SUPPLEMENTARY DATA

Data Source and Search

The following search items were used: (((((AMG 145* OR evolocumab* OR REGN727* OR alirocumab * SAR236553* OR RN316* OR PF04950615* OR bococizumab* OR antibody to proprotein convertase subtilisin/kexin type 9* OR antibody to PCSK9*)) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups)) NOT animals) AND Randomized Controlled Trial[ptyp] AND Humans[Mesh]) AND (Randomized Controlled Trial[ptyp] AND Humans[Mesh]).

During the search strategy, English, French, Spanish, and Portuguese languages were selected. However, all the relevant articles were published in English, conducted on human subjects, and classified as RCTs.

Definitions

Diabetes worsening was characterized according to each investigator definition. Generally, these definitions included the following MedDRA terms: "Diabetes mellitus inadequate control" and "Diabetic metabolic decompensation" as used by Kastelein *et al* (1) or the High-Level Group Term "diabetes complications" as used by Robinson *et al* (2).

Data Extraction and Quality Assessment

Two investigators who were not involved in any of the selected studies independently abstracted data by using pre-specified forms and independently appraised the accuracy of the abstractions and resolved any discrepancies by consensus after discussion with the third investigator. The following items were extracted from included studies: first author's name, year of publication, study design, characteristic of patients, sample size, duration of intervention and type of control, drug dose, clinical outcomes, and adverse events. If a trial was published more than once, we included the last report. If patients were recruited from parent trials, they were not accounted in duplicity. The Cochrane Collaboration tool for assessing risk of bias (3) was utilized to assess for different forms of bias within the included studies in our meta-analysis and study quality was assessed with the GRADE system (4). Two unblinded investigators independently appraised the potential risk of bias of the RCTs by using methods described in the Cochrane Collaboration guidelines (3).

Our co-primary outcomes were (i) incident type 2 diabetes and (ii) a compound endpoint of incident type 2 diabetes and worsening type 2 diabetes as defined by each author. The secondary outcomes were the change in FBG or glycosylated hemoglobin from baseline to the end of each study. High-intensity background statin therapy was defined as daily use of atorvastatin, 40 mg or more; rosuvastatin, 20 mg or more (or ≥5 mg for the YUKAWA study, which was defined for a Japanese population).

Included and Excluded studies

Using Medline/PubMed, Cochrane Library databases, and ClinicalTrials.gov, we identified 133 citations using the previously defined search terms. Three additional citations were obtained from conference annals (5). Implementing our inclusion/exclusion criteria, we evaluated 136 abstracts, of which we assessed 59 as full-text publications. We excluded 39 studies due to: duplication of data (n=4), enrolled patients with homozygosity for genes implicated in familial hypercholesterolemia (n=2), phase 1 RCT design (n=3), no RCT design (n=3), publication of study designs (n=10), RCT not designed to treat hypercholesterolemia (n=3) and RCT with no incident data of type 2 diabetes (n=14).

We excluded 39 studies due to: duplication of data (n=4) (6–9), enrolled patients with homozygosity for genes implicated in familial hypercholesterolemia (n=2) (10,11), phase 1 RCT design (n=3) (12–14), no RCT design (n=3) (15–17), publication of a study design (n=10) (18–27), RCT not designed to treat hypercholesterolemia (n=3) (28–30). Also, studies by Ballantyne *et al* (NCT01592240), Stroes *et al* (GAUSS-2), Nissen *et al* (GAUSS-3), Robinson *et al* (LAPLACE-2), Desai *et al* (LAPLACE-TIMI 57), McKenney *et al* (NCT01288443), Koren *et al* (MENDEL-2), Raal *et al* (RUTHERFORD-2), Raal *et al* (NCT01439880), Hirayama *et al* (YUKAWA), Kastelein *et al* (NCT01890967), Stein *et al* (NCT01026597, NCT01074372, and NCT01161082), Moriarty *et al* (ODYSSEY ALTERNATIVE) could not be included in our meta-analysis as they did not share data on incident diabetes mellitus or the values for fasting plasma glucose or glycosylated hemoglobin (n=3,674) (31–44). Most of these studies (90%), however, were included when we performed the inclusion of pooled studies such as the OSLER-1, OSLER-2, and Colhoun *et al*.

Data Synthesis and Analysis

Dichotomous variables are reported as percentages while continuous variables are reported as mean ± SD or median (interquartile range). Baseline data were obtained by weighted calculation. To identify potential effects of PCSK9i therapy on incident diabetes, we calculated an overall risk ratio (RR) with both random- and fixed-effect models meta-analyses. Odds ratios and risk ratios were universally identical during data analysis. We assessed statistical heterogeneity between trials with I^2 statistic (with 95% CIs) (45), which provides a measure of the proportion of overall variation that is attributable to between-trial heterogeneity. We used risk estimates obtained with both random- and fixed-effects meta-analysis because one can be used as sensitivity analysis to the other. We used meta-regression analyses to investigate potential sources of heterogeneity between trials. Factors that we investigated were baseline age, prevalence of type 2 diabetes at baseline, LDL-C at the end of each study and the change in LDL-C after treatment, and these factors were decided before the meta-analysis

was undertaken. We also evaluated the percentage of individuals on high-dose statin regimen, and the percentage of individuals on ezetimibe in meta-regressions as post-hoc analyses. To test for publication bias, we formed funnel plots and undertook the Egger test. For the summary treatment effect estimate, a 2-tailed *P* value less than 0.05 was considered statistically significant.

Additional results

For our co-primary outcome meta-analysis, we included 20 RCT(46–54,1,55–58,2) with 68,123 patients and 96,063 patients-years that were randomized to treatment group using PCSK9i (n=35,514) plus ezetimibe (n=30), statin (n=268). Control group was randomized to placebo (n=30,032), ezetimibe (n=337), statin (n=250), statin and ezetimibe (n=203) or standard therapy (n=1,489). All included studies had a low risk of bias as assessed by the Cochrane Collaboration tool for assessing risk of bias (59) (Table S1B) and all studies were deemed High Quality by the GRADE system (60).

The included patients in our study had a mean age of 60.1±10%, 58% were male, 84% were whites, 39% had coronary artery disease, 61% had hypertension, 28% had diabetes mellitus, 29% had heterozygous familial hypercholesterolemia and 18% were current smokers. The included patients also had a mean baseline LDL-C of 126±32 mg/dL, total cholesterol of 208±40 mg/dL, FBG of 103±10 mg/dL (5.72±0.55 mmol/L) and HbA1c of 5.89±0.04% (40.9 mmol/mol).

PCSK9 inhibitors and glycemic levels

By including the patient-level meta-analysis of Colhoun *et al* (61), a pooled analysis with non-diabetic individuals from 10 phase 3 RCTs, and excluding the overlapping RCTs such as ODYSSEY ALTERNATIVE, COMBO I, COMBO II, OPTIONS I, OPTIONS II, LONG TERM, FH I, FH II and HIGH FH, we observed equivalent results. Since most of the clinical trials from ODYSSEY family did not publish the changes in FPG and HbA1c during follow-up, pooling these data could add new information on the impact of these studies. After inclusion of this meta-analysis data, the use of PCSK9i still had a small, but significant effect on both FBG [SMD of 0.14 (0.12-0.14), I^2=82%, p<0.001] and HbA1c levels [SMD of 0.08 (0.06-0.10), I^2=80%, p<0.001] (Figures S3A-B). In the pooled analysis, the alirocomab individual-level meta-analysis counted for 13% of the overall sample size and despite of that it greatly increased the heterogeneity from 0 to 82% for FBG and from 15 to 80% for HbA1c (Figures S3A-B).

