BMJ Open

Effect of adjunctive glucose-lowering drugs on body weight in people with type 1 diabetes: a systematic review and network meta-analysis protocol

Christian Laugesen [1], Ajenthen G. Ranjan [1], Signe Schmidt [1], Lauge Neimann Rasmussen [2], Ole Nørgaard [2], Robin Christensen [3,4], Kirsten Nørgaard [1]

To cite: Laugesen C, Ranjan AG, Schmidt S, *et al*. Effect of adjunctive glucose-lowering drugs on body weight in people with type 1 diabetes: a systematic review and network meta-analysis protocol. *BMJ Open* 2020;**10**:e038970. doi:10.1136/bmjopen-2020-038970

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-038970).

Received 30 March 2020
Revised 29 July 2020
Accepted 17 October 2020

[1]Clinical Research, Steno Diabetes Center Copenhagen, Gentofte, Denmark
[2]Education, Diabetes Knowledge Center, Steno Diabetes Center Copenhagen, Gentofte, Denmark
[3]Musculoskeletal Statistics Unit, the Parker Institute, Frederiksberg and Bispebjerg Hospital, Copenhagen, Denmark
[4]Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark

Correspondence to
Dr Christian Laugesen; christian.laugesen@regionh.dk

ABSTRACT

Introduction Obesity increases the risk of comorbidities and diabetes-related complications and, consequently, efforts to prevent and reduce excess weight in people with type 1 diabetes are essential. The aim of this systematic review and network meta-analysis is to assess the effect of adjunctive glucose-lowering drugs on body weight and other important health outcomes in people with type 1 diabetes.

Methods and analysis This systematic review and network meta-analysis will include randomised controlled trials (RCTs) evaluating the use of adjunctive glucose-lowering drugs for treatment of people with type 1 diabetes. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform will be searched from inception to present. Key eligibility criteria include: RCT study design; adult participants with type 1 diabetes; treatment with a glucose-lowering drug for ≥24 weeks; and comparison of the intervention to placebo, usual care or another glucose-lowering drug. The primary outcome is change in body weight. Other major outcomes include change in HbA1c and total daily insulin dose and risk of hypoglycaemia and other adverse events. Dual study selection, data extraction and risk of bias assessment will be performed. Results from the meta-analysis will be presented as weighted mean differences for continuous outcomes and risk ratios for dichotomous outcomes. Sources of heterogeneity will be explored by subgroup and sensitivity analysis. A network meta-analysis for the primary outcome will be performed using an arm-based random-effects model based on the Bayesian framework while assessing for transitivity across studies and consistency between direct and indirect estimates. The overall quality of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach for each outcome.

Ethics and dissemination No ethical assessment is required. The results of this review will be disseminated through peer-reviewed publication and conference presentation.

PROSPERO registration number CRD42020158676

Strengths and limitations of this study

- This systematic review and network meta-analysis will comprehensively evaluate the effect on body weight, glycaemic control and adverse events of all adjunctive glucose-lowering drug classes for treatment of type 1 diabetes.
- The thorough and transparent methodological approach undertaken will minimise the risk of possible biases. Quality of evidence will be assessed to provide confidence in the effect estimates.
- To be able to assess meaningful changes in body weight, eligible studies are limited to those of interventions with a duration of ≥24 weeks.
- Common to any meta-analysis, some study heterogeneity across and within drug classes may exist.

INTRODUCTION

Rationale

Several studies have demonstrated a concerning trend in the prevalence of obesity in people with type 1 diabetes.[1–3] The Type 1 Diabetes Exchange registry and the Pittsburgh Epidemiology of Diabetes Complications Study found that around 50%–60% of the adult population with type 1 diabetes was either overweight or obese,[1 4] and the prevalence of obesity among people with type 1 diabetes has been shown to increase at a faster rate compared with the general population.[5] Weight management is an important health-related topic of interest as excess body weight increases the risk of several adverse health outcomes; there is solid evidence that obesity is associated with increased mortality, increased risk of cardiovascular disease and a lower health-related quality of life in the general population.[6 7] Although less is known about the health consequences in people with type 1 diabetes, several studies indicate that increasing body mass index (BMI) is

associated with increased mortality and risk of cardiovascular disease, heart failure and microvascular complications in this population.[8–11] Consequently, efforts to prevent and reduce excess weight in people with type 1 diabetes are essential.

Several approaches to reduce weight have been investigated. Lifestyle interventions such as diets and exercise intensification are key therapeutic avenues to reduce body weight, but these can often be difficult to implement for the same reasons as in people without diabetes. Further, the risk of hypoglycaemia also constitutes a significant barrier for many people with type 1 diabetes with respect to implementing the lifestyle changes. As insulin induces weight gain and pump therapy is associated with lower total daily insulin dose (TDD),[12] this would theoretically cause less weight gain. However, studies have not been able to demonstrate any significant differences in body weight between people using pump and injection therapy.[13 14]

Despite aforementioned strategies, weight management remains difficult. Therefore, additional approaches to managing body weight can be beneficial. In people with type 2 diabetes, some glucose-lowering agents have shown to reduce weight.[15] Several studies have investigated the effects of various adjunctive therapies on glycaemic control and body weight in people with type 1 diabetes, and numerous systematic reviews have evaluated the outcomes of specific drug classes. However, a complete and comparative overview of the weight-reducing and glycaemic effects of agents across all adjunctive glucose-lowering drug classes is warranted.

