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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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Title:

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 GLP-1 RA or SGLT-2i compared to 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 (6,986 patients) proved eligible. Studies fulfilling criteria for SGLT-2i were not identified. Five studies (2,690 patients) evaluated preferences for GLP-1 RA compared to other glucose-lowering medications. 12 studies (4,296 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 to once-daily liraglutide. Comparing different attributes of GLP-1 RA drugs and devices, cardiovascular risk reduction, glucose lowering potential, once-weekly and simple administered regimes 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 regimes 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: CRD42020159284

ARTICLE SUMMARY

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 in order 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 SGLT-2 inhibitors.

BACKGROUND

The American Diabetes Association and the European Association for the Study of Diabetes have highlighted the importance of providing a patient-centered 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-centered practice.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose co-transporter-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 hypoglycemia.[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.[2] 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 to each other or other drug treatments for type 2 diabetes. 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 judgments 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 (PRISMA) checklist for writing this review.[13] The protocol was registered in the Prospective Register of Systematic reviews (PROSPERO) with the following registration code: CRD42020159284.

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 to 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) randomized 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. **(Supplemental material 1)** A previously published filter for studies regarding values and preferences was added in order 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 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

None.

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 6,986 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 2,690 patients evaluated preferences for GLP-1 RA versus other glucose-lowering drugs.[21, 22, 26, 27, 33] Furthermore, twelve studies comprising a total of 4,296 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.[19, 20, 23-25, 28-32, 34, 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 one 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, or odds ratios where used as units of measurement to quantify values and preferences.[20, 23-26, 33-35] The next most frequent methodology was the Time-Trade-Off (TTO) approach in four studies.[19, 28, 29, 32] Utilities, health state disutilities and relative importance were the units of measurement in these studies. Other methodologies employed were willingness to pay[26], online surveys[21], questionnaires[30], crossover trials[27, 31], and case-note surveys.[22] **(Table 1, Table 2)**

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.[19-27, 30, 32, 34] Only 5 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.[28, 29, 31, 33, 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 3)**

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[33], sitagliptin[21, 22], vildagliptin[27], rosiglitazone, and glimepiride.[26] From these, one study was found to be at low risk of bias.[33] Two studies were performed on the injection-naïve population[21, 33], one on injection-experienced[27] and the remaining two on a mixed population.[22, 26] Among the studies which presented drug profiles as part of their methodology, all studies described efficacy (defined as a change in HbA1c), proportion of side effects, weight change, dosing frequency, and delivery system. Four studies described hypoglycemia risk[21, 22, 26, 33], and three included blood pressure change in the studied drugs profile.[21, 22, 26] From the five studies, two described the all above-mentioned attributes on their drug profiles.[22, 26] **(Table 4)** Shown below is a subdivision of the drug comparisons that were assessed in these studies:

GLP-1 RA compared to DPP-4i

Three studies evaluated preferences between orally administered DPP-4i (sitagliptin and vildagliptin) and GLP-1 RA (liraglutide).[21, 22, 27] Preference for DPP-4i in both injection naïve and experienced patients was observed in two out of three studies.[21, 27] 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 2)**

Insulin Glargine compared to GLP-1 RA

Two studies evaluated preferences between liraglutide or dulaglutide and insulin glargine, both of them showed preference for GLP-1 RA.[26, 33] The first study found that 75% of participants preferred a dulaglutide profile when compared to insulin glargine where among patients who preferred the former, the most important reasons were type of delivery

system and dosing frequency, with relative importance (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%). [33] **(Table 2)**

In the second study (willingness to pay analysis), participants were prepared to pay an extra 3.36 euros/day for liraglutide over insulin glargine where weight change was the most important attribute leading to liraglutide preference (2.35 euros/day). In this study, liraglutide was presented as the best profile among all subdomains.[26] The risk for hypoglycemia was not an important attribute for patients' preference in both studies.

Other glucose-lowering treatments compared to 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 euros/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.[26]

Different GLP-1 RA medications

12 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 discrete choice experiments [20, 23-25, 34, 35] and four were time-trade-offs.[19, 28, 29, 32] The remaining two were a questionnaire [30] and a crossover trial.[31]

Liraglutide vs Exenatide

Four studies evaluated this comparison.[26, 32, 34, 35] Overall, participants preferred once-daily liraglutide compared to twice-daily exenatide. However, they preferred once-weekly exenatide compared to 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 hypoglycemia.[32] 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 to 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 2)** A willingness-to-pay analysis demonstrated that participants were willing to pay an extra 0.81 euros/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 euros/day).[26]

Liraglutide vs Dulaglutide

Three studies evaluated this comparison, one of them only compared device characteristics.[23, 24, 30] A preference for dulaglutide was observed in all three.

In two studies, one in Japan and the other in the United Kingdom (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 to a once-daily application with a multi-use 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 hypoglycemia 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).[23, 24] **(Table 2)** In the third one, a survey comparing medication devices was applied on patients experienced to both treatments and revealed a preference for the dulaglutide device. **(Table 2)** In this case, participants' preference was chosen based on their own experience.[30]

Dulaglutide vs Semaglutide

Three studies evaluated this comparison where two of them evaluated device attributes [19, 31] and the other added clinical attributes to the drug profiles.[20] 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 analyzed 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".[19] A crossover trial comparing both injection devices found that 84.2% of participants preferred the dulaglutide profile, mainly due to its "ease of use".[31]

In contrast, one study comparing both drugs using five attributes (method of administration, HbA1c change, reduction in 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 (versus no risk reduction for dulaglutide), and with a multi-dose prefilled pen with dose adjustment (versus 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.[20] **(Table 2)**

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 2)** Hauber et al 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.[25] Furthermore, Matza et al. performed two studies with consistent main findings; each administration requirement (needle handling, reconstitution and waiting) was associated with higher disutilities when compared to an oral health state.[28, 29]

DISCUSSION

In this systematic review, we found no direct evidence to inform judgments 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 analyzing 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 micro- or macrovascular outcomes.[36]

The evidence on burden of treatment serves as a reminder to guideline panels often restricting judgments 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 favoring 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 specialized 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 emphasized issues about the applicability of findings of this review to the BMJ Rapid Recommendations.

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 to GLP-1 RA (the first SGLT-2i to be FDA-approved was canagliflozin in 2013, compared to 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 individualize 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 emphasize the importance of standardizing 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.

CONTRIBUTORSHIP STATEMENT

Conceiving of the research idea: JGGG, RRG, LL, RAM, SCP, SL, QH; First draft of the research protocol: JGGG, ADGC, JMMA, RCS, NAAV, RRG; Final version of the research protocol: all authors; Search strategy design: NAAV; Study selection process: JGGG, ADGC, JMMA, RCS; Data extraction process: JGGG, ADGC, JMMA, RCS; Data synthesis: JGGG, ADGC, JMMA, RCS; First draft of the manuscript: JGGG, ADGC, JMMA, RCS, RRG; Final version of the manuscript: all authors.

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PATIENT CONSENT

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ETHICS APPROVAL

Not required

DATA SHARING STATEMENT

No additional data available

TRANSPARENCY

The manuscript's guarantors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained. This manuscript has not been deposited as a preprint.

DISSEMINATION TO PARTICIPANTS AND RELATED PATIENT AND PUBLIC COMMUNITIES

The paper informs a Rapid Recommendation on the use of SGLT-2 inhibitors and GLP-1 receptor agonists that will be released on a digital platform (www.magicproject.org) and made available to organizations to adapt for their own materials and purposes.

