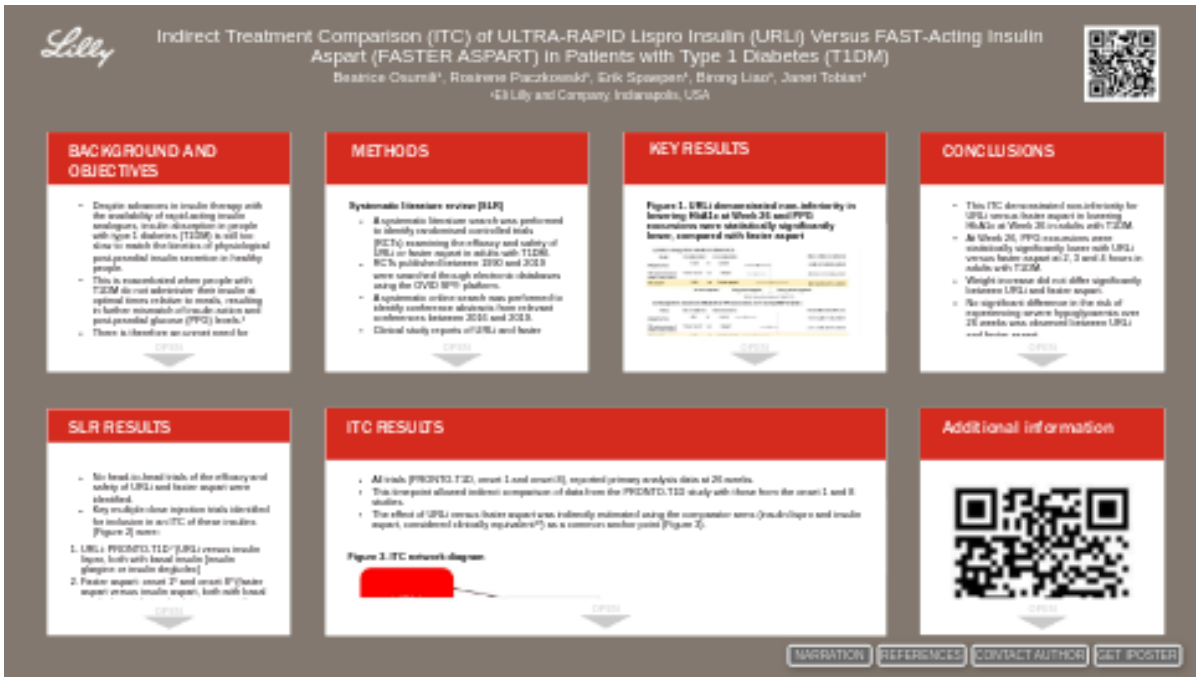
Indirect Treatment Comparison (ITC) of ULTRA-RAPID Lispro Insulin (URLi) Versus FAST-Acting Insulin Aspart (FASTER ASPART) in Patients with Type 1 Diabetes (T1DM)



Beatrice Osumili[1], Rosirene Paczkowski[1], Erik Spaepen[1], Birong Liao[1], Janet Tobian[1]

[1]Eli Lilly and Company, Indianapolis, USA

PRESENTED AT:

BACKGROUND AND OBJECTIVES

- Despite advances in insulin therapy with the availability of rapid-acting insulin analogues, insulin absorption in people with type 1 diabetes (T1DM) is still too slow to match the kinetics of physiological post-prandial insulin secretion in healthy people.
- This is exacerbated when people with T1DM do not administer their insulin at optimal times relative to meals, resulting in further mismatch of insulin action and post-prandial glucose (PPG) levels.[1]
- There is therefore an unmet need for insulin formulations with more rapid onset of action after dosing in order to optimally control PPG.
- Ultra-rapid lispro insulin (URLi) has shown a faster onset of action that more closely mimics the action of endogenous insulin in people without T1DM, compared with insulin lispro.[2]
- We performed an indirect treatment comparison (ITC) to compare the efficacy and safety of the currently available faster-acting insulin analogues URLi (Eli Lilly and Company) and fast-acting insulin aspart (faster aspart; Novo Nordisk) in people with T1DM.

