Supplementary appendix

Weekly vs. daily dipeptidyl peptidase-4 inhibitor therapy for type 2 diabetes: Systematic review and meta-analysis

Tomohide Yamada, Nobuhiro Shojima, Hisashi Noma, Toshimasa Yamauchi, Takashi Kadowaki

Contents

SUPPLEMENTARY DATA

Supplementary Appendix 1. Protocol for systematic review

Weekly vs. daily dipeptidyl peptidase-4 inhibitor therapy for type 2 diabetes: Systematic review and meta-analysis

Information	Topic	Date	PRISMA-P Item*
ADMINISTRATIVE INFORMATION			
Title			
Weekly vs. daily dipeptidyl peptidase-4 inhibitor therapy for type 2 diabetes: Systematic review and meta-analysis	Identification	August 2017	1a
Registration			
PROSPERO (CRD42017069004)	-	August 2017	2
Authors			
Tomohide Yamada (bqx07367@yahoo.co.jp)	Contact	August 2017	3a
Hisashi Noma			
Nobuhiro Shojima			
Takashi Kadowaki			
All Authors contributed to this protocol. TYamada is a guarantor of the review	Contribution		3b
Amendments			
-	-	-	4
Support			
TY was funded by the Japan Diabetes Society, Japan Society for the Promotion of Science (16K20965), and Japan Foundation for Applied Enzymology.	Sources	August 2017	5a
NA	Sponsor		5b
The funding sources had no role in this study.	Role of sponsor/funder		5c
INTRODUCTION			
Rationale			
Once-weekly dipeptidyl peptidase-4 inhibitors (weekly DPP-4is) were recently developed in addition to the once-daily agents, and weekly DPP-4is may improve compliance by reducing the burden of medication. Omarigliptin and trelagliptin are the weekly DPP4is currently available on the market in Japan. We performed a meta-analysis to assess the efficacy and safety of weekly DPP-4is compared with daily DPP-4is and placebo for type 2 diabetes.	-	August 2017	6
Objectives			
We performed a systematic review and meta-analysis to determine the efficacy and safety of weekly DPP-4 inhibitor therapy compared with placebo and daily DPP-4 inhibitors in type 2 diabetes.	-	August 2017	7
METHODS			
Eligibility criteria			

Randomized trials that fulfilled the following criteria were eligible: (1) comparison of weekly DPP-4 inhibitor therapy with placebo or daily DPP-4 inhibitors for ≥12 weeks in adult patients (≥18 years old) with type 2 diabetes, and (2) reporting efficacy and safety outcomes of interest. Studies were excluded if other aspects of treatment were targeted, if the design was not double-blind (e.g., open-label or cross-over), or if the follow-up period was <12 weeks. Studies of children and observational studies were also ineligible.	-	August 2017	8

Information sources			
We searched PubMed, the Cochrane library, and EMBASE for original reports of RCTs that compared weekly DPP-4 inhibitors for type 2 diabetes with placebo or daily DPP-4 inhibitors.	-	August 2017	9
Search Strategy			
Medline (1946- 16 September, 2017) and Embase (1947- 16 September, 2017) on ProQuest Dialog (dipeptidyl peptidase inhibitor OR mk-3012 OR omarigliptin OR SYR-472 OR trelagliptin OR DPP) AND (randomized controlled trial OR controlled clinical trial OR randomized) Cochrane library (~Issue 9 of 12, September 2017) '(dipeptidyl peptidase inhibitor OR mk-3012 OR omarigliptin OR SYR-472 OR trelagliptin OR DPP) AND (randomized controlled trial OR controlled clinical trial OR randomized) in Title, Abstract, Keywords in Trials'	-	September 2017	10
Study Records			
Two authors (TY, NS) will independently perform the searches. Literature search results will be uploaded.	Data management	August 2016	11a
Two authors (TY, NS) will independently screen titles/abstracts and obtain full reports for 1) reports meeting inclusion criteria; 2) those requiring further discussion. Any discrepancies will be resolved through discussion.	Selection Process	August 2017	11b
Extracted data will be independently (TY, NS) add into digital pre-defined forms (Excel).	Data collection process	August 2017	11c
Data Items			
Efficacy outcomes were the changes from baseline of HbA1c, fasting plasma glucose, 2-h postmeal glucose, body weight, achieving HbA1c < 7.0%. Safety outcomes were the occurrence of hypoglycemic events, severe hypoglycemic events, pancreatitis, and diarrhea. Data were extracted according to the definitions used in each study.	-	August 2017	12
Outcomes and Prioritization			
The arm-specific mean difference from baseline and odds ratio (OR) were employed as measures of effect for continuous and dichotomous variables, respectively.	-	August 2017	13
Risk of Bias in Individual Studies			
We used the risk of trial bias assessment scheme recommended by the Cochrane Collaboration for assessment of study quality.	-	August 2017	14
Data Synthesis			

