# Real-life relevance of 2nd-generation basal insulin analogs in high-risk patients

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SAGLB.TJO.19.06.0790c
Date of approval: September 2019

# Disclosures

- Advisor or consultant for Amgen, AstraZeneca, Bayer, Berlin-Chemie AG/Menarini Group, Boehringer-Ingelheim, Lilly, Merck Sharp & Dohme, NAPP, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Servier
- Speaker or a member of a speakers bureau for Amgen, AstraZeneca, Bayer, Berlin-Chemie AG/Menarini Group, Boehringer-Ingelheim, Lilly, Merck Sharp & Dohme, NAPP, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, and Servier
- Received grants for clinical research from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, and Servier

# Objectives

1. Describe the value of RWE
2. Consider the relevance of results from the latest RCTs and real-world trials for Gla-300 vs 1$^{st}$ and 2$^{nd}$-generation BI analogs
3. Discuss the clinical implications of these results with a particular focus on high-risk populations

# How confident are you that real-world data provides important information regarding a treatment's effectiveness?

1. Very confident
2. Somewhat confident
3. Neutral
4. Not very confident
5. Not confident at all

# From efficacy to effectiveness: The need for real-world evidence

# RCT vs real-world data

"Data that are **collected** outside the controlled constraints of conventional randomized clinical trials to evaluate what is happening in normal clinical practice"[1]

Ever-increasing role in decisions that affect patients' access to therapies[2]

**Randomised controlled trials**

**Can it work?[3]**

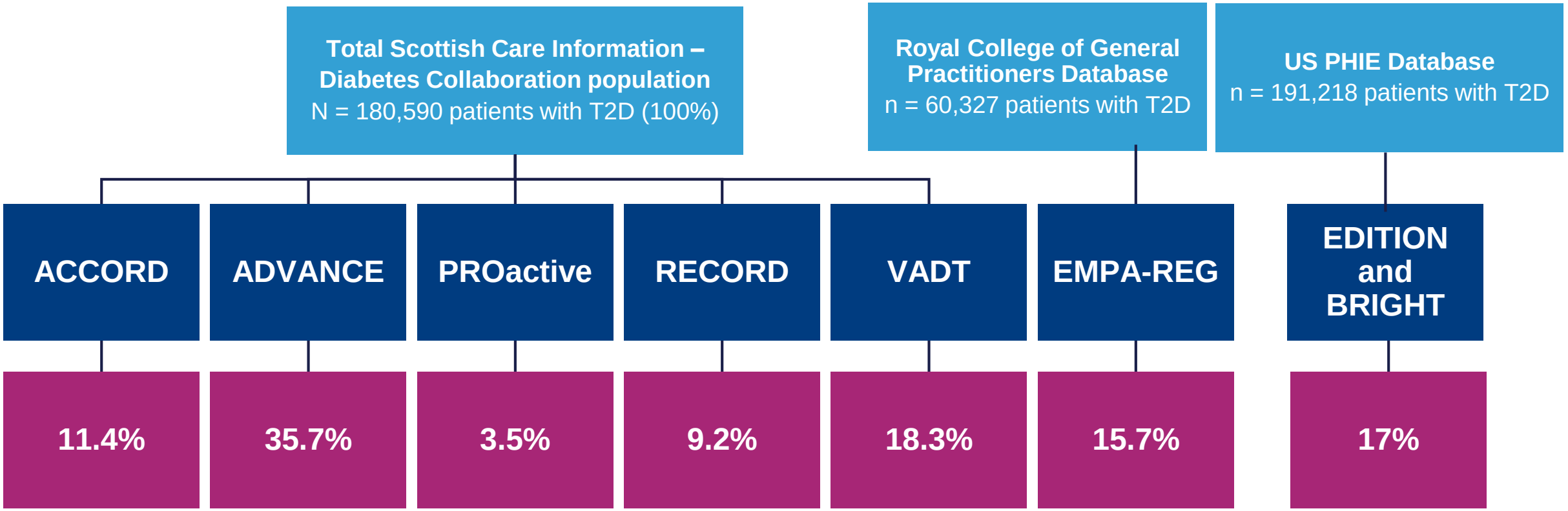
**Real-world data**

**Does it work?[3]**

1. ABPI. At: http://abpi.org.uk/media/1378/vision-for-real-world-data.pdf (Last accessed: September 2019);
2. Peperell K, et al. Value Health 2012;15:A460–1; 3. Luce BR, et al. Milbank Q 2010:88:256–76

# The majority of patients are not represented in RCTs

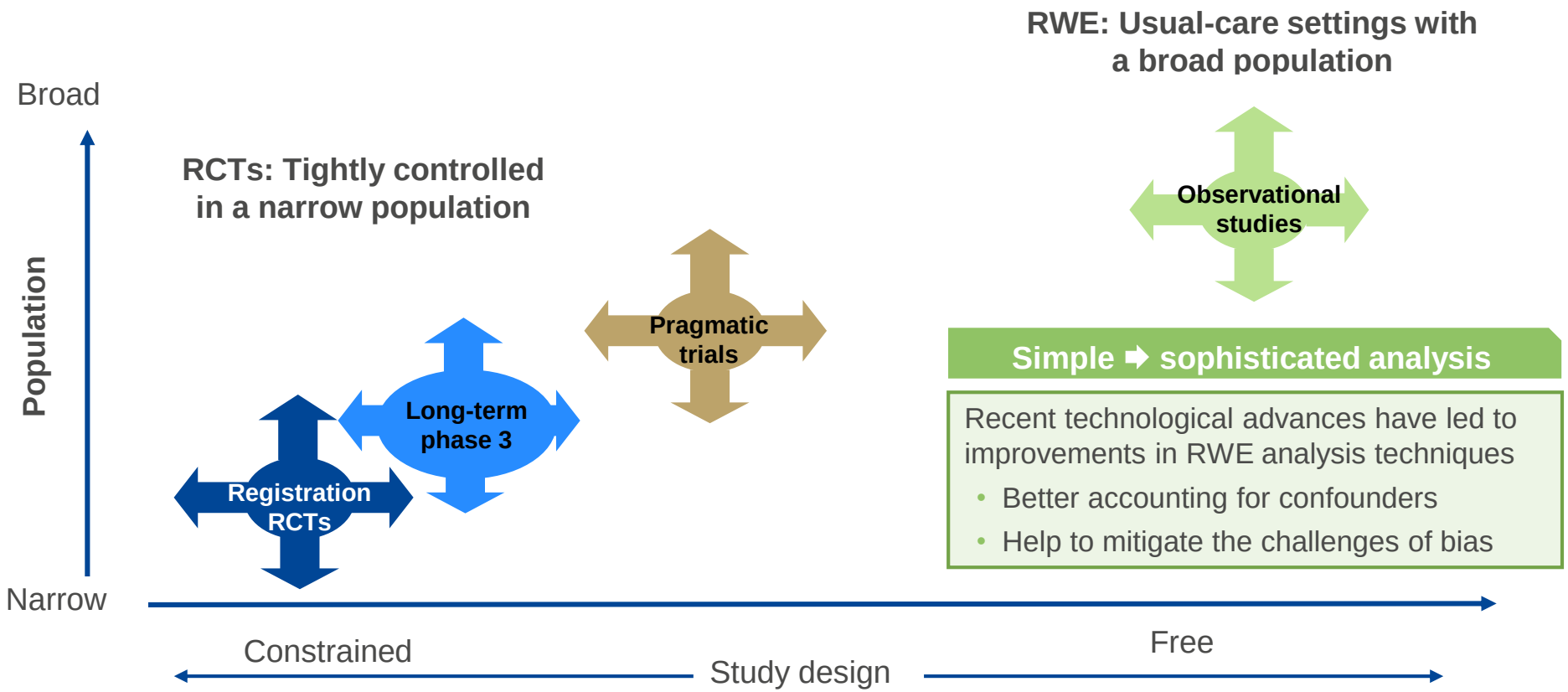
How many real-world patients with T2D would be eligible for landmark diabetes RCTs?