METHODS

Systematic literature review (SLR)

- A systematic literature search was performed to identify randomised controlled trials (RCTs) examining the efficacy and safety of URLi or faster aspart in adults with T1DM.
- RCTs published between 1990 and 2019 were searched through electronic databases using the OVID SP® platform.
- A systematic online search was performed to identify conference abstracts from relevant conferences between 2016 and 2019.
- Clinical study reports of URLi and faster aspart were also assessed.
- Studies that only compared different regimens/doses of the same drug were excluded.
- The SLR methods were consistent with recommendations published in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, the Centre for Reviews and Dissemination and the Cochrane Collaboration.[3–5]
- For RCTs, the risk of bias was assessed using the Cochrane risk of bias tool.

ITC

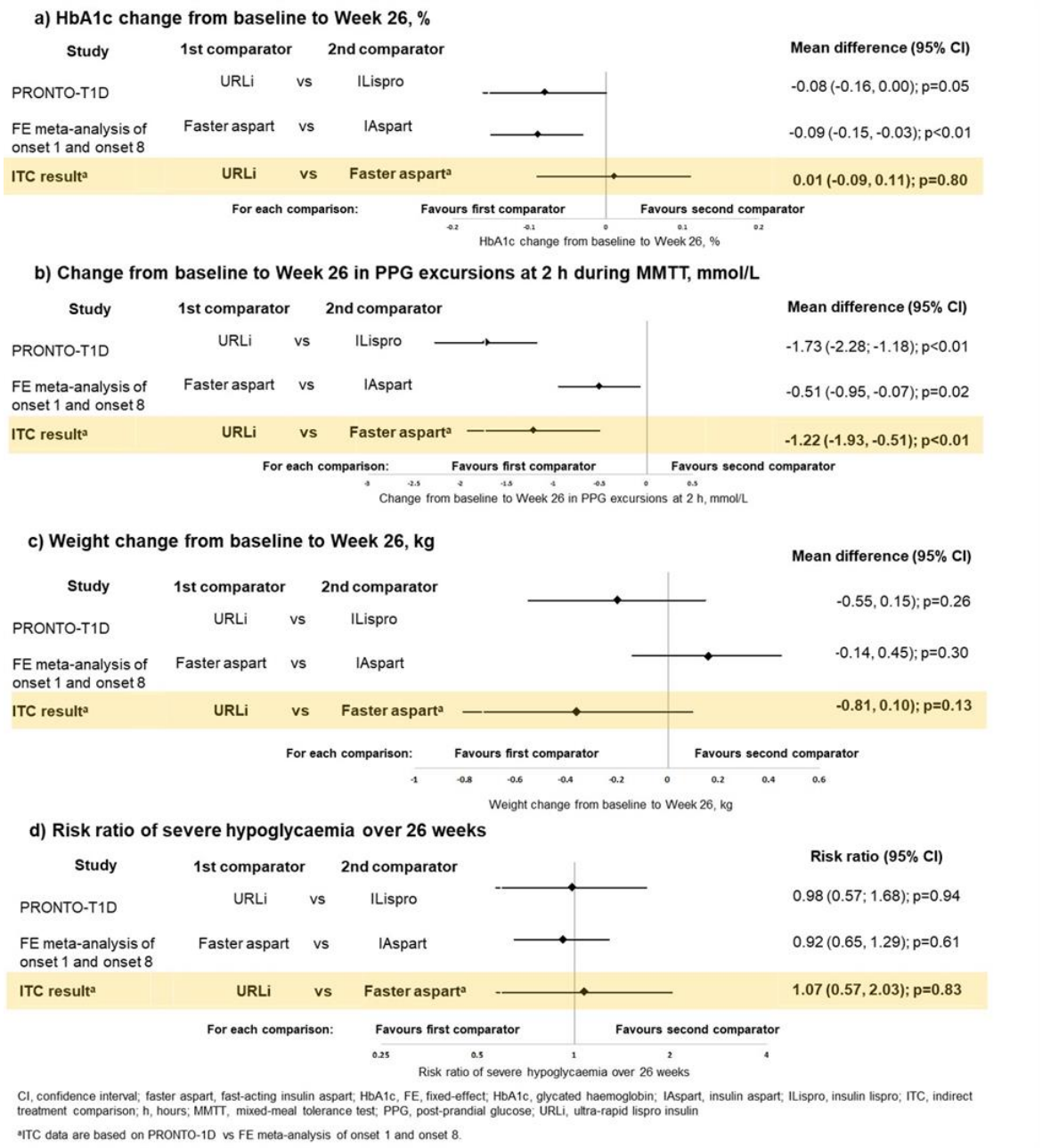
- The Bucher method was used to perform an ITC comparing relative treatment effects of URLi versus faster aspart based on relevant studies identified from the SLR.
- The Bucher method requires an effect estimate for each study (comparison) and the standard error (SE) of this effect.
- Continuous endpoints were analysed using modelled (mixed-model for repeated measures [MMRM] or analysis of variance [ANOVA]) least square means of the treatment difference and corresponding SEs.
- Binary endpoints (incidence of severe hypoglycaemia) were analysed using the normal approximation formula[6] to calculate the SE of the natural log of the relative risk, using the number of people with the event and total number of people per arm for each study relative risk.