Meta-analysis: Meta-analysis was performed by a frequentist-based approach with a multivariate random effects model (White IR (2009) Multivariate random-effects meta-analysis. Stata J 9:40–56). Heterogeneity was assessed by the I^2 statistic(0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.) (Higgins JP, Thompson SG, Deeks JJ et al (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions. Version 5.1.0. Cochrane Collaboration, 2011. http://handbook.cochrane.org/. (accessed 1 December 2016)) Summary effect sizes and their 95% confidence intervals were calculated by using the random effects model of DerSimonian and Laird. Studies lacking data on the standard deviation (or standard error) were excluded from analysis. Publication bias was estimated visually by drawing funnel plots, and also by performing Begg's test and Egger's weighted regression test. The arm-specific difference of the mean value from baseline and the odds ratio (OR) were employed as measures of effect for continuous and dichotomous variables, respectively. We added 0.5 if no events were reported in the treatment group of a study. All statistical analyses were performed with Stata V.14.0 software and $P < 0.05$ was considered to indicate significance. This research was carried out according to a predetermined protocol and followed the standard guidelines for conduct and reporting of systematic reviews and meta-analyses.	-	August 2017	15a,b
Additional analyses: NA	-	August 2017	15c
Summary planned if quantitative synthesis not appropriate: NA	-	August 2017	15d
Meta-bias(es)			
Tables will show the availability of data for each study and outcome (selective reporting)	-	August 2017	16
Confidence in cumulative evidence			
Results will be commented in view of study limitations and available evidence	-	August 2017	17

* Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349:g7647. doi: 10.1136/bmj.g7647

SUPPLEMENTARY DATA

Supplementary Appendix 2. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
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.	Appendix 1
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.	2, Appendix 1
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.	2, Appendix 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2, Appendix 1
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).	2, Appendix 1
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.	2, Appendix 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2, Appendix 1
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.	2, Appendix 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Appendix 1
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.	Appendix 1

Section/topic	#	Checklist item	Reported on page #

Supplementary Appendix 2. PRISMA checklist

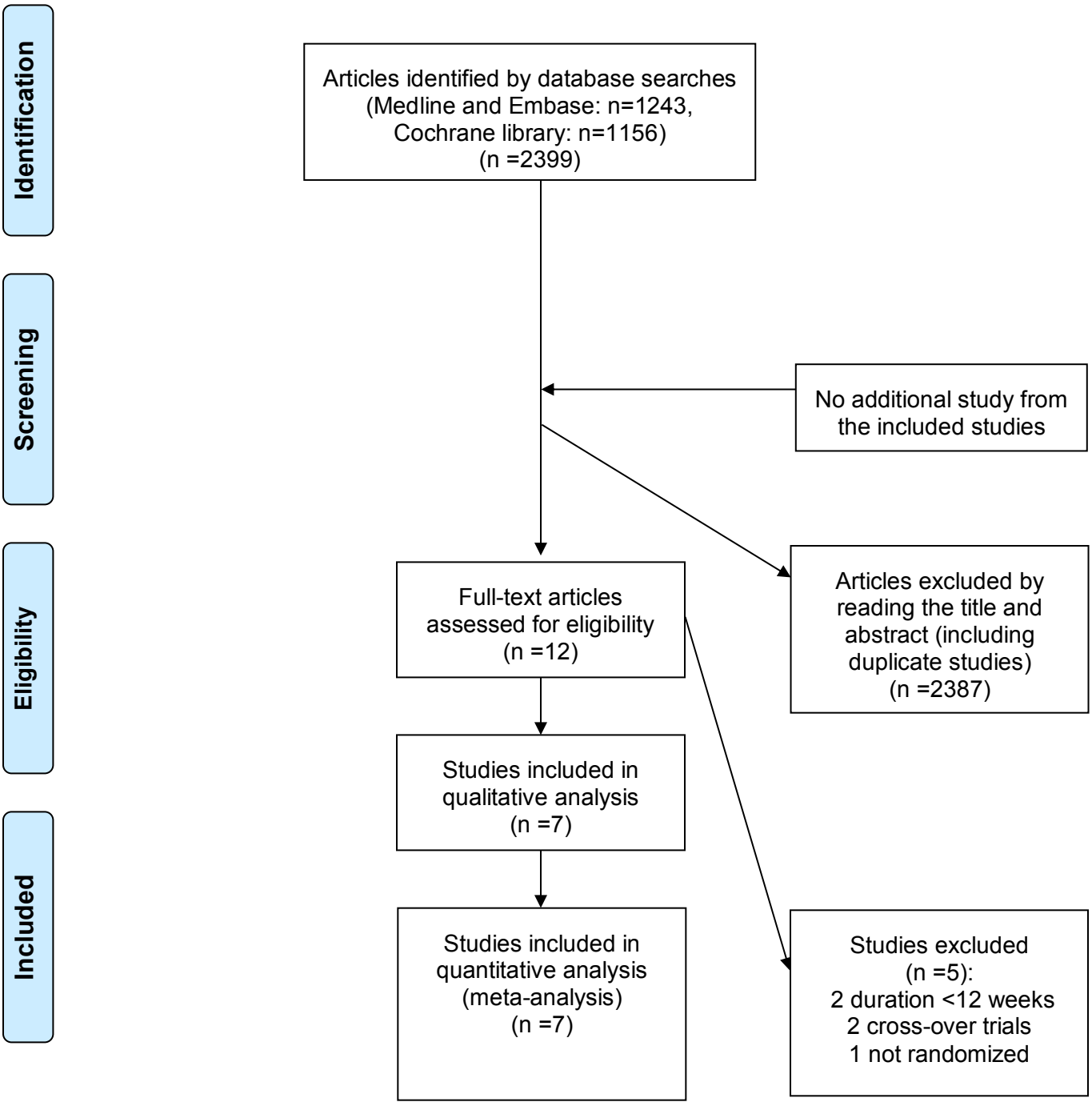
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2, Appendix 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2, Appendix 1
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.	3, Appendix 3
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.	3, Appendix 4-7
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).	3, Appendix 4-7
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.	3-4, Appendix 4-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	3-4, Figure 1, 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3, Appendix 8, 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
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).	3
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).	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	3
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.	4