Exploratory meta-regression analyses on PCSK9i effect on incident type 2 diabetes

The absolute value of LDL-C at the end of each study was inversely associated with the risk of type 2 diabetes; for each 10% lower of LDL-C levels increased the type 2 diabetes risk by 3.8% [(0.5-6.3), p=0.024]. As shown in Table S5, the LDL-lowering effect by PCSK9i was also negatively associated with the risk of worsening diabetes or new-onset type 2 diabetes among individuals who had a LDL-C decrease ≥ 50%. For this subgroup, each 10% decrease in LDL-C levels increased the risk of type 2 diabetes by 5.5% [(0.7-11.0), p=0.029] in age- and gender-adjusted meta-regression analysis (Figure S5A). Finally, the duration of PCSK9i therapy was also associated with increased risk of type 2 diabetes, and each one-month therapy was associated with 0.97% [(0.12-2.07), p=0.026] increased risk (Figure S5B) across trials during 48 to 114 weeks.

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SUPPLEMENTARY DATA

Supplementary Table S1A. Study characteristics of included trials

Study (first author)	Publication year	RCT phase	Included patients	Patient groups	Groups for analysis	Follow-up length	Patient profile
DESCARTES (Blom DJ)	2014	3	901	302 placebo; 599 evolocumab [420 QM]	Placebo PCSK9i	52 weeks	Hyperlipidemia according to the NCEP
FOURIER (Sabatine MS)	2017	3	27,564	13,780 placebo; 13,784 evolocumab [140 Q2W or 420 QM]	Placebo PCSK9i	114 weeks	Atherosclerotic cardiovascular disease with hypercholesterolemia under treatment by statin
GAUSS (Sullivan D)	2012	2	157	32 placebo; 95 alirocumab [280 QM (n=32), 350 QM (n=31), 420 QM (n=32)]; 30 alirocumab + ezetimibe [420 QM + 10 mg]	Placebo Ezetimibe PCSK9i	12 weeks	Hypercholesterolemia with statin intolerance
GLAGOV (Nicholls SJ)	2016	3	968	484 placebo; 484 evolocumab [420 QM]	Placebo PCSK9i	78 weeks	Coronary disease diagnosed by angiography
MENDEL-2 (Koren M)	2012	2	406	90 placebo; 45 ezetimibe; 271 evolocumab [70 Q2W (n=45), 105 Q2W (n=46), 140 Q2W (n=45), 280 QM (n=45), 350 QM (n=45), 420 QM (n=45)]	Placebo Ezetimibe PCSK9	12 to 14 weeks	Hypercholesterolemia with fasting LDL ≥2.6 mmol/L and < 4.9 mmol/L, triglycerides <4.5 mmol/L and 10 year Framingham risk score for CHD of up to 10%.
NCT01266876 (Stein EA)	2012	2	77	15 placebo; 62 alirocumab [150 Q2W (n=16), 150 QM (n=15), 200 QM (n=16), 300 QM (n=15)]	Placebo PCSK9i	20 weeks	Heterozygous for FH
NCT01288469 (Roth EM)	2012	2	92	31 placebo; 61 atorvastatin + alirocumab [10 + 150 Q2W (n=31), 80 mg + 150 Q2W (n=30)]	Placebo Atorvastatin + PCSK9i	16 weeks	Hypercholesterolemia (LDL ≥100 mg/dL)
ODYSSEY CHOICE II (Stroes E)	2016	3	233	58 placebo; 175 alirocumab [75-150 Q2W (n=116), 150 Q2W-QM (n=59)]	Placebo PCSK9i	24 weeks	Inadequately controlled hypercholesterolemia under treatment other than statin
ODYSSEY COMBO I (Kereiakes DJ)	2015	3	316	107 placebo; 209 alirocumab [75-150 Q2W]	Placebo PCSK9i	52 weeks	Established CHD or equivalent risk and hypercholesterolemia
ODYSSEY COMBO II (Cannon CP)	2015	3	720	241 ezetimibe; 479 alirocumab [75-150 Q2W]	Ezetimibe PCSK9i	52 weeks	High CV risk with inadequately controlled hypercholesterolemia
ODYSSEY FH I and FH II (Kastelein JJP)	2015	3	FH I: 485 FH II: 248	FH I: 163 placebo; 322 alirocumab [75-150 Q2W] FH II: 81 placebo; 167 alirocumab [75-150 Q2W]	Placebo PCSK9i	78 weeks	Heterozygous for FH with previous history of CV events
ODYSSEY JAPAN	2016	3	216	72 placebo; 144 alirocumab [75-150 Q2W]	Placebo	52 weeks	Heterozygous for FH, non-FH at

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(Teramoto T)					PCSK9i		high CV risk with coronary disease or category III
ODYSSEY LONG TERM (Robinson JG)	2015	3	2341	788 placebo; 1553 alirocumab [150 Q2W]	Placebo PCSK9i	78 weeks	Heterozygous for FH or established CHD or CHD risk equivalent
ODYSSEY MONO (Roth EM)	2015	3	103	51 ezetimibe; 52 alirocumab [75-150 Q2W]	Ezetimibe PCSK9i	32 weeks	Hypercholesterolemia on no lipid-lowering therapy
ODYSSEY OPTIONS I (Bays H)	2015	3	355	102 ezetimibe + atorvastatin [20 mg (n=55), 40 mg (47)]; 57 atorvastatin [40 mg]; 47 atorvastatin [80 mg]; 45 rosuvastatin [40 mg]; 104 alirocumab + atorvastatin [75/150 Q2W + 20 mg (n=57), 75/150 Q2W + 40 mg (n=47)]	Ezetimibe Atorvastatin Rosuvastatin PCSK9i	24 weeks	Very high CVD risk and with LDL ≥70 mg/dL or high CVD risk and with LDL ≥100 mg/dL
ODYSSEY OPTIONS II (Farnier M)	2016	3	305	101 rosuvastatin [20 mg (n=48), 40 mg (n=53)]; 101 rosuvastatin + ezetimibe [10 mg (n=48), 20 mg (n=53)]; 103 alirocumab + rosuvastatin [75/150 Q2W + 10 mg (n=49), 75/150 Q2W + 20 mg (n=54)]	Rosuvastatin Ezetimibe PCSK9i	24 weeks	Hypercholesterolemia at very high or high CV risk receiving rosuvastatin 10 or 20 mg/day for, at least, 4 weeks
OSLER 1 and 2 (Sabatine MS)	2015	2 and 3	4465	1489 standard therapy; 2976 evolocumab [OSLER 1: 420 QM and OSLER 2: 140 Q2W or 420 QM]	Standard therapy PCSK9i	48 weeks (OSLER 1) 56 weeks (OSLER 2)	Patients who had completed 1 of 12 phase 2 or 3 studies
RUTHERFORD (Raal F)	2012	2	329	109 placebo; 220 evolocumab [140 Q2W (n=110), 420 QM (n=110)]	Placebo PCSK9i	12 weeks	Heterozygous for FH with hypercholesterolemia with LDL ≥100 mg/dL despite statin therapy with or without ezetimibe.
SPIRE 1 and 2 (Ridker PM)	2017	3	27,438	13,718 placebo; 13,720 bococizumab [150 Q2W]	Placebo PCSK9i	40 weeks	Previous CV event or high-risk conditions for CV
YUKAWA-2 (Kiyosue A)	2016	3	404	202 placebo; 202 evolocumab [140 Q2W (n=101), 420 QM (n=101)]	Placebo PCSK9i	12 weeks	Hyperlipidemia or mixed dyslipidemia and high CV risk

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Supplementary Table S1B. Risk of Bias of Individual Randomized Controlled Trials.

