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REVIEW ARTICLE

What have we learnt from "real world" data, observational studies and meta-analyses

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The incretin therapies glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-IV (DPP-IV) inhibitors are now well-established as second and third-line therapies and in combination with insulin for the treatment of type 2 diabetes. Over the last decade, there is accumulating evidence of their efficacy and safety from both large multicentre randomized clinical trials (RCT) and observational studies. Cardiovascular outcome trials have confirmed that several of these agents are also non-inferior to placebo with the GLP-1 RA liraglutide and semaglutide recently found to be superior in terms of major adverse cardiovascular events. Observational studies and post-marketing surveillance provide real world evidence of safety and effectiveness of these agents and have provided reassurance that signals for pancreatitis and pancreatic cancer seen in clinical trials are not of major concern in large patient populations. Well-designed real world studies complement RCTs and systematic reviews but appropriate data and methodologies, which are constantly improving, are necessary to answer appropriate clinical questions relating to the use of incretin therapies.

KEYWORDS

antidiabetic drug, clinical trial, cohort study, DPP-IV inhibitor, GLP-1 analogue, incretin therapy

1 | INTRODUCTION

There has been an expanding evidence base for the efficacy, safety, tolerability and cardiovascular outcomes and mortality of incretin therapies since the 1980s. They are now well-established in international diabetes treatment algorithms as second or third-line therapies and in combination with insulin.[1] Pharmaceutical companies have spent billions of dollars on conducting large-scale phase III clinical trial programmes of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-IV (DPP-IV) inhibitors to confirm efficacy and safety with cardiovascular safety established with US Food and Drug Agency (FDA) mandated cardiovascular outcome trials. Numerous systematic reviews and meta-analyses of data from these clinical trials have been published and real-world data are emerging from post-marketing surveillance studies and observational cohort studies from around the world.

Randomized controlled trials (RCTs) are considered gold standard as randomization avoids bias, ensuring that treatment groups are similar in every respect other than the investigative treatment, blinding ensures that the assessment of outcomes is not affected by knowledge of the participant's assigned treatment, and there is high internal validity. However, real world studies have been recognized by the FDA and European Medicines Agency (EMA) as a necessary and important source of evidence for regulatory decision making and publication of draft evidence.[2]

Real world data are collected outside the controlled restrictions of RCTs and are therefore more representative of usual clinical practice.[3] Specific differences that can be identified include the fact that there is a clear sequence of outcomes with RCT and a wider range of outcomes with real world studies, follow-up is longer with real world studies and in general they are cheaper to conduct compared with RCTs. RCTs are often highly selective and exclude elderly patients (65 years and older), those with co-morbidities or taking other drugs whereas in real world practice, patients are often older than 65 years, suffer from multiple diseases and take several drugs and can be classified as "diverse and complex."[4]

This review will consider what has been learnt from these two important but different sources of evidence for determining the place of incretin therapies in current type 2 diabetes management.

2 | INCRETIN THERAPIES

Incretin therapies comprise subcutaneously injectable GLP-1 RA and oral DPP-IV inhibitors and have been licensed for use since 2005 and 2006 in the United States and 2006 and 2007 in Europe, respectively. GLP-1 RA optimize the incretin effect, a physiological secretion of the gut hormones GLP-1 and gastric inhibitory polypeptide (GIP) secondary to an oral glucose load, a mechanism impaired in type 2 diabetes mellitus (T2DM). DPP-IV inhibitors attenuate the effects of physiological GLP-1 and GIP by preventing rapid enzymatic degradation following secretion. Due to the glucose-dependent mechanism of action, these agents are not associated with an excess risk of hypoglycaemia unless combined with insulin secretagogues or insulin. Furthermore, DPP-IV inhibitors tend to be weight neutral whereas GLP-1 RA are associated with weight loss. GLP-1 RA have several extra-pancreatic effects including reduced hepatic and gastric glucose output, increased insulin secretion from pancreatic beta cells, reduced glucagon secretion from pancreatic alpha cells and increased satiety through appetite centres in the brain.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are either short-acting (lixisenatide, exenatide twice daily) or long-acting (liraglutide daily or once weekly exenatide, dulaglutide, albiglutide and semaglutide) in duration depending on amino acid homology and plasma half-life. Current international T2DM treatment guidelines place both GLP-1 RA and DPP-1 V inhibitors as second-line or third-line agents after metformin and they can be used in combination with insulin.[1] Large-scale multicentre clinical programmes have evaluated the efficacy, safety and tolerability of GLP-1 RA, for example, LEAD[5–7] studies for liraglutide and AWARD[8–10] for dulaglutide. Similar programmes have been conducted for DPP-IV inhibitors such as sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin.[11]

3 | HIERARCHY OF EVIDENCE

3.1 | Clinical research trials

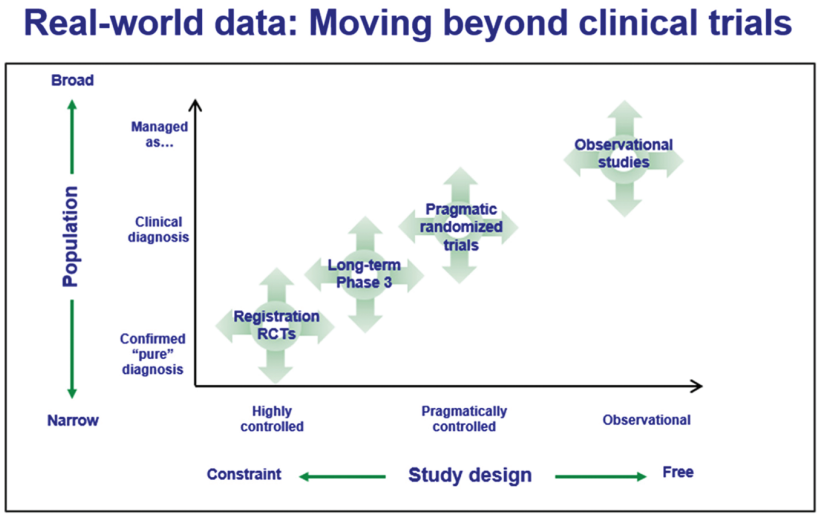
A RCT is considered the gold standard when assessing new interventions and therefore systematic reviews and meta-analyses with homogeneity of RCT are the highest level of evidence. Real-world data and observational studies provide important clinical data and outcomes beyond that gained from RCT and help us to understand the true impact of the intervention including its effectiveness, cost-effectiveness and adverse effects (Figure 1). Whereas RCT answer the question "can it work?" real world data are more concerned with answering "does it work?"[12] The primary focus of RCTs is efficacy, safety, quality and cost-effectiveness. Real world studies extend this to assess effectiveness, safety, quality, cost-effectiveness, natural history, compliance and adherence as well as identifying service models and patient preference (Table 1).

