

Supplementary materials

Table 1 Search strategy for cohort studies in MEDLINE and EMBASE through OVID

Search No.	Query	Items
1	glucose.ti. or glucose.ab.	911361
2	Glycosuria.ti. or Glycosuria.ab.	4093
3	Hyperglycemia.ti. or Hyperglycemia.ab.	85456
4	FPG.ti. or FPG.ab.	12538
5	OGTT.ti. or OGTT.ab.	20232
6	Glycosylated Haemoglobin.ti. or Glycosylated Haemoglobin.ab.	5084
7	glycosylated hemoglobin.ti. or glycosylated hemoglobin.ab.	14271
8	glycated hemoglobin.ti. or glycated hemoglobin.ab.	12573
9	Glycated Haemoglobin.ti. or Glycated Haemoglobin.ab.	5997
10	glycohaemoglobin.ti. or glycohaemoglobin.ab.	231
11	glycohemoglobin.ti. or glycohemoglobin.ab.	1831
12	HbA1c.ti. or HbA1c.ab.	75206
13	Type 2 diabetes.ti. or Type 2 diabetes.ab.	232282
14	Type II diabetes.ti. or Type II diabetes.ab.	17394
15	Non?insulin dependent diabetes.ti. or Non?insulin dependent diabetes.ab.	2422
16	niddm.ti. or niddm.ab.	14910
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	1137583
18	Complication*.ti. or Complication*.ab.	1781888
19	Macro-vascular disease.ti. or Macro-vascular disease.ab.	73
20	Macrovascular disease.ti. or Macrovascular disease.ab.	2688
21	cardiovascular disease.ti. or cardiovascular disease.ab.	239229

22	Heart disease.ti. or Heart disease.ab.	321400
23	Coronary artery disease.ti. or Coronary artery disease.ab.	178144
24	myocardial infarction.ti. or myocardial infarction.ab.	378154
25	Angina.ti. or Angina.ab.	115402
26	Heart attack.ti. or Heart attack.ab.	8889
27	Heart failure.ti. or Heart failure.ab.	346540
28	Cerebrovascular disease.ti. or Cerebrovascular disease.ab.	32163
29	stroke.ti. or stroke.ab.	477663
30	death.ti. or death.ab.	1357780
31	Mortality.ti. or Mortality.ab.	1437828
32	CVD.ti. or CVD.ab.	62945
33	CAD.ti. or CAD.ab.	80572
34	CHD.ti. or CHD.ab.	52121
35	IHD.ti. or IHD.ab.	12085
36	"MI".ti. or "MI".ab.	102969
37	"HF".ti. or "HF".ab.	85314
38	Micro-vascular disease.ti. or Micro-vascular disease.ab.	56
39	Microvascular disease.ti. or Microvascular disease.ab.	3295
40	Retinal.ti. or Retinal.ab.	287805
41	Retinopath*.ti. or Retinopath*.ab.	85477
42	Vision*.ti. or Vision*.ab.	216180
43	Blind*.ti. or Blind*.ab.	604473
44	Retinopathy.ti. or Retinopathy.ab.	83669
45	Nephropathy.ti. or Nephropathy.ab.	108188
46	Nephropath*.ti. or Nephropath*.ab.	114577
47	Kidney.ti. or Kidney.ab.	804656
48	Renal.ti. or Renal.ab.	1214804
49	Neuropath*.ti. or Neuropath*.ab.	265712
50	Neuropathy.ti. or Neuropathy.ab.	141459

51	Foot ulcer.ti. or Foot ulcer.ab.	3507
52	Amputation.ti. or Amputation.ab.	61865
	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or	
	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or	
53	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or	7834048
	48 or 49 or 50 or 51 or 52	
54	cohort.ti. or cohort.ab.	992397
55	Cohort*.ti. or Cohort*.ab.	1089981
56	Prospective.ti. or Prospective.ab.	1118011
57	Longitudinal.ti. or Longitudinal.ab.	427198
58	Followed.ti. or Followed.ab.	1974867
59	Follow-up.ti. or Follow-up.ab.	1949700
60	Incidence.ti. or Incidence.ab.	1477253
61	Incidence stud*.ti. or Incidence stud*.ab.	3154
62	exp cohort analysis/	2087203
63	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61	6398285
64	54 or 55 or 56 or 57 or 60 or 61 or 62	4698094
65	17 and 53 and 63	81056
66	17 and 53 and 64	64581
67	limit 65 to human	72021
68	limit 66 to human	60014
69	54 or 55 or 56 or 57 or 60 or 61	3549445
70	17 and 53 and 102	56166
71	limit 103 to human	51708
72	Hemoglobin A.ti. or Hemoglobin A.ab.	4629
73	Haemoglobin A.ti. or Haemoglobin A.ab.	968
74	17 or 72 or 73	1141649
75	74 and 53 and 69	56273
76	limit 75 to human	51758