Study (first author)	Multicenter trial	Adequate Sequence Generation	Allocation concealment	Blinding			Incomplete Data Outcome Addressed?	Selective Outcome Reporting	Free of Other Bias
				Patient	Physician	Adjudication of outcomes			
DESCARTES (Blom DJ)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
FOURIER (Sabatine MS)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
GAUSS (Sullivan D)	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes
GLAGOV (Nicholls SJ)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
MENDEL-2 (Koren M)	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes
NCT01266876 (Stein EA)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
NCT01288469 (Roth EM)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY CHOICE II (Stroes E)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY COMBO I (Kereiakes DJ)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY COMBO II (Cannon CP)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY FH I and FH II (Kastelein JJP)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY JAPAN (Teramoto T)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY LONG TERM (Robinson JG)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY MONO (Roth EM)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY OPTIONS I (Bays H)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY OPTIONS II (Farnier M)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
OSLER 1 and 2 (Sabatine MS)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
RUTHERFORD (Raal F)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

SPIRE 1 and 2 (Ridker PM)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
YUKAWA-2 (Kiyosue A)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes

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Supplementary Table S2. Participants characteristics.

Study (first author)	Age (years)	Female (%)	Caucasian (%)	Known CAD (%)	Hypertension (%)	Familial hypercholesterolemia (%)	Diabetes mellitus (%)	Background statin therapy	
								Any statin (%)	High-intensity (%)
DESCARTES (Blom DJ)	56±10	52	81	15	50	__	12	88	45
FOURIER (Sabatine MS)	62±9	25	85	81	80	__	37	100	69
GAUSS (Sullivan D)	62±8	46	93	__	59	__	20	16	0
GLAGOV (Nicholls SJ)	60±9	28	94	35	83	__	21	98	59
MENDEL-2 (Koren M)	53±12	69	83	0	29	__	0.2	0	0
NCT01266876 (Stein EA)	53±10	39	95	42	__	__	4	100	77
NCT01288469 (Roth EM)	57±10	60	87	3	51	__	15	100	48
ODYSSEY CHOICE II (Stroes E)	63±10	44	94	50	61	12	16	29	__
ODYSSEY COMBO I (Kereiakes DJ)	63±9	34	82	78	__	__	43	99.7	63
ODYSSEY COMBO II (Cannon CP)	62±9	26	85	90	__	__	31	99.9	67
ODYSSEY FH I and FH II (Kastelein JJP)	FH I: 52±13 FH II: 53±13	FH I: 44 FH II: 53	FH I: 91 FH II: 98	FH I: 46 FH II: 36	FH I: 43 FH II: 32	FH I: 100 FH II: 100	FH I: 12 FH II: 4	100	83
ODYSSEY JAPAN (Teramoto T)	61±9	39	__	35	__	19	68	100	__
ODYSSEY LONG TERM (Robinson JG)	60±10	38	93	69	__	18	34	99.9	44
ODYSSEY MONO (Roth EM)	63±9	47	90	0	__	__	4	0	0
ODYSSEY OPTIONS I (Bays H)	63±10	35	72	56	78	__	50	100	50
ODYSSEY OPTIONS II (Farnier M)	61±10	61	84	58	55	13	41	100	55

OSLER 1 and 2 (Sabatine MS)	58±11	49	13	20	52	10	13	99.9	27
RUTHERFORD (Raal F)	50±13	42	89	21	—	78	0	100	88
SPIRE 1 and 2 (Ridker PM)	63	30	—	—	81	4	48	93	84
YUKAWA-2 (Kiyosue A)	62±10	39	100	13	74	6	49	100	50

SUPPLEMENTARY DATA

Supplementary Table S3. Baseline characteristics of patients.

Study (first author)	Total cholesterol (mg/dL)		LDL-C (mg/dL)		Fasting plasma glucose (mg/dL)		HbA1c (%)	
	Control	PCSK9i	Control	PCSK9i	Control	PCSK9i	Control	PCSK9i
DESCARTES (Blom DJ)	—	—	104±22	104±22	—	—	—	—
FOURIER (Sabatine MS)	168±38	168±38	92±29	92±29	—	—	—	—
GAUSS (Sullivan D)	274±39	284±58	181±36	194±55	—	—	—	—
GLAGOV (Nicholls SJ)	166±6	166±6	92±5	93±5	107±6	104±4	5.9±0.2	5.8±0.1
MENDEL-2 (Koren M)	—	—	143±23	143±22	93±10	94±9	—	—
NCT01266876 (Stein EA)	234±40	233±47	151±40	156±38	99±11	100±12	—	—
NCT01288469 (Roth EM)	201±26	205±25	121±18	123±18	106±27	105±20	6.03±0.77	5.84±0.53
ODYSSEY CHOICE II (Stroes E)	245±51	243±59	157±47	159±51	—	—	—	—
ODYSSEY COMBO I (Kereiakes DJ)	181±36	178±36	105±32	100±30	—	—	—	—
ODYSSEY COMBO II (Cannon CP)	186±42	186±42	104±35	108±35	—	—	6.07±0.77	6.05±0.75
ODYSSEY FH I and FH II (Kastelein JJP)	—	—	FH I: 144±4 FH II: 134±5	FH I: 145±3 FH II: 135±3	—	—	FH I: 5.75±0.62 FH II: 5.60±0.49	FH I: 5.68±0.56 FH II: 5.61±0.43
ODYSSEY JAPAN (Teramoto T)	228±35	224±31	143±27	143±27	—	—	—	—
ODYSSEY LONG TERM (Robinson JG)	—	—	122±41	123±43	—	—	—	—
ODYSSEY MONO (Roth EM)	224±30	222±34	138±24	141±27	97±9	101±14	5.6±0.4	5.7±0.5
ODYSSEY OPTIONS I (Bays H)	—	—	103±33	110±36	—	—	—	—
ODYSSEY OPTIONS II (Farnier M)	—	—	110±42	113±29	—	—	—	—
OSLER 1 and 2 (Sabatine MS)	205(61)	202(59)	121(54)	120(51)	—	—	—	—
RUTHERFORD (Raal F)	—	—	151±40	158±46	—	—	—	—
SPIRE 1 and 2 (Ridker PM)	179(46)	179(46)	109(38)	109(38)	—	—	—	—
YUKAWA-2 (Kiyosue A)	—	—	103±28	109±35	113±2	116±2	6.21±0.06	6.14±0.05

SUPPLEMENTARY DATA

Supplementary Table S4. Egger Bias Analysis.