PUBLISHING LICENCE

Not required

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FIGURE LEGENDS

Figure 1: Study selection flow diagram

Figure 2: Risk of bias assessment

BOX 1: LINKED RESOURCES IN THE BMJ RAPID RECOMMENDATIONS CLUSTER

- Reference to this values and preferences systematic review here.
- Reference to guideline paper: SGLT-2 inhibitors or GLP -1 receptor agonists for adults with type 2 diabetes at different risk of cardiovascular and renal outcomes: a clinical practice guideline. Li S, Vandvik PO, Hao Q, et al. In submission The BMJ
- Reference to prognostic systematic review: Risk prediction models for cardiovascular and renal outcomes in patients with type 2 diabetes: A systematic review. Buchan T, Malik A, Chan C, et al. In submission The BMJ

- Reference to systematic review and network meta-analysis for SGLT-2 inhibitors and GLP-1 receptor agonists for type 2 diabetes: Sodium-Glucose Transport Protein 2 (SGLT-2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) receptor agonists for type 2 diabetes: A systematic review and network meta-analysis of randomised controlled trials. Palmer SC, Tendal B, Mustafa RA, et al. In submission The BMJ
- 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

Table 1: Demographic and study characteristics

Author, year	Country	N	Injection experience	Age (yrs)	Female (%)	Race (%)	BMI	HbA1c	Years of diagnosis	Assessment approach	Drugs evaluated
Boye, 2019[19]	Italy	216	M	60.5 (9.9)¥	42.1	White: 98.60 Other: 0.9	ND	ND	ND	TTO	Dulaglutide QW Semaglutide QW
Brooks, 2019[20]	Japan	161	N	55 (48-63)Ω	16	ND	25.9 (23.9-28.9)Ω	8.3 (7.4-9.1) Ω	<1 yr: 1% 1-5 yrs: 24% 5-10 yrs: 38% >10 yrs: 37%	DCE	Dulaglutide QW Semaglutide QW
DiBonaventura, 2010[21]	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, 2013[22]	United Kingdom	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, 2015[23]	United Kingdom	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 yr: 5.8% 1-5 yrs: 35.8% 5-10 yrs: 34.6% >10 yrs: 23.9%	DCE	Liraglutide QD Dulaglutide QW
Gelhorn 2016[24]	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 yr: 3.9% <1-5 yrs: 32.4% 5-10 yrs: 29.1% >10 yrs: 34.6%	DCE	Dulaglutide QW Liraglutide QD
Hauber, 2015[25]	United States	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, 2012[26]	Sweden	840	M	ND	ND	ND	ND	ND	ND	WTP via DCE	Liraglutide QD Rosiglitazone Glimepiride Insulin glargine Exenatide BID
Ludemann, 2015[27]	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)¥	Crossover trial	Vildagliptin Liraglutide QD
Matza, 2017[28]	United Kingdom	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, 2018a[29]	Italy	238	M	60.2 (9.3)¥	41.2	White:100	ND	ND	ND	TTO	QW GLP-1 RA injection devices
Matza, 2018b[30]	United States	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, 2020[31]	United States	310	N	60 (10.8)¥	48.4	White: 50 Black/African american: 33.9	ND	7.29 (1.4)¥	8.06 (6.7)¥	Crossover trial	Dulaglutide QW Semaglutide QW
Polster, 2010[32]	United States	382	M	52.7 (8.8)¥	52	White: 89.2	ND	7.3 (no SD)	7.6 (5.3)¥	TTO	Liraglutide QD Exanetide BID
Poon, 2018[33]	United Kingdom	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 yr: 7.3%, 1-5 yrs: 36.6% 5-10 yrs:28.9% > 10 yrs: 27.2%	DCE	Dulaglutide QW Insulin glargine
Qin, 2017a[34]	Germany and United	510	E	57 (11)¥	48.6	White: 93.5 Asian/Asian	34.2 (7.5)¥	7.4 (1.9)¥	7.2 (5.9)¥	DCE	Liraglutide QD Exenatide QW

	Kingdom					British: 3.3					
Qin, 2017b[35]	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

N: Injection naïve; E: Injection experienced; M: Mixed; ND: No Data; DCE: Discrete Choice Experiment; TTO: Time Trade Off; WTP: Willingness-to-pay; QD: Once daily administration; QW: Once weekly administration; BID: Twice daily administration; [¥]mean/standard deviation; [+]range; "[Ω]median/interquartile range; [€]Demographic characteristics shown for full sample; only 58 participants were included in the preferences analysis

Table 2: 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, 2019[19]	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, 2019[20]	Dulaglutide: 20 % Semaglutide: 80 %	Utility coefficient (SE)	0-No 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, 2010[21]	Sitagliptin: 84.4% Liraglutide: 15.6 %	Ranked importance (SD)	0-No limit	Effectiveness of medication (1.6% 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 cost of medication: 3.42 (1.43)
Evans, 2013[22]	Liraglutide: 62.5 % Sitagliptin: 37.5 %	Most important attribute according to preferred drug	0-100%	Liraglutide: Weight Loss, 61% Sitagliptin: Oral administration, 66%
Gelhorn, 2015[23]	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% Weight change: 5.9% HbA1c change: 3.6% Low blood sugar events (hypoglycemia): 3.0%
Gelhorn, 2016[24]	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 hypoglycemia: 7.4% Weight change: 6.2 % HbA1c change: 1.0%
Hauber, 2016[25]	NA	Relative importance	0-No limit	Weekly injection frequency (vs. daily) Shorter and thinner needle (vs. longer and thicker) Eliminating injection site reactions
Jendle, 2012[26]	Overall participants were willing to pay more for liraglutide compared to all other drugs. (BID EXN, RGL, GLI, INS)	Prepared to pay an extra ∈/day for liraglutide	0-No 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: 0.65, 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 Hypoglycemia rate: EXN: 0.07, GLI: 0.03, INS: 0.03, RGL: 0.0
Lüdemann, 2015 [27]	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 diarrhea): VG: 67.8%, LG: 41.4% Blood sugar lowering: VG: 77.4%, LG: 75.9% Weight loss and blood pressure decrease: VG: 64.6% , LG: 65.5%
Matza, 2017[28]	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, 2018a[29]	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, 2018b[30]	Dulaglutide: 70.7%Ω Liraglutide: 22.4% Ω	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, 2020[31]	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, 2010[32]	Liraglutide: 0.97 (CI 0.96-0.98) Exenatide BID: 0.94 (CI 0.92-0.955)	Relative Importance* (Health Utility)	0-100%	Efficacy: 39% (0.016) Nausea: 30% (0.011) Hypoglycemia: 17% (0.006) Dosing schedule: 14% (0.005)
Poon, 2018¥[33]	Dulaglutide: 75% Insulin glargine: 25%	Relative Importance	0-100%	Delivery system : 19.8 % GI effects: 18.2% Dosing frequency: 17.7% Weight change: 15.6% HbA change: 14.2 % Frequency of pancreatitis: 12.3% Frequency of hypoglycemia: 2.2%
Qin, 2017a[34]	Exenatide QW: 78.60% Liraglutide: 21.40%	Odds Ratio (95% CI)	0-No 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) Multi use pen: 1.709 (1.55-1.88) Needle size, device size, and titration were not significant in patient's preference
Qin, 2017b[35]	Liraglutide: 21.40% Exenatide QW: 78.60%	Odds Ratio (95% CI)	0-No limit	Less side effects: 2.66 Efficacy: <1.5 Hba1c): 2.57 Weekly dosing frequency: 2.25 Multi use pen: 1.709

VG: Prefered vildagliptin; LG: Prefered liraglutide; *Definition of relative importance relative importance is calculated by dividing the difference in the average TTO utility for the best and worst levels for each attribute across all possible scenarios and across all respondents by the sum of those mean differences; ** Preference elicited assuming equal efficacy between drugs 1.2 improvement in HbA1c; ΩPreference for overall ease of use; ¥Risk of pancreatitis considered in study profile for GLP-1 RA, we advise to take results with caution ; #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; RGL: Rosiglitazone; GLI: Glimepiride; INS: Insulin Glargine; EXN: Exenetide; BID: Twice daily; QW: Once weekly; CI: Confidence interval; SD: Standard Deviation; SE "Standard Error; DID-EQ : Diabetes Injection Device Experience Questionnaire.

Table 3: GRADE assessment of the certainty of evidence

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
GLP-1 RA (liraglutide) compared to DPP-4i (sitagliptin, vildagliptin)									
3	observational studies [a]	very serious [b]	serious [c]	very serious [d]	serious [e]	none	Higher preference for DPP-4i over liraglutide was observed in two out of three studies.	⨁◯◯◯ VERY LOW	
GLP-1 RA (liragltuide, dulaglutide) compared to Insulin Glargine									
2	observational studies	serious [f]	not serious	very serious [d]	serious [e]	none	Higher preference for GLP-1RA was observed in both studies.	⨁◯◯◯ VERY LOW	
Other glucose-lowering treatments compared to GLP1-RA									
1	observational studies	very serious [g]	not serious [h]	very serious [d]	serious [e]	none	GLP-1 RA were preferred over other study drugs. (Pioglitaz one, glimepiride)	⨁◯◯◯ VERY LOW	
Liraglutide vs Exenatide									
4	observational studies	very serious [i]	not serious	very serious [d,j]	serious [e]	none	Liraglutide was preferred over twice-daily exenatide, however once-weekly exenatide was preferred over liraglutide.	⨁◯◯◯ VERY LOW	
Liraglutide vs Dulaglutide									
3	observational studies	very serious [k]	not serious	very serious [d,l]	serious [e]	none	In all three studies, a preference for dulaglutide over liraglutide was shown.	⨁◯◯◯ VERY LOW	
Dulaglutide vs Semaglutide									
3	observational studies	very serious [m]	very serious [n]	very serious [d,o]	serious [e]	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 [p]	not serious	not serious	serious [e]	none	As administration requirements for GLP-1 RA injection devices increase, preferences decrease. Patients strongly preferr weekly over daily injection devices.	⨁◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

