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ORIGINAL ARTICLE

Incretin-based medications for type 2 diabetes: an overview of reviews

J.-M. Gamble[1], A. Clarke[1], K. J. Myers[1], M. D. Agnew[1], K. Hatch[2], M. M. Snow[1] & E. M. Davis[1]

[1] *School of Pharmacy, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada*
[2] *Allyn and Betty Taylor Library, Western University, London, Ontario, Canada*

Aims: To summarize evidence from and assess the quality of published systematic reviews evaluating the safety, efficacy and effectiveness of incretin-based medications used in the treatment of type 2 diabetes.

Methods: We identified systematic reviews of randomized controlled trials or observational studies published in any language that evaluated the safety and/or effectiveness of glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl-peptidase-4 (DPP-4) inhibitors. Data sources used include the Cochrane Library, PubMed, EMBASE, Web of Science, International Pharmaceutical Abstracts, table of contents of diabetes journals, and hand-searching of reference lists and clinical practice guidelines. The methodological quality of systematic reviews was independently assessed by two reviewers using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. Our study protocol was registered with PROSPERO (2013:CRD42013005149). The primary outcomes were pooled treatment effect estimates for glycaemic control, macrovascular and microvascular complications, and hypoglycaemic events.

Results: We identified 467 unique citations of which 84 systematic reviews met our inclusion criteria. There were 51 reviews that evaluated GLP-1 receptor agonists and 64 reviews that evaluated DPP-4 inhibitors. The median (interquartile range) AMSTAR score was 6 (3) out of 11 for quantitative and 1 (1) for non-quantitative reviews. Among the 66 quantitative systematic reviews, there were a total of 718 pooled treatment effect estimates reported for our primary outcomes and 1012 reported pooled treatment effect estimates for secondary outcomes.

Conclusions: Clinicians and policy makers, when using the results of systematic reviews to inform decision-making with regard to round clinical care or healthcare policies for incretin-based medications, should consider the variability in quality of reviews.

Keywords: systematic review, incretin therapy

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Introduction

Incretin-based medications are relatively new medications used in the management of type 2 diabetes. The first incretin-based medication approved was the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide, receiving US Food and Drug Administration (FDA) approval in April 2005 and European Medicines Agency (EMA) approval in November 2006. Shortly thereafter, the first dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, received FDA and EMA approval (in October 2006 and March 2007, respectively). In 2015, there are several GLP-1 receptor agonists and DPP-4 inhibitors available to treat type 2 diabetes.

The DPP-4 inhibitors and GLP-1 receptor agonists lower blood glucose via prolongation of the 'incretin effect', in which a significantly greater insulin release is induced after an oral glucose load than with an intravenous glucose infusion. This effect is driven by intestinal hormones called incretins, namely GLP-1, the most active agent, and glucose-dependent insulinotropic peptide [1]. Incretins are released when glucose is consumed orally and, under normal physiological conditions, their effect is short-lived as they are degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) within 2–3 min. DPP-4 inhibitors (often called 'incretin enhancers') increase effective levels of GLP-1 by targeting and inactivating DPP-4, thus enhancing the incretin effect and stimulating the release of insulin in response to a rise in blood sugar. Alternatively, the GLP-1 receptor agonists (often called 'incretin mimetics') mimic the effect of natural GLP-1 receptors and exert their effect through direct action on GLP-1 receptors expressed on pancreatic tissue, thus stimulating insulin secretion.

Clinical practice guidelines recommend that incretin-based medications be used as either second- or third-line therapies after the failure of other antihyperglycaemic regimens, particularly metformin monotherapy [2–4]. Despite a paucity of evidence on the long-term clinical outcomes for incretin-based medications [5–7], there is an overwhelming volume of knowledge synthesis literature, primarily systematic reviews of randomized controlled trials. Given that existing systematic reviews would be expected to vary in their quality, design and applicability to practice [8], we decided to conduct an overview of systematic reviews. Overviews of systematic reviews present the best available evidence on a subject in one resource and formally assess the quality of systematic reviews [9,10];

Correspondence to: John-Michael Gamble, Health Sciences Centre, School of Pharmacy, Memorial University of Newfoundland, 300 Prince Philip Drive, St. John's, Newfoundland and Labrador A1B 3V6, Canada.
E-mail: jgamble@mun.ca

therefore, we aimed to summarize evidence from and assess the quality of published systematic reviews evaluating the safety and efficacy or effectiveness of incretin-based medications used in the treatment of type 2 diabetes.

Materials and Methods

The protocol for this overview is registered with the PROSPERO international prospective register of systematic reviews (PROSPERO 2013:CRD42013005149) [11].

Eligibility Criteria

Systematic reviews of randomized controlled trials or observational studies, which evaluated the safety, efficacy and/or effectiveness of incretin-based medications, were included, specifically, any DPP-4 inhibitor (sitagliptin, saxagliptin, vildagliptin, linagliptin or alogliptin) or GLP-1 receptor agonist (exenatide, liraglutide or lixisenatide). We considered a review to be a 'systematic review' if there was a specific research question, pre-defined search strategy and eligibility criteria included in the published article. Reviews lacking any of these elements were excluded.

Our primary outcomes were glycaemic control [i.e. glycated haemoglobin (HbA1c), fasting plasma glucose and proportion achieving a target value], macrovascular complications (i.e. cardiovascular mortality, non-fatal and fatal myocardial infarction, fatal and non-fatal stroke), microvascular complications (i.e. renal disease, neuropathy and retinopathy) and hypoglycaemia. Secondary outcomes included all-cause mortality, quality of life, weight change, cancer, pancreatitis, infections, hypersensitivity reactions, gastrointestinal adverse effects, blood pressure control and lipid control. We did not restrict the language of reviews. For non-English-language reviews we attempted to contact the corresponding author and first author via email, but we were unable to find valid contact information for 3 of the 11 non-English-language reviews.