Endpoints

- The primary endpoint in this ITC was the change from baseline to Week 26 in glycated haemoglobin (HbA1c), at a non-inferiority margin of 0.4%.
- Other ITC endpoints included changes from baseline to Week 26 in PPG excursions (1 to 4 hours during a mixed-meal tolerance test [MMTT]) and weight.
- Incidence of severe hypoglycaemia over 26 weeks.
- Sensitivity analyses were performed for each endpoint to assess the effect of heterogeneity between the included studies.

KEY RESULTS

Figure 1. URLi demonstrated non-inferiority in lowering HbA1c at Week 26 and PPG excursions were statistically significantly lower, compared with faster aspart



CI, confidence interval; faster aspart, fast-acting insulin aspart; HbA1c, FE, fixed-effect; HbA1c, glycated haemoglobin; lAspart, insulin aspart; lLispro, insulin lispro; ITC, indirect treatment comparison; h, hours; MMTT, mixed-meal tolerance test; PPG, post-prandial glucose; URLi, ultra-rapid lispro insulin

[a]ITC data are based on PRONTO-1D vs FE meta-analysis of onset 1 and onset 8.

CONCLUSIONS

- This ITC demonstrated non-inferiority for URLi versus faster aspart in lowering HbA1c at Week 26 in adults with T1DM.
- At Week 26, PPG excursions were statistically significantly lower with URLi versus faster aspart at 2, 3 and 4 hours in adults with T1DM.
- Weight increase did not differ significantly between URLi and faster aspart.
- No significant difference in the risk of experiencing severe hypoglycaemia over 26 weeks was observed between URLi and faster aspart.

Limitations

The key limitation of this analysis was the low number of included studies.

- Only three studies provided the required efficacy and safety data to allow indirect comparison of URLi and faster aspart.
- Although information published after the cut-off date for the systematic literature review (December 2019) may change the estimates from this analysis, no such later data were identified.

Other limitations were based on differences between the trial designs:

- Differences in basal insulin use: insulin degludec or insulin glargine in PRONTO-T1D compared with insulin detemir in onset 1 and insulin degludec in onset 8.
- Differences in liquid test meal content used for MMTTs for PRONTO-T1D compared with the onset trials (100 g carbohydrate in PRONTO-T1D, ~80 g carbohydrate in the onset trials).
- Differences in prandial insulin dose calculation: in PRONTO-T1D the dose was individualised for each patient compared with onset 1 and 8 where the dose was calculated (0.1 U/kg) for each patient.

