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Review

Comparing once-weekly semaglutide to incretin-based therapies in patients with type 2 diabetes: a systematic review and meta-analysis

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ABSTRACT

Aims. – Our aim was to compare once-weekly semaglutide to incretin-based therapies – defined as either dipeptidyl peptidase-4 inhibitors (DPP-4i) or other glucagon-like peptide-1 receptor agonist (GLP-1RA) – in patients with type 2 diabetes.

Methods. – We searched for randomized trials comparing once-weekly semaglutide to other incretin-based therapies in patients with type 2 diabetes. We pooled trials that compared semaglutide to other GLP-1RA together, and those comparing semaglutide to DPP-4i together. The primary outcome was the change in haemoglobin A_{1c} over time.

Results. – Five trials met our inclusion criteria. There was a significantly greater reduction in haemoglobin A_{1c} favouring semaglutide when compared to other GLP-1RA or DPP-4i [MD (95% CI) = −0.38% (−0.62, −0.15) and −1.14% (−1.53, −0.75) respectively]. There was a significantly greater weight loss favouring semaglutide when compared to other GLP-1RA or DPP-4i [MD (95% CI) = −2.50 kg (−3.91, −1.09) and −3.19 kg (−3.66, −2.72) respectively]. The proportion of patients achieving glycaemic goals and goal weight loss was greater in semaglutide-treated patients when compared to either other GLP-1RA or DPP-4i. However, semaglutide-treated patients had a significantly higher incidence of gastrointestinal side effects.

Conclusions. – While both once-weekly semaglutide and other incretin-based therapies can reduce haemoglobin A_{1c}, semaglutide causes a more potent haemoglobin A_{1c} reduction and greater weight loss when compared to other incretin-based therapies. However, this potent effect of semaglutide was associated with a higher incidence of gastrointestinal side effects. Additional studies are needed to determine whether this marked reduction in both haemoglobin A_{1c} and body weight may translate into improved cardiovascular outcomes.

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Introduction

Both Glucagon-like peptide-1 Receptor Agonists (GLP-1RA), as incretin mimetics, and dipeptidyl peptidase-4 inhibitors (DPP-4i), as incretin enhancers, potentiate the action of or act at the receptor for the incretin hormone GLP-1, an important pathway for regulation of appetite, glucose, insulin and other metabolic parameters [1]. Since introductions in 2005 (for exenatide, the first GLP-1RA) and 2006 (for sitagliptin, the first DPP-4i), incretin-based therapies have become widely used and are now recommended by multiple guidelines [2–4]. Semaglutide is a GLP-1RA that is structurally similar to liraglutide but is less susceptible to degradation by DPP-4 enzymes and thus is more stable. In December 2017, semaglutide was approved by the US Food and Drug Administration (FDA) for patients with type 2 diabetes as a once-weekly subcutaneous injection.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; ADA, american diabetes association; MD, mean difference; CI, confidence interval; RR, relative risk; FDA, food and drug administration; NCT, national clinical trial; SD, standard deviation.

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While both GLP-1RA and DPP-4i effect the incretin system, there are differences between them, and GLP-1RA have been shown to have a more potent haemoglobin A1c-lowering effect in patients with type 2 diabetes [1,5]. There may also be important within group differences between GLP-1RAs [6]. Given the potential for therapeutically important differences between the newer agent, semaglutide, and other incretin-based therapies, the authors performed this systematic review and meta-analysis to compare the efficacy and safety of once-weekly semaglutide to other incretin-based therapies in patients with type 2 diabetes.

Materials and methods

In accordance with the PRISMA statement recommendations for reporting systematic review and meta-analysis [7], the systematic review and meta-analysis was registered on PROSPERO (CRD42018092590).

Data sources and search

We searched MEDLINE (1966–2018), the Cochrane Central Register of Controlled trials, EMBASE (1947–2018), Web of Science, and CINAHL looking for randomized trials directly comparing once-weekly semaglutide to other incretin-based therapies in patients with type 2 diabetes.

An experienced librarian (KS) iteratively developed keywords in the domains of semaglutide, DPP-4i, and GLP-1RA based upon drug registries, expert consultation, and terminology identified in known, relevant studies, and then combined the keywords with controlled vocabulary from PubMed/MEDLINE (Table S1; see supplementary materials associated with this article on line). One author (KS) mapped and implemented the search strategy across identified databases. In addition, we searched clinicaltrials.gov to identify clinical trials and checked for data availability of any relevant trials. The date of the last database search was March 14th, 2018. The reference lists of eligible articles were also screened to identify any additional published studies.

