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Values, preferences and burden of treatment for the initiation of GLP-1 receptor agonists and SGLT-2 inhibitors in adult patients with type 2 diabetes: a systematic review

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ABSTRACT

Objectives Assess values, preferences and burden of treatment that patients with type 2 diabetes consider when initiating glucagon-like peptide-1 receptor agonists (GLP-1 RA) or sodium-glucose cotransporter-2 inhibitors (SGLT-2i) compared with other glucose-lowering options.

Methods Paired reviewers independently included studies reporting quantitative or qualitative methods to assess values, preferences and burden of treatment reported by patients with type 2 diabetes regarding the initiation of GLP-1 RA or SGLT-2i over other alternatives. A systematic search in MEDLINE, Scopus, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials from inception until May 2020 was performed by an experienced librarian. Risk of bias was assessed with a specifically designed tool for values and preferences studies.

Results 17 studies (7296 patients) proved eligible. Studies fulfilling criteria for SGLT-2i were not identified. Five studies (2662 patients) evaluated preferences for GLP-1 RA compared with other glucose-lowering medications. 12 studies (4634 patients) evaluated preferences between, at least, two kinds of GLP-1 RA or their injection devices based on the following attributes: efficacy, dose, application frequency, device characteristics. Among studies comparing GLP-1 RA to other glucose-lowering medications, some preferences were observed for dypeptil peptidase-4 inhibitors compared with once daily liraglutide. Comparing different attributes of GLP-1 RA drugs and devices, cardiovascular risk reduction, glucose lowering potential, once weekly and simple administered regimens were the most preferred.

Conclusions As no evidence for preferences on SGLT-2i was available, only preferences for GLP-1 RA were assessed; however, evidence is still limited for the latter. Studies comparing preferences for GLP1-RA to other glucose-lowering alternatives only included twice daily or once daily injection regimens of GLP-1 RA drugs. According to our findings, once weekly alternatives are widely preferred than the formers. The extent to which patients with type 2 diabetes value reduced adverse cardiovascular and kidney outcomes, weighed benefits against harms and burden of treatment is limited and with very low certainty.

PROSPERO registration number CRD42020159284.

Strengths and limitations of this study

- In the design of the search strategy, we employed a previously published filter for studies evaluating values and preferences.
- Risk of bias assessment of included studies was performed in accordance with a specific tool for assessing values and preferences studies.
- The GRADE approach was employed to evaluate the certainty of our results.
- Results are mostly based on studies graded at high risk of bias.
- We did not found studies evaluating preferences for initiation of sodium-glucose cotransporter-2 inhibitors.

BACKGROUND

The American Diabetes Association and the European Association for the Study of Diabetes have highlighted the importance of providing a patient-centred approach in patients with type 2 diabetes.[1] To support clinicians in providing holistic care, it is important to understand the values and preferences that are considered by patients when choosing a particular treatment option.[2] More specifically, evidence on how patients weigh the balance of benefits, harms and burden of treatment can inform patient-centred practice.

Box 1 Linked resources in the BMJ rapid recommendations cluster

- Reference to this values and preferences systematic review here.
- Reference to guideline paper[37]
- Reference to prognostic systematic review[38]
- Reference to systematic review and network meta-analysis for SGLT-2i and GLP-1 receptor agonists for type 2 diabetes[39]
- Reference to MAGICapp public guideline: to appear at www.magicapp.org
- Reference to MAGIC multiple comparisons evidence summaries and decision aids: www.magicevidence.org/match-it

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are two new drug classes of medications to treat type 2 diabetes that are rapidly changing clinical practice because of demonstrable reductions in cardiovascular and kidney outcomes, without increasing hypoglycaemic.[3–10] These drugs have notable differences in their benefits and harms and how patients are required to administer them. While GLP-1 RA are mostly injected, SGLT-2i are taken orally. The extent to which these treatments impact patients and carers (treatment burden) is often ignored both in the clinical decision-making process and clinical practice guidelines. Moreover, understanding the values and preferences that patients consider in the process of initiating either of both therapies is still inconclusive, and a thorough and integrative analysis of the available evidence could assist both patients and clinicians in the integral management of the disease.[11]

As a result of the aforementioned, we performed this systematic review to inform a clinical practice guideline (BMJ Rapid Recommendation) on the values and preferences that patients consider in the process of initiating GLP-1 RA and SGLT-2i when compared with each other or other drug treatments for type 2 diabetes (box 1). The goal of the BMJ Rapid Recommendations project is to create rapid and trustworthy recommendations regarding medical topics of interest by identifying relevant studies which might change practice and are of interest to readers.[12] These guidelines were also informed by a linked systematic review and network meta-analysis on effectiveness and a systematic review on risk prediction models. Together these reviews confirmed, with overall high certainty evidence, benefits of SGLT-2i and GLP-1 RA while demonstrating that absolute benefits differ across patients with different risks for cardiovascular and renal outcomes. In this context, our systematic review was performed to inform judgements on the values that patients consider when balancing benefits, harms and burdens of treatment for SGLT-2i and GLP-1 RA.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for writing this review.[13]

Eligibility criteria

We included any study design using quantitative or qualitative analysis to report values and preferences held by patients with type 2 diabetes mellitus when initiating GLP-1 RA or SGLT-2i treatments or alternative glucose-lowering therapy. We excluded: (1) cost-effectiveness studies (as preferences are not directly assessed), (2) studies that report data that is not patient-reported (as they do not reflect the overall patient perspective), (3) studies assessing patient satisfaction on a specific treatment rather than preferences for it when compared with other choices, (4) studies that elicited or explored treatment preferences without reporting the process or factors considered in the decision (as results could be biased due to lack of assessment of values driving the preference), (5) studies of patients with a previously stated preference for GLP-1 RA or SGLT-2i (as results can be biased toward one treatment choice due to previous experience with it) and (6) randomised clinical trials that evaluated patient preferences of a given intervention over a previous treatment (due to possible differences in experiencing each treatment).

Search strategy

A systematic search strategy was performed on MEDLINE, Scopus, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials from inception until May 2020. An experienced search specialist designed and conducted the search strategy using a combination of keywords and Medical Subject Headings terms related to values and preferences considered by patients with type 2 diabetes mellitus for initiating GLP-1 RA or SGLT-2i (online supplemental material 1). A previously published filter for studies regarding values and preferences was added to narrow the obtained studies.[14]

Study selection

After excluding duplicated studies, three reviewers independently and in duplicate screened the title and abstract of retrieved records. Potentially eligible reports were then reviewed in full text. Differences were reconciled by either consensus or discussion with a third reviewer. To ensure an adequate inter-rater agreement, the investigators performed calibration exercises until acceptable agreement was achieved with Cohen's kappa coefficient >0.7. Study selection process was performed in the Distiller Systematic Review Software (Evidence Partners DistillerSR, Ottawa, Canada).

Data collection

A web-based extraction form for data collection was used following piloting to ensure adequate inter-rater agreement and later modifications according to reviewers' input. Paired data extractors worked independently to abstract study characteristics, participants' baseline characteristics, methods used to measure values and preferences, and number and percentage of patients who chose to take the medication according to their values and

preferences. Disagreements in the data collection process were resolved by either consensus or arbitration by a third reviewer.