Endpoint	Egger 2-tailed p-value
Incident type 2 diabetes mellitus	0·42
Incident type 2 diabetes mellitus or worsening diabetes	0·84
Fasting plasma glucose change from baseline	0·14
HbA1c change from baseline	0·29

Supplementary Table S5. Meta-regression analyses on study-level association between baseline age, prevalence of T2DM at baseline, duration of treatment, LDL-C at the end of each study and change in LDL-C vs the risk ratio (log) incident T2DM and worsening diabetes.

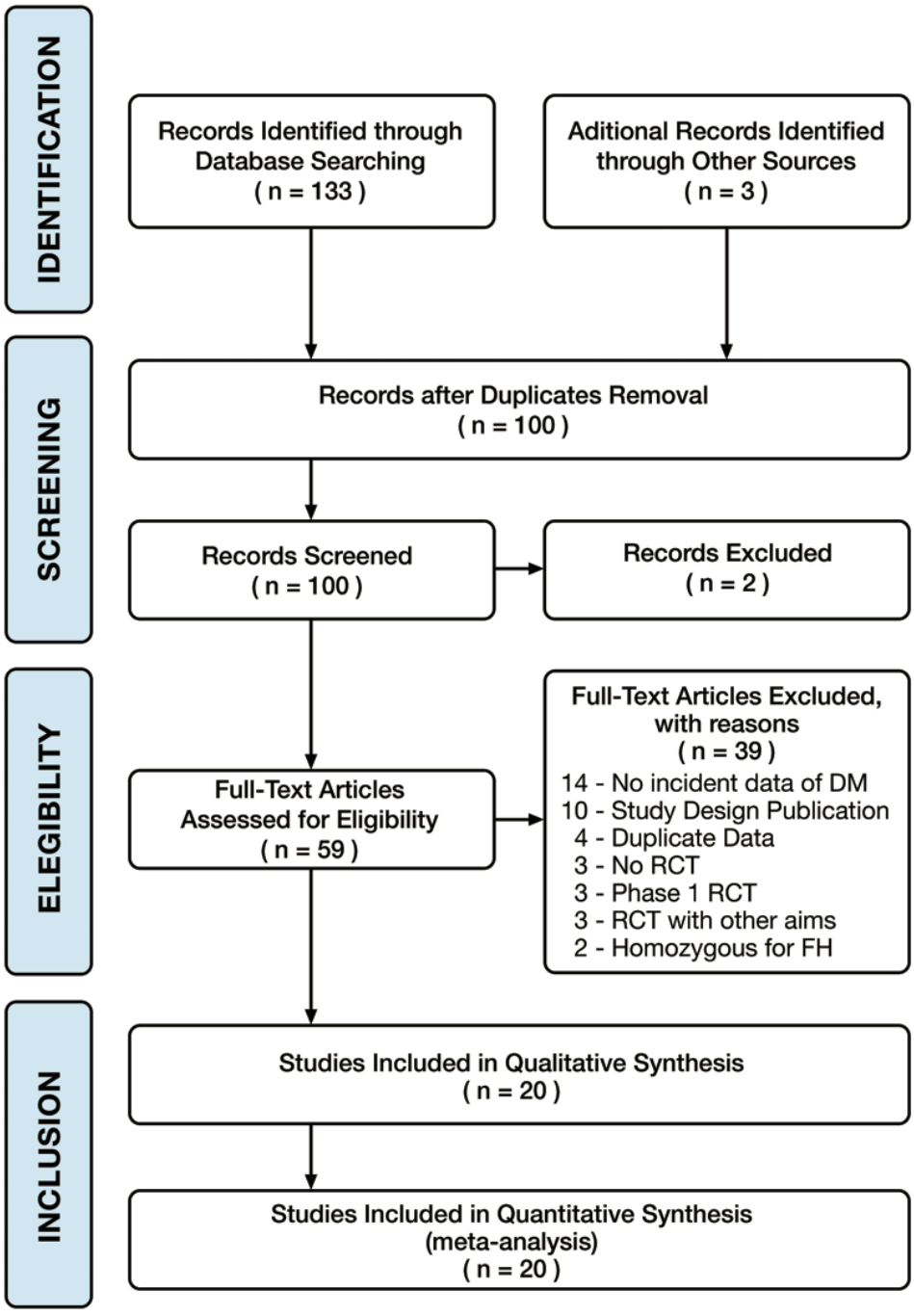
Variable	Regression	p-value
Baseline age	-0.019 (-0.0983 to 0.0588) + 0.09	0.610
Women in the study	+0.011 (-0.0124 to 0.0341) + 0.29	0.320
Prevalence of T2DM at baseline	-0.0039 (0.0172 to 0.0092) + 0.26	0.470
Percentage of individuals on high-dose statin regimen**	-0.0062 (-0.0160 to 0.0037) + 0.48	0.200
Percentage of individuals on ezetimibe	-0.0021 (-0.0289 to 0.0168) + 0.21	0.462
Duration of treatment (per month)	+0.0051 (0.0006 to 0.0095) - 4.31	0.026*
LDL-C at the end of each study (per 10 mg/dL)	-0.0144 (-0.0266 to 0.0022) + 0.15	0.024*
Change in LDL-C (per 10 mg/dL)	-0.0235 (-0.0441 to -0.0029) – 1.16	0.029*

* Adjusted by the percentage of women in the study and mean age of study participants.