Study selection

After de-duplication of records, all retrieved articles were screened for inclusion. We included randomized trials that compared once-weekly subcutaneous semaglutide to any other incretin-based therapy (i.e., any other DPP-4i or GLP-1RA) in patients with type 2 diabetes. Included studies were required to report a change in haemoglobin A_{1c} over time. We included trials that are not fully published but registered at clinicaltrials.gov unless results were not submitted. We excluded trials investigating oral or daily semaglutide since once-weekly subcutaneous semaglutide is the FDA-approved treatment schedule. We excluded reviews, retrospective studies, letters to the editors, and conference abstracts. No date or language limits were applied.

Data extraction and quality assessment

Two authors (BMM and DMC) reviewed eligible articles. The quality of the included trials was assessed using the risk of bias tables suggested by the Cochrane Collaboration [8]. We also used the 7-point modified Oxford Score [9–11]. We resolved discrepancies by discussion.

We then created a data collection sheet including:

- author name;
- national clinical trial (NCT) identifier;
- duration of the trial;
- haemoglobin A_{1c} eligibility;
- inclusion/exclusion criteria;
- dose of once-weekly semaglutide;
- name/dose of incretin-based therapy;
- primary outcome of the trial;
- baseline age, haemoglobin A_{1c}, body weight, systolic and diastolic blood pressure, and duration of diabetes;
- change in haemoglobin A_{1c} over time;
- change in body weight over time;
- change in fasting plasma glucose over time;
- change in blood pressure over time;
- number of patients achieving haemoglobin $A_{1c} < 7.0\%$ and $\leq 6.5\%$;
- number of patients achieving haemoglobin $A_{1c} < 7.0\%$ without severe hypoglycaemia or weight gain;
- number of patients with body weight loss $\geq 5\%$ and $\geq 10\%$;
- number of patients requiring rescue medications; and;
- incidence of side effects.

Data synthesis and statistical analysis

The primary outcome of interest in this meta-analysis was the change in haemoglobin A_{1c} over time. Secondary outcomes were the change in body weight, change in fasting plasma glucose, change in blood pressure, number of patients achieving goal haemoglobin $A_{1c} < 7.0\%$ and $\leq 6.5\%$, number of patients achieving goal haemoglobin $A_{1c} < 7.0\%$ without hypoglycaemia or weight gain, numbers of patients with body weight loss $\geq 5\%$ and $\geq 10\%$, number of patients requiring rescue medications, and incidence of side effects.

Given the expected differences between GLP-1RA and DPP-4i [12,13], separate analyses were performed according to whether semaglutide was compared to other GLP-1RA or DPP-4i. In dose-finding trials, we only combined the groups investigating doses approved by the FDA. If the dose-ranging trial did not investigate the specific FDA-approved dose, the closest approved doses were used instead. If results were reported as standard error or confidence intervals (CI), we converted this data to standard deviation (SD) according to equations recommended by the Cochrane Collaboration [8]. In articles reporting outcomes only in graphic format, data were extracted from the graph.

Continuous data were summarized as mean difference (MD) between treatment arms with 95% CI. If the value 0 was included in the 95% CI, we considered that the difference between the semaglutide and other incretin-based therapies was not statistically significant. Dichotomous data were summarized as relative risk (RR) with 95% CI. If the value 1 was included in the 95% CI, we considered that the difference between the semaglutide and other incretin-based therapies was not statistically significant. Analyses were performed using the Review Manager (RevMan, Version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). We used a random effects model. For statistically significant outcomes and side effects, the number needed to treat (NNT) and number needed to harm (NNH) were calculated respectively to estimate the overall clinical impact. We considered I^2 test was $> 50\%$. Forest plots were used to graphically represent and evaluate treatment effects.

Results

The initial searches yielded 651 citations, with 390 studies remaining after duplicates were removed (Fig. 1). Five trials [14–18] with 3769 patients (2161 received semaglutide and 1608 received incretin-based therapy) met our inclusion criteria. The characte-

