Canada's Drug and
Health Technology Agency

Supplemental Materials

Sodium-Glucose Cotransporter-2 Inhibitors for Type 2 Diabetes Mellitus

Streamlined Drug Class Review

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Abbreviations

AE	adverse event
AMSTAR2	A MeaSurement Tool to Assess systematic Reviews 2
CI	confidence interval
CUA	cost utility analysis
DPP-4	dipeptidyl peptidase-4
FMEC	Formulary Management Expert Committee
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRIPP2	Guidance for Reporting Involvement of Patients and the Public 2
NMA	network meta-analysis
NPDUIS	National Prescription Drug Utilization Information System
OR	odds ratio
pCPA	pan-Canadian Pharmaceutical Alliance
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SGLT2	sodium glucose cotransporter-2
SMD	standardized mean difference
SR	systematic review

Note that the appendices have not been copy-edited.

Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: August 31, 2023

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments.

Limits:

- Publication date limit: 2016-present
- Language limit: English
- Conference abstracts: excluded

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were Type 2 diabetes and Sodium-Glucose Transporter 2 Inhibitors, including specific drug names as well as general terms for these drugs.

CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. Conference abstracts were excluded from the search results.

Table 1: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1. diabetes mellitus/ or diabetes mellitus, type 2/ or diabetes mellitus, lipoatrophic/
2. (familial partial lipodystroph* or berardinelli-seip congenital lipodystroph* or dunnigan syndrome* or koberling-dunnigan syndrome* or MODY* or NIDDM or T2DM or T2D or DM2 or DMT2).ti,kf.
3. (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).ti,kf.
4. ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).ti,kf.
5. ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).ti,kf.
6. ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).ti,kf.
7. or/1-6

8. (empagliflozin* or Jardiance* or Jardianz* or Glimpacare* or Gibtulio* or Dzhardins* or Diacurimap* or Synjardy* or Trijardy*).ti,ab,kf,ot,hw,rn,nm.
9. (dapagliflozin* or forxiga* or farxiga* or edistride* or Ebymect* or Qternmet* or Xigduo*).ti,ab,rn,nm,kf,ot,hw.
10. (canagliflozin* or canagliflocin* or Invokana* or Invokamet* or Vokanamet * or canaglu* or sulisent*).ti,ab,rn,nm,kf,ot,hw.
11. *Sodium-Glucose Transporter 2 Inhibitors/
12. ((SGLT2* adj2 inhibitor*) or gliflozin*).ti,kf.
13. (sodium adj3 glucose adj2 (transporter* or co-transporter* or cotransporter*) adj2 inhibitor*).ti,kf.
14. or/8-13
15. 7 and 14
16. 15 use medall
17. diabetes mellitus/ or non insulin dependent diabetes mellitus/ or lipoatrophic diabetes mellitus/
18. (familial partial lipodystroph* or berardinelli-seip congenital lipodystroph* or dunnigan syndrome* or koberling-dunnigan syndrome* or MODY* or NIDDM or T2DM or T2D or DM2 or DMT2).ti,kf.
19. (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).ti,kf.
20. ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).ti,kf.
21. ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).ti,kf.
22. ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).ti,kf.
23. or/17-22
24. *Empagliflozin/ or *empagliflozin plus metformin/
25. (empagliflozin* or Jardiance* or Jardianz* or Glimpacare* or Gibtulio* or Dzhardins* or Diacurimap* or Synjardy* or Trijardy*).ti,ab,kf,dq.
26. *dapagliflozin/ or *dapagliflozin plus metformin/
27. (dapagliflozin* or forxiga* or farxiga* or edistride* or Ebymect* or Qternmet* or Xigduo*).ti,ab,kf,dq.
28. *canagliflozin/ or *canagliflozin plus metformin/
29. (canagliflozin* or canagliflocin* or Invokana* or Invokamet* or Vokanamet* or canaglu* or sulisent*).ti,ab,kf,dq.
30. *sodium glucose cotransporter 2 inhibitor/
31. ((SGLT2* adj2 inhibitor*) or gliflozin*).ti,kf.
32. (sodium adj3 glucose adj2 (transporter* or co-transporter* or cotransporter*) adj2 inhibitor*).ti,kf.
33. or/24-32

34. 23 and 33
35. (conference abstract or conference review).pt.
36. 34 not 35
37. 16 or 36
38. network meta-analysis/
39. (meta-analysis/ or meta-analysis as topic/ or "meta analysis (topic)"/) and network.ti,ab,kf.
40. ((indirect or indirect treatment or mixed treatment or bayesian) adj3 comparison*).ti,ab,kf.
41. (network* adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
42. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
43. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
44. umbrella review*.ti,ab,kf.
45. nma.ti,ab,kf.
46. (Multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
47. (Multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
48. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
49. MPES.ti,ab,kf.
50. or/38-49
51. 37 and 50
52. (systematic review or meta-analysis).pt.
53. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
54. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
55. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
56. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
57. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
58. (handsearch* or hand search*).ti,ab,kf.
59. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
60. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.

61. (meta regression* or metaregression*).ti,ab,kf.
62. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
63. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
64. (cochrane or (health adj2 technology assessment) or evidence report).jw.
65. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
66. (outcomes research or relative effectiveness).ti,ab,kf.
67. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
68. [(meta-analysis or systematic review).md.]
69. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
70. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
71. umbrella review*.ti,ab,kf.
72. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
73. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
74. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
75. or/52-74
76. 37 and 75
77. 51 or 76
78. limit 77 to yr="2016 -Current"
79. limit 78 to english language

Grey Literature

Search dates: August 17-31, 2023

Keywords: canagliflozin, invokana, canagliflozin-metformin, invokamet, empagliflozin, jardiance, emplagliflozin-metformin, synjardy, dapagliflozin, forxiga, dapagliflozin-metformin, xigduo, sodium-glucose cotransporter-2 (SGLT2) inhibitors), type 2 diabetes

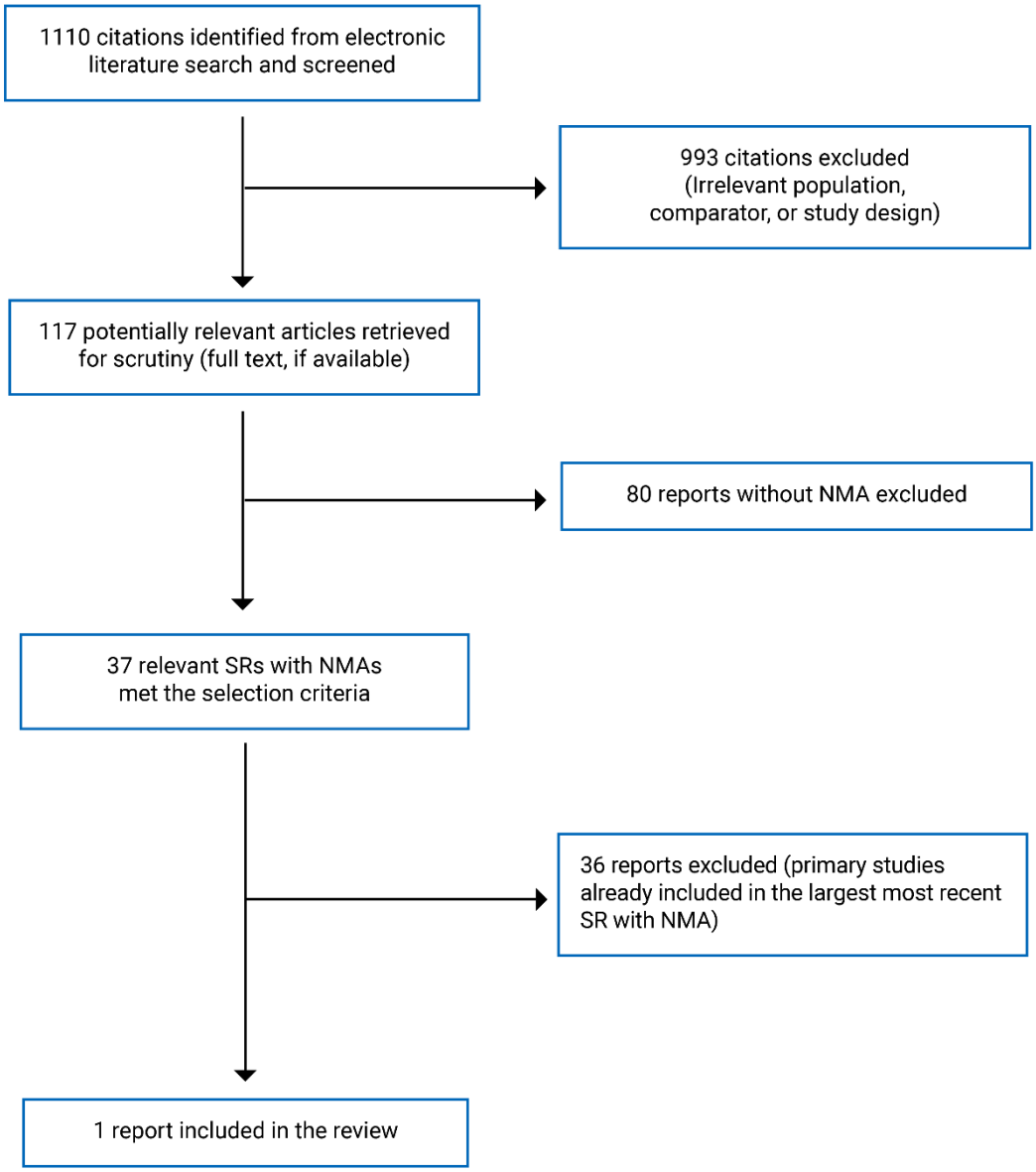
Limits: Publication years: 2016-present, English language

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Selection of Included Studies

Figure 1: Flowchart of Selected Reports



Appendix 3: List of Excluded Publications

Table 2: Characteristics of Excluded Systematic Reviews and Network Meta-Analyses