** High-dose statin regimen: atorvastatin 40-80mg/day or rosuvastatin 20-40mg/day

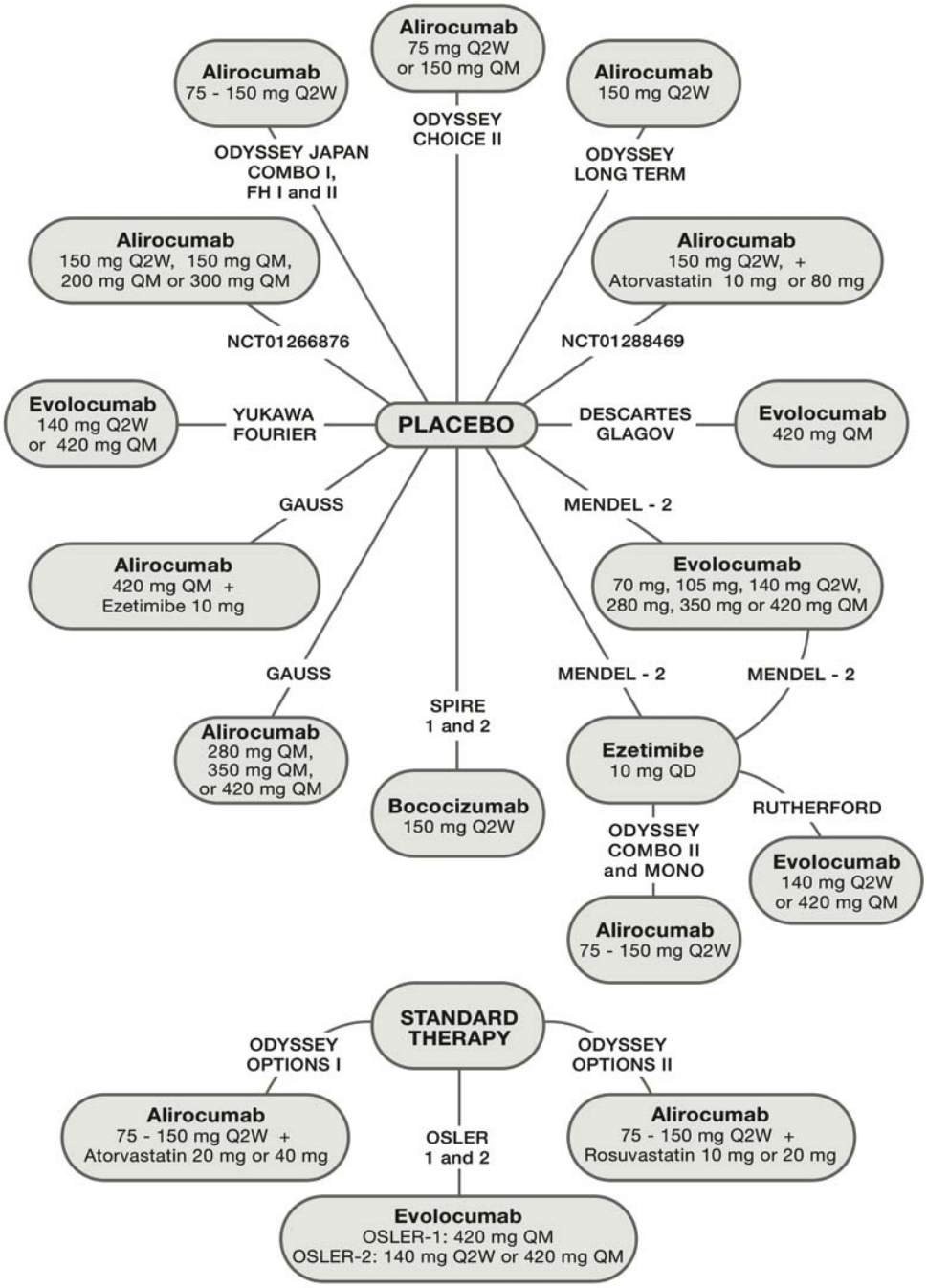
SUPPLEMENTARY DATA

Supplementary Figure S1A. Flow diagram.



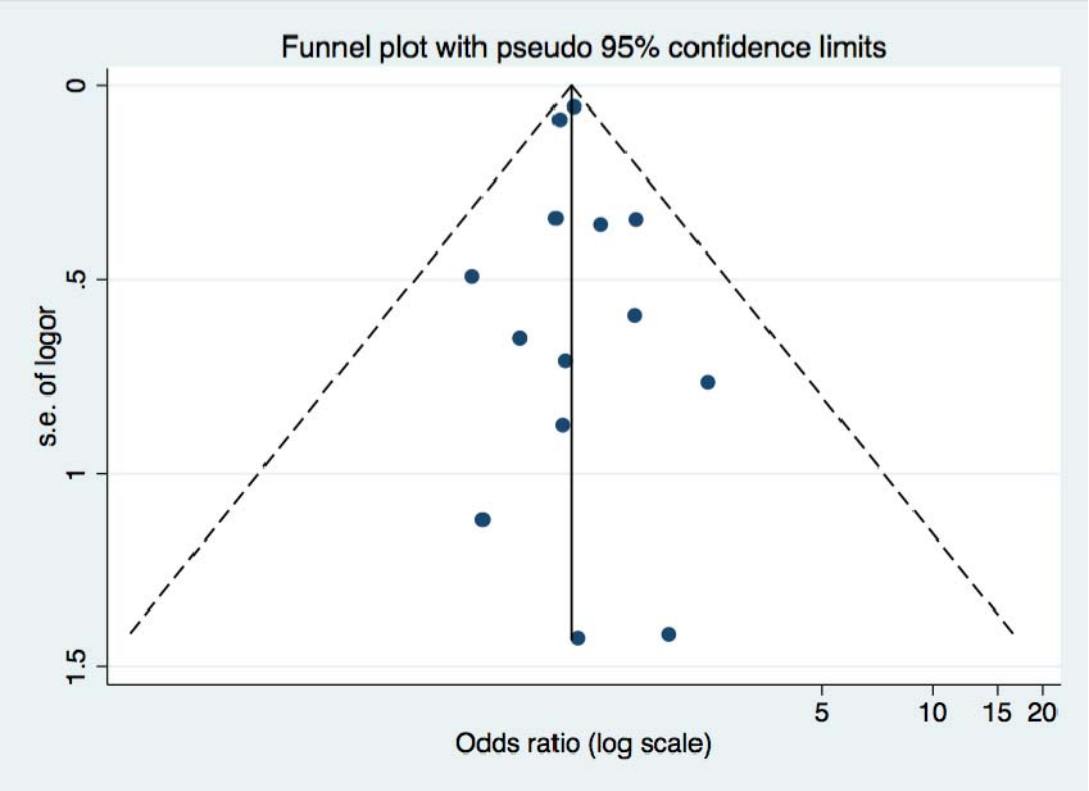
SUPPLEMENTARY DATA

Supplementary Figure S1B. Network diagram.

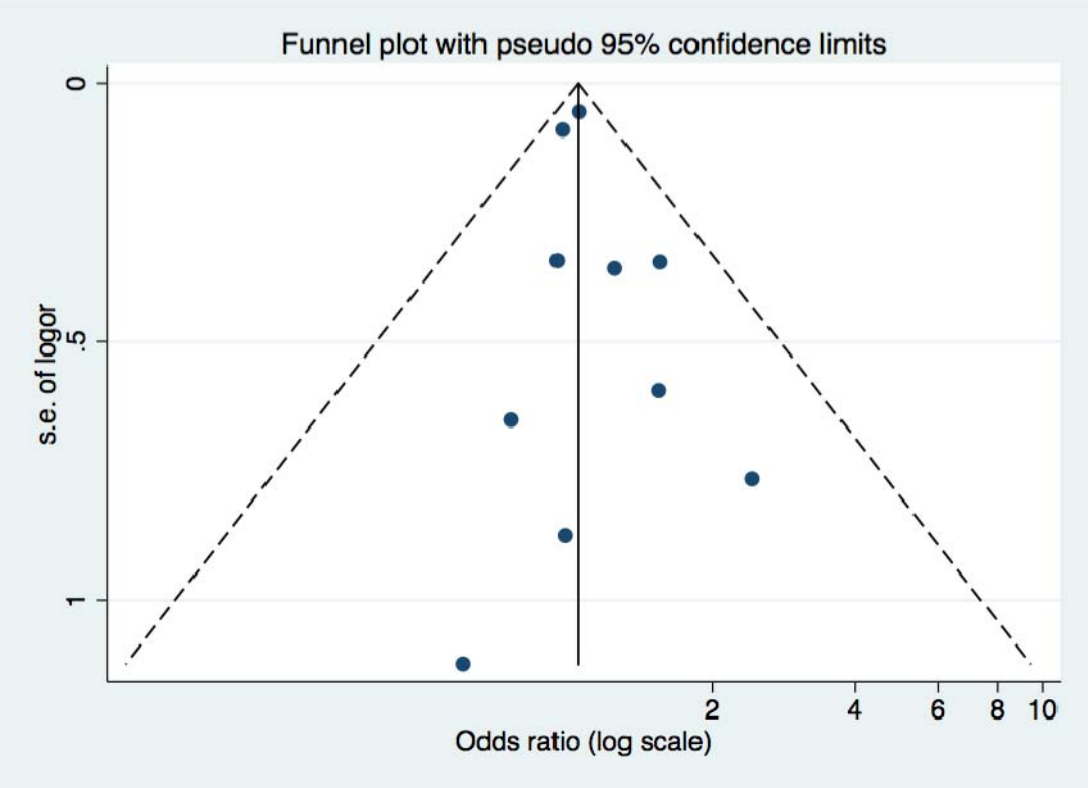


SUPPLEMENTARY DATA

Supplementary Figure S2A. Funnel plots for worsening or incident diabetes mellitus.