Outcome definition

The term 'values and preferences' was defined according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group definition: 'the process that individuals use in considering the potential benefits, harms, costs, limitations and inconvenience of the management options in relation to one another'.[15] In order to broaden our scope, the following definition was also considered: 'given a choice, the selection of one alternative a priori'.[16] We considered reporting of the following attributes: benefits, harms, costs, limitations or inconvenience related to available treatment options.

Risk of bias assessment

Two independent reviewers working in duplicate adjudicated risks of bias in individual studies based on our main outcome, using a tool proposed by the GRADE working group. It evaluates the following four domains: selection of participants into the study, completeness of data measurement instrument and data analysis.[17] Disagreements were resolved by consensus or arbitration by a third reviewer.

Certainty of evidence assessment

To assess the certainty of evidence for the different drug profile comparisons that were included in this review, we followed the constructs proposed by the GRADE working group which are: study design, risk of bias, inconsistency, indirectness, imprecision and other methodological considerations. An overall certainty of evidence grade was then obtained (very low, low, low-moderate, high).[18]

Data synthesis

Due to the nature of the research question and design of the included studies, our results are reported as a narrative synthesis since a pooled analysis is not feasible.

Patient and public involvement

Patients or members of the public were not involved with the design of this study.

RESULTS

Search strategy and study selection

A total of 11 162 records were retrieved in the search and screened using the title and abstract. (figure 1) From these, 86 full-text articles were assessed for eligibility and 17 studies comprising 7296 patients were included in this review[19–35] (table 1). We did not identify studies reported values and preferences of SGLT-2i and all eligible studies evaluated GLP-1 RA.

Study characteristics

All studies employed quantitative methods to assess outcomes of interest. Five studies comprising a total of 2662 patients evaluated preferences for GLP-1 RA versus other glucose-lowering drugs.[19–23] Furthermore, 12 studies comprising a total of 4634 patients evaluated preferences between, at least, two different GLP-1 RA medications or related injection devices, taking into account clinical attributes and/or device-related ones such as dosing, application frequency or characteristics of the application device.[24–35] Mean age of participants in the included studies ranged between 52.7 and 63.9 years. Most studies reporting duration of diabetes and included patients at least 1 year after diagnosis.

Employed methodologies to elicit values and preferences

The most frequently employed methodology to elicit patients' preferences was discrete choice experiment (DCE) (eight studies) where utilities, relative importance (RI) or ORs where used as units of measurement to quantify values and preferences.[21 23 25–28 34 35] The next most frequent methodology was the time-trade-off (TTO) approach in four studies.[24 29 31 33] Utilities, health state disutilities and RI were the units of measurement in these studies. Other methodologies employed were willingness to pay,[21] online surveys,[19] questionnaires,[30] crossover trials[22 32] and case-note surveys[20] (table 1).

Risk of bias and certainty of evidence assessment

Overall, 12 studies were found at high-risk of bias due to the usage of non-validated instruments for eliciting preferences and invalid representation of efficacy and safety of the drug profiles.[19–22 24–28 30 33 34] Only five studies were found at low risk of bias, these studies used a previously validated survey to measure preferences between different GLP-1 RA on both injection naïve and experienced patients[23 29 31 32 35] (figure 2).

We evaluated the certainty of evidence regarding the following drug profile comparisons: GLP-1 RA versus dypeptil peptidase-4 inhibitors (DPP-4i), insulin glargine and other glucose-lowering therapies, liraglutide versus exenatide and dulaglutide, dulaglutide versus semaglutide and studies evaluating attributes of GLP-1RA injection devices. The certainty of evidence was judged to be very low in all cases due to concerns regarding study design, risk of bias and imprecision in all cases. In addition, concerns regarding inconsistency and indirectness were identified in most of the evidence for the different drug profile comparisons (table 2).

Preferences for GLP-1 RA versus other types of glucose-lowering medications

Overall, five studies evaluated preferences for a GLP-1 RA versus other treatments of type 2 diabetes, such as insulin glargine,[23] sitagliptin,[19 20] vildagliptin,[22] rosiglitazone and glimepiride.[21] From these, one study was found to be at low risk of bias.[23] Two studies were performed on the injection-naïve population,[19 23] one on injection-experienced[22] and

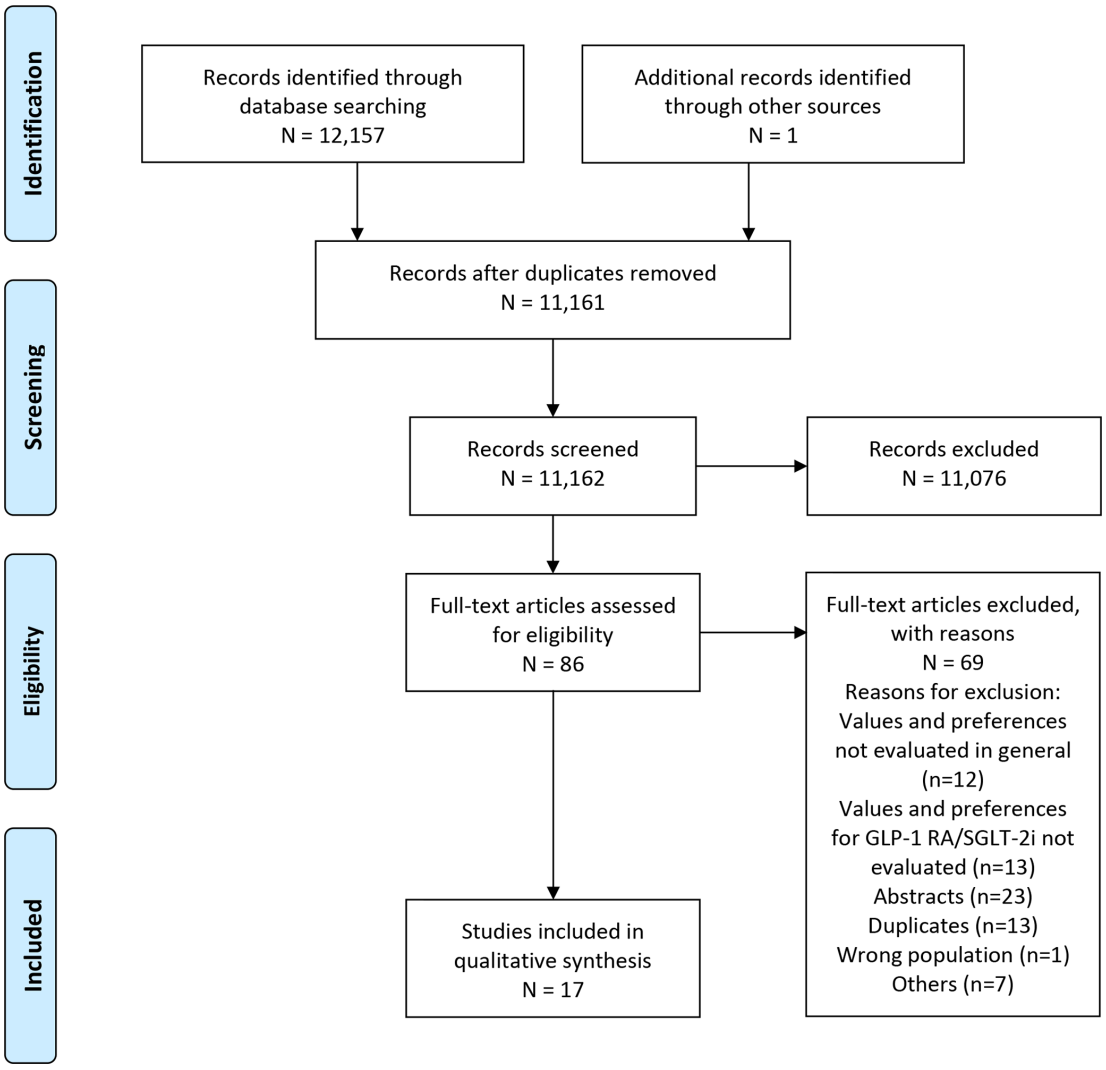

Figure 1 Study selection flow diagram. GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