Sources and Searching

Potentially relevant systematic reviews were identified through a comprehensive search of bibliographic electronic databases and other sources. First, we searched the following databases: the Cochrane Library, PubMed, EMBASE, Web of Science and International Pharmaceutical Abstracts from inception to 31 October 2013. Where applicable, a systematic review filter was used within the database search strategy. Second, we searched the tables of contents from the following diabetes journals from 2005 to October 2013: *Diabetes Care*, *Diabetologia*, *Diabetic Medicine*, *Diabetes Research and Clinical Practice*, *Diabetes, Obesity and Metabolism*, *Diabetes* and the *Journal of Clinical Endocrinology*. Third, we hand-searched the references of included systematic reviews and recent clinical practice guidelines (Canadian Diabetes Association 2013 guidelines and the American Diabetes Association 2013 Standards of Medical Care in Diabetes). The search strategy was formulated and executed with assistance from a health sciences librarian (K. H.) and is available in the PROSPERO protocol [11].

Study Selection

Two independent reviewers (K.J.M. and M.D.A.) screened the titles and abstracts of all citations identified by our search strategy. Two independent reviewers using a standardized study eligibility form further reviewed the full texts of citations that were potentially relevant. Disagreements were resolved by consensus or by a third reviewer (J.M.G.). Study selection is summarized in Figure 1.

Data Extraction

Two independent reviewers extracted relevant review-level data from the eligible systematic reviews and recorded it on standardized forms developed for the present overview. Disagreement was resolved by consensus or through consultation with a third party. Information was extracted from each included systematic review on bibliographic details, research question(s)/objective(s), search strategies, number of included studies, interventions and comparisons evaluated, outcomes reported and methods of analysis used. One reviewer (M.D.A.) extracted all pooled estimates from each included systematic review and a second reviewer (J.M.G.) verified all estimates. We only extracted estimates calculated from traditional pairwise meta-analytical techniques pooling results from $\geq$2 studies (i.e. indirect and mixed treatment effect estimates were excluded).

Quality Assessment

Two independent reviewers (M.D.A. and A.C.) assessed the quality of included systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist [12]. AMSTAR is a validated tool consisting of 11 questions that assess criteria such as the extensiveness of the literature search, whether the quality of the included studies was assessed and documented, and the probability of publication bias in the included studies [12]. All discordant AMSTAR scores between reviewers were resolved by consensus. Although we did not exclude non-English-language systematic reviews, we were unable to derive AMSTAR scores for the included non-English-language reviews. Consistent with previous studies, we considered studies with an AMSTAR score between 0 and 4 to be low quality, studies with an AMSTAR score between 5 and 8 to be of moderate quality, and studies with an AMSTAR score between 9 and 11 to be of high quality [13–15].

Analysis

We conducted a descriptive analysis of our results, whereby we summarized the characteristics of the systematic reviews according to the class of incretin-based agent and outcomes assessed. We tabulated the number of systematic reviews and number of pooled estimates of treatment effect for all placebo and active treatment comparisons for both GLP-1 receptor agonists and DPP-4 inhibitors. We calculated summary statistics and plotted the reported pooled point estimates and 95% confidence intervals (CIs) from individual high-quality systematic reviews for all outcomes of interest. Furthermore, in the absence of high-quality reviews, we plotted pooled estimates from reviews irrespective of their AMSTAR score. In the case