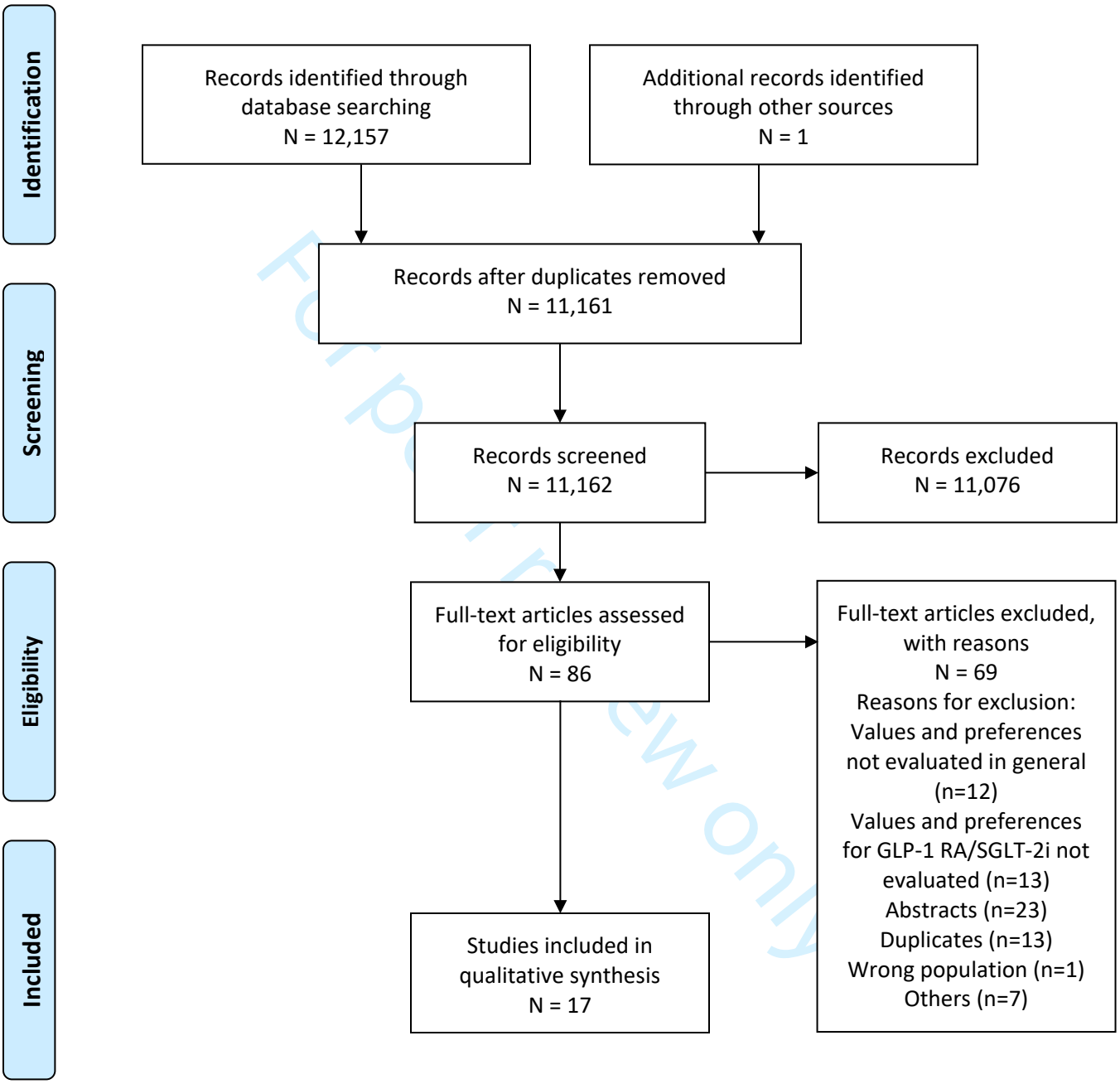
a. One study presented a cross-over design

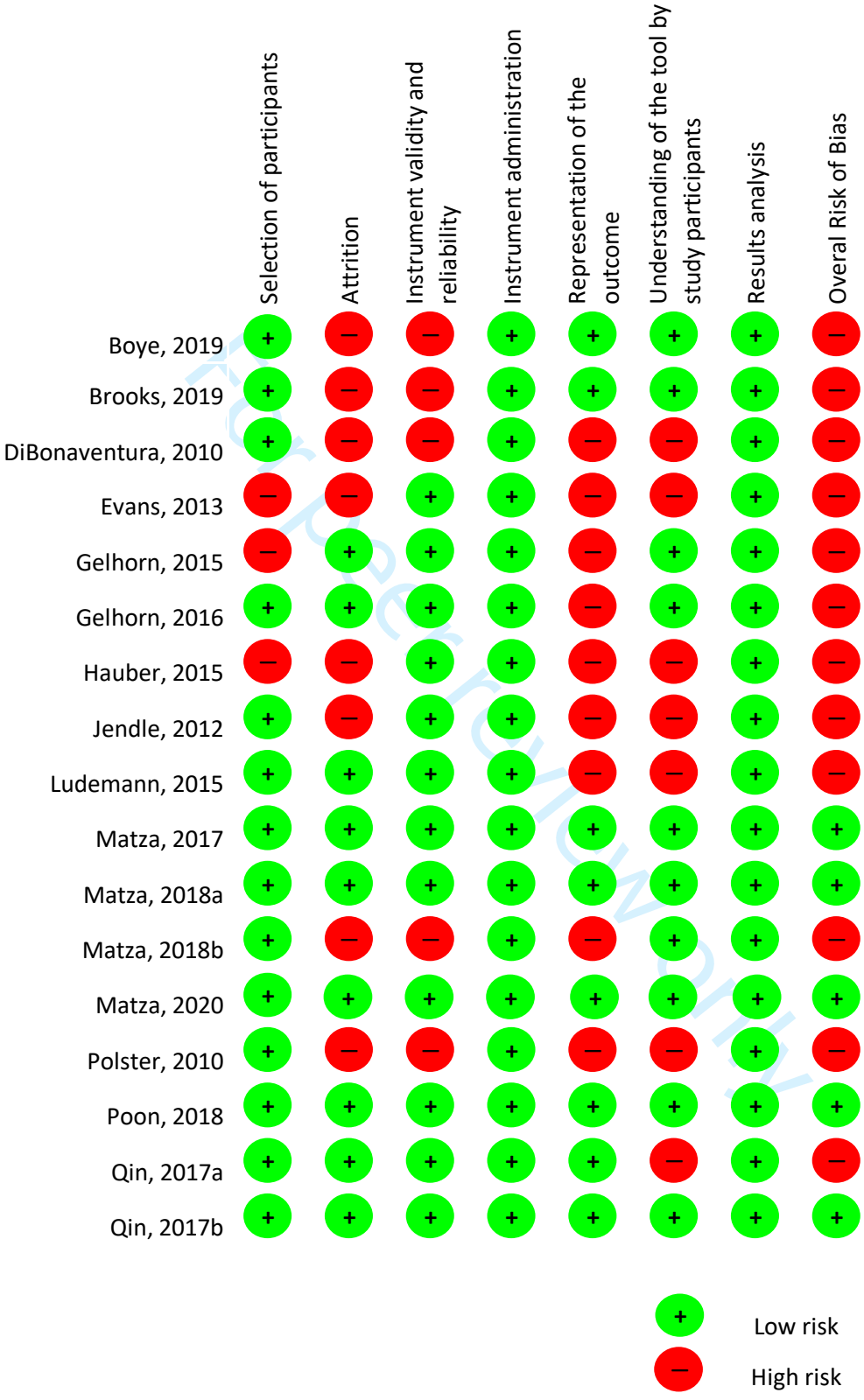
b. Two studies presented a high risk of bias in the attrition item. One of the studies presented a high risk of bias in the item of instrument validity and reliability (1340 participants) which was the biggest one. The three studies presented a high risk of bias in two out of six items assessed (representation of the outcome and understanding of the tool by study participants). Therefore, we judged the trials to have very serious methodological limitations.
c. Two of the studies included patients naive 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´s decisions differed between studies (liraglutide weight reduction effect was omitted in the study where patients preferred sitagliptin). None of the included studies reported confidence intervals of the point estimate neither statistical hypothesis tests to further assess inconsistency. Wejudged the evidence to have serious inconsistency.
d. Drug profile did not fully represent the best available evidence at the moment.
e. Although the evaluated sample size was optimal, the confidence interval of the point of estimate was not reported. We judge serious imprecision in the evidence.
f. One of two studies was judged as overall low risk of bias. (232 patients) The otherstudy was at high risk in the attrition domain, representation of outcomes and understanding of the tool by study participants. (840 patients) Wejudge risk of bias to be serious for this outcome.
g. 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.
h. Since no further evidence is presented it is not feasible to classify inconsistency.
i. 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. Wejudge the evidence to have serious methodological limitations.
j. In all studies, medication profiles were presented with varying benefits and harms which were not based on the best available evidence at the moment.
k. Two of the three studies were at high risk of bias due to concerns regarding selection of participants and evaluation of the outcomes.
l. 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.
m. Two studies were classified as high risk of bias due to concerns regarding attrition rate and instrument validity and reliability for evaluating patient preferences.
n. The direction of patient preferences tended to vary across studies where in two of them, strong preferences for semaglutide were observed. However, in the other study, strong preference for dulaglutide was reported.
o. 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.
p. 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.