Reference	Number of included studies	Number of studies in NMA	Number of included drug classes	Number of patients	Population	Outcomes
Yang et al. 2023	27	27	7	50237	T2DM and CKD	Cardiorenal
Sabouret et al. 2023	11	0	2	98572	T2DM	Mortality, Cardiorenal
Nguyen et al. 2023	29	0	3	50938	T2DM and CKD	Cardiorenal
Ghosal et al. 2023	16	0	3	NR	T2DM	Renal
Brondal et al. 2023	NR	NR	4	NR	T2DM	Mortality, Cardiorenal
Zhang et al. 2022	18	0	3	51496	T2DM and CKD	Mortality, Cardiorenal
Yang et al. 2022	98	0	3	186335	T2DM	Renal
Tornyos et al. 2022	29	0	1	88418	T2DM	Mortality, Cardiovascular
Tian et al. 2022	10	0	1	68723	T2DM	Mortality, Cardiorenal
Teo et al. 2022	111	0	2	103922	T1DM or T2DM	Cardiovascular, HbA1C, Safety
Qiu et al., 2022	N/A	0	2	NR	T2DM	Mortality, Cardiorenal
Li et al., 2022	36	0	2	85701	T2DM	A fib event
Guigliano et al. 2022	23	0	3	181143	T2DM or no DM	Mortality, Cardiorenal
Wei et al. 2021	NR	NR	2	NR	T2DM	Mortality, Cardiorenal
Tsapas et al. 2021	424	0	9	276336	T2DM	Body weight, Blood Pressure

Reference	Number of included studies	Number of studies in NMA	Number of included drug classes	Number of patients	Population	Outcomes
Tager et al. 2021	64	0	1	74874	T2DM	Mortality, Cardiovascular
Qiu et al. 2021	NR	0	2	NR	T2DM	Mortality, Cardiovascular
Palmer et al. 2021	764	0	2	421346	T2DM	Mortality, Cardiorenal, Safety
Mannucci et al. 2021	NR	0	At least 5	NR	T2DM	HbA1C, body weight, hypoglycemia
Lin et al. 2021	21	0	3	170930	CHF and CKD	Mortality, Cardiorenal
Hu et al. 2021	15	0	2	125796	T2DM	Mortality, Cardiorenal
Duan et al. 2021	14	0	2	NR	T2DM	Mortality, Cardiorenal
Bae et al. 2021	17	0	2	87263	T2DM	Renal
Tsapas et al. 2020	453	0	9	NR	T2DM	Mortality, Cardiorenal, HbA1c
Hussein et al. 2020	64	0	2	31384	T2DM	HbA1c, Body Weight, Blood Pressure, Safety
Wang et al. 2019	29	0	1	11999	T2DM	Change in weight
Kanter et al. 2019	21	0	2	NR	T2DM	HbA1c, weight, blood pressure
Hussein et al. 2019	8	0	2	60082	T2DM	Mortality, Cardiorenal
Fei et al. 2019	14	0	3	121047	T2DM	Mortality, Cardiorenal
Alfayez et al. 2019	9	0	3	87162	T2DM	Mortality, Cardiorenal
Zhang et al. 2018	236	0	3	176310	T2DM	Mortality, Cardiorenal

Reference	Number of included studies	Number of studies in NMA	Number of included drug classes	Number of patients	Population	Outcomes
Kramer et al. 2018	9	0	3	87162	T2DM	Heart Failure Hospitalization
Fei et al. 2018	7	0	3	62268	T2DM	Mortality, Cardiovascular
Wang et al. 2017	8	0	At least 4	NR	T2DM	HbA1c, Triglycerides, Safety
Min et al. 2017	14	0	3	6980	T2DM	HbA1c, body weight, glucose, safety
Lee et al. 2017	73	0	5	101183	T2DM	Mortality, Cardiovascular

HbA1C = glycated hemoglobin; NMA = network meta-analysis; NR = not reported; T2DM = Type 2 Diabetes Mellitus

Appendix 4: Critical Appraisal

Table 3: AMSTAR 2 — A Critical Appraisal Tool for Systematic Reviews That Include Randomized or Non-Randomized Studies of Health Care Interventions or Both[1]

For Study by Shi et al. 2023[2]		
Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: • Population • Intervention • Comparator group • Outcome	Optional (recommended) Timeframe for follow-up	**Yes**
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes The authors state that they had a written protocol or guide that included ALL the following: • review question(s) • a search strategy • inclusion/exclusion criteria • a risk of bias assessment	**For Yes** As for partial yes, plus the protocol should be registered and should also have specified: • a meta-analysis/synthesis plan, if appropriate, and • a plan for investigating causes of heterogeneity • justification for any deviations from the protocol **Page 3 Methods: A protocol detailing predefined eligibility criteria, which differed slightly from the previously published network meta-analysis,2 was registered with PROSPERO (CRD42022325948).**	**Yes** Partial Yes No
Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: • Explanation for including only RCTs • OR explanation for including only NRSI • OR explanation for including only RCTs and NRSI		**Yes** No

For Study by Shi et al. 2023[2]		
Did the review authors use a comprehensive literature search strategy?		
• searched at least 2 databases (relevant to research question) • provided key word and/or search strategy • justified publication restrictions (e.g., language) **Page 6: Search strategy and information sources**	For Yes, should also have (all the following): • searched the reference lists/ bibliographies of included studies • searched trial/study registries • included/consulted content experts in the field • where relevant, searched for grey literature • conducted search within 24 months of completion of the review	Yes **Partial Yes** No
Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: • at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include • OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. **Page 6: Study selection: Pairs of reviewers (QS, KNo, QF, ZQ, and FY) independently screened identified hits at the title and abstract and full text levels, with discrepancies resolved by a senior reviewer (SL).**		**Yes** No
Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: • at least two reviewers achieved consensus on which data to extract from included studies • OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.		**Yes** No

For Study by Shi et al. 2023[2]		
Page 6: Data collection and data items: Using a standardised extraction form, the paired trained reviewers (QS, KNo, YM, QF, ZQ, XZ, XC, ZC, XL, and SH) independently extracted the following data		
Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: • provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: • Justified the exclusion from the review of each potentially relevant study	Yes Partial Yes **No**
Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): • described populations • described interventions • described comparators • described outcomes • described research designs	For Yes, should also have ALL the following: • described population in detail • described intervention in detail (including doses where relevant) • described comparator in detail (including doses where relevant) • described study's setting • timeframe for follow-up **All the information provided in supplemental appendix**	**Yes** Partial Yes No
The review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from: • unconcealed allocation, and • lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) **Cochrane RoB was used**	For Yes, must also have assessed RoB from: • allocation sequence that was not truly random, and • selection of the reported result from among multiple measurements or analyses of a specified outcome **(unclear)**	Yes **Partial Yes** No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: • from confounding, and	For Yes, must also have assessed RoB:	Yes Partial Yes No

For Study by Shi et al. 2023[2]		
• from selection bias	• methods used to ascertain exposures and outcomes, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	Includes only RCTs
Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: • Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information, but it was not reported by study authors also qualifies		**Yes** No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		

RCTs
For Yes:
• The authors justified combining the data in a meta-analysis
  ○ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  ○ AND investigated the causes of any heterogeneity
 	
Page 7: Data synthesis: methods for meta-analyses reported (include justification of approach, assessment of heterogeneity, transitivity and other assumptions prior to conducting the NMA)
		Yes
		No
		No meta-analysis conducted

For NRSI
For Yes:
• The authors justified combining the data in a meta-analysis
  ○ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  ○ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  ○ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review
		Yes
		No
		No meta-analysis conducted

For Study by Shi et al. 2023[2]	
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: • included only low risk of bias RCTs • OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. **Sensitivity analysis was performed excluding studies with high RoB**	**Yes** No No meta-analysis conducted
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: • included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	**Yes** No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: • There was no significant heterogeneity in the results • OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	**Yes** No
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: • performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias **Page 7: data analysis: Comparison adjusted funnel plots evaluated global small study effects, which could reflect publication bias.** **Page 8: The evidence did not suggest global publication bias and intransitivity for any outcome**	**Yes** No No meta-analysis conducted
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: • The authors reported no competing interests OR	**Yes** No

For Study by Shi et al. 2023[2]	
• The authors described their funding sources and how they managed potential conflicts of interest	

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008.

Table 4: ISPOR Questionnaire to Assess Relevance and Credibility of Network Meta-Analysis Study[3] (for Shi et al. 2023)

For Shi et al. 2023[2] — Network Meta-analysis	
Relevance	**Yes / No / Can't answer**
Is the population relevant?	**Yes**
	Yes, include only Type 2 DM population. Also, some results are analyzed by risk strata that may provide additional context when reviewing the evidence.
Are any relevant interventions missing?	**No**
	No, all comparators/interventions included in our PICO are included in the NMA.
Are any relevant outcomes missing?	**No**
	No missing outcomes. Decision maker has requested to see additional outcome on HbA1C which will be evaluated by including a supplemental NMA. Follow up of 24 weeks or longer.
Is the context (settings and circumstances) applicable?	**Yes**
	Yes, data sources include up to 14 October 2022.
Credibility	
Did the researchers attempt to identify and include all relevant RCTs?	**Yes**
	Target RCTs between all interventions. Multiple databases were searched (MEDLINE, EMBASE, Cochrane Central).
Do the trials for the interventions of interest form one connected network of RCTs?	**Yes**
Is it apparent that poor quality studies were included, thereby leading to bias?	**No**
	Risk of Bias assessment were conducted at the study level.
Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No**
	Publication bias assessment was conducted.

For Shi et al. 2023[2] — Network Meta-analysis	
Relevance	**Yes / No / Can't answer**
	Global inconsistency, intransitivity and incoherence were all assessed.
Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparisons in the network?	**No** The authors reported that the evidence did not suggest intransitivity for any outcome.
If there are systematic differences in treatment effect modifiers, were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?	**Not applicable**
Analysis	
Were statistical methods used that preserve within-study randomization? (no naïve comparisons)	**Yes**
If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed?	**Yes** Global inconsistency was assessed.
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the NMA?	**Yes**
With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Not applicable**
Was a valid rationale provided for the use of random-effects or fixed-effect models?	**Yes** Conducted a random effect network meta-analysis using a frequentist graph theoretical approach.
If a random-effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes** The global heterogeneity was evaluated with generalized methods of moments estimate of variance between studies and tested by the design-based decomposition of Cochran's Q statistic.
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with prespecified covariates performed?	**Yes** The authors calculated indirect estimates from the network by node splitting and back calculation methods.
Reporting Quality and Transparency	
	Yes

For Shi et al. 2023[2] — Network Meta-analysis	
Relevance	**Yes / No / Can't answer**
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Study characteristics and patient characteristics are provided.
Are the individual study results reported?	Yes, in the appendix.
Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	**No** They are reported together.
Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	**Yes** In the appendix
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**For some results only**
Is the effect of important patient characteristics on treatment effects reported?	**Yes** Results are reported by risk factors.
Interpretation	
Are the conclusions fair and balanced?	**Yes**
Conflict of Interest	
Were there any potential conflicts of interest?	**No**

Table 5: ISPOR Questionnaire to Assess Relevance and Credibility of Network Meta-Analysis Study[3] (for Palmer et al. 2021)

Network Meta-analysis — For Study by Palmer et al.[4]	
Relevance	**Yes / No / Can't answer**
Is the population relevant?	**Yes**
	For adults with type 2 diabetes.
Are any relevant interventions missing?	**No**
	Although main interventions for comparison are SGLT2 inhibitors and GLP-1 receptor agonists. The NMA has included other interventions of interest.
Are any relevant outcomes missing?	**No**
	Only using this NMA as supplemental to provide results on HbA1C.
Is the context (settings and circumstances) applicable?	**Yes**
	Including relevant RCTs in Type 2 DM. This is an older NMA but still relevant in our setting.
Credibility	
Did the researchers attempt to identify and include all relevant RCTs?	**Yes**
	The search strategy targeted RCTs comparing SGLT2 or GLP-1 receptor agonists with placebo. Included MEDLINE, EMBASE, Cochrane Central up to August 11, 2020.
Do the trials for the interventions of interest form one connected network of RCTs?	**Yes**
	See Figure 2 in the publication. All nodes are connected except for bolus insulin and alpha glucosidase inhibitor which are not interventions of interest in this review.
Is it apparent that poor quality studies were included, thereby leading to bias?	**No**
	Only included RCT and risk of bias appraisal has been done for each trial.
Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No**
	Appendix 5: Evaluations of network inconsistency and heterogeneity. Appendix 6: Direct, indirect and network treatment estimates.

