## Online-only Supplement


*eTable 1. PRISMA Checklist* ..... 3

*eTable 2. Search Terms* ..... 5

*eTable 3. Definitions of Certain Outcomes and Adverse Events* ..... 6

*eTable 4. Categorization of Dosing Levels for GLP1RAs and Other Drugs* ..... 7

*eTable 5. Characteristics of Randomized Trials of GLP1RA vs. Placebo* ..... 8

*eTable 6. Characteristics of Randomized Trials of GLP1RA vs. Other Anti-hyperglycemic Medication* ..... 9

*eTable 7. Inclusion Criteria of Randomized Trials* ..... 11

*eTable 8. Participant Characteristics: Randomized Trials of GLP1RA vs. Placebo* ..... 14

*eTable 9. Participant Characteristics: Randomized Trials of GLP1RA vs. Other Anti-hyperglycemic Medication* ..... 21

*eTable 10: Number of GLP1RA vs. Placebo trials available for each outcome and subgroup analysis* ..... 32

*eTable 11: Number of GLP1RA vs. Other Anti-hyperglycemic Medication trials available for each outcome and subgroup analysis* ..... 33

*eTable 12. Risk of Bias GLP1RA vs. Placebo for $HbA_{1c}$ [a]* ..... 34

*eTable 13. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for $HbA_{1c}$[a]* ..... 35

*eTable 14. Risk of Bias GLP1RA vs. Placebo for Mortality*[a] ..... 37

*eTable 15. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Mortality*[a] ..... 38

*eTable 16. Risk of Bias GLP1RA vs. Placebo for 3-point MACE*[a] ..... 39

*eTable 17. Risk of Bias GLP1RA vs. Placebo for Any Myocardial Infraction Event*[a] ..... 40

*eTable 18. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Any Myocardial Infraction Event*[a] ..... 40

*eTable 19. Risk of Bias GLP1RA vs. Placebo for Stroke*[a] ..... 41

*eTable 20. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Stroke*[a] ..... 41

*eTable 21. Risk of Bias GLP1RA vs. Placebo for Any Renal Event*[a] ..... 42

*eTable 22. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Any Renal Event*[a] ..... 42

*eTable 23. Risk of Bias GLP1RA vs. Placebo for Gastrointestinal Event Leading to Treatment Discontinuation[a]* ..... *43*

*eTable 24. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Gastrointestinal Event Leading to Treatment Discontinuation[a]* ..... *44*

*eFigure 1. Funnel Plots for Cardiovascular Risk Factors for GLP1RA vs. Placebo* ..... *45*

*eFigure 2. Funnel Plots for Microvascular Outcomes, Macrovascular Outcomes, Mortality, and Adverse Events for GLP1RA vs. Placebo* ..... *46*

*eFigure 3. Funnel Plots for Cardiovascular Risk Factors for GLP1RA vs. Other Anti-hyperglycemic Medication* ..... *47*

*eFigure 4. Funnel Plots for Microvascular Outcomes, Macrovascular Outcomes, Mortality, and Adverse Events for GLP1RA vs. Other Anti-hyperglycemic Medication*..... *48*

*eTable 25. Effects of GLP1RAs on Cardiovascular Risk Factors, Mortality, Macrovascular and Microvascular Outcomes, and Adverse Events[a]*..... *49*

*eTable 26. Subgroup Analyses: GLP1RA vs. Placebo*..... *51*

*eTable 27. Subgroup Analyses: GLP1RA vs. Other Anti-hyperglycemic Medication* ..... *52*

eTable 1. PRISMA Checklist

| Section and 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. | 2 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| 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. | 3 |
| 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. | 4 |
| 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. | 3 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | eTable 2 |
| 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). | 3-4 |
| 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. | 4-5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4-5, eTables 3-4 |
| 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. | 4 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5 |
| 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. | 4-5 |
| 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). | 4-5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5 |
| 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. | 5, Figure 1 |
| 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. | 5-6, eTables 5-11 |
| 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). | 6, eTables 12-24 |
| 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. | 6-7, Table 1, Figures 2-5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6-7, eTable 25 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6, Table 1, eFigures 1-4 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 6-7, eTables 26-27 |
| 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). | 7-8, Table 1 |
| 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). | 8-9 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 |
| 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. | 9 |

eTable 2. Search Terms

| | |
|---|---|
| PubMed (inception to 7/15/2019) | Search (((((("Diabetes Mellitus"[Mesh] OR diabetes OR T2DM OR T2D OR IDDM OR NIDDM OR diabet*[tw] OR "noninsulin-dependent" OR "noninsulin dependent" OR "non-insulin-dependent" OR "non-insulin dependent" OR "non-insulin-resistant" OR "noninsulin-resistant" OR "non-insulin-resistance" OR "non-insulin-responsive"))) AND (("Glucagon-like peptide 1"[MeSH] OR GLP-1 OR GLP-1s OR GLP1 OR GLP1s OR GLP1RA OR GLP1RAs OR "glucagon-like peptide-1 receptor agonist" OR "glucagon-like peptide-1 receptor agonists" OR exenatide OR liraglutide OR lixisenatide OR taspoglutide OR semaglutide OR dulaglutide OR albiglutide OR Byetta OR Bydureon OR Eperzan OR Tanzeum OR Victoza OR Saxenda OR Xultophy OR Lyxumia OR Adlyxin OR Ozempic OR Trulicity OR Soliqua OR Suliqua OR IDegLira OR LixiLan OR iGlarLixi)))) |
| Scopus (inception to 7/15/2019) | ( TITLE-ABS-KEY ( diab* OR t2d* OR *iddm OR "noninsulin-dependent" OR "noninsulin dependent" OR "non-insulin-dependent" OR "non-insulin dependent" OR "non-insulin-resistant" OR "noninsulin-resistant" OR "non-insulin-resistance" OR "non-insulin-responsive" ) ) AND ( ( TITLE-ABS-KEY ( glucagon* AND peptide* ) ) OR ( TITLE-ABS-KEY ( glp* ) ) OR ( TITLE-ABS-KEY ( exenatide OR liraglutide OR lixisenatide OR taspoglutide OR semaglutide OR dulaglutide OR albiglutide ) ) OR ( TITLE-ABS-KEY ( byetta OR bydureon OR eperzan OR tanzeum OR victoza OR saxenda OR xultophy OR lyxumia OR adlyxin OR ozempic OR trulicity OR soliqua OR suliqua OR ideglira OR lixilan OR iglarlixi ) ) ) |

eTable 3. Definitions of Certain Outcomes and Adverse Events

| Complication or Adverse Event | Definition |
|---|---|
| MACE | |
| 3-component MACE | Cardiovascular death, myocardial infarction, or stroke |
| 5-component MACE | Cardiovascular death, myocardial infarction, stroke, heart failure, or unstable angina |
| 6-component MACE | Cardiovascular death, myocardial infarction, stroke, heart failure, unstable angina, or revascularization |
| End-stage renal disease | Chronic kidney disease stage 5, estimated glomerular filtration rate ≤ 15 ml/min, or renal failure |
| Any renal event | Nephropathy, acute kidney injury, acute renal failure, dialysis, or end-stage renal disease.<br><br>If studies reported more than one of these outcomes, we included the result for the outcome with the highest prevalence (e.g., nephropathy rather than end-stage renal disease) |
| Hypoglycemia | |
| Any hypoglycemia | Glucose level ≤3.9 mmol/L or study-defined non-severe hypoglycemia |
| Severe hypoglycemia | Requiring medical assistance or study-defined severe hypoglycemia |
| Gastrointestinal event leading to treatment discontinuation | Diarrhea, nausea, vomiting, or gastrointestinal composite (defined by study)<br><br>If studies reported more than one of these outcomes, we included the result for the outcome with the highest prevalence |
| Any pancreatitis | Acute pancreatitis, chronic pancreatitis, or unspecified pancreatitis |

Abbreviations: MACE, major adverse cardiovascular event

eTable 4. Categorization of Dosing Levels for GLP1RAs and Other Drugs

| **Medication** | **Dosing** |
|---|---|
| Albiglutide | |
| 30 mg daily | Low |
| 50 mg daily | High |
| Dulaglutide | |
| 0.75 mg daily | Low |
| 1.5 mg daily | High |
| Exenatide | |
| 2 mg weekly | High |
| 5 mcg twice daily | Low |
| 10 mcg twice daily | High |
| Liraglutide | |
| ≤ 1.2 mg daily | Low |
| ≥ 1.8 mg daily | High |
| Lixisenatide | |
| 10 mcg daily | Low |
| 20 mcg daily | High |
| Semaglutide | |
| ≤ 0.5 mg daily | Low |
| 1 mg daily | High |
| Taspoglutide | |
| 10 mg daily | Low |
| 20 mg daily | High |
| Oral semaglutide | |
| ≤ 7 mg daily | Low |
| 14 mg daily | High |
| Glibenclamide (UK) /Glyburide | |
| ≤ 10 mg daily | Low |
| ≥ 15 mg daily | High |
| Glimepiride | |
| ≤ 4 mg daily | Low |
| ≥ 6 mg daily | High |
| Pioglitazone | |
| ≤ 30 mg daily | Low |
| 45 mg daily | High |
| Sitagliptin | |
| ≤ 50 mg daily | Low |
| 100 mg daily | High |

eTable 5. Characteristics of Randomized Trials of GLP1RA vs. Placebo

| Trial Name | Main Drug and Dose Category | Background Medication | Location | Study Period (Month/Year) | Screened, N | Randomized, N | Run-in Period | Length of Follow-up | Withdrawn, N (%) |
|---|---|---|---|---|---|---|---|---|---|
| Derosa 2013 | Exenatide<br>High dose | Metformin | Italy | 4/2008-4/2010 | NR | 171 | Y | 52 weeks | 2 (1.2) |
| ELIXA | Lixisenatide<br>High dose | Standard care | Multi-continent | 7/2010-8/2013 | 7718 | 6068 | Y | Median 25 months | 215 (3.5) |
| EXSCEL | Exenatide<br>N/A | 0-3 other drugs | Multi-continent | 6/2010-5/2017 | 15185 | 14752 | N | 3.2 years | 565 (3.8) |
| GetGoal-F1 | Lixisenatide<br>High dose | Metformin | Multi-continent | 9/2008-1/2011 | 884 | 484 | Y | 76 weeks | 103 (21.3) |
| GetGoal-P | Lixisenatide<br>High dose | Pioglitazone ± metformin | Multi-continent | 9/2008-6/2011 | 906 | 484 | Y | 76 weeks | 59 (12.2) |
| HARMONY 1 | Albiglutide<br>Low dose | Pioglitazone ± metformin | Multi-continent | 1/2009-1/2013 | 450 | 310 | Y | 52 weeks<br>3 years | 52 wk: 53 (17.1)<br>3 yr: 113 (36.5) |
| HARMONY 2 | Albiglutide<br>High dose | No other drugs | North America | 1/2009-11/2013 | 479 | 309 | Y | 52 weeks<br>3 years | 52 wk: 61 (19.7)<br>3 yr: 118 (38.2) |
| HARMONY 3 | Albiglutide<br>High dose | Metformin | Multi-continent | 2/2009-3/2013 | 1525 | 1049 | Y | 104 weeks<br>3 years | 104 wk: 305 (29.1)<br>3 yr: 421 (40.1) |
| HARMONY 5 | Albiglutide<br>High dose | Metformin + glimepiride 4 mg | Multi-continent | 2/2009-4/2013 | 992 | 685 | Y | 52 weeks<br>3 years | 52 wk: 162 (23.6)<br>3 yr: 297 (43.4) |
| Harmony Outcomes | Albiglutide<br>High dose | Standard care | Multi-continent | 7/2015-3/2018 | 10793 | 9463 | N | 16 months | 265 (2.8) |
| LEADER | Liraglutide<br>High dose | Standard care | Multi-continent | 9/2010-4/2012 | 12076 | 9340 | Y | 3 years | 298 (3.2) |
| NCT00395746 | Liraglutide<br>Low dose | Sulfonlyurea | Japan | 11/2006-4/2008 | 308 | 267 | N | 52 weeks | 36 (13.5) |
| PIONEER 4 | Oral semaglutide<br>High dose | Metformin ± SGLT2 | Multi-continent | 8/2016-2/2017 | 950 | 711 | N | 52 weeks | 26 (3.7) |
| PIONEER 6 | Oral semaglutide<br>High dose | Standard care | Multi-continent | 1/2017-9/2018 | 3418 | 3183 | N | Median 15.9 months | 11 (0.3) |
| REWIND | Dulaglutide<br>High dose | 1 or 2 other drugs ± insulin | Multi-continent | 7/2011-8/2018 | 12133 | 9901 | Y | Median 5.4 years | 34 (0.3) |
| SCALE | Liraglutide<br>High dose | 0-3 other drugs | Multi-continent | 6/2011-1/2013 | 1361 | 846 | N | 56 weeks | 247 (29.2) |
| SUSTAIN-6 | Semaglutide<br>High dose* | Standard care | Multi-continent | 2/2013-3/2016 | 4346 | 3297 | Y | 104 weeks | 65 (2.0) |

eTable 6. Characteristics of Randomized Trials of GLP1RA vs. Other Anti-hyperglycemic Medication