the remaining two on a mixed population.[20 21] Among the studies which presented drug profiles as part of their methodology, all studies described efficacy (defined as a change in glycosilated hemoglobin [HbA1c]), proportion of side effects, weight change, dosing frequency and delivery system. Four studies described hypoglycaemic risk,[19–21 23] and three included blood pressure change in the studied drugs profile.[19–21] From the five studies, two described the all above-mentioned attributes on their drug profiles[20 21] (table 3). Shown below is a subdivision of the drug comparisons that were assessed in these studies.

Glp-1 RA compared with DPP-4i

Three studies evaluated preferences between orally administered DPP-4i (sitagliptin and vildagliptin) and GLP-1 RA (liraglutide).[19 20 22] Preference for DPP-4i in both injection naïve and experienced patients was observed in two out of three studies.[19 22] Attributes ranked as the most important for choosing a DPP-4i over GLP-1 RA were its oral administration route and lesser frequency of side effects. For patients choosing GLP-1 RA, the most important attributes were blood sugar/HbA1c lowering effect and weight loss effect (table 4).

Insulin glargine compared with GLP-1 RA

Two studies evaluated preferences between liraglutide or dulaglutide and insulin glargine, both of them showed preference for GLP-1 RA.[21 23] The first study found that 75% of participants preferred a dulaglutide profile when compared with insulin glargine where among patients who preferred the former, the most important reasons were type of delivery system and dosing frequency, with RI (proportion of the variance in the medication decision accounted by each attribute) of 24.5% and 19.2% for each attribute, respectively. Moreover, in patients who preferred insulin, most important reasons for choice were lesser frequency of gastrointestinal adverse effects (RI: 45.3%) and pancreatitis (RI: 26.5%).[23] (table 4)

In the second study (willingness-to pay-analysis), participants were prepared to pay an extra €3.36/day for liraglutide over insulin glargine where weight change was the most important attribute leading to liraglutide preference

Table 1 Demographic and study characteristics

Author, year	Country	N	Injection experience	Age (years)	Female (%)	Race (%)	BMI	HbA1c	Years of diagnosis	Assessment approach	Drugs evaluated
Boye *et al*[24] 2019	Italy	216	M	60.5 (9.9)*	42.1	White: 98.60 Other: 0.9	ND	ND	ND	TTO	Dulaglutide QW Semaglutide QW
Brooks *et al*[25] 2019	Japan	161	N	55 (48–63)‡	16	ND	25.9 (23.9-28.9)‡	8.3 (7.4-9.1)‡	<1 year: 1% 1–5 years: 24% 5–10 years: 38%>10 yrs: 37%	DCE	Dulaglutide QW Semaglutide QW
Dibonaventura *et al*[19] 2010	International	1340	N	55.3 (12.1)*	46.8	White: 90.5 Other:9.5	ND	ND	6.2 (5.9)*	Online survey	Sitagliptin Liraglutide QD
Evans *et al*[20] 2013	UK	188	M	63.9 (5.9)*	42.8	ND	36.7 (5.9)*	8.9 (1.1)*	8.5 (3.3)*	Case-note survey	Sitagliptin Liraglutide QD
Gelhorn *et al*[27] 2015	UK	243	N	60.5 (10.9)*	23.9	White: 72 Asian: 15.2	29.8 (5.4)*	<7%: 28.8% 7.1%–8%: 25.5% 8.1%–9%:11.1%>9%: 6.6% NR: 28%	<1 year: 5.8% 1–5 years: 35.8% 5–10 years: 34.6%>10 yrs: 23.9%	DCE	Liraglutide QD Dulaglutide QW
Gelhorn *et al*[28] 2016	Japan	182	N	58.9 (10)*	35.7	ND	26.1 (5)*	<7%: 53.3% 7.1%–8%: 31.3% 8.1–9: 8.8%>9 %: 6.6%	<1 year: 3.9%<1–5 years: 32.4% 5–10 years: 29.1%>10 yrs: 34.6%	DCE	Dulaglutide QW Liraglutide QD
Hauber *et al*[26] 2015	USA	643	M	52.7 (15)*	48.3	ND	ND	<7%: 34.5% 7%–9%: 44.1%>9%: 12.8%	ND	DCE	GLP-1 RA in general
Jendle *et al*[21] 2012	Sweden	840	M	ND	ND	ND	ND	ND	ND	WTP via DCE	Liraglutide QD Rosiglitazone Glimepiride Insulin glargine Exenatide Twice daily
Lüdemann *et al*[22] 2015	Germany	62	E	60.3 (11.1)*	53.2	White: 98.4 Others: 1.6	31.2 (3.5)*	7.4 (0.5)*	7.5 (6.3)*	Cross-over trial	Vildagliptin Liraglutide QD
Matza *et al*[29] 2017	UK	209	M	60.4 (8.9)*	42.6	White: 86.6 Other: 14.4	ND	ND	ND	TTO	QW GLP-1 RA injection devices
Matza *et al*[31] 2018a	Italy	238	M	60.2 (9.3)*	41.2	White:100	ND	ND	ND	TTO	QW GLP-1 RA injection devices
Matza *et al*[30] 2018b	USA	404/58§	E	60.7 (11.4)*	54	White: 78 African/ American: 14.6	ND	ND	13.7 (9.0)*	Questionnaire	Liraglutide QD Dulaglutide QW
Matza *et al*[32] 2020	USA	310	N	60 (10.8)*	48.4	White: 50 Black/African american: 33.9	ND	7.29 (1.4)*	8.06 (6.7)*	Cross-over trial	Dulaglutide QW Semaglutide QW
Polster*et al*[33] 2010	USA	382	M	52.7 (8.8)*	52	White: 89.2	ND	7.3 (no SD)	7.6 (5.3)*	TTO	Liraglutide QD Exenatide Twice daily
Poon *et al*[23] 2018	UK	232	N	61.8 (10.8)*	25.9	White: 78 Asian: 13.8	29.8 (6.1)*	<7%: 30.6% 7.1%–8%: 22% 8.1%–9%: 12.5%>9% : 4.7% NR : 30.2%	< 1 year: 7.3%, 1–5 years: 36.6% 5–10 years:28.9%>10 years: 27.2%	DCE	Dulaglutide QW Insulin glargine
Qin *et al*[34] 2017a	Germany and UK	510	E	57 (11)*	48.6	White: 93.5 Asian/ Asian British: 3.3	34.2 (7.5)*	7.4 (1.9)*	7.2 (5.9)*	DCE	Liraglutide QD Exenatide QW
Qin *et al*[35] 2017b	International	1482	N	56 (11.4)*	32	White: 51.60 Asian: 40.7	ND	7.4 (2.3)*	7 (0.5–61.9)†	DCE	Liraglutide QD Exenatide QW

*Mean/SD.
†Range.
‡Median/IQR.
§Demographic characteristics shown for full sample; only 58 participants were included in the preferences analysis.
BID, twice daily administration; BMI, body mass index; DCE, discrete choice experiment; E, Injection experienced; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, Glycosilated hemoglobin; M, mixed; N, injection naïve; ND, no data; QD, once daily administration; QW, once weekly administration; TTO, time trade-off; WTP, willingness-to-pay.