3.1.1 | Efficacy and tolerability

The glycaemic efficacy of incretin therapies has been demonstrated by a number of systematic reviews and meta-analyses (Table 2). Some have been conducted using GLP-1 RA alone and others on DPP-IV inhibitors. With time, there has been greater diversity in the clinical trials included in systematic reviews and meta-analyses in terms of study duration, geographical spread, comparison of at least 2 active treatments and phase III trials.

The first systematic review and meta-analysis of incretin therapy was published in 2007.[13] A total of 29 studies of at least 12 weeks' duration were identified between 1966 and 2007 where GLP-1 RA and DPP-IV inhibitors were compared with placebo or another glucose-lowering therapy and found that GLP-1 RA reduced HbA1c by −0.97% (95% CI −1.13% to −0.81%) and DPP-IV inhibitors −0.74% (95% CI, −0.85% to −0.62%). DPP-IV inhibitors were weight neutral but GLP-1 RA reduced weight by 1.4 kg compared with placebo and 4.8 kg compared with insulin. Longer-term effects could not be evaluated in this early systematic review as 26 out of 29 studies were 30 weeks or less in duration.

One systematic review and meta-analysis of 80 phase III clinical studies conducted from 2005 investigating the efficacy of GLP-1 RA (exenatide twice daily and once weekly, liraglutide once daily) and DPP-IV inhibitors (sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin) found with pooled analysis that there was a significant reduction in glycated haemoglobin (HbA1c) and fasting plasma glucose



Adapted from Roche et al. *Lancet Respir Med* 2013;1(10):e29–30

RCT, randomized controlled trial

FIGURE 1 Real world data: moving beyond clinical trials

TABLE 1 RCT data vs real world data

	RCTs	Real world studies
Type of trial	Experimental/interventional	Observational/non-interventional
Primary focus	Efficacy, safety, quality and cost-effectiveness	Effectiveness, safety, quality, cost-effectiveness, natural history, compliance and adherence, service models, patient preference
Patient population	Narrow, restricted and motivated	Diverse, large and unrestricted
Monitoring	Intense (ICH-GCP compliant)	Not required (?)
Comparators	Gold standard/placebo	None/standard clinical practice/multiple iterations
Outcomes	Clear sequence	Wide range
Data collection confounders	Standardized, controlled	Routine, recruitment bias (?)
Validity	Internal	External
Randomization and Blinding	Yes	No
Follow-up	Short (?)	Long
Cost	$$$$	$

(FPG) with both incretin therapies.[14] For GLP-1 RA, mean HbA1c reduction from baseline was −1.1% to −1.6%, mean FPG reduction −1.16 to −2.12 mmol/L and mean weight reduction −2.03 to −2.41 kg. With DPP-IV inhibitors mean HbA1c reduction was −0.6% to −1.10%, mean FPG reduction −0.87 to −1.57 mmol/L and mean weight reduction −0.16 to −0.64 kg. However, there was considerable heterogeneity between studies related to blinding, treatment discontinuation criteria and medication management.

Another systematic review and meta-analysis of 27 studies (n = 6015) of at least 16 to 30 weeks in duration, where incretin therapy was added to metformin, found a significantly greater HbA1c reduction in patients on long-acting GLP-1 RA than short-acting GLP-1 RA and DPP-IV inhibitors (−1.2% vs 0.8% vs 0.7%, respectively, both $P < 0.0001$).[15] As expected, both short- and long-acting GLP-1 RA reduced weight whereas DPP-IV inhibitors were weight neutral. Conclusions could not be made for lipids, blood pressure and heart rate due to inconsistencies in reporting and except for gastrointestinal (GI) symptoms with GLP-1 RA, adverse effects were rarely observed.

A meta-analysis of the effect of GLP-1 RA on body weight examined 29 studies (n = 10 275) of at least 24 weeks' duration that reported body weight data at either 6 months and/or 12 months.[16] In the 19 studies in patients with diabetes, GLP-1 RA were associated with significant BMI reduction of 1.2 kg/m^2 (95% CI −1.5 to −0.8, $P < 0.001$) at 6 months and 1.9 kg/m^2 (95% CI −3.0 to −0.8, $P < 0.001$) at 12 months compared with placebo and all other glucose-lowering agents but not thiazolidinediones (due to a small number of trials). However, there was no difference between exenatide and liraglutide in terms of body weight reduction.

Network meta-analysis, also known as mixed treatments comparison or multiple treatments comparison meta-analysis, can be used to compare multiple treatments (≥3 or more) using both direct and indirect comparisons and in so doing, increase the number and complexity of comparisons between studies.[17] A network meta-analysis compared the efficacy of liraglutide 1.2 and 1.8 mg once daily with exenatide once weekly and found that the estimated mean HbA1c differences were −0.14% between exenatide and liraglutide 1.2 mg and −0.03% between exenatide and liraglutide 1.8 mg.[18]

A recent systematic review of 34 trials including 14 463 participants on the following GLP-1 RA: albiglutide, dulaglutide, twice daily and once-weekly exenatide, liraglutide, lixisenatide, semaglutide and taspoglutide, and comparing with placebo or another GLP-1 RA, showed that longer acting GLP-1 RA dulaglutide, liraglutide and once-weekly exenatide were more effective at improving glycaemic control (1.21%; 95% CI 1.05, 1.36; 1.15%; 1.03, 1.27; 1.08%; 0.89, 1.27, respectively) than short acting twice daily exenatide (0.70%; 0.59, 0.81) and lixisenatide (0.55%; 0.42, 0.68) (Figure 2).[19] Greatest weight loss was achieved with liraglutide (1.96 kg; 95% CI 1.25, 2.67) and vomiting was least commonly seen with once weekly exenatide (Figure 3). The combination of insulin and incretin therapies has great therapeutic potential with complementary actions and additive effects on glycaemic control and weight. Basal insulin targets FPG levels while incretins lower postprandial glucose, resulting in glycaemic improvement with lower insulin requirements and less weight gain.[20] Basal insulin analogues achieve HbA1c targets of <7% in approximately 50% to 60% of patients, result in modest weight increase of 1 to 3 kg, lower hypoglycaemia risk compared with NPH insulin, control nocturnal and FPG and are generally simple to initiate. In comparison, GLP-1 RA are also relatively simple to initiate, with greater effects on postprandial glucose, reduced risk of hypoglycaemia, have weight lowering or neutral effects and achieve HbA1c targets in around 40% to 60% of patients.