Network Meta-analysis — For Study by Palmer et al.[4]	
Relevance	**Yes / No / Can't answer**
Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparisons in the network?	**Yes** Evidence presented by risk strata: • Very low risk (no or few than 3 cardiovascular risk factors) • Low risk (three or more cardiovascular risk factors) • Moderate risk (cardiovascular disease) • High risk (chronic kidney disease) • Very high risk (cardiovascular and chronic kidney disease)
If there are systematic differences in treatment effect modifiers, were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?	Appendix 6: Direct, indirect and network treatment estimates. The authors assessed agreement between direct and indirect estimates in every closed loop of evidence using node splitting approaches and for the entire network using a design-by-treatment interaction model.
Analysis	
Were statistical methods used that preserve within-study randomization? (no naïve comparisons)	**Yes** Appendix 6: Direct, indirect and network treatment estimates.
If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed?	**Yes** Appendix 6: Direct, indirect and network treatment estimates.
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the NMA?	**Yes** Appendix 5: Evaluations of network inconsistency and heterogeneity.
With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes** Appendix 5: Evaluations of network inconsistency and heterogeneity.
Was a valid rationale provided for the use of random-effects or fixed-effect models?	**Yes** • The direct comparison of two treatments, the authors conducted a frequentist pairwise meta-analysis using a restricted maximum likelihood estimation and reported, with corresponding 95% confidence intervals, odds ratios for dichotomous outcomes, mean differences for continuous outcomes and standardized mean difference for health related QOL.

Network Meta-analysis — For Study by Palmer et al.[4]	
Relevance	**Yes / No / Can't answer**
	• The authors conducted NMA using frequentist methods with restricted maximum likelihood estimation to quantify network heterogeneity, assuming a common heterogeneity estimate within a network. • Agreement between direct and indirect estimates was assessed in every closed loop of evidence using node splitting approaches and for the entire network using a design-by-treatment interaction model.
If a random-effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes**
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with prespecified covariates performed?	**Yes**
	Appendix 5: Evaluations of network inconsistency and heterogeneity.
Reporting Quality and Transparency	
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes**
	Appendix 6: Direct, indirect and network treatment estimates.
Are the individual study results reported?	**Yes**
Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	**Yes**
	Appendix 6: Direct, indirect and network treatment estimates.
Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	**Yes**
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No**
Is the effect of important patient characteristics on treatment effects reported?	**Yes**
Interpretation	
Are the conclusions fair and balanced?	**Yes**
Conflict of Interest	
Were there any potential conflicts of interest?	**No**

Appendix 5: Drugs Included in the National Prescription Drug Utilization System Database Search

Table 6: Drugs Included in the National Prescription Drug Utilization System Database Search

ATC Level 4	ATC	Name
A10AB Insulins and analogues for injection, fast-acting	A10AB01	insulin (human)
A10AB Insulins and analogues for injection, fast-acting	A10AB03	insulin (pork)
A10AB Insulins and analogues for injection, fast-acting	A10AB04	insulin lispro
A10AB Insulins and analogues for injection, fast-acting	A10AB05	insulin aspart
A10AB Insulins and analogues for injection, fast-acting	A10AB06	insulin glulisine
A10AC Insulins and analogues for injection, intermediate-acting	A10AC01	insulin (human)
A10AC Insulins and analogues for injection, intermediate-acting	A10AC03	insulin (pork)
A10AC Insulins and analogues for injection, intermediate-acting	A10AC04	insulin lispro
A10AD Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	A10AD01	insulin (human)
A10AD Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	A10AD03	insulin (pork)
A10AD Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	A10AD04	insulin lispro
A10AD Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	A10AD05	insulin aspart
A10AE Insulins and analogues for injection, long-acting	A10AE01	insulin (human)
A10AE Insulins and analogues for injection, long-acting	A10AE03	insulin (pork)
A10AE Insulins and analogues for injection, long-acting	A10AE54	insulin glargine and lixisenatide
A10AF Insulins and analogues for inhalation	A10AF01	insulin (human)
A10BA Biguanides	A10BA02	metformin
A10BD Combinations of oral blood glucose lowering drugs	A10BD07	metformin and sitagliptin
A10BD Combinations of oral blood glucose lowering drugs	A10BD10	metformin and saxagliptin
A10BD Combinations of oral blood glucose lowering drugs	A10BD11	metformin and linagliptin

ATC Level 4	ATC	Name
A10BD Combinations of oral blood glucose lowering drugs	A10BD15	metformin and dapagliflozin
A10BD Combinations of oral blood glucose lowering drugs	A10BD20	metformin and empagliflozin
A10BF Alpha glucosidase inhibitors	A10BF01	acarbose
A10BG Thiazolidinediones	A10BG02	rosiglitazone
A10BG Thiazolidinediones	A10BG03	pioglitazone
A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH01	sitagliptin
A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH03	saxagliptin
A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH05	linagliptin
A10BJ Glucagon-like peptide-1 (GLP-1) analogues	A10BJ03	lixisenatide
A10BJ Glucagon-like peptide-1 (GLP-1) analogues	A10BJ06	semaglutide
A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK01	dapagliflozin
A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK02	canagliflozin
A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK03	empagliflozin
A10BX Other blood glucose lowering drugs, excl. insulins	A10BX02	repaglinide

Appendix 6: Public Claimants and Expenditures for Antihyperglycemic Agents

Table 7: Claimants for Antihyperglycemic Agents by Class ATC4 (2019-2022)

Treatment	2019	2020	2021	2022
Alpha glucosidase inhibitors	6,246	4,520	4,648	4,700
Biguanides	870,625	876,295	913,753	943,245
Combinations of oral blood glucose lowering drugs	194,120	201,066	208,203	215,343
Dipeptidyl peptidase 4 (dpp-4) inhibitors	205,436	200,869	198,507	188,463
Glucagon-like peptide-1 (glp-1) analogues	24,721	68,814	130,696	204,258
Insulins and analogues for injection, fast-acting	177,846	174,115	176,430	174,938
Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	39,205	33,758	29,786	25,991
Insulins and analogues for injection, intermediate-acting	43,558	36,800	32,884	28,976
Insulins and analogues for injection, long-acting	254,216	261,411	272,632	280,054
Other blood glucose lowering drugs, excl. insulins	10,143	9,373	9,553	9,026
Sodium-glucose co-transporter 2 (sglt2) inhibitors	212,592	256,891	324,151	403,436
Sulfonylureas	317,091	308,301	312,408	312,754
Thiazolidinediones	5,935	4,554	3,589	3,341

Table 8: Expenditures for Antihyperglycemic Agents by Class ATC4 (2019-2022)

Treatment	2019 ($)	2020 ($)	2021 ($)	2022 ($)
Alpha glucosidase inhibitors	1,151,949	908,214	676,953	679,987
Biguanides	40,208,916	40,966,518	41,202,115	42,062,929
Combinations of oral blood glucose lowering drugs	182,496,309	194,709,259	203,221,913	207,430,454
Dipeptidyl peptidase 4 (dpp-4) inhibitors	181,510,557	181,050,203	177,921,208	167,601,951
Glucagon-like peptide-1 (glp-1) analogues	12,942,271	111,684,036	216,075,303	356,572,651
Insulins and analogues for injection, fast-acting	76,174,663	76,179,145	75,896,662	74,298,068
Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	25,182,332	21,597,869	18,636,249	16,496,585
Insulins and analogues for injection, intermediate-acting	12,882,976	10,850,007	9,084,051	7,643,953
Insulins and analogues for injection, long-acting	196,183,647	204,042,669	205,553,289	205,347,755

Treatment	2019 ($)	2020 ($)	2021 ($)	2022 ($)
Other blood glucose lowering drugs, excl. insulins	1,153,219	1,128,338	1,054,828	1,000,272
Sodium-glucose co-transporter 2 (sglt2) inhibitors	157,230,404	200,322,242	250,453,872	312,727,026
Sulfonylureas	23,078,370	22,828,288	22,345,230	21,974,399
Thiazolidinediones	1,828,477	1,312,247	1,139,265	1,045,770

Table 9: Average Cost of Utilization per Beneficiary for Antihyperglycemic Agents by Molecule (2022)

Treatment	Average Annual Cost of Utilization per Beneficiary ($)
Alpha-glucosidase Inhibitors	
ACARBOSE	194
Biguanides	
METFORMIN	83
Combination	
METFORMIN AND LINAGLIPTIN	906
METFORMIN AND SAXAGLIPTIN	888
METFORMIN AND SITAGLIPTIN	1146
METFORMIN AND DAPAGLIFLOZIN	752
METFORMIN AND EMPAGLIFLOZIN	840
DPP-4i	
LINAGLIPTIN	865
SAXAGLIPTIN	629
SITAGLIPTIN	1100
GLP-1 Agonists	
LIXISENATIDE	622
SEMAGLUTIDE	1968
Insulin	
INSULIN (HUMAN)	476
INSULIN (PORK)	959
INSULIN ASPART	577
INSULIN DEGLUDEC	1022
INSULIN DETEMIR	1045
INSULIN GLARGINE	693
INSULIN GLARGINE AND LIXISENATIDE	1348