T2D, Type 2 diabetes mellitus; PHIE, Predictive Health Intelligence Environment

Saunders C, et al. Diabet Med 2013;30:300–8; McGovern A, et al. Diabetes Ther. 2017 Apr;8:365–76. doi: 10.1007/s13300-017-0254-7 [Epub ahead of print]; Mauricio D, et al. Poster presented at ADA 2019;135-LB

# Continuum of clinical research from RCT efficacy to RWE effectiveness




RWE: Helps to answer questions that RCTs do not address

# Different stakeholders have different interests in real-world evidence

## PRESCRIBER

How a treatment performs in **real life practice** across different age **groups**, genders, races and ethnicities, disease severities and comorbid conditions to inform use in everyday clinical practice[1]



## REGULATORY AUTHORITY

How clinical setting and provider and health-system characteristics influence treatment **effects and outcomes**[2]; real-world **safety**[1]

## PAYER

**Economic impact** (budget impact model, short term models, health care resource utilisation/cost data), reimbursement;[3] pricing;[3] cost-effectiveness;[1] formulary placement[1]

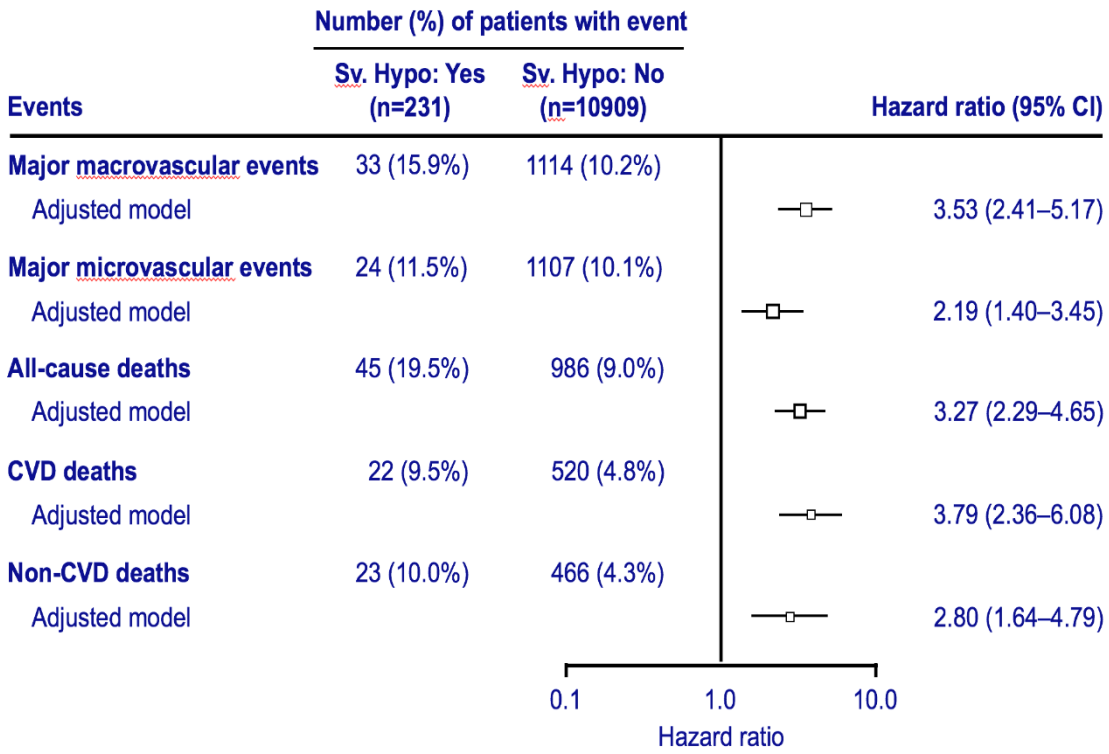
## PATIENT

To what extent a treatment is likely to work for **patients like them** in real life[4]

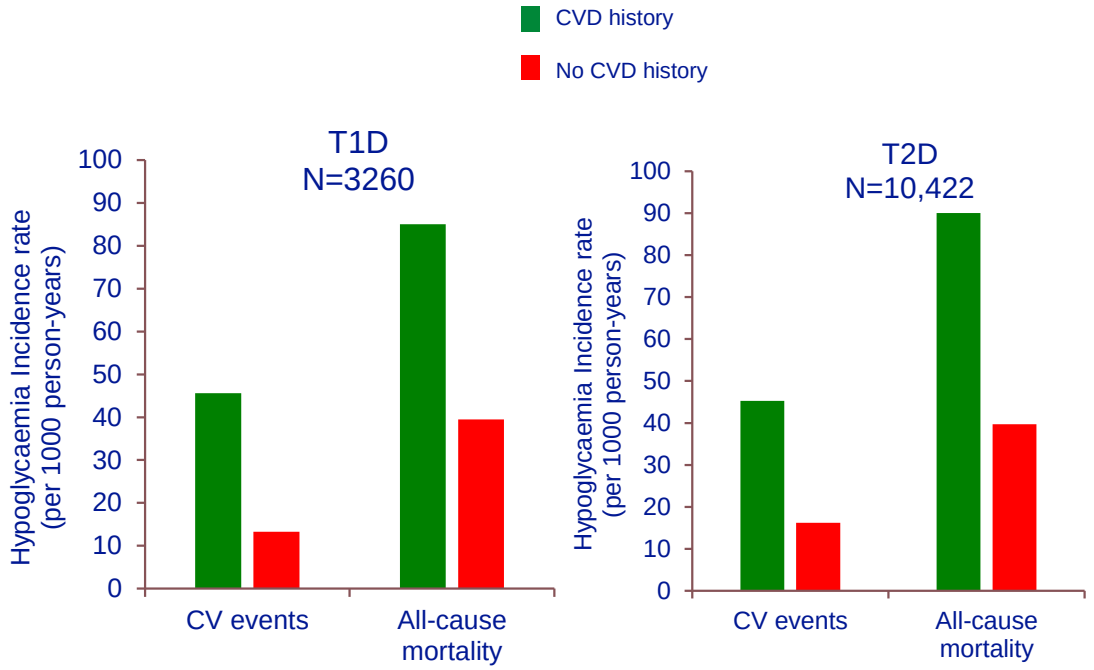
1. Cziraky M, Pollock M. Applied Clinical Trials 2015. Available at: http://www.appliedclinicaltrialsonline.com/real-world-evidence-studies. Last accessed April 2018; 2. Sherman RE et al. N Engl J Med 2016:375:2293–7; 3. ISPOR. Real-Life Data: A Growing Need. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp. Last accessed April 2018; 4. de Lusignan S, et al. J Innov Health Inform 2015;22:368–73

# Real-world evidence can provide confirmation of findings from RCTs in the real-world setting

Number of patients: 11,140




Number of patients: 13,682




Data are unadjusted incidence rates. CV, cardiovascular; CVD, cardiovascular disease; T1D, type 1 diabetes; T2D, type 2 diabetes.