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

For more information, visit: **www.prisma-statement.org**.

SUPPLEMENTARY DATA

Supplementary Appendix 3. Literature search and study selection



SUPPLEMENTARY DATA

Supplementary Appendix 4. Characteristics of the trials investigated

Author, year	Sample size, n	Study duration, weeks	Treatment, mg/day	Men, %	Age, y	Duration of DM, y	HbA1c, %	BMI, kg/m^2	BW, kg	FPG, mmol/l	2hr PPG, mmol/l
Shanker 2017 (1)	402	24	OMA 25, Placebo	51	57	7.8	8.1	32.5	91.0	9.3	13.2
Gantz 2017 (2)	414	24	OMA 25, SITA50, Placebo	67	60	7.8	8.0	25	66.7	8.9	13.5
Chacra 2017 (3)	213	24	OMA 25, Placebo	62	65	15.0	8.3	30.1	82.1	9.5	NA
Goldenberg 2016 (4)	642	24	OMA 25, SITA100	51	58	7.3	7.5	32	89.5	8.7	NA
Sheu 2015 (5)	685	12	OMA 0.25, OMA 1.0, OMA 3.0, OMA 10, OMA 25, Placebo	57	55	5.4	8.0	29.8	82.3	9.5	13.1
Inagaki 2015 (6)	243	24	TRELA 100, ALO 25, Placebo	77	60	7.0	7.8	24.9	67.9	9.1	13.6
Inagaki 2014 (7)	321	12	TRELA 12.5, TRELA 25, TRELA 50, TRELA 100, TRELA 200, Placebo	60	60	6.5	8.1	25.4	NA	9.1	14.1

DM; diabetes mellitus, BMI; body mass index, BW; body weight, FPG; fasting plasma glucose, 2hr PPG; 2-hour postprandial glucose, OMA; omarigliptin, TRELA; trelagliptin, SITA; sitagliptin, ALO; alogliptin, NA; not available

SUPPLEMENTARY DATA

Reference

1. Shankar RR, Inzucchi SE, Scarabello V, Gantz I, Kaufman KD, Lai E, Ceesay P, Suryawanshi S, Engel SS. A randomized clinical trial evaluating the efficacy and safety of the once-weekly dipeptidyl peptidase-4 inhibitor omarigliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Curr Med Res Opin. 2017 Oct;33(10):1853-1860. doi: 10.1080/03007995.2017.1335637. Epub 2017 Jun 23. PubMed PMID: 28547998.