Table 2 Search strategy for systematic review of RCTs in CENTRAL

Search No.	Query	Items
1	Type 2 diabetes.ab. or Type 2 diabetes.ti.	238391
2	Type II diabetes.ab. or Type II diabetes.ti.	17685
3	type-2 diabetes.ab. or type-2 diabetes.ti.	238391
4	1 or 2 or 3	255197
5	systematic review.ti. or systematic review.pt.	151961
6	meta-analysis.ti. or meta-analysis.pt.	184675
7	meta analyses.ti. or meta analyses.pt.	5317
8	5 or 6 or 7	285496
9	trial.ab.	990802
10	randomly.ab.	630216
11	randomized.ab.	948840
12	9 or 10 or 11	2071903
13	Complication*.ti. or Complication*.ab.	1816453
14	Macro-vascular disease.ti. or Macro-vascular disease.ab.	73
15	Macrovascular disease.ti. or Macrovascular disease.ab.	2570
16	cardiovascular disease.ti. or cardiovascular disease.ab.	245030
17	Heart disease.ti. or Heart disease.ab.	327904
18	Coronary artery disease.ti. or Coronary artery disease.ab.	182637
19	myocardial infarction.ti. or myocardial infarction.ab.	386719
20	Angina.ti. or Angina.ab.	117995
21	Heart attack.ti. or Heart attack.ab.	9045
22	Heart failure.ti. or Heart failure.ab.	355371
23	Cerebrovascular disease.ti. or Cerebrovascular disease.ab.	32715

24	stroke.ti. or stroke.ab.	488698
25	death.ti. or death.ab.	1387252
26	Mortality.ti. or Mortality.ab.	1470285
27	CVD.ti. or CVD.ab.	64754
28	CAD.ti. or CAD.ab.	82570
29	CHD.ti. or CHD.ab.	53359
30	IHD.ti. or IHD.ab.	12285
31	"MI".ti. or "MI".ab.	105221
32	"HF".ti. or "HF".ab.	87557
33	Micro-vascular disease.ti. or Micro-vascular disease.ab.	58
34	Microvascular disease.ti. or Microvascular disease.ab.	3387
35	Retinal.ti. or Retinal.ab.	294682
36	Retinopath*.ti. or Retinopath*.ab.	87179
37	Vision*.ti. or Vision*.ab.	220206
38	Blind*.ti. or Blind*.ab.	616242
39	Retinopathy.ti. or Retinopathy.ab.	85342
40	Nephropathy.ti. or Nephropathy.ab.	110032
41	Nephropath*.ti. or Nephropath*.ab.	116490
42	Kidney.ti. or Kidney.ab.	821978
43	Renal.ti. or Renal.ab.	1238897
44	Neuropath*.ti. or Neuropath*.ab.	270673
45	Neuropathy.ti. or Neuropathy.ab.	143928
46	Foot ulcer.ti. or Foot ulcer.ab.	3582
47	Amputation.ti. or Amputation.ab.	62721
48	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	7992503
49	4 and 8 and 12 and 48	819

eTable 3: Scale of quality assessment for cohort or trials comparing the incidence of macrovascular and microvascular complications in type 2 diabetes patients

Study population

1. Were participants representative for the general type 2 diabetes patients?

Yes: The participants represented the general type 2 diabetes patients.

No: The participants had some certain characteristic.

Unclear: The representativeness of participants was not clearly stated.

Outcome measurements

2. Were relevant outcomes appropriately measured with objective methods?

Yes: The outcome was measured using the objective methods.

No: The methods used to measure the outcomes were subjective.

Unclear: we could not figure out the methods used to measure study's outcomes.

Results

3. Were patients with prevalent outcomes excluded in analysis?

Yes: These patients were excluded and only the population at risk were included in analysis.

No: They were not excluded.

Unclear: No related information about these patients.

4. Did the study deal with the loss to follow-up appropriately?

Yes: The study dealt with the patients lost to follow-up well.

No: The patients lost to follow-up are neglect.

Unclear: The information of loss follow-up people was unclear.