Objectives

The primary objective of this systematic review and meta-analysis is to assess the effect of adjunctive (non-insulin) glucose-lowering drugs on body weight in adults with type 1 diabetes. To assess the comparative effectiveness of each drug class with respect to the primary outcome, a network meta-analysis (NMA) using both direct and indirect trial evidence will be performed (if applicable). The secondary objectives are to assess the effect of adjunctive glucose-lowering drugs on glycaemic (HbA1c), non-glycaemic (change in TDD) and safety outcomes (risk of hypoglycaemia, diabetic ketoacidosis and serious adverse events (SAEs)).

METHODS

The protocol was developed and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[16] and registered with the International Prospective Register of Systematic Reviews (PROSPERO). In the event of protocol amendments, these will be submitted to PROSPERO accompanied by a description of the change and rationale.

Patient and public involvement

No patients or public entities were involved in the conception of this systematic review and meta-analysis protocol.

Eligibility criteria

Study design

Only randomised controlled trials (RCTs) are eligible for inclusion, excluding cluster RCTs and controlled (non-randomised) clinical trials. Results from the first period of crossover studies will be included if they are reported explicitly and are otherwise in accordance with the inclusion criteria.

Report characteristics

Both abstracts and full-text articles will be considered for eligibility. No limitations regarding year of publication will be applied.

Records in languages other than English (LOEs) will be screened on title and abstract level. When abstracts are not available in English, Danish, Swedish, Norwegian or German (languages spoken by the review team), LOE abstracts will be translated using Google Translate (https://translate.google.com/). LOE abstracts which are deemed relevant based on this assessment will be reported in the supplemental material of the review specifying the languages identified by Google Translate, but are excluded from the analysis unless the full text-publication is published in a language spoken by the review team (ie, Danish, Swedish, Norwegian, German and English). Although this limitation might introduce bias, our review team has limited language skills, does not have funding to hire professional translation facilities (see support statement above), and is not a part of an institution, for example, university, with informal access to people with the additional language skills potentially needed. The risk of bias due to this limitation will be discussed in the review.[17 18]

Participants

Studies examining adult (≥18 years) men and non-pregnant women with type 1 diabetes will be eligible for inclusion.

Interventions

Studies examining treatment with any adjunctive (non-insulin) glucose-lowering drug (defined as pharmacological therapy primarily intended to lower blood glucose) in combination with insulin therapy for a duration of ≥24 weeks will be eligible for inclusion. Studies examining adjunctive glucose-lowering drugs with a simultaneous co-intervention (eg, diet or exercise intervention) will only be eligible for inclusion if the co-intervention is applied in all study arms.

Drug classes of a priori interest are based on the sources listed in the Search strategy section and include:

- α-Glucosidase inhibitors.
- Amylin mimetics.
- Biguanides.
- Bile acid sequestrants.

- Dopamine-2 agonists.
- Dipeptidyl peptidase-4 inhibitors.
- Gastric inhibitory peptide analogues.
- Glucagon-like peptide-1 receptor agonists.
- Meglitinides.
- Sodium-glucose co-transporter–1 and 2 inhibitors.
- Somatostatin analogues.
- Sulfonylureas.
- Thiazolidinediones.

Comparators

Studies comparing the experimental intervention with placebo, usual care (without placebo) or another glucose-lowering drug will be eligible for inclusion.

Outcomes

Eligibility of trials will not be restricted by outcome criteria. Thus, studies meeting the remaining eligibility criteria will be included irrespective of the outcomes reported; this will enable assessment of the risk of selective outcome reporting. The predefined outcome measurements of the meta-analysis are listed in the Outcomes section.

Setting

There will be no restrictions on type of setting.

Information sources

The following databases will be searched from inception to present:

- MEDLINE (Ovid).
- EMBASE (Ovid).
- Cochrane Central Register of Controlled Trials.
- Cochrane Database of Systematic Reviews, which covers WHO International Clinical Trials Registry Platform database and ClinicalTrials.gov.

In addition, reference lists of included studies will be used as sources to identify eligible studies. Study authors or organisations will be contacted for information about unpublished studies if required.

Search strategy

The search strategy was developed by two health information specialists with input from the remaining project team. The MEDLINE search strategy (table 1) will be adapted to the syntax and subject headings of the other databases.

The glucose-lowering drugs (drug classes as well as individual drugs) used in the search strategy are based on (1) American Diabetes Association's (ADA) 'Pharmacological Approaches to Glycaemic Treatment—Standards of Medical Care in Diabetes' (2020),[19] (2) drugs listed as diabetes medicine in the European Medicines Agency's public assessment reports[20] and on drugs.com,[21 22] and (3) authors' subject matter expertise. The intervention criteria used for selection of studies are based on the definitions listed in the Eligibility criteria section. Thus, eligible interventions are not limited to the drugs included in the search strategy.

Study records

Data management

Literature search results will be uploaded to EPPI-Reviewer V.4.0[23], which will be used for screening. The health information specialists will provide members of the review team with adequate training in the software and support during the review process.

Selection process

The search strategy described will be used to obtain study titles and abstracts for potentially eligible trials. Two reviewers will independently screen titles and abstracts to identify studies for full-text assessment and subsequently determine whether each study meets the eligibility criteria by assessing full-text articles. Reasons for excluding studies after full-text review will be documented. Disagreement will be resolved first by discussion and then by consulting a third review author for arbitration. In studies where a subset of the included participants meets the inclusion criteria, data deriving separately from the eligible subgroup will be included. If subgroup data are not reported, study authors will be contacted with enquires to share subgroup data if available. In case it is not possible to gain access to the relevant subgroup data, the study is excluded. A PRISMA flow diagram[24] will be produced to document and transparently illustrate the selection process.