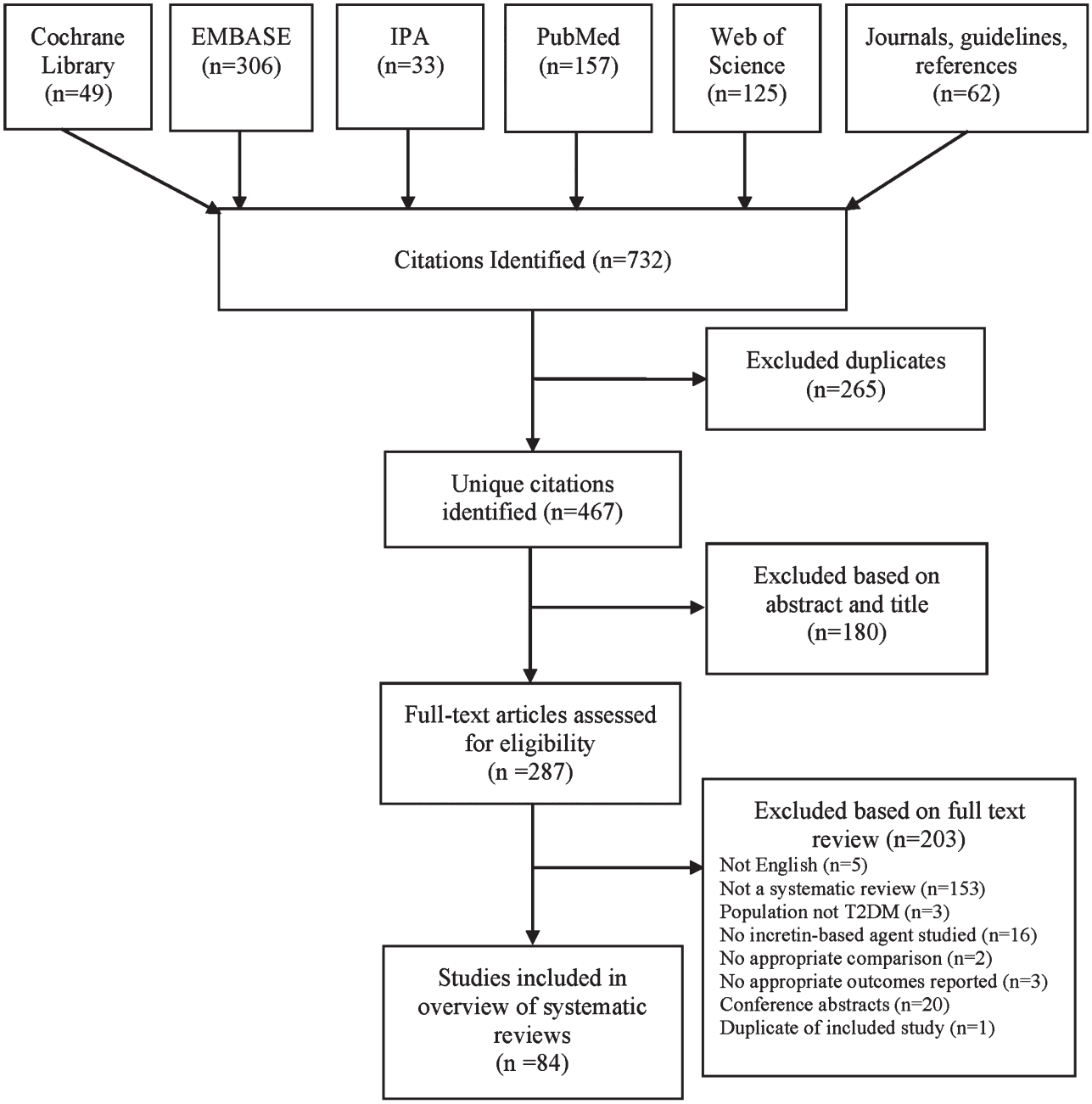

Figure 1. Flow diagram of study selection. IPA, International Pharmaceutical Abstracts; T2DM, type 2 diabetes mellitus.

where a systematic review reported multiple pooled estimates for the same treatment comparison, we plotted the estimate based on the greatest number of studies. If both random and fixed effects were reported, we plotted the random effects estimate.

Results

We identified 467 unique citations of which 84 systematic reviews met our inclusion criteria (Figure 1, Tables S1 and S2). There were 64 reviews that evaluated one or more DPP-4 inhibitors (alogliptin, n = 57; linagliptin, n = 33; saxagliptin, n = 42; sitagliptin, n = 22; vildagliptin, n = 25) and 51 reviews that evaluated one or more GLP-1 receptor agonists (exenatide, n = 47; liraglutide, n = 40; lixisenatide, n = 4). The first systematic reviews were published in 2007 and, since 2010, there have been >10 systematic reviews published per year evaluating the safety, efficacy or effectiveness of incretin-based medications (Table S3). Almost half of the systematic reviews did not report a funding source (n = 36, 43%); however, ~20% (n = 17) of the systematic reviews were funded by academia/government and 18% were funded by industry (n = 15). The median [interquartile range (IQR)] number of databases searched was 3 (6) and the median (IQR) number of studies included was

25 (24.75). There were 1730 pooled treatment effect estimates reported from the 66 quantitative reviews, whereby the most frequently reported estimates (28%) were for glycaemic control (Figure S1).

Quality Assessment

The distribution of AMSTAR scores for quantitative and qualitative systematic reviews is shown in Figure S2. The median (IQR) AMSTAR score was 6 (3) out of a possible 11 for quantitative reviews and 1 (1) out of a possible 11 for qualitative reviews. Only 5 (6%) systematic reviews received an AMSTAR score >8 (high quality) and almost half (n = 39, 46%) received an AMSTAR of <5 (low quality). High-quality reviews included reviews published by expert groups in knowledge synthesis such as the Cochrane Collaboration and the Canadian Agency for Drugs and Technologies in Health, as well as academic research teams [16–20].

Glycaemic Control

Among the 66 quantitative systematic reviews, there were a total of 477 pooled estimates reported for glycaemic control for DPP-4 inhibitors (n = 291) and GLP-1 receptor agonists (n = 186; Tables S4 and S5). Pooled treatment effects for glycaemic control were reported using five different measures: (i) change in HbA1c [n = 289 pooled estimates (184 for DPP-4 inhibitors, 105 for GLP-1 receptor agonists)]; (ii) change in fasting plasma glucose [n = 91 pooled estimates (59 for DPP-4 inhibitors, 32 for GLP-1 receptor agonists)]; (iii) change in postprandial glucose (n = 14 pooled estimates for DPP-4 inhibitors); (iv) proportion achieving HbA1c <7% [n = 80 pooled estimates (32 for DPP-4 inhibitors, 48 for GLP-1 receptor agonists)]; and (v) proportion achieving a 1% decrease in HbA1c from baseline (n = 2 pooled estimates for DPP-4 inhibitors, n = 1 for GLP-1 receptor agonists).

Figure 2 shows the weighted mean difference (WMD) and 95% CIs in change in HbA1c from all high-quality quantitative systematic reviews for DPP-4 inhibitor sitagliptin and for GLP-1 receptor agonists exenatide, liraglutide and taspoglutide. Two high-quality systematic reviews reported a WMD of −0.79 (95% CI −0.92 to −0.66) [20] and −0.81 (95% CI −0.94 to −0.68) [21] for DPP-4 inhibitors compared with placebo. Similar reductions in HbA1c were seen for DPP-4 inhibitors with metformin (WMD −0.78, 95% CI −0.96 to −0.60) [17]; however, when DPP-4 inhibitors were compared with other active comparators such as sulphonylureas (WMD 0.05, 95% CI −0.04 to 0.14) and thiazolidinediones (WMD −0.10, 95% CI −0.16 to −0.04), no clinically significant reductions in HbA1c were observed in high-quality systematic reviews [17]. High-quality systematic reviews also found that GLP-1 receptor agonists reduced HbA1c compared with placebo (11 WMD estimates, minimum WMD −0.72, maximum WMD −1.26) and metformin (WMD −0.75, −0.96 to −0.54), but did not reduce HbA1c compared with insulin. Pooled estimates from six systematic reviews found that GLP-1 receptor agonists significantly reduced HbA1c compared with DPP-4 inhibitors (n = 8 pooled estimated, minimum WMD −0.4, maximum WMD −0.6, all p values <0.05). In addition, two reviews reported summary estimates for long-acting exenatide, which was more effective at lowering HbA1c compared with short-acting exenatide and a mixed comparator group (File S1).