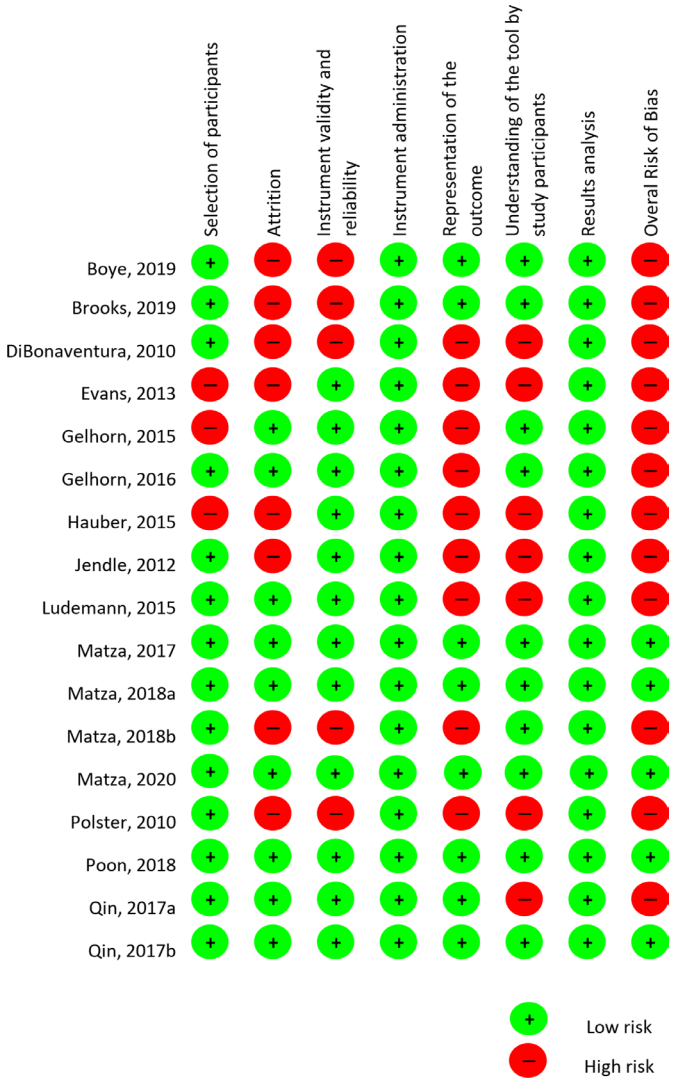

Figure 2 Risk of bias assessment.

(€2.35/day). In this study, liraglutide was presented as the best profile among all subdomains.[21] The risk for hypoglycaemic was not an important attribute for patients' preference in both studies.

Other glucose-lowering treatments compared with GLP1-RA

One study evaluated the preference for liraglutide and other oral treatments, including rosiglitazone and glimepiride. Participants were prepared to pay an extra €2.64 and €1.94/day for liraglutide over rosiglitazone and glimepiride, respectively. The main component for preference of liraglutide over both drugs was its weight loss effect. The only attribute which leads participants to pay more for rosiglitazone and glimepiride over liraglutide was the oral administration route.[21]

Different GLP-1 RA medications

Twelve studies evaluating preferences between different GLP-1 RA medications were included. Attributes that were included in these were related to dosing frequency and device type, but some also included efficacy, safety, and price as attributes. Drug profiles examined in these studies were extended release (weekly) and twice daily exenatide, once daily liraglutide and once weekly semaglutide and dulaglutide. Six of them were DCEs[25–28 34 35] and four were TTOs.[24 29 31 33] The remaining two were a questionnaire[30] and a cross-over trial.[32]

Liraglutide versus exenatide

Four studies evaluated this comparison.[21 33–35] Overall, participants preferred once daily liraglutide compared with twice daily exenatide. However, they preferred once weekly exenatide compared with once daily liraglutide.

One survey found that 96% of included participants preferred once daily liraglutide over twice daily exenatide, where liraglutide also was presented as the drug having better efficacy, less rates of nausea and hypoglycaemic.[33] Two other surveys (one on injection naïve and the other on injection experienced users) reported that when assuming equal efficacy within both profiles (1.2 decreases in HbA1c), 78.6% of injection experienced users preferred once weekly exenatide compared with a profile matching liraglutide.[34] Among injection-naïve participants, 77% preferred the profile matching exenatide.[35] In both studies, attributes determining preference were better efficacy, lesser frequency of side effects and weekly dosing frequency. Moreover, even when efficacy was assumed to be better for liraglutide (1.2 vs 0.8 decrease in HbA1c), patients still preferred a weekly exenatide matching profile. (table 4) A willingness-to-pay analysis demonstrated that participants were willing to pay an extra €0.81/day for once daily liraglutide over twice daily exenatide where once daily administration (lesser dosing frequency) was the main component driving the preference (€1.04/day).[21]

Liraglutide versus dulaglutide

Three studies evaluated this comparison, one of them only compared device characteristics.[27 28 30] A preference for dulaglutide was observed in all three.

In two studies, one in Japan and the other in the UK most of the population preferred the profile representing dulaglutide (94.5% and 83.1% for Japanese and UK population, respectively). Its profile consisted of a once weekly injection with a single-use prefilled pen compared with a once daily application with a multiuse pen that required dose titration for liraglutide. Slightly greater efficacy (reported difference in proportions of patients reaching treatment goals across groups was <3%), greater weight loss effect, and lesser frequency of nausea and hypoglycaemic were also attributes included on the dulaglutide profile. In both samples, the most important attributes for choosing a medication were dosing frequency (RI: 41.6%, 44.1% for the UK and Japanese population, respectively) and type of delivery system (RI: 35.5%, 26.3% for the UK and Japanese population, respectively)[27 28] (table 4). In the third one, a survey comparing medication devices was applied on patients experienced to both treatments and revealed a