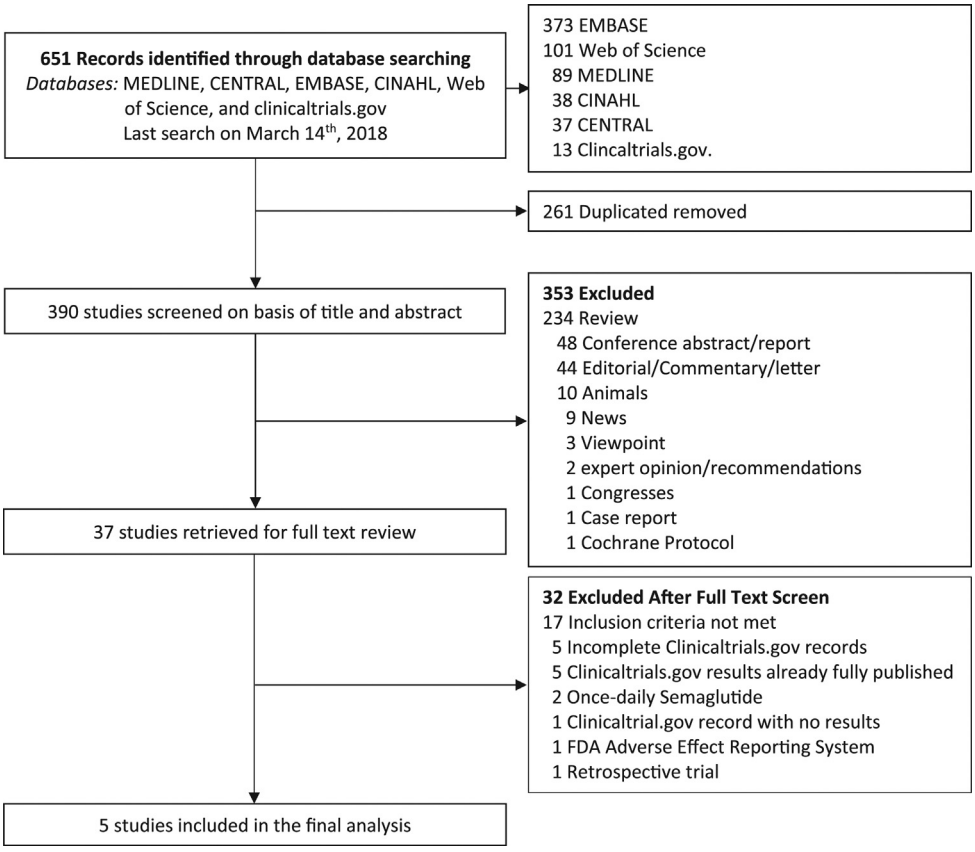

Fig. 1. Study selection flow chart.

ristics of the included trials are shown in Table 1 and the risk of bias in table S2 (see supplementary materials associated with this article on line).

Of the 5 trials [14–18], one [16] was a phase 2 dose-finding trial. Three trials [14,16,17] compared semaglutide to another GLP-1RA (liraglutide [16], exenatide [14], or dulaglutide [17]), while two trials [15,18] compared semaglutide to a DPP-4i (sitagliptin). Three trials [14,15,17] investigated semaglutide as add-on therapy, one [16] as added to either diet/exercise or metformin, and one [18] as monotherapy. The primary outcome for four trials [14–17] was the change in haemoglobin A_{1c} over time, and one [18] was the treatment-emergent adverse events.

Semaglutide compared to other GLP-1RA

Change in haemoglobin A_{1c}

Three trials [14,16,17] comparing semaglutide to other GLP-1RA and reported a change in haemoglobin A1c over time. Pooled results showed a statistically significant reduction in haemoglobin A1c favouring semaglutide compared to other GLP-1RA [MD (95% CI) = −0.38% (−0.62, −0.15), I^2 = 81%, Fig. 2]. On pooling the means of the haemoglobin A1c reduction among different trials, there was an absolute haemoglobin A_{1c} reduction of −1.5% with semaglutide versus −1.1% with other GLP-1RA.

Change in weight outcomes

The change in body weight over time, number of patients achieving body weight loss of ≥ 5%, and number of patients achieving body weight loss of ≥ 10% were reported in three trials [14,16,17]. Pooled results for the change in body weight showed a statistically significant reduction favouring semaglutide compared to other GLP-1RA [MD (95% CI) = −2.50 kg (−3.91, −1.09), I^2 = 90%, Fig. 3]. On pooling the means of the change in body weight among the trials, there was an absolute body weight reduction of −4.7 kg with semaglutide versus −2.3 Kg with other GLP-1RA. The number of patients achieving body weight loss of ≥ 5% and ≥ 10% was significantly higher in semaglutide-treated patients compared to other GLP-1RA [RR (95% CI) = 2.37 (1.74, 3.23), I^2 = 76%, NNT = 4 and 4.08 (3.04, 5.46), I^2 = 0%, NNT = 8 respectively] (Fig. 4).

Change in fasting plasma glucose and blood pressure outcomes

The change in fasting plasma glucose and blood pressure was investigated in 3 [14,16,17] and 2 [14,17] trials, respectively. Pooled results for the change in fasting blood glucose showed a statistically significant reduction favouring semaglutide compared to other GLP-1RA [MD (95% CI) = −0.51 mmol/L (−0.81, −0.20), I^2 = 51%]. Pooled results for the change in systolic and diastolic blood pressure showed a significant reduction favouring semaglutide compared to other GLP-1RA [MD (95% CI) = −1.60 mmHg (−2.84, −0.36), I^2 = 10% and −1.03 mmHg (−1.78, −0.28), I^2 = 0% respectively].