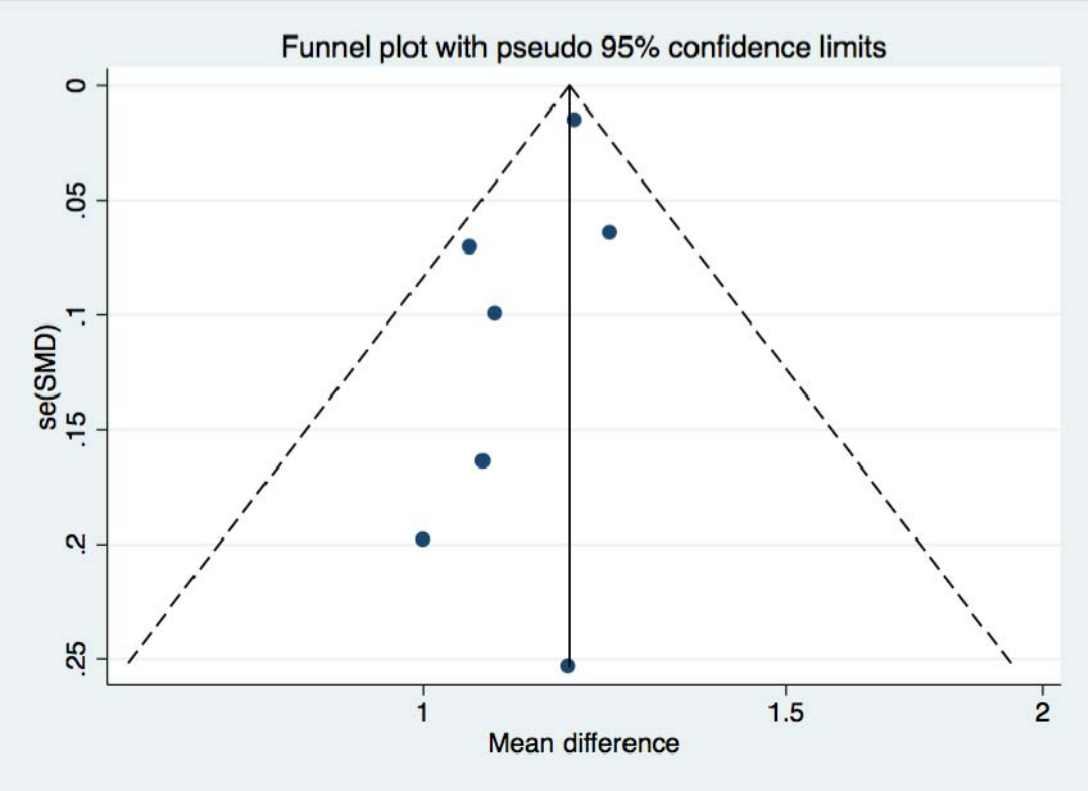


Supplementary Figure S2B. Funnel plots for incident diabetes mellitus.

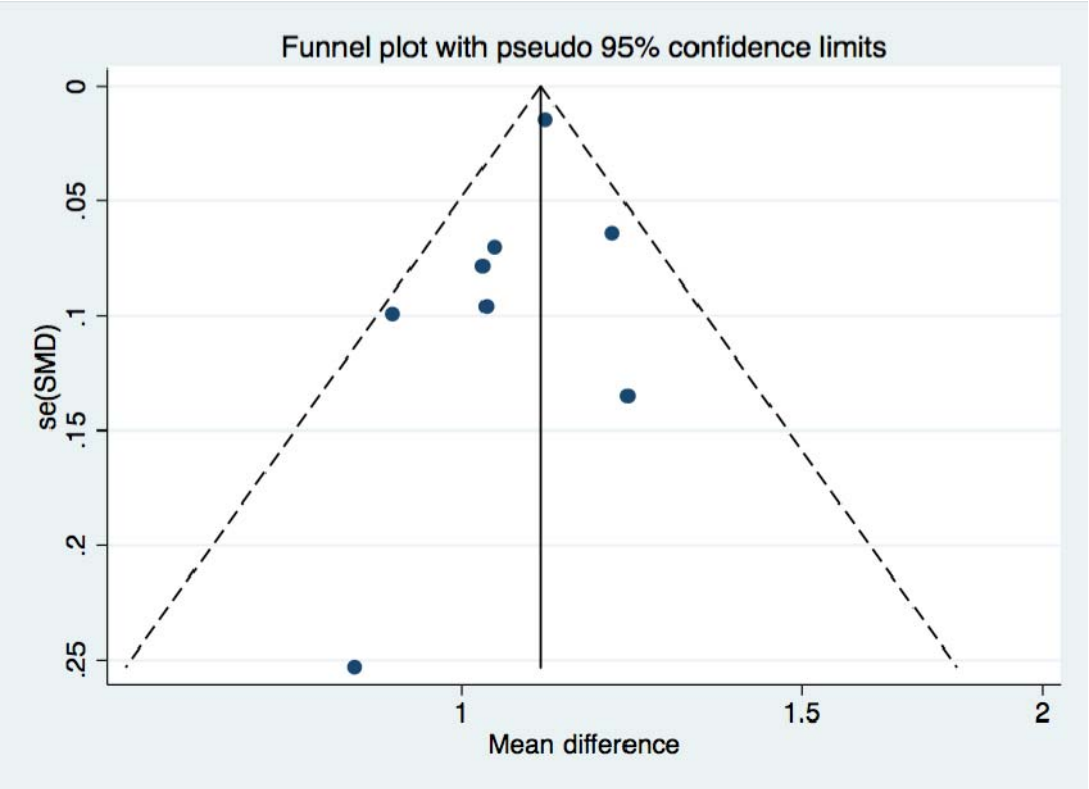


SUPPLEMENTARY DATA

Supplementary Figure S2C. Funnel plots for fasting plasma glucose change.