Macrovascular and Microvascular Complications

A total of 83 pooled treatment effect estimates from 10 systematic reviews reported on macrovascular outcomes, of which none received a high-quality AMSTAR score (Tables S6 and S7; Figures 3 and 4). The majority of pooled treatment estimates for macrovascular outcomes suggested a potential decreased risk (41/45 DPP-4 inhibitors and 28/38 for GLP-1 receptor agonists); however, only 18/41 and 3/28 pooled treatment effect estimates suggesting macrovascular benefit were statistically significant for DPP-4 inhibitors and GLP-1 receptor agonists, respectively.

Point estimates for the risk of a cardiovascular event, as defined by each systematic review, were consistent with both a decreased (minimum point estimate for DPP-4 inhibitors vs placebo 0.86; minimum point estimate for GLP-1 receptor agonists vs placebo 0.46) and increased (maximum point estimate for DPP-4 inhibitors vs placebo 1.05; maximum point estimate for GLP-1 receptor agonists vs placebo 2.19) risk. There were a limited number of systematic reviews reporting on the risk of cardiovascular mortality (n = 2 for DPP-4 inhibitors; n = 1 for GLP-1 receptor agonists), the risk of non-fatal or fatal myocardial infarction (n = 1 for DPP-4 inhibitors; n = 1 for GLP-1 receptor agonists), or the risk of non-fatal or fatal stroke (n = 1 for DPP-4 inhibitors; n = 1 for GLP-1 receptor agonists). All the pooled estimates for cardiovascular mortality, non-fatal or fatal myocardial infarction, or non-fatal or fatal stroke were statistically non-significant, although imprecise, whereby CIs contained treatment effects consistent with clinically significant benefits and harms. There were no pooled estimates reported for microvascular complications.

Hypoglycaemia

There were a total of 156 pooled estimates reported for hypoglycaemia (Table S8) for DPP-4 inhibitors (n = 107) and GLP-1 receptor agonists (n = 49). Results from high-quality systematic reviews showed that neither DPP-4 inhibitors nor GLP-1 receptor agonists were associated with significant differences in hypoglycaemia except when compared against medications known to cause significant hypoglycaemia (Figure 5). Specifically, compared with sulphonylureas, DPP-4 inhibitors were associated with a 90% relative reduction in the odds of hypoglycaemia (odds ratio 0.1, 95% CI 0.07 to 0.13) [17]. Similarly, GLP-1 receptor agonists were associated with a significant reduction in the risk of hypoglycaemia compared to sulphonylureas (relative risk 0.13, 95% CI 0.07 to 0.25) [16] and insulin (odds ratio 0.22, 95% CI 0.71 to 0.07) [17]. One review compared DPP-4 inhibitors with GLP-1 receptor agonists and found no difference in the risk of hypoglycaemia [22].

Secondary Outcomes

Secondary outcomes associated with consistent statistically significant treatment effects included weight change and gastrointestinal symptoms, especially for GLP-1 receptor