Table 2 GRADE assessment of the certainty of evidence

Certainty assessment									
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Impact**	**Certainty**	**Importance**
GLP-1 RA (liraglutide) compared with DPP-4i (sitagliptin, vildagliptin)									
3	Observational studies*	Very serious†	Serious‡	Very serious§	Serious¶	None	Higher preference for DPP-4i over liraglutide was observed in two out of three studies.	⊕◯◯◯ VERY LOW	
GLP-1 RA (liraglutide, dulaglutide) compared with Insulin Glargine									
2	Observational studies	Serious**	Not serious	Very serious§	Serious¶	None	Higher preference for GLP-1 RA was observed in both studies.	⊕◯◯◯ VERY LOW	
Other glucose-lowering treatments compared with GLP-1 RA									
1	Observational studies	Very serious††	Not serious‡‡	Very serious§	Serious¶	None	GLP-1 RA were preferred over other study drugs. (rosiglitazone, glimepiride)	⊕◯◯◯ VERY LOW	
Liraglutide vs exenatide									
4	Observational studies	Very serious§§	Not serious	Very serious§,¶¶	Serious¶	None	Liraglutide was preferred over twice-daily exenatide; however, once weekly exenatide was preferred over liraglutide.	⊕◯◯◯ VERY LOW	
Liraglutide versus dulaglutide									
3	observational studies	very serious***	not serious	very serious§,†††	serious¶	none	In all three studies, a preference for dulaglutide over liraglutide was shown.	⊕◯◯◯ VERY LOW	
Dulaglutide versus semaglutide									
3	Observational studies	Very serious‡‡‡	Very serious§§§	Very serious§,¶¶¶	Serious¶	None	A strong preference for dulaglutide was observed in two studies; however, these studies only presented injection attributes to participants. In the other study, a strong preference for semaglutide was observed where not only injection attributes but also clinical attributes of each drug profile were presented.	⊕◯◯◯ VERY LOW	
Studies evaluating attributes of GLP-1 RA injection devices									
3	Observational studies	Serious****	Not serious	Not serious	Serious¶	None	As administration requirements for GLP-1 RA injection devices increase, preferences decrease. Patients strongly prefer weekly over daily injection devices.	⊕◯◯◯ VERY LOW	

Continued

Table 2 Continued

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty	Importance
Certainty assessment									

*One study presented a cross-overdesign.
†Two studies presented a high risk of bias in the attrition item. One of the studies presented a high risk of bias in the item of instrument validity and reliability (1340 participants) which was the biggest one. The three studies presented a high risk of bias in two out of six items assessed (representation of the outcome and understanding of the tool by study participants). Therefore, we judged the trials to have very serious methodological limitations.
‡Two of the studies included patients naïve to injectable medications and demonstrated a preference for DPP-4i over liraglutide. In another study, more participants preferred liraglutide over vildagliptin and included patients naive to injectable medications. The harms and benefits presented for patient'sdecisions differed between studies (liraglutide weight reduction effect was omitted in the study where patients preferred sitagliptin). None of the included studies reported CIs of the point estimate neither statistical hypothesis tests to further assess inconsistency. We judged the evidence to have serious inconsistency.
§Drug profile did not fully represent the best available evidence now.
¶Although the evaluated sample size was optimal, the CI of the point of estimate was not reported. We judge serious imprecision in the evidence.
**One of two studies was judged as overall low risk of bias (232 patients). The other study was at high risk in the attrition domain, representation of outcomes and understanding of the tool by study participants. (840 patients). We judge risk of bias to be serious for this outcome.
††The study was classified overall high risk of bias due to concerns regarding the attrition rate, representation of the outcome and understanding of the tool by study participants.
‡‡Since no further evidence is presented, it is not feasible to classify inconsistency.
§§One out of four studies presented low risk of bias in all the evaluated items (1482 patients). The other three studies (510, 382, 840 patients) presented a high risk of bias in the items of attrition, representation of the outcome and understanding the tool by study participants. We judge the evidence to have serious methodological limitations.
¶¶In all studies, medication profiles were presented with varying benefits and harms which were not based on the best available evidence now.
***Two of the three studies were at high risk of bias due to concerns regarding selection of participants and evaluation of the outcomes.
†††Serious concerns on indirectness are present due to heterogeneity among populations, where two of them were injection naive and another one was injection experienced. Furthermore, two studies presented drug profiles with only clinical variables and the other presented drug profiles with only device characteristics.
‡‡‡Two studies were classified as high risk of bias due to concerns regarding attrition rate and instrument validity and reliability for evaluating patient preferences.
§§§The direction of patient preferences tended to vary across studies wherein two of them, strong preferences for semaglutide were observed. However, in the other study, strong preference for dulaglutide was reported.
¶¶¶Two studies presented only device attributes as part of the treatment profile. However, the third study also added clinical attributes to the drug profile. This difference could have altered the direction of results across studies.
****Two of the three studies were classified as overall low risk of bias and the other one as high risk of bias due to concerns regarding selection of participants, attrition rate and representation of the outcome and understanding of the tool by study participants.
DPP-4i, dypeptil peptidase-4 inhibitors; GLP-1 RA, Glucagon-like peptide-1 receptor agonists.

preference for the dulaglutide device (table 4). In this case, participants' preference was chosen based on their own experience.[30]

Dulaglutide versus semaglutide

Three studies evaluated this comparison where two of them evaluated device attributes[24 32] and the other added clinical attributes to the drug profiles.[25] Overall, among devices, participants preferred the one accompanying dulaglutide. When clinical attributes when considered in the drug profile, participants preferred semaglutide.

In a survey comparing device characteristics by providing hypothetical health states with each one, 88% of participants preferred the health state with the dulaglutide device over the semaglutide device, as the first one was considered 'less complicated' and 'quicker'. Considering that the study exclusively analysed preferences regarding injection devices, no information regarding efficacy, side effects and price was assessed on either of the health states, assuming that they were all equal regarding these characteristics. Dulaglutide consisted of a one-dose injection with no needle handling and no dose adjustment. Patients who preferred semaglutide profile considered that a one-dose injection would make them 'buy too many pens'.[24] A cross-over trial comparing both injection devices found that 84.2% of participants preferred the dulaglutide profile, mainly due to its 'ease of use'.[32]

In contrast, one study comparing both drugs using five attributes (method of administration, HbA1c change, reduction in cardiovascular (CV) risk, weight change and common side effects) reported that 80% of participants preferred the semaglutide profile, which was presented as the more efficient (1.9% vs 1.4% reduction in HbA1c), with greater weight loss effect, greater rate of nausea, 26% CV risk reduction (vs no risk reduction for dulaglutide), and with a multidose prefilled pen with dose adjustment (vs a single-dose prefilled pen with no dose adjustment representing dulaglutide). CV risk reduction followed by HBA1c reduction and rate of side effects were the most important attributes leading to their choice based on coefficient utilities[25] (table 4).