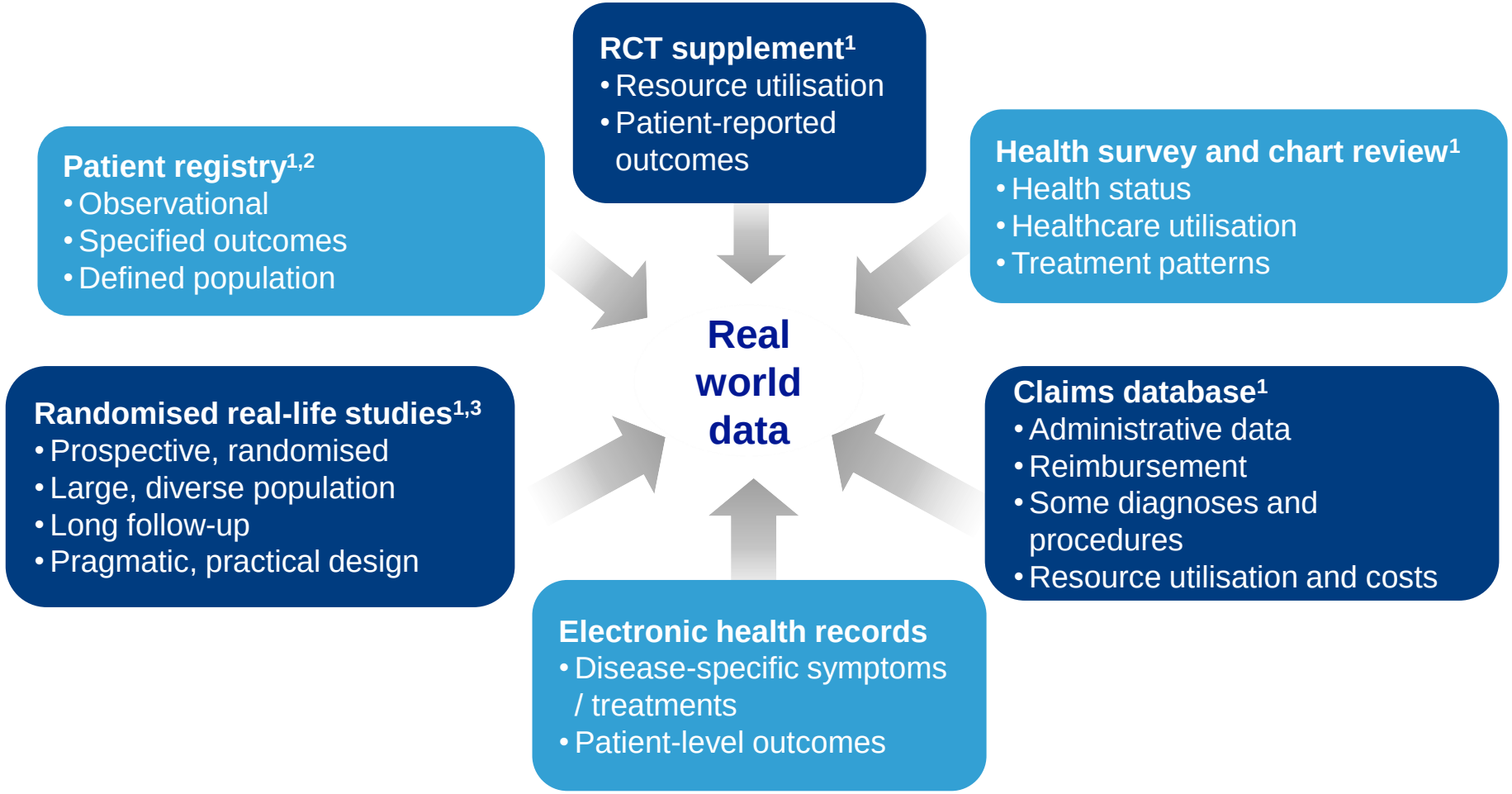
Zoungas S, et al. N Engl J Med. 2010;363:1410–8; Khunti K, et al. Diabetes Care. 2015;38:316–22.

# Today real-world evidence trials are well designed and provide robust data

In the past, real-world evidence has been widely seen as **poor quality and unreliable**, often with good reason

With the use of **robust methodologies and new technologies**, we have entered a new era of **reliable real-world evidence**

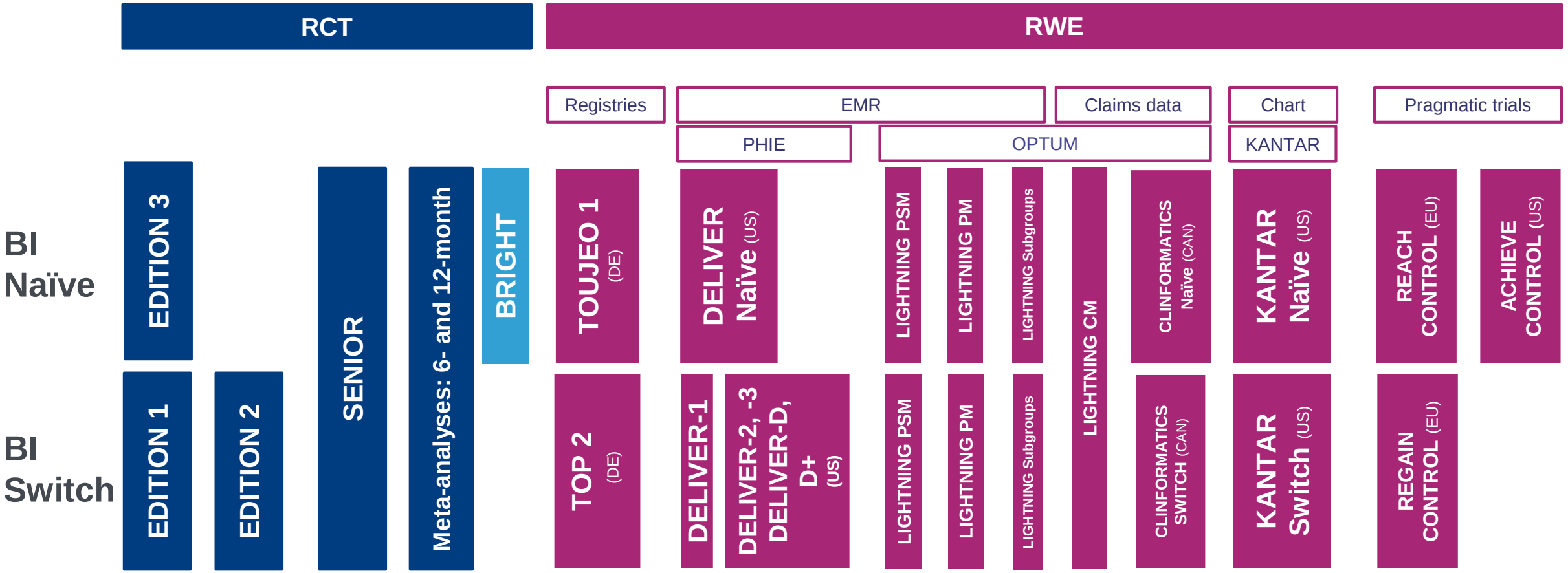
# Sources of real-world evidence




1. ISPOR Using 'Real World' Data Task Force. At: www.ispor.org/workpaper/RWD_TF/RWTFDraftReport.pdf. Accessed January 2018;
2. Gliklich RE, Dreyer NA (eds). Registries for evaluating patient outcomes: a user's guide. 2nd ed. Rockville, MD: AHRQ. 2010;
3. Tunis SR et al. JAMA 2003;290:1624-32