Treatment	Average Annual Cost of Utilization per Beneficiary ($)
INSULIN GLULISINE	467
INSULIN LISPRO	564
Insulins and analogues for injection, fast-acting	92
Meglitinides	
REPAGLINIDE	164
SGLT2i	
CANAGLIFLOZIN	1039
DAPAGLIFLOZIN	830
EMPAGLIFLOZIN	900
Sulfonylureas	
GLIBENCLAMIDE	94
GLICLAZIDE	117
GLIMEPIRIDE	527
TZDs	
PIOGLITAZONE	412
ROSIGLITAZONE	804

Appendix 7: Anticipated Absolute Effect for Selected Outcome: Non-Fatal Stroke

Table 10: Anticipated Absolute Effect for Non-Fatal Stroke

Population	Outcome	Intervention	Comparator	Relative Effect	Baseline (5 years)	Anticipated Absolute Effects (5 years)	Grade
Adults with 3 or fewer cardiovascular risk factors	Non-fatal stroke	SGLT2 inhibitors	GLP-1 receptor agonists	1.16 (1.00, 1.35)	26 per 1000 persons	4 more (0 to 9) per 1000 persons	Moderate
Adults with more than 3 cardiovascular risk factors	Non-fatal stroke	SGLT2 inhibitors	GLP-1 receptor agonists	1.16 (1.00, 1.35)	50 per 1000 persons	8 more (0 to 16 more) per 1000 persons	Low
Adults with cardiovascular disease not chronic kidney disease	Non-fatal stroke	SGLT2 inhibitors	GLP-1 receptor agonists	1.16 (1.00, 1.35)	93 per 1000 persons	14 more (0 to 29 more) per 1000 persons	Moderate
Adults with chronic kidney disease but not cardiovascular disease	Non-fatal stroke	SGLT2 inhibitors	GLP-1 receptor agonists	1.16 (1.00, 1.35)	104 per 1000 persons	15 more (0 to 32 more) per 1000 persons	Moderate
Adults with established cardiovascular disease and chronic kidney disease	Non-fatal stroke	SGLT2 inhibitors	GLP-1 receptor	1.16 (1.00, 1.35)	166 per 1000 persons	22 more (0 to 46 more) per 1000 persons	Moderate

Appendix 8: Re-Analysis to Compare SGLT2 Inhibitors With Semaglutide and/or Dulaglutide: Proposal and Results

Comparisons of efficacy and safety between SGLT2 inhibitors, Semaglutide, or Dulaglutide: proposal and results for a network meta-analysis

Proposal

We performed a frequentist random effect network meta-analysis for drug treatments on adults with type 2 diabetes.

Types of Participants

We included trials enrolling adults with type 2 diabetes.

Types of Interventions and Controls

We included the trials if they compared SGLT2 inhibitors, semaglutide, or dulaglutide with each other or standard treatment with or without placebo. During analysis of scenario 1, semaglutide and dulaglutide were treated as one drug class label as “Semaglutide/Dulaglutide”. In analysis of scenario 2, dulaglutide was excluded. SGLT2 inhibitors include Bexagliflozin, Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Henagliflozin, Ipragliflozin, Luseogliflozin, Sotagliflozin, and Tofogliflozin. Standard treatments include standard care (i.e., lifestyle modification) and standard drug treatments (e.g., metformin and/or sulfonylureas) other than the drug of interest in the randomised trial.

Types of Outcomes

Primary Outcomes

1. all-cause death
2. cardiovascular death
3. non-fatal stroke
4. end-stage kidney disease
5. Secondary outcomes
6. non-fatal myocardial infarction
7. admission to hospital for heart failure
8. health-related quality of life, such as diabetes-related quality of life or SF-36.
9. Analysis of Scenario 1 included both primary outcomes and secondary outcomes, while Scenario 2 only analysed primary outcomes. We measured the binary outcomes using odds ratios. We measured

the quality of life score with standardised mean differences. We adopted the outcome definition reported in the original trials. End-stage kidney disease was defined as one of following criteria: long-term dialysis, kidney transplantation, a sustained eGFR <15 ml per minute per 1.73 m^2, a sustained percent decline in eGFR of at least 40% or a doubling of serum creatinine, or kidney-related death.

Types of Studies

Parallel group randomized controlled trials published in English were eligible.

Follow-Up and Assessment Time Points

We included trials with at least 24 weeks of follow-up. We assessed the outcomes at maximum follow-up.

Results for Scenario 1

Figure 2: Re-Analysis of Scenario 1 With Semaglutide and Dulaglutide — Forest Plot of Binary Outcomes

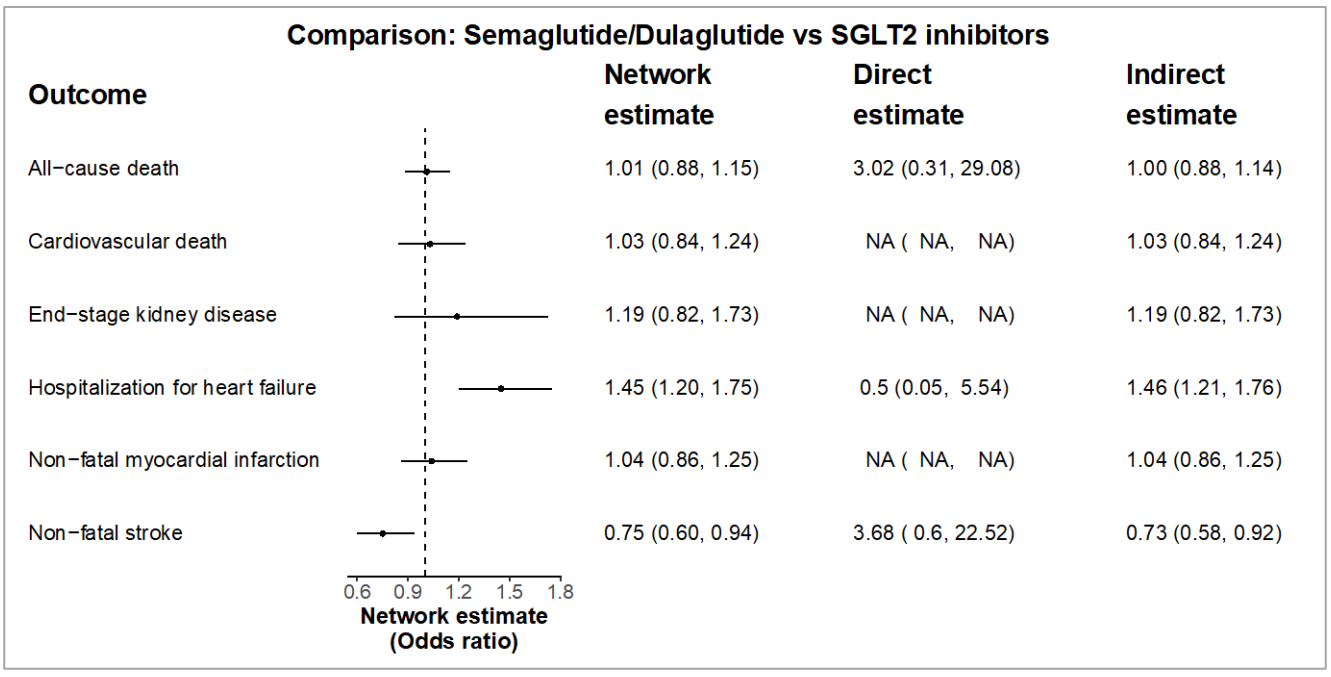
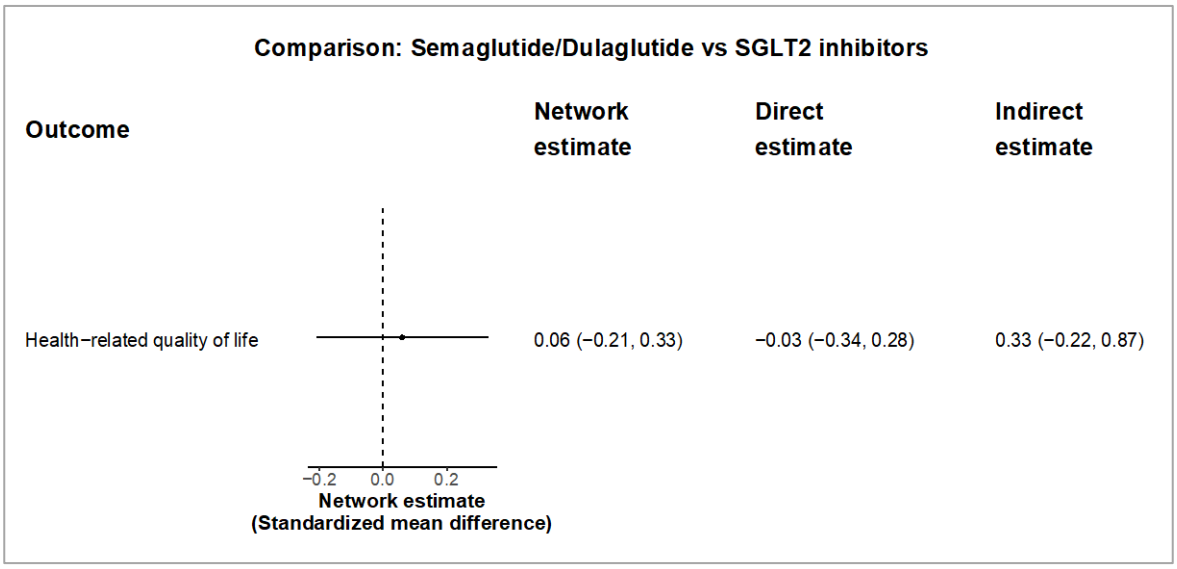
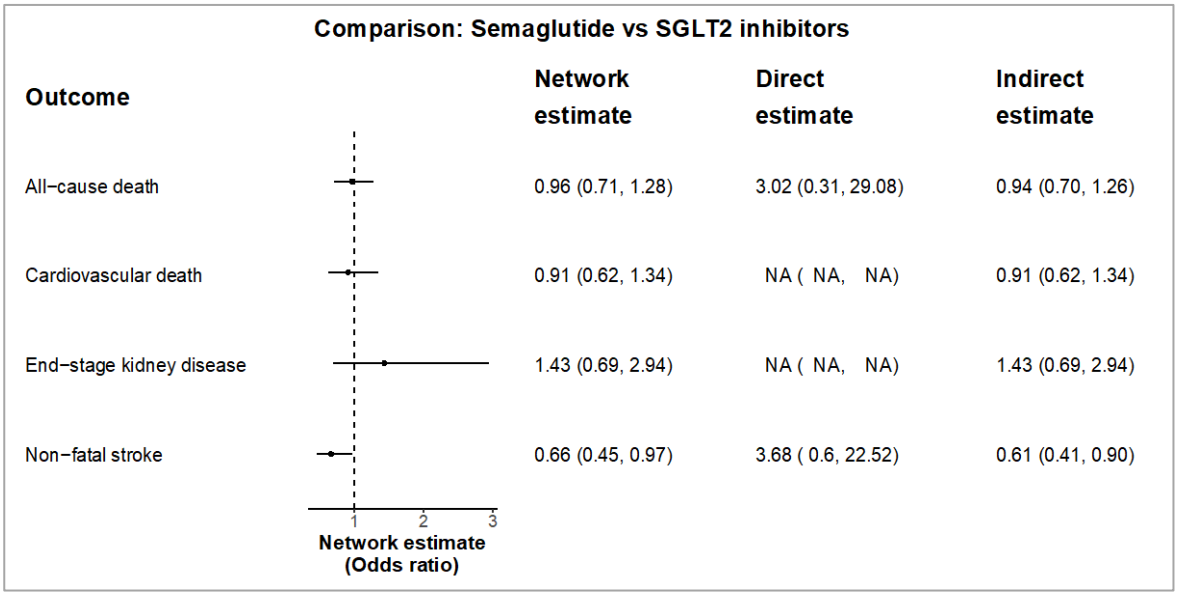