Studies evaluating attributes of GLP-1 RA injection devices and administration regimes

Three studies fell into this category, none of which evaluated a specific drug profile; conversely, these studies evaluated patients' preferences for injection devices based on different device attributes (table 4). One found that among a mixed population of injection naïve and injection experienced patients, changing injection frequency from daily to weekly was the most important attribute for choice of treatment.[26] The other two found consistent main findings; each administration requirement (needle handling, reconstitution and waiting) was associated with higher disutilities when compared with an oral health state.[29 31]

Table 3 Drug evidence profiles presented to participants in studies comparing GLP-1 RA to other glucose-lowering therapies

Author, year	Preferred therapy	Change in HbA1c	Adverse Effects (%)	Weight change (kg)	Hypoglycaemic (%)	Blood pressure changes (mmHg)	Dosing Frequency	Type of delivery system	Population experience
Dibonaventura *et al*[19] 2010	SG	SG: −1.4% LG: −2.4%	LG: Nausea 11%–19%, Vomit 5%–7%, Diarrhoea 8%–15% SG: No adverse effects	SG: 0 LG: −3.5	SG: Low risk LG: Low risk	SG: 0 LG: −2 to −3	SG: QD LG. QD	SG: Oral LG: Injected	Injection naive
Evans *et al*[20] 2013	LG	LG: −1 to −1.5% SG: −0.5 to 1%	LG: 10%–15% feelings of sickness, 8%–15% diarrhea SG: No side effects	LG: −3.4 SG: No effect	LG: Low risk SG: Low risk	LG: Small reduction SG: No effect	LG: QD SG: QD	LG: Injected SG: Oral	Mixed
Jendle *et al*[21] 2012*	LG	LG: −1.1% RGL: −0.3% GLM: −0.7% INS: −0.9% EXN: −0.8%	LG: 4.1% RGL: 0.2% GLM: 0.8% INS: 0.1% EXN: 12.2%	LG: −1.5 RGL:+1.9 GLM:+1.04 INS:+1.5 EXN: −2.2	LG: 0.2 RGL: 0.1 GLM: 1.3 INS: 1.4 EXN: 2.6	LD: −2.5 RGL: −0.3 GLM:+0.41 INS:+1.6 EXN: −3.8	LD: QD EX: Twice daily GL: OD RS: OD INS:MD	LD: Injected RGL: Oral GLM: Oral EXN: Injected INS: Injected	Mixed
Lüdemann *et al*[22] 2015†	VG	VG: −0.3% LG: −0.5%	VG: 15% LG: 37.5%	VG: −0.1 LG: −2.2	ND	ND	VG: QD LG: QD	VG: Oral LG: Injected	Injection experienced
Poon *et al*[23] 2018	DG	DG: 53.2% achieve HbA1c goal INS: 30.9% achieve HbA1c goal.	DG: Nausea 15.4% Pancreatitis 0.7% in first 18 months INS: Nausea 1.5%, Pancreatitis 0%	DG: −1.87 INS:+1.44	DG: 5 events in 1 year INS: 8 events in 1 year	ND	DG: QW INS: MD	DG: Single prefilled pen ready. INS: Multiple dose prefilled pens, titration required.	Injection naive

*Only listed nausea as an adverse effect, blood pressure change assessed as systolic blood pressure change.
†Attribute values are results from the cross-over trial.
BID, twice daily; DG, dulaglutide; EXN, exenatide; GLM, glimepiride; GLP-1 RA, glucagon-like peptide-1 receptor agonists; INS, insulin; LG, liraglutide; MD, multiple daily; ND, no data; OD, once daily; QD, once daily; QW, once weekly; RGL, rosiglitazone; SG, sitagliptin; VG, vildagliptin.

Table 4 Drug preferences and attributes leading to preference among included studies

Author, year	Drug preference (as measured)	Unit of measurement for drug attribute assessment	Scale	Attributes (attribute weight)
Boye *et al*[24] 2019	Dulaglutide: 88.4% Semaglutide: 11.6%	Utility (95% CI)	0–1 0=death 1=full health	Oral : 0.9 (0.89–0.91) oral+dulaglutide device : 0.89 (0.88–0.9) oral+semaglutide device : 0.88 (0.87–0.89)
Brooks *et al*[25] 2019	Dulaglutide: 20% Semaglutide: 80%	Utility coefficient (SE)	0No Limit	Cardiovascular disease reduction: 1.08 (0.05) HbA1c reduction: 0.60 (0.07) avoidance of nausea: 0.55 (0.08) Method of administration: 0.05 (0.05)
Dibonaventura *et al*[19] 2010	Sitagliptin: 84.4% Liraglutide: 15.6%	Ranked importance (SD)	0No limit	Effectiveness of medication (0.6% difference in HBA1c): 4.49 (0.84) Experience of prescribing Physician with medication: 4.11 (0.96) side effects: 3.92 (1.17) method of administration (oral vs injectable): 3.86 (1.23) Out-of-pocket costs of medication: 3.42 (1.43)
Evans *et al*[20] 2013	Liraglutide: 62.5% Sitagliptin: 37.5%	Most important attribute according to preferred drug	0%–100%	Liraglutide: weight loss, 61% sitagliptin: oral administration, 66%
Gelhorn *et al*[27] 2015	Dulaglutide: 83.1% Liraglutide: 16.9%	Relative importance	0%–100%	Dosing frequency: 41.6% type of delivery system: 35.5% frequency of nausea: 10.4% wt change: 5.9% HbA1c change: 3.6% low blood sugar events (hypoglycaemic): 3.0%
Gelhorn *et al*[28] 2016	Dulaglutide: 94.5% Liraglutide: 5.5%	Relative importance	0%–100%	Dosing frequency: 44.1%, type of delivery system: 26.3% frequency of nausea: 15.1% frequency of hypoglycaemic: 7.4% wt change: 6.2% HbA1c change: 1.0%
Hauber *et al*[26] 2015	NA	Relative importance	0No limit	Weekly injection frequency (vs daily) shorter and thinner needle (vs longer and thicker) eliminating injection site reactions
Jendle *et al*[21] 2012	Overall participants were willing to pay more for liraglutide compared with all other drugs. (twice daily EXN, RGL, GLI, INS)	Prepared to pay an extra Î/ day for liraglutide	0No limit	Change in body weight RGL: 2.7, INS: 2.35, GLI: 1.87, EXN: −0.46 method of administration EXN:1.04, INS: 0.0, RGL: −1.3, GLI: −0.82 change in HBA1c RGL: 0.95, GLI: 0.43, EXN: 0.27, INS: 0.04 change in systolic BP: INS: 0.65, GLI: 0.46, RGL: 0.34, EXN: −0.2 nausea EXN: 0.08, GLI: −0.03, RGL: −0.04, INS: −0.04 hypoglycaemic rate: EXN: 0.07, GLI: 0.03, INS: 0.03, RGL: 0.0
Lüdemann *et al* [22] 2015	Vildagliptin: 51.7% Liraglutide: 48.3%	Patient preference according to drug choice	0% to 100% (Important and Very important.)§	How you take the medication: VG: 71%, LG: 44.8% Side effects (nausea, vomiting and diarrhoea): VG: 67.8%, LG: 41.4% blood sugar lowering: VG: 77.4%, LG: 75.9% wt loss and blood pressure decrease: VG: 64.6%, LG: 65.5%
Matza *et al*[29] 2017	NA	Health-State utility*	0–1 0=death 1=full health	A: 0.88; B: 0.85; C: 0.86; D: 0.86; E: 0.87; F: 0.87; G: 0.87
Matza *et al*[31] 2018a	NA	Health-State utility*	0–1 0=death 1=full health	A: 0.9; B: 0.86; C: 0.87; D: 0.87; E: 0.88; F: 0.88; G: 0.8
Matza *et al*[30] 2018b	Dulaglutide: 70.7%‡ Liraglutide: 22.4%‡	DID-PQ scores	Prefer/strongly prefer drug percentage 0% to 100%	Ease of fitting the injection: 72.1% DG ease preparing injection: 67.2% DG time to prepare: 67.2% DG confidence of using correctly: 65.5% DG ease of bringing injection device: 63.8% DG confidence injection: 60.3% DG needle size: 60.4% DG
Matza *et al*[32] 2020	Dulaglutide: 84.2% Semaglutide: 12.3%	Patient preference	0%–100%	Dulaglutide preference: device's ease of use 92.7%, reasons related to the needle 33.3%, ease of learning to use the device 17.6% liraglutide preference: device can be used multiple times 39.5%, ease of use 26.3%, less generation of plastic waste 26.3%
Polster *et al*[33] 2010	Liraglutide: 0.97 (CI 0.96 to 0.98) Exenatide Twice daily: 0.94 (CI 0.92 to 0.955)	Relative Importance† (Health Utility)	0%–100%	Efficacy: 39% (0.016) nausea: 30% (0.011) hypoglycaemic: 17% (0.006) dosing schedule: 14% (0.005)
Poon *et al*[23] 2018	Dulaglutide: 75% Insulin glargine: 25%	Relative Importance	0%–100%	Delivery system: 19.8% GI effects: 18.2% dosing frequency: 17.7% wt change: 15.6% HbA1change: 14.2% frequency of pancreatitis: 12.3% frequency of hypoglycaemic: 2.2%
Qin *et al*[34] 2017a	Exenatide QW: 78.60% Liraglutide: 21.40%	OR (95% CI)	0No limit	Less side effects: 2.66 (2.51–2.82) Efficacy (<1.5 pts HbA1c): 2.57 (2.36–2.804) Once weekly dosing frequency: 2.25 (2.13–2.38) multiuse pen: 1.709 (1.55–1.88) needle size, device size and titration were not significant in patient's preference
Qin *et al*[35] 2017b	Liraglutide: 21.40% Exenatide QW: 78.60%	OR (95% CI)	0No limit	Less side effects: 2.66 efficacy (<1.5 Hba1c): 2.57 weekly dosing frequency: 2.25 multiuse pen: 1.709