In general, DPP-IV inhibitors are associated with the same level of adverse effects as placebo even in longer term trials of up to 104 weeks.[21] A recent network meta-analysis of 165 RCT found that DPP-IV inhibitors were associated with fewer GI side-effects than metformin, alpha glucosidase inhibitors and GLP-1 RA.[22] Compared with placebo, there was no increase of GI side-effects with sitagliptin (OR = 0.95; 95% CI 0.64-1.14), saxagliptin (OR = 0.96; 95% CI 0.80-1.15) or linagliptin (OR = 1.11; 95% CI, 0.92-1.35).

GLP-1 RA are associated with increased GI side-effects especially on initiation and with short-acting agents. The evidence suggests that GI side-effects although initially troublesome resolve after a few weeks. It is important to discuss expectations with patients before initiation of these therapies, in particular stressing that nausea is likely to be mild and transient, resolving within a few weeks, that it may be a symptom of fullness and that reducing portion sizes and fat content might alleviate discomfort. It may be useful for patients to keep a log of nausea-inducing foods and slow titration is also likely to

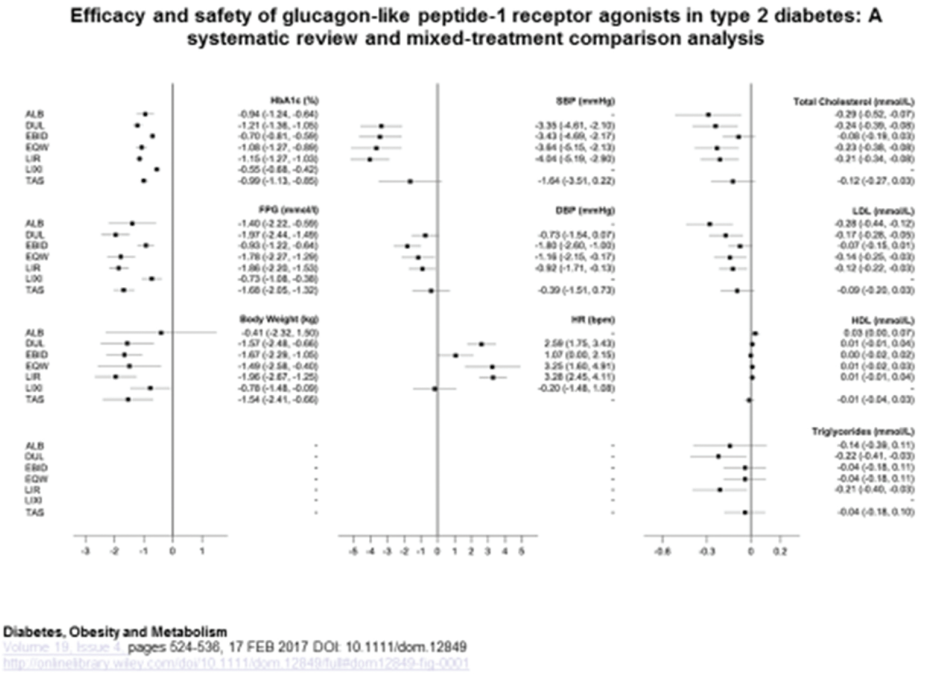


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FIGURE 2 Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis

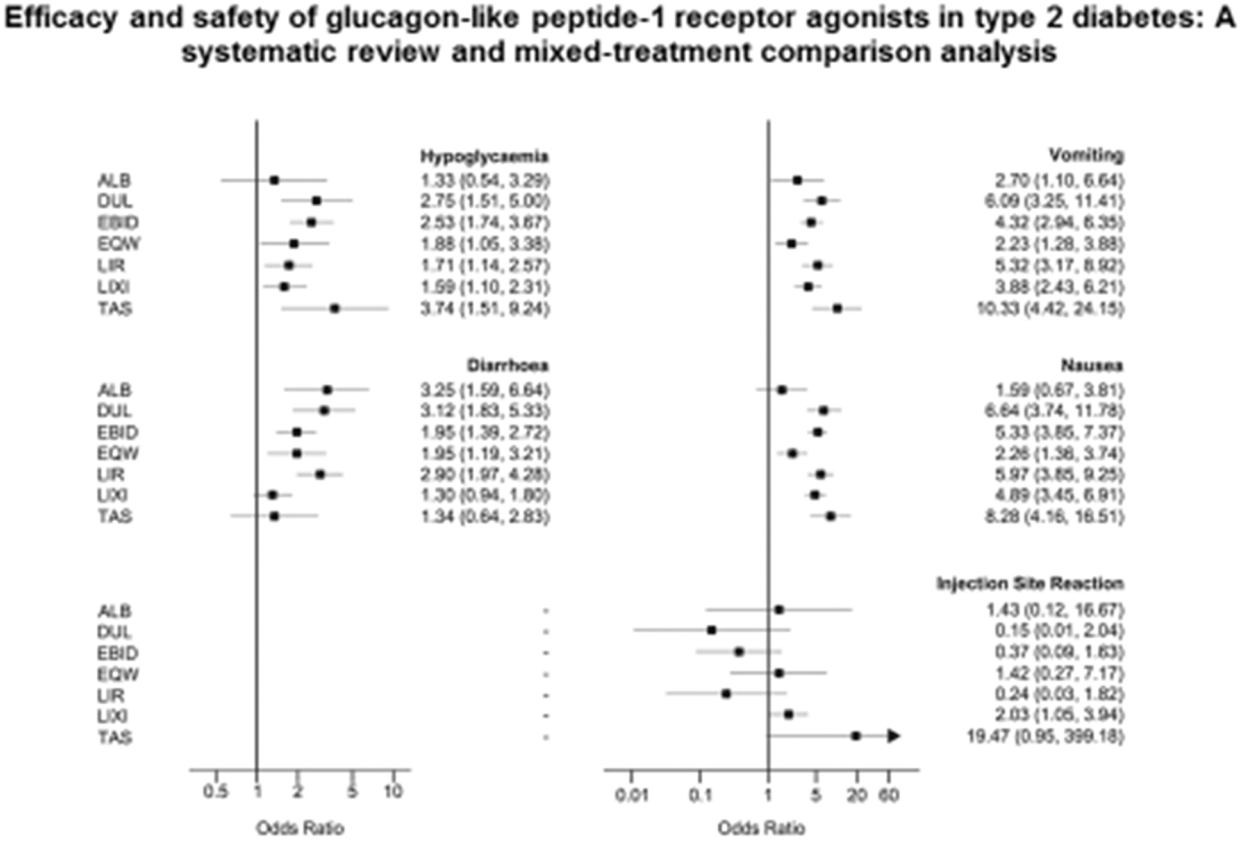

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FIGURE 3 Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis

help. Severe persistent abdominal pain may however be an early sign of acute pancreatitis which again is shown by systematic reviews and observational studies to be a relatively rare but important adverse effect of GLP-1 RA. In general, GLP-1 RA should be avoided in severe GI disease including gastroparesis.

3.1.2 | Safety

There is ongoing controversy as to whether GLP-1 RA are associated with pancreatitis and pancreatic cancer.[23,24] A systematic review and meta-analysis of 60 studies (n = 353 639) evaluated 55 RCT and 5 observational studies and found that incretin therapies were not associated with increased risk of pancreatitis (GLP-1 RA: OR 1.05, 95% CI 0.37-2.94, vs control; DPP-IV inhibitors: OR 1.06, 0.46-2.45, vs control).[25]

3.1.3 | Cardiovascular outcomes and mortality

The cardiovascular effects of GLP-1 RA include beneficial lowering of blood pressure which is rapid and may be through direct vascular or natriuretic mechanisms but is probably not related to weight loss although this may contribute to sustained reductions. These agents also have beneficial effects on lipids which are largely mediated through weight loss and effects on inflammatory markers as well as other cardioprotective effects which are not yet well understood.

As a class, DPP-IV inhibitors have shown cardiovascular safety but not improved major adverse cardiovascular outcomes (MACE) outcomes with some concern regarding increased hospitalization with heart failure with saxagliptin and alogliptin resulting in alerts from the FDA to avoid these agents in certain patient circumstances such as pre-existing heart or renal failure. It is beneficial therefore to examine systematic reviews and meta-analyses of incretin therapies on cardiovascular outcomes and mortality to determine whether the evidence supports the findings of individual trials. However, making comparisons between and conducting statistical analyses of multiple trials is affected by heterogeneity of studies due to differences in methodology, trial duration, outcome measures and sample size (Table 2).

Overall, cardiovascular safety is not affected by incretin therapies as confirmed by a recent systematic review of 11 pooled analyses, 17 meta-analyses and 8 RCTs of patients exposed to DPP-IV inhibitors or GLP-1 RA up to 4 years.[26] A systematic review found a non-significant increased risk in hospitalization for congestive heart failure with DPP-IV inhibitors (HR 1.14, 95% CI 0.97-1.34, P = 0.10)[27] but the meta-analysis was significantly affected by heterogeneity (I^2 = 44.9, P = 0.16) amongst the trials for saxagliptin,[28] alogliptin[29] and sitagliptin.[30]

A systematic review of 189 RCT (n = 155 145) assessed the impact of incretin therapies (both GLP-1 RA and DPP-IV inhibitors) on all-cause mortality in patients with T2DM.[31] No difference in all-cause mortality was detected when comparing incretin therapies with control (OR 0.96, 95% CI 0.90-1.02, I^2 = 0%); although there was the suggestion of improved mortality with GLP-1 RA this was not strongly supported by subgroup analysis.

The impact of incretin therapies on inflammatory markers such as C-reactive protein (CRP) and tumour necrosis factor-alpha (TNF-α) may explain the positive findings from the LEADER[32] and SUSTAIN-6[33] studies on cardiovascular outcomes. A systematic review and meta-analysis of 7 treatment arms of clinical trials identified a significant reduction in CRP levels with GLP-1 RA therapy (weighted mean difference −2.14 (mg/dL), 95% CI −3.51, −0.78, P = 0.002; I^2 96.1%).[34] DPP-IV inhibition is also associated with significant reductions in TNF-alpha levels with no difference between vildagliptin and sitagliptin.[35]

Some of the trials have identified unexpected adverse events such as increased heart rate with GLP-1 RA with pooled analysis suggesting an association with atrial fibrillation. However, a systematic review and meta-analysis of 113 trials found that GLP-1 RA were not significantly associated with atrial fibrillation (Mantel-Haenzsel OR 0.87, 95% CI 0.71-1.05, P = 0.15).[36]

3.2 | Cohort/real world studies

Observational cohort studies can provide real world data on the efficacy and safety of therapies in large patient populations and are more representative of the clinical burden of care. Participants of clinical trials, enrolled following assessment of strict inclusion and exclusion criteria, tend to be more interested in their disease and have greater motivation to attend appointments, take prescribed medication and report adverse events. Real world data can be obtained from a number of sources for example electronic health records provide patient-level outcomes and disease-specific symptoms and treatments, health surveys give indicators of health status, healthcare utilization and treatment patterns.[37] Claims databases provide administrative data, diagnoses, procedures and costs and patient registries are a source of observational data and specified outcomes in a defined population. Practical clinical trials which are prospective and randomized provide outcomes in a large diverse population with a long follow-up duration and finally supplements to RCTs allow additional data collection, resource utilization and patient-reported outcomes. Importantly, a meta-analysis of adverse effects data derived from RCTs compared with observational studies concluded that there was no difference generally in risk estimates of adverse effects between meta-analysis of RCTs and meta-analysis of observational studies.[38]

Adverse events which are identified during large clinical trials can be further evaluated in observational studies which have the benefit of much larger patient numbers taking medication in the real world without regular study visits or healthcare provider input. Post-marketing surveillance can also identify signals for cancer and other diseases not seen during clinical trials.