Data collection process

Baseline characteristics and outcome data will be collected independently by two reviewers using predefined and piloted extraction forms. Appropriate software (eg, Microsoft Excel or EPPI-Reviewer) will be used to collect the data. If more than one publication reports on a specific trial, reports will be collected and grouped, and relevant data from each report will be used in the analyses. Any discrepancy between published versions will be highlighted. If outcomes are not reported as defined in this protocol, conversion to the relevant metric is not statistically possible, and it is not possible to obtain these data after contact to the study authors, the study will still be included in the systematic review (ie, qualitative synthesis).

Data items

The following data items will be collected: publication data (title, first author, year and source of publication, ClinicalTrials.gov identifier (NCT), source of funding), trial design, baseline characteristics of the study population (sample size, sex, age, duration of type 1 diabetes, body weight, BMI, HbA1c, total daily insulin dose, treatment modality), details of the intervention(s) (generic drug name, dose, frequency, treatment duration), the comparator used and the outcome measures (listed below). Data items needed for assessment of the risk of bias will also be collected. For crossover studies, data will be extracted for the first period only because of possible carry-over effects.

Table 1 MEDLINE search (Ovid interface)

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	75 008
2	(((autoimmune$ or insulin-dependent$ or insulindependent$ or juvenile$ or type-1 or type-i) adj3 diabet$) or dm1 or iddm$ or t1d? or td1).ti,ab,kw,kf.	83 666
3	or/1–2	109 351
4	((add-on$ or addon$ or adjunct$) adj3 (therap$ or treatment$)).ti,ab,kw,kf.	29 534
5	Hypoglycemic Agents/	63 885
6	(anti-diabetic$ or antidiabetic$ or anti-hyperglyc?emic$ or antihyperglyc?emic$ or hypoglyc?emic$).ti,ab,kw,kf.	48 317
7	or/5–6	90 420
8	exp alpha-Glucosidases/	4578
9	((alpha-glucosidas$ or alphaglucosidas$) adj3 inhibit$).ti,ab,kw,kf.	3925
10	Acarbose/	1329
11	(acarbose$ or bay-g-5421$ or bay-g5421$ or bayg-5421$ or bayg5421$ or glucobay$ or glucor$ or glumida$ or prandase$ or precise$).ti,ab,kw,kf.	233 207
12	(voglibos$ or basen$).ti,ab,kw,kf.	492
13	or/10–12	233 830
14	exp Amylin Receptor Agonists/	2438
15	amylin$.ti,ab,kw,kf.	2086
16	(pramlintid$ or ac-?137$ or ac?137$ or symlin$).ti,ab,kw,kf.	389
17	or/14–16	3277
18	Biguanides/	3189
19	biguanid$.ti,ab,kw,kf.	3071
20	exp Buformin/	154
21	(buformin$ or butylbiguanid$ or adebit$ or gliporal$ or silubin$).ti,ab,kw,kf.	266
22	exp Metformin/	13 011
23	(metformin$ or dimethyl$guanidin$ or glucophage$).ti,ab,kw,kf.	19 940
24	exp Phenformin/	1474
25	(phenformin$ or fenformin$ or phenylethylbiguanide$).ti,ab,kw,kf.	1193
26	or/18–25	26 861
27	exp Colesevelam Hydrochloride/	199
28	(c?olesevelam$ or gt-31104$ or gt31-104$ or gt31104$ or c?olestagel$ or welc?ol$).ti,ab,kw,kf.	267
29	or/27–28	302
30	exp Bromocriptine/	6950
31	(bromo#r#ptin$ or bromoergocr#ptin$ or cb-154$ or cb154$ or parlodel$).ti,ab,kw,kf.	7735
32	or/30–31	9362
33	exp Dipeptidyl-Peptidase IV Inhibitors/	4661
34	(((dipeptidyl-peptidase$ or dipeptidylpeptidase$ or dpp$) adj3 inhibit$) or gemigliptin$ or gliptin$ or lc15-0444$ or lc150444$).ti,ab,kw,kf.	6931
35	(alogliptin$ or syr-322$ or syr322$ or incresync$ or nesina$ or vipdomet$ or vipidia$).ti,ab,kw,kf.	469
36	(anagliptin$ or suiny$).ti,ab,kw,kf.	79
37	dutogliptin$.ti,ab,kw,kf.	15
38	(evogliptin$ or da-1229$ or da1229$ or suganon$).ti,ab,kw,kf.	36
39	(gosogliptin$ or pf-??734200$ or pf??734200$ or satrx$).ti,ab,kw,kf.	11
40	exp Linagliptin/	396
41	(linagliptin$ or bi-1356$ or bi1356$ or jentadueto$ or tra?jenta$).ti,ab,kw,kf.	722
42	(omarigliptin$ or mk-3102$ or mk3102$ or marizev$).ti,ab,kw,kf.	46