Proportion of patients achieving glycaemic targets

The number of patients achieving a haemoglobin $A_{1c} < 7.0\%$, a haemoglobin $A_{1c} \leq 6.5\%$, and a composite outcome of haemoglobin $A_{1c} < 7.0\%$ without hypoglycaemia or weight gain was investigated in 3 [14,16,17], 3 [14,16,17], and 2 [14,17] trials respectively. Pooled results for the number of patients achieving a haemoglobin $A_{1c} \leq 7.0\%$, a haemoglobin $A_{1c} \leq 6.5\%$, and a composite outcome of haemoglobin $A_{1c} \leq 7.0\%$ with no hypoglycaemia or weight gain favoured semaglutide compared to other GLP-1RA [RR (95% CI) = 1.33 (1.06, 1.68), I^2 = 88%, NNT = 6, 1.52 (1.09, 2.12), I^2 = 87%, NNT = 6, and 1.63 (1.10, 2.43), I^2 = 93%, NNT = 5 respectively] (figure S1; see supplementary materials associated with this article on line).

Table 1
Characteristics of included trials.

Author	Groups dose (*n*)	1ry outcome	Baseline age (years)	Baseline A_{1c} (%)	Baseline weight (kg)	Baseline SBP (mmHg)	Baseline DBP (mmHg)
Ahmann A [14] (NCT01885208)	Sema 1 mg qw (404) Exen ER 2 mg qw (405)	Change in A_{1c} over 56 w	Sema1: 56.4(20–82)[a] Exen: 56.7(21–83)[b]	Sema1: 8.4(6.7–11.1)[a] Exen: 8.3(6.5–11.2)[b]	Sema1: 96.2(49.9–198.3)[b] Exen: 95.4 (53.2–171.9)[a]	133.5 (14.5)[b]	79.9 (8.7)[b]
Ahren B [15] (NCT01930188)	Sema 0.5 mg qw (409) Sema 1 mg qw (409) Sita 100 mg qd (407)	Change in A_{1c} over 56 w	Sema0.5: 54.8(10.2) Sema1: 56.0(9.4) Sita: 54.6(10.4)	Sema0.5: 8.0(0.9) Sema1: 8.0 (0.9) Sita: 8.2(0.9)	Sema0.5: 89.9(20.4) Sema1: 89.2(20.7) Sita: 89.3(19.7)	132.6 (14.9)[c]	80.7 (9.2)[b]
Nauck M [16] (NCT00696657)	Sema 0.4 mg qw (48) Sema 0.8 mg qw Sema 0.8 mg with dose escalation(DE)[c] (43) Lira 1.2 mg qd (45) Lira 1.8 mg qd (50)	Change in A_{1c} over 12 w	Sema0.4: 53.8(10.2) Sema0.8: 55.0(9.7) Sema0.8DE: 55.9(7.9) Lira1.2: 54.8(9.2) Lira1.8: 54.3(10.1)	Sema0.4: 8.1(0.9) Sema0.8: 8.2(0.9) Sema0.8DE: 8.0(0.8) Lira1.2: 8.0(0.8) Lira1.8: 8.1(0.7)	Sema0.4: 87.0(14) Sema0.8: 85.9(15.1) Sema0.8DE: 85.7(12.6) Lira1.2: 90.5(13.5) Lira1.8: 87.2(13.1)	Not reported	Not reported
Pratley R [17] (NCT02648204)	Sema 0.5 mg qw (301) Sema 1 mg qw (300) Dula 0.75 mg qw (299) Dula 1.5 mg qw (299)	Change in A_{1c} over 40 w	Sema0.5: 56.0(10.9) Sema1: 55(10.6) Dula0.75: 55(10.4) Dula1.5: 56(10.6)	Sema0.5: 8.3(0.9) Sema1: 8.2(0.9) Dula0.75: 8.2(0.9) Dula1.5: 8.2(0.9)	Sema0.5: 96.4(24.4) Sema1: 95.5(20.9) Dula0.75: 95.6(23.0) Dula1.5: 93.4(21.8)	Sema0.5: 134(14.8) Sema1: 133(14.5) Dula0.75: 133(14.0) Dula1.5: 132(13.6)	Sema0.5: 81(9.0) Sema1: 82(9.1) Dula0.75: 81(8.9) Dula1.5: 80(8.4)
Seino Y [18] (NCT02254291)	Sema 0.5 mg qw (103) Sema 1 mg qw (102) Sita 100 mg qd (103)	Number of adverse events during 30 w	Sema0.5: 58.8(10.4) Sema1: 58.1(11.6) Sita: 57.9(10.1)	Sema0.5: 8.2(1) Sema1: 8.0(0.9) Sita: 8.2(0.9)	Sema0.5: 67.8(11.7) Sema1: 70.8(16.4) Sita: 69.4(12.9)	Not reported	Not reported

Data is presented as mean and standard deviation unless reported otherwise.
A_{1c}: haemoglobin A_{1c}; kg: kilogram; SBP: systolic blood pressure; mmHg: millimetre mercury; DBP: diastolic blood pressure; Sema: semaglutide; qw: every week; Exen ER: exenatide extended-release; Sita: sitagliptin; qd: every day; Lira: liraglutide; Dula: dulaglutide.