3.2.1 | Efficacy and tolerability

One of the first observational studies performed to assess efficacy, safety and tolerability of GLP-1 RA in the real world was the nationwide exenatide audit launched in December 2008 and conducted by the Association of British Clinical Diabetologists (ABCD) (Table 3).[39] A national password-protected online website hosted by ABCD collected anonymized data of the use of exenatide in combination with insulin in clinical practice in the United Kingdom and included 6717 patients from 126 centres with information on HbA1c, weight, adverse events, treatment satisfaction and exenatide discontinuation. Data were available on 4857 patients of which 39.6% were on insulin

TABLE 2 Selected systematic reviews and meta-analyses of incretin therapies

Authors	Number of studies	Baseline characteristics of population	Interventions	Comparators	Main findings	Limitations
Aroda et al 2012[14]	80 studies; *N* = 23 592; study duration 12 to 104 weeks	Mean baseline HbA1c 7.2 to 10.3%; females 23% to 64%; 30% to 100% white; diabetes duration 0.3 to 14.8 years	Exenatide twice daily and once weekly, liraglutide; sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin	Placebo or another glucose lowering therapy	**HbA1c:** *GLP-1 RA* −1.1% to −1.6%; *DPP-IV inhibitors* −0.6% to −1.1% **Weight:** *GLP-1 RA* > 2.0 kg; *DPP-IV inhibitors* −0.2 to −0.6 kg	Lack of adjustment for placebo use, interstudy heterogeneity due to differences in methodology
Deacon et al 2012[15]	27 randomized controlled trials; *N* = 6015; study duration at least 16 to 30 weeks	Mean baseline HbA1c 8.1% to 8.5%	Exenatide twice daily and once weekly, liraglutide; sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin (all as add-on to metformin)	Placebo or another glucose lowering therapy	**HbA1c:** *Long acting GLP-1 RA* −1.2%; *Short acting GLP-1 RA* −0.8%; *DPP-IV inhibitors* −0.7% **Weight:** *Long acting GLP-1 RA* −2.3 kg; *Short acting GLP-1 RA* −3.9 kg; *DPP-IV inhibitors* −0.5 kg	No detailed safety evaluation; no conclusions on lipids, blood pressure and heart rate due to inconsistencies of reporting
Monami et al 2012[16]	29 studies; *N* = 10 245; study duration at least 24 weeks	Mean baseline HbA1c 5.6 to 8.8%; age 29 to 59 years; diabetes duration 0 to 12 years	Exenatide; liraglutide	Placebo or another glucose lowering therapy	**Weight:** BMI reduction at 6 months; 1.2 kg/m^2 (95% CI −1.5 to −0.8, $P < 0.001$); BMI reduction at 12 months; 1.9 kg/m^2 (95% CI −3.0 to −0.8, $P < 0.001$); no difference between exenatide and liraglutide	No other parameters apart from weight assessed by authors
Scott et al 2013[18]	22 RCT; *N* = 11 049; study duration at least 24 weeks	Mean baseline HbA1c 7.5% to 8.7%; females 31.6% to 62.5%; mean BMI 26.1 to 34.0 kg/m^2; diabetes duration 0.3 to 14.8 years	Liraglutide once daily (OD); exenatide once weekly (QW)	Placebo	**HbA1c:** Exenatide QW vs liraglutide 1.2 mg OD mean difference adjusted for baseline HbA1c −0.14 (95% −0.34 to 0.06); Exenatide QW vs liraglutide 1.8 mg OD mean difference adjusted for baseline HbA1c −0.03 (95% −0.14 to 0.18)	Non-English literature not included; baseline included as a co-variate in change from baseline analysis
Wu et al 2017[22]	165 RCT; *N* = 122 072; study duration 4 weeks to 206 weeks	Mean age (SD) 57.6 (5.22) years; mean diabetes duration 6.6 (3.5) years; mean baseline HbA1c 8.1% (0.6%)	Alogliptin; linagliptin; saxagliptin; sitagliptin; tenegliptin; vildagliptin	Placebo or other glucose lowering therapy	Significant reduction in GI side-effects compared with GLP-1 RA and same as placebo alogliptin (OR = 0.26; 95% CI, 0.15–0.44), linagliptin (OR = 0.43; 95% CI, 0.25–0.74), saxagliptin (OR = 0.28; 95% CI, 0.17–0.46), sitagliptin (OR = 0.24; 95% CI, 0.17–0.35), and vildagliptin (OR = 0.27; 95% CI, 0.18–0.41)	Only trials in English included; none of included studies designed to assess comparative effect of DPP-IV inhibitors on GI side-effects

Abbreviations: BMI, body mass index; CI, confidence interval; DPP-IV, dipeptidyl peptidase-IV; *GLP-1*, glucagon-like peptide-1; OR, odds ratio; RCT, randomized clinical trial.