Continued

Table 1 Continued

#	Searches	Results
43	(saxagliptin$ or bms-477118$ or bms477118$ or komboglyze$ or onglyza$ or qtern$).ti,ab,kw,kf.	676
44	exp Sitagliptin Phosphate/	1353
45	(sitagliptin$ or mk-0431$ or mk0431$ or efficib$ or janumet$ or januvia$ or ristaben$ or ristfor$ or tesavel$ or velmetia$ or xelevia$).ti,ab,kw,kf.	2271
46	(teneligliptin$ or tenelia$).ti,ab,kw,kf.	146
47	(trelagliptin$ or syr-472$ or syr472$ or zafatek$).ti,ab,kw,kf.	43
48	exp Vildagliptin/	621
49	(vildagliptin$ or nvp-laf237$ or nvplaf237$ or eucreas$ or galvus$ or icandra$ or jalra$ or xiliarx$ or zomarist$).ti,ab,kw,kf.	1011
50	or/33–49	9018
51	exp Gastric Inhibitory Polypeptide/	2513
52	((gastric$ adj3 inhibit$ adj3 polypeptid$) or ((glucose-dependent$ or glucosedependent$) adj3 (insulin-releas$ or insulinreleas$ or insulintropic$) adj3 (polypeptide$ or peptide$)) or gip).ti,ab,kw,kf.	3852
53	(tirzepatid$ or ly-3298176$ or ly3298176$).ti,ab,kw,kf.	3
54	or/51–53	4368
55	exp Glucagon-Like Peptide 1/	8398
56	exp Glucagon-Like Peptide-1 Receptor/	2789
57	(glp-1$ or glp1$ or ((glucagon-like or glucagonlike) adj3 peptid$)).ti,ab,kw,kf.	15 628
58	(albiglutid$ or eperzan$ or tanzeum$).ti,ab,kw,kf.	193
59	(dulaglutid$ or ly-2189265$ or ly2189265$ or trulicity$).ti,ab,kw,kf.	350
60	Exenatide/	2364
61	(exenatid$ or ac-2993$ or ac2993$ or itca-650$ or itca650$ or exendin-4$ or (ex4 adj1 peptid$) or bydureon$ or byetta$).ti,ab,kw,kf.	3358
62	Liraglutide/	1597
63	(liraglutid$ or nn-2211$ or nn2211$ or saxenda$ or victoza$ or xultophy$).ti,ab,kw,kf.	2621
64	(lixisenatid$ or aqve-10010$ or aqve10010$ or ave-?010$ or ave?010$ or zp-10$ or zp10$ or adlyxin$ or lyxumia$ or suliqua$).ti,ab,kw,kf.	444
65	(semaglutid$ or nn-9535$ or nn9535$ or ozempic$).ti,ab,kw,kf.	335
66	(taspoglutid$ or itm-077 or itm077$).ti,ab,kw,kf.	59
67	or/55–66	18 473
68	(meglitinid$ or glinitid$ or hb-699$ or hb699$).ti,ab,kw,kf.	327
69	(miglitol$ or bay-m-1099? or bay-m1099? or baym-1099? or baym1099? or glyset? or diastabol$ or plumarol$).ti,ab,kw,kf.	318
70	(mitiglinid$ or miti-glinid$ or kad-1229$ or kad1229$ or s-21403$ or s21403$).ti,ab,kw,kf.	144
71	exp Nateglinide/	389
72	(nateglinid$ or nate-glinid$ or senaglinid$ or a?–4166$ or a?4166$ or djn-608$ or djn608$ or fastic$ or starlix$ or starsis$ or trazec$).ti,ab,kw,kf.	665
73	(repaglinid$ or repa-glinid$ or ag-ee-388$ or ag-ee388$ or agee388$ or ag-ee-623$ or ag-ee623$ or ag-ee623$ or enyglid$ or gluconorm$ or prandin$ or novonorm$).ti,ab,kw,kf.	764
74	or/68–73	1975
75	exp Sodium-Glucose Transporter 2 Inhibitors/	2143
76	(((sodium-glucose$ or sodiumglucose$) adj3 (transporter$ or co-transporter$ or cotransporter$)) or sglt$ or gliflozin$).ti,ab,kw,kf.	5883
77	exp Canagliflozin/	583
78	(canagliflozin$ or ta-7284$ or ta7284$ or invokana$ or vokanamet$).ti,ab,kw,kf.	986
79	(dapagliflozin$ or bms-512148$ or bms512148$ or ebymect$ or edistride$ or forxiga$ or xigduo$).ti,ab,kw,kf.	1086