2. Gantz I, Okamoto T, Ito Y, Okuyama K, O'Neill EA, Kaufman KD, Engel SS, Lai E; and the Omarigliptin Study 020 Group. A randomized, placebo- and sitagliptin-controlled trial of the safety and efficacy of omarigliptin, a once-weekly dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes. Diabetes Obes Metab. 2017 Apr 27. doi: 10.1111/dom.12988. [Epub ahead of print] PMID: 28449368.

3. Chacra A, Gantz I, Mendizabal G, Durlach L, O'Neill EA, Zimmer Z, Suryawanshi S, Engel SS, Lai E. A randomised, double-blind, trial of the safety and efficacy of omarigliptin (a once-weekly DPP-4 inhibitor) in subjects with type 2 diabetes and renal impairment. Int J Clin Pract. 2017 Jun;71(6). doi: 10.1111/ijcp.12955. Epub 2017 Apr 27. PMID: 28449320.

4. Goldenberg R, Gantz I, Andryuk PJ, O'Neill EA, Kaufman KD, Lai E, Wang YN, Suryawanshi S, Engel SS. Randomized clinical trial comparing the efficacy and safety of treatment with the once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor omarigliptin or the once-daily DPP-4 inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2017 Mar;19(3):394-400. doi: 10.1111/dom.12832. Epub 2017 Jan 17. PMID: 28093853 PMCID: PMC5347923

5. Sheu WH, Gantz I, Chen M, Suryawanshi S, Mirza A, Goldstein BJ, Kaufman KD, Engel SS. Safety and Efficacy of Omarigliptin (MK-3102), a Novel Once-Weekly DPP-4 Inhibitor for the Treatment of Patients With Type 2 Diabetes. Diabetes Care. 2015 Nov;38(11):2106-14. doi: 10.2337/dc15-0109. Epub 2015 Aug 26. PMID: 26310692.

6. Inagaki N, Onouchi H, Maezawa H, Kuroda S, Kaku K. Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: a randomised, double-blind, phase 3, non-inferiority study. Lancet Diabetes Endocrinol. 2015 Mar;3(3):191-7. doi: 10.1016/S2213-8587(14)70251-7. Epub 2015 Jan 19. PMID: 25609193

7. Inagaki N, Onouchi H, Sano H, Funao N, Kuroda S, Kaku K. SYR-472, a novel once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor, in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014 Feb;2(2):125-32. doi: 10.1016/S2213-8587(13)70149-9. Epub 2013 Nov 1. PMID: 24622716

SUPPLEMENTARY DATA

Supplementary Appendix 5. Clinical outcomes of the trials investigated

Author, year	Outcomes							
	HbA1c (%)	Fasting plasma glucose (mmol/l)	2hr postmeal glucose (mmol/l)	Body weight (kg)	Diarrhea	Pancreatitis	Hypoglycemia	Severe hypoglycemia
Shanker 2017 (1)	A	A	A	A	NA	A	A	A
Gantz 2017 (2)	A	A	A	A	A	A	A	A
Chacra 2017 (3)	A	A	NA	A	NA	A	A	A
Goldenberg 2016 (4)	A	A	NA	A	A	A	A	A
Sheu 2015 (5)	A	A	A	A	NA	A	A	A
Inagaki 2015 (6)	A	A	A	A	A	A	A	A
Inagaki 2014 (7)	A	A	A	NA	A	A	A	A

A; data available, NA; data not available

SUPPLEMENTARY DATA

Supplementary Appendix 6. Incidence of events in the trials investigated

1. Achieving HbA1c < 7.0%

Author, year	Weekly DPP-4is (n/N)	Daily DPP-4is (n/N)
Gantz 2017 (2)	(78/166)	(62/165)
Goldenberg 2016 (4)	(175/322)	(168/320)
Inagaki 2015 (6)	(26/101)	(30/92)

Author, year	Weekly DPP-4is (n/N)	Placebo (n/N)
Shanker 2017 (1)	(76/201)	(38/201)
Gantz 2017 (2)	(78/166)	(6/83)
Chacra 2017 (3)	(107/29)	(106/20)
Sheu 2015 (5)	(38/114)	(25/114)
Inagaki 2015 (6)	(26/101)	(2/50)
Inagaki 2014 (7)	(18/54)	(0/55)

2. Diarrhea

Author, year	Weekly DPP-4is (n/N)	Daily DPP-4is (n/N)
Gantz 2017 (2)	(2/166)	(3/165)
Goldenberg 2016 (4)	(3/322)	(9/320)
Inagaki 2015 (6)	(2/101)	(3/92)

Author, year	Weekly DPP-4is (n/N)	Placebo (n/N)
Gantz 2017 (2)	(2/166)	(3/83)
Inagaki 2015 (6)	(2/101)	(1/50)
Inagaki 2014 (7)	(1/54)	(0/55)