TABLE 3 Selected observational studies of incretin therapies

Authors	Study population	No. of participants	Intervention	Comparator	Baseline characteristics	Main findings	Conclusion
Thong et al 2011,[39] United Kingdom	Patient data entered by UK physicians on password-protected online database hosted by Association of British Clinical Diabetologists (ABCD)	6717	Exenatide with insulin (n = 1921) twice daily	Non-insulin treated	Male 54.9%; Caucasian 84.4%; age 54.9 (10.6) years; diabetes duration 8 (5-13) years; HbA1c 9.47 (1.69)%; weight 113.8 (23.4) kg; BMI 39.8 (8.0) kg/m^2	HbA1c reduction 3 months −0.74% (P < 0.001); 6 months −0.75% (P < 0.001) Weight 3 months −4.4 kg (P < 0.001); 6 months −6.5 kg (P < 0.001)	Addition of exenatide to obese insulin-treated patients improved glycaemic control and weight but was associated with significant insulin discontinuation, dose reduction and greater sulphonylurea discontinuation
Ryder et al 2012,[40] United Kingdom	Patient data entered by UK physicians on password-protected online database hosted by ABCD	3010	Liraglutide (n = 2303) once daily	Non-insulin treated	Male 54.1%; Caucasian 90.4%; age 55.4 (11.2) years; diabetes duration 9 (5-13) years; HbA1c 9.32 (1.72)%; weight 111.1 (23.0) kg; BMI 39.1 (7.5) kg/m^2	HbA1c reduction 3 months −1.05% (P < 0.001); 6 months −0.93% (P < 0.001) Weight 3 months −3.1 kg (P < 0.001); 6 months −3.7 kg (P < 0.001)	Greater HbA1c reduction but less weight reduction compared with exenatide
Gautier et al 2015,[42] France	Data collected from CEGEDIM database in mainland France	3590	Liraglutide (n = 3152)	Other glucose-lowering treatments	Male 53%; age 58.7 (10.5) years; diabetes duration 9.7 (6.7) years; HbA1c 8.5 (1.5)%; weight 95.6 (19.9) kg; BMI 34.1 (6.9) kg/m^2	29.5% (95% CI 27.7 to 31.2) achieved primary endpoint of HbA1c < 7.0%; at 2 years HbA1c reduction 1.01% (P < 0.001); body weight reduction 4.1 kg (P < 0.0001)	Liraglutide as effective in real world clinical practice as in RCTs
Saab et al 2015,[43] Middle East	Data extracted from EDGE study which enrolled patients from 27 countries	4780	Vildagliptin (n = 2513)	Other oral glucose-lowering agents	Male 61.6%; diabetes duration 4.2 (4.0) years; HbA1c 8.5 (1.3) %; BMI 29.4 (4.7) kg/m^2	Primary endpoint of HbA1c < 7% achieved in 76.1% with vildagliptin compared with 61.6% in comparator group OR 1.98 (95% CI 1.75 to 2.25, P < 0.0001); at 12 months HbA1c reduced significantly in both cohorts (−1.7% vs −1.4% respectively); low risk of adverse events both cohorts	Vildagliptin was well-tolerated with good safety profile in a real world study
Toh et al 2016,[51] United States	Patients enrolled on health insurance and health system schemes in US FDA Mini-Sentinel program	1 113 211	Saxagliptin (n = 78 553); sitagliptin (n = 210 178)	Other glucose-lowering therapies including pioglitazone, sulphonylureas and insulin	Male 53.8% to 57.9%; mean age 58.3 to 59.4 years	Hazard ratios from disease risk score (DRS)–stratified analyses 0.83 (95% CI, 0.70 to 0.99) for saxagliptin vs sitagliptin, 0.63	No increased risk of hospitalization for heart failure with saxagliptin or sitagliptin compared with comparators

(*Continues*)

TABLE 3 (Continued)

Authors	Study population	No. of participants	Intervention	Comparator	Baseline characteristics	Main findings	Conclusion
						(CI, 0.47 to 0.85) for saxagliptin vs pioglitazone, 0.69 (CI, 0.54 to 0.87) for saxagliptin vs sulfonylureas, and 0.61 (CI, 0.50 to 0.73) for saxagliptin vs insulin	

Abbreviations: BMI, body mass index; CI, confidence interval; FDA, US Food and Drug Agency; OR, odds ratio; RCT, randomized clinical trial.

and exenatide and showed that compared with non-insulin treated patients, mean (±standard error) latest HbA1c and weight reduction (median 26 weeks) were 0.51 ± 0.06 vs 0.94 ± 0.04% ($P < 0.001$) and 5.8 ± 0.2 vs 5.5 ± 0.1 kg ($P = 0.278$) and in the insulin treated patients there was more treatment dissatisfaction (20.8 vs 5.7%, $P < 0.001$), hypoglycaemia (8.9 vs 6.1%, $P < 0.001$), exenatide discontinuation (31.0 vs 13.9%, $P < 0.001$), and GI side-effects (28.4 vs 25.0%, $P = 0.008$).

In 2009, ABCD launched a liraglutide audit which had collected data by April 2011 from 264 centres.[40] At 6 months, liraglutide was associated with an HbA1c reduction of 0.93% compared with 0.75% with exenatide, a statistically significant difference. At baseline, patients in both exenatide and liraglutide audits were heavier with worse glycaemic control compared with the phase III clinical studies for these agents. Efficacy was similar with both agents with greater weight loss demonstrated in those with BMI > 40 kg/m^2 who were not included in RCTs. The differences between the 2 GLP-1 RA in terms of effects on weight and HbA1c reductions have been attributed by the authors to greater clinician confidence with regard to adjusting glucose-lowering therapies including less discontinuation of thiazolidinediones with time bearing in mind that the liraglutide audit data were collected 2 years after the exenatide data. In particular, up to 40% of patients were using insulin with liraglutide in that audit whereas it was only 25% in the exenatide audit. Total GI side-effects were less frequently observed with liraglutide (16.4% vs 23.7%, respectively), and there were fewer cases of pancreatitis (1 vs 4 cases, respectively).

The findings of the exenatide and liraglutide are in agreement with a head-to-head study between these 2 agents where maximum doses of liraglutide 1.8 mg once daily compared with exenatide 10 mcg twice daily resulted in lower HbA1c concentration (1.12% vs 0.79%, respectively, with an estimated treatment difference of −0.33; 95% CI −0.47 to −0.18; $P < 0.0001$).[5] However, in this study, liraglutide was more effective at achieving weight loss (−3.24 kg vs −2.87 kg, respectively).

ABCD also conducted an audit on the safety and efficacy of liraglutide 1.2 mg daily in 1791 patients with mild and moderate renal impairment and found that at 6 months there were significant reductions in HbA1c (−1.0 to −1.1%) and weight (−3.6 to −3.8 kg) which was not affected by degree of renal function.[41] Minor hypoglycaemia was not more commonly reported in those with renal impairment and GI side effects were likely to occur at all stages of renal function although those with mild and moderate renal impairment were more likely to discontinue liraglutide (adjusted OR 2.32 [95% CI 1.45-3.74] and 2.37 [95% CI 0.97-5.81]), respectively.