| Trial Name | Main Drug and Dose Category | Comparator | Background Medication | Location | Study Period (Month/Year) | Screened, N | Randomized, N | Run-in Period | Length of Follow-up | Withdrawn, N (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Arturi 2016 | Liraglutide<br>High dose | Sitagliptin | Metformin ± sulfonylurea | Italy | NR | NR | 32 | Y | 52 weeks | NR |
| AWARD-2 | Dulaglutide<br>High dose | Insulin glargine | Metformin + glimepiride | Multi-continent | 2/2010-11/2012 | NR | 810 | Y | 52 weeks<br>78 weeks | 52 wk: 67 (8.3)<br>78 wk: 84 (10.4) |
| AWARD-3 | Dulaglutide<br>High dose | Metformin | No other drugs | Multi-continent | 5/2010-6/2012 | NR | 807 | Y | 52 weeks | 156 (19.3) |
| AWARD-4 | Dulaglutide<br>High dose | Insulin glargine | Insulin (majority also metformin) | Multi-continent | 12/2010-9/2012 | 1256 | 884 | Y | 52 weeks | 202 (22.9) |
| AWARD-5 | Dulaglutide<br>High dose | Sitagliptin | Metformin | Multi-continent | 8/2008-5/2010 | NR | 1098 | Y | 52 weeks<br>104 weeks | 52 wk: 202 (18.4)<br>104 wk: 359 (32.7) |
| AWARD-7 | Dulaglutide<br>High dose | Insulin glargine | Insulin lispro | Multi-continent | 8/2012-11/2015 | 1324 | 577 | Y | 52 weeks | 97 (16.8) |
| Derosa 2010 | Exenatide<br>High dose | Glibenclamide | Metformin | Italy | NR | NR | 128 | Y | 52 weeks | 12 (9.4) |
| Derosa 2011 | Exenatide<br>High dose | Glimepiride | Metformin | Italy | NR | NR | 111 | N | 52 weeks | 10 (9.0) |
| DUAL I | Liraglutide<br>High dose | Insulin degludec | Metformin ± pioglitazone | Multi-continent | 5/2011-11/2012 | 3004 | 1663 | N | 52 weeks | 451 (27.1) |
| DURATION-3 | Exenatide<br>N/A | Insulin glargine | Metformin ± sulfonylurea | Multi-continent | 5/2008-1/2012 | 659 | 467 | Y | 84 weeks<br>3 years | 84 wk: 132 (28.3)<br>3 yr: 163 (34.9) |
| HARMONY 3 | Albiglutide<br>High Dose | Sitagliptin | Metformin | Multi-continent | 2/2009-3/2013 | 1525 | 1049 | Y | 104 weeks<br>3 years | 104 wk: 305 (29.1)<br>3 yr: 421 (40.1) |
| HARMONY 4 | Albiglutide<br>High dose | Insulin glargine | Metformin ± sulfonylurea | Multi-continent | 2/2009-3/2013 | 1060 | 779 | Y | 52 weeks<br>3 years | 52 wk: 180 (23.1)<br>3 yr: 273 (35.0) |
| HARMONY 5 | Albiglutide<br>High dose | Pioglitazone | Metformin + glimepiride 4 mg | Multi-continent | 2/2009-4/2013 | 992 | 685 | Y | 52 weeks<br>3 years | 52 wk: 162 (23.6)<br>3 yr: 297 (43.4) |
| HARMONY 6 | Albiglutide<br>High dose | Insulin lispro | Insulin glargine ± other drugs | Multi-continent | 9/2009-5/2012 | 920 | 586 | Y | 52 weeks | 81 (13.8) |
| HARMONY 8 | Albiglutide<br>High dose | Sitagliptin | Other drugs permitted | Multi-continent | 5/2010-5/2012 | 771 | 507 | Y | 52 weeks | 119 (23.5) |
| LEAD-2 | Liraglutide<br>Low dose | Glimepiride | Metformin | Multi-continent | 5/2006-11/2008 | 1662 | 1091 | Y | 104 weeks | 466 (42.7) |
| LEAD-3 (Mono) | Liraglutide<br>High dose | Glimepiride | None specified | North America | 2/2006-11/2007 | NR | 746 | Y | 52 weeks<br>104 weeks | 52 wk: 259 (34.7)<br>104 wk: 424 (56.8) |

| Trial Name | Main Drug and Dose Category | Comparator | Background Medication | Location | Study Period (Month/Year) | Screened, N | Randomized, N | Run-in Period | Length of Follow-up | Withdrawn, N (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| NCT00082407 | Exenatide High dose | Insulin aspart | Metformin + sulfonylurea | Multi-continent | 11/2003-4/2005 | 641 | 505 | N | 52 weeks | 79 (15.6) |
| NCT00097500 | Exenatide High dose | Insulin glargine | Metformin | Europe | 9/2004-9/2007 | 150 | 69 | N | 52 weeks<br>156 weeks | 52 wk: 10 (14.5)<br>156 wk: 33 (47.8) |
| NCT00393718 | Liraglutide Low dose | Glibenclamide | No other drugs | Japan | 11/2006-5/2008 | 464 | 411 | Y | 52 weeks | 65 (15.8) |
| NCT00700817 | Liraglutide High dose | Sitagliptin | Metformin | Multi-continent | 6/2008-12/2009 | 1302 | 665 | N | 52 weeks | 229 (34.4) |
| NCT01512108 | Liraglutide Low dose | Other drugs | Glinide, metformin, glucosidase inhibitor, or thiazolidinedione | Japan | 1/2012-4/2013 | 435 | 363 | N | 52 weeks | 31 (8.5) |
| NCT01648582 | Dulaglutide High dose | Insulin glargine | Metformin ± sulfonylurea | Multi-continent | 7/2012-12/2014 | 1121 | 774 | Y | 52 weeks | 102 (13.2) |
| PIONEER 3 | Oral semaglutide High dose | Sitagliptin | Metformin ± sulfonylurea | Multi-continent | 2/2016-3/2018 | 2463 | 1864 | N | 52 weeks<br>78 weeks | 52 wk: NR<br>78 wk: 109 (5.8) |
| PIONEER 7 | Oral semaglutide High dose | Sitagliptin | 1 or 2 other drugs | Multi-continent | 9/2016-3/2019 | 804 | 504 | Y | 52 weeks | 19 (3.8) |
| Su 2014 | Exenatide High dose | Insulin glargine | Metformin | China | 11/2009-9/2012 | NR | 60 | N | 52 weeks | NR |
| SUSTAIN (JAPAN) | Semaglutide High dose | Other drugs | 0-1 other drugs | Japan | 8/2014-2/2016 | 665 | 601 | Y | 56 weeks | 56 (9.3) |
| SUSTAIN 2 | Semaglutide High dose | Sitagliptin | 1 or 2 other drugs | Multi-continent | 12/2013-8/2015 | 1796 | 1231 | Y | 56 weeks | 213 (17.3) |
| T-Emerge 4 | Taspoglutide High dose | Sitagliptin | Metformin | Multi-continent | 10/2008-3/2011 | 1034 | 666 | Y | 52 weeks | 191 (28.7) |
| Yan 2015 | Liraglutide Low dose | Insulin glargine | Repaglinide + metformin | China | 5/2010-12/2012 | NR | 52 | N | 72 weeks | 3 (5.8) |

Abbreviations: NR, not reported

eTable 7. Inclusion Criteria of Randomized Trials

| Trial Name | Age (years) | Baseline $HbA_{1c}$ (%) | BMI ($kg/m^2$) | eGFR ($mL/min/m^2$) | Must have high CV risk | Must have pre-existing CVD, CHF, or CKD |
|---|---|---|---|---|---|---|
| GLP1RA vs. Placebo | | | | | | |
| Derosa (2013) | ≥18 | >7.5 | ≥25 & <34.9 | NR | No | No |
| ELIXA (2015) | ≥30 | 5.5-11.0 | NR | ≥30 | Yes | CVD |
| EXSCEL (2017, 2019) | ≥18 | 6.5-10.0 | NR | ≥30 | No | No |
| GetGoal-F1 (2013) | 24-79 | 7.0-10.0 | NR | NR | No | No |
| GetGoal-P (2013) | ≥18 | 7.0-10.0 | NR | NR | No | No |
| HARMONY 1 (2014, 2017) | ≥18 | 7.0-10.0 | 20-45 | NR | No | No |
| HARMONY 2 (2016, 2017) | ≥18 | 7.0-10.0 | 20-45 | NR | No | No |
| HARMONY 3 (2014, 2017) | ≥18 | 7.0-10.0 | 20-45 | >60 | No | No |
| HARMONY 5 (2015, 2017) | ≥18 | 7.0-10.0 | 20-45 | >60 | No | No |
| Harmony Outcomes (2018) | ≥40 | >7.0 | NR | ≥30 | Yes | CVD |
| LEADER (2016) | ≥50 | ≥7.0 | NR | <60 | Yes | CVD, CHF, or CKD |
| NCT00395746 (2011) | ≥20 | 7.4-10.4 | NR | NR | No | No |
| PIONEER 4 (2019) | ≥18 | 7.0-9.5 | NR | ≥60 | No | No |
| PIONEER 6 (2019) | ≥50 | NR | NR | ≥30 | Yes | CVD or CKD |
| REWIND (2019) | ≥50 | ≤9.5 | ≥23 | ≥15 | Yes | CVD or CKD |
| SCALE (2015) | ≥18 | 7-10.0 | ≥27 | NR | No | No |
| SUSTAIN-6 (2016) | ≥50 | ≥7.0 | NR | NR | Yes | CVD, CHF, or CKD |
| GLP1RA vs Other Anti-hyperglycemic Medications | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Arturi (2016) | 45-75 | ≥7.0 & <10.0 | NR | NR | No | CVD or CHF |
| AWARD-2 (2015) | ≥18 | 7.0-11.0 | 23-45 | NR | No | No |
| AWARD-3 (2014) | ≥18 | 6.5-9.5 | NR | NR | No | No |
| AWARD-4 (2015, 2019) | ≥18 | 7.0-11.0 | 23-45 | NR | No | No |
| AWARD-5 (2014, 2015) | 18-75 | 7.0-9.5 | 25-40 | NR | No | No |
| AWARD-7 (2018) | ≥18 | 7.5-10.5 | 23-45 | ≥15 & <60 | No | CKD |
| Derosa (2010) | ≥18 | >8.0 | ≥25 & <30 | NR | No | No |
| Derosa (2011) | ≥18 | >8.0 | ≥25 & <30 | NR | No | No |
| DUAL I (2015) | ≥18 | 7.0-10.0 | ≤40 | NR | No | No |
| DURATION-3 (2012, 2015) | ≥18 | 7.1-11.0 | 23-45 | NR | No | No |
| HARMONY 3 (2014, 2017) | ≥18 | 7.0-10.0 | 20-45 | >60 | No | No |
| HARMONY 4 (2014, 2017) | ≥18 | 7.0-10.0 | 20-45 | >60 | No | No |
| HARMONY 5 (2015, 2017) | ≥18 | 7.0-10.0 | 20-45 | >60 | No | No |
| HARMONY 6 (2017) | 18-75 | 7.0-10.5 | 20-45 | >60 | No | No |
| HARMONY 8 (2014) | ≥18 | 7.0-10.0 | 20-45 | ≥15 & <90 | No | No |
| LEAD-2 (2013) | 18-80 | 7.0-11.0 | ≤40 | NR | No | No |
| LEAD-3 (Mono) (2009, 2011) | 18-80 | 7.0-11.0 | ≤45 | NR | No | No |
| NCT00082407 (2007) | 30-75 | 7.0-11.0 | 25-40 | NR | No | No |
| NCT00097500 (2009, 2016, 2019) | 30-75 | 6.6-9.5 | 25-40 | NR | No | No |
| NCT00393718 (2011) | ≥20 | 7.0-10.0 | <35 | NR | No | No |
| NCT00700817 (2011) | 18-80 | 7.5-10.0 | ≤45 | NR | No | No |
| NCT01512108 (2014, 2018) | ≥20 | 7.0-10.0 | <40 | NR | No | No |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT01648582 (2011) | ≥18 | 7.0-11.0 | 19-35 | NR | No | No |
| PIONEER 3 (2013) | ≥18 | 7.0-10.5 | NR | ≥60 | No | No |
| PIONEER 7 (2019) | ≥18 | 7.5-9.5 | NR | ≥60 | No | No |
| Su (2014) | 35-70 | 8-10 | 26-36 | NR | No | No |
| SUSTAIN (JAPAN) (2018) | ≥20 | 7.0-10.5 | NR | ≥30 | No | No |
| SUSTAIN 2 (2017) | ≥18 | 7.0-10.5 | ≥18 | ≥60 | No | No |
| T-Emerge 4 (2012) | 18-75 | 7.0-10.0 | 23-45 | NR | No | No |
| Yan (2015) | 40-60 | <9.0 | 18-30 | NR | No | No |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; BMI, body mass index; eGFR, estimated glomerular filtration rate; CV, cardiovascular; CVD, cardiovascular disease; CHF, congestive heart disease; CKD, chronic kidney disease; NR, not reported