Continued

Table 1 Continued

#	Searches	Results
80	(empagliflozin$ or bi-10773$ or bi10773$ or glyxambi$ or jardiance$ or synjardy$).ti,ab,kw,kf.	1147
81	(ertugliflozin$ or pf-04971729$ or pf04971729$ or steglatro$ or steglujan$ or segluromet$).ti,ab,kw,kf.	98
82	(ipragliflozin$ or asp-1941$ or asp1941$ or suglat$).ti,ab,kw,kf.	205
83	licogliflozin$.ti,ab,kw,kf.	4
84	(luseogliflozin$ or ts-071$ or ts071$ or lusefi$).ti,ab,kw,kf.	102
85	remogliflozin$.ti,ab,kw,kf.	25
86	sergliflozin$.ti,ab,kw,kf.	15
87	(sotagliflozin$ or lx-4211$ or lx4211$ or zynquista$).ti,ab,kw,kf.	66
88	(tofogliflozin$ or csg-452$ or csg452$ or apleway$ or deberza$).ti,ab,kw,kf.	107
89	or/75–88	6739
90	exp Somatostatin/	19052
91	(somatostatin$ or (somatotropin$ adj3 (factor$ or hormone$)) or srih-14$ or srih14$ or somatofalk$ or stilamin$).ti,ab,kw,kf.	30432
92	exp Octreotide/	7507
93	(octreotid$ or compound-201–995$ or compound-201995$ or compound201-995$ or compound 201995$ or san$–201–995$ or san$–201995$ or san$201–995$ or san201995 or sm?–201–995$ or sm?–201995$ or sm?201–995$ or sm?201995$ or sandostatin$).ti,ab,kw,kf.	8680
94	or/90–93	38435
95	exp Sulfonylurea Compounds/	18994
96	sulfonylurea$.ti,ab,kw,kf.	7883
97	Acetohexamide/	238
98	(acetohexamid$ or d#melor$ or gamadiabet$).ti,ab,kw,kf.	203
99	Carbutamide/	532
100	(aminophenurobutan$ or bu#arban$ or butylcarbamid$ or diabetal$ or glucidoral$ or glybutamid$ or oran#l$ or sulfaninylbutylurea$).ti,ab,kw,kf.	92
101	Chlorpropamide/	1819
102	(c?lorpropamid$ or diabinese$ or glucamid$ or insogen$ or meldian$).ti,ab,kw,kf.	1504
103	(glibornurid$ or ro-6–4563$ or ro6-4563$ or ro-64563$ or ro64563$ or gluborid$ or glutril$).ti,ab,kw,kf.	95
104	Gliclazide/	884
105	(gl##lazid$ or s-1702$ or s1702$ or s-852$ or s852$ or diabrezid$ or diaglyk$ or diamicron$ or diaikron$ or diabrezid$ or glyade$).ti,ab,kw,kf.	1394
106	(gl#mepirid$ or hoe-490$ or hoe490$ or amar#l$ or roname$).ti,ab,kw,kf.	2446
107	Glipizide/	731
108	(gl#pizid$ or k-4024$ or k4024$ or glucotrol$ or gl#diazinamid$ or glupitel$ or melizide$ or min?diab$ or ozidia$).ti,ab,kw,kf.	1077
109	(gl###idon$ or ar-df-26$ or ardf-26$ or ar-df26$ or ardf26$ or beglynor$ or glurenor$).ti,ab,kw,kf.	179
110	Glyburide/	6168
111	(glyburid$ or hb-419$ or hb419$ or hb-420$ or hb420$ or daonil$ or diabeta$ or euglucon$ or gl#benclamid$ or maninil$ or micronase$ or neogluconin$).ti,ab,kw,kf.	10267
112	Tolazamide/	168
113	(tolazamid$ or norglycin$ or tol#nase$).ti,ab,kw,kf.	169
114	Tolbutamide/	5250
115	(tolbutamid$ or artosin$ or diabetol$ or diaval$ or dolipol$ or orabet$ or orinase$ or rastinon$).ti,ab,kw,kf.	7043
116	or/95–115	32466
117	exp Thiazolidinediones/	11549
118	(thiazolidinedion$ or glitazon$).ti,ab,kw,kf.	6432

Continued

Table 1 Continued

#	Searches	Results
119	(pioglitazon$ or u-72107a$ or u72107a$ or ad-4833$ or ad4833$ or actos$ or competact$ or glidipion$ or glubrava$ or glustin$ or paglitaz$ or sepioglin$ or tandemact$).ti,ab,kw,kf.	5431
120	(rosiglitazon$ or brl-49653$ or brl49653$ or avaglim$ or avandamet$ or avandia$ or nyracta$ or venvia$).ti,ab,kw,kf.	5807
121	(troglitazon$ or cs-045$ or cs045$ or prelay$ or rezulin$).ti,ab,kw,kf.	2348
122	or/117–121	17 693
123	exp Topiramate/	2715
124	(topiramat$ or mcn-4853? or mcn4853? or usl-255? or usl255? or epitomax$ or topamax$).ti,ab,kw,kf.	4608
125	or/123–124	4936
126	or/4–125	465 776
127	("randomized controlled trial" or "controlled clinical trial").pt.	591 452
128	(groups or placebo or randomi#ed or randomly or trial).ab.	2 807 236
129	"drug therapy".fs.	2 190 159
130	Cross-Over Studies/	47 393
131	(cross-over or crossover).ti,ab,kw,kf.	84 179
132	or/127–131	4 706 281
133	exp Animals/ not Humans/	4 683 296
134	132 not 133	4 081 128
135	and/3,126,134	9978

Outcomes

Primary outcome:

- Change in body weight (or BMI) from baseline to end of the intervention.

Other major outcomes:

- Change in HbA1c from baseline to end of the intervention.
- Risk of mild hypoglycaemia.
- Risk of severe hypoglycaemia.
- Change in TDD (or TDD/kg body weight) from baseline to end of the intervention.
- Risk of diabetic ketoacidosis (DKA).
- Risk of SAEs.
- Drop-out rate.
- Withdrawals due to adverse events.

The criteria used for the classification of mild/severe hypoglycaemia, DKA and SAEs will follow the definitions applied by the respective study authors. In cases where outcomes are reported on various time points during the study (eg, at 26 and 52 weeks), the outcome closest to the end of the active intervention will be used (ie, only data respecting the original randomised design will be included; excluding early rescues and open label extension phases).