An observational multicentre prospective study of 3152 French adults with T2DM who were about to start treatment with liraglutide and were randomly recruited from the Centre de Gestion, de Documentation, d'Informatique et de Marketing (CEGEDIM) database in which 29.5% of patients reached the HbA1c target of <7% after 2 years of follow-up.[42] There were significant improvements in HbA1c, FPG, weight and BMI from baseline (8.46% [±1.46] to 7.44% [±1.20]; 180 [±60] to 146 [±44] mg/dL; 95.2 [±20.0] to 91.1 [±19.6] kg; 34.0 [±7.2] to 32.5 [±6.9] kg/m^2; respectively, all $P < 0.0001$). Gastrointestinal symptoms occurred at a frequency of 10.9% with a reduction of hypoglycaemic episodes of ≥1 from 6.9% to 4.4% and treatment satisfaction scores also increased.

The DPP-IV inhibitor vildagliptin was investigated for effectiveness and tolerability in a large observational study of 45, 868 patients in the Middle East (Bahrain, Jordan, Kuwait, Lebanon, Oman, Palestine and United Arab Emirates) and was found to result in greater numerical reduction in HbA1c compared with other oral glucose-lowering agents (1.7% vs 1.4%, respectively) with no difference in adverse events between cohorts.[43]

Benefits on glycaemic control and body weight need to be balanced against cost-effectiveness when considering the use of incretin therapies. A real world study of data collected from 4490 patients enrolled with 2 large health insurers in the United States compared treatment patterns and outcomes between liraglutide and insulin glargine.[44] After 6 months, both liraglutide and glargine resulted in improvements in HbA1c (−0.51% vs −1.24%, respectively), there was a significant increase in diabetes-related costs with liraglutide ($2089 vs $3258, $P < 0.001$) compared with glargine ($3492 vs $3550, $P = 0.890$). However, mean weight increased by 1.17 kg with glargine whereas there was mean weight loss of 2.74 kg with liraglutide.

3.2.2 | Safety

The concerns around pancreatic safety of incretin therapies and the emergence of safety signals from post-marketing surveillance led to independent evaluations by the FDA and EMA of extensive data from toxicology studies in rodents and non-rodents as well as clinical safety databases.[45] The FDA evaluation examined 41 000 participants

exposed to incretin drugs in over 200 trials and the EMA reviewed all studies undertaken in the European Union with these agents. The overall conclusion was that the data provided reassurance that there was no compelling evidence that GLP-1 RA and DPP-IV inhibitors were linked with an increased risk of pancreatitis and pancreatic cancer although both agencies would continue to monitor the association as a safety signal.

An international multicentre population-based cohort study conducted in Canada, United Kingdom and United States analysed 1 532 513 patients to identify whether incretin therapies resulted in more acute pancreatitis than 2 or more glucose-lowering agents and found that there was no increased risk with either DPP-IV inhibitors (pooled adjusted HR, 1.09; 95% CI, 0.86-1.22) or GLP-1 RA (pooled adjusted HR, 1.04; 95% CI, 0.81-1.35).[46]

Systematic review and meta-analysis of 1 324 515 patients and 5195 episodes of acute pancreatitis from 9 observational studies found no association with acute pancreatitis (OR 1.03, 95% CI 0.87-1.20).[47] Another review of the literature concluded that the current literature was inadequate and longer-term studies will be necessary to evaluate this association further.[48]

Another systematic review sought to answer this concern by evaluating data from 6 observational studies (n = 2 229 470), 5 in the United States and 1 in Italy, comparing incretin therapies with other treatment and pancreatitis risk.[49] The review found no difference in overall risk of pancreatitis (OR 1.08, 95% CI 0.84-1.40) between incretin users and others but limitations included lack of differentiation between DPP-IV inhibitors and GLP-1 RA, low number of incretin users and relatively short study duration.

With regard to pancreatic cancer, in a multicentre cohort study including 972 384 patients initiated on glucose-lowering drugs in Canada, United Kingdom and United States, there was no increased risk of this outcome with incretin therapies compared with patients on sulphonylureas (pooled adjusted HR 1.02, 95% CI 0.84-1.23) and no association with a duration response.[50]

3.2.3 | Cardiovascular outcomes and mortality

Data from observational studies of incretin-based therapies have been conflicting. An observational study examined the risk of hospitalization for heart failure with saxagliptin and sitagliptin by reviewing 18 health insurance and health system data partners in US FDA's Mini-Sentinel programme which comprised 78 553 patients on saxagliptin and 298, 124 patients on sitagliptin.[51] The study showed that, contrary to evidence from cardiovascular outcome trials (CVOT) for these agents, there was no increased risk of hospitalization for heart failure compared with other agents such as pioglitazone, sulphonylureas or insulin and regardless of pre-existing cardiovascular disease.

Another analysis used healthcare data obtained from 3 countries, specifically from the Clinical Practice Research Datalink (CPRD) linked to the Hospital Episodes Statistics database in the United Kingdom, the MarketScan database containing data from health insurance plans in the United States, and databases of physician billing claims, hospital discharge abstracts and drug prescriptions from 4 sites in Canada to investigate the association between heart failure and incretin therapies.[52] The study found that in 1 499 650 patients with 29 741 episodes of heart failure requiring hospitalization with an incidence rate of 9.2 events per 1000 persons per year, there was no increased risk of this outcome compared with other oral glucose lowering agents for GLP-1 RA (HR 0.95, 95% CI, 0.83-1.10) or DPP-IV inhibitors (HR 0.84, 95% CI, 0.69-1.02) (Table 3).

