SUPPLEMENTARY APPENDIX

Systematic review

Data sources and search terms

The following online databases were searched (1997 to 5 May 2017): MEDLINE via Ovid, EMBASE via Ovid, the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials via The Cochrane Library, and the ClinicalTrials.gov results database. Search strategies were adapted for each database and included keywords (Medical Subject Heading or EMTREE) and free-text terms (multiple field search) as follows: (type 2 diabetes AND [insulin or glucagon-like peptide-1 receptor ((GLP-1)) agonists]) AND treatment initiation. Terms were combined with OR or AND, and truncation symbols were used wherever possible. As an example, the following search terms were used for MEDLINE: "diabetes mellitus, type 2" (MeSH) OR "type 2 diabetes", "type II diabetes", "non-insulin dependent diabetes", "NIDDM" (all free-text); "biphasic insulins", "insulin aspart", "insulin detemir", "insulin glargine", "insulin lispro", "insulin, long-acting", "insulin, short-acting", "insulin, isophane", "insulin, regular, human" (all MeSH) OR "basal insulin", "premixed insulin", "aspart", "lispro", "detemir", "glargine", "glulisine", "degludec", "neutral protamine Hagedorn", "NPH", "NPL", "insulin analog*" (all free-text) OR "liraglutide", "dulaglutide", "exenatide", "semaglutide", "lixisenatide", "glucagon-like peptide-1 (receptor* or agonist* or analog*)", "GLP-1 (receptor* or agonist* or analog*)" (free-text); "insulin-naive", "naive", "initiat*", "start*" (all free-text).

Published evidence was restricted to English-language publications and studies with 30 or more participants per treatment arm (Giugliano D, Chiodini P, Maiorino MI*, et al. Endocrine*. 2016;51:417-428).

Eligibility criteria

The inclusion criteria were as follows: randomized controlled trials, nonrandomized studies, and prospective observational or cohort studies; male and female adult (≥18 years) patients with type 2 diabetes mellitus (T2DM) who were injection-naive, had inadequate glycemic control with OAM, and required initiation with injectable therapy; studies or subgroup analyses of populations in East Asian countries/regions (defined as those conducted in China, Japan, the Republic of Korea, Hong Kong, or Taiwan) and from Caucasian countries; studies with insulin, insulin and oral antihyperglycemic medication (OAMs), insulin and GLP-1 agonist, GLP-1 agonist, or GLP-1 agonist and OAMs treatment arms, and studies reporting baseline data for blood glucose (BG) excursions or for pre- and postprandial BG levels before injectable treatment. There was no restriction on treatment duration as only baseline data before patients commenced injectable treatment were to be extracted.

The exclusion criteria were as follows: evidence from other study designs (eg, retrospective studies, case series, case reports) and from narrative reviews, letters, editorials, commentaries, conference abstracts, meta-analyses, and systematic reviews; studies on East Asian patients residing in Caucasian countries or where the race/ethnicity of the study population was not reported or could not be reported separately; studies not reporting baseline data for BG excursions or not reporting sufficient data to allow calculation of baseline BG excursions.

Screening and data extraction

Searches were collated using bibliographic management software and duplicates were removed. An initial screen of the title and abstract of each publication was conducted by one reviewer to identify potential publications for inclusion. Confirmation of inclusion was

obtained after a review of the full text of all potential publications. Authors were consulted in instances where inclusion was uncertain and authors reviewed and approved the final list of articles identified for inclusion in the review.

One person extracted all data into a prespecified spreadsheet. A quality control check of all extracted data was conducted by a second independent reviewer and any disagreements were resolved by consensus. Data extracted included study characteristics, population characteristics (including definition of OAM failure), BG measures (eg, self-monitored or other; serum, plasma, or whole blood) and BG outcomes (pre- and postprandial for breakfast, lunch, dinner, and/or daily average).

Reference lists from relevant systematic reviews and meta-analyses were screened manually to identify publications not retrieved by the literature search strategies.

Search results

The search strategy retrieved 2056 publications, of which 2051 did not meet the eligibility criteria and were excluded for one or more reasons. The reasons for exclusion were as follows: duplicate publication or publication reporting data reported in another publication (n=631), not publication or study type (n=608), no relevant outcomes reported (n=287), not population type (n=224), not ethnicity type (n=125), publication not in English (n=105), fewer than 30 participants reported (n=46), and insufficient data to calculate BG excursion (n=25). Five publications from 5 clinical studies were eligible for inclusion (Supplementary Table).