3. Pancreatitis

Author, year	Weekly DPP-4is (n/N)	Daily DPP-4is (n/N)
Gantz 2017 (2)	(0/166)	(0/165)
Goldenberg 2016 (4)	(0/322)	(0/320)
Inagaki 2015 (6)	(0/101)	(0/92)

Author, year	Weekly DPP-4is (n/N)	Placebo (n/N)
Shanker 2017 (1)	(0/201)	(1/201)
Gantz 2017 (2)	(0/166)	(0/83)
Chacra 2017 (3)	(0/107)	(0/106)
Sheu 2015 (5)	(0/114)	(0/114)
Inagaki 2015 (6)	(0/101)	(0/50)
Inagaki 2014 (7)	(0/54)	(0/55)

4. Severe hypoglycemia

Author, year	Weekly DPP-4is (n/N)	Daily DPP-4is (n/N)
Gantz 2017 (2)	(0/166)	(0/165)
Goldenberg 2016 (4)	(0/322)	(0/320)
Inagaki 2015 (6)	(0/101)	(0/92)

Author, year	Weekly DPP-4is (n/N)	Placebo (n/N)
Shanker 2017 (1)	(1/201)	(2/201)
Gantz 2017 (2)	(0/166)	(0/83)
Chacra 2017 (3)	(6/107)	(8/106)
Sheu 2015 (5)	(0/114)	(0/114)
Inagaki 2015 (6)	(0/101)	(0/50)
Inagaki 2014 (7)	(0/54)	(0/55)

5. Hypoglycemia

Author, year	Weekly DPP-4is (n/N)	Daily DPP-4is (n/N)
Gantz 2017 (2)	(0/166)	(1/165)
Goldenberg 2016 (4)	(12/322)	(15/320)
Inagaki 2015 (6)	(0/101)	(1/92)

Author, year	Weekly DPP-4is (n/N)	Placebo (n/N)
Shanker 2017 (1)	(7/201)	(5/201)
Gantz 2017 (2)	(0/166)	(0/83)
Chacra 2017 (3)	(22/107)	(19/106)
Sheu 2015 (5)	(0/114)	(3/114)
Inagaki 2015 (6)	(0/101)	(0/50)
Inagaki 2014 (7)	(0/54)	(0/55)