eTable 8. Participant Characteristics: Randomized Trials of GLP1RA vs. Placebo

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | HbA$_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| **Derosa (2013)** | | | | | | | | | |
| Exenatide 10 ug bid | 86 | 57.3 (7.7)<br>NR | 43 (50.0) | NR<br>NR | 86 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 31.9 (1.7)<br>NR<br>NR | 89.0 (9.7) | 8.1 (0.8)<br>NR | 0.63 (0.23)<br>NR |
| Placebo | 85 | 56.7 (7.3)<br>NR | 41 (48.2) | NR<br>NR | 85 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 31.7 (1.5)<br>NR<br>NR | 90.5 (10.3) | 7.9 (0.6)<br>NR | 0.65 (0.26)<br>NR |
| **ELIXA (2015)** | | | | | | | | | |
| Lixisenatide 10-20 ug daily | 3034 | 59.9 (9.7)<br>NR | 2111 (69.6) | 865 (28.5)<br>NR | 2258 (74.4)<br>118 (3.9)<br>404 (13.3)<br>254 (8.4)<br>NR | 30.1 (5.6)<br>NR<br>NR | 84.6 (19.2) | 7.7 (1.3)<br>NR | 9.2 (8.2)<br>NR |
| Placebo | 3034 | 60.6 (9.6)<br>NR | 2096 (69.1) | 903 (29.8)<br>NR | 2318 (76.4)<br>103 (3.4)<br>367 (12.1)<br>246 (8.1)<br>NR | 30.2 (5.8)<br>NR<br>NR | 85.1 (19.6) | 7.6 (1.3)<br>NR | 9.4 (8.3)<br>NR |
| **EXSCEL (2017, 2019)** | | | | | | | | | |
| Exenatide 2 mg weekly | 7356 | NR<br>62 (NR) | 4562 (62) | 1506 (20.5)<br>5849 (79.5) | 5554 (75.5)<br>442 (6.0)<br>725 (9.9)<br>56 (0.8)<br>577 (7.8) | NR<br>2659 (36.5)<br>4628 (63.5) | NR | NR<br>8 (NR) | NR<br>12 (7-17) |
| Placebo | 7356 | NR<br>62 (NR) | 4587 (62) | 1520 (20.6)<br>5875 (79.4) | 5621 (76.0)<br>436 (5.9)<br>727 (9.8)<br>52 (0.7) | NR<br>2704 (37.0)<br>4611 (63.0) | NR | NR<br>8 (NR) | NR<br>12 (7-18) |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | HbA$_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| | | | | | 557 (7.5) | | | | |
| **GetGoal-F1 (2013)** | | | | | | | | | |
| Lixisenatide 20 ug daily (1 step) | 161 | 55.4 (8.9)<br>NR | NR (44) | NR<br>NR | NR (88)<br>NR (1)<br>NR (8)<br>NR (4)<br>NR | 33.0 (5.8)<br>NR<br>NR | 90.3 (19.0) | 8 (0.9)<br>NR | 5.8 (3.9)<br>NR |
| Placebo | 162 | 58.2 (9.8)<br>NR | NR (45) | NR<br>NR | NR (93)<br>NR (1)<br>NR (6)<br>NR (1)<br>NR | 32.4 (5.5)<br>NR<br>NR | 87.9 (17.3) | 8 (0.8)<br>NR | 6.2 (4.7)<br>NR |
| **GetGoal-P (2013)** | | | | | | | | | |
| Lixisenatide 10-20 ug daily | 323 | 56.0 (9.5)<br>NR | NR (53) | 87 (NR)<br>236 (NR) | 273 (85)<br>14 (4)<br>14 (4)<br>22 (7)<br>NR | 33.7 (6.7)<br>NR<br>NR | 92.9 (22.9) | 8.1 (0.9)<br>NR | 8.1 (5.4)<br>NR |
| Placebo | 161 | 55.3 (9.5)<br>NR | NR (51) | 41 (NR)<br>120 (NR) | 132(82)<br>9 (6)<br>8 (5)<br>12 (8)<br>NR | 34.4 (7.0)<br>NR<br>NR | 96.7 (25.6) | 8.1 (0.8)<br>NR | 8.1 (5.6)<br>NR |
| **HARMONY 1 (2014, 2017)** | | | | | | | | | |
| Albiglutide 30 mg weekly | 150 | 55.2 (10.0)<br>NR | 92 (61.3) | 38 (25.3)<br>NR | 109 (72.7)<br>19 (12.7)<br>6 (4.0)<br>19 (12.7)<br>NR | 33.6 (5.9)<br>NR<br>NR | 97.6 (22.0) | 8.1 (1.0)<br>NR | 8.0 (5.6)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| Placebo | 151 | 54.9 (9.4)<br>NR | 88 (58.3) | 37 (24.5)<br>NR | 108 (71.5)<br>20 (13.2)<br>6 (4.0)<br>17 (11.3)<br>NR | 34.7 (5.6)<br>NR<br>NR | 100.2 (23.1) | 8.1 (0.9)<br>NR | 7.9 (6.1)<br>NR |
| **HARMONY 2 (2016, 2017)** | | | | | | | | | |
| Albiglutide 50 mg weekly | 99 | 52.0 (11.8)<br>NR | 50 (50.5) | 26 (26.3)<br>NR | 78 (78.8)<br>14 (14.1)<br>1 (1.0)<br>NR<br>NR | 33.9 (5.5)<br>NR<br>NR | 97.1 (17.8) | 8.2 (0.9)<br>NR | 4.2 (4.6)<br>NR |
| Placebo | 101 | 53.1 (11.7)<br>NR | 58 (57.4) | 29 (28.7)<br>NR | 79 (78.2)<br>14 (13.9)<br>5 (5.0)<br>NR<br>NR | 33.0 (5.4)<br>NR<br>NR | 95.4 (19.9) | 8.0 (0.9)<br>NR | 4.3 (4.0)<br>NR |
| **HARMONY 3 (2014, 2017)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 315 | 54.3 (10.1)<br>NR | 135 (44.7) | 99 (32.8)<br>NR | 214 (70.9)<br>53 (17.5)<br>18 (6.0)<br>NR<br>NR | 32.7 (5.6)<br>NR<br>NR | 89.6 (18.4) | 8.1 (0.8)<br>NR | 6.0 (4.3)<br>NR |
| Placebo | 104 | 56.1 (10.0)<br>NR | 50 (49.5) | 32 (31.7)<br>NR | 64 (63.4)<br>23 (22.8)<br>5 (5.0)<br>NR<br>NR | 32.8 (5.4)<br>NR<br>NR | 91.6 (19.3) | 8.2 (0.9)<br>NR | 6.7 (6.6)<br>NR |
| **HARMONY 5 (2015, 2017)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 281 | 54.5 (9.5)<br>NR | 135 (49.8) | NR<br>NR | 180 (66.4)<br>34 (12.5)<br>36 (13.3)<br>23 (8.5)<br>NR | 32.4 (5.5)<br>NR<br>NR | 90.9 (20.2) | 8.19 (0.91)<br>NR | 8.5 (6.3)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| Placebo | 116 | 55.7 (9.6)<br>NR | 70 (60.9) | NR<br>NR | 80 (69.6)<br>10 (8.7)<br>15 (13.0)<br>10 (8.7)<br>NR | 31.8 (4.9)<br>NR<br>NR | 89.9 (18.8) | 8.26 (0.98)<br>NR | 9.3 (6.1)<br>NR |
| **Harmony Outcomes (2018)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 4731 | 64.1 (8.7)<br>NR | 3304 (70) | NR<br>NR | 3295 (70)<br>111 (2)<br>228 (5)<br>92 (2)<br>1005 (21) | 32.3 (5.9)<br>NR<br>NR | NR | 8.76 (1.5)<br>NR | 14.1 (8.6)<br>NR |
| Placebo | 4732 | 64.2 (8.7)<br>NR | 3265 (69) | NR<br>NR | 3288 (69)<br>114 (2)<br>242 (5)<br>100 (2)<br>988 (21) | 32.3 (5.9)<br>NR<br>NR | NR | 8.72 (1.5)<br>NR | 14.2 (8.9)<br>NR |
| **LEADER (2016)** | | | | | | | | | |
| Liraglutide 1.8 mg daily | 4668 | 64.2 (7.2)<br>NR | 3011 (64.5) | 68 (11.7)<br>540 (13.2) | 3616 (77.0)<br>370 (8.0)<br>471 (10.0)<br>211 (4.5)<br>580 (12.4) | 32.5 (6.3)<br>NR<br>NR | 91.9 (21.2) | 8.7 (1.6)<br>NR | 12.8 (8.0)<br>NR |
| Placebo | 4672 | 64.4 (7.2)<br>NR | 2992 (64.0) | 86 (15.5)<br>608 (14.8) | 3622 (77.5)<br>407 (8.7)<br>465 (10.0)<br>178 (3.8)<br>554 (11.8) | 32.5 (6.3)<br>NR<br>NR | 91.1 (20.8) | 8.7 (1.5)<br>NR | 12.9 (8.1)<br>NR |
| NCT00395746 (2011) | | | | | | | | | |
| Liraglutide 0.9 mg daily | 88 | 61.3 (11.0)<br>NR | 59 (67.0) | NR<br>NR | 0 (0)<br>0 (0)<br>88 (100)<br>0 (0)<br>0 (0) | 24.4 (3.8)<br>NR<br>NR | 64.5 (12.0) | 8.61 (0.78)<br>NR | 11.6 (7.7)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | HbA$_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| Placebo | 88 | 58.6 (9.7)<br>NR | 57 (64.8) | NR<br>NR | 0 (0)<br>0 (0)<br>88 (100)<br>0 (0)<br>0 (0) | 24.9 (4.0)<br>NR<br>NR | 66.8 (13.7) | 8.85 (0.99)<br>NR | 10.1 (7.3)<br>NR |
| **PIONEER 4 (2019)** | | | | | | | | | |
| Oral semaglutide 14 mg daily | 285 | 56 (10)<br>NR | 147 (52) | 17 (6)<br>268 (94) | 208 (73)<br>12 (4)<br>39 (14)<br>3 (1)<br>NR | 32.5 (5.9)<br>NR<br>NR | 92.9 (20.6) | 8.0 (0.7)<br>NR | 7.8 (5.7)<br>NR |
| Placebo | 142 | 57 (10)<br>NR | 74 (52) | 5 (4)<br>137 (96) | 99 (70)<br>8 (6)<br>19 (13)<br>4 (3)<br>NR | 32.9 (6.1)<br>NR<br>NR | 93.2 (20.0) | 7.9 (0.7)<br>NR | 7.8 (5.5)<br>NR |
| **PIONEER 6 (2019)** | | | | | | | | | |
| Oral semaglutide 14 mg daily | 1591 | 66 (7)<br>NR | 1084 (68.1) | NR<br>NR | 1148 (72.2)<br>89 (5.6)<br>324 (20.4)<br>30 (1.9)<br>NR | 32 (6.6)<br>650 (40.9)<br>940 (59.1) | 91.0 (21.4) | 8.2 (1.6)<br>NR | 14.7 (8.5)<br>NR |
| Placebo | 1592 | 66 (7)<br>NR | 1092 (68.6) | NR<br>NR | 1152 (72.4)<br>103 (6.5)<br>306 (19.2)<br>31 (1.9)<br>NR | 32 (6.4)<br>629 (39.5)<br>963 (60.5) | 90.8 (21.0) | 8.2 (1.6)<br>NR | 15.1 (8.5)<br>NR |
| **REWIND (2019)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 4949 | 66.2 (6.5)<br>NR | 2643 (53.4) | NR<br>NR | 3754 (75.9)<br>NR<br>NR<br>NR<br>NR | 32.3 (5.7)<br>NR<br>NR | NR | 7.3 (1.1)<br>NR | 10.5 (7.3)<br>9.5 (5.5-14.5) |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| Placebo | 4952 | 66.2 (6.5)<br>NR | 2669 (53.9) | NR<br>NR | 3744 (75.6)<br>NR<br>NR<br>NR<br>NR | 32.3 (5.8)<br>NR<br>NR | NR | 7.4 (1.1)<br>NR | 10.6 (7.2)<br>9.5 (5.5-14.5) |
| **SCALE (2015)** | | | | | | | | | |
| Liraglutide 3.0 mg daily | 423 | 55.0 (10.8)<br>NR | 220 (52.0) | 46 (10.9)<br>375 (88.7) | 353 (83.5)<br>44 (10.4)<br>11 (2.6)<br>13 (3.1)<br>NR | 37.1 (6.5)<br>NR<br>NR | 105.7 (21.9) | 7.9 (0.8)<br>NR | 7.5 (5.7)<br>NR |
| Placebo | 212 | 54.7 (9.8)<br>NR | 97 (45.8) | 24 (11.3)<br>187 (88.2) | 175 (82.5)<br>27 (12.7)<br>4 (1.9)<br>5 (2.4)<br>NR | 37.4 (7.1)<br>NR<br>NR | 106.5 (21.3) | 7.9 (0.8)<br>NR | 6.7 (5.1)<br>NR |
| **SUSTAIN-6 (2016)** | | | | | | | | | |
| Semaglutide 0.5 mg weekly | 826 | 64.6 (7.3) | 495 (59.9) | 132 (16.0)<br>694 (84.0) | 693 (83.9)<br>54 (6.5)<br>63 (7.6)<br>16 (1.9)<br>NR | 32.7 (6.3)<br>NR<br>NR | 91.8 (20.25) | 8.7 (1.39)<br>NR | 14.3 (8.21)<br>NR |
| Semaglutide 1.0 mg weekly | 822 | 64.7 (7.1)<br>NR | 518 (63.0) | 124 (15.1)<br>698 (84.9) | 691 (84.1)<br>54 (6.6)<br>58 (7.1)<br>19 (2.3)<br>NR | 32.9 (6.2)<br>NR<br>NR | 92.9 (21.05) | 8.7 (1.51)<br>NR | 14.1 (8.17)<br>NR |
| Placebo 0.5 mg | 824 | 64.8 (7.6) | 482 (58.5) | 117 (14.2)<br>707 (85.8) | 676 (82.0)<br>54 (6.6)<br>80 (9.7)<br>14 (1.7)<br>NR | 32.9 (6.4)<br>NR<br>NR | 91.8 (20.35) | 8.7 (1.49) | 14 (8.54)<br>NR |

| **Trial Arms** | **N** | **Age (years)** | **Male** | **Ethnicity** | **Race** | **BMI (kg/m$^2$)** | **Weight (kg)** | **HbA$_{1c}$ (%)** | **Diabetes Duration (years)** |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)*<br>*Median (IQR)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* | *Mean (SD)*<br>*Median (IQR)* |
| Placebo<br>1.0 mg | 825 | 64.4 (7.5)<br>NR | 507 (61.5) | 137 (16.6)<br>688 (83.4) | 676 (81.9)<br>59 (7.2)<br>72 (8.7)<br>18 (2.2)<br>NR | 32.7 (6.0)<br>NR<br>NR | 91.9 (20.75) | 8.7 (1.45)<br>NR | 13.2 (7.44)<br>NR |

eTable 9. Participant Characteristics: Randomized Trials of GLP1RA vs. Other Anti-hyperglycemic Medication