Continued

Table 4 Continued

Author, year	Drug preference (as measured)	Unit of measurement for drug attribute assessment	Scale	Attributes (attribute weight)

*VG: preferred vildagliptin; LG: preferre dliraglutide

†Definition of relative importance relativeimportance is calculated by dividing the difference in the average TTO utilityfor the best and worst levels for each attribute across all possible scenarios and across all respondents by the sum of those mean differences

‡Preference for overall ease of use
§Health state A: oral treatment only; health state B: reconstitution, waiting, needle handling; health state C: reconstitution,waiting; health state D: reconstitution, needle handling; health state E: reconstitution; health state F: needle handling; health state G: no inconveniences
¶
**Risk of pancreatitis considered in study profile for GLP-1 RA, we advise to take results with caution
BID, twice daily; DID-EQ, Diabetes Injection Device Experience Questionnaire; EXN, exenatide; GLI, glimepiride; INS, insulin glargine; QW, once weekly; RGL, rosiglitazone.

DISCUSSION

In this systematic review, we found no direct evidence to inform judgements about how patients with type 2 diabetes considering SGLT-2i and GLP-1 RA value established benefits on cardiovascular and kidney outcomes, weighed against harms and burdens of treatments. Taking this into account, several evidence evaluating preferences for GLP-1 RA was found where patients consistently showed resistance to injectables and complicated devices, preferring oral medications or weekly injected devices, which reflects on potential burdens of treatment likely to impact their treatment choices. However, these results demonstrate a major shortcoming of our systematic review; none of the studies presented patients with best current evidence on benefits and harms of these drugs, making any inferences about values and preferences of highly limited value as analysing the state of evidence on a certain medication at a specific point in time does not necessarily reflect the state of the same in the future with respect to it, therefore, treatment profiles could vary depending on the year in which the preference study was performed. Furthermore, studies defined efficacy of different drugs based on their glucose-lowering potential and for almost all did not assess patient-important microvascular or macrovascular outcomes.[36]

The evidence on burden of treatment serves as a reminder to guideline panels often restricting judgements of values and preferences to benefits and harms and clinicians leaving this factor out of the equation in assisting patients in making well-informed treatment choices.[2] Indeed, the BMJ Rapid Recommendations put great emphasis on this evidence, directly impacting recommendations favouring SGLT-2i over GLP-1 RA.

This review has multiple strengths. We used of a previously validated search strategy to perform systematic reviews and meta-analysis of patients' preferences studies. Additionally, we followed high methodological standards in conducting the review and evaluated each study's quality with a specialised tool for patients' preference studies and performed a further comprehensive analysis of the certainty of evidence by following the GRADE working group constructs. Finally, we considered the consistency of the evidence presented in the included studies to elicit patients' preferences with the current best available evidence when drawing conclusions. This approach emphasised issues about the applicability of findings of this review to the BMJ Rapid Recommendations (Box 1).

We acknowledge there are several important limitations in our study. Our results are based mostly on studies graded at high risk of bias due to important methodological concerns. As a result, when assessing the certainty of evidence, all preferences in each drug comparison are graded at a very low certainty. More importantly, most of the included studies drew conclusions that could be influenced by conflict of interest. Moreover, there was no information regarding other important second-line treatments for diabetes such as SGLT-2i, therefore, we could

not directly establish preferences between SGLT-2i and GLP-1 RA which would be very important due to both drugs' increasing popularity among patients and clinicians. Some explanations on the absence of studies evaluating preferences for and among SGLT-2i could be that they are relatively new when compared with GLP-1 RA (the first SGLT-2i to be approved by the Food and Drug Administration was canagliflozin in 2013, compared with exenatide in 2005) and that as GLP-1 RA tend to have similar efficacy profiles, industry-based studies could have been carried out to assess preferences between treatments based on other attributes.

Overall, there is still not enough evidence to demonstrate a patient preference tendency between GLP-1 RA and SGLT-2i. Clinicians should individualise the use of these medications to each patient individual context, taking into consideration the best current evidence on efficacy and side effects all the while considering treatment burden, patient preferences, among other factors in the process of shared decision making. Furthermore, when opting to use GLP-1 RA, it would be optimal to consider weekly versions due to higher preferences observed for these in the present study.

Further studies are needed to elicit patients' values and preferences among wider spectrum of oral and injectable diabetes treatments. There is a specific and urgent need to assess patient's values and preferences between weekly injected GLP-1 RAs and all other classes of oral glucose-lowering medications including SGLT-2i. Furthermore, our review highlights the need for information about treatment efficacy based on systematic reviews rather than single studies. Additionally, our review findings emphasise the importance of standardising the way in which drug profiles are presented in values and preferences studies, where we suggest that attributes such as efficacy, side effects, mode of administration and dosage, cost, among other important variables to be constantly included in the building of drug profiles so that precise and trustworthy results are ensured.