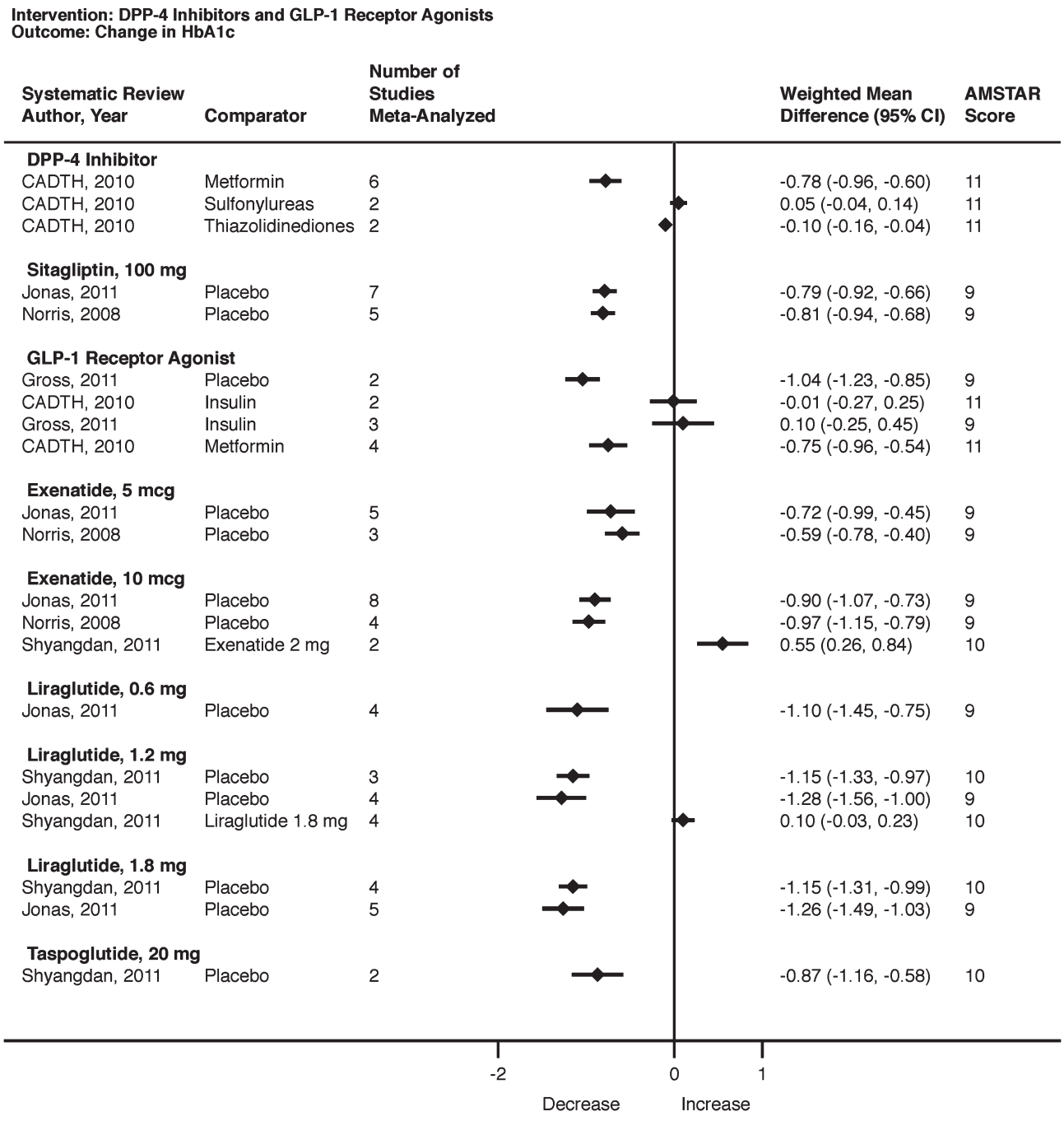

Figure 2. Results from high-quality quantitative systematic reviews for weighted mean differences in glycated haemoglobin (HbA1c) between dipeptidyl-peptidase-4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists and comparators. AMSTAR, Assessment of Multiple Systematic Reviews; CADTH, Canadian Agency for Drugs and Technologies in Health.

agonists. Of 168 effect estimates from reviews that evaluated change in weight for DPP-4 inhibitors and GLP-1 receptor agonists, 128 (76%) were statistically significant [16/25 estimates (64%) from high-quality reviews]. In general, GLP-1 receptor agonists were associated with significant weight loss when compared with placebo or an active comparator, whereas DPP-4 inhibitors were only associated with significant weight loss when compared with drugs known to cause weight gain (e.g. sulphonylureas, thiazolidinediones). GLP-1 receptor agonists were associated with significant weight loss (~2 kg) compared with DPP-4 inhibitors in two systematic reviews [23,24]. Findings from high-quality systematic reviews showed that DPP-4 inhibitors were not associated with significant differences in nausea, vomiting and diarrhoea compared with placebo. By contrast, all treatment effect estimates from high-quality systematic reviews showed that GLP-1 receptor agonists were associated with significant nausea, vomiting and diarrhoea.

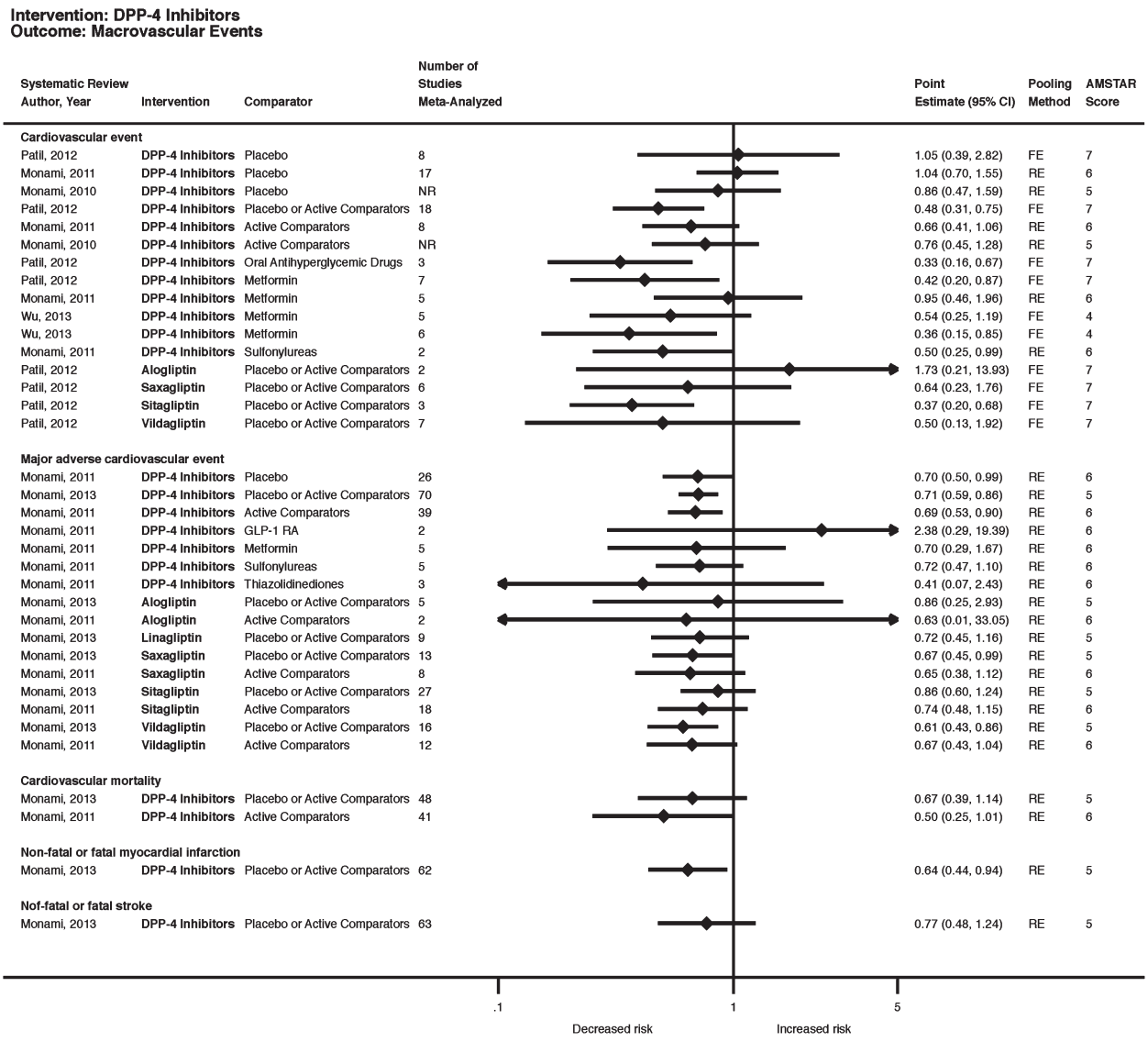

Figure 3. Results from quantitative systematic reviews for the relative treatment effect of dipeptidyl-peptidase-4 (DPP-4) inhibitors versus comparators for macrovascular events. AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; FE, fixed effects; NR, not reported; RE, random effects.