Table 4: 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)	Hypoglycemia (%)	Blood pressure changes (mmHg)	Dosing Frequency	Type of delivery system	Population experience
DiBonaventura, 2010 [21]	SG	SG: -1.4% LG: -2.4%	LG: Nausea 11-19%, Vomit 5-7%, Diarrhea 8-15% SG: No adverse effects	SG: 0 LG: -3.5	SG: Low risk LG: Low risk	SG: 0 LG: -2,-3	SG: QD LG. QD	SG: Oral LG: Injected	Injection naive
Evans, 2013 [22]	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, 2012Ω [26]	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: BID GL:OD RS:OD INS:MD	LD: Injected RGL: Oral GLM: Oral EXN: Injected INS: Injected	Mixed
Lüdemann, 2015* [27]	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, 2018 [33]	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 one year	ND	DG: QW INS: MD	DG: Single prefilled pen ready. INS: Multiple dose prefilled pens, titration required.	Injection naive

Ω Only listed nausea as an adverse effect, blood pressure change assessed as systolic blood pressure change; *Attribute values are results from the crossover trial; ND: No Data; QD: Once daily; BID: Twice daily; QW: Once weekly; MD: Multiple daily; OD: Once daily; LG: Liraglutide; VG: Vidagliptin; RGL: Rosiglitazone; GLM: Glimepiride; INS: Insulin; EXN: Exenatide; SG: Sitagliptin; DG: Dulaglutide





Supplemental Material 1: Example of the employed search strategy

Scopus GLP-1 RA

(TITLE-ABS-KEY ("Attitude to Health" OR "Patient Participation" OR preference* OR "Patient Preference" OR choice OR choices OR value* OR "health state values" OR valuation* OR expectation* OR attitude* OR acceptab* OR knowledge OR "point of view" OR "user participation" OR "users participation" OR "users' participation" OR "user's participation" OR "patient participation" OR "patients' participation" OR "patients participation" OR "patient's participation" OR "patient perspective*" OR "patients perspective*" OR "patients' perspective*" OR "patient's perspective*" OR "patient perce*" OR "patients perce*" OR "patients' perce*" OR "patient's perce*" OR "health perception*" OR "user view*" OR "users view*" OR "users' view*" OR "user's view*" OR "patient view*" OR "patients view*" OR "patients' view*" OR "patient's view*") OR ((patient* OR user* OR men OR women) AND ("Decision Making" OR "decision mak*" OR "decisions mak*" OR (decision* AND mak*) OR "avoidance learning") OR (("discrete choice" OR "decision board*" OR "decision analy*" OR "decision-support" OR "decision tool*" OR "decision aid*" OR "discrete-choice*" OR decision*) AND (patient* OR user* OR men OR women))) OR (" decision support technique" OR (health AND utilit*) OR gamble* OR "prospect theory" OR "preference score" OR "preference elicitation" OR "health utilit*" OR (utility AND (value* OR score* OR estimate*)) OR "health state" OR "feeling thermometer*" OR "best-worst scaling" OR "best worst scaling" OR "best worst" OR "TTO" OR "time trade-off" OR "probability trade-off" OR "choice Behavior") OR ("preference based" OR "preference score" OR multiattribute OR "multi attribute" OR "EuroQoL 5D" OR euroqol5d OR eq5d OR "EQ 5D" OR sf6d OR "SF 6D" OR hui OR 15d) OR (sf36 OR "SF 36" OR sf12 OR "SF 12" OR hrqol OR qol OR "quality of life" OR "Quality of Life")) AND TITLE-ABS ((("Albiglutide" OR "Tanzeum" OR "Dulaglutide" OR "Trulicity" OR "Exenatide" OR "Byetta" OR "Extended-release exenatide" OR "Bydureon" OR "Liraglutide" OR "Victoza" OR "Lixisenatide" OR "Adlyxin" OR "Semaglutide" OR "Ozempic") OR ("albugon" OR "albumin GLP 1" OR "albumin glucagon like peptide 1" OR "albumin glucagon like peptide 1 fusion protein" OR "eperzan" OR "GLP 1 albumin" OR "glucagon like peptide 1 albumin" OR "glucagon like peptide 1 albumin fusion protein" OR "gsk 716155" OR "gsk 716155a" OR "gsk-716155" OR "gsk-716155a" OR "gsk716155" OR "gsk716155a" OR "naliglutide" OR "syncria" OR "tanzeum") OR ("dulaglutide" OR "ly 2189265" OR "ly2189265" OR "trulicity") OR ("exenatide" OR "exendin 4" OR "ac

2993" OR "ac 2993a" OR "ac2993" OR "ac2993a" OR "bydureon" OR "bydureon pen" OR "byetta" OR "exenatide synthetic" OR "ly 2148568" OR "ly2148568") OR ("liraglutide" OR "glucagon like peptide 1 [7-37][26 (6 n hexadecanoyl gamma glutamyllysine) 34 arginine]" OR "liraglutide recombinant" OR "n26 (hexadecanoyl gamma glutamyl)glucagon like peptide 1 [7-37][34 arginine]" OR "nn 2211" OR "nn2211" OR "nnc 90 1170" OR "nnc 90-1170" OR "nnc90 1170" OR "nnc90-1170" OR "saxenda" OR "victoza") OR ("lixisenatide" OR "adlyxin" OR "aqve 10010" OR "aqve10010" OR "ave 0010" OR "ave0010" OR "des 38 proline exendine 4 [1-39]peptidylpentalysyllysinamide" OR "lyxumia" OR "zp 10" OR "zp10") OR ("semaglutide" OR "glucagon like peptide 1 [7-37][8 (2 amino 2 methylpropanoic acid) 26 [6 n [18 [n (17 carboxyheptadecanoyl) gamma glutamyl] 10 oxo 3,6,12,15 tetraoxa 9,18 diazaoctadecanoyl]lysine] 34 arginine]" OR "nn 9535" OR "nn9535" OR "ozempic"))) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

Scopus SGLT2-i

(TITLE-ABS-KEY ("Attitude to Health" OR "Patient Participation" OR preference* OR "Patient Preference" OR choice OR choices OR value* OR "health state values" OR valuation* OR expectation* OR attitude* OR acceptab* OR knowledge OR "point of view" OR "user participation" OR "users participation" OR "users' participation" OR "user's participation" OR "patient participation" OR "patients' participation" OR "patients participation" OR "patient's participation" OR "patient perspective*" OR "patients perspective*" OR "patients' perspective*" OR "patient's perspective*" OR "patient perce*" OR "patients perce*" OR "patients' perce*" OR "patient's perce*" OR "health perception*" OR "user view*" OR "users view*" OR "users' view*" OR "user's view*" OR "patient view*" OR "patients view*" OR "patients' view*" OR "patient's view*") OR ((patient* OR user* OR men OR women) AND ("Decision Making" OR "decision mak*" OR "decisions mak*" OR (decision* AND mak*) OR "avoidance learning") OR (("discrete choice" OR "decision board*" OR "decision analy*" OR "decision-support" OR "decision tool*" OR "decision aid*" OR "discrete-choice*" OR decision*) AND (patient* OR user* OR men OR women))) OR (" decision support technique" OR (health AND utilit*) OR gamble* OR "prospect theory" OR "preference score" OR "preference elicitation" OR "health utilit*" OR (utility AND (value* OR score* OR estimate*)) OR "health state" OR "feeling thermometer*" OR "best-worst scaling" OR "best worst scaling" OR "best worst" OR "TTO" OR "time trade-off" OR "probability trade-off" OR "choice Behavior") OR ("preference based" OR "preference score" OR multiattribute OR "multi attribute" OR "EuroQoL 5D" OR euroqol5d OR eq5d OR "EQ 5D" OR sf6d OR "SF