[a] Data is presented as mean and minimum–maximum.

[b] Data is the overall mean for the study groups.

[c] There was a fixed 1 to 2-week dose-escalation from 0.4 to 0.8 mg.

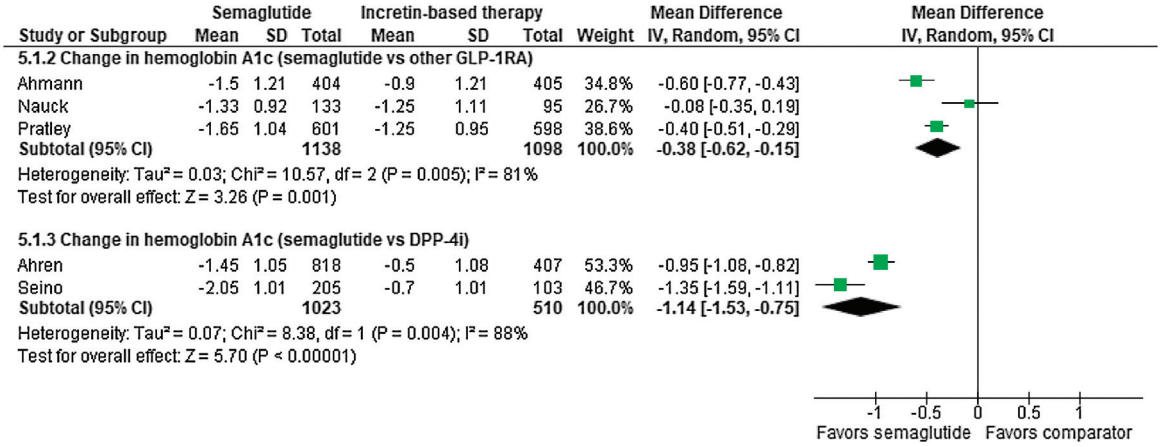

Fig. 2. Change in haemoglobin A_{1c} over time. GLP-1RA: glucagon-like peptide-1 receptor agonist; DPP-4i: dipeptidyl peptidase-4 inhibitor; SD: standard deviation; CI: confidence interval.

Two trials [14,17] reported the number of patients requiring rescue medications with pooled results showing a significantly lower incidence with semaglutide compared to other GLP-1RA [RR (95% CI) = 0.58 (0.39, 0.84), I^2 = 0%, NNT = 35].

Adverse effects

There was no statistically significant difference in the incidence of adverse events, serious adverse events, diarrhoea, or acute pancreatitis. However, semaglutide-treated patients had a significantly higher incidence of adverse effects leading to discontinuation of study drug, nausea, and vomiting. Data are presented in figure S2 (see supplementary materials associated with this article on line).

Semaglutide compared to DPP-4i

Change in haemoglobin A_{1c}

Two trials [15,18] comparing semaglutide to DPP-4i reported a change in haemoglobin A1c over time. Pooled results showed a statistically significant reduction in haemoglobin A1c favouring semaglutide compared to DPP-4i [MD (95% CI) = −1.14% (-1.53, -0.75), I^2 = 88%, Fig. 2]. On pooling the means of the haemoglobin A1c reduction among different trials, there was an absolute haemoglobin A_{1c} reduction of −1.8% with semaglutide versus -0.6% with DPP-4i.

Change in weight outcomes

The change in body weight over time, number of patients achieving body weight loss of ≥ 5%, and number of patients achieving body weight loss of ≥ 10% were reported in two trials [15,18]. Pooled results for the change in body weight showed a statistically significant reduction favouring semaglutide compared to DPP-4i [MD (95% CI) = −3.19 kg (−3.66, −2.72), I^2 = 0%, Fig. 3]. On pooling the means of the change in body weight among the trials, there was an absolute body weight reduction of −4.1 kg with semaglutide versus −0.95 kg with DPP-4i. The number of patients achieving body weight loss of ≥ 5% and ≥ 10% was significantly higher in semaglutide-treated patients compared to DPP-4i [RR (95% CI) = 3.97 [1.88, 8.36], I^2 = 75%, NNT = 3 and 8.89 (1.52, 52.14), I^2 = 50%, NNT = 7 respectively] (Fig. 4).