Several reviews also reported a statistically significant reduction in systolic [17/27 estimates (63%) were significant] and diastolic [6/13 estimates (46%) were significant] blood pressure; however, there were no statistically significant changes in systolic blood pressure within the four high-quality reviews. Only one review reported on blood pressure change for DPP-4 inhibitors and did not find a significant difference. Many reviews also found reductions in total cholesterol for both DPP-4 inhibitors [8/12 estimates (67%) statistically significant] and GLP-1 receptor agonists [5/8 estimates (63%) statistically significant]; however, high-quality studies did not find significant differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglyceride levels.

Many of the secondary outcomes were not associated with statistically significant treatment effects. Specifically, all but 2 of 27 and 1 of 26 pooled treatment effect estimates were non-significant for all-cause mortality and cancer outcomes, respectively. There was not a single statistically significant pooled treatment effect estimate from among the 20 effect estimates (7 for DPP-4 inhibitors and 13 for GLP-1 receptor agonists) reported in the three quantitative systematic reviews that evaluated pancreatitis. Similarly, very few significant effects were reported by systematic reviews for infections, of which upper respiratory tract infections [6/64 estimates (9%) significant; 0/8 from high-quality reviews], influenza [1/10 estimates (10%) significant; no high-quality reviews], and urinary tract infections [1/15 estimates (7%) significant; 0/2 from high-quality reviews] were most commonly reported.

Other clinically relevant outcomes of interest, not defined *a priori*, included bone fractures and change in heart rate. Specifically, one systematic review that pooled 28 trials reported a 40% relative risk reduction in fracture occurrence for DPP-4 inhibitors compared with placebo or active comparators [25]. Another systematic review reported that GLP-1

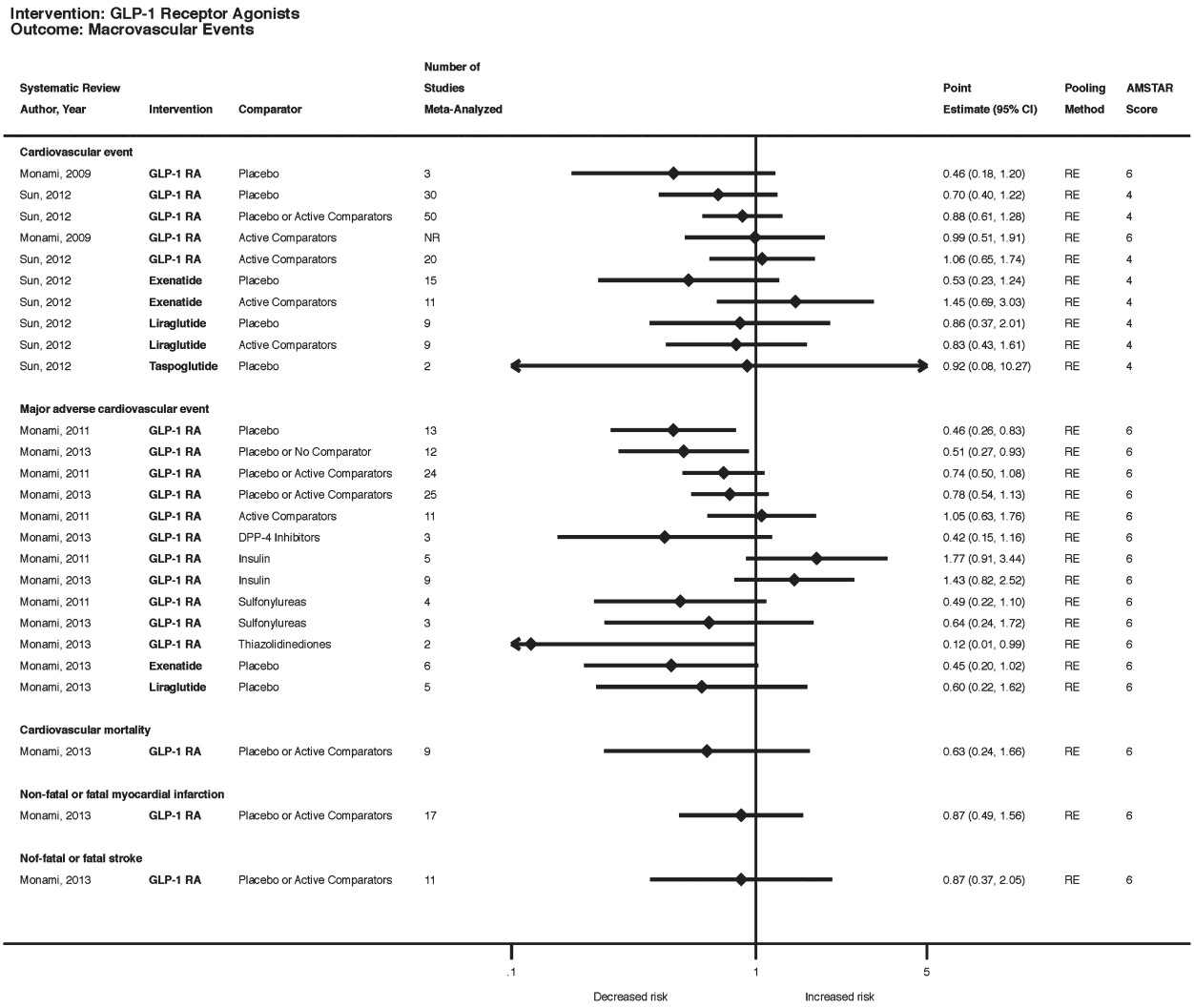

Figure 4. Results from quantitative systematic reviews for the relative treatment effect of glucagon-like peptide 1 (GLP-1) receptor agonists (RA) versus comparators for macrovascular events. AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; FE, fixed effects; NR, not reported; RE, random effects.

receptor agonists increased heart rate compared with placebo and active comparators by 1.86 and 1.90 beats per minute, respectively [26]. Additional summary results for secondary outcomes are reported in File S3.