6D" OR hui OR 15d) OR (sf36 OR "SF 36" OR sf12 OR "SF 12" OR hrqol OR qol OR "quality of life" OR "Quality of Life")) AND ((TITLE-ABS-KEY ((t2dm OR niddm OR t2d OR dm2) OR ((non-insulin OR noninsulin OR slow-onset OR ketosis-resistant OR maturity) W/2 diabet*) OR (type W/2 ("2" OR ii) W/2 diabet*))) AND ((TITLE-ABS-KEY (sodium* W/2 glucose* W/1 (transport* OR cotransport* OR co-transport*) W/2 inhibit*)) OR (TITLE-ABS-KEY ((sglt2* OR sglt-2* OR slc5a2) W/3 inhibit*)) OR (TITLE-ABS-KEY (atigliflozin OR bexaglifozin OR "bi 44874" OR canagliflozin* OR dapagliflozin* OR empagliflozin* OR ertugliflozin* OR ipragliflozin* OR mizagliflozin OR tofogliflozin* OR luseogliflozin* OR serglifozin OR sotagliflozin* OR gliflozin* OR "ta 7284" OR ta7284 OR invokana OR jnj28431754 OR "jnj* 28431754")))) AND NOT (PMID (0*) OR PMID (1*) OR PMID (2*) OR PMID (3*) OR PMID (4*) OR PMID (5*) OR PMID (6*) OR PMID (7*) OR PMID (8*) OR PMID (9*)) AND ORIG-LOAD-DATE AFT 20200510 AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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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Primary Subject Heading:	Diabetes and endocrinology
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Keywords:	DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES &

	ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY

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Title:

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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Keywords:

Type 2 diabetes, values, preferences, GLP-1 Receptor Agonists, SGLT-2 Inhibitors patient-important outcomes, patient-centered care

Word count: 3,679

ABSTRACT

Objectives: Assess values, preferences and burden of treatment that patients with type 2 diabetes consider when initiating GLP-1 RA or SGLT-2i compared to 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 (6,986 patients) proved eligible. Studies fulfilling criteria for SGLT-2i were not identified. Five studies (2,690 patients) evaluated preferences for GLP-1 RA compared to other glucose-lowering medications. 12 studies (4,296 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 to once-daily liraglutide. Comparing different attributes of GLP-1 RA drugs and devices, cardiovascular risk reduction, glucose lowering potential, once-weekly and simple administered regimes 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 regimes 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: CRD42020159284

ARTICLE SUMMARY

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 SGLT-2 inhibitors.

BACKGROUND

The American Diabetes Association and the European Association for the Study of Diabetes have highlighted the importance of providing a patient-centered 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-centered practice.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose co-transporter-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 hypoglycemia. (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 to 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 judgments 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 (PRISMA) checklist for writing this review. (13) The protocol was registered in the Prospective Register of Systematic reviews (PROSPERO) with the following registration code: CRD42020159284.

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 to 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) randomized 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 **(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 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 6,986 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 2,690 patients evaluated preferences for GLP-1 RA versus other glucose-lowering drugs. (19-23) Furthermore, twelve studies comprising a total of 4,296 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 one 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, or odds ratios 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 relative importance 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 5 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 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 HbA1c), proportion of side effects, weight change, dosing frequency, and delivery system. Four studies described hypoglycemia 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 to 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 to 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 to insulin glargine

where among patients who preferred the former, the most important reasons were type of delivery system and dosing frequency, with relative importance (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 euros/day for liraglutide over insulin glargine where weight change was the most important attribute leading to liraglutide preference (2.35 euros/day). In this study, liraglutide was presented as the best profile among all subdomains. (21) The risk for hypoglycemia was not an important attribute for patients' preference in both studies.

Other glucose-lowering treatments compared to 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 euros/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

12 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 discrete choice experiments (25-28, 34, 35) and four were time-trade-offs. (24, 29, 31, 33) The remaining two were a questionnaire (30) and a crossover trial. (32)

Liraglutide vs Exenatide

Four studies evaluated this comparison. (21, 33-35) Overall, participants preferred once-daily liraglutide compared to twice-daily exenatide. However, they preferred once-weekly exenatide compared to 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 hypoglycemia. (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 to 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 euros/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 euros/day). (21)

Liraglutide vs 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 United Kingdom (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 to a once-daily application with a multi-use 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 hypoglycemia 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 preference for the dulaglutide device. **(Table 4)** In this case, participants' preference was chosen based on their own experience. (30)

Dulaglutide vs 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 analyzed 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 crossover 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 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 (versus no risk reduction for dulaglutide), and with a multi-dose prefilled pen with dose adjustment (versus 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 to an oral health state. (29, 31)

DISCUSSION

In this systematic review, we found no direct evidence to inform judgments 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 analyzing 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 micro- or macrovascular outcomes. (36)

The evidence on burden of treatment serves as a reminder to guideline panels often restricting judgments 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 favoring 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 specialized 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 emphasized 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 to GLP-1 RA (the first SGLT-2i to be FDA-approved was canagliflozin in 2013, compared to 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 individualize 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 emphasize the importance of standardizing 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.

CONTRIBUTORSHIP STATEMENT

Conceiving of the research idea: JGGG, RRG, LL, RAM, SP, SL, QH, PV; First draft of the research protocol: JGGG, ADGC, JMMA, RCS, NAV, RRG; Final version of the research protocol: all authors; Search strategy design: NAV; Study selection process: JGGG, ADGC, JMMA, RCS; Data extraction process: JGGG, ADGC, JMMA, RCS; Data synthesis: JGGG, ADGC, JMMA, RCS; First draft of the manuscript: JGGG, ADGC, JMMA, RCS, RRG; Final version of the manuscript: all authors.

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This systematic review did not receive any funding.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JGGG, ADGC, JMMA, LL, RCS, RAM, SP, SL, QH, NAV, PV, RRG: no support from any organization for the submitted work; no

financial relationships with any organizations that might have an interest in the submitted work in the previous three years. SL was supported by grants from the National Natural Science Foundation of China (grant number 21534008), Sichuan Science and Technology Program (grant number 2019YFH0150), and 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (grant number ZYGD18022 and 2020HXF011). But none of the grant contributes to this work.

PATIENT CONSENT

Not required

ETHICS APPROVAL

Not required

DATA SHARING STATEMENT

No additional data available

TRANSPARENCY

The manuscript's guarantors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained. This manuscript has not been deposited as a preprint.

DISSEMINATION TO PARTICIPANTS AND RELATED PATIENT AND PUBLIC COMMUNITIES

The paper informs a Rapid Recommendation on the use of SGLT-2 inhibitors and GLP-1 receptor agonists that will be released on a digital platform (www.magicproject.org) and made available to organizations to adapt for their own materials and purposes.

PUBLISHING LICENCE

Not required

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FIGURE LEGENDS

Figure 1: Study selection flow diagram

Figure 2: Risk of bias assessment

BOX 1: LINKED RESOURCES IN THE BMJ RAPID RECOMMENDATIONS CLUSTER

- Reference to this values and preferences systematic review here.
- Reference to guideline paper: SGLT-2 inhibitors or GLP -1 receptor agonists for adults with type 2 diabetes at different risk of cardiovascular and renal outcomes: a clinical practice guideline. Li S, Vandvik PO, Hao Q, et al. In submission The BMJ
- Reference to prognostic systematic review: Risk prediction models for cardiovascular and renal outcomes in patients with type 2 diabetes: A systematic review. Buchan T, Malik A, Chan C, et al. In submission The BMJ
- Reference to systematic review and network meta-analysis for SGLT-2 inhibitors and GLP-1 receptor agonists for type 2 diabetes: Sodium-Glucose Transport Protein 2 (SGLT-2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) receptor agonists for type 2 diabetes: A systematic review and network meta-analysis of randomised controlled trials. Palmer SC, Tendal B, Mustafa RA, et al. In submission The BMJ
- 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