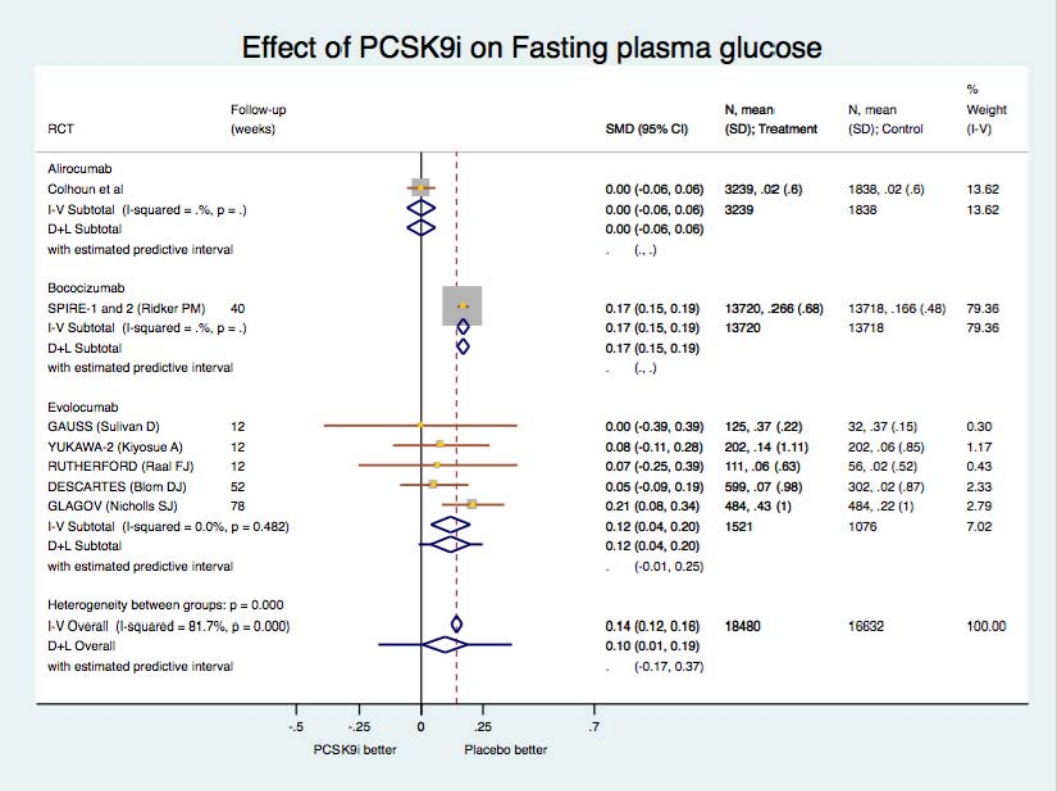


Supplementary Figure S2D. Funnel plots for HbA1c change.

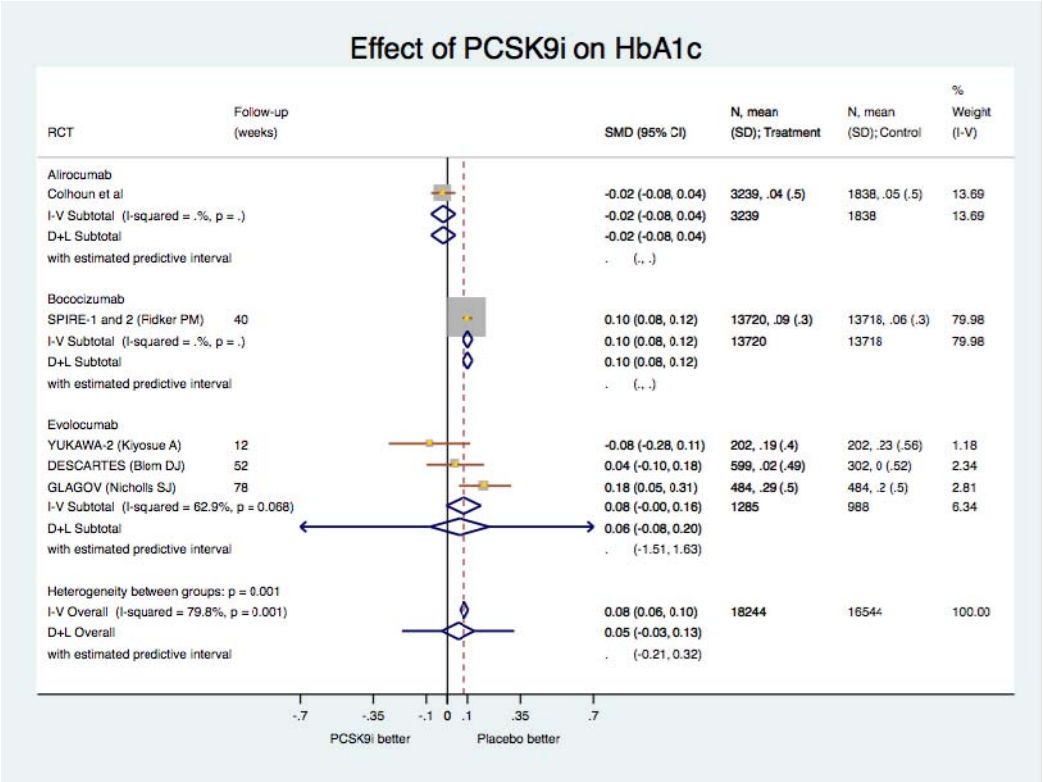


SUPPLEMENTARY DATA

Supplementary Figure S3A. Fasting plasma glucose change including the pooled analysis by Colhoun *et al.*