# Real-world evidence for basal insulins

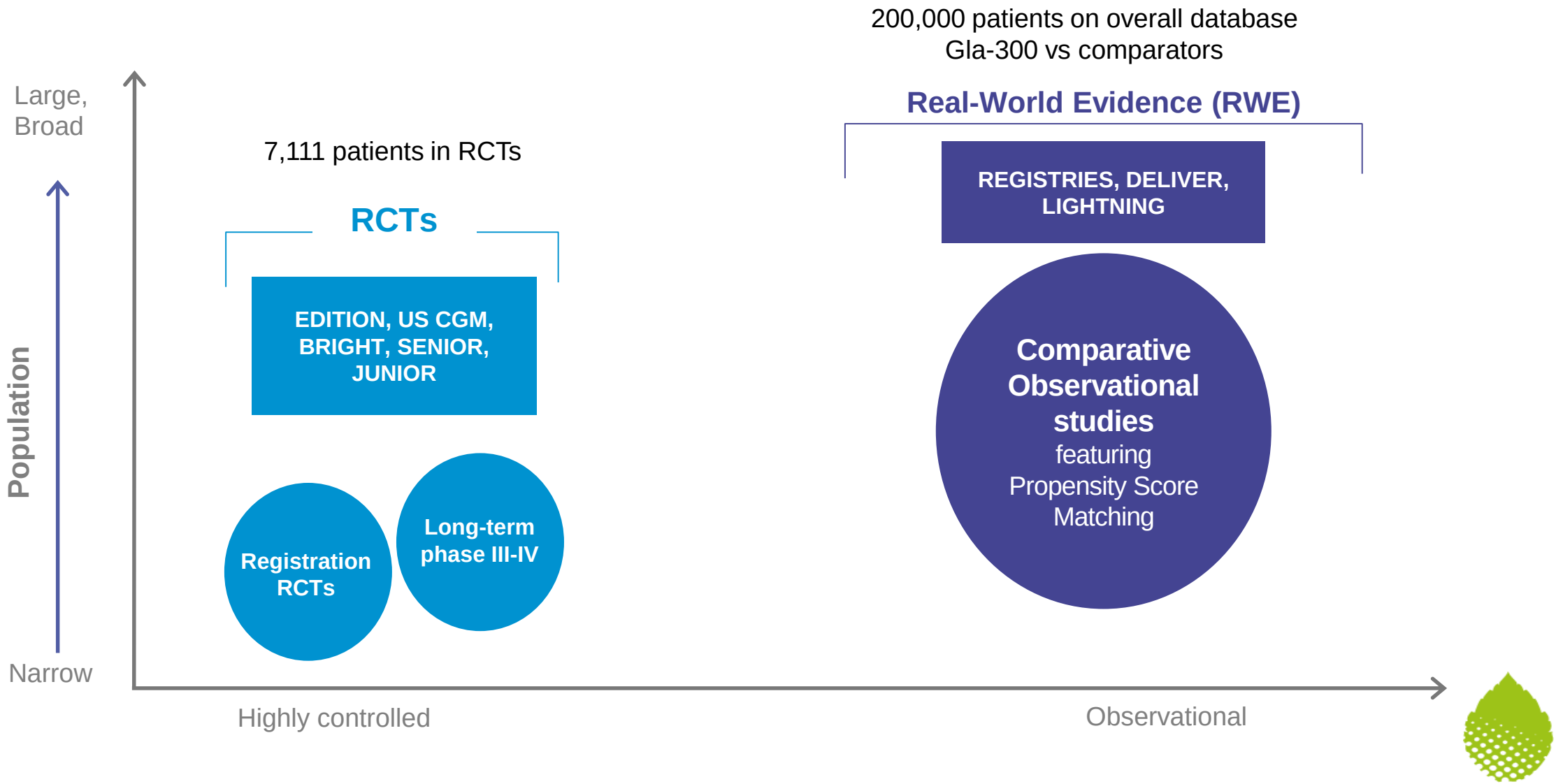
# There is a growing evidence base available for Gla-300




CM, Cost modelling; EMR, Electronic medical records; FPG, Fasting plasma glucose; RCT, Randomised controlled trial

Riddle MC et al. Diabetes Care 2014;37:2755–62; Yki-Järvinen H et al. Diabetes Care 2014;37:3235–43 Bolli GB et al. Diabetes Obes Metab 2015;17:386-94; Ritzel R et al. Diabetes Obes Metab 2015;17:859–67 Seufert J et al. ADA 2017:1023-P; Ritzel R, et al. Diabetes Obes Metab 2018;20:541–48;Ye F et al. ADA 2016:943-P; Zhou FL et al. Diabetes Obes Metab. 2018;20:1293–97; Blonde L et al. Poster presented at WCIRDC 2017; Meneghini L et al. Poster presented at ATTD 2018; Meneghini L, et al. ADA 78th Scientific Sessions 2018; 97-LB; Ritzel R, et al. Diabetes Care 2018; doi: 10.2337/dc-180168 [Epub ahead of print]; Sullivan SD, et al. ADA 78th Scientific Sessions 2018; 1056-P; Sullivan SD, et al. ADA 78th Scientific Sessions 2018; 1057-P; Sullivan SD et al Diabetes Obes Metab. 2019 May 30. doi: 10.1111/dom.13793. [Epub ahead of print]; Sullivan SD, et al. Diabetes 2019;68(S1); Sullivan SD, et al. Poster presented at EASD 2019; 900-P

# From efficacy to effectiveness



# Considering RCTs and RWE studies: From efficacy to effectiveness

| | BRIGHT | DELIVER-NAÏVE D |
|---|---|---|
| **TRIAL OBJECTIVES:** | *To evaluate the efficacy and safety of **Gla-300 versus IDeg-100** in **insulin-naïve** patients with **T2D** inadequately controlled on OADs ± GLP-1 RAs* | *To compare glycaemic control, hypoglycaemia and treatment discontinuation of **Gla-300** and **IDeg** in a real-world study in **insulin-naïve** adults with **T2D*** |
| **GLYCAEMIC CONTROL:** | ***HbA1c improved similarly** from **baseline values of 8.7%** in the Gla-300 group and **8.6%** in the IDeg-100 group to **7.0%***<br><br>*LSM difference 0.05% (95% CI 20.15 to 0.05)* | *Mean(SD) **HbA1c decreases were comparable** in the Gla-300 and IDeg cohorts*<br><br>***−1.67%** [2.22] and **−1.58%** [2.20]; p=0.51* |
| **HYPOGLYCAEMIA:** | ***Hypoglycaemia** incidence and event rates over 24 weeks were **comparable with both insulins*** | *Overall and inpatient/emergency department-associated **hypoglycaemia** were **similar in both cohorts** over 24 weeks of follow ups* |