Figure 3: Re-Analysis of Scenario 1 With Semaglutide and Dulaglutide — Forest Plot of Health-Related Quality of Life



Results for Scenario 2

Figure 4: Re-Analysis of Scenario 2 With Semaglutide — Forest Plot of Binary Outcomes



Appendix 9: Re-Analysis to Compare SGLT2 Inhibitors With Semaglutide and Dulaglutide – Scenario 1: Forest Plots

These forest plots presenting relative effect of individual trial and pooled relative effects of each comparison.

Figure 5: Forest Plot — Scenario 1 for All-Cause Death

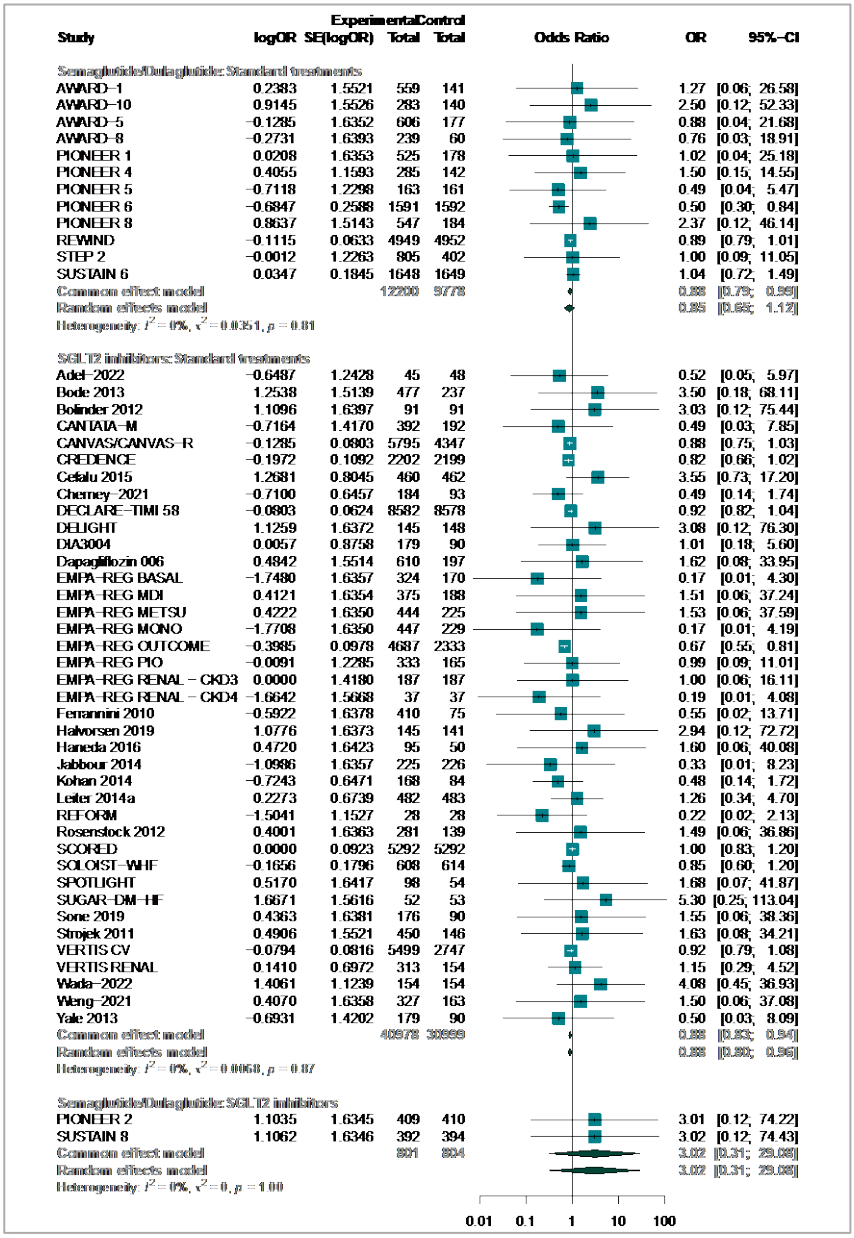


Figure 6: Forest Plot — Scenario 1 for Cardiovascular Death

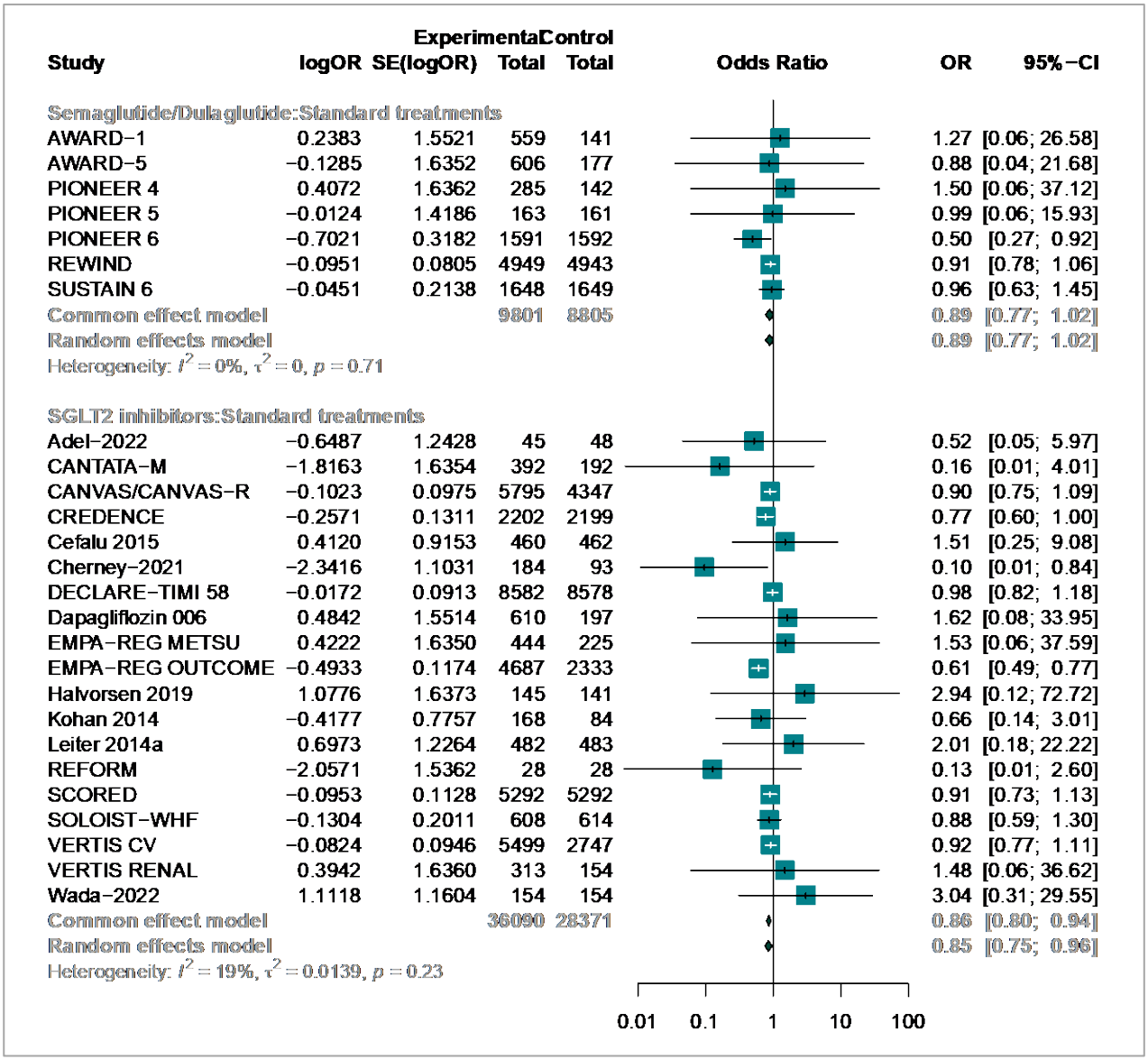


Figure 7: Forest Plot — Scenario 1 for Non-Fatal Stroke

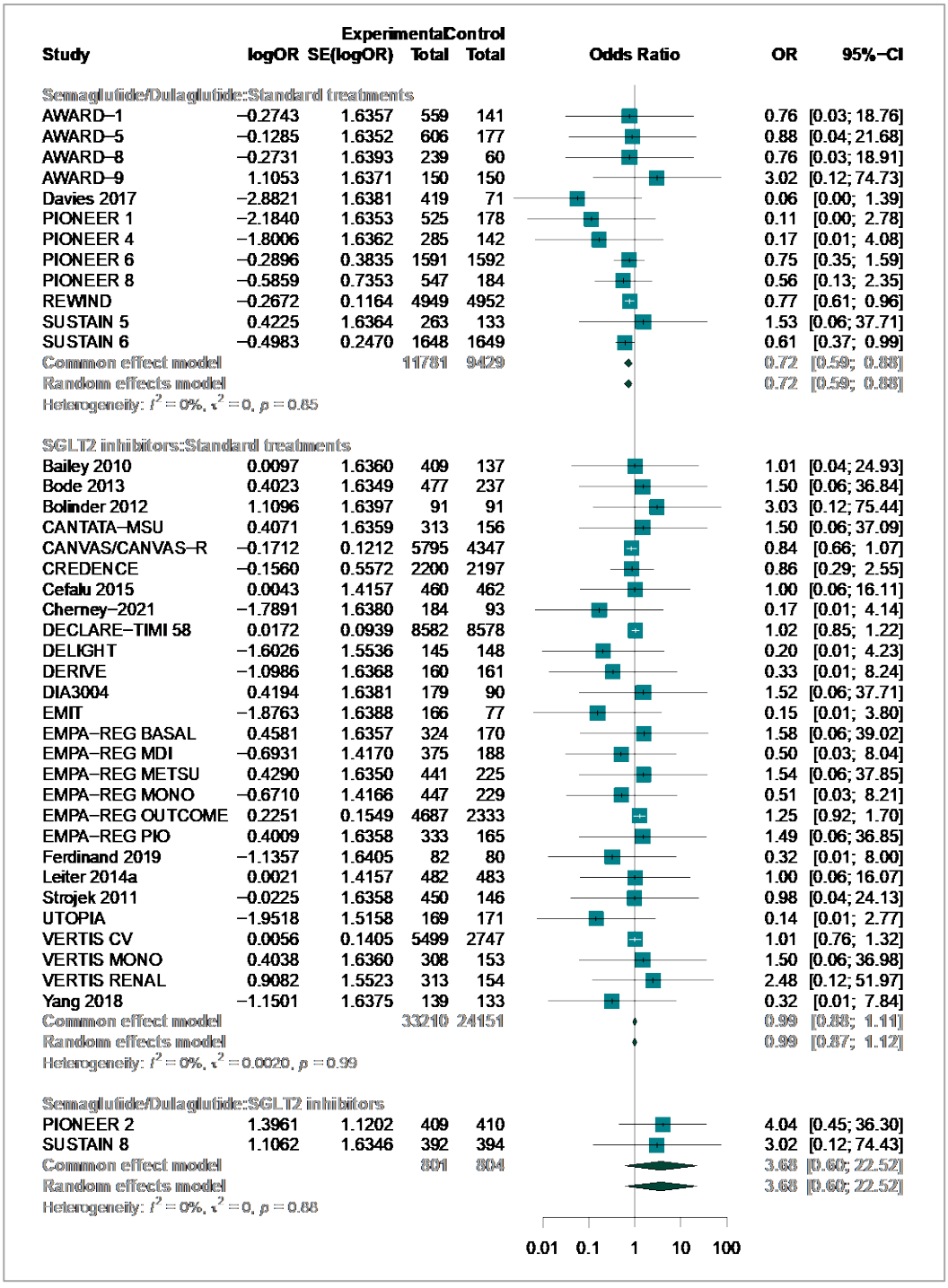


Figure 8: Forest Plot — Scenario 1 for End-Stage Kidney Disease

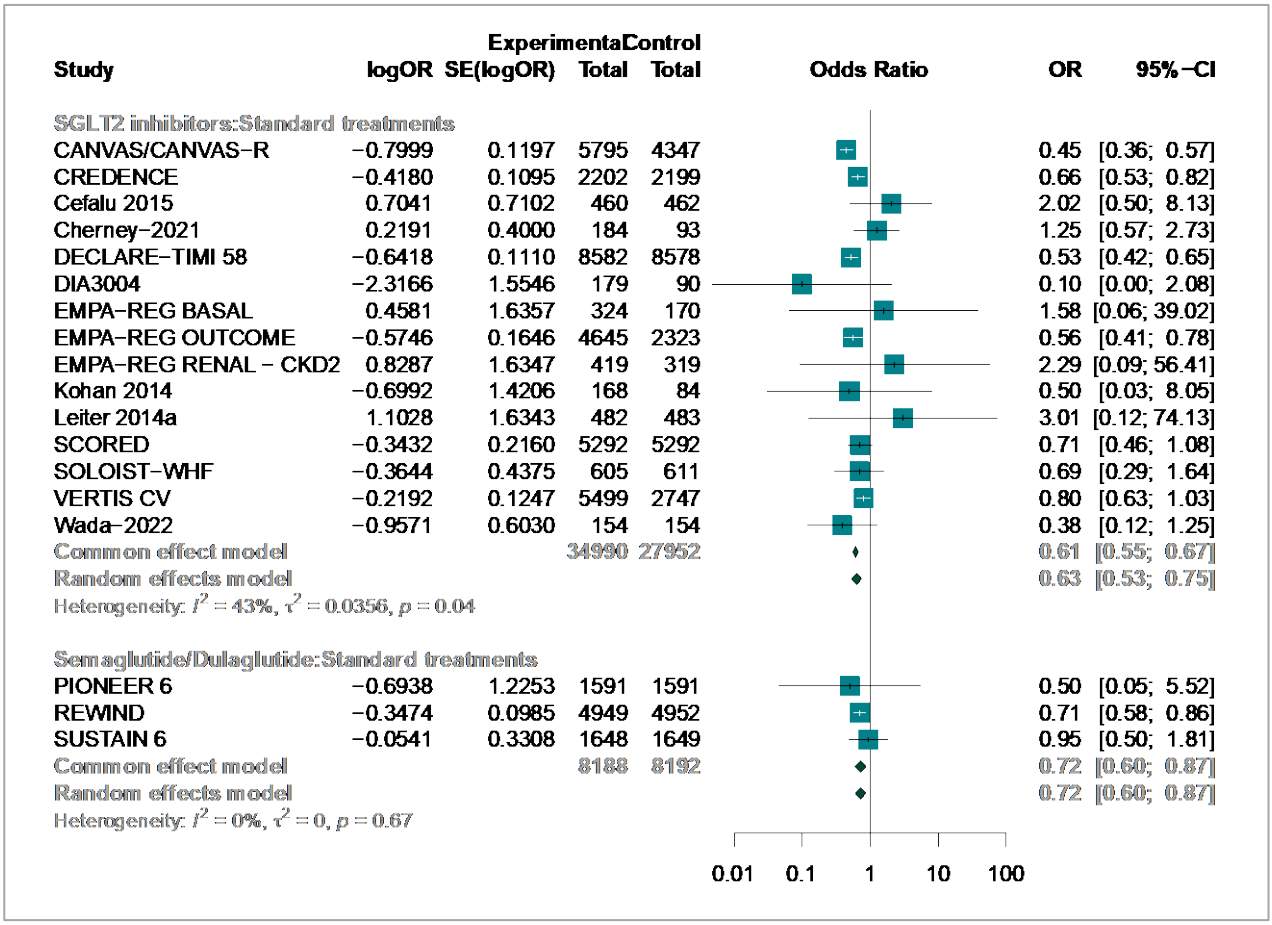


Figure 9: Forest Plot — Scenario 1 for Non-Fatal Myocardial Infarction