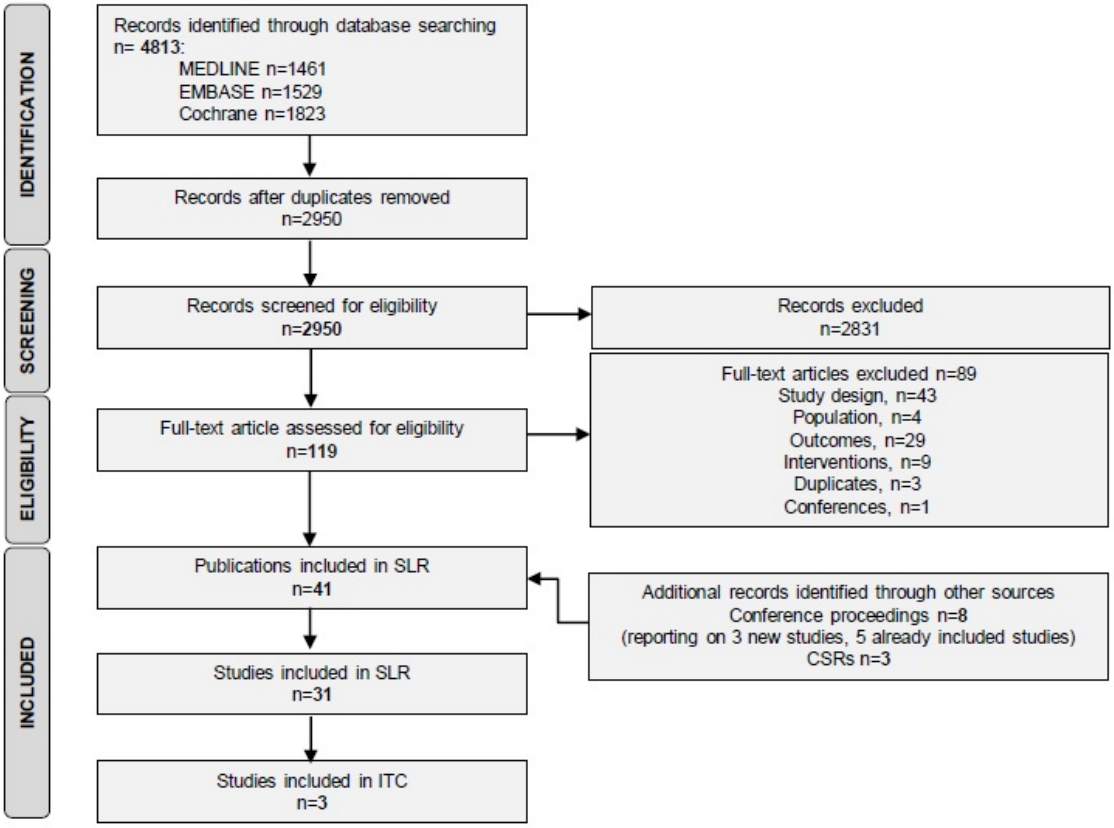
Although the 26-week timeframe for clinical trial data was typical of T1DM trials and long enough to assess effects on HbA1c, a longer timeframe would be needed to assess effects on long-term complications.

SLR RESULTS

- No head-to-head trials of the efficacy and safety of URLi and faster aspart were identified.
- Key multiple dose injection trials identified for inclusion in an ITC of these insulins (Figure 2) were:

1. URLi: PRONTO-T1D[7] (URLi versus insulin lispro, both with basal insulin [insulin glargine or insulin degludec]
2. Faster aspart: onset 1[8] and onset 8[9] (faster aspart versus insulin aspart, both with basal insulin [onset 1, insulin detemir; onset 8, insulin degludec])

Figure 2. PRISMA diagram

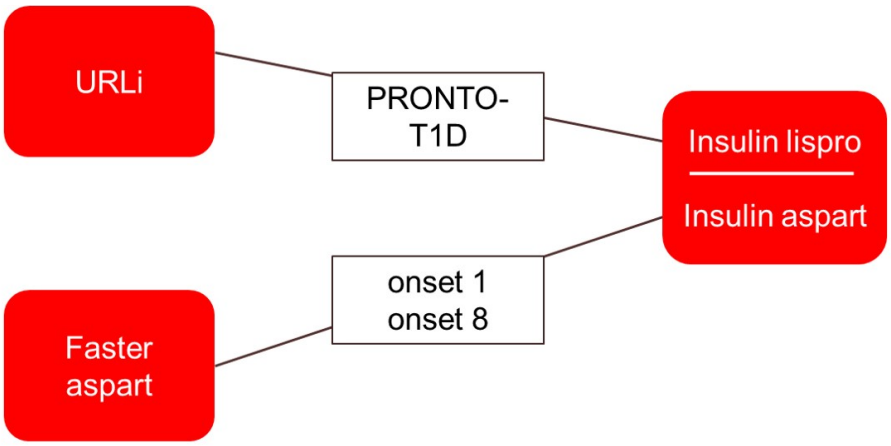


CSR, clinical study report; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ITC, indirect treatment comparison; SLR, systematic literature review

ITC RESULTS

- All trials (PRONTO-T1D, onset 1 and onset 8), reported primary analysis data at 26 weeks.
- This timepoint allowed indirect comparison of data from the PRONTO-T1D study with those from the onset 1 and 8 studies.
- The effect of URLi versus faster aspart was indirectly estimated using the comparator arms (insulin lispro and insulin aspart, considered clinically equivalent[10]) as a common anchor point (Figure 3).