Discussion

Overviews of systematic reviews serve to synthesize knowledge generated from reviews on a common topic and are suited to guide researchers, clinicians and policy makers toward the best summary of the evidence. To our knowledge this is the first study to systematically summarize and assess the quality of systematic reviews evaluating incretin-based medications used to treat type 2 diabetes. There was significant variation in the quality of reviews, as measured by the AMSTAR instrument, with the majority of reviews being of low or moderate quality. Despite 66 quantitative systematic reviews being conducted, which reported >1700 pooled treatment effect estimates on >90 different outcomes, our knowledge regarding the effect of DPP-4 inhibitors and GLP-1 receptor agonists on the occurrence of patient important outcomes remains limited. Although some of the included systematic reviews evaluated patient important outcomes such as macrovascular disease, infections and serious adverse events, >35% of all pooled treatment effect estimates measured blood glucose: either glycaemic control or hypoglycaemia.

The present study confirms several clinically relevant effects of incretin-based medications. First, compared with placebo or metformin, DPP-4 inhibitors and GLP-1 receptor agonists were consistently associated with a pooled weighted mean reduction in HbA1c of >0.5%, which is often considered a clinically important change in HbA1c; however, the magnitude of glycaemic lowering is limited to about a 0.5–1.5% absolute decrease in HbA1c for both DPP-4 inhibitors and GLP-1 receptor agonists, whereby the latter appear to have a stronger glucose-lowering effect. Second, incretin-based medications were not associated with a clinically significant risk of hypoglycaemia compared with placebo or active comparators.

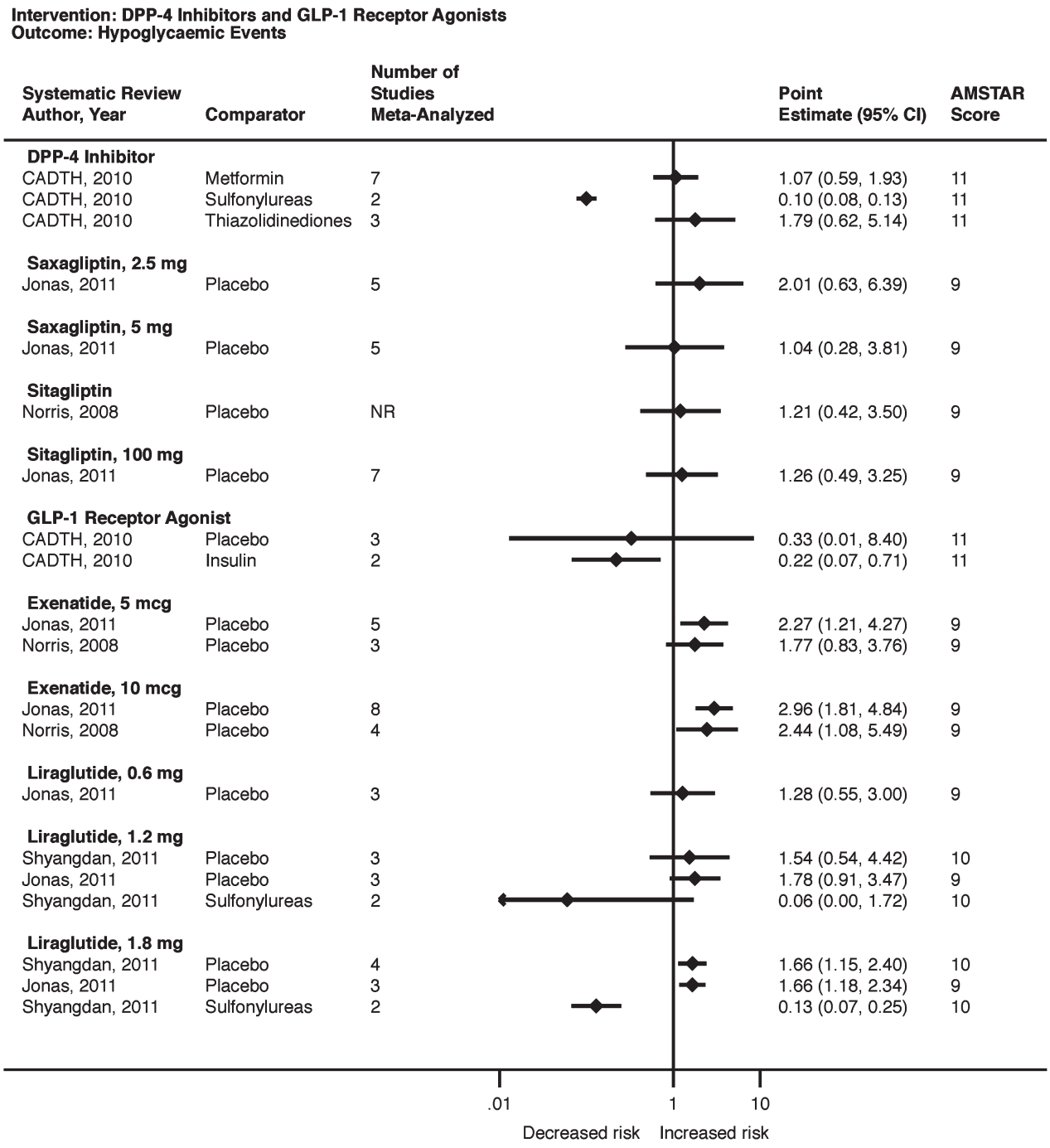

Figure 5. Results from high-quality quantitative systematic reviews for the relative treatment effect of dipeptidyl-peptidase-4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists versus comparators for hypoglycaemic events. AMSTAR, Assessment of Multiple Systematic Reviews; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; NR, not reported.

In fact, compared with sulphonylureas and insulin, two agents known to increase the risk of hypoglycaemia, incretin-based medications were associated with a reduced risk of hypoglycaemia. Third, our findings also confirm the well-known gastrointestinal adverse effects of incretin-based medications, notably GLP-1 receptor agonists which have a two-to-threefold increased risk of nausea and diarrhoea, and a three-to-fourfold increased risk of vomiting compared with placebo.