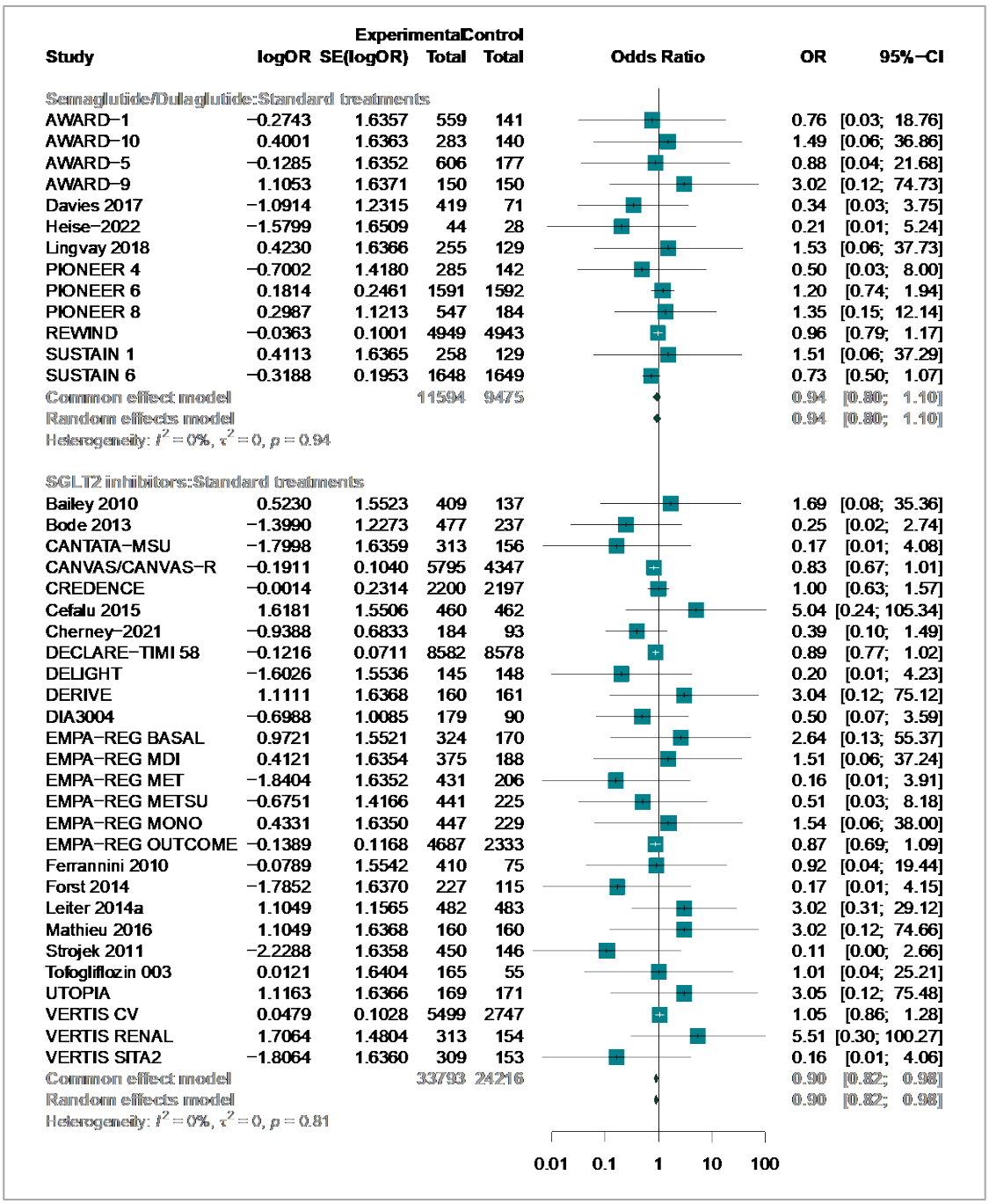


Figure 10: Forest Plot — Scenario 1 for Hospitalization for Heart Failure

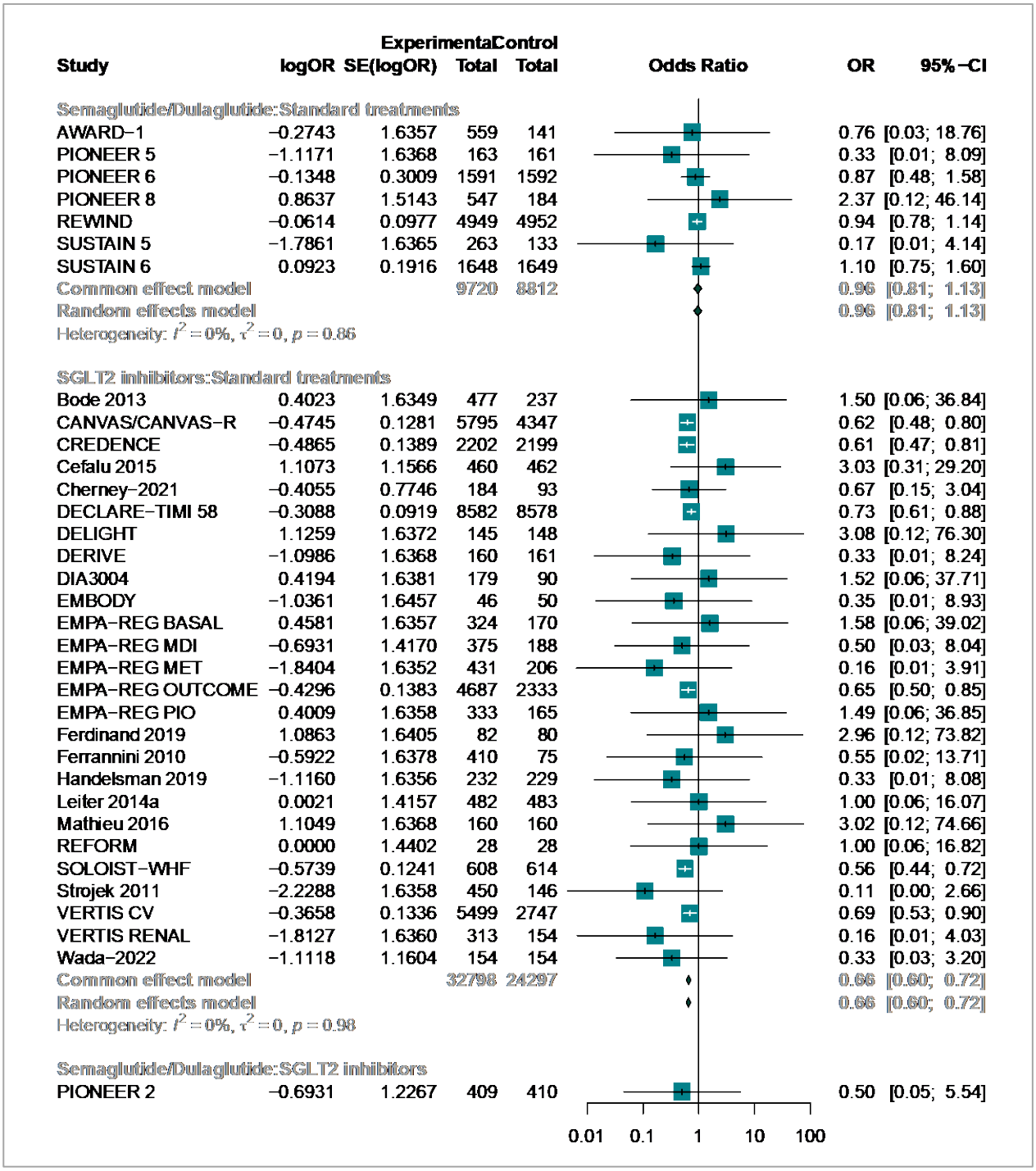
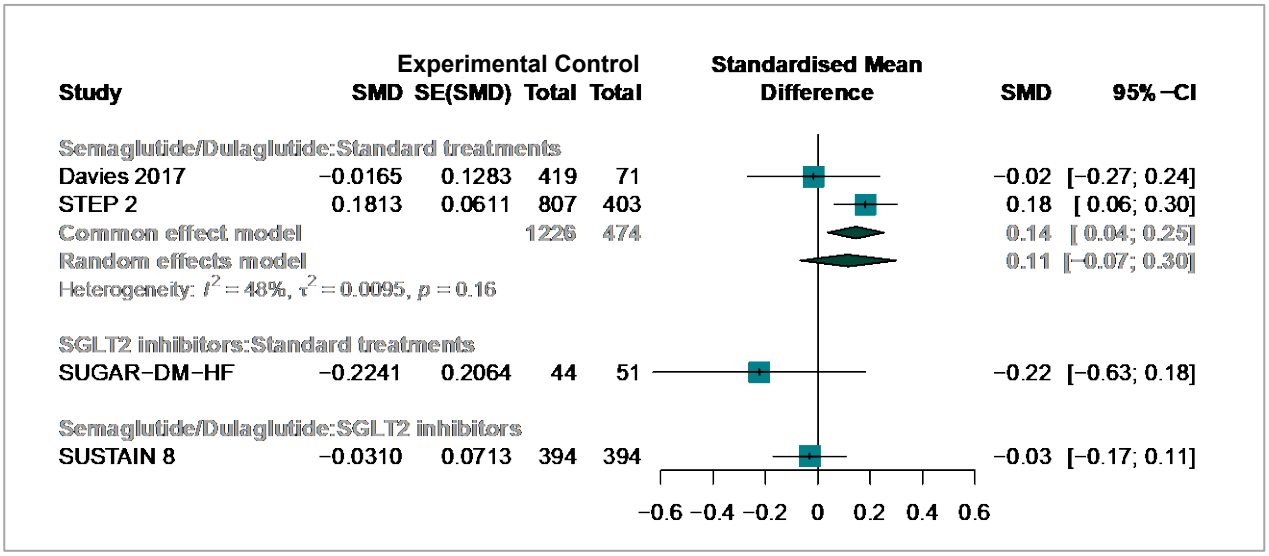


Figure 11: Forest Plot — Scenario 1 for Health-Related Quality of Life



Appendix 10: Re-Analysis to Compare SGLT2 Inhibitors With Semaglutide — Scenario 2: Forest Plots

These forest plots presenting relative effect of individual trial and pooled relative effects of each comparison.