| **Trial Arms** | **N** | **Age (years)** | **Male** | **Ethnicity** | **Race** | **BMI (kg/m$^2$)** | **Weight (kg)** | **HbA$_{1c}$ (%)** | **Diabetes Duration (years)** |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| **Arturi (2016)** | | | | | | | | | |
| Liraglutide 1.8 mg daily | 10 | 59.5 (9) | 7 (NR) | NR<br>NR | 10 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 33.2 (2.0)<br>NR<br>NR | NR | 8.2 (1.0) | NR<br>NR |
| Sitagliptin 100 mg daily | 10 | 60.5 (10) | 6 (NR) | NR<br>NR | 10 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 30.9 (2.8)<br>NR<br>NR | NR | 8.3 (0.9) | NR<br>NR |
| **AWARD-2 (2015)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 273 | 56 (10) | 144 (53) | 98 (36)<br>175 (64) | 193 (71)<br>1 (NR)<br>48 (18)<br>31 (11)<br>NR | 31 (5)<br>NR<br>NR | 85 (18) | 8.2 (1) | 9 (6)<br>NR |
| Insulin glargine | 262 | 57 (9) | 134 (51) | 97 (37)<br>165 (63) | 184 (70)<br>2 (1)<br>43 (16)<br>33 (13)<br>NR | 32 (6)<br>NR<br>NR | 88 (20) | 8.1 (1) | 9 (6)<br>NR |
| **AWARD-3 (2014)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 269 | 56 (10) | 114 (42) | 90 (33)<br>179 (67) | 201 (75)<br>17 (6)<br>21 (8)<br>30 (11)<br>NR | 34 (6)<br>NR<br>NR | 93 (19) | 7.6 (0.9) | 3 (2)<br>NR |
| Metformin 1,500-2000 mg daily | 268 | 55 (10) | 121 (45) | 95 (35)<br>173 (65) | 201 (75)<br>14 (5)<br>20 (8)<br>33 (12) | 33 (5)<br>NR<br>NR | 92 (19) | 7.6 (0.8) | 3 (2)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| | | | | | NR | | | | |
| **AWARD-4 (2015, 2019)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 295 | 58.9 (9.6) | 160 (54) | 102 (35)<br>NR | 231 (78)<br>32 (11)<br>9 (3)<br>23 (NR)<br>NR | 32.0 (5.1)<br>NR<br>NR | 91.0 (18.2) | 8.4 (1.08) | 12.8 (7.2)<br>NR |
| Insulin glargine | 296 | 59.9 (9.1) | 165 (56) | 100 (34)<br>NR | 231 (78)<br>26 (9)<br>14 (5)<br>25 (NR)<br>NR | 32.4 (5.3)<br>NR<br>NR | 90.8 (18.9) | 8.5 (1.03) | 13.0 (6.8)<br>NR |
| **AWARD-5 (2014, 2015)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 304 | 54 (10) | 146 (48) | NR<br>NR | 157 (52)<br>16 (5)<br>77 (25)<br>0 (0)<br>54 (18) | 31 (5)<br>NR<br>NR | 87 (17) | 8.1 (1.1) | 7 (6)<br>NR |
| Sitagliptin 100 mg daily | 315 | 54 (10) | 151 (48) | NR<br>NR | 158 (50)<br>7 (2)<br>80 (25)<br>2 (1)<br>67 (21) | 31 (4)<br>NR<br>NR | 86 (17) | 8.1 (1.1) | 7 (5)<br>NR |
| **AWARD-7 (2018)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 193 | 64.7 (8.8) | 104 (54) | 78 (NR)<br>114 (NR) | 134 (71)<br>26 (14)<br>7 (4)<br>22 (11)<br>78 (41) | 32.1 (4.8)<br>NR<br>NR | 88.1 (16.0) | 8.6 (0.9) | 17.6 (8.7)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | HbA$_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Insulin glargine | 194 | 64.3 (8.4) | 93 (48) | 79 (NR)<br>115 (NR) | 137 (71)<br>26 (14)<br>5 (3)<br>25 (13)<br>79 (41) | 32.4 (5.3)<br>NR<br>NR | 88.2 (18.5) | 8.6 (1.0) | 18.7 (8.7)<br>NR |
| **Derosa (2010)** | | | | | | | | | |
| Exenatide 10 ug bid | 63 | 57 (8) | 30 (NR) | NR<br>NR | 63 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 28.7 (1.5)<br>NR<br>NR | 82.0 (8.3) | 8.8 (0.7) | NR<br>NR |
| Gilbenclamide 5 mg tid | 65 | 56 (7) | 33 (NR) | NR<br>NR | 65 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 28.5 (1.4)<br>NR<br>NR | 82.4 (9.1) | 8.9 (0.8) | NR<br>NR |
| **Derosa (2011)** | | | | | | | | | |
| Exenatide 10 ug bid | 57 | 56 (7) | 28 (NR) | NR<br>NR | 57 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 28.4 (1.3)<br>NR<br>NR | 80.2 (7.5) | 8.7 (0.7) | NR<br>NR |
| Glimepiride 2 mg tid | 54 | 55 (6) | 26 (NR) | NR<br>NR | 54 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 28.5 (1.4)<br>NR<br>NR | 81.4 (8.1) | 8.8 (0.8) | NR<br>NR |
| **DUAL I (2015)** | | | | | | | | | |
| Liraglutide 1.8 mg daily | 413 | 55.0 (10.2) | 208 (50.2) | NR<br>NR | NR (62.3)<br>NR (6.8)<br>NR (28.1)<br>NR (2.9)<br>NR | 31.3 (4.8)<br>NR<br>NR | 87.4 (18.0) | 8.3 (0.9) | 7.2 (6.1)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Insulin degludec | 414 | 54.9 (9.7) | 200 (48.4) | NR<br>NR | NR (62.2)<br>NR (5.6)<br>NR (29.1)<br>NR (3.2)<br>NR | 31.2 (5.3)<br>NR<br>NR | 87.4 (19.2) | 8.3 (1.0) | 7.0 (5.3)<br>NR |
| **DURATION-3 (2012, 2015)** | | | | | | | | | |
| Exenatide 2 mg weekly | 233 | 58 (10) | 120 (NR) | NR<br>NR | 190 (82)<br>2 (1)<br>13 (6)<br>0 (0)<br>28 (12) | 32 (5)<br>NR<br>NR | 91.2 (18.6) | 8.3 (1.1) | 8 (6)<br>NR |
| Insulin glargine | 234 | 58 (9) | 123 (NR) | NR<br>NR | 189 (85)<br>1 (NR)<br>14 (6)<br>0 (0)<br>19 (9) | 32 (5)<br>NR<br>NR | 90.6 (16.4) | 8.3 (1.0) | 8 (6)<br>NR |
| **HARMONY 3 (2014, 2017)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 315 | 54.3 (10.1) | 135 (44.7) | 99 (32.8)<br>NR | 214 (70.9)<br>53 (17.5)<br>18 (6.0)<br>NR<br>NR | 32.7 (5.6)<br>NR<br>NR | 89.6 (18.4) | 8.1 (0.8) | 6.0 (4.3)<br>NR |
| Sitagliptin 100 mg daily | 313 | 54.3 (9.8) | 139 (46.0) | 111 (36.8)<br>NR | 225 (74.5)<br>35 (11.6)<br>20 (6.6)<br>NR<br>NR | 32.5 (5.4)<br>NR<br>NR | 90.3 (19.1) | 8.1 (0.8) | 5.8 (4.8)<br>NR |
| **HARMONY 4 (2014, 2017)** | | | | | | | | | |
| Albuglutide 30-50 mg daily | 516 | 55.8 (9.3) | 286 (56.7) | 81 (16.1)<br>423 (83.9) | 349 (69.3)<br>130 (25.8)<br>25 (5.0)<br>6 (1.2)<br>NR | 33.2 (5.6)<br>NR<br>NR | 95.1 (19.7) | 8.28 (0.90) | 8.9 (6.5)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Insulin glargine | 263 | 54.7 (9.8) | 132 (54.8) | 38 (15.8)<br>203 (84.2) | 160 (66.4)<br>64 (26.6)<br>15 (6.2)<br>2 (0.8)<br>NR | 33.0 (5.4)<br>NR<br>NR | 94.6 (19.1) | 8.36 (0.95) | 8.4 (5.7)<br>NR |
| **HARMONY 5 (2015, 2017)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 281 | 54.5 (9.5) | 135 (49.8) | NR<br>NR | 180 (66.4)<br>34 (12.5)<br>36 (13.3)<br>23 (8.5)<br>NR | 32.4 (5.5)<br>NR<br>NR | 90.9 (20.2) | 8.19 (0.91) | 8.5 (6.3)<br>NR |
| Pioglitazone 30-45 mg daily | 288 | 55.7 (9.4) | 148 (53.4) | NR<br>NR | 203 (73.3)<br>24 (8.7)<br>39 (14.1)<br>11 (4.0)<br>NR | 32.2 (5.7)<br>NR<br>NR | 91.0 (21.2) | 8.29 (0.88) | 9.2 (6.1)<br>NR |
| **HARMONY 6 (2017)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 281 | 54.8 (9.1) | 132 (46) | 75 (26)<br>NR | 176 (62)<br>39 (14)<br>48 (17)<br>31 (11)<br>NR | NR<br>NR<br>NR | 92.5 (21.5) | 8.5 (0.9) | 11 (7)<br>NR |
| Insulin lispro | 285 | 56.3 (8.9) | 136 (48) | 70 (25)<br>NR | 174 (62)<br>34 (12)<br>50 (18)<br>24 (9)<br>NR | NR<br>NR<br>NR | 91.6 (21.0) | 8.4 (0.9) | 11 (6)<br>NR |
| **HARMONY 8 (2014)** | | | | | | | | | |
| Albiglutide 30-50 mg weekly | 249 | 63.2 (8.37) | 136 (54.6) | NR<br>NR | 113 (45.4)<br>36 (14.5)<br>84 (33.7)<br>17 (6.8)<br>NR | 30.4 (5.5)<br>NR<br>NR | 83.3 (19.9) | 8.1 (1.0) | 10.8 (7.4)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Sitagliptin<br>100 mg daily | 246 | 63.5 (9.02) | 130 (52.8) | NR<br>NR | 114 (46.3)<br>42 (17.1)<br>76 (30.9)<br>16 (6.5)<br>NR | 30.4 (5.8)<br>NR<br>NR | 82.8 (20.6) | 8.2 (0.9) | 11.6 (8.5)<br>NR |
| **LEAD-2 (2013)** | | | | | | | | | |
| Liraglitude<br>1.8 mg daily | 241 | 57 (9) | NR (54) | NR<br>NR | NR (88)<br>NR (4)<br>NR (8)<br>NR (1)<br>NR | 31.1 (4.8)<br>NR<br>NR | NR | 8.3 (1) | 7 (5)<br>NR |
| Glimepiride<br>4 mg daily | 244 | 57 (9) | NR (57) | NR<br>NR | NR (89)<br>NR (2)<br>NR (9)<br>NR (1)<br>NR | 31.2 (4.6)<br>NR<br>NR | NR | 8.4 (1) | 8 (5)<br>NR |
| **LEAD-3 (Mono) (2009, 2011)** | | | | | | | | | |
| Liraglutide<br>1.8 mg daily | 247 | 52.0 (10.8) | 121 (49) | 87 (35)<br>NR | 186 (75)<br>30 (12)<br>12 (6)<br>19 (7)<br>NR | 32.8 (6.3)<br>NR<br>NR | 92.8 (20.7) | 8.3 (1.1) | 5.3 (5.1)<br>NR |
| Glimepiride<br>8 mg daily | 248 | 53.4 (10.9) | 133 (54) | 93 (38)<br>NR | 197 (77)<br>30 (12)<br>9 (4)<br>7 (7)<br>NR | 33.2 (5.6)<br>NR<br>NR | 93.4 (19.2) | 8.4 (1.2) | 5.6 (5.1)<br>NR |
| **NCT00082407 (2007)** | | | | | | | | | |
| Exenatide<br>10 ug bid | 253 | 59 (9) | NR (53) | NR<br>NR | NR<br>NR<br>NR<br>NR<br>NR | 30.6 (4.0)<br>NR<br>NR | 85.5 (15.7) | 8.6 (1.0) | 9.8 (6.3)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Insulin aspart | 248 | 58 (9) | NR (49) | NR<br>NR | NR<br>NR<br>NR<br>NR<br>NR | 30.2 (4.2)<br>NR<br>NR | 83.4 (15.6) | 8.6 (1.1) | 10.0 (6.2)<br>NR |
| **NCT00097500 (2009, 2016, 2019)** | | | | | | | | | |
| Exenatide 5-20 ug tid | 36 | 58.4 (1.4) | NR (63.9) | NR<br>NR | 36 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 30.9 (0.7)<br>NR<br>NR | 90.6 (2.1) | 7.6 (0.1) | 5.7 (0.8)<br>NR |
| Insulin glargine | 33 | 58.3 (1.3) | NR (66.7) | NR<br>NR | 33 (100)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 30.1 (0.6)<br>NR<br>NR | 92.4 (2.4) | 7.4 (0.1) | 4.0 (0.6)<br>NR |
| **NCT00393718 (2011)** | | | | | | | | | |
| Liraglutide 0.9 mg daily | 268 | 58.2 (10.4) | 183 (68.3) | NR<br>NR | 0 (0)<br>0 (0)<br>268 (100)<br>0 (0)<br>0 (0) | 24.9 (3.7)<br>NR<br>NR | 66.2 (12.6) | 9.32 (1.08) | 8.1 (6.7)<br>NR |
| Glibenclamide 1.25-2.50 mg daily | 132 | 58.5 (10.4) | 86 (65.2) | NR<br>NR | 0 (0)<br>0 (0)<br>132 (100)<br>0 (0)<br>0 (0) | 24.6 (3.8)<br>NR<br>NR | 65.4 (12.9) | 9.18 (0.97) | 8.5 (6.8)<br>NR |
| **NCT00700817 (2011)** | | | | | | | | | |
| Liraglutide 1.8 mg daily | 221 | 55 (9.1) | 116 (52) | 34 (15)<br>NR | 193 (87)<br>16 (7)<br>4 (2)<br>8 (4)<br>NR | 33.1 (5.1)<br>NR<br>NR | 94.6 (18.1) | 8.4 (0.7) | 6.4 (5.4)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Sitagliptin 100 mg daily | 219 | 55 (9.0) | 120 (55) | 35 (16)<br>NR | 199 (91)<br>10 (5)<br>2 (1)<br>8 (4)<br>NR | 32.6 (5.4)<br>NR<br>NR | 93.1 (18.9) | 8.5 (0.7) | 6.3 (5.4)<br>NR |
| **NCT01512108 (2014)** | | | | | | | | | |
| Liraglutide 0.9 mg daily | 243 | 59.6 (11.6) | 182 (75.8) | NR<br>NR | 0 (0)<br>0 (0)<br>243 (100)<br>0 (0)<br>0 (0) | 25.7 (4.2)<br>NR<br>NR | 69.4 (14.2) | 8.1 (0.8) | 7.8 (5.8)<br>NR |
| Other oral antidiabetic drug | 120 | 59.2 (10.2) | 80 (66.7) | NR<br>NR | 0 (0)<br>0 (0)<br>120 (100)<br>0 (0)<br>0 (0) | 25.5 (3.7)<br>NR<br>NR | 68.2 (13.6) | 8.1 (0.8) | 8.5 (6.6)<br>NR |
| **NCT01648582 (2011)** | | | | | | | | | |
| Dulaglutide 1.5 mg weekly | 258 | 55.0 (9.6) | 135 (53.4) | NR<br>NR | 18 (7.1)<br>NR<br>213 (84.2)<br>NR<br>22 (8.7) | 26.6 (3.7)<br>NR<br>NR | 73.6 (13.0) | 8.5 (1.2) | 7.9 (4.8)<br>NR |
| Insulin glargine | 259 | 55.4 (9.2) | 139 (55.6) | NR<br>NR | 17 (6.8)<br>NR<br>209 (83.6)<br>NR<br>24 (9.6) | 26.7 (3.5)<br>NR<br>NR | 73.4 (13.1) | 8.3 (1.1) | 8.4 (5.3)<br>NR |
| **PIONEER 3 (2013)** | | | | | | | | | |
| Oral semaglutide 14 mg daily | 465 | 57 (10) | 247 (53.1) | 75 (16.1)<br>NR | 317 (68.2)<br>45 (9.7)<br>61 (13.1)<br>20 (4.3)<br>NR | 32.3 (6.3)<br>NR<br>NR | 91.2 (21.7) | 8.3 (0.9) | 8.7 (6.1)<br>7.4 (4.0-12.2) |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | HbA$_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Sitagliptin<br>100 mg daily | 467 | 58 (10) | 238 (51.0) | 93 (19.9)<br>NR | 333 (71.3)<br>39 (8.4)<br>59 (12.6)<br>12 (2.6)<br>NR | 32.5 (6.2)<br>NR<br>NR | 90.9 (21.0) | 8.3 (0.9) | 8.8 (6.0)<br>7.9 (4.3-12.2) |
| **PIONEER 7 (2019)** | | | | | | | | | |
| Oral semaglutide<br>3-14 mg daily | 253 | 56.9 (9.7) | 145 (57) | 48 (19)<br>205 (81) | 195 (77)<br>22 (9)<br>34 (13)<br>2 (1)<br>NR | 31.5 (6.5)<br>NR<br>NR | 88.9 (19.6) | 8.3 (0.6) | 8.6 (6.3)<br>NR |
| Sitagliptin<br>100 mg daily | 251 | 57.9 (10.1) | 140 (56) | 57 (23)<br>194 (77) | 186 (74)<br>25 (10)<br>38 (15)<br>2 (1)<br>NR | 31.5 (6.1)<br>NR<br>NR | 88.4 (20.1) | 8.3 (0.6) | 9.0 (6.2)<br>NR |
| **Su (2014)** | | | | | | | | | |
| Exenatide<br>10 ug tid | 30 | 45.8 (12.3) | NR | NR<br>NR | 0 (0)<br>0 (0)<br>30 (100)<br>0 (0)<br>0 (0) | 28.6 (3.5)<br>NR<br>NR | NR | 8.15 (1.58) | NR<br>NR |
| Insulin glargine | 30 | 46.1 (11.3) | NR | NR<br>NR | 0 (0)<br>0 (0)<br>30 (100)<br>0 (0)<br>0 (0) | 28.1 (3.4)<br>NR<br>NR | NR | 8.17 (1.28) | NR<br>NR |
| **SUSTAIN (JAPAN) (2018)** | | | | | | | | | |
| Semaglutide<br>1.0 mg weekly | 241 | 58.7 (10.2) | NR (72.2) | NR<br>NR | 0 (0)<br>0 (0)<br>241 (100)<br>0 (0)<br>0 (0) | 26.4 (4.7)<br>NR<br>NR | 71.7 (15.9) | 8.1 (1.0) | 9.4 (6.5)<br>NR |