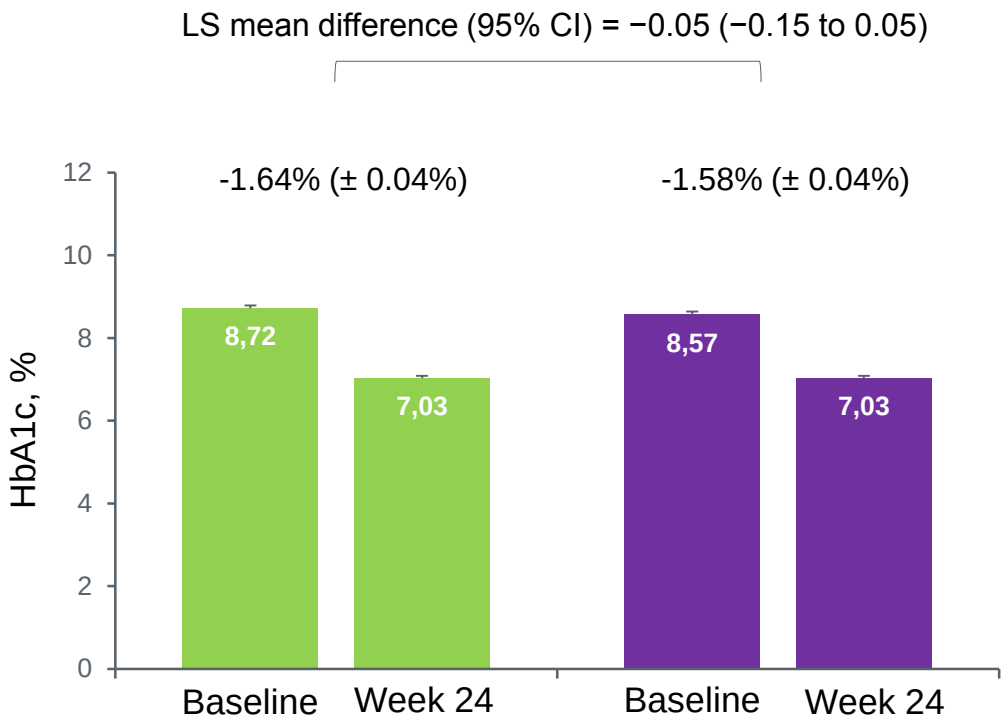
OADs: Oral antidiabetic drugs

Rosenstock J, et al. Diabetes Care 2018;41:2147–54; Sullivan SD, et al. Diabetes Obes Metab 2019;21:2123–32

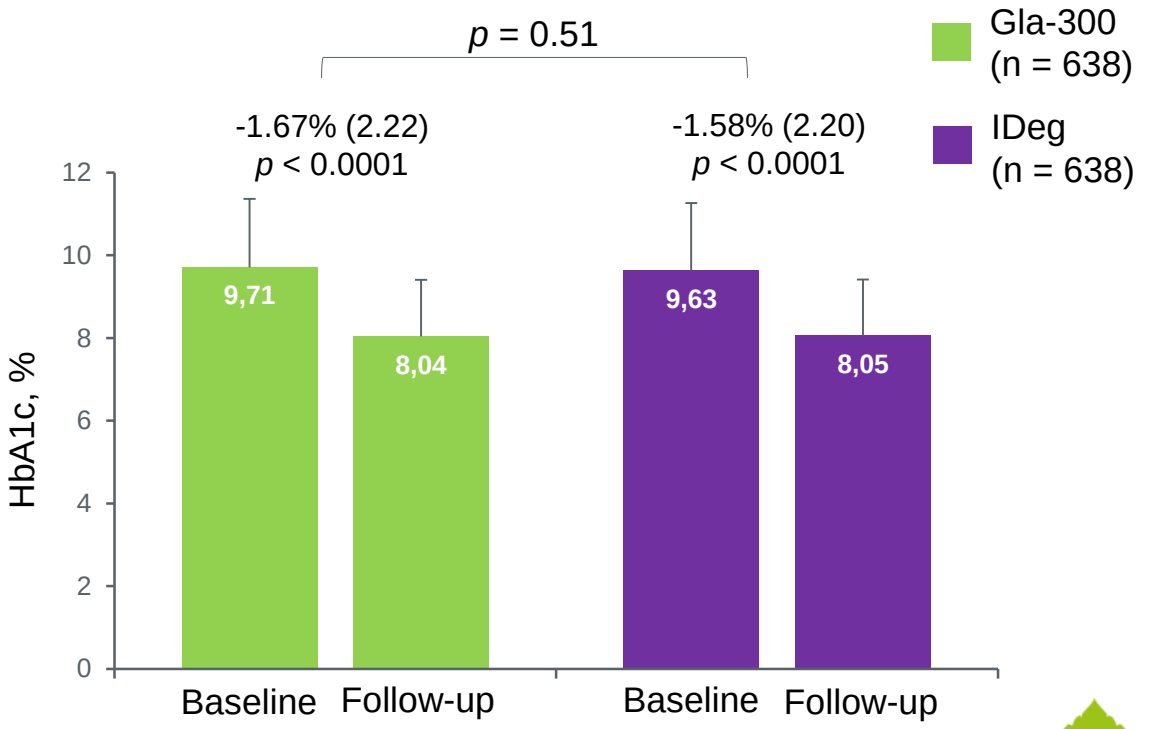
BRIGHT was an open-label, randomised, active controlled, 2-arm parallel group 24 week noninferiority study in insulin naive adults with T2D. Patients were randomised to receive Gla-300 (n=466) or IDeg-100 (n=463); DELIVER Naive D was a retrospective observational study that used electronic medical record data to compare glycaemic control, hypoglycaemia and treatment discontinuation of Gla-300 and IDeg in a real-world study of insulin-naïve adults with type 2 diabetes (N=1276)

# Similar glycaemic improvement for Gla-300 and IDeg in BRIGHT and real-world setting

## BRIGHT




## DELIVER-NAÏVE D



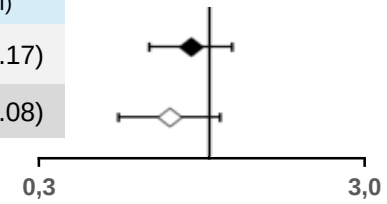

Rosenstock J, et al. Diabetes Care 2018;41:2147–54; Sullivan SD, et al. Diabetes Obes Metab 2019;21:2123–32

# Similar hypoglycaemia incidence and rates for Gla-300 and IDeg in BRIGHT and real-world setting

## BRIGHT

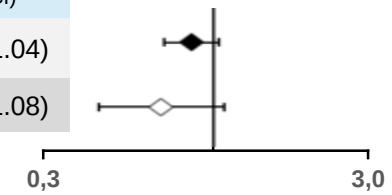
**Anytime hypoglycaemia (0–24 weeks)**

| | Incidence, n (%) | | |
|---|---|---|---|
| | Gla-300 | IDeg | OR (95% CI) |
| Confirmed (≤70 mg/dL) | 66.5 | 69.0 | 0.88 (0.66,1.17) |
| Confirmed (<54 mg/dL) | 14.7 | 18.4 | 0.76 (0.53,1.08) |




Favours Gla-300 Favours IDeg

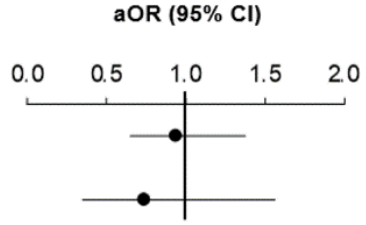
| | Events, (PPPY) | | |
|---|---|---|---|
| | Gla-300 | IDeg | RR (95% CI) |
| Confirmed (≤70 mg/dL) | 9.34 | 10.83 | 0.86 (0.71,1.04) |
| Confirmed (<54 mg/dL) | 0.61 | 0.88 | 0.69 (0.45,1.08) |




Favours Gla-300 Favours IDeg

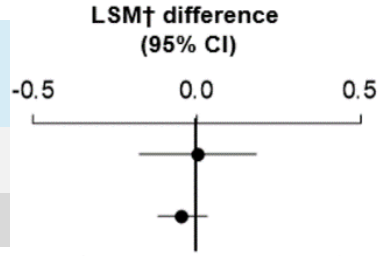
## DELIVER-NAÏVE D

| | Incidence, n (%) | | |
|---|---|---|---|
| | Gla-300 (n = 638) | IDeg (n = 638) | aOR (95% CI) |
| All hypo | 66 (10.3) | 71 (11.1) | 0.94 (0.64,1.37) |
| Inpatient/ ED hypo | 13 (2.0) | 16 (2.5) | 0.73 (0.34,1.56) |