Figure 12: Forest Plot — Scenario 2 for All-Cause Death

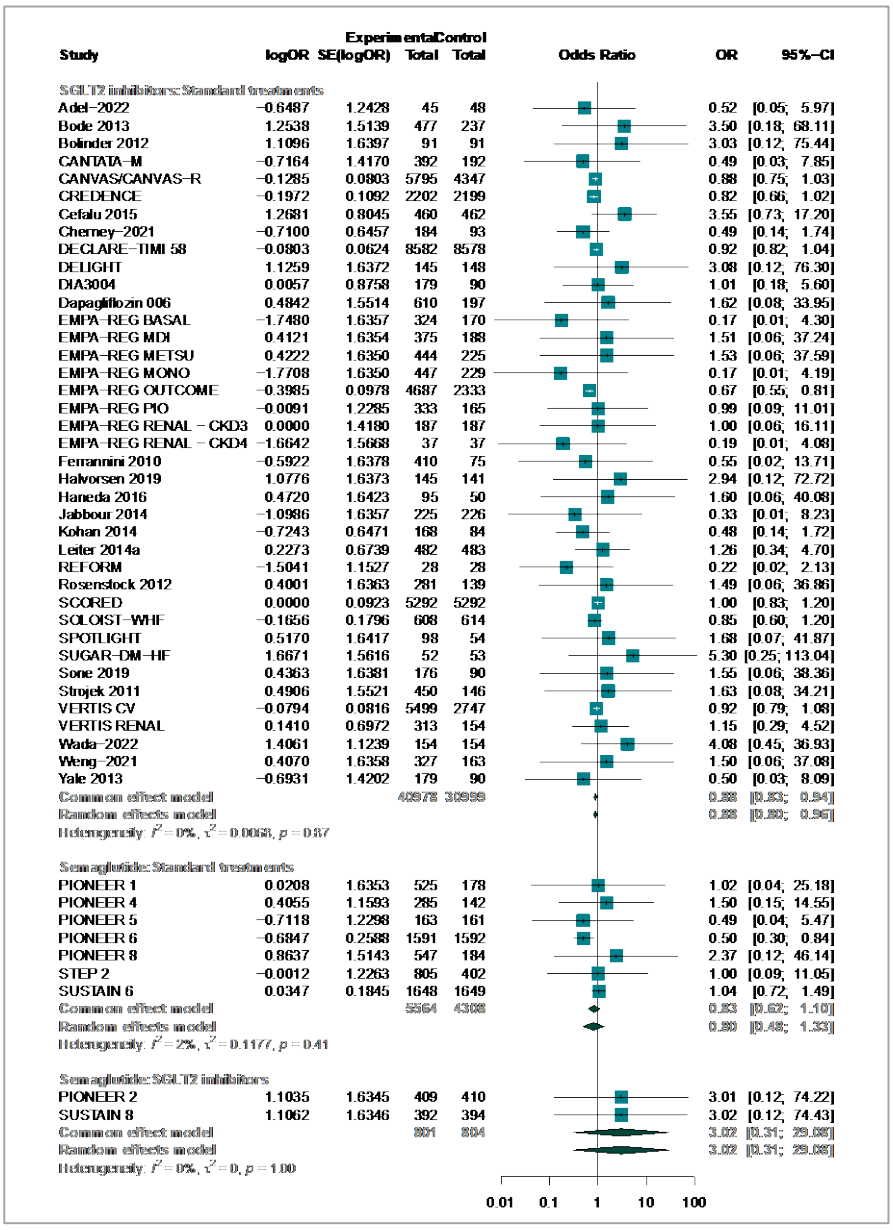


Figure 13: Forest Plot — Scenario 2 for Cardiovascular Death

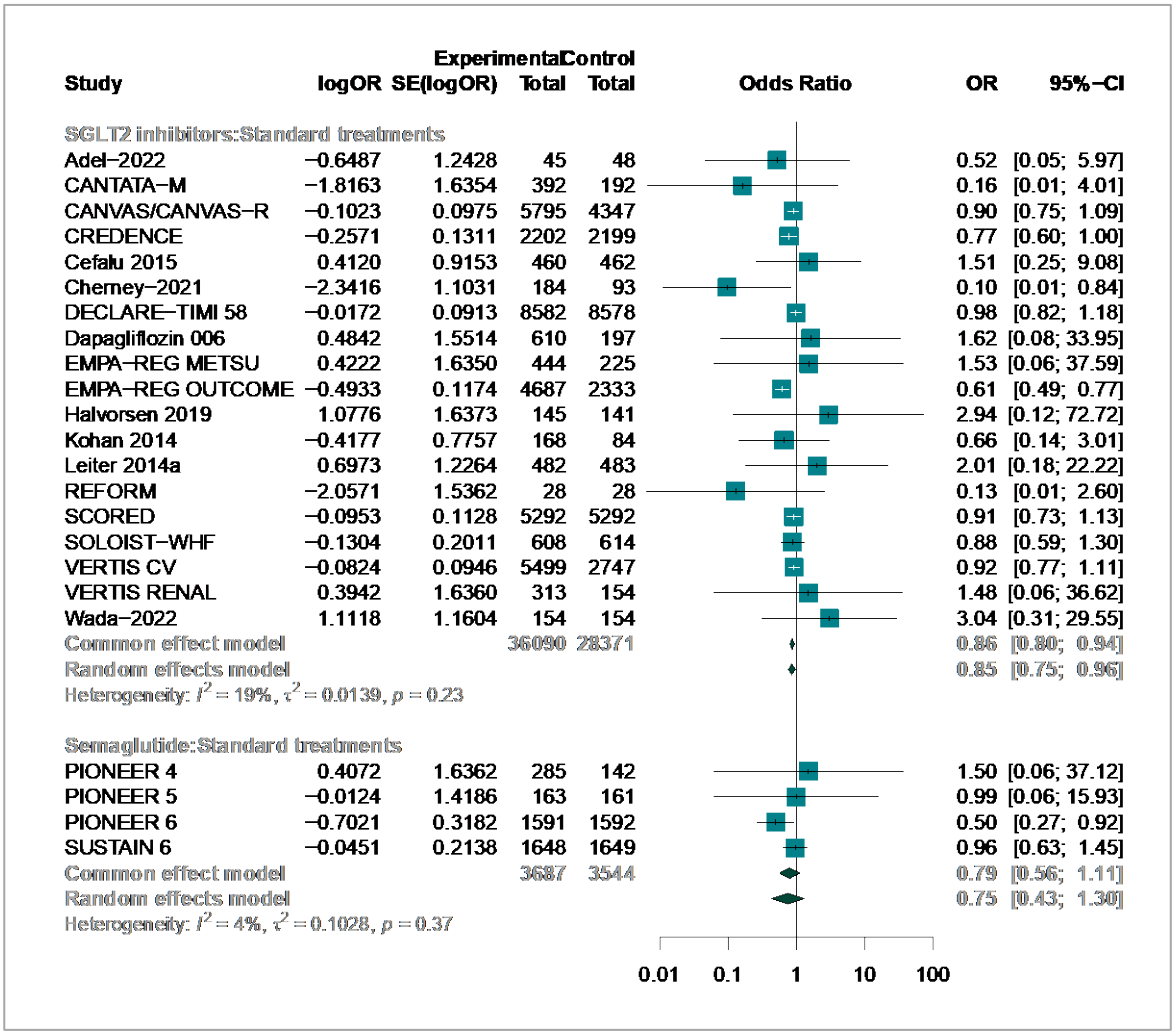


Figure 14: Forest Plot — Scenario 2 for Non-Fatal Stroke

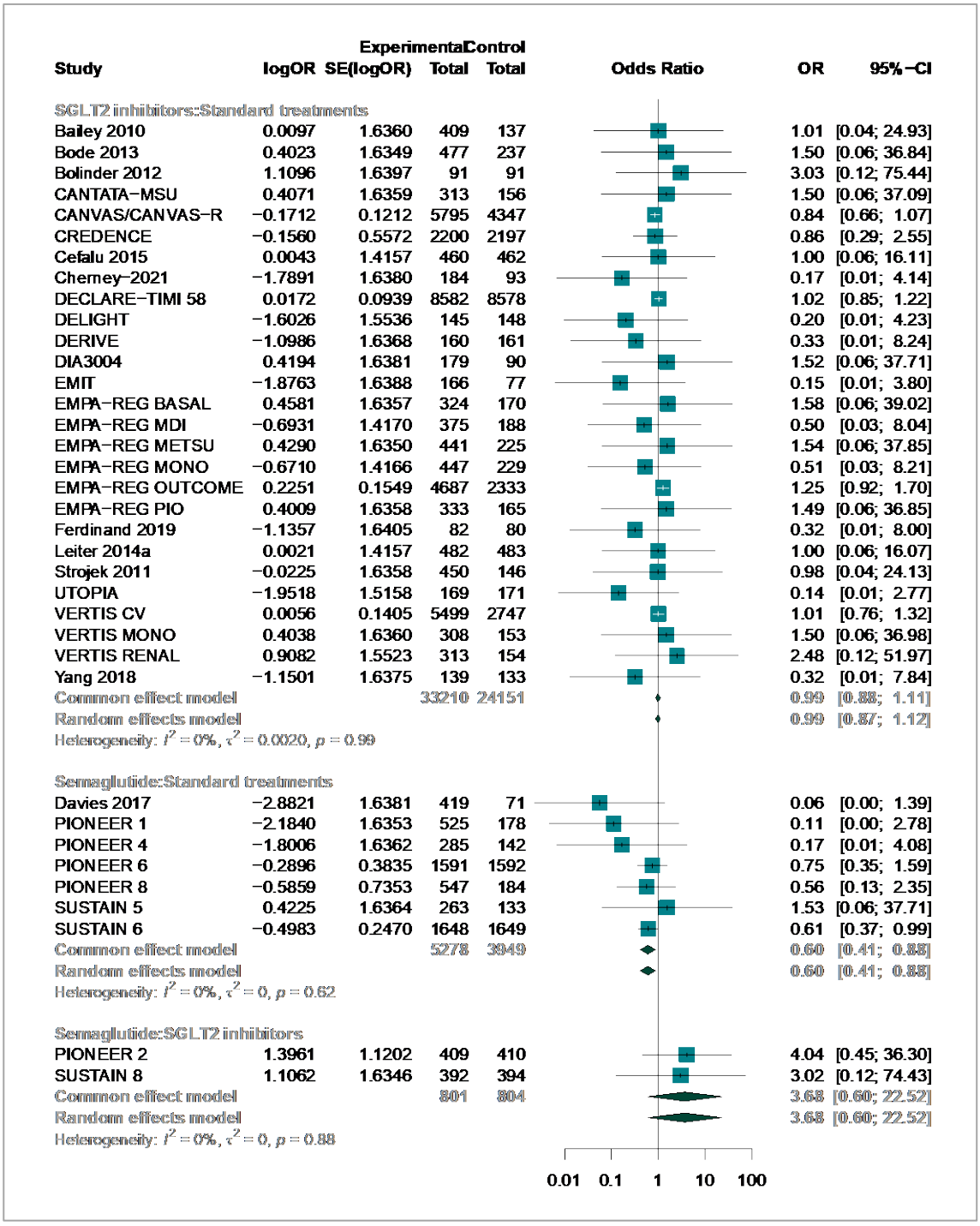
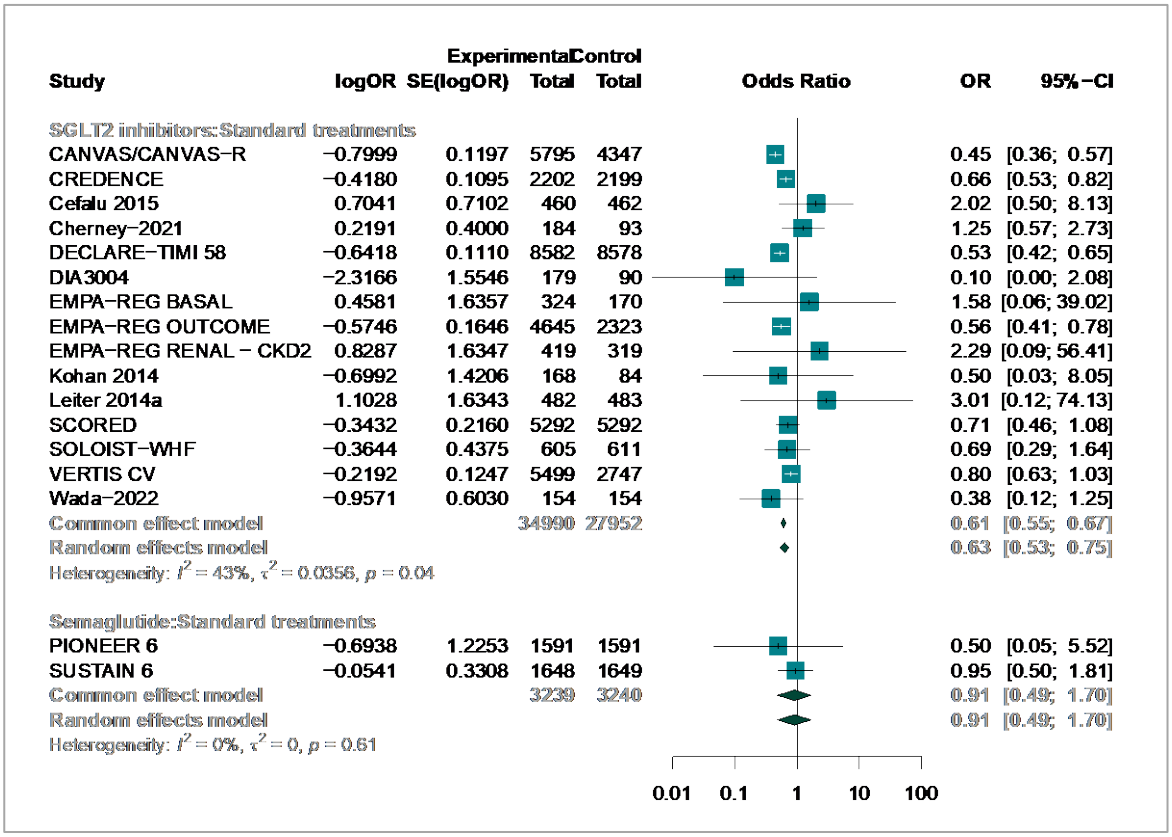


Figure 15: Forest Plot — Scenario 2 for End-Stage Kidney Disease



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