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REFERENCES

1 Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Spectrum* 2012;25:154–71.
2 Stiggelbout AM, Van der Weijden T, De Wit MPT, *et al*. Shared decision making: really putting patients at the centre of healthcare. *BMJ* 2012;344:e256.
3 Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–44.
4 Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine* 2016;375:311–22.
5 Bethel MA, Patel RA, Merrill P, *et al*. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol* 2018;6:105–13.
6 Ahrén B, Masmiquel L, Kumar H, *et al*. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on

to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (sustain 2): a 56-week, double-blind, phase 3A, randomised trial. *Lancet Diabetes Endocrinol* 2017;5:341–54.
7 Diamant M, Van Gaal L, Stranks S, *et al*. Once Weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010;375:2234–43.
8 Fonseca VA, Alvarado-Ruiz R, Raccah D, *et al*. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). *Diabetes Care* 2012;35:1225–31.
9 Hernandez AF, Green JB, Janmohamed S, *et al*. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;392:1519–29.
10 Marre M, Shaw J, Brändle M, *et al*. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med* 2009;26:268–78.
11 Thieu VT, Robinson S, Kennedy-Martin T, *et al*. Patient preferences for glucagon-like peptide 1 receptor-agonist treatment attributes. *Patient Prefer Adherence* 2019;13:561–76.
12 Siemieniuk RA, Agoritsas T, Macdonald H, *et al*. Introduction to BMJ rapid recommendations. *BMJ* 2016;354:i5191.
13 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
14 Selva A, Sanabria AJ, Pequeño S, *et al*. Incorporating patients' views in Guideline development: a systematic review of guidance documents. *J Clin Epidemiol* 2017;88:102–12.
15 Andrews J, Guyatt G, Oxman AD, *et al*. Grade guidelines: 14. going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013;66:719–25.
16 Joy SM, Little E, Maruthur NM, *et al*. Patient preferences for the treatment of type 2 diabetes: a scoping review. *Pharmacoeconomics* 2013;31:877–92.
17 Zhang Y, Alonso-Coello P, Guyatt GH, *et al*. Grade guidelines: 19. assessing the certainty of evidence in the importance of outcomes or values and preferences-Risk of bias and indirectness. *J Clin Epidemiol* 2019;111:94–104.
18 Murad MH, Mustafa RA, Schünemann HJ, *et al*. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med* 2017;22:85–7.
19 Dibonaventura MD, Wagner J-S, Girman CJ, *et al*. Multinational Internet-based survey of patient preference for newer oral or injectable type 2 diabetes medication. *Patient Prefer Adherence* 2010;4:397.
20 Evans M, McEwan P, O'Shea R, O'Shea R, *et al*. A retrospective, case-note survey of type 2 diabetes patients prescribed incretin-based therapies in clinical practice. *Diabetes Ther* 2013;4:27–40.
21 Jendle J, Torffvit O, Ridderstråle M. Willingness to pay for diabetes drug therapy in type 2 diabetes patients: based on lead clinical programme results. *J Med Econ* 2012;15:1–5.
22 Lüdemann J, Dütting ED, Dworak M. Patient preference and tolerability of a DPP-4 inhibitor versus a GLP-1 analog in patients with type 2 diabetes mellitus inadequately controlled with metformin: a 24-week, randomized, multicenter, crossover study. *Ther Adv Endocrinol Metab* 2015;6:141–8.
23 Poon JL, Boye KS, Thieu VT. Preferences for attributes of medications among patients with type 2 diabetes: a cross-medication class comparison of injection therapies. *Curr Res Diabetes Obes J* 2018;6:1–13.
24 Boye KS, Matza LS, Stewart KD, *et al*. Patient preferences and health state utilities associated with dulaglutide and semaglutide injection devices among patients with type 2 diabetes in Italy. *J Med Econ* 2019;22:806–13.
25 Brooks A, Langer J, Tervonen T, *et al*. Patient preferences for GLP-1 receptor agonist treatment of type 2 diabetes mellitus in Japan: a discrete choice experiment. *Diabetes Ther* 2019;10:735–49.
26 Hauber AB, Nguyen H, Posner J, *et al*. A discrete-choice experiment to quantify patient preferences for frequency of glucagon-like peptide-1 receptor agonist injections in the treatment of type 2 diabetes. *Curr Med Res Opin* 2016;32:251–62.
27 Gelhorn HL, Poon J-L, Davies EW, *et al*. Evaluating preferences for profiles of GLP-1 receptor agonists among injection-naïve type 2 diabetes patients in the UK. *Patient Prefer Adherence* 2015;9
28 Gelhorn HL, Bacci ED, Poon JL, *et al*. Evaluating preferences for profiles of glucagon-like peptide-1 receptor agonists among injection-naive type 2 diabetes patients in Japan. *Patient Prefer Adherence* 2016;10:1337–48.
29 Matza LS, Boye KS, Stewart KD, *et al*. Health state utilities associated with attributes of Weekly injection devices for treatment of type 2 diabetes. *BMC Health Serv Res* 2017;17:1–10.
30 Matza LS, Boye KS, Currie BM, *et al*. Patient perceptions of injection devices used with dulaglutide and liraglutide for treatment of type 2 diabetes. *Curr Med Res Opin* 2018;34:1457–64.
31 Matza LS, Boye KS, Jordan JB, *et al*. Patient preferences in Italy: health state utilities associated with attributes of Weekly injection devices for treatment of type 2 diabetes. *Patient Prefer Adherence* 2018;12:971–9.
32 Matza LS, Boye KS, Stewart KD, *et al*. Assessing patient preference between the dulaglutide Pen and the semaglutide Pen: a crossover study (prefer). *Diabetes Obes Metab* 2020;22:355–64.
33 Polster M, Zanutto E, McDonald S, *et al*. A comparison of preferences for two GLP-1 products--liraglutide and exenatide--for the treatment of type 2 diabetes. *J Med Econ* 2010;13:655–61.
34 Qin L, Chen S, Flood E, *et al*. Glucagon-Like peptide-1 receptor agonist treatment attributes important to injection-experienced patients with type 2 diabetes mellitus: a preference study in Germany and the United Kingdom. *Diabetes Ther* 2017;8:335–53.
35 Qin L, Chen S, Flood E, *et al*. Glucagon-Like peptide-1 receptor agonist treatment attributes important to injection-naïve patients with type 2 diabetes mellitus: a multinational preference study. *Diabetes Ther* 2017;8:321–34.
36 Rodríguez-Gutiérrez R, Montori VM. Glycemic control for patients with type 2 diabetes mellitus: our evolving faith in the face of evidence. *Circ Cardiovasc Qual Outcomes* 2016;9:504–12.
37 Li S, Vandvik PO, Hao Q. Sodium-Glucose cotransporter-2 inhibitors (SGLT-2i) glucagon-like peptide-1 (GLP-1) receptor agonists for adults with type 2 diabetes at different risk of cardiovascular and renal outcomes: a clinical practice guideline. *BMJ*.
38 Buchan T, Malik A, Chan C, *et al*. Risk prediction models for cardiovascular and renal outcomes in patients with type 2 diabetes: a systematic review. *BMJ*.
39 Palmer SC, Tendal B, Mustafa RA, *et al*. Sodium-Glucose transport protein 2 inhibitors and GLP-1 receptor agonists for type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *BMJ*.