East Asian and Caucasian BG excursion data were available for breakfast, lunch, and dinner from 3 studies [12, 15, 17]. No East Asian BG excursion data were available in studies reporting the daily average [14, 16, 17]. BG levels were measured by self-monitored BG in 3 studies [12, 16, 17] and blood samples in 1 study [15]; 1 study did not report how BG was measured [14].

SUPPLEMENTARY TABLE Eligible clinical studies retrieved from the systematic review of the literature

Publication (Definition of inadequate glycemic control)	Relevant study population	Treatment allocation (N)	Patient characteristics at baseline				Mean (SD) blood glucose excursion at baseline, mmol/L			
			Mean age (yr)	Mean diabetes duration (yr)	Mean body weight (kg)	Mean HbA1c (%)	Morning	Lunch	Dinner	Daily
Ji *et al. Diabetes Metab Syndr Obes*. 2016;9:243-9. (HbA1c 7.0-10.9% on OAMs without insulin, ≥90 days)	East Asian	Glargine + lispro (44)	54.4	9.4	65.7	8.8	5.2 (2.7)	3.2 (3.0)	2.5 (2.8)	NR
		LM25 (45)	57.2	10.0	67.8	8.9	5.0 (2.5)	3.6 (2.6)	3.2 (3.0)	NR
	Caucasian	Glargine + lispro (61)	61.7	10.6	82.1	8.9	4.0 (2.4)	1.6 (2.2)	2.0 (2.6)	NR
		LM25 (69)	58.6	12.6	84.0	8.9	3.7 (2.4)	1.2 (2.6)	1.7 (2.7)	NR
Franek *et al. Diabetic Medicine*. 2016;33:497-505. (HbA1c 7.0-10.0% on met ±1 OAM, ≥12 wk)	Caucasian	IDegAsp + met (197)	59.0	9.6	88.0	8.5	3.6 (2.6)	2.1 (2.9)	2.6 (1.7)	2.6 (1.7)
		BIAsp 30 + met (197)	58.8	9.4	88.5	8.3	3.5 (2.7)	2.4 (3.1)	2.2 (2.9)	2.7 (1.8)
Kann *et al. Exp Clin Endocrinol Diabetes*. 2006;114:527-32. (HbA1c 7.1-12% on SU ±met or met)	Caucasian	BIAsp 30 + met (128)	61.5	10.3	84.2	9.2	NR	NR	NR	2.5 (1.9)
		Glargine + glimepiride (127)	61.0	10.2	86.6	8.9	NR	NR	NR	2.0 (1.8)
Kapitza *et al. Diabetes Obes Metab*. 2013:642-9 (HbA1c 6.5-9.0% on stable dose of met)	Caucasian	Lixisenatide (70)	59.7	6.7†	92.9	7.4	4.9 (NR)	NR	NR	NR
		Liraglutide (77)	60.5	6.7†	91.2	7.2	4.9 (NR)	NR	NR	NR
Lalic *et al. Exp Opin Pharmacother*. 2007;8:2895-2901 (HbA1c ≥8.5%; secondary OAM failure with OAM)	Caucasian	BIAsp 30 (prior BG + SU/glinide) (42)	56.0	11.0	77.8	10.4	NR	NR	NR	2.0 (1.9)
		BIAsp 30 (prior SU) (29)	56.7	9.0	74.2	11.1	NR	NR	NR	3.2 (1.7)

Abbreviations: α-GI, alpha-glucosidase inhibitor; BIAsp 30, biphasic insulin aspart (30% soluble insulin aspart); BG, biguanide; BMI, body mass index; DPP-IV, dipeptidyl peptidase IV; HbA1c, glycated hemoglobin; IDegAsp, Insulin degludec/insulin aspart; LM25, insulin lispro mix (25% insulin lispro and 75% insulin lispro protamine); max, maximum; met, metformin; NR, not reported; OAM, oral antihyperglycemic medication; SD, standard deviation; SU, sulfonylurea medication; yr, year; wk, week.

†Reported as median.