| Trial Arms | N | Age (years) | Male | Ethnicity | Race | BMI (kg/m$^2$) | Weight (kg) | $HbA_{1c}$ (%) | Diabetes Duration (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Other oral antidiabetic agent | 120 | 59.2 (10.1) | NR (74.2) | NR<br>NR | 0 (0)<br>0 (0)<br>120 (100)<br>0 (0)<br>0 (0) | 26.7 (4.6)<br>NR<br>NR | 72.2 (14.9) | 8.1 (0.9) | 9.3 (7.0)<br>NR |
| **SUSTAIN 2 (2017)** | | | | | | | | | |
| Semaglutide 1.0 mg weekly | 409 | 56.0 (9.4) | 205 (50) | 67 (16)<br>342 (84) | 279 (68)<br>24 (6)<br>99 (24)<br>NR<br>NR | 32.5 (6.6)<br>NR<br>NR | 89.2 (20.7) | 8.0 (0.9) | 6.7 (5.6)<br>NR |
| Sitagliptin 100 mg daily | 407 | 54.6 (10.4) | 208 (51) | 73 (18)<br>334 (82) | 281 (69)<br>17 (4)<br>102 (25)<br>NR<br>NR | 32.5 (5.8)<br>NR<br>NR | 89.3 (19.7) | 8.2 (0.9) | 6.6 (5.1)<br>NR |
| **T-Emerge 4 (2012)** | | | | | | | | | |
| Taspoglutide 20 mg weekly | 187 | 56.8 (8.8) | 98 (52) | 35 (19)<br>152 (81) | 153 (82)<br>8 (4)<br>14 (7)<br>12 (6)<br>NR | 32.3 (5)<br>NR<br>NR | 91.8 (18.0) | 7.97 (0.86) | 5.7 (4.7)<br>NR |
| Sitagliptin 100 mg daily | 177 | 55.5 (9.9) | 105 (59) | 29 (16)<br>148 (84) | 135 (76)<br>10 (6)<br>19 (11)<br>13 (7)<br>NR | 32.4 (5)<br>NR<br>NR | 92.5 (19.7) | 7.94 (0.85) | 6.0 (5.0)<br>NR |
| **Yan (2015)** | | | | | | | | | |
| Liraglutide 1.2 mg daily | 26 | 50 (3) | 15 (NR) | NR<br>NR | 0 (0)<br>0 (0)<br>26 (100)<br>0 (0)<br>0 (0) | 24.8 (2.9)<br>NR<br>NR | 66.2 (9.3) | 10.7 (1.5) | NR<br>NR |

| **Trial Arms** | **N** | **Age (years)** | **Male** | **Ethnicity** | **Race** | **BMI (kg/m$^2$)** | **Weight (kg)** | **HbA$_{1c}$ (%)** | **Diabetes Duration (years)** |
|---|---|---|---|---|---|---|---|---|---|
| | | *Mean (SD)* | *N (%)* | *Hispanic or Latino, N (%)*<br><br>*Not Hispanic or Latino, N (%)* | *White, N (%)*<br>*Black, N (%)*<br>*Asian, N (%)*<br>*Other, N (%)*<br>*Hispanic, N (%)* | *Mean (SD)*<br>*<30, N (%)*<br>*≥30, N (%)* | *Mean (SD)* | *Mean (SD)* | *Mean (SD)*<br>*Median (IQR)* |
| Insulin glargine | 26 | 51 (3) | 13 (NR) | NR<br>NR | 0 (0)<br>0 (0)<br>26 (100)<br>0 (0)<br>0 (0) | 23.3 (2.9)<br>NR<br>NR | 64.3 (9.0) | 10.5 (1.4) | NR<br>NR |

Abbreviations: NR, not reported

eTable 10: Number of GLP1RA vs. Placebo trials available for each outcome and subgroup analysis

| | GLP1RA vs Placebo | High GLP1RA Dose | Background Medication | ASCVD Population Only | | Average Baseline $HbA_{1c}$ | | | Study Duration | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≥ 1 Other Drug | ≥ 50% ASCVD history | < 50% ASCVD history | < 8 | 8.0-8.5 | > 8.5 | 1-year | > 1-year |
| **Cardiovascular risk factors** | | | | | | | | | | |
| $HbA_{1c}$ | 14 | 12 | 9 | - | - | 2 | 9 | 4 | - | - |
| Weight | 11 | 9 | 7 | - | - | - | - | - | - | - |
| Heart rate | 10 | 9 | 3 | 5 | 5 | - | - | - | - | - |
| **Adverse events** | | | | | | | | | | |
| Any hypoglycemia | 12 | 11 | 7 | - | - | 2 | 8 | 2 | 6 | 6 |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; ASCVD, atherosclerotic cardiovascular disease

eTable 11: Number of GLP1RA vs. Other Anti-hyperglycemic Medication trials available for each outcome and subgroup analysis

| | GLP1RA vs other anti-hyperglycemic medication | High GLP1RA Dose | Background Medication | Comparison | | | Average Baseline $HbA_{1c}$ | | | Baseline BMI | | Study Duration | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≥ 1 Other Drug | SU | DDP-4I | Insulin | < 8 | 8.0-8.5 | > 8.5 | ≥ 30 | < 30 | 1-year | > 1-year |
| **Cardiovascular risk factors** | | | | | | | | | | | | | |
| $HbA_{1c}$ | 28 | 23 | 24 | 5 | 8 | 11 | 3 | 19 | 6 | - | - | - | - |
| Weight | 22 | 18 | 19 | 4 | 7 | 8 | - | - | - | 16 | 6 | - | - |
| Heart rate | 17 | 14 | 14 | 2 | 7 | 5 | - | - | - | - | - | - | - |
| **Adverse events** | | | | | | | | | | | | | |
| Any hypoglycemia | 23 | 20 | 19 | 4 | 6 | 10 | 3 | 16 | 4 | - | - | 17 | 6 |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; ASCVD, atherosclerotic cardiovascular disease; SU, sulfonylurea; DPP-4I, dipeptyl peptidase-4 inhibitor; BMI, body mass index

eTable 12. Risk of Bias GLP1RA vs. Placebo for $HbA_{1c}$ [a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| Derosa (2013)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| ELIXA (2015)[b] | Median 25 months | Low | Low | Low | Low | High | High |
| EXSCEL (2017)[b] | 3.2 years | Low | Low | Low | Low | Moderate | Moderate |
| GetGoal-F1 (2013)[b] | 76 weeks | Low | Low | Low | Low | Moderate | Moderate |
| GetGoal-P (2013)[b] | 76 weeks | Low | Low | Low | Low | High | High |
| HARMONY 1 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 1 (2017)[b] | 156 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 2 (2016) | 52 weeks | Low | Low | Low | Low | High | High |
| HARMONY 2 (2017)[b] | 156 weeks | Low | Low | Low | Low | High | High |
| HARMONY 3 (2014) | 104 weeks | Low | Low | Low | Low | High | High |
| HARMONY 3 (2017)[b] | 156 weeks | Low | Low | Low | Low | High | High |
| HARMONY 5 (2015)[b] | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 5 (2017)[b] | 156 weeks | Low | Low | Low | Low | High | High |
| Harmony Outcomes (2018)[b] | 16 months | Low | Low | Low | Low | High | High |
| LEADER (2016)[b] | 36 months | Low | Low | Low | Low | Moderate | Moderate |
| NCT00395746 (2011)[b] | 52 weeks | Low | Moderate | Low | Low | High | High |
| PIONEER 4 (2019)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 6 (2019)[b] | Median 15.9 months | Low | Low | Low | Low | Moderate | Moderate |
| REWIND (2019)[b] | Median 5.4 years | Low | Low | Low | Low | Low | Low |
| SCALE (2015)[b] | 56 weeks | Low | Low | Low | Low | High | High |
| SUSTAIN-6 (2016)[b] | 104 weeks | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had moderate concern, then overall bias was high. If fewer than three domains had moderate concern, then overall bias was moderate concern. If one or more domains had high bias, then overall bias was high.
[b] For trials that reported multiple timepoints, the timepoint with the lowest risk of bias was selected for analyses. If risk of bias was equal, the longest follow-up timepoint was selected.