Table 1: Demographic and study characteristics

Author, year	Country	N	Injection experience	Age (yrs)	Female (%)	Race (%)	BMI	HbA1c	Years of diagnosis	Assessment approach	Drugs evaluated
Boye, 2019[24]	Italy	216	M	60.5 (9.9)¥	42.1	White: 98.60 Other: 0.9	ND	ND	ND	TTO	Dulaglutide QW Semaglutide QW
Brooks, 2019[25]	Japan	161	N	55 (48-63)Ω	16	ND	25.9 (23.9-28.9)Ω	8.3 (7.4-9.1) Ω	<1 yr: 1% 1-5 yrs: 24% 5-10 yrs: 38% >10 yrs: 37%	DCE	Dulaglutide QW Semaglutide QW
DiBonaventura, 2010[19]	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, 2013[20]	United Kingdom	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, 2015[27]	United Kingdom	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 yr: 5.8% 1-5 yrs: 35.8% 5-10 yrs: 34.6% >10 yrs: 23.9%	DCE	Liraglutide QD Dulaglutide QW
Gelhorn 2016[28]	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 yr: 3.9% <1-5 yrs: 32.4% 5-10 yrs: 29.1% >10 yrs: 34.6%	DCE	Dulaglutide QW Liraglutide QD
Hauber, 2015[26]	United States	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, 2012[21]	Sweden	840	M	ND	ND	ND	ND	ND	ND	WTP via DCE	Liraglutide QD Rosiglitazone Glimepiride Insulin glargine Exenatide BID
Ludemann, 2015[22]	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)¥	Crossover trial	Vildagliptin Liraglutide QD
Matza, 2017[29]	United Kingdom	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, 2018a[31]	Italy	238	M	60.2 (9.3)¥	41.2	White:100	ND	ND	ND	TTO	QW GLP-1 RA injection devices
Matza, 2018b[30]	United States	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, 2020[32]	United States	310	N	60 (10.8)¥	48.4	White: 50 Black/African american: 33.9	ND	7.29 (1.4)¥	8.06 (6.7)¥	Crossover trial	Dulaglutide QW Semaglutide QW
Polster, 2010[32]	United States	382	M	52.7 (8.8)¥	52	White: 89.2	ND	7.3 (no SD)	7.6 (5.3)¥	TTO	Liraglutide QD Exenatide BID
Poon, 2018[23]	United Kingdom	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 yr: 7.3%, 1-5 yrs: 36.6% 5-10 yrs:28.9% > 10 yrs: 27.2%	DCE	Dulaglutide QW Insulin glargine
Qin, 2017a[34]	Germany and United Kingdom	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, 2017b[35]	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

N: Injection naïve; E: Injection experienced; M: Mixed; ND: No Data; DCE: Discrete Choice Experiment; TTO: Time Trade Off; WTP: Willingness-to-pay; QD: Once daily administration; QW: Once weekly administration; BID: Twice daily administration; ¥mean/standard deviation; ⁺range; “Ωmedian/interquartile range; €Demographic characteristics shown for full sample; only 58 participants were included in the preferences analysis

Table 2: GRADE assessment of the certainty of evidence

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
GLP-1 RA (liraglutide) compared to DPP-4i (sitagliptin, vildagliptin)									
3	observational studies [a]	very serious [b]	serious [c]	very serious [d]	serious [e]	none	Higher preference for DPP-4i over liraglutide was observed in two out of three studies.	⨁◯◯◯ VERY LOW	
GLP-1 RA (liraglutide, dulaglutide) compared to Insulin Glargine									
2	observational studies	serious [f]	not serious	very serious [d]	serious [e]	none	Higher preference for GLP-1RA was observed in both studies.	⨁◯◯◯ VERY LOW	
Other glucose-lowering treatments compared to GLP1-RA									
1	observational studies	very serious [g]	not serious [h]	very serious [d]	serious [e]	none	GLP-1 RA were preferred over other study drugs. (rosiglitazone, glimepiride)	⨁◯◯◯ VERY LOW	
Liraglutide vs Exenatide									
4	observational studies	very serious [i]	not serious	very serious [d,j]	serious [e]	none	Liraglutide was preferred over twice-daily exenatide; however once-weekly exenatide was preferred over liraglutide.	⨁◯◯◯ VERY LOW	
Liraglutide vs Dulaglutide									
3	observational studies	very serious [k]	not serious	very serious [d,l]	serious [e]	none	In all three studies, a preference for dulaglutide over liraglutide was shown.	⨁◯◯◯ VERY LOW	
Dulaglutide vs Semaglutide									
3	observational studies	very serious [m]	very serious [n]	very serious [d,o]	serious [e]	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 [p]	not serious	not serious	serious [e]	none	As administration requirements for GLP-1 RA injection devices increase, preferences decrease. Patients strongly prefer weekly over daily injection devices.	⨁◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

a. One study presented a cross-over design

b. 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.

c. Two of the studies included patients naive 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´s decisions differed between studies (liraglutide weight reduction effect was omitted in the study where patients preferred sitagliptin). None of the included studies reported confidence

intervals of the point estimate neither statistical hypothesis tests to further assess inconsistency. We judged the evidence to have serious inconsistency.

d. Drug profile did not fully represent the best available evidence now.
e. Although the evaluated sample size was optimal, the confidence interval of the point of estimate was not reported. We judge serious imprecision in the evidence.
f. 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) Wejudge risk of bias to be serious for this outcome.
g. 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.
h. Since no further evidence is presented it is not feasible to classify inconsistency.
i. 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. Wejudge the evidence to have serious methodological limitations.
j. In all studies, medication profiles were presented with varying benefits and harms which were not based on the best available evidence now.
k. Two of the three studies were at high risk of bias due to concerns regarding selection of participants and evaluation of the outcomes.
l. 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.
m. Two studies were classified as high risk of bias due to concerns regarding attrition rate and instrument validity and reliability for evaluating patient preferences.
n. The direction of patient preferences tended to vary across studies where in two of them, strong preferences for semaglutide were observed. However, in the other study, strong preference for dulaglutide was reported.
o. 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.
p. 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.

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)	Hypoglycemia (%)	Blood pressure changes (mmHg)	Dosing Frequency	Type of delivery system	Population experience
DiBonaventura, 2010 [19]	SG	SG: -1.4% LG: -2.4%	LG: Nausea 11-19%, Vomit 5-7%, Diarrhea 8-15% SG: No adverse effects	SG: 0 LG: -3.5	SG: Low risk LG: Low risk	SG: 0 LG: -2, -3	SG: QD LG. QD	SG: Oral LG: Injected	Injection naive
Evans, 2013 [20]	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, 2012Ω [21]	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: BID GL: OD RS: OD INS:MD	LD: Injected RGL: Oral GLM: Oral EXN: Injected INS: Injected	Mixed
Lüdemann, 2015* [22]	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, 2018 [23]	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 one year	ND	DG: QW INS: MD	DG: Single prefilled pen ready. INS: Multiple dose prefilled pens, titration required.	Injection naive

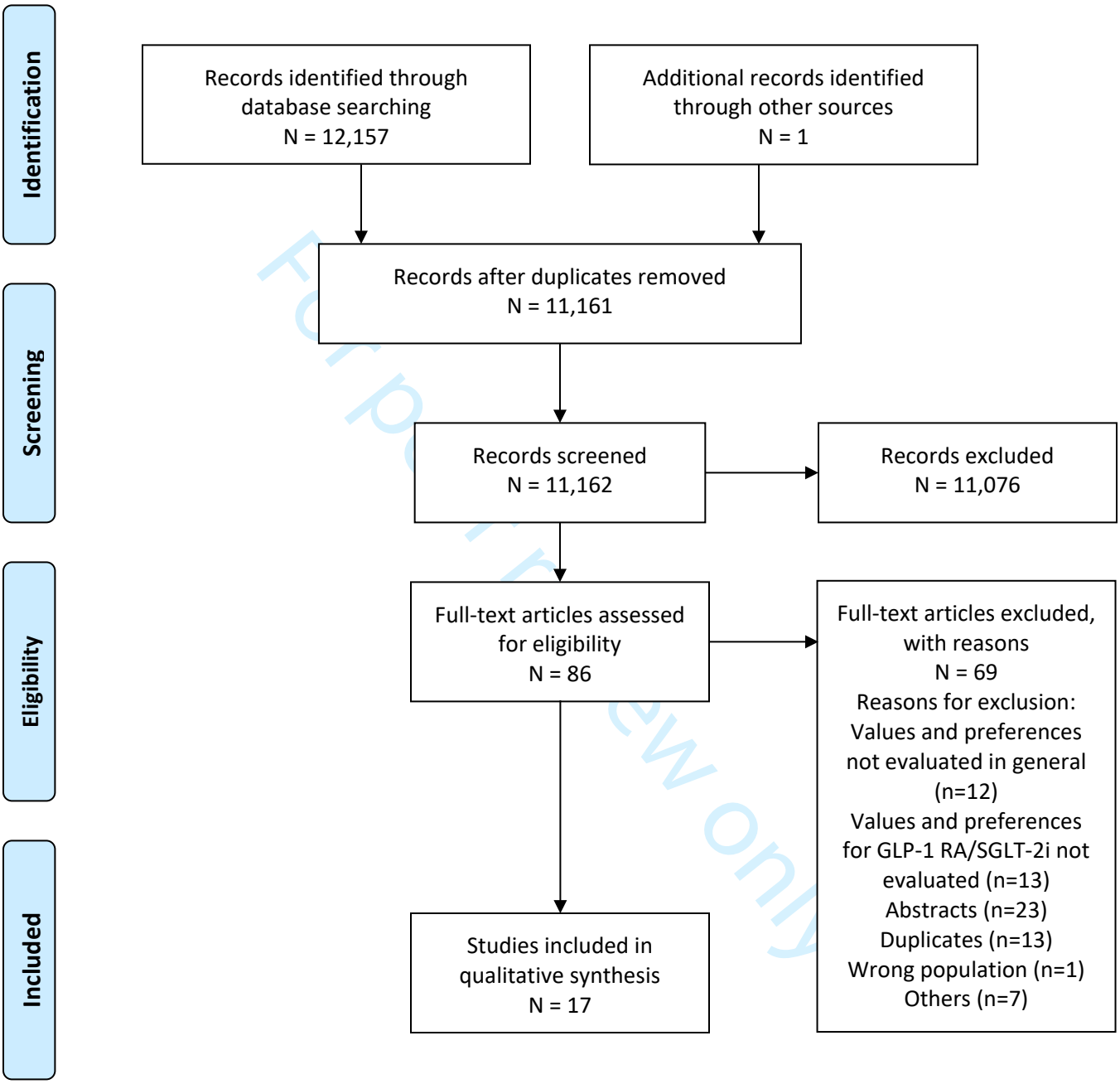
Ω Only listed nausea as an adverse effect, blood pressure change assessed as systolic blood pressure change; *Attribute values are results from the crossover trial; ND: No Data; QD: Once daily; BID: Twice daily; QW: Once weekly; MD: Multiple daily; OD: Once daily; LG: Liraglutide; VG: Vildagliptin; RGL: Rosiglitazone; GLM: Glimepiride; INS: Insulin; EXN: Exenatide; SG: Sitagliptin; DG: Dulaglutide