Change in fasting plasma glucose and blood pressure outcomes

The change in fasting plasma glucose and blood pressure was investigated in one [15] and 2 [15,18] trials, respectively. In the one trial [15] reporting the fasting plasma glucose there was a reduction of −2.35 mmol/L with semaglutide versus −1.1 mmol/L with DPP-4i. There was a statistically significant reduction in systolic but not diastolic blood pressure with semaglutide compared to DPP-4i [MD (95% CI) = −3.37 mmHg (−4.72, −2.01), I^2 = 0% and −0.87 mmHg (−1.79, 0.04), I^2 = 0% respectively].

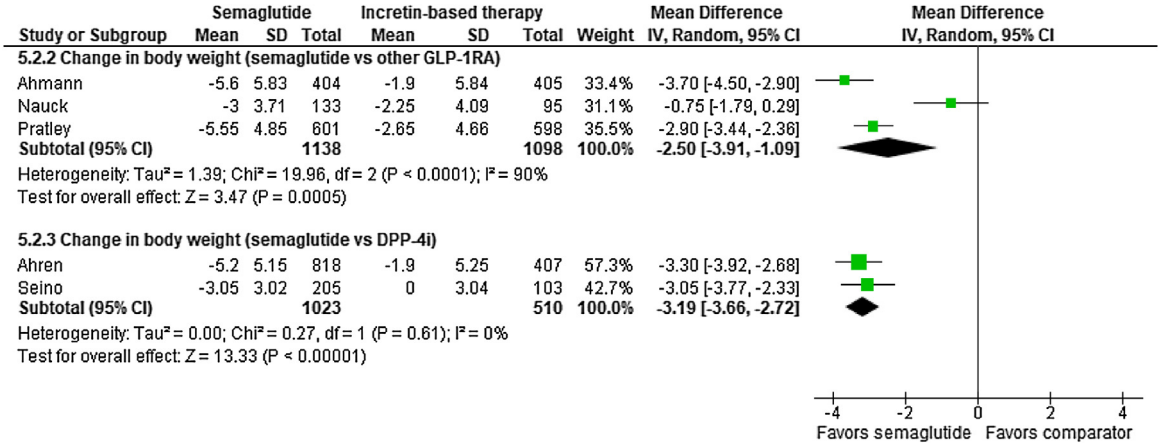

Fig. 3. Change in body weight over time. GLP-1RA: Glucagon-like peptide-1 receptor agonist; DPP-4i: dipeptidyl peptidase-4 inhibitor; SD: standard deviation; CI: confidence interval.