Although our overview of reviews included several reviews that found non-significant differences in macrovascular events, all-cause mortality, cancer and pancreatitis, results from the included reviews must be interpreted in the light of their limitations. Trials included within these systematic reviews were not designed to measure differences in these outcomes and, as such, the outcomes would not have been formally adjudicated within the trials. Furthermore, small sample sizes and

short durations of follow-up precluded many of the individual trials from being able to detect any differences in these outcomes among therapies, with many trials reporting zero events. Alternatively, small sample bias such as publication bias may be at play. Indeed, the results of many included reviews appear to overestimate the cardiovascular benefits of DDP-4 inhibitors when compared with the neutral findings of two recent randomized controlled trials, which evaluated the risk of cardiovascular outcomes among two different DPP-4 inhibitors, saxagliptin (SAVOR-TIMI 53) and alogliptin (EXAMINE) versus placebo [27,28]. Likewise, significant differences in blood pressure, cholesterol, heart rate and fracture risk must be interpreted cautiously until higher-quality evidence is available. These exploratory findings need to be corroborated by mechanistic studies, robustly designed observational studies, and data from ongoing randomized controlled trials.

The present study has several implications for both policy makers and clinicians. The former may be responsible for allocating research funds or commissioning evidence reviews or health technology assessments. The policy makers responsible for making formulary decisions based on drug coverage may also use the results from systematic reviews of treatment effects, while clinicians often use systematic reviews as a source for making evidence-informed treatment decisions. Indeed, one of the founding principles of evidence-based medicine is that not all levels of evidence are considered equal. As such, rigorous systematic reviews of medical interventions are considered to be high-quality scientific evidence useful to help inform patient care decisions, implement healthcare policies, and develop clinical practice guidelines [29]. The popularity of systematic reviews and meta-analyses for informing clinicians and policymakers about the effects of medical interventions has led to multiple reviews being conducted on the same topic [30]. Indeed, we found >80 systematic reviews evaluating the effects of incretin-based medications. It is important to note that, although duplication is a risk, the included reviews reported on a broad range of outcomes and undertook various methods to summarize and quantify the drug effects of incretin-based medications.

Although the present study used the standard rigorous methods for conducting systematic reviews such as a published protocol, a comprehensive search strategy, and screening and quality assessment by two independent reviewers, it has several limitations. First, we limited our data extraction to the level of the systematic review, which was our unit of analysis for this study. This precluded us from meta-analysing individual study results. In addition, we did not evaluate the degree of overlap among individual studies included within the reviews. As the present study was focused on summarizing and assessing the quality of systematic reviews, we felt that extracting individual study-level data was beyond the scope of our review. Second, given the large number of pooled estimates for numerous outcomes reported over the 84 systematic reviews, we were limited in the amount of detail we could include in our manuscript. Nonetheless, we have included numerous supplemental tables for interested readers to examine the results in more depth, and we anticipate follow-up publications. Readers interested in quickly identifying a review of interest could use the figure showing the results of their outcome of interest and subsequently identify the study author and year in Table S1, which contains a link to the reference number in File S2. Third, although some reviews did report results for formulation-specific and dose–response effects among individual agents, there is a lack of high-quality comparative evidence for long-acting formulations (e.g. exenatide 2 mg vs basal insulin) as well as for dose–response effects.

The present overview of reviews provides an evidence-based assessment and synthesis of published systematic reviews on the safety, efficacy and effectiveness of incretin-based medications. The evidence to date does not suggest any definitive benefits of incretin-based medications, beyond glucose-lowering, for patients with type 2 diabetes. The present overview of systematic reviews provides a pragmatic means to arrive at a high-quality systematic review about incretin-based medications. Moreover, despite the vast number of systematic reviews published, there is still a dearth of evidence regarding important outcomes for patients with type 2 diabetes treated with incretin-based medications.

Acknowledgements

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An abstract of this paper was presented as a poster at the 17th Annual Canadian Diabetes Association Professional Conference and Annual Meetings held in Winnipeg, Manitoba from 22–25 October 2014.

Conflict of Interest

The authors have no conflict of interest to declare. Furthermore, none of the authors were involved with any of the included or excluded reviews with this study.

Author contributions were as follows: J. M. G., E. M. D., K. J. M., M. D. A. and K. H. were involved in the concept and design of the study. J. M. G., A. C., K. J. M., M. D. A. were responsible for screening, data extraction, and analyses of the data. J. M. G. and A. C. were responsible for drafting the first version of the manuscript. All authors contributed to the interpretation of data and provided revisions to the manuscript. J. M. G. will act as guarantor for the study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Frequency of outcomes of pooled treatment effects reported from 66 quantitative systematic reviews evaluating the safety and/or effectiveness of glucagon-like peptide 1 receptor agonists and/or dipeptidyl-peptidase-4 inhibitors.

Figure S2. Assessment of Multiple Systematic Reviews scores for systematic reviews with and without a meta-analysis.

Table S1. Characteristics and quality assessment of included systematic reviews.

Table S2. References of excluded studies.

Table S3. Summary characteristics of 84 systematic reviews that evaluated either glucagon-like peptide 1 receptor agonists, dipeptidyl-peptidase-4 inhibitors or both.

Table S4. Summary results of the effect of dipeptidyl-peptidase-4 inhibitors on glycaemic control compared with placebo and active comparators.

Table S5. Summary results of the effect of glucagon-like peptide 1 receptor agonists on glycaemic control compared with placebo and active comparators.

Table S6. Summary results of the effect of dipeptidyl-peptidase-4 inhibitors on the risk of macrovascular events compared with placebo and active comparators.

Table S7. Summary results of the effect of glucagon-like peptide 1 receptor agonists on the risk of macrovascular events compared with placebo and active comparators.

Table S8. Summary results of the effect of dipeptidyl-peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists on the risk of hypoglycaemic events compared with placebo and active comparators.

File S1. Dose-specific exenatide effect estimates.

File S2. References of included studies.

File S3. Summary results for secondary outcomes.

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