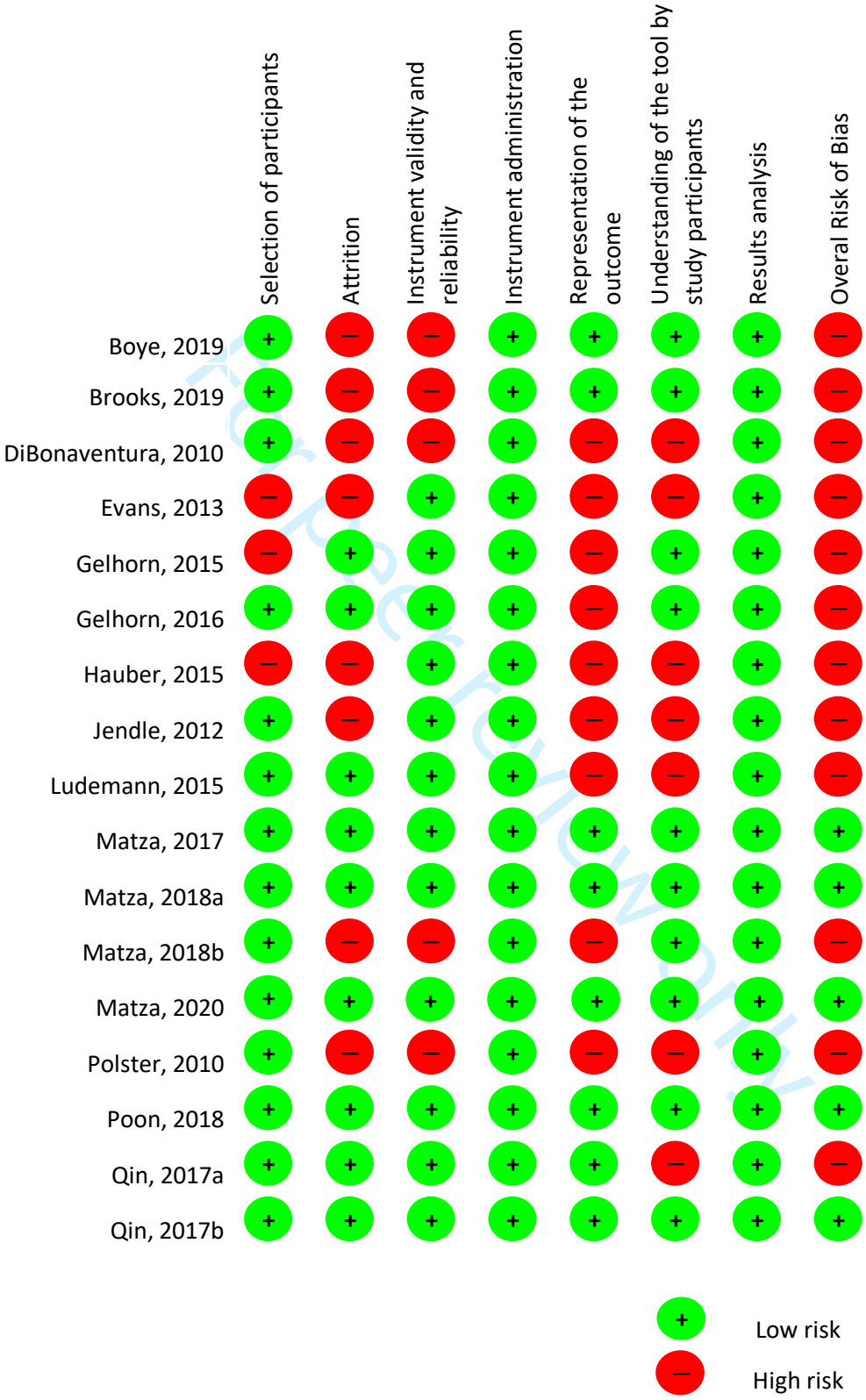
Table 4: Drug preferences and attributes leading to preference among included studies

Author, year	Drug preference (as measured)	Unit of measurement for drug attribute assessment	Scale	Attributes (Attribute Weight)
Boye, 2019[24]	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, 2019[25]	Dulaglutide: 20 % Semaglutide: 80 %	Utility coefficient (SE)	0-No 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, 2010[19]	Sitagliptin: 84.4% Liraglutide: 15.6 %	Ranked importance (SD)	0-No 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, 2013[20]	Liraglutide: 62.5 % Sitagliptin: 37.5 %	Most important attribute according to preferred drug	0-100%	Liraglutide: Weight Loss, 61% Sitagliptin: Oral administration, 66%
Gelhorn, 2015[27]	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% Weight change: 5.9% HbA1c change: 3.6% Low blood sugar events (hypoglycemia): 3.0%
Gelhorn 2016[28]	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 hypoglycemia: 7.4% Weight change: 6.2 % HbA1c change: 1.0%
Hauber, 2015[26]	NA	Relative importance	0-No limit	Weekly injection frequency (vs. daily) Shorter and thinner needle (vs. longer and thicker) Eliminating injection site reactions
Jendle, 2012[21]	Overall participants were willing to pay more for liraglutide compared to all other drugs. (BID EXN, RGL, GLI, INS)	Prepared to pay an extra ∈/day for liraglutide	0-No 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 Hypoglycemia rate: EXN: 0.07, GLI: 0.03, INS: 0.03, RGL: 0.0
Ludemann, 2015[22]	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 diarrhea): VG: 67.8%, LG: 41.4% Blood sugar lowering: VG: 77.4%, LG: 75.9% Weight loss and blood pressure decrease: VG: 64.6%, LG: 65.5%
Matza, 2017[29]	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, 2018a[31]	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, 2018b[30]	Dulaglutide: 70.7%Ω Liraglutide: 22.4% Ω	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, 2020[32]	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, 2010[32]	Liraglutide: 0.97 (CI 0.96-0.98) Exenatide BID: 0.94 (CI 0.92-0.955)	Relative Importance* (Health Utility)	0-100%	Efficacy: 39% (0.016) Nausea: 30% (0.011) Hypoglycemia: 17% (0.006) Dosing schedule: 14% (0.005)
Poon, 2018[23]	Dulaglutide: 75% Insulin glargine: 25%	Relative Importance	0-100%	Delivery system: 19.8 % GI effects: 18.2% Dosing frequency: 17.7% Weight change: 15.6% HbA1change: 14.2 % Frequency of pancreatitis: 12.3% Frequency of hypoglycemia: 2.2%
Qin, 2017a[34]	Exenatide QW: 78.60% Liraglutide: 21.40%	Odds Ratio (95% CI)	0-No 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) Multi use pen: 1.709 (1.55-1.88) Needle size, device size, and titration were not significant in patient's preference
Qin, 2017b[35]	Liraglutide: 21.40% Exenatide QW: 78.60%	Odds Ratio (95% CI)	0-No limit	Less side effects: 2.66 Efficacy (<1.5 Hba1c): 2.57 Weekly dosing frequency: 2.25 Multi-use pen: 1.709

VG: Preferred vildagliptin; LG: Preferred liraglutide; *Definition of relative importance relative importance is calculated by dividing the difference in the average TTO utility for the best and worst levels for each attribute across all possible scenarios and across all respondents by the sum of those mean differences; ** Preference elicited assuming equal efficacy between drugs 1.2 improvement in HbA1c; ΩPreference for overall ease of use; ¥Risk of pancreatitis considered in study profile for GLP-1 RA, we advise to take results with caution ; #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; RGL: Rosiglitazone; GLI: Glimepiride; INS: Insulin Glargine; EXN: Exenatide; BID: Twice daily; QW: Once weekly; CI: Confidence interval; SD: Standard Deviation; SE "Standard Error; DID-EQ : Diabetes Injection Device Experience Questionnaire.