Outcome measures were chosen based on clinical relevancy and use of outcome reporting from relevant literature. In the section 'Non-insulin Treatments for Type 1 Diabetes' of ADA's 'Standards of Medical Care 2020', body weight, HbA1c and DKA are used to describe the agents.[19] Risk of hypoglycaemia and SAEs are essential outcome measurements when evaluating glucose-lowering drugs and TDD is a valuable outcome measure with respect to interpreting the primary outcome (body weight). Lastly, drop-out rate and withdrawals due to adverse events are widely used components in the assessment of adverse effects.[25]

Geometry of the network

A network graph will be used to present the evidence base for the primary outcome following our systematic review: treatments will be represented by nodes and head-to-head studies between treatments are represented by edges.[26] The sizes of edges and nodes are proportional to the available numbers of studies comparing the different interventions and the numbers of patients studied with each treatment. The description of the network of interventions will include numerical summary statistics to describe the current evidence available for the competing interventions and to identify gaps and potential bias. At the level of drug classes, it will be examined whether head-to-head comparisons are between agents in the same class or between agents in different classes. In the networks of drug class comparisons, each drug class will be drawn by a node and randomised comparisons between drug classes shown by links between the nodes.

Assessment of risk of bias

Two reviewers will independently assess the risk of bias for each study using the Cochrane Risk of Bias tool.[27] Each study will be rated as having a low, high or unclear risk of bias for each of the following aspects: sequence generation, allocation concealment, blinding of participants,

blinding of personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. Disagreement will be resolved first by discussion and then by consulting a third review author for arbitration.

Data synthesis

Measures of treatment effect: contrast-based comparisons

When each study uses the same outcome measure and the units of that measure are intuitively interpretable (eg, body weight in kilograms and HbA1c in percentages), presenting differences in means is usually desirable. Thus, the meta-analyses for the continuous outcomes measuring on the same scale will be conducted by calculating the weighted mean difference with 95% CIs.[28] For binary (dichotomous) outcomes, risk ratios will be the preferred measure of relative effect and, where applicable, control group risks will be used to generate absolute risks.[29]

Handling of missing data

RCT level: an intention-to-treat (ITT) analysis estimates the effect of treatment assignment in a particular trial, not the effect of the treatment itself. ITT effects are agnostic about post-randomisation decisions, including treatment discontinuation and the use of concomitant therapies prohibited by the study protocol. The true effect of selecting a new management strategy is a combination of biological effects, variations in compliance or adherence and other patient characteristics that influence efficacy. For all the meta-analyses, estimates apparently derived from the ITT population will be used; that is, if these analyses did not explicitly (and appropriately) handle the missing data in a specific trial, this will be noted as a risk of attrition bias.

Meta-analysis level: for missing standard deviations (SDs) of mean changes and where the p value is provided for a comparison between the treatment and control groups, the SD will be calculated by converting the p value into a t value with appropriate degrees of freedom (df). If neither the SDs nor the p values are available, a SD will be imputed based on studies with comparable measurement methods, duration and measurement error. Missing outcome data that were probably measured will be retrieved by contacting the corresponding authors of the RCTs via email. Where this is unsuccessful, missing data will be calculated from the raw numbers given in tables and/or estimated from bar charts if possible. The overall robustness of the findings will be assessed by manually imputing a 'no change' into the analysis. Thus, consistence between the sensitivity analyses and the primary analyses will strengthen the robustness of the results.

Assessment of heterogeneity

Statistical heterogeneity will be assessed using the inconsistency index (I^2), where an I^2 value of more than 50% indicates significant heterogeneity. Sources of heterogeneity will be explored by subgroup and sensitivity analysis. Random-effects models will be applied per default, but the 95% CIs will be compared with the point estimate from the corresponding fixed-effects meta-analysis. Agreement between the models will indicate robustness against small-study bias.

Data synthesis (meta-analysis)

Each outcome will be combined using appropriate statistical software according to the statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions. Data will be combined into nodes for each drug class using a random-effects model as a substantial variability in the trial methodology and subsequent treatment effects across studies may be expected. If heterogeneity is substantial, confidence in the estimates will be rated down in the Summary of Findings table as recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. For the primary outcome (change in body weight), a random-effects NMA will also be conducted to assess the comparative effectiveness of the adjunctive glucose-lowering drugs. Local and global methods for evaluation of inconsistency will be employed. Quality of evidence contributing to network estimates of the primary outcomes will also be assessed using GRADE.

When two drugs are compared with a common standard, the difference in effect between these two drugs with respect to the common standard forms the basis of indirect comparisons. Indirect treatment comparisons in a meta-analysis can be analysed by various methods according to the different networks applied, including the star, ladder, closed and partially closed-loop designs. We will perform mixed-effects models using an arm-based, random-effects model within an empirical Bayes framework.[30] The linear mixed model incorporates a vector of random-effects and a design matrix for the random-effects. Allowance will be made for differences in heterogeneity of effects between different drugs by specifying that the linear predictor varies at the level of study and the drug across study. Heterogeneity for the indirect comparison analyses will be evaluated using estimated tau-squared, which measures the statistical heterogeneity across the population of studies. If the collected data do not allow for an NMA of the primary outcome, this will be stated in the manuscript.