SUPPLEMENTARY DATA

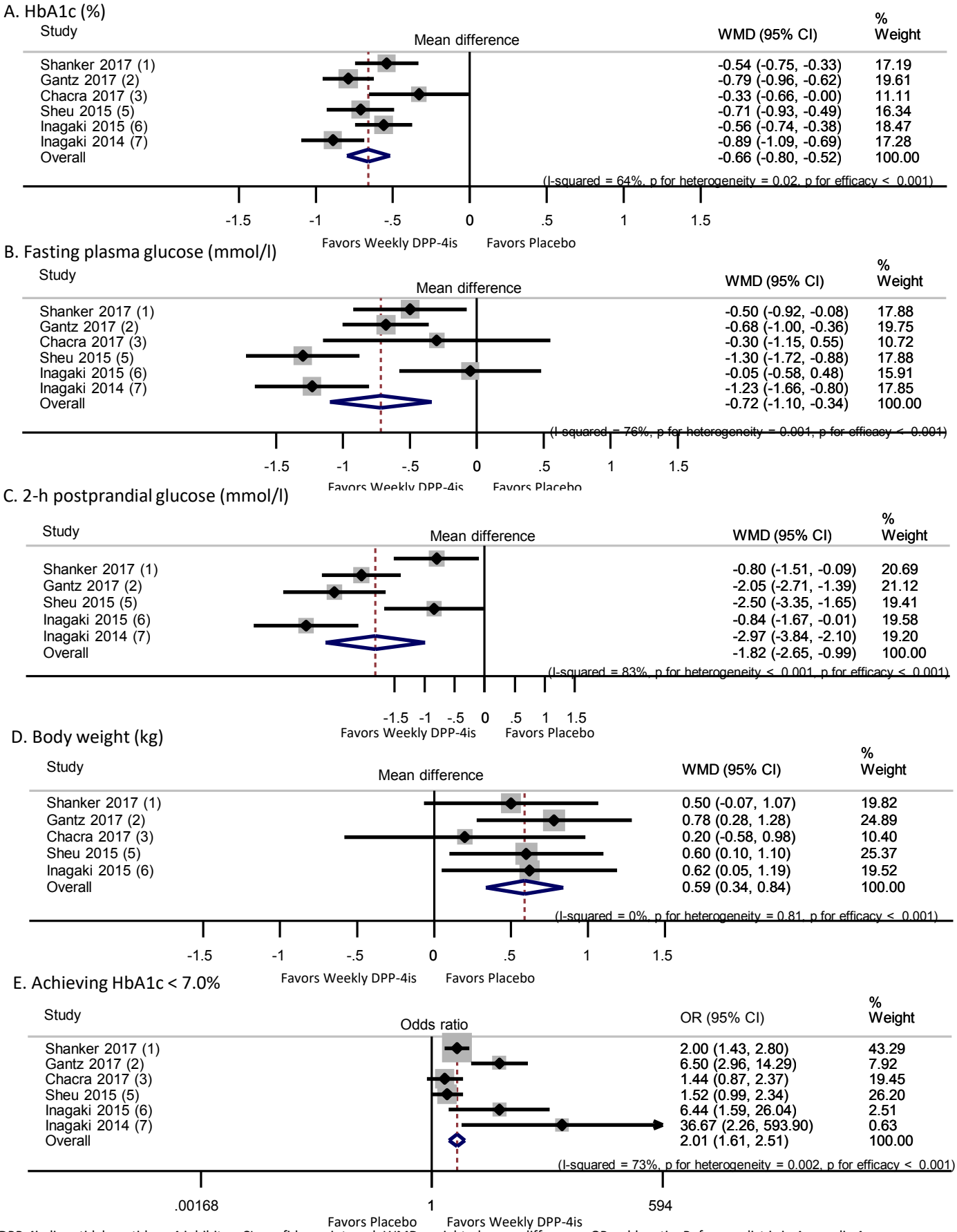
Supplementary Appendix 7. Risk of bias

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Sponsorship bias	Other bias
Shanker 2017 (1)	U	U	L	U	L	U	H	L
Gantz 2017 (2)	U	U	L	U	L	U	H	L
Chacra 2017 (3)	U	U	L	U	L	U	H	L
Goldenberg 2016 (4)	U	U	L	U	L	U	H	L
Sheu 2015 (5)	U	U	L	U	L	U	H	L
Inagaki 2015 (6)	L	L	L	L	L	U	H	L
Inagaki 2014 (7)	L	L	L	L	L	U	H	L

L = Low Risk; H = High Risk; U = Unclear Risk.

SUPPLEMENTARY DATA

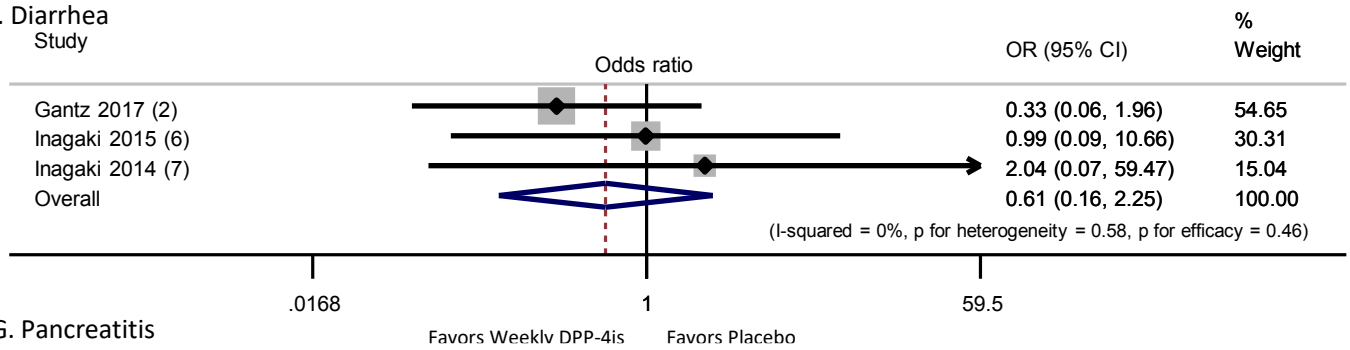
Supplementary Appendix 8. Meta-analysis comparing weekly DPP-4is with placebo for type 2 diabetes