Competing interest and source of support

5. Were both competing interest and source of support for the study reported?

Yes: Both competing interest and source of support (financial or other) received for the study are reported, or the absence of any competing interest and source of support was acknowledged.

No: there was no information available about competing interests and sources of support.

Partly report: only one of these elements was reported.

*: The scale is adapted from the scale of the Institute of Health Economics and Newcastle-Ottawa Quality Assessment Scale. One point was assigned to each item if it was met by the study being assessed and 3.5 or above out of 5 scores were regarded as high quality.

Table 4 Data for the incidence of each type of major cardiovascular events in eligible studies

Id	Author	Myocardial infarction (MI)			Stroke			Cardiovascular disease (CVD)			Total cases	Population
		definition	case	No.	definition	case	No.	definition	case	No.		
1	Accord intensive	nonfatal MI	186	5128	nonfatal stroke	67	5128	CVD death	135	5128	388	5128
2	Accord standard	nonfatal MI	235	5123	nonfatal stroke	61	5123	CVD death	94	5123	390	5123
3	Advance intensive	nonfatal MI	153	5571	nonfatal stroke	214	5571	CVD death	253	5571	620	5571
4	Advance standard	nonfatal MI	156	5569	nonfatal stroke	209	5569	CVD death	289	5569	654	5569
5	Bethel 2007	MI	265	33772	Stroke	313	33772	—	—	—	578	33772
6	Cheng 2015	MI	1801	226310	Stroke	13513	226310	—	—	—	15314	226310
7	Gordon 2017	MI	231	10484	Stroke	158	10484	—	—	—	389	10484
8	Hasen 2013	MI	429	1259	Stroke	302	1318	—	—	—	731	1318 ^a
9	Johnson 2013	MI	249	15951	Stroke	225	15951	—	—	—	474	15951
10	Kanaya 2011	MI	6088	58632	Stroke	4825	61479	—	—	—	10913	61479 ^a
11	Leal 2013	MI	814	3773	Stroke	339	3902	—	—	—	1153	3902 ^a

12	Marre Placebo	nonfatal MI	59	2469	nonfatal stroke	84	2469	CVD death	133	2469	276	2469
13	Marre Ramipril	nonfatal MI	52	2443	nonfatal stroke	89	2443	CVD death	141	2443	282	2443
14	Martin 2007	AMI	109	3142	Stroke	181	3142	—	—	—	290	3142
15	VADT intensive	MI	64	892	Stroke	28	892	—	—	—	92	892
16	VADT standard	MI	78	899	Stroke	36	899	—	—	—	114	899

Table 5 Data for the incidence of each type of severe microvascular complications in eligible studies

ID	Author	Serious retinopathy			Serious nephropathy			Serious diabetic foot			Total case	Population
		definition	case	No.	definition	case	No.	definition	case	No.		
1	Accord intensive	Severe loss of vision	258	4651	Renal failure	107	5085	–	(43) b	5128 c	408	4651 a
2	Accord standard	Severe loss of vision	273	4689	Renal failure	112	5108	–	(43) b	5123 c	428	4689 a
3	Advance intensive	New or worsening retinopathy	332	5571	New or worsening nephropathy	230	5571	–	(47) b	5571 c	609	5571
4	Advance standard	New or worsening retinopathy	349	5569	New or worsening nephropathy	292	5569	–	(47) b	5571 c	688	5569
5	Bethel 2007	Loss vision or blindness	53	33,772	ESRD	268	33,772	Amputation	33	33,772	354	33,772
6	Cheng 2015	Photocoagulation	2272	226,310	ESRD	617	22,6310	Amputation	23	226,310	2912	226,310

7	Gordon 2017	Blindness	9	10,484	Renal failure	111	10,484	Amputation	38	10,484	158	10,484
8	Hasen 2013	Retinal photocoagulation or renal failure				181	1378	Amputation or PVD death	69	1372	250	1372 ^a
9	Johnson 2013	Blindness or laser therapy	125	15,951	Dialysis	77	15,951	Amputation	95	15,951	297	15,951
10	Kanaya 2011	—	(477) ^b	64,211 ^c	ESRD	2340	63,438	Amputation	2291	63,279	5108	63,279 ^a
11	Leal 2013	Blindness	141	3886	Renal failure	81	4011	Amputation	149	3995	371	3886 ^a
12	Marre Placebo	Loss of vision	8	2469	ESRD	12	2469	Amputation	26	2469	46	2469
13	Marre Ramipril	Loss of vision	8	2443	ESRD	11	2443	Amputation	28	2443	47	2443
14	Martin 2007	Blindness	13	3142	Dialysis	39	3142	Amputation	26	3142	78	3142
15	VADT intensive	Photocoagulation	50	719	Dialysis	7	882	Amputation	11	892	68	719 ^a
16	VADT standard	Photocoagulation	66	746	Dialysis	11	884	Amputation	17	899	94	746 ^a

ESRD: End stage renal disease; PVD: Peripheral vascular disease; —: data is not available

a: We choose the smallest number of population at risk for SMICs;

b: use the average incidence estimated from all other studies to figure out the missing cases of the SMICs;

c: use the numbers of patients at baseline as the subtotal numbers for the missing.