Reporting the NMA

An NMA will be performed within the 'frequentist framework' to synthesise the available evidence from the entire network of trials (reporting on change in body weight) by integrating direct and indirect estimates for each comparison into a single summary treatment effect. A frequentist random-effects model will be used (ie, empirical Bayes based on mixed-effects models) applying the methodology of multivariate meta-analysis to assess the comparative effectiveness of eligible interventions.

To check that the model fits the data well, hypothesis tests based on deviance statistics will be used. Issues of

incoherence (direct and indirect effect estimates are not similar) will be identified by comparing direct evidence (ie, estimates from pairwise comparisons) with indirect evidence (ie, estimates from NMA).[31] In this approach, incoherence will be assessed locally by statistical evaluation of the difference between direct and indirect estimates for a specific comparison in the loop. A common heterogeneity estimate across the network will be assumed. In case of incoherence in a closed loop of evidence, the certainty of evidence of each estimate will enable us to decide which estimate to believe.

Treatment rankings

An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimise potential biases. Following the NMA, information about the hierarchy of competing interventions (drug classes) in terms of their mutual mean difference and their 95% CIs (and credibility intervals) will be provided. As recommended by the GRADE Working Group,[32] mutual rankings can be judged along with corresponding estimates of pairwise comparisons between interventions. Rankings (eg, the surface under the cumulative ranking (SUCRA) curve) might unfortunately be misinterpreted since these may exaggerate small differences in relative effects, especially if they are based on limited information. For these reasons, standard forest plots will be used to summarise findings for all contrast-based meta-analyses. The large number of treatment comparisons coming from arm-based NMAs will be presented using a league table (ie, a tabular approach used to succinctly present all possible pairwise comparisons between treatments) as suggested by PRISMA Extension Statement for Reporting Network Meta-analyses.[26] The primary attention will be on reporting differences between means of a specific drug class of interest versus 'management as usual'/placebo.

Using the GRADE approach instead of the SUCRA curve, the adjunctive glucose-lowering drug classes will be evaluated first based on their effectiveness versus placebo, second versus other competing interventions and finally according to GRADE certainty of evidence ratings. Based on this, drug classes will be sorted into three groups: among the most effective (superior to both placebo and to at least one intervention superior to placebo or no treatment); superior to placebo, but not superior to any other intervention; or no more effective than placebo.

Subgroup and sensitivity analysis

Outcomes will be reported separately for each drug class. Subgroup analysis will be used to explore possible sources of heterogeneity based on the duration of intervention and dose administered. A meta-regression analysis will be performed to evaluate the potential influence of glycaemic control at baseline, duration of diabetes and baseline body weight. Selection of a statistical model for NMAs where comparisons between treatments are largely based on single studies can represent a challenge. Sensitivity analysis will be performed in order to explore the sources of heterogeneity based on internal validity components (eg, full-text publications vs abstract) and risk of bias (high vs low risk of bias). Performance of additional analyses retains an important role in establishing the robustness of our findings. Various ways to structure the treatment network (such as lumping and splitting in relation to name of active drug and potentially dose levels, method of administration or exclusion of certain doses) will be reconsidered, accounting for the effect of covariates on summary effect measures (using meta-regression analysis) and use of different statistical models (including a Bayesian approach, where different prior distributions will be chosen). Findings from such analyses will be reported so that readers have all available information for judging robustness of primary findings.

Meta-biases

For outcomes reported in ≥10 studies, comparison-adjusted funnel plots will be drawn. If funnel plot asymmetry is observed, reasons for its prevalence (eg, selective reporting, publication bias, heterogeneity and inconsistency) will be examined.

Confidence in cumulative evidence

The certainty associated with the comparisons will be assessed using the GRADE approach.[33] For both direct and indirect comparisons, the starting point for certainty in the estimates will be high (further research is very unlikely to change the authors' confidence in the estimate of effect), but can be rated down to moderate (further research is likely to have an important impact on the authors' confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on the authors' confidence in the estimate of effect and is likely to change the estimate) or very low (any estimate of effect is very uncertain). The certainty of the evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate. Interventions will be categorised from most to least effective interventions: superior to both placebo and alternatives; superior to placebo, but inferior to alternatives; and no better than placebo. The GRADE assessment will be conducted by three reviewers.

ETHICS AND DISSEMINATION

As no primary data collection will be undertaken, no ethical assessment is required. Data will be processed according to protocol, merged into at least one scientific article and published in an international peer-reviewed scientific journal. The analysis will be reported according to PRISMA guidelines.

Contributors CL is the guarantor. CL, AGR, SS and KN drafted the protocol manuscript. LNR and ON critically reviewed the methodological content and developed the search strategy in collaboration with CL, AGR, SS and KN. RC

provided statistical and methodological expertise. All authors read, provided feedback and approved the final protocol.

Funding CL, AGR, SS, LNR, ON and KN are employed by Steno Diabetes Center Copenhagen (SDCC), who is the sponsor of the research initiative. SDCC is owned by the Capital Region of Denmark and supported by a donation from the Novo Nordisk Foundation (NNF16SA0024138). The Musculoskeletal Statistics Unit at the Parker Institute, Bispebjerg and Frederiksberg Hospital (RC), is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL).

Disclaimer The funders have not been involved in the conception or any other part of the systematic review, and no external funding has been received for this research initiative.