The safety of DPP-IV inhibitors with regard to heart failure hospitalization has also been confirmed in another very large observational retrospective registry study of 127 555 patients in the Nationwide OsMed Health-DB Database covering 32 health services in 16 Italian regions (HR 0.70; 95% CI 0.52-0.94; P = 0.018).[53] The findings of these massive observational studies of real world data provides some reassurance regarding this serious outcome, despite the conflicting results from RCTs for DPP-IV inhibitors..[28–30,54]

The UK Prospective Diabetes Study Risk Engine has been used in an observational retrospective study in 170 patients with type 2 diabetes in Italy on sitagliptin to evaluate cardiovascular risk evolution and found analysis of variance testing showed a significant effect on increased CV risk at 12 months (P = 0.003) and 48 months (P = 0.04).[55]

An observational propensity score-matched study of 414 213 participants aged 65 years or more identified from the National Health Insurance Research Database in Taiwan showed that compared with matched controls, DPP-IV inhibitors in this older age group were associated with less all-cause mortality risk (HR 0.54, 95% CI 0.52-0.56), MACE outcomes (HR 0.79, 95% CI 0.75-0.83), myocardial infarction (HR 0.79, 95% CI 0.72-0.87) and ischaemic stroke (HR 0.79, 95% CI 0.75-0.84).[56] A Medicare cohort of the same age group in the United States was evaluated to determine cardiovascular risk in those initiated on DPP-IV inhibitors (n = 50 726) compared with sulphonylureas (n = 68 382) and thiazolidinediones (n = 13 526) over a 12-month period.[57] Over this short duration, no differences were found in a composite outcome of myocardial infarction, stroke and all-cause mortality with adjusted HR 0.75 (95% CI 0.72-0.79) for DPP-IV inhibitors vs sulphonylureas and adjusted HR 0.95 (95% CI 0.86-1.03) for DPP-IV inhibitors vs thiazolidinediones.

3.3 | Special circumstances

There has been some interest in the use of incretin therapies in the management of type 1 diabetes. A systematic review and meta-analysis of 12 RCT (n = 2903) in patients with type 1 diabetes found that incretin drugs significantly reduced HbA1c (mean difference [MD] −0.20, 95% CI −0.30 to −0.10), weight (MD −2.83, −4.00 to 1.65) and insulin dose (MD −4.55, −6.15 to −2.94).[58] Importantly, there was no significant increase in the rate of ketoacidosis or severe hypoglycaemia. However, more evidence is needed before incretin therapies will be established as part of the treatment for type 1 diabetes.

The management of older people (>65 years) with diabetes, who are not always included in large-scale clinical trials, is often complicated by co-morbidities including cardiac and renal impairment, polypharmacy, frailty and social issues. Issues with hypoglycaemia and self-administration of injectable therapies also need consideration. However, in view of their safety, DPP-IV inhibitors are commonly prescribed in the elderly. A population based study of

12 881 very old (>80 years) people with diabetes using UK CPRD data shows that DPP-IV inhibitor prescriptions have increased whereas sulphonylurea use has declined.[59] A systematic review of 30 studies including 1 RCT, 17 intervention studies and 12 observational studies evaluated the safety and effectiveness of DPP IV inhibitors in this population and found similar or greater safety compared with placebo or any other glucose-lowering therapies including insulin but only for short term outcomes such as hypoglycaemia or adverse events.[59] The authors concluded that other than the surrogate endpoint of improved glycaemic control, data on clinically relevant benefits of DPP-4 inhibitors in the treatment of type 2 diabetes mellitus in older adults is scarce.[60] Pooled analysis of phase III trials for liraglutide[61] and dulaglutide in people with diabetes >65 years have shown that they can be used safely and effectively in this cohort.[62]

Patients with type 2 diabetes often have co-existing renal disease and the efficacy and safety of incretin therapies needs to be ascertained. A systematic review and meta-analysis has evaluated the use of incretin therapies compared with placebo or active comparator in moderate or severe chronic kidney disease (CKD) by examining 13 studies (n = 6390).[63] Although there was increased risk of hypoglycaemia in CKD compared with placebo (n = 7; relative risk [RR], 1.38; 95% CI, 1.01-1.89; I^2 = 0%), there was no difference when compared with active comparators (n = 4; RR, 0.24; 95% CI, 0.03-1.94; I^2 = 52%) but the review was limited by the relatively small number of heterogeneous studies.

GLP-1 RA have been associated with improvement in outcomes from non-alcoholic fatty liver disease (NAFLD) through a number of possible mechanisms including improved insulin sensitivity, anti-inflammatory properties and weight loss mediated by satiety, reduced appetite and delayed gastric emptying. A systematic review found improvement in markers of hepatic inflammation in 4 studies (n = 136) of people with NAFLD and type 2 diabetes.[64] In the 2 studies examining exenatide and liraglutide, there was a significant reduction in serum alanine transaminase (ALT) concentrations with treatment (mean reduction 12.2 IU/L, 95% CI 4.9-19.4, P < 0.001) and in the 2 sitagliptin treated groups ALT was reduced by 17.7 IU/L (95% CI 12.4-23.1, P < 0.001). A phase 2 clinical trial with liraglutide 1.8 mg daily showed histological resolution of NAFLD changes after 48 weeks of treatment.[65]

A small (n = 58) observational study comparing the effect of metformin in combination with one of liraglutide, exenatide, sitagliptin, pioglitazone and gliclazide on NAFLD found no difference between therapies on qualitative ultrasonographic evaluation after 6 months.[66]

4 | CONCLUSION

While RCTs continue to provide high-quality evidence of the efficacy and safety of incretin therapies, it is only through systematic reviews and meta-analyses that findings can be understood in aggregate. However, there can be considerable variation in quality of systematic reviews, and this needs to be considered by stakeholders involved in making clinical and health economic decisions regarding incretin therapies.[67] Beyond research, real world data in the form of observational studies complement RCTs and provide information on a larger scale than is feasible in clinical trials although multiple confounding factors and variations in care can affect the results. Furthermore, pragmatic RCTs can overcome the criticisms of real world evidence. Systematic reviews confirm that GLP-1 RA are safe and effective but as a group do not improve cardiovascular outcomes despite evidence from individual cardiovascular outcome trials. Head-to-head studies might identify the reasons for this. In conclusion, well-designed real world studies complement RCTs and systematic reviews but appropriate data and methodologies, which are constantly improving, are necessary to answer appropriate clinical questions. Clinicians need to be aware of the strengths and limitations of these two types of data before making informed decisions for the clinical care of their patients.

Conflict of interest

Dr S.C. has received speaker fees, educational funding or both from Janssen, Eli Lilly, Novo Nordisk, Astra Zeneca, Takeda and Boehringer Ingelheim, and grants in support of investigator-initiated trials from Boehringer Ingelheim and Janssen. Prof. M.J.D. reports personal fees from Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Janssen, Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc., and grants from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim and Janssen. Prof. K.K. has acted as a consultant and speaker for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim. He has received grants in support of investigator and investigator-initiated trials from Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp & Dohme and Roche. K.K. has served on advisory boards for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim..

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