eTable 13. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for $HbA_{1c}$[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| Arturi (2016)[b] | 52 weeks | Low | Moderate | Low | Low | Low | Moderate |
| AWARD-2 (2015)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| AWARD-2 (2015) | 78 weeks | Low | Low | Low | Low | Moderate | Moderate |
| AWARD-3 (2014)[b] | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| AWARD-4 (2015, 2019)[b] | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| AWARD-5 (2014)[b] | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| AWARD-5 (2015)[b] | 104 weeks | Low | Low | Low | Low | High | High |
| AWARD-7 (2018)[b] | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| Derosa (2010)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| Derosa (2011)[b] | 52 weeks | Low | Moderate | Low | Low | Low | Moderate |
| DUAL I (2015)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| DURATION-3 (2012) | 84 weeks | Low | Moderate | Low | Low | High | High |
| DURATION-3 (2014)[b] | 156 weeks | Low | Moderate | Low | Low | High | High |
| HARMONY 3 (2014) | 104 weeks | Low | Low | Low | Low | High | High |
| HARMONY 3 (2017)[b] | 156 weeks | Low | Low | Low | Low | High | High |
| HARMONY 4 (2014) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| HARMONY 4 (2017)[b] | 156 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| HARMONY 5 (2015)[b] | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 5 (2017) | 156 weeks | Low | Low | Low | Low | High | High |
| HARMONY 6 (2017)[b] | 52 weeks | Low | Low | Low | Low | High | High |
| HARMONY 8 (2014)[b] | 52 weeks | Low | Low | Low | Low | High | High |
| LEAD-2 (2013)[b] | 104 weeks | Low | Low | Low | Low | Moderate | Moderate |
| LEAD-3 (Mono) (2009) | 52 weeks | Low | Low | Low | Low | High | High |
| LEAD-3 (Mono) (2011)[b] | 104 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| NCT00082407 (2007)[b] | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| NCT00097500 (2009, 2016, 2019)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| NCT00097500 (2016)[b] | 156 weeks | Low | Low | Low | Low | High | High |
| NCT00393718 (2011)[b] | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| NCT00700817 (2011)[b] | 52 weeks | Low | Low | Low | Low | High | High |
| NCT01512108 (2014[b], 2018) | 52 weeks | Low | Moderate | Low | Low | Low | Moderate |
| NCT01648582 (2011)[b] | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| PIONEER 3 (2013) | 52 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 3 (2013)[b] | 78 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 7 (2019)[b] | 52 weeks | Low | Low | Low | Low | Low | Low |
| Su (2014)[b] | 52 weeks | Low | Low | Low | Moderate | Low | Moderate |
| SUSTAIN (JAPAN) (2018)[b] | 56 weeks | Low | Low | Low | Low | High | High |
| SUSTAIN 2 (2017)[b] | 56 weeks | Low | Low | Low | Low | Moderate | Moderate |
| T-Emerge 4 (2012)[b] | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| Yan (2015)[b] | 72 weeks | Low | Low | Low | Low | Low | Low |

[a] Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had moderate concern, then overall bias was high. If fewer than three domains had moderate concern, then overall bias was moderate concern. If one or more domains had high bias, then overall bias was high.
[b] For trials that reported multiple timepoints, the timepoint with the lowest risk of bias was selected for analyses. If risk of bias was equal, the longest follow-up timepoint was selected.

eTable 14. Risk of Bias GLP1RA vs. Placebo for Mortality[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| ELIXA (2015) | Median 25 months | Low | Low | Low | Low | Low | Low |
| EXSCEL (2017) | 3.2 years | Low | Low | Low | Low | Low | Low |
| GetGoal-F1 (2013) | 76 weeks | Low | Low | Low | Low | Moderate | Moderate |
| GetGoal-P (2013) | 76 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 1 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 2 (2016) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 3 (2014) | 104 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 5 (2017) | 156 weeks | Low | Low | Low | Low | Moderate | Moderate |
| Harmony Outcomes (2018) | 16 months | Low | Low | Low | Low | Low | Low |
| LEADER (2016) | 36 months | Low | Low | Low | Low | Low | Low |
| NCT00395746 (2011) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| PIONEER 4 (2019) | 52 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 6 (2019) | Median 15.9 months | Low | Low | Low | Low | Low | Low |
| REWIND (2019) | Median 5.4 years | Low | Low | Low | Low | Low | Low |
| SCALE (2015) | 56 weeks | Low | Low | Low | Low | Moderate | Moderate |
| SUSTAIN-6 (2016) | 104 weeks | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 15. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Mortality[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| Arturi (2016) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| AWARD-2 (2015) | 52 weeks | Low | Low | Low | Low | Low | Low |
| AWARD-2 (2015) | 78 weeks | Low | Low | Low | Low | Low | Low |
| AWARD-3 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| AWARD-4 (2015) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| AWARD-5 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| AWARD-7 (2018) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| DURATION-3 (2014) | 156 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| HARMONY 3 (2014) | 104 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 4 (2014) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| HARMONY 8 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| LEAD-2 (2013) | 104 weeks | Low | Low | Low | Low | Moderate | Moderate |
| LEAD-3 (Mono) (2011) | 104 weeks | Low | Moderate | Low | Low | High | High |
| NCT00082407 (2007) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| NCT00393718 (2011) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| NCT00700817 (2011) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| NCT01512108 (2014) | 52 weeks | Low | Moderate | Low | Low | Low | Moderate |
| NCT01648582 (2011) | 52 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| PIONEER 3 (2013) | 78 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 7 (2019) | 52 weeks | Low | Low | Low | Low | Low | Low |
| SUSTAIN (JAPAN) (2018) | 56 weeks | Low | Low | Low | Low | Low | Low |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SUSTAIN 2 (2017) | 56 weeks | Low | Low | Low | Low | Moderate | Moderate |
| T-Emerge 4 (2012) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

## eTable 16. Risk of Bias GLP1RA vs. Placebo for 3-point MACE[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| EXSCEL (2017) | 3.2 years | Low | Low | Low | Low | Low | Low |
| Harmony Outcomes (2018) | 16 months | Low | Low | Low | Low | Low | Low |
| LEADER (2016) | 36 months | Low | Low | Low | Low | Low | Low |
| PIONEER 6 (2019) | Median 15.9 months | Low | Low | Low | Low | Low | Low |
| REWIND (2019) | Median 5.4 years | Low | Low | Low | Low | Low | Low |
| SUSTAIN-6 (2016) | 104 weeks | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 17. Risk of Bias GLP1RA vs. Placebo for Any Myocardial Infraction Event[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| ELIXA (2015) | Median 25 months | Low | Low | Low | Low | Low | Low |
| EXSCEL (2017) | 3.2 years | Low | Low | Low | Low | Low | Low |
| Harmony Outcomes (2018) | 16 months | Low | Low | Low | Low | Low | Low |
| LEADER (2016) | 36 months | Low | Low | Low | Moderate | Low | Moderate |
| PIONEER 4 (2019) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| PIONEER 6 (2019) | Median 15.9 months | Low | Low | Low | Low | Low | Low |
| REWIND (2019) | Median 5.4 years | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 18. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Any Myocardial Infraction Event[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| DUAL I (2015) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| DURATION-3 (2014) | 156 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| LEAD-3 (Mono) (2011) | 104 weeks | Low | Moderate | Low | Low | High | High |
| PIONEER 3 (2013) | 78 weeks | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 19. Risk of Bias GLP1RA vs. Placebo for Stroke[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| ELIXA (2015) | Median 25 months | Low | Low | Low | Low | Low | Low |
| EXSCEL (2017) | 3.2 years | Low | Low | Low | Low | Low | Low |
| Harmony Outcomes (2018) | 16 months | Low | Low | Low | Low | Low | Low |
| LEADER (2016) | 36 months | Low | Low | Low | Moderate | Low | Moderate |
| PIONEER 4 (2019) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| PIONEER 6 (2019) | Median 15.9 months | Low | Low | Low | Low | Low | Low |
| REWIND (2019) | Median 5.4 years | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 20. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Stroke[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| AWARD-5 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| DURATION-3 (2012) | 156 weeks | Low | Moderate | Low | Low | Moderate | Moderate |
| PIONEER 3 (2013) | 78 weeks | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 21. Risk of Bias GLP1RA vs. Placebo for Any Renal Event[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| EXSCEL (2017) | 3.2 years | Low | Low | Low | Low | Low | Low |
| Harmony Outcomes (2018) | 16 months | Low | Low | Low | Low | Moderate | Moderate |
| LEADER (2016) | 36 months | Low | Low | Low | Low | Low | Low |
| PIONEER 4 (2019) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| PIONEER 6 (2019) | Median 15.9 months | Low | Low | Low | Low | Low | Low |
| REWIND (2019) | Median 5.4 years | Low | Low | Low | Low | Low | Low |
| SCALE (2015) | 56 weeks | Low | Low | Low | Low | Moderate | Moderate |
| SUSTAIN-6 (2016) | 104 weeks | Low | Low | Low | Low | Low | Low |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 22. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Any Renal Event[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| AWARD-7 (2018) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| LEAD-2 (2013) | 104 weeks | Low | Low | Low | Low | Moderate | Moderate |
| PIONEER 3 (2013) | 78 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 7 (2019) | 52 weeks | Low | Low | Low | Low | Low | Low |
| T-Emerge 4 (2012) | 52 weeks | Low | Low | Low | Low | High | High |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 23. Risk of Bias GLP1RA vs. Placebo for Gastrointestinal Event Leading to Treatment Discontinuation[a]

| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| Derosa (2013) | 52 weeks | Low | Low | Low | Low | Low | Low |
| ELIXA (2015) | Median 25 months | Low | Low | Low | Low | Low | Low |
| HARMONY 1 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 2 (2016) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| HARMONY 3 (2014) | 104 weeks | Low | Low | Low | Low | Moderate | Moderate |
| LEADER (2016) | 36 months | Low | Low | Low | Low | Low | Low |
| PIONEER 4 (2019) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| PIONEER 6 (2019) | Median 15.9 months | Low | Low | Low | Low | Low | Low |
| SUSTAIN-6 (2016) | 104 weeks | Low | Low | Low | Low | Low | Low |

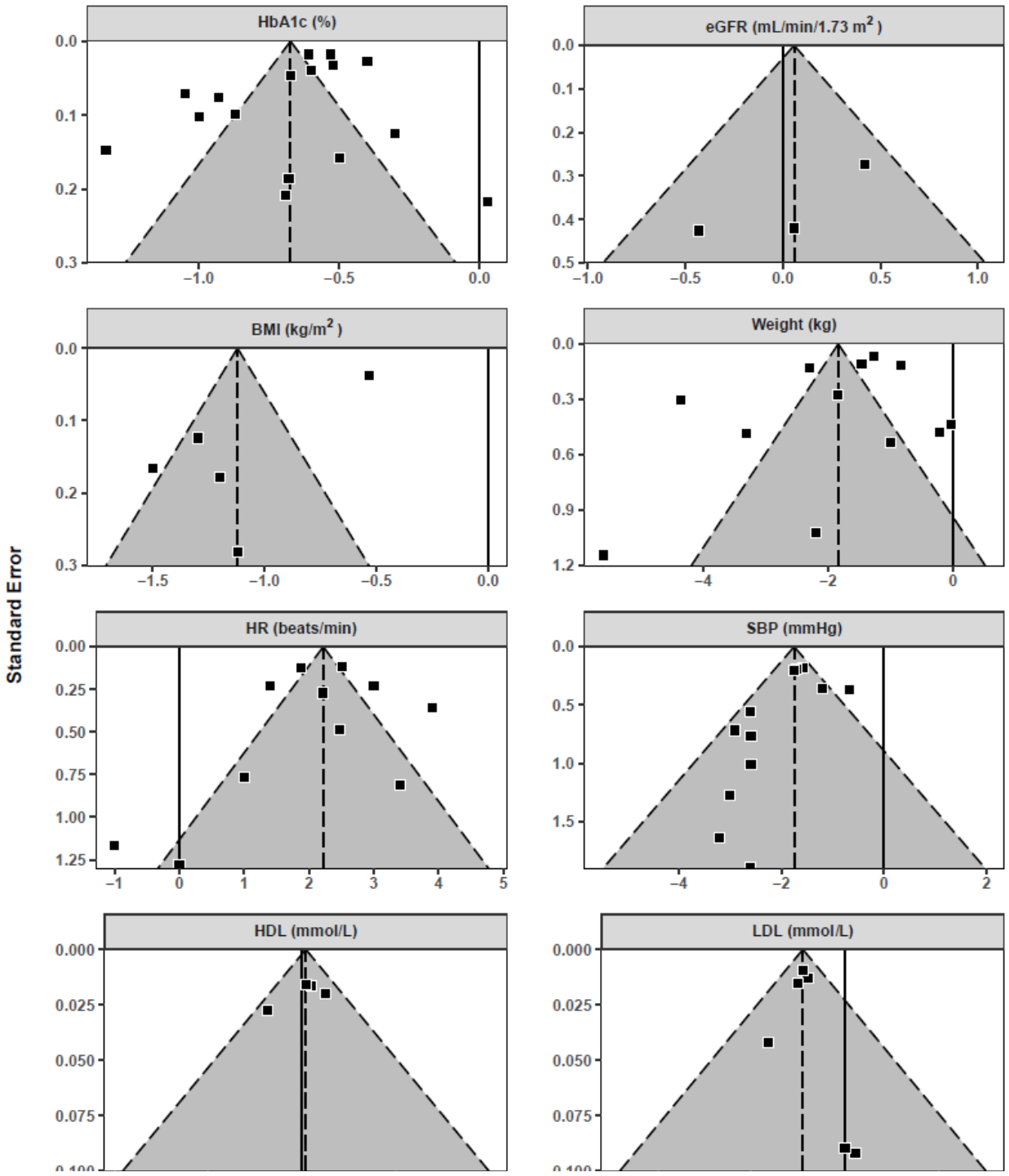
[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

eTable 24. Risk of Bias GLP1RA vs. Other Anti-hyperglycemic Medications for Gastrointestinal Event Leading to Treatment Discontinuation[a]