Favours Gla-300 Favours IDeg

| | Events, (PPPY) | | LSMs† | |
|---|---|---|---|---|
| | Gla-300 (n = 638) | IDeg (n = 638) | Gla-300 | IDeg |
| All hypo | 143 (0.43) | 138 (0.43) | 0.44 | 0.44 |
| Inpatient/ ED hypo | 19 (0.06) | 32 (0.10) | 0.06 | 0.10 |



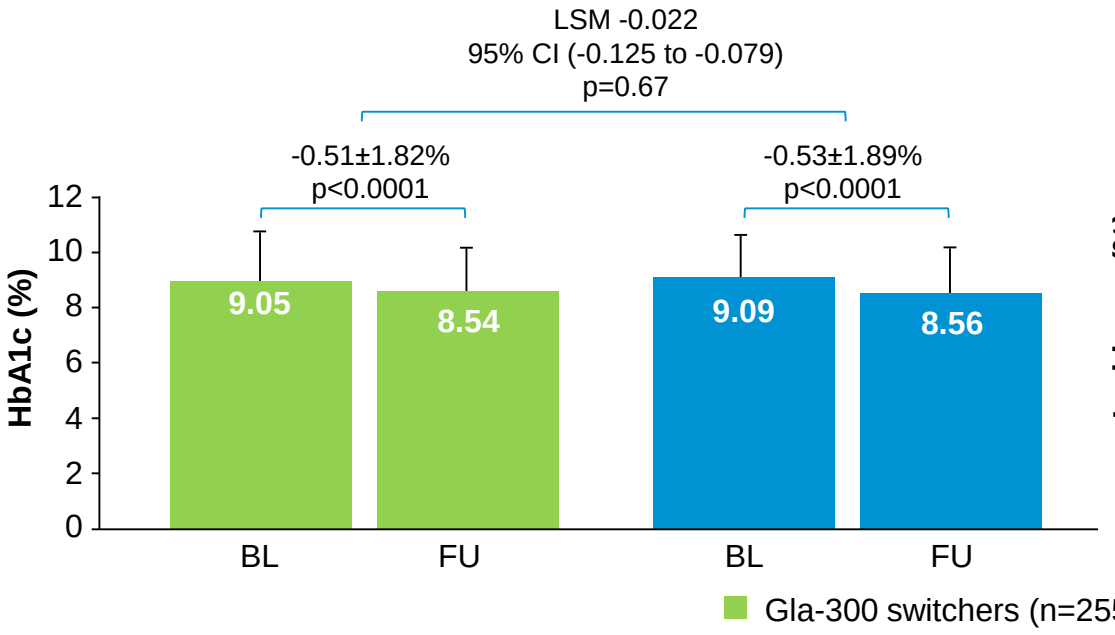

Favours Gla-300 Favours IDeg

Overall 202 (43.7%) and 221 (47.8%) in the Gla-300 and IDeg-100 arms respectively reported adverse events during the 24 week BRIGHT study
No other safety outcomes outside of hypoglycaemia were reported in the DELIVER-naïve D study
In DELIVER-naïve D, Hypoglycaemia (ICD-9-CM/ICD-10-CM diagnoses and/or blood glucose ≤70 mg/dL) was assessed as all captured events and those associated with an inpatient or emergency department (ED) encounter.
Rosenstock J, et al. Diabetes Care 2018;41:2147–54; Sullivan SD, et al. Diabetes Obes Metab 2019;21:2123–32

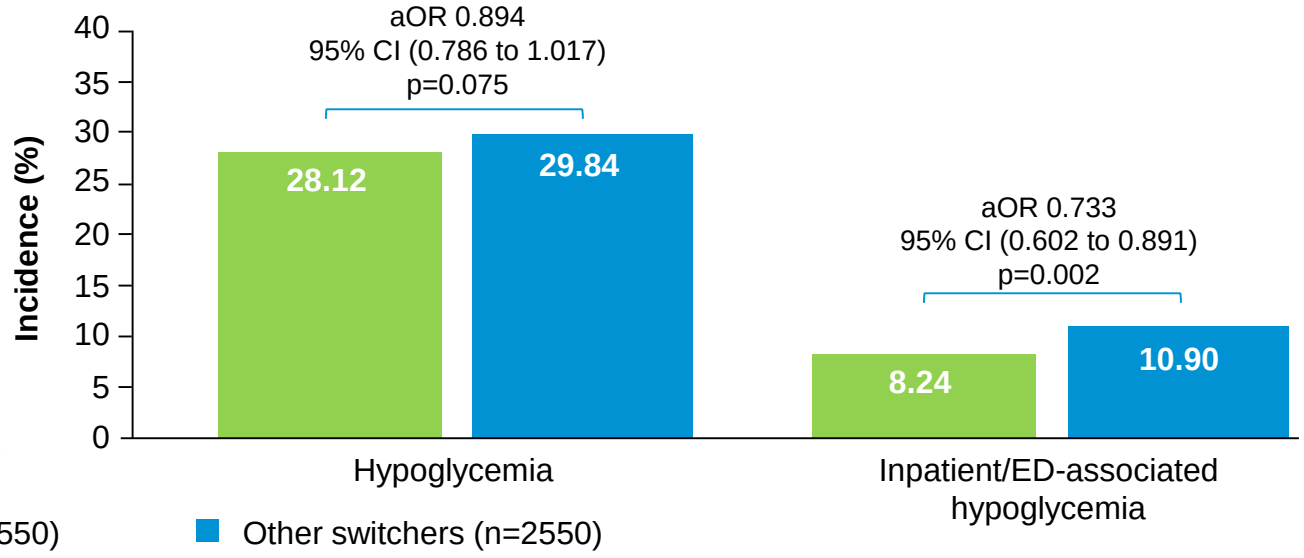
# DELIVER-HIGH RISK study: Lower risk of hypoglycaemia when switching to Gla-300 vs 1st-generation BIs

Objectives: To compare the long-term clinical outcomes for patients with T2D and high hypoglycaemia risk on first-generation BIs who were switched to Gla-300 or other first-generation BIs (other switchers)