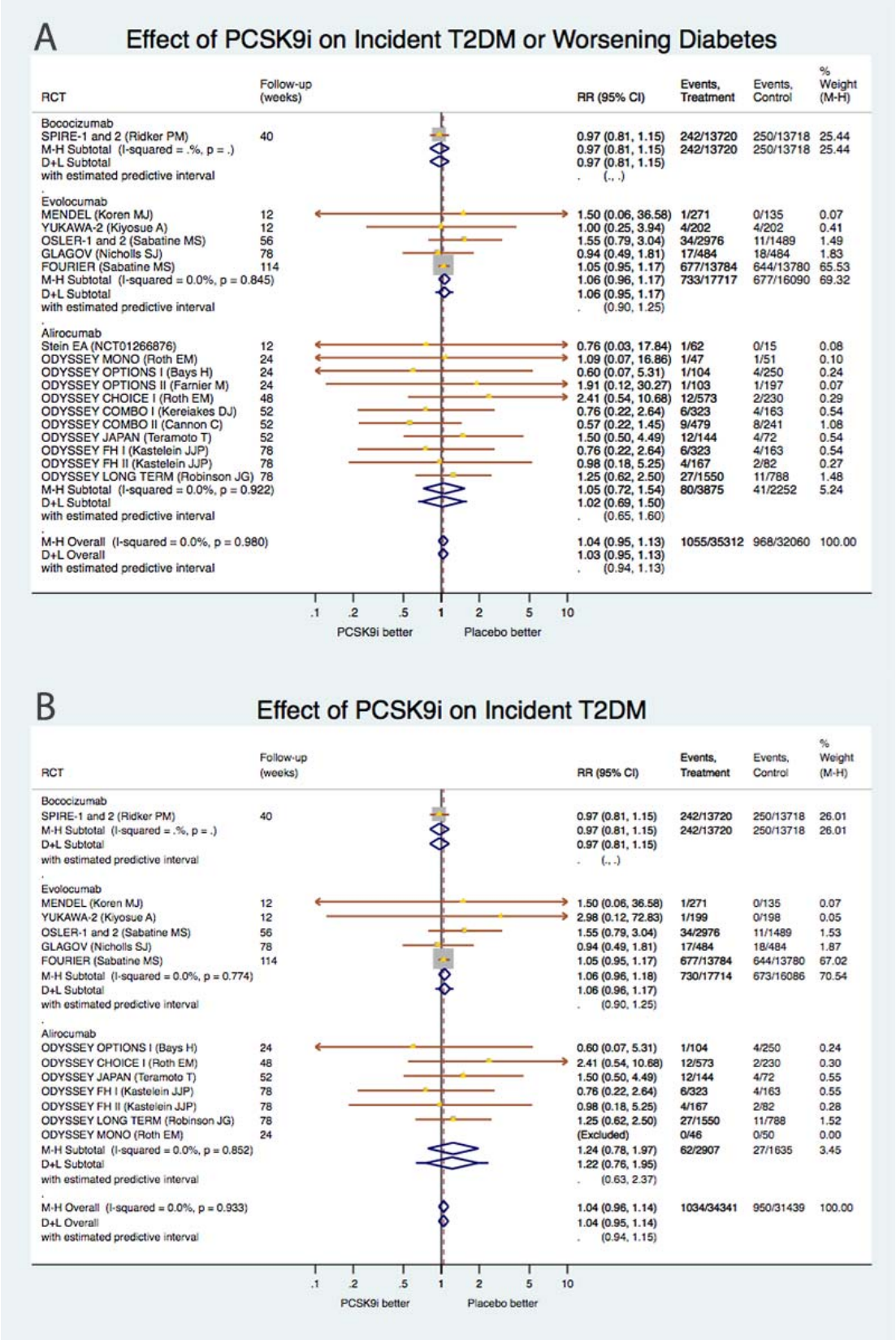


Supplementary Figure S3B. HbA1c change including the pooled analysis by Colhoun *et al.*



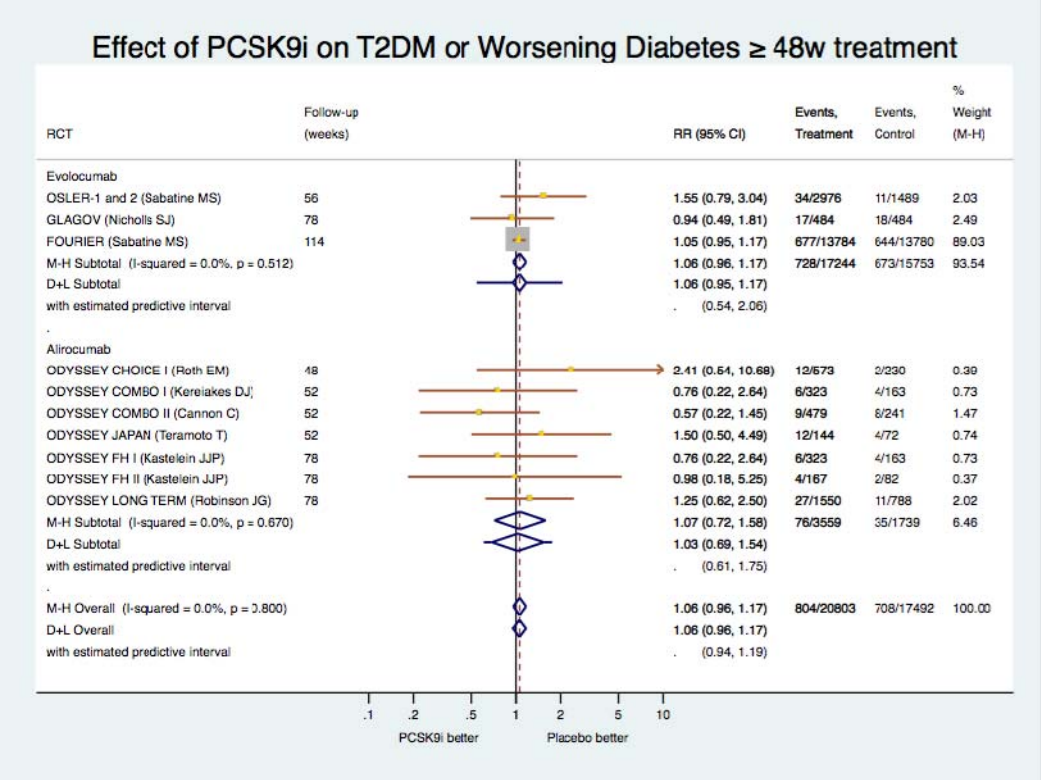
SUPPLEMENTARY DATA

Supplementary Figure S4A-B. Worsening or incident diabetes mellitus



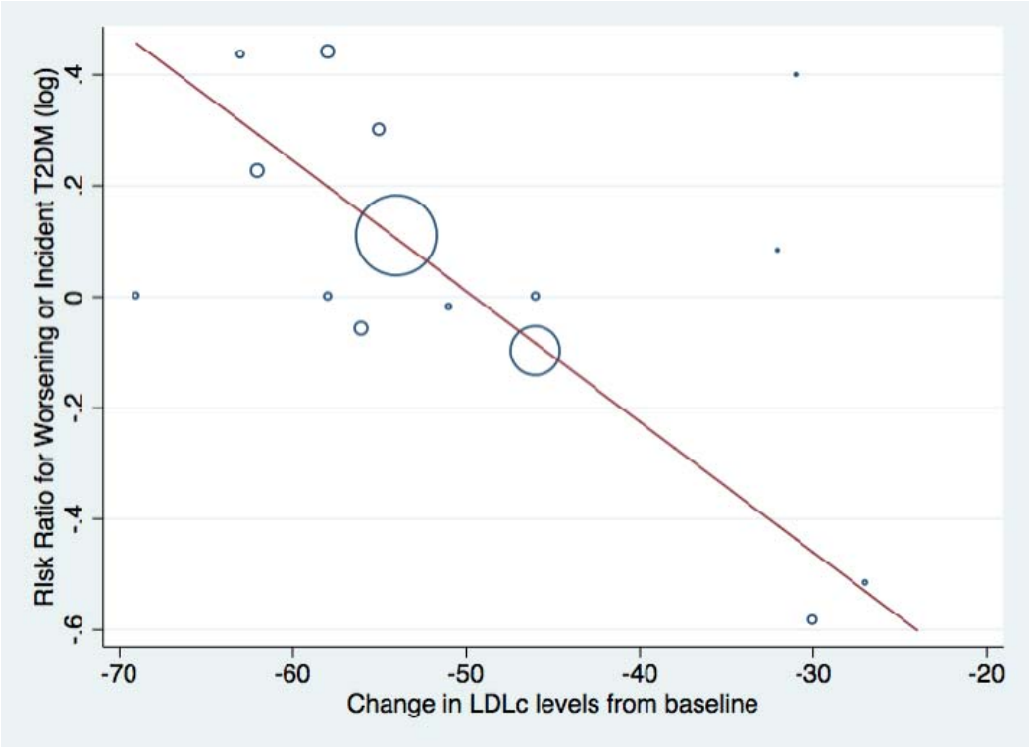
SUPPLEMENTARY DATA

Supplementary Figure S4C. Worsening or incident diabetes mellitus – studies with 48 weeks or more.



SUPPLEMENTARY DATA

Supplementary Figure S5A. Meta-regression analysis: Percent change in LDL-C levels from baseline *vs.* the risk of worsening diabetes or new-onset T2DM.



Supplementary Figure S5B. Meta-regression analysis: Duration of treatment *vs.* the risk of worsening diabetes or new-onset T2DM.