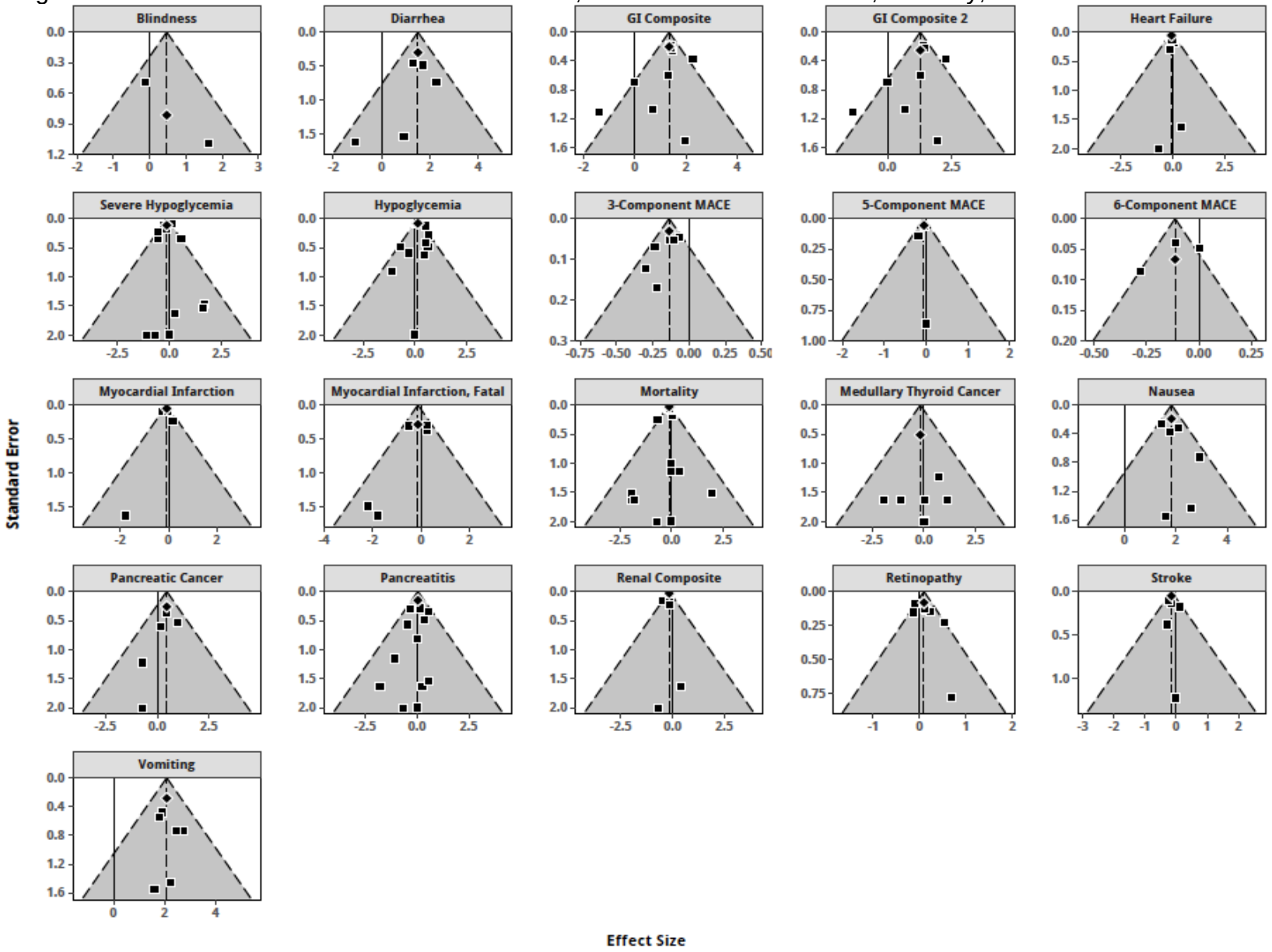
| Trial Name | Follow-up | Sequence Generation | Blinding | Detection Bias | Reporting | Attrition Bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| Arturi (2016) | 52 weeks | Low | Moderate | Low | Low | Low | Moderate |
| AWARD-3 (2014) | 52 weeks | Low | Low | Low | Low | Moderate | Moderate |
| AWARD-4 (2015) | 52 weeks | Low | Moderate | Low | Low | High | High |
| AWARD-5 (2014) | 52 weeks | Low | Low | Low | Low | High | High |
| Derosa (2010) | 52 weeks | Low | Low | Low | Low | Low | Low |
| Derosa (2011) | 52 weeks | Low | Moderate | Low | Low | Low | Moderate |
| DURATION-3 (2014) | 156 weeks | Low | Moderate | Low | Low | High | High |
| HARMONY 3 (2014) | 104 weeks | Low | Low | Low | Low | High | High |
| HARMONY 6 (2017) | 52 weeks | Low | Low | Low | Low | High | High |
| LEAD-3 (Mono) (2009) | 52 weeks | Low | Low | Low | Low | High | High |
| NCT00393718 (2011) | 52 weeks | Low | Moderate | Low | Low | High | High |
| PIONEER 3 (2019) | 78 weeks | Low | Low | Low | Low | Low | Low |
| PIONEER 7 (2019) | 52 weeks | Low | Low | Low | Low | Low | Low |
| SUSTAIN 2 (2017) | 56 weeks | Low | Low | Low | Low | Moderate | Moderate |
| T-Emerge 4 (2012) | 52 weeks | Low | Low | Low | Low | High | High |

[a]Risk of bias for each of the five domains was determined using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (BMJ 2011;343:d5928). Overall risk-of-bias was determined as follows: If all five domains had low bias, then overall bias was low. If three or more domains had some concern, then overall bias was high. If fewer than three domains had some concern, then overall bias was some concern. If one or more domains had high bias, then overall bias was high.

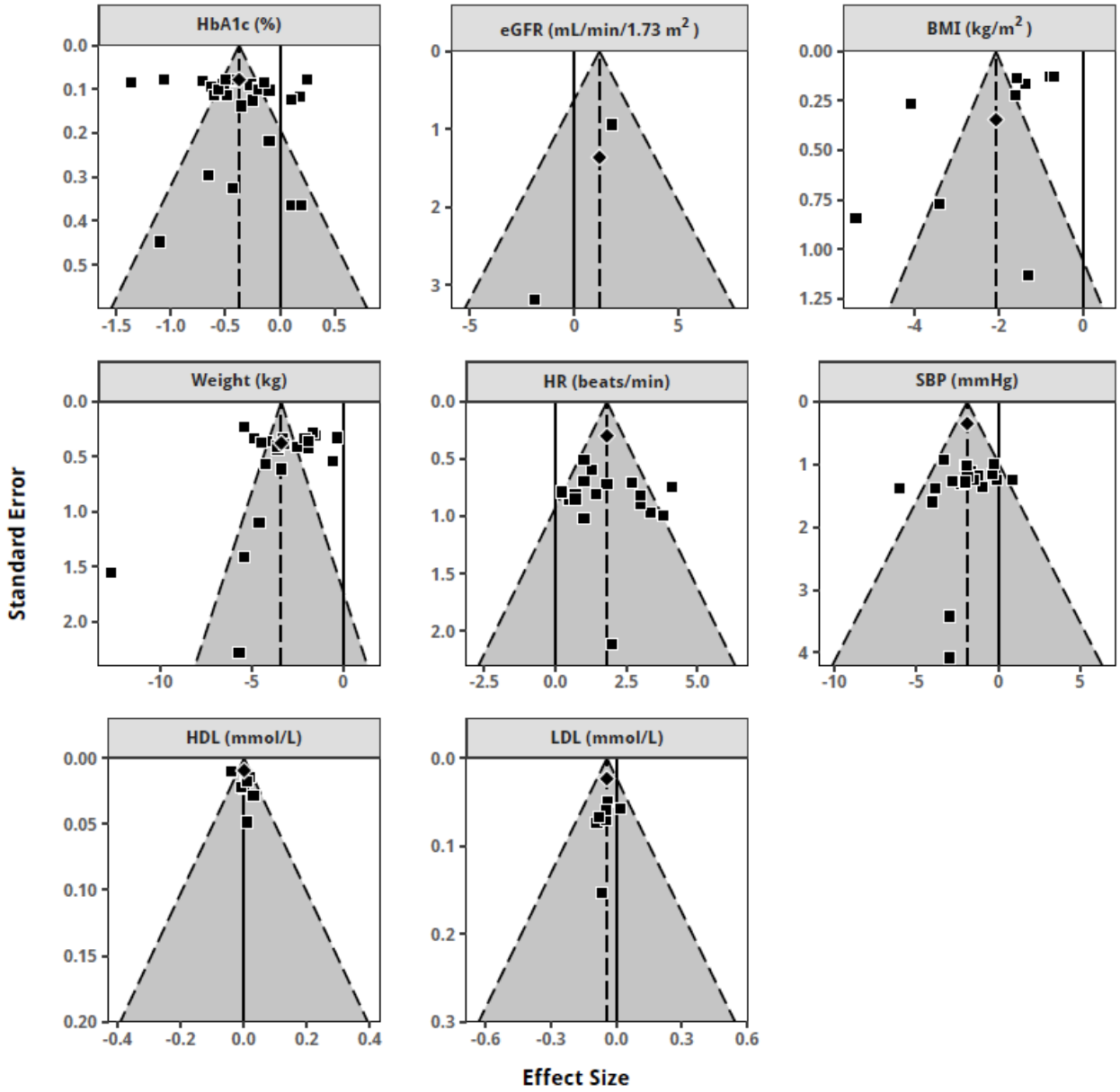
eFigure 1. Funnel Plots for Cardiovascular Risk Factors for GLP1RA vs. Placebo



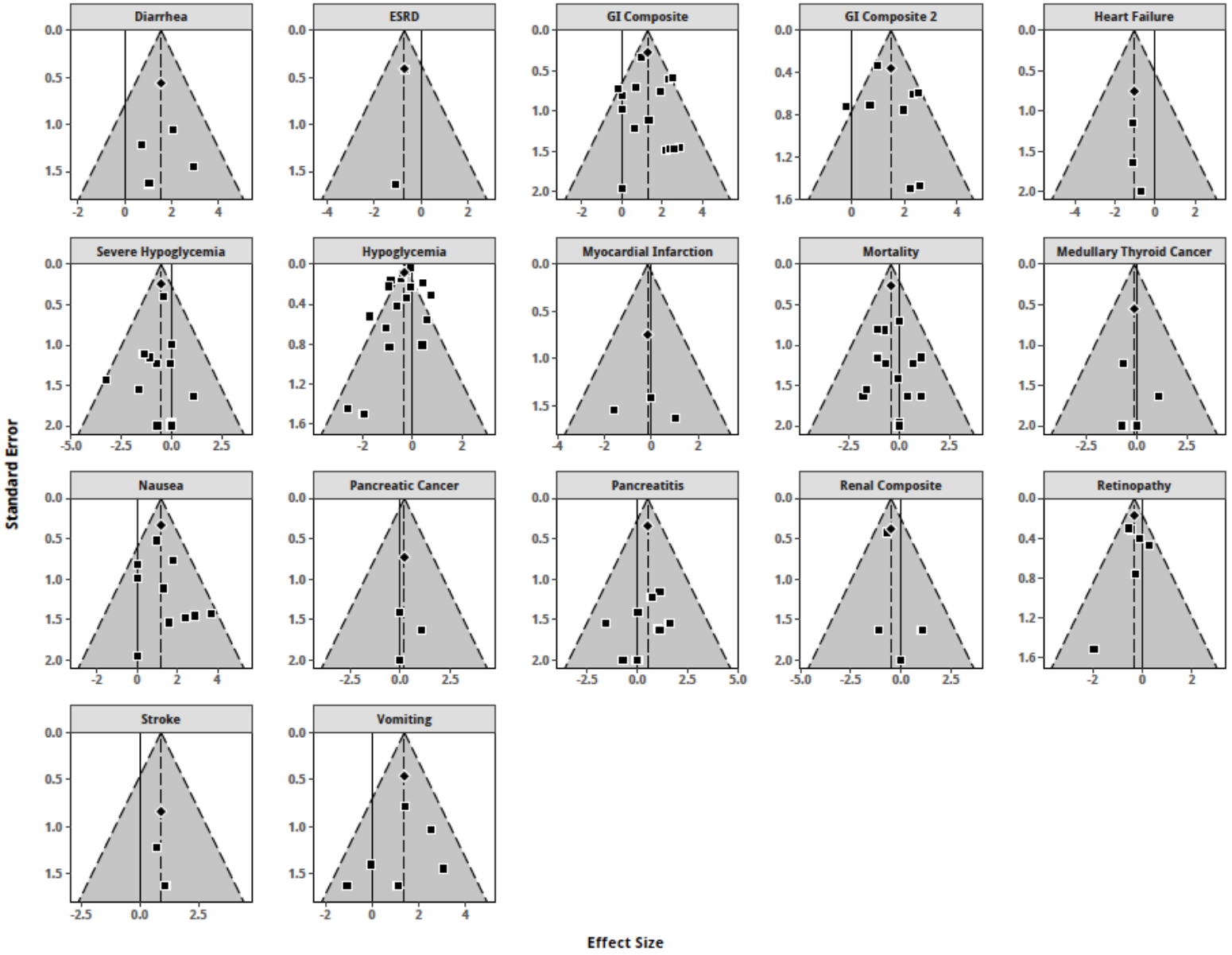
eFigure 2. Funnel Plots for Microvascular Outcomes, Macrovascular Outcomes, Mortality, and Adverse Events for GLP1RA vs. Placebo



eFigure 3. Funnel Plots for Cardiovascular Risk Factors for GLP1RA vs. Other Anti-hyperglycemic Medication



eFigure 4. Funnel Plots for Microvascular Outcomes, Macrovascular Outcomes, Mortality, and Adverse Events for GLP1RA vs. Other Anti-hyperglycemic Medication



eTable 25. Effects of GLP1RAs on Cardiovascular Risk Factors, Mortality, Macrovascular and Microvascular Outcomes, and Adverse Events[a]