## HbA1c reduction




## Hypoglycaemia incidence



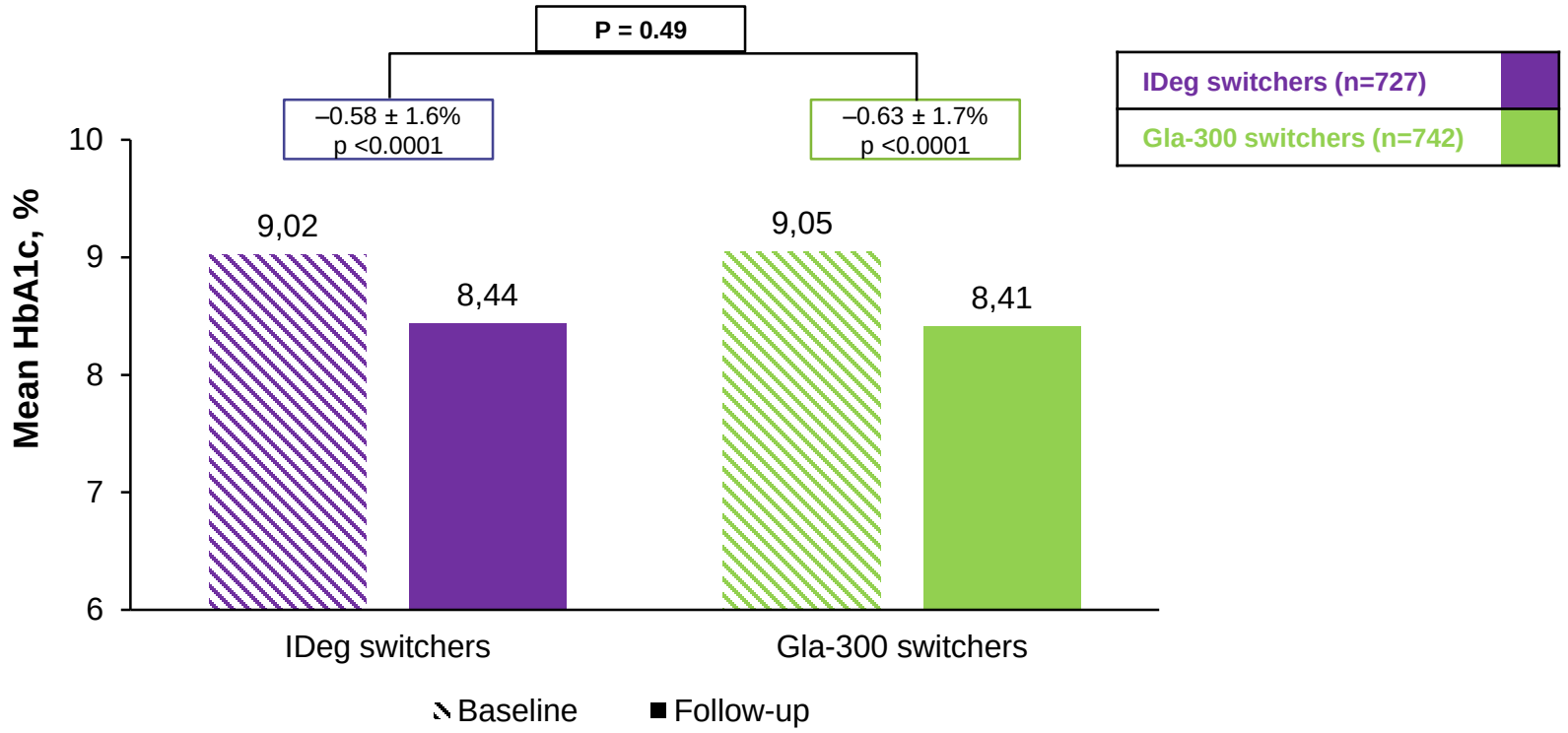

Switching to Gla-300 vs other BIs in patients with T2D and increased risk of hypoglycaemia – similar HbA1c reduction and goal attainment, significantly lower risk of ED/hospitalisation-related hypoglycaemia, 1 year after switching

FU, follow-up. Sub-groups: Uncontrolled HbA1c, prandial insulin, moderate-to-severe renal impairment, hypoglycaemia risk, ASCVD, older adults, sulphonylurea use

Sullivan SD, et al. ADA 79th Scientific Sessions 2019, Abstract 133-LB

# DELIVER D+: Similar glycaemic improvement for Gla-300 and IDeg in patients switching BI

**Mean HbA1c levels for Gla-300 and IDeg cohorts at baseline and follow-up (3 to 6 months after index date)**

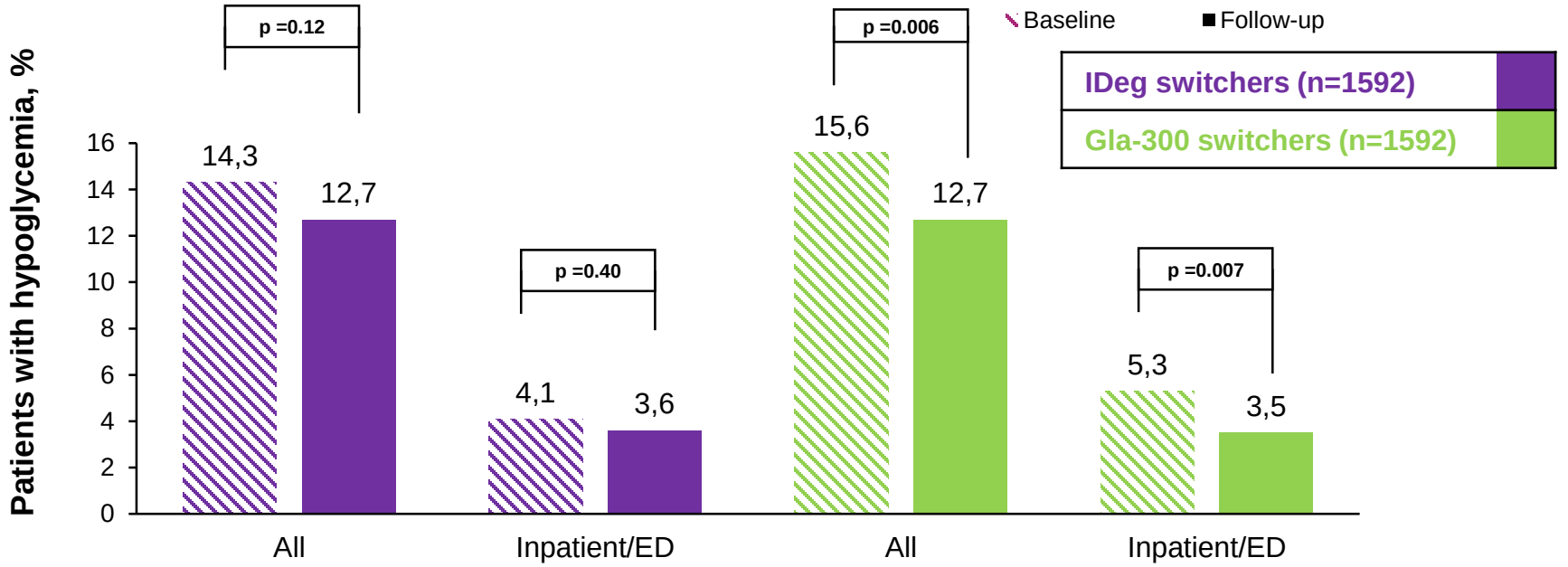



**Mean HbA1c levels decreased significantly from baseline to 3- and 6-month follow-up in both Gla-300 and IDeg cohorts**

Sullivan SD, et al. Diabetes Obes Metab 2018;20:2148–58
DELIVER D+ was a retrospective, observational study of adults with T2D who switched from Gla-100 or IDet to either Gla-300 or IDeg-100. Each matched cohort comprised 1592 patients

# DELIVER D+: Similar hypoglycaemia rates for Gla-300 and IDeg in patients switching BI

- There was a significant reduction in the unadjusted hypoglycaemia incidence (all and inpatient/ED-associated) in the Gla-300 cohort only between baseline and 6-month follow-up
- Hypoglycaemia event rates were similar between cohorts from baseline to 6-month follow-up (aRR 0.94, 95% CI 0.78–1.14, p=0.56)