Table 6 The results of quality assessment of studies comparing the incidences of major cardiovascular events and severe microvascular complications in type 2 diabetes patients

		Measure Representative for general type 2 diabetes	outcomes appropriately with objective methods	Exclude patients with prevalent outcomes in analysis	Deal with the loss to follow-up appropriately	Report competing and support study	both interest source of for the	Total marks
ACCORD	0	1	0.5	1	1		3.5	
ADVANCE	0	1	0	1	1		3	
Bethel 2007	1	1	0	1	1		4	
Cheng 2015	1	1	1	1	0.5		4.5	
Gordon 2017	0	1	0	1	0.5		2.5	
Hansen 2013	1	1	0.5	1	1		4.5	
Johnson 2013	0	1	0	0.5	0.5		2	
Kanaya 2011	1	1	1	1	1		5	
Leal 2013	0	0.5	1	0.5	1		3	
Marre 2004	0	1	0	1	1		3	
Martin	1	1	0	0	1		3	

2007

VADT

0

1

0.5

1

1

3.5

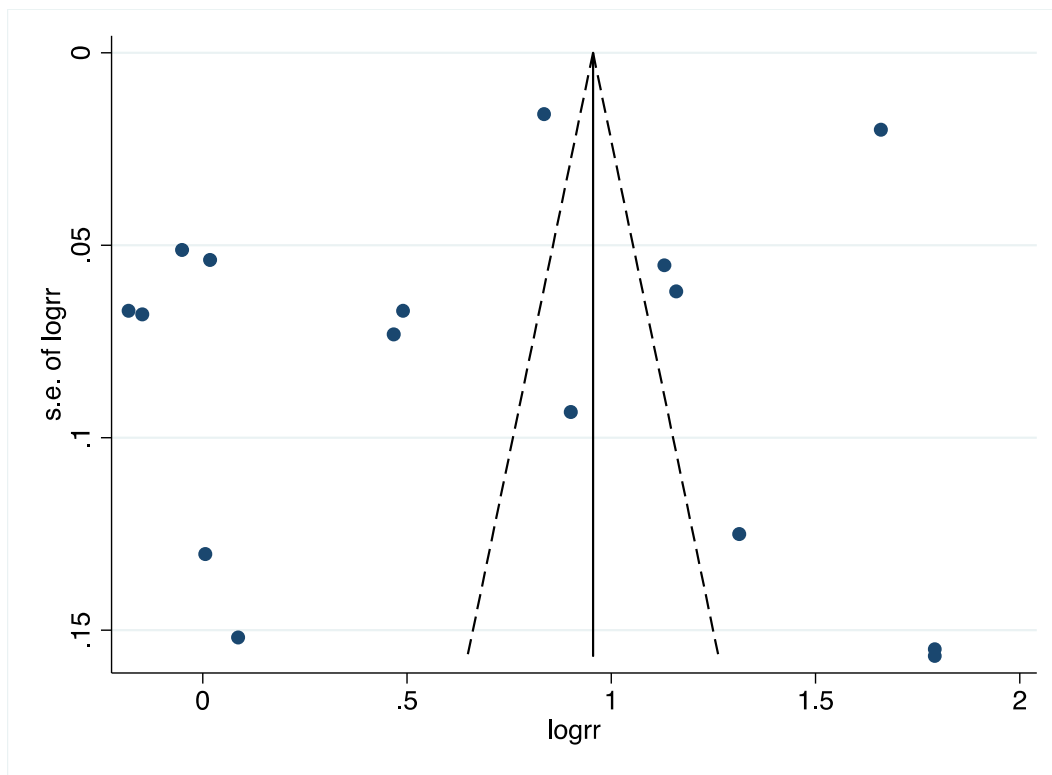


Figure 1 Funnel plot of studies comparing the incidence of major cardiovascular events over severe microvascular complications in type 2 diabetes patients.