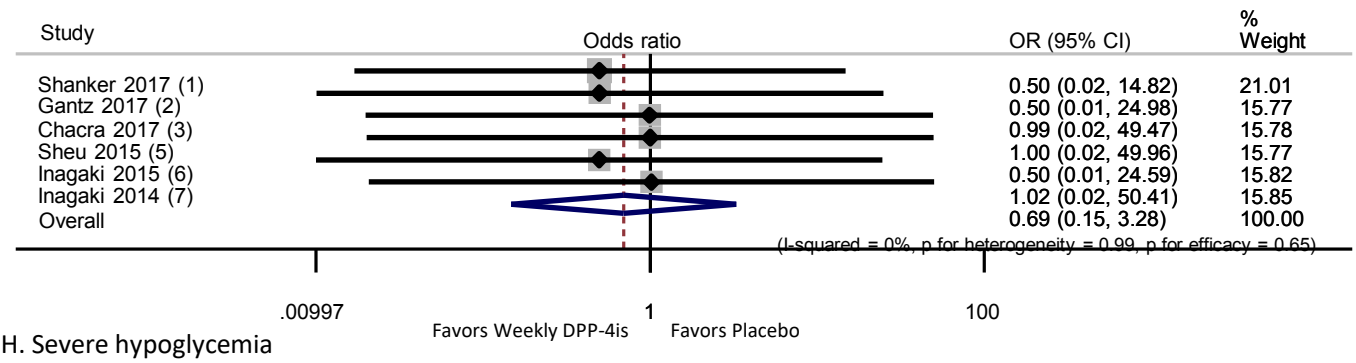
DPP-4i; dipeptidyl peptidase-4 inhibitor, CI; confidence interval, WMD; weighted mean difference, OR; odds ratio. Reference list is in Appendix 4.

Supplementary Appendix 8 (continued). Meta-analysis comparing weekly DPP-4is with placebo for type 2 diabetes