Competing interests CL, AGR, SS, LNR, ON and RC have nothing to disclose. KN owns shares in Novo Nordisk and has received research grants and fees for lecturing from Novo Nordisk and Zealand Pharma. No other potential conflicts of interest relevant to this article were reported.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Christian Laugesen http://orcid.org/0000-0001-9253-9457
Ajenthen G. Ranjan http://orcid.org/0000-0002-2253-6071
Signe Schmidt http://orcid.org/0000-0002-6968-6675
Lauge Neimann Rasmussen http://orcid.org/0000-0001-9584-2443
Ole Nørgaard http://orcid.org/0000-0002-1681-4338
Robin Christensen http://orcid.org/0000-0002-6600-0631
Kirsten Nørgaard http://orcid.org/0000-0003-1620-8271

REFERENCES

1 Conway B, Miller RG, Costacou T, *et al*. Temporal patterns in overweight and obesity in type 1 diabetes. *Diabet Med* 2010;27:398–404.
2 Baskaran C, Volkening LK, Diaz M, *et al*. A decade of temporal trends in overweight/obesity in youth with type 1 diabetes after the diabetes control and complications trial. *Pediatr Diabetes* 2015;16:263–70.
3 Minges KE, Whittemore R, Weinzimer SA, *et al*. Correlates of overweight and obesity in 5529 adolescents with type 1 diabetes: the T1D exchange clinic registry. *Diabetes Res Clin Pract* 2017;126:68–78.
4 Foster NC, Beck RW, Miller KM, *et al*. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. *Diabetes Technol Ther* 2019;21:66–72.
5 , Nathan DM, Zinman B, *et al*, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-Day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med* 2009;169:1307–16.
6 , Whitlock G, Lewington S, *et al*, Prospective Studies Collaboration. Body-Mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083–96.
7 Dixon JB. The effect of obesity on health outcomes. *Mol Cell Endocrinol* 2010;316:104–8.
8 Conway B, Miller RG, Costacou T, *et al*. Adiposity and mortality in type 1 diabetes. *Int J Obes* 2009;33:796–805.
9 Edqvist J, Rawshani A, Adiels M, *et al*. Bmi, mortality, and cardiovascular outcomes in type 1 diabetes: findings against an obesity paradox. *Diabetes Care* 2019;42:1297–304.
10 Vestberg D, Rosengren A, Olsson M, *et al*. Relationship between overweight and obesity with hospitalization for heart failure in 20,985 patients with type 1 diabetes: a population-based study from the Swedish national diabetes registry. *Diabetes Care* 2013;36:2857–61.
11 SA P, G A, F S. Obesity is associated with retinopathy and macrovascular disease in type 1 diabetes. Obes Res clin Pract. *Obes Res Clin Pract* 2014;8.
12 Teló GH, Dougher CE, Volkening LK, *et al*. Predictors of changing insulin dose requirements and glycaemic control in children, adolescents and young adults with type 1 diabetes. *Diabet Med* 2018;35:1355–63.
13 Alderisio A, Bozzetto L, Franco L, *et al*. Long-Term body weight trajectories and metabolic control in type 1 diabetes patients on insulin pump or multiple daily injections: a 10-year retrospective controlled study. *Nutr Metab Cardiovasc Dis* 2019;29:1110–7.
14 Andersen HU, Hangaard S, Hommel E, *et al*. Six-Year follow-up after insulin pump initiation: HbA1c is significantly reduced without weight gain. *J Diabetes Sci Technol* 2018;12:535–6.
15 Van Gaal L, Scheen A. Weight management in type 2 diabetes: current and emerging approaches to treatment. *Diabetes Care* 2015;38:1161–72.
16 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
17 Neimann Rasmussen L, Montgomery P. The prevalence of and factors associated with inclusion of non-English language studies in Campbell systematic reviews: a survey and meta-epidemiological study. *Syst Rev* 2018;7:129.
18 Walpole SC. Including papers in languages other than English in systematic reviews: important, feasible, yet often omitted. *J Clin Epidemiol* 2019;111:127–34.
19 American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020;43:S98–110.
20 EMA. The European Medicines Agency's public assessment reports (EPARs). Available: https://www.ema.europa.eu/en/medicines [Accessed 03 Mar 2020].
21 Drugs.com. Medication for diabetes, type 2, 2019. Available: https://www.drugs.com/condition/diabetes-mellitus-type-ii.html
22 Drugs.com. Medication for Diabetes, type 1 [Internet], 2019. Available: https://www.drugs.com/condition/diabetes-mellitus-type-i.html
23 Thomas J, Brunton J, Graziosi S. *EPPI-Reviewer 4.0: software for research synthesis. EPPI-Centre software*. London: Social Science Research Unit, Institute of Education, University of London, 2010.
24 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
25 Peryer G, Golder S, Junqueira DR, *et al*. Adverse effects. In: *Cochrane Handbook for systematic reviews of interventions 2019*, 2019: 493–505.
26 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
27 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
28 Guyatt GH, Thorlund K, Oxman AD, *et al*. Grade guidelines: 13. preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 2013;66:173–83.
29 Guyatt GH, Oxman AD, Santesso N, *et al*. Grade guidelines: 12. preparing summary of findings tables-binary outcomes. *J Clin Epidemiol* 2013;66:158–72.
30 Platt RW, Leroux BG, Breslow N. Generalized linear mixed models for meta-analysis. *Stat Med* 1999;18:643–54.
31 Bucher HC, Guyatt GH, Griffith LE, *et al*. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683–91.
32 Puhan MA, Schünemann HJ, Murad MH, *et al*. A grade Working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.
33 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.