chronic obstructive pulmonary disease. Frequency on each of these is displayed in the table below.

Reported serious adverse events with frequencies ≥1%

	Insulin degludec				IGlar U100			
	N	%	E	R	N	%	E	R
Number of patients	3818				3819			
PYO	7568				7558			
Number of patients with events	1473	38.6	3341	44.15	1517	39.7	3745	49.55
Atrial fibrillation	47	1.2	55	0.73	56	1.5	75	0.99
Acute myocardial infarction	98	2.6	111	1.47	115	3.0	123	1.63
Angina pectoris	36	0.9	37	0.49	48	1.3	53	0.70
Angina unstable	87	2.3	94	1.24	79	2.1	93	1.23
Coronary artery disease	80	2.1	85	1.12	89	2.3	91	1.20
Myocardial infarction	48	1.3	51	0.67	66	1.7	68	0.90
Cardiac failure congestive	134	3.5	177	2.34	143	3.7	206	2.73
Non-cardiac chest pain	47	1.2	48	0.63	54	1.4	63	0.83
Cellulitis	52	1.4	64	0.85	61	1.6	72	0.95
Pneumonia	90	2.4	99	1.31	90	2.4	102	1.35
Fall	54	1.4	57	0.75	55	1.4	59	0.78
Hypoglycemia	64	1.7	77	1.02	49	1.3	66	0.87
Ischemic stroke	43	1.1	44	0.58	45	1.2	50	0.66
Transient ischemic attack	28	0.7	29	0.38	42	1.1	44	0.58
Acute kidney injury	70	1.8	79	1.04	95	2.5	110	1.46
Chronic obstructive pulmonary disease	42	1.1	54	0.71	56	1.5	70	0.93

DEVOTE DEGLUDEC CARDIOVASCULAR OUTCOMES TRIAL

Full analysis set (all randomized patients); six and one of the reported hypoglycemic serious adverse events for insulin degludec and IGlar U100, respectively, were not categorized as severe hypoglycemia by the Event Adjudication Committee. E, number of events; N, number of patients with events; %, proportion of patients with events; PYO, patient-years of observation; R, events per 100 patient-years of observation

Presented at the American Diabetes Association 77th Scientific Sessions, Session 3-CT-SY22. June 12 2017, San Diego, CA, USA

CONCLUSION AND CLINICAL IMPLICATIONS

John Buse, MD (University of North Carolina, Chapel Hill, NC)

Dr. John Buse delivered concluding remarks on the DEVOTE full results, putting this trial into context with BEGIN, SWITCH 1 and SWITCH 2, and our knowledge to-date of how hypoglycemia affects CV risk and patient quality of life. One of the most important takeaways, in his view and ours, is that the significant 40% risk reduction for severe hypoglycemia at a similar A1c level and the 53% risk reduction for severe hypoglycemia overnight corroborate Tresiba's hypoglycemia benefit as reported in BEGIN, SWITCH 1, and SWITCH 2. Novo Nordisk has submitted SWITCH 1 and SWITCH 2 data to the FDA for inclusion on the Tresiba label (decision expected by July), and this label update was recently EMA-approved. Novo Nordisk has also submitted the DEVOTE data to both the FDA and the EMA. Busy patients/providers deserve ready access to information on empirically-grounded benefits, such as lower risk for hypoglycemia, particularly significant hypoglcyemia, a key outcome beyond A1c metric. Fear of hypoglycemia affects patients and providers alike, with 79% of type 1 patients and 58% of type 2 patients who experience a severe episode opting to decrease their insulin dose (leading to suboptimal glycemic control). Similarly, 72% of PCPs and 79% of diabetes care specialists endorse that they would treat patients more aggressively if hypoglycemia was not a concern. Dr. Buse also shared findings from a large, systematic metaanalysis that linked hypoglycemia to a significantly increased risk for all-cause mortality (HR=1.8, 95% CI: 1.5-2.2), CV mortality (HR=2.2, 95% CI: 2.0-2.4), and major CV events (HR=2.3, 95% CI: 1.1-5.0). While the decrease in hypoglycemia seen in DEVOTE wasn't sufficient to significantly lower CV events and CV death for people on Tresiba vs. Lantus, Dr. Buse emphasized that reducing the severity and frequency of hypoglycemia could have an independent positive impact on a patient's cardiovascular health. What's more, helping patients avoid hypoglycemia allows for best practice diabetes management and substantially improves quality of life for people living with this chronic disease. Although cost wasn't explicitly mentioned during Dr. Buse's presentation, we know hypoglycemia incurs major avoidable costs on the healthcare system due to hospitalizations, emergency care, productivity loss, and more. We imagine the profound hypoglycemia benefit in DEVOTE could come into play for Tresiba in formulary negotiations - we'd surely love to see a health economic analysis predicting cost-savings. Dr. Buse announced that further analysis from DEVOTE, focused on the associations between glycemic control, glycemic variability, and outcomes, will be presented at EASD 2017 in Lisbon, Portugal. We can't wait.

INDEPENDENT COMMENTARY

Elizabeth Seaquist, MD (University of Minnesota, Minneapolis, MN)

University of Minnesota and the International Hypoglycemia Study Group's Dr. Elizabeth Seaquist provided a thoughtful and balanced independent commentary on the DEVOTE results. She praised the strengths of the trial design, including the randomized, double-blinded, event-driven, and treat-to-target design with well-defined endpoints. She highlighted the large size of the trial as well (n=7,637 at 434 sites on five continents), commenting that the study's "generalizability to patients with type 2 diabetes is assured." The very low dropout rate (2%), standardized titration protocol, rigorous adjudication of severe hypoglycemia, and systematic collection of adverse events also improved Dr. Seaquist's confidence in the findings and conclusions. That said, Dr. Seaquist also pointed out several weaknesses in the data that was collected - one was directed more at the design of the trial while the other two were directed at the limited clinical information provided by the trial. On the first, Dr. Seaquist noted investigators in the trial could modify the titration protocol based on clinical judgement and it's unclear if these modifications were applied in a standardized way between the two arms of the trial. In terms of the information included in the endpoints, Dr. Seaquist underscored that data on moderate symptomatic hypoglycemia and on hypoglycemic events with blood glucose levels ≤54 mg/dl were not collected. The former is the most common kind of hypoglycemia experienced by patients and the lack of inclusion of this endpoint makes it difficult to assess the impact of Tresiba on more common forms of hypoglycemia. The latter information would be important and useful to have since it's known that impaired awareness of hypoglycemia is more likely to develop with recurrent episodes of hypoglycemia with blood glucose ≤54 mg/dl. Dr. Seaquist also highlighted additional questions that should be addressed using the DEVOTE data, including (i) Was the reduction in severe hypoglycemia in the Tresiba arm associated with a reduction in healthcare costs?; and (ii) Was the reduction in severe hypoglycemia in the Tresiba arm associated with improved quality of life/ sleep and reduced fear of hypoglycemia (this is yet another question that would have been aided by greater collection of hypoglycemia data in our view)? Furthermore, she highlighted several questions that DEVOTE leaves unanswered: (i) Does Tresiba reduce hypoglycemia more relative to Lantus in patients with severe renal impairment?; (ii) What is the relative impact of Tresiba vs. Lantus on severe hypoglycemia in insulin-naïve patients?; and (iii) How do the effects of Tresiba on glycemic control and hypoglycemia in type 2 diabetes compare to Toujeo (U300 insulin glargine)?

--by Abigail Dove, Helen Gao, Payal Marathe, and Kelly Close