| GLP1RA vs. Placebo | Patient N | Trial N | Weighted Mean Difference / Pooled Relative Risk (95% CI) | PQ | $I^2$ Statistic |
|---|---|---|---|---|---|
| Cardiovascular Risk Factors | | | | | |
| $HbA_{1c}$ (%) | 48575 | 15 | -0.67 (-0.77 to -0.58) | 0 | 93% |
| Weight (kg) | 47096 | 11 | -1.84 (-2.37 to -1.30) | 0 | 95% |
| BMI ($kg/m^2$) | 11114 | 4 | -1.12 (-1.67 to -0.57) | 0.09 | 96% |
| SBP (mmHg) | 49929 | 10 | -1.75 (-2.14 to -1.35) | 0 | 48% |
| HR (beats per minute) | 49929 | 10 | 2.22 (1.69 to 2.75) | 0.84 | 88% |
| LDL (mmol/L) | 25246 | 4 | -0.04 (-0.06 to -0.03) | 0.07 | 0% |
| HDL (mmol/L) | 793 | 2 | 0.00 (-0.03 to 0.04) | 0 | 43% |
| eGFR ($mL/min/1.73m^2$) | 19364 | 2 | 0.06 (-0.77 to 0.88) | 0.14 | 65% |
| All-Cause Mortality | 59338 | 16 | 0.87 (0.82 to 0.93) | 0.59 | 0% |
| Macrovascular Outcomes | | | | | |
| 3-component MACE | 49936 | 6 | 0.87 (0.82 to 0.93) | 0.40 | 23% |
| 5-component MACE | 9678 | 3 | 0.95 (0.85 to 1.06) | 0.59 | 0% |
| 6-component MACE | 18705 | 3 | 0.89 (0.78 to 1.02) | 0.01 | 77% |
| Any Myocardial Infarction | 53136 | 7 | 0.93 (0.84 to 1.03) | 0.14 | 43% |
| Fatal Myocardial Infarction | 37664 | 5 | 0.88 (0.50 to 1.55) | 0.13 | 45% |
| Heart Failure | 37705 | 7 | 0.94 (0.84 to 1.04) | 0.94 | 0% |
| Stroke | 53134 | 7 | 0.86 (0.78 to 0.95) | 0.72 | 0% |
| Microvascular Outcomes | | | | | |
| Retinopathy | 50363 | 7 | 1.10 (0.93 to 1.29) | 0.08 | 47% |
| Blindness | 18049 | 2 | 1.61 (0.32 to 8.12) | 0.15 | 53% |
| Any Renal Event | 51001 | 8 | 0.85 (0.80 to 0.90) | 0.72 | 0% |
| Adverse Events | | | | | |
| Any Hypoglycemia | 20374 | 12 | 1.15 (0.98 to 1.35) | 0 | 70% |
| Severe Hypoglycemia | 55790 | 15 | 0.89 (0.68 to 1.16) | 0.09 | 62% |
| Any GI Event Leading to Treatment Discontinuation | 21732 | 9 | 3.84 (2.59 to 5.70) | 0.03 | 52% |
| Any Pancreatitis | 57694 | 16 | 1.05 (0.78 to 1.43) | 0.93 | 0% |
| Pancreatic Cancer | 30780 | 5 | 1.61 (0.96 to 2.71) | 0.68 | 0% |
| Medullary Thyroid Carcinoma | 49907 | 11 | 0.77 (0.22 to 2.61) | 0.98 | 0% |
| GLP1RA vs. other anti-hyperglycemic medication | Patient N | Trial N | Mean Difference / Relative Risk (95% CI) | PQ | $I^2$ Statistic |
| Cardiovascular Risk Factors | | | | | |
| $HbA_{1c}$ (%) | 11832 | 28 | -0.37 (-0.53 to -0.22) | 0 | 93% |
| Weight (kg) | 9965 | 22 | -3.39 (-4.13 to -2.66) | 0 | 94% |
| BMI ($kg/m^2$) | 2998 | 9 | -2.07 (-2.74 to -1.39) | 0 | 96% |

| | | | | | |
|---|---|---|---|---|---|
| SBP (mmHg) | 9901 | 20 | -1.90 (-2.57 to -1.22) | 0.08 | 32% |
| HR (beats per minute) | 8982 | 17 | 1.81 (1.23 to 2.39) | 0 | 57% |
| LDL (mmol/L) | 3528 | 8 | -0.04 (-0.09 to 0.00) | 0.96 | 0% |
| HDL (mmol/L) | 4029 | 9 | 0.00 (-0.02 to 0.02) | 0.01 | 58% |
| eGFR (mL/min/1.73m$^2$) | 440 | 2 | 1.21 (-1.46 to 3.87) | 0.27 | 19% |
| All-Cause Mortality | 11171 | 22 | 0.68 (0.42 to 1.11) | 0.99 | 0% |
| Macrovascular Outcomes | | | | | |
| Any Myocardial Infarction | 2713 | 4 | 0.89 (0.24 to 3.24) | 0.69 | 0% |
| Heart Failure | 2630 | 4 | 0.39 (0.09 to 1.66) | 1 | 0% |
| Stroke | 2011 | 3 | 2.17 (0.48 to 9.76) | 0.97 | 0% |
| Microvascular Outcomes | | | | | |
| Retinopathy | 3375 | 6 | 0.72 (0.52 to 1.00) | 0.60 | 0% |
| Any Renal Event | 2679 | 5 | 0.61 (0.29 to 1.27) | 0.69 | 0% |
| ESRD | 1320 | 2 | 0.51 (0.23 to 1.10) | 0.81 | 0% |
| Adverse Events | | | | | |
| Any Hypoglycemia | 12229 | 23 | 0.73 (0.63 to 0.86) | 0 | 80% |
| Severe Hypoglycemia | 13246 | 27 | 0.57 (0.35 to 0.93) | 1 | 0% |
| Any GI Event | 7146 | 15 | 3.32 (1.95 to 5.65) | 0.09 | 42% |
| Any Pancreatitis | 11725 | 22 | 1.91 (0.95 to 3.85) | 1 | 0% |
| Pancreatic Cancer | 3477 | 6 | 1.44 (0.23 to 9.12) | 1 | 0% |
| Medullary Thyroid Carcinoma | 5674 | 11 | 0.96 (0.17 to 5.29) | 1 | 0% |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; GI, gastrointestinal; ESRD end-stage renal disease

[a]Meta-analyses were not conducted for outcomes with <2 trials. For GLP1RA vs. placebo, these included ESRD (1 study), bone fracture (0 studies), and foot ulcer (1 study). For GLP1RA vs. other drugs, these included fatal myocardial infarction (0 studies), 3-component MACE (1 study), 5-component MACE (0 studies), 6-component MACE (0 studies), blindness (0 studies), bone fracture (1 study), and foot ulcer (0 studies).

eTable 26. Subgroup Analyses: GLP1RA vs. Placebo

| GLP1RA vs. Placebo | Patient N | Trial N | Mean Difference / Relative Risk (95% Cl) | $I^2$ Statistic |
|---|---|---|---|---|
| High Dose GLP1RA | | | | |
| $HbA_{1c}$ (%) | 33348 | 12 | -0.65 (-0.76 to -0.54) | 93% |
| Weight (kg) | 32045 | 9 | -1.94 (-2.67 to -1.20) | 96% |
| HR (beats per minute) | 35177 | 9 | 2.11 (1.42 to 2.80) | 88% |
| Any Hypoglycemia | 20073 | 11 | 1.13 (0.97 to 1.33) | 68% |
| Combination Therapy (Background Medication) | | | | |
| $HbA_{1c}$ (%) | 12554 | 9 | -0.72 (-0.85 to -0.59) | 84% |
| Weight (kg) | 11894 | 7 | -1.69 (-2.62 to -0.77) | 87% |
| HR (beats per minute) | 10725 | 3 | 0.99 (-0.43 to 2.40) | 72% |
| Any Hypoglycemia | 2489 | 7 | 1.16 (0.71 to 1.89) | 36% |
| No 'Standard Care' Approach Permitted | | | | |
| $HbA_{1c}$ (%) | 3472 | 10 | -0.71 (-0.89 to -0.52) | 87% |
| Average Baseline $HbA_{1c}$ < 8% | | | | |
| $HbA_{1c}$ (%) | 10524 | 2 | -0.76 ( -1.07 to -0.45) | 94% |
| Any Hypoglycemia | 6702 | 2 | 1.31 (0.89 to 1.94) | 88% |
| Average Baseline $HbA_{1c}$ 8.0 to 8.5% | | | | |
| $HbA_{1c}$ (%) | 17425 | 9 | -0.60 ( -0.73 to -0.48) | 82% |
| Any Hypoglycemia | 2685 | 8 | 1.22 (0.79 to1.87) | 26% |
| Average Baseline $HbA_{1c}$ > 8.5% | | | | |
| $HbA_{1c}$ (%) | 20626 | 4 | -0.79 (-1.07 to -0.52) | 97% |
| Any Hypoglycemia | 10987 | 2 | 0.96 (0.92 to 1.01) | 0% |
| Study Duration 1 year | | | | |
| Any Hypoglycemia | 2117 | 6 | 1.63 (1.32 to 2.01) | 0% |
| Study Duration > 1 year | | | | |
| Any Hypoglycemia | 18257 | 6 | 1.01 (0.92 to 1.11) | 39% |
| ≥ 50% ASCVD History | | | | |
| HR (beats/min) | 38385 | 5 | 2.63 (1.94 to 3.32) | 91% |
| < 50% ASCVD History | | | | |
| HR (beats/min) | 11544 | 5 | 1.35 (0.22 to 2.49) | 69% |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; HR, heart rate; ASCVD, atherosclerotic cardiovascular disease

eTable 27. Subgroup Analyses: GLP1RA vs. Other Anti-hyperglycemic Medication

| GLP1RA vs. other anti-hyperglycemic medication | Patient N | Trial N | Mean Difference / Relative Risk (95% CI) | $I^2$ Statistic |
|---|---|---|---|---|
| High Dose GLP1RA | | | | |
| $HbA_{1c}$ (%) | 10082 | 23 | -0.39 (-0.57 to -0.21) | 94% |
| Weight (kg) | 8700 | 18 | -3.54 (-4.30 to -2.79) | 93% |
| HR (beats per minute) | 7681 | 14 | 1.69 (1.08 to 2.30) | 55% |
| Any Hypoglycemia | 11237 | 20 | 0.79 (0.68 to 0.91) | 76% |
| Combination Therapy (Background Medication) | | | | |
| $HbA_{1c}$ (%) | 10040 | 24 | -0.32 (-0.47 to -0.18) | 95% |
| Weight (kg) | 8710 | 19 | -3.49 (-4.34 to -2.65) | 95% |
| HR (beats per minute) | 7590 | 14 | 1.91 (1.29 to 2.53) | 55% |
| Any Hypoglycemia | 10342 | 19 | 0.70 (0.60 to 0.83) | 79% |
| Sulfonylurea | | | | |
| $HbA_{1c}$ (%) | 1596 | 5 | -0.28 (-0.56 to 0.00) | 75% |
| Weight (kg) | 1111 | 4 | -5.37 (-8.00 to -2.73) | 95% |
| HR (beats per minute) | 979 | 2 | 0.45 (-0.68 to 1.58) | 0% |
| Any Hypoglycemia | 1222 | 4 | 0.34 (0.23 to 0.50) | 0% |
| DPP-4I | | | | |
| $HbA_{1c}$ (%) | 4289 | 8 | -0.62 (-0.80 to -0.44) | 86% |
| Weight (kg) | 4269 | 7 | -2.13 (-2.91 to -1.35) | 87% |
| HR (beats per minute) | 3925 | 7 | 1.58 (0.86 to 2.29) | 34% |
| Any Hypoglycemia | 4263 | 6 | 1.22 (0.86 to 1.75) | 50% |
| Insulin | | | | |
| $HbA_{1c}$ (%) | 4147 | 11 | -0.22 (-0.37 to -0.07) | 77% |
| Weight (kg) | 3322 | 8 | -4.13 (4.93 to 3.35) | 83% |
| HR (beats per minute) | 2820 | 5 | 2.25 (1.11 to 3.40) | 66% |
| Any Hypoglycemia | 5298 | 10 | 0.67 (0.56 to 0.80) | 85% |
| Average Baseline $HbA_{1c}$ < 8% | | | | |
| $HbA_{1c}$ (%) | 970 | 3 | -0.30 (-0.57 to -0.03) | 74% |
| Any Hypoglycemia | 970 | 3 | 0.81 (0.54 to 1.23) | 17% |
| Average Baseline $HbA_{1c}$ 8.0 to 8.5% | | | | |
| $HbA_{1c}$ (%) | 9309 | 19 | -0.45 (-0.65 to -0.26) | 95% |
| Any Hypoglycemia | 10078 | 16 | 0.74 (0.62 to 0.89) | 84% |
| Average Baseline $HbA_{1c}$ > 8.5% | | | | |
| $HbA_{1c}$ (%) | 1553 | 6 | -0.15 (-0.39 to 0.09) | 67% |
| Any Hypoglycemia | 1344 | 4 | 0.24 (0.04 to 1.38) | 0% |
| Study Duration 1 year | | | | |
| Any Hypoglycemia | 9214 | 17 | 0.80 (0.69 to 0.93) | 75% |
| Study Duration > 1 year | | | | |
| Any Hypoglycemia | 3015 | 6 | 0.50 (0.30 to 0.85) | 77% |
| Baseline BMI ≥30 $kg/m^2$ | | | | |

| | | | | |
|---|---|---|---|---|
| Weight (kg) | 8578 | 16 | -3.23 (-3.96 to -2.49) | 93% |
| Baseline BMI < 30 kg/$m^2$<br>Weight (kg) | 1387 | 6 | -4.28 (-6.25 to -2.32) | 95% |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; HR, heart rate; DPP-4I, dipeptyl peptidase-4 inhibitor; BMI, body mass index