Figure 3. ITC network diagram



Faster aspart, fast-acting insulin aspart; ITC, indirect treatment comparison; URLi, ultra-rapid lispro insulin

Baseline characteristics

- Baseline characteristics of participants from the PRONTO-T1D, onset 1 and onset 8 studies are presented in Table 1.
- No important differences that could have affected the analysis were observed between the characteristics of patients included in these individual trials.

Table 1. Baseline characteristics from studies included in the ITC

	PRONTO-T1D[7] (NCT03214367)		onset 1[8] (NCT01831765)		onset 8[9] (NCT02500706)	
	URLi + IGlargine / degludec	ILispro + IGlargine / degludec	Faster aspart + IDetemir	IAspart + IDetemir	Faster aspart + degludec	IAspart + degludec
Primary analysis	26-week, double-blind, non-inferiority		26-week, double-blind, non-inferiority		26-week, double-blind, non-inferiority	
Sample size, n						
Mealtime	451	442	381	380	342	342
Post-mealtime	329	-	382	-	341	-
Age (years), mean (SD)	44.09 (13.71)	44.50 (13.62)	46.10 (13.80)	43.70 (14.00)	41.48 (14.42)	40.77 (14.77)
Male, %	55.4	57.9	56.4	62.6	53.8	52.8
Duration of diabetes (years), mean (SD)	18.76 (12.26)	19.13 (12.04)	20.90 (12.90)	19.30 (11.80)	17.58 (12.45)	16.74 (11.00)
HbA1c (%), mean (SD)	7.34 (0.65)	7.33 (0.67)	7.62 (0.71)	7.58 (0.68)	7.46 (0.68)	7.41 (0.79)
Weight (kg), mean (SD)	77.3 (16.21)	77.3 (16.73)	78.56 (14.89)	80.15 (15.21)	72.59 (16.56)	71.79 (17.04)

faster aspart, fast-acting insulin aspart; h, hours; HbA1c, glycated haemoglobin; IAspart, insulin aspart; IDetemir, insulin detemir; IGlargine, insulin glargine; ILispro, insulin lispro; SD, standard deviation; URLi, ultra-rapid lispro insulin

ITC results

Efficacy

- ITC of URLi versus faster aspart showed a mean difference of 0.01% (95% confidence interval [CI] -0.09%, 0.11%) for HbA1c change from baseline at 26 weeks (Figure 1); the 95% CI was within the non-inferiority margin (0.4%).
- At Week 26, reductions in PPG excursions (mmol/L) were larger with URLi versus faster aspart at all timepoints (Table 2).
- This difference between treatments was statistically significant from 2 hours onwards.
- Mean difference at 2 hours was -1.22 (95% CI -1.93, -0.51) mmol/L, p<0.01 (Figure 1).
- No statistically significant between-treatment differences were observed regarding weight increase (mean difference -0.36 [95% CI -0.81, 0.10] kg; Figure 1).

Safety

- No statistically significant between-treatment difference was observed regarding the risk ratio of experiencing severe hypoglycaemia over 26 weeks (1.07 [95% CI 0.57, 2.03], p=0.83; Figure 1)
- Accordingly, the odds ratio for experiencing severe hypoglycaemia over 26 weeks with URLi versus faster aspart was 1.08 (95% CI 0.55, 2.12), p=0.82.