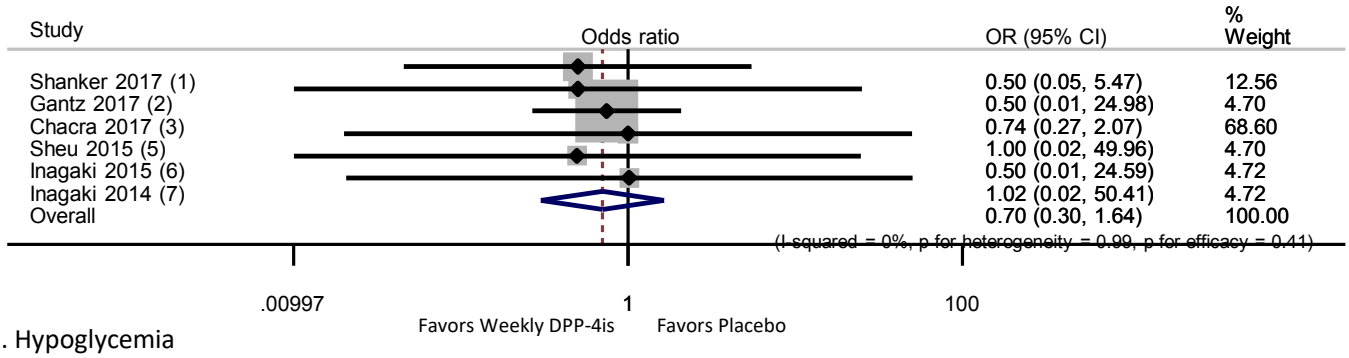
F. Diarrhea



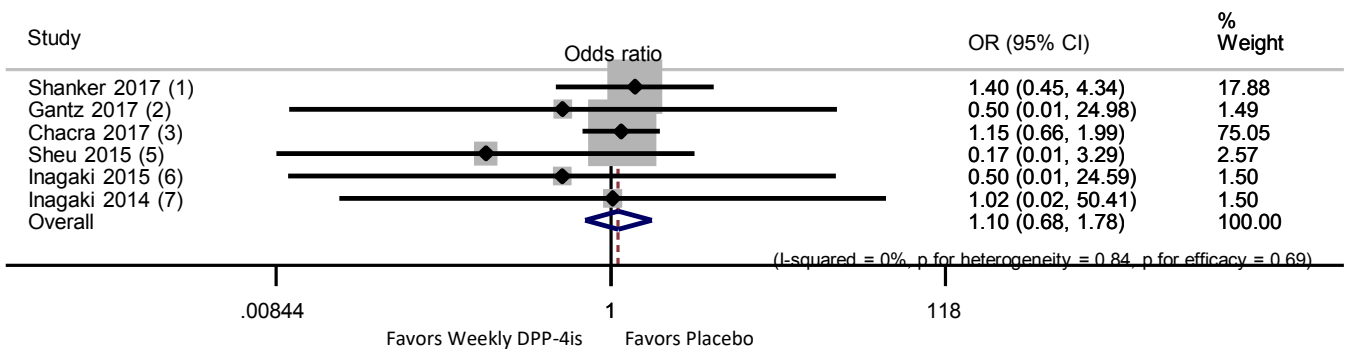
G. Pancreatitis



H. Severe hypoglycemia



I. Hypoglycemia

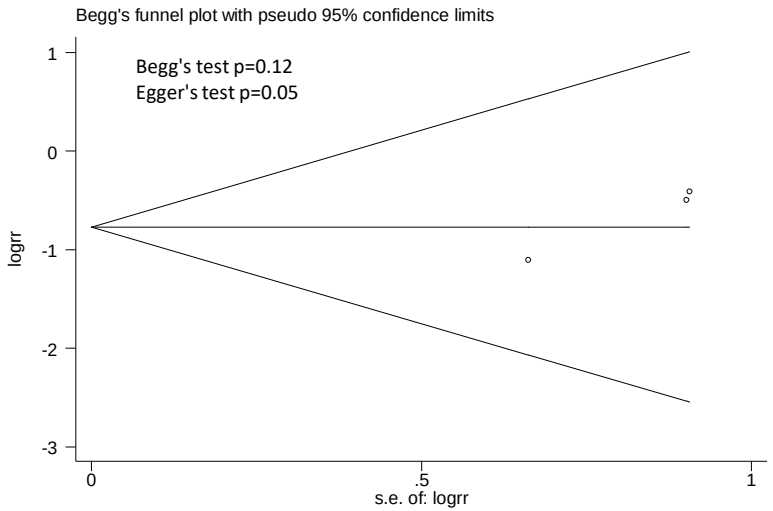


DPP-4i; dipeptidyl peptidase-4 inhibitor, CI; confidence interval, WMD; weighted mean difference, OR; odds ratio. The OR was employed as a measure of effect for dichotomous variables. When performing meta-analysis, we added 0.5 if no events were reported in the treatment group of a study. Reference list is in Appendix 4.S

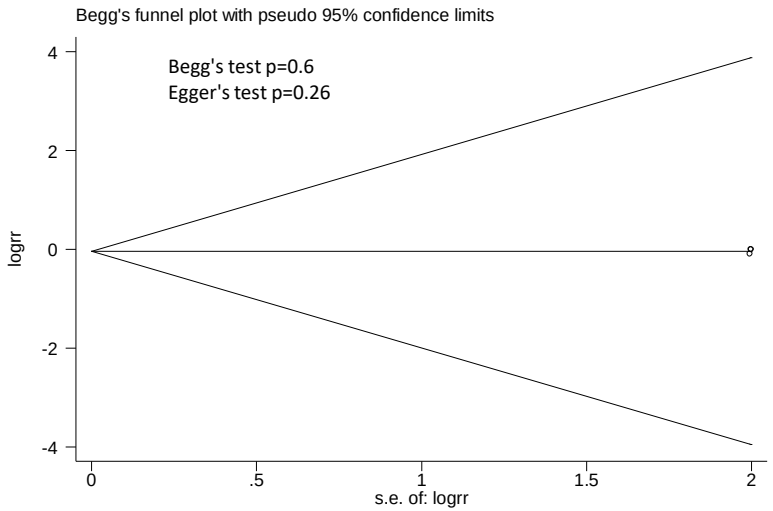
SUPPLEMENTARY DATA

Supplementary Appendix 9. Funnel plots and the results of Begg's test and Egger's test

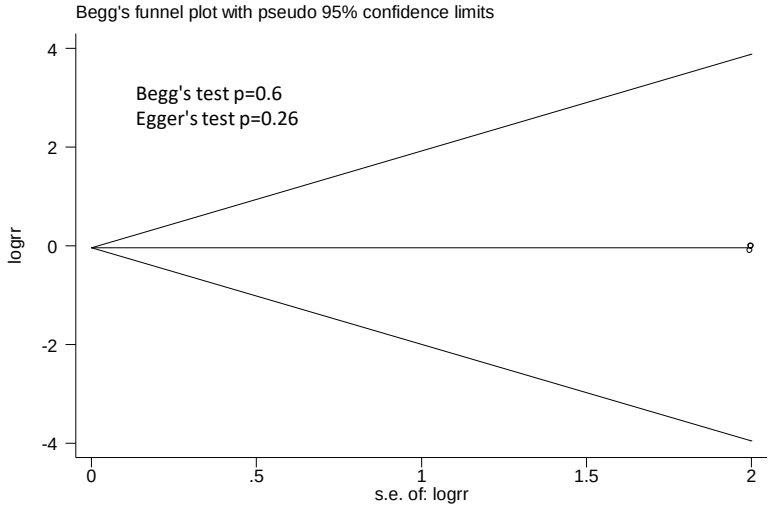
A. Diarrhea



B. Pancreatitis



C. Severe hypoglycemia



D. Hypoglycemia