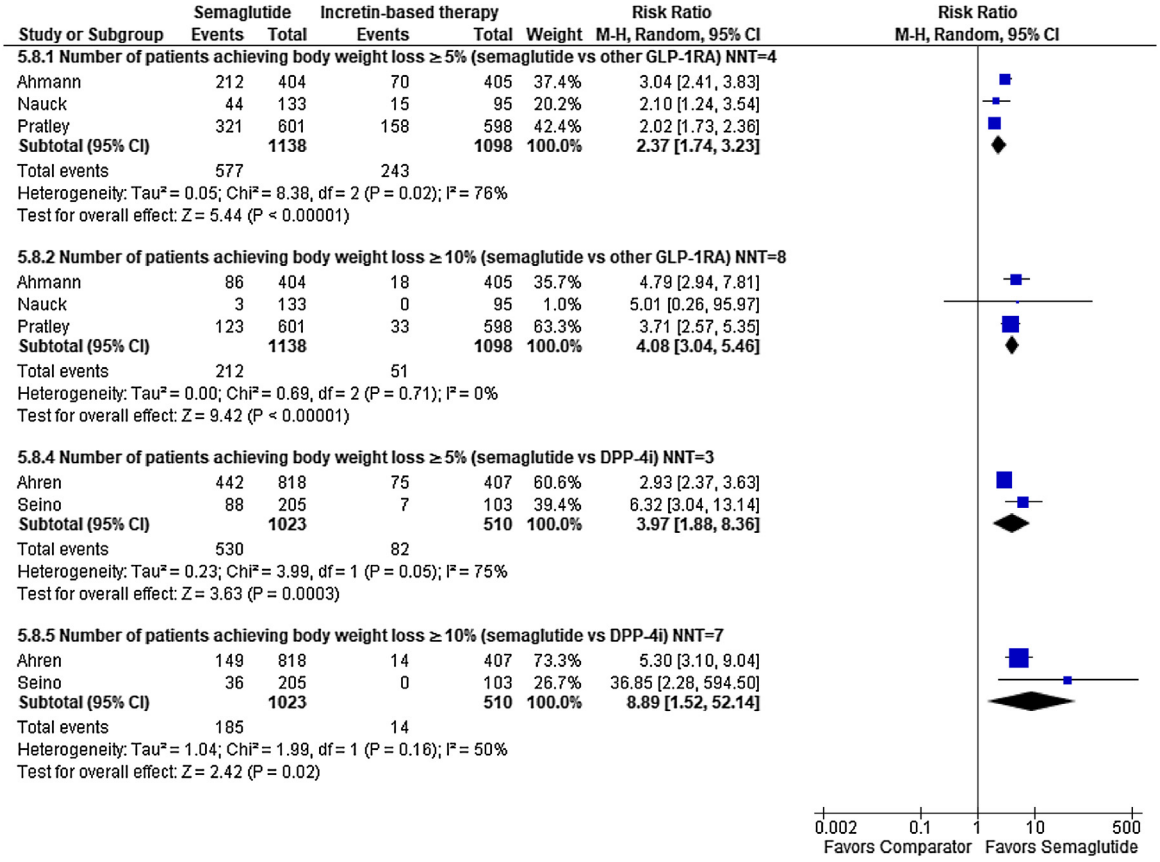

Fig. 4. Number of patients achieving body weight loss goals for once-weekly semaglutide compared to incretin-based therapies. GLP-1RA: glucagon-like peptide-1 receptor agonist; DPP-4i: dipeptidyl peptidase-4 inhibitor; CI: confidence interval; NNT: number needed to treat.

Proportion of patients achieving glycaemic targets

The number of patients achieving a haemoglobin $A_{1c} < 7.0\%$, a haemoglobin $A_{1c} \leq 6.5\%$, and a composite outcome of haemoglobin $A_{1c} < 7.0\%$ without hypoglycaemia or weight gain were all investigated in 2 trials [15,18]. Pooled results for the number of patients achieving a haemoglobin $A_{1c} < 7.0\%$, a haemoglobin $A_{1c} \leq 6.5\%$, and a composite outcome of haemoglobin $A_{1c} < 7.0\%$ with no hypoglycaemia or weight gain favoured semaglutide compared to DPP-4i [RR (95% CI) = 2.22 (1.77, 2.77), I^2 = 58%, NNT = 3, 3.70 (2.14, 6.39), I^2 = 80%, NNT = 3, and 3.17 (1.94, 5.19), I^2 = 80%, NNT = 3 respectively] (figure S1; see supplementary materials associated with this article on line).

Two trials [15,18] reported the number of patients requiring rescue medications with pooled results showing a significantly lower incidence with semaglutide compared to DPP-4i [RR (95% CI) = 0.19 (0.13, 0.28), I^2 = 0%, NNT = 8].

Adverse effects

There was no statistically significant difference in the incidence of adverse events, serious adverse events, or acute pancreatitis. Semaglutide-treated patients had a significantly higher incidence of adverse effects leading to discontinuation of study drug, vomiting, and diarrhoea. Although the incidence of nausea was higher in semaglutide-treated patients, the comparison of results was not statistically significant. Data are presented in figure S3 (see supplementary materials associated with this article on line).

Discussion

The present systematic review and meta-analysis suggests that once-weekly semaglutide produces greater reductions in haemoglobin A_{1c}, weight, and blood pressure when compared to other GLP-1RA or DPP-4i while requiring less need for rescue medications. In addition, the number of patients achieving glycaemic goals (either haemoglobin $A_{1c} < 7.0\%$ or $\leq 6.5\%$) was higher in semaglutide-treated patients compared to either other GLP-1RA or DPP-4i. Furthermore, the number of patients achieving weight loss $\geq 5\%$ and $\geq 10\%$ was higher in semaglutide-treated patients compared to other GLP-1RA or DPP-4i. However, while semaglutide seems more potent compared to other incretin-based therapies, it was associated with an increased risk for nausea, vomiting, diarrhoea and adverse effects leading to discontinuation of the medication. These findings need to be placed in the context of previous literature and available guidelines.

The potent effect of semaglutide on glycaemic control and other endpoints relative to other incretin-based therapies needs to be considered in the context of the association between improved glycaemic control and outcomes. The Diabetes Control and Complications Trial (DCCT) [19,20] in patients with type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) [21,22] in patients with type 2 diabetes concluded that glycaemic control can reduce complications. As a result, most guidelines [2–4] recommended a glycaemic goal (either $< 7.0\%$ or $\leq 6.5\%$) to reduce complications, although goals can be individualized. While early medications focused on glycaemic control, with the introduction of GLP-1RA such as semaglutide, the potential now exists also to lower weight (thus indirectly improving insulin resistance) [3,4,23]. Therefore, while achieving haemoglobin A_{1c} goals is clearly important, in the future this may be insufficient, and selection of specific therapies may be guided by the potential to impact multiple targets that may impact future health outcomes.