Table 2. Analyses of trial data and ITC results

	PRONTO-T1D (URLi vs ILispro) Estimate (95% CI)	onset 1 (faster aspart vs IAspart) Estimate (95% CI)	onset 8 (faster aspart vs IAspart) Estimate (95% CI)	FE meta-analysis of onset 1, onset 8 (faster aspart vs IAspart) Estimate (95% CI)	ITC (URLi vs faster aspart[a]) Estimate (95% CI)
HbA1c change from baseline to Week 26 (MD), %	-0.08 (-0.16, 0.00); p=0.05	-0.15 (-0.23, -0.07); p<0.01	-0.02 (-0.11, 0.07); p=0.66	-0.09 (-0.15, -0.03); p<0.01	**0.01 (-0.09, 0.11); p=0.80**
Change from baseline to Week 26 in PPG excursions during MMTT (MD), mmol/L					
1 h	-1.55 (-1.96, -1.14); p<0.01	-1.18 (-1.65, -0.71); p<0.01	-0.90 (-1.36, -0.44); p<0.01	-1.04 (-1.36, -0.71); p<0.01	**-0.51 (-1.04, 0.01); p=0.05**
2 h	-1.73 (-2.28, -1.18); p<0.01	-0.67 (-1.30, -0.04); p=0.04	-0.35 (-0.98, 0.28); p=0.27	-0.51 (-0.95, -0.07); p=0.02	**-1.22 (-1.93, -0.51); p<0.01**
3 h	-1.46 (-2.08, -0.84); p<0.01	0.07 (-0.59, 0.73); p=0.84	-0.16 (-0.82, 0.50); p=0.63	-0.05 (-0.51, 0.42); p=0.85	**-1.41 (-2.19, -0.64); p<0.01**
4 h	-0.86 (-1.51, -0.21); p<0.01	0.19 (-0.45, 0.83); p=0.56	-0.14 (-0.74, 0.46); p=0.64	0.01 (-0.42, 0.45); p=0.95	**-0.87 (-1.66, -0.09); p=0.03**
Weight change from baseline to Week 26 (MD), kg	-0.20 (-0.55, 0.15); p=0.26	0.12 (-0.31, 0.55); p=0.58	0.19 (-0.22, 0.60); p=0.36	0.16 (-0.14, 0.45); p=0.30	**-0.36 (-0.81, 0.10); p=0.13**
RR of severe hypoglycaemia over 26 weeks	0.98 (0.57, 1.68); p=0.94	0.80 (0.47, 1.32); p=0.38	1.03 (0.64, 1.65); p=0.89	0.92 (0.65, 1.29); p=0.61	**1.07 (0.57, 2.03); p=0.83**

CI, confidence interval; faster aspart, fast-acting insulin aspart; FE, fixed-effect; HbA1c, glycated haemoglobin; IAspart, insulin aspart; ILispro, insulin lispro; ITC, indirect treatment comparison; MD, mean difference; MMTT, mixed-meal tolerance test; PPG, post-prandial glucose; RR, risk ratio; URLi, ultra-rapid lispro insulin
[a]ITC data are based on PRONTO-1D vs FE meta-analysis of onset 1 and onset 8.

Sensitivity analyses

- Sensitivity analyses were performed for each endpoint, in which ITC estimates were created combining the PRONTO-T1D results with results of the separate onset studies rather than the meta-analysis pooled estimate of the onset studies.
  - PRONTO-T1D and onset 1
  - PRONTO-T1D and onset 8
- There was little heterogeneity between the onset 1 and onset 8 study endpoint results.
- As a consequence, the ITC results of these sensitivity analyses were similar to the primary analysis results.

ADDITIONAL INFORMATION

REFERENCES

1. Slattery D, et al. Diabetic Med. 2018;35:306–316.
2. Heise T, et al. Diabetes Obes Metab. 2020; 22: 1789–1798.
3. Hutton B, et al. Ann Intern Med. 2015; 162: 777–784.
4. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. 2009. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (accessed 6 October 2020).
5. Higgins JPT and Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, 2011. Available at: https://handbook-5-1.cochrane.org/ (accessed 9 October 2020).
6. Altman DG. Practical Statistics for Medical Research. 1991. Chapman and Hall.
7. Klaff L, et al. Diabetes Obes Metab. 2020;22:1799–1807.
8. Russell-Jones D, et al. Diabetes care. 2017;40:943–950.
9. Buse JB, et al. Diabetes Obes Metab. 2018;20:3885–2893.
10. Homko C, et al. Diabetes Care 2003;26:2027–2031.