**DELIVER D+ CONCLUSION**

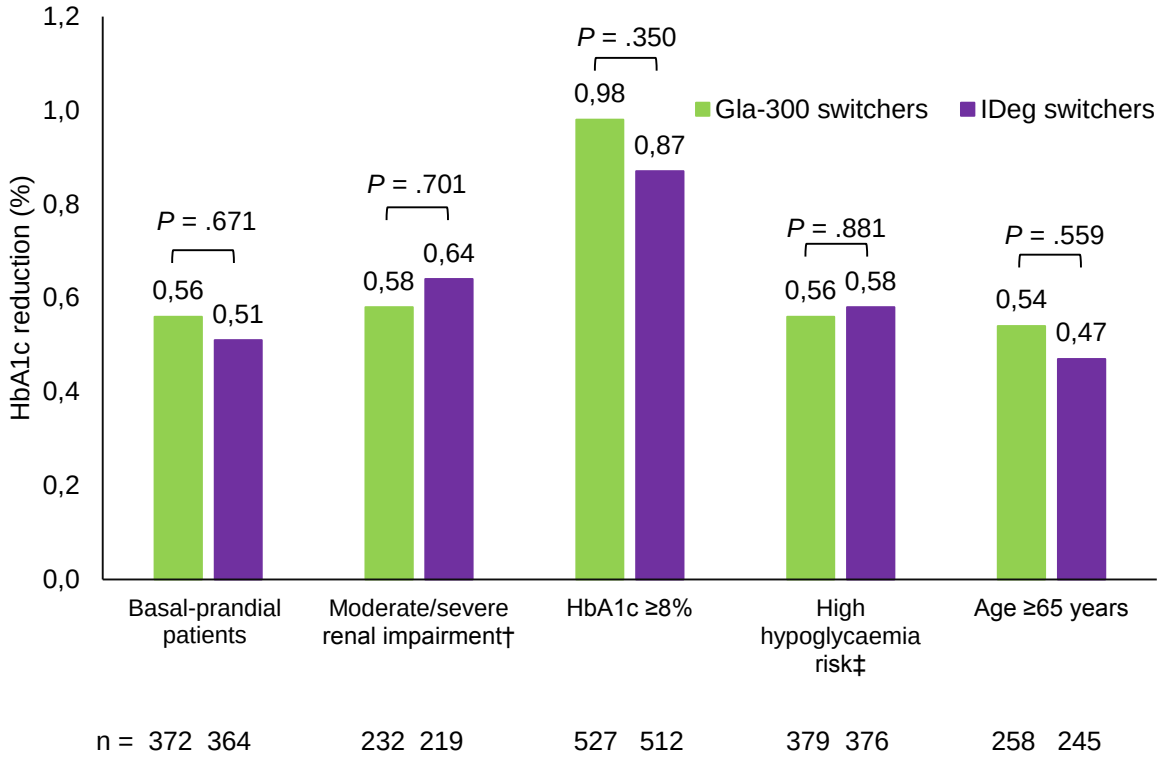
Comparable glycaemic control was seen between Gla-300 and IDeg switchers. Generally, comparable incidences and rates of hypoglycaemia during the 6-month follow-up were seen in both cohorts but only Gla-300 saw a significant reduction in hypoglycaemia incidence from baseline to study end

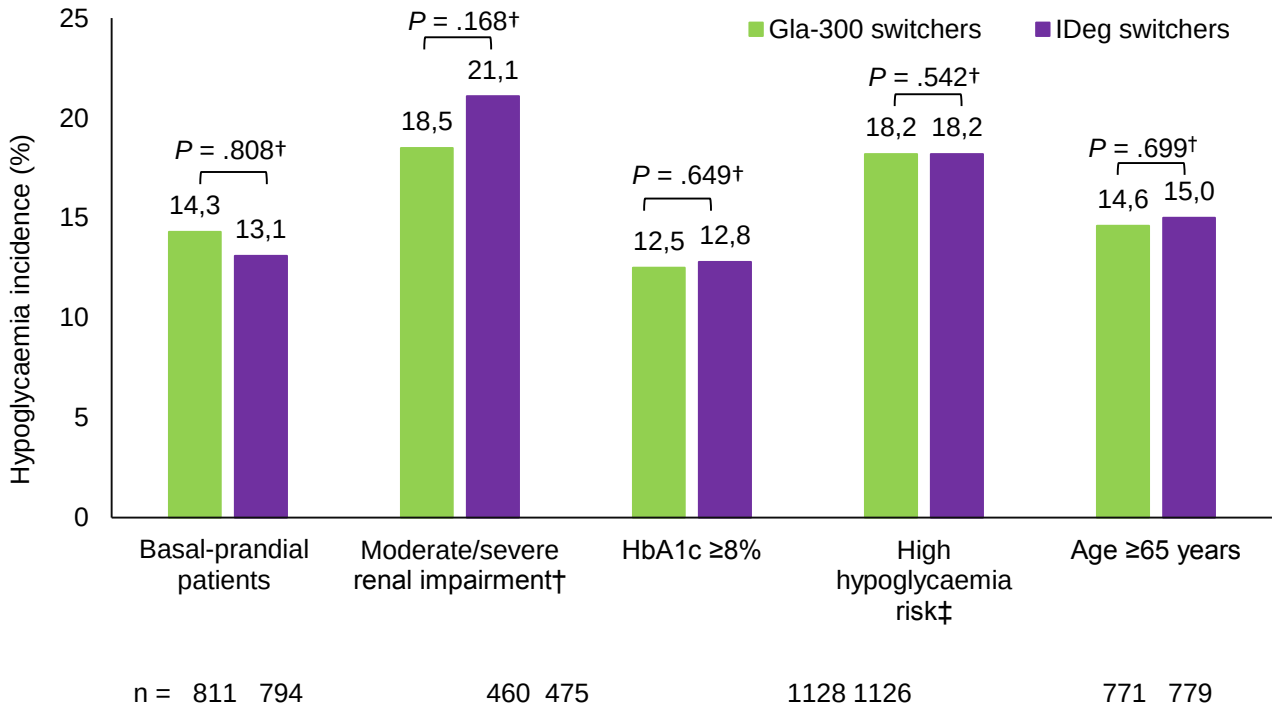
aRR, adjusted for baseline hypoglycaemia rate ratio

In DELIVER D+, hypoglycaemia events (based on ICD-9/ICD-10 diagnoses or blood glucose ≤3.9 mmol/L [70 mg/dL] reported in the EMRs; both all hypoglycaemia events and those associated with an inpatient or emergency department [ED] encounter) were analysed for all patients. No other safety data was reported as part of the analysis

Sullivan SD, et al. Diabetes Obes Metab 2018;20:2148–58

# DELIVER D+ sub-analysis: Similar glycaemic control and hypoglycaemia risk in high-risk subgroups who had switched to either Gla-300 or IDeg




†eGFR <60 mL/min/1.73 m2 or nephropathy.
‡At least one of: ≥1 severe hypoglycaemic (inpatient/ED) episode within prior 12 months; moderate renal impairment (eGFR 30–59 mL/min/1.73 m2); exposure to insulin for >4 years; recent episode of hypoglycaemia (ICD diagnosis and/or glucose ≤70 mg/dL) within the previous 12 weeks).
Sullivan SD, et al. Diabetes Obes Metab 2018;20:2148–58

# Summary

1. Many patients commonly seen in practice are usually excluded from RCTs
2. There is a comprehensive programme of RWE available for Gla-300
3. The results from RCTs and RWE comparing Gla-300 and IDeg are consistent
4. Sub-analyses suggest that 2$^{nd}$-generation BI analogs may offer similar benefits in high-risk patients to those observed in the overall diabetes population

55th EASD Annual Meeting

# Diabetes journey: Innovative solutions for individual needs

Monday
16th September 2019

Fira Barcelona Gran Via
Barcelona, Spain

SANOFI