The comparison of the effects of semaglutide vs. other incretin-based therapies on weight, blood pressure, and glycaemic control also have the potential to impact cardiovascular risk. In 2009, the FDA required all new diabetes medications to provide cardiovas-

cular safety data [24]. In December 2015, the authors reporting the ELIXA [25] trial concluded that lixisenatide compared to placebo did not alter cardiovascular disease in patients with type 2 diabetes who had a myocardial infarction or unstable angina within 180 days. However, both the LEADER [26] (liraglutide versus placebo), and SUSTAIN-6 [27] (semaglutide versus placebo) trials demonstrated a lower incidence of the 3-point composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes and high cardiovascular risk. In September 2017, the authors of the EXSCEL [28] trial concluded that exenatide compared to placebo did not alter cardiovascular disease in patients with type 2 diabetes with or without previous cardiovascular disease (although results were favouring exenatide). Thus, both LEADER [26] and SUSTAIN-6 [27] showed cardiovascular benefit, EXSCEL [28] had possible cardiovascular benefit (as results favoured a lower incidence of cardiovascular events), and ELIXA [25] showed no difference on cardiovascular outcomes. With respect to DPP-4i, SAVOR-TIMI 53 [29] (investigating saxagliptin) and EXAMINE [30] (investigating alogiptin) showed concern for increased hospitalization for heart failure while TECOS [31] (investigating sitagliptin) did not affect the risk for heart failure. Thus, sitagliptin did not reduce cardiovascular risk, but the data showed increased concern for hospitalization for heart failure in patients taking saxagliptin and alogliptin [32].

Our review suggests that once-weekly semaglutide causes a robust reduction in haemoglobin A_{1c} (about 1.5–1.8%), weight loss (approximately 4.5 kg), a greater proportion of patients achieving glycaemic goals, and fewer rescue medications when compared to either other GLP-1RA or DPP-4i. In addition, and as shown above, semaglutide was not only safe but has been shown to reduce cardiovascular risk [32]. These findings suggest that semaglutide may have advantages over other incretin-based therapies if patients can tolerate the gastrointestinal side effects and are willing to use an injectable medication. However, in patients with history of nausea, vomiting, and diarrhoea, the use of another incretin-based therapy may be favoured over semaglutide.

We identified multiple limitations in our review. There was significant heterogeneity among the included trials in several of the analyses. This is probably due to pooling different GLP-1RA (liraglutide, dulaglutide, and exenatide) together. In addition, this may be secondary to differences is the design of included trials since some compared semaglutide to incretin-based therapy as monotherapy while others as add-on therapy. Furthermore, there was a limited number of included trials in the analysis, and more comparative research is needed. Publication bias cannot be excluded, as testing is unreliable in the presence of a small number of studies [33–35]. Finally, this review did not examine the costs of treatment, and both insurance coverage and out-of-pocket patient costs may have an important influence on determining therapeutic options in a given patient.

Our review identified areas for future research. Large trials comparing semaglutide to SGLT-2i in patients with type 2 diabetes who fail metformin may be needed. In addition, the initial combination of metformin, semaglutide, and either pioglitazone or an SGLT-2i may be investigated. This regimen may have effects on both hyperglycaemia and insulin resistance. Additional research is also focusing on the potential for GLP-1RA and DPP-4i to spare beta-cells in the pancreas, prolonging their survival, and perhaps influencing both native insulin production and the time course of developing complications [36]. Much more research is needed to understand the comparative effects of these medications in this important area of treatment.

In conclusion, while once-weekly semaglutide and other incretin-based therapies can both reduce haemoglobin A_{1c} in patients with type 2 diabetes, semaglutide, in the doses studied, causes greater haemoglobin A_{1c} reduction and weight loss. Whether this potency advantage continues over many years of treatment is unknown, and longer-term trials are needed. However, the potency of semaglutide also results in an increased incidence of nausea, vomiting, and diarrhoea. In patients with no concern for nausea, vomiting, or diarrhoea, once-weekly semaglutide may be preferred over other incretin-based therapies because of the magnitude of reduction in haemoglobin A_{1c} and weight and because of the drug's cardiovascular risk reduction. The extent to which these potential advantages will result in long-term reductions in diabetes complications will await large comparative trials and long-term follow-up studies.

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Author contributions

BMM was involved in the concept, study design, conduct of the study, extracting data, data analysis, and manuscript preparation.

DMC was involved in conduct of the study, extracting data, data analysis, and manuscript preparation.

KS was involved in literature search and manuscript preparation.

RJT and JRP were involved in manuscript preparation and review.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2018.09.002.

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