Supplemental Material 1: Example of the employed search strategy

Scopus GLP-1 RA

(TITLE-ABS-KEY ("Attitude to Health" OR "Patient Participation" OR preference* OR "Patient Preference" OR choice OR choices OR value* OR "health state values" OR valuation* OR expectation* OR attitude* OR acceptab* OR knowledge OR "point of view" OR "user participation" OR "users participation" OR "users' participation" OR "user's participation" OR "patient participation" OR "patients' participation" OR "patients participation" OR "patient's participation" OR "patient perspective*" OR "patients perspective*" OR "patients' perspective*" OR "patient's perspective*" OR "patient perce*" OR "patients perce*" OR "patients' perce*" OR "patient's perce*" OR "health perception*" OR "user view*" OR "users view*" OR "users' view*" OR "user's view*" OR "patient view*" OR "patients view*" OR "patients' view*" OR "patient's view*") OR ((patient* OR user* OR men OR women) AND ("Decision Making" OR "decision mak*" OR "decisions mak*" OR (decision* AND mak*) OR "avoidance learning") OR (("discrete choice" OR "decision board*" OR "decision analy*" OR "decision-support" OR "decision tool*" OR "decision aid*" OR "discrete-choice*" OR decision*) AND (patient* OR user* OR men OR women))) OR (" decision support technique" OR (health AND utilit*) OR gamble* OR "prospect theory" OR "preference score" OR "preference elicitation" OR "health utilit*" OR (utility AND (value* OR score* OR estimate*)) OR "health state" OR "feeling thermometer*" OR "best-worst scaling" OR "best worst scaling" OR "best worst" OR "TTO" OR "time trade-off" OR "probability trade-off" OR "choice Behavior") OR ("preference based" OR "preference score" OR multiattribute OR "multi attribute" OR "EuroQoL 5D" OR euroqol5d OR eq5d OR "EQ 5D" OR sf6d OR "SF 6D" OR hui OR 15d) OR (sf36 OR "SF 36" OR sf12 OR "SF 12" OR hrqol OR qol OR "quality of life" OR "Quality of Life")) AND TITLE-ABS ((("Albiglutide" OR "Tanzeum" OR "Dulaglutide" OR "Trulicity" OR "Exenatide" OR "Byetta" OR "Extended-release exenatide" OR "Bydureon" OR "Liraglutide" OR "Victoza" OR "Lixisenatide" OR "Adlyxin" OR "Semaglutide" OR "Ozempic") OR ("albugon" OR "albumin GLP 1" OR "albumin glucagon like peptide 1" OR "albumin glucagon like peptide 1 fusion protein" OR "eperzan" OR "GLP 1 albumin" OR "glucagon like peptide 1 albumin" OR "glucagon like peptide 1 albumin fusion protein" OR "gsk 716155" OR "gsk 716155a" OR "gsk-716155" OR "gsk-716155a" OR "gsk716155" OR "gsk716155a" OR "naliglutide" OR "syncria" OR "tanzeum") OR ("dulaglutide" OR "ly 2189265" OR "ly2189265" OR "trulicity") OR ("exenatide" OR "exendin 4" OR "ac

2993" OR "ac 2993a" OR "ac2993" OR "ac2993a" OR "bydureon" OR "bydureon pen" OR "byetta" OR "exenatide synthetic" OR "ly 2148568" OR "ly2148568") OR ("liraglutide" OR "glucagon like peptide 1 [7-37][26 (6 n hexadecanoyl gamma glutamyllysine) 34 arginine]" OR "liraglutide recombinant" OR "n26 (hexadecanoyl gamma glutamyl)glucagon like peptide 1 [7-37][34 arginine]" OR "nn 2211" OR "nn2211" OR "nnc 90 1170" OR "nnc 90-1170" OR "nnc90 1170" OR "nnc90-1170" OR "saxenda" OR "victoza") OR ("lixisenatide" OR "adlyxin" OR "aqve 10010" OR "aqve10010" OR "ave 0010" OR "ave0010" OR "des 38 proline exendine 4 [1-39]peptidylpentalysyllysinamide" OR "lyxumia" OR "zp 10" OR "zp10") OR ("semaglutide" OR "glucagon like peptide 1 [7-37][8 (2 amino 2 methylpropanoic acid) 26 [6 n [18 [n (17 carboxyheptadecanoyl) gamma glutamyl] 10 oxo 3,6,12,15 tetraoxa 9,18 diazaoctadecanoyl]lysine] 34 arginine]" OR "nn 9535" OR "nn9535" OR "ozempic"))) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

Scopus SGLT2-i

(TITLE-ABS-KEY ("Attitude to Health" OR "Patient Participation" OR preference* OR "Patient Preference" OR choice OR choices OR value* OR "health state values" OR valuation* OR expectation* OR attitude* OR acceptab* OR knowledge OR "point of view" OR "user participation" OR "users participation" OR "users' participation" OR "user's participation" OR "patient participation" OR "patients' participation" OR "patients participation" OR "patient's participation" OR "patient perspective*" OR "patients perspective*" OR "patients' perspective*" OR "patient's perspective*" OR "patient perce*" OR "patients perce*" OR "patients' perce*" OR "patient's perce*" OR "health perception*" OR "user view*" OR "users view*" OR "users' view*" OR "user's view*" OR "patient view*" OR "patients view*" OR "patients' view*" OR "patient's view*") OR ((patient* OR user* OR men OR women) AND ("Decision Making" OR "decision mak*" OR "decisions mak*" OR (decision* AND mak*) OR "avoidance learning") OR (("discrete choice" OR "decision board*" OR "decision analy*" OR "decision-support" OR "decision tool*" OR "decision aid*" OR "discrete-choice*" OR decision*) AND (patient* OR user* OR men OR women))) OR (" decision support technique" OR (health AND utilit*) OR gamble* OR "prospect theory" OR "preference score" OR "preference elicitation" OR "health utilit*" OR (utility AND (value* OR score* OR estimate*)) OR "health state" OR "feeling thermometer*" OR "best-worst scaling" OR "best worst scaling" OR "best worst" OR "TTO" OR "time trade-off" OR "probability trade-off" OR "choice Behavior") OR ("preference based" OR "preference score" OR multiattribute OR "multi attribute" OR "EuroQoL 5D" OR euroqol5d OR eq5d OR "EQ 5D" OR sf6d OR "SF

6D" OR hui OR 15d) OR (sf36 OR "SF 36" OR sf12 OR "SF 12" OR hrqol OR qol OR "quality of life" OR "Quality of Life")) AND ((TITLE-ABS-KEY ((t2dm OR niddm OR t2d OR dm2) OR ((non-insulin OR noninsulin OR slow-onset OR ketosis-resistant OR maturity) W/2 diabet*) OR (type W/2 ("2" OR ii) W/2 diabet*))) AND ((TITLE-ABS-KEY (sodium* W/2 glucose* W/1 (transport* OR cotransport* OR co-transport*) W/2 inhibit*)) OR (TITLE-ABS-KEY ((sglt2* OR sglt-2* OR slc5a2) W/3 inhibit*)) OR (TITLE-ABS-KEY (atigliflozin OR bexaglifozin OR "bi 44874" OR canagliflozin* OR dapagliflozin* OR empagliflozin* OR ertugliflozin* OR ipragliflozin* OR mizagliflozin OR tofogliflozin* OR luseogliflozin* OR sergliflozin OR sotagliflozin* OR gliflozin* OR "ta 7284" OR ta7284 OR invokana OR jnj28431754 OR "jnj* 28431754")))) AND NOT (PMID (0*) OR PMID (1*) OR PMID (2*) OR PMID (3*) OR PMID (4*) OR PMID (5*) OR PMID (6*) OR PMID (7*) OR PMID (8*) OR PMID (9*)) AND ORIG-LOAD-DATE AFT 20200510 AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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