Appendix 1. Search strategies

The Cochrane Library

1. MeSH descriptor Diabetes mellitus, type 2explode all trees
2. MeSH descriptor Insulin resistanceexplode all trees
3. ((impaired in All Text and glucosein All Text and toleranc* in All Text) or (glucosein All Text and intoleranc* in All Text) or (insulin*in All Text and resistanc* in All Text))
4. (obes* in All Text near/6 diabet*in All Text)
5. (MODY in All Text or NIDDMin All Text or TDM2 in All Text)
6. ((non in All Text and insulin*in All Text and depend* in All Text) or (noninsulin*in All Text and depend* in All Text) or (nonin All Text and insulindepend* in All Text) or noninsulindepend*in All Text)
7. (typ* in All Text and (2in All Text near/6 diabet* in All Text))
8. (typ* in All Text and (IIin All Text near/6 diabet* in All Text))
9. (non in All Text and (keto*in All Text near/6 diabet* in All Text))
10. (nonketo* in All Text near/6 diabet*in All Text)
11. (adult* in All Text near/6 diabet*in All Text)
12. (matur* in All Text near/6 diabet*in All Text)
13. (late in All Text near/6 diabet*in All Text)
14. (slow in All Text near/6 diabet*in All Text)
15. (stabl* in All Text near/6 diabet*in All Text)
16. (insulin* in All Text and (defic*in All Text near/6 diabet* in All Text)
17. (plurimetabolic in All Text and syndrom*in All Text)
18. (pluri in All Text and metabolicin All Text and syndrom* in All Text)
19. (#1 or #2 or #3or #4 or #5 or #6 or #7or #8 or #9 or #10)
20. (#11 or #12 or #13or #14 or #15 or #16 or #17or #18)
21. (#19 or #20)
22. MeSH descriptor Diabetes insipidusexplode all trees
23. (diabet* in All Text and insipidusin All Text)
24. (#22 or #23)
25. (#21 and not #24)
26. MeSH descriptor Blood glucoseexplode all trees
27. MeSH descriptor Hyperglycemiaexplode all trees
28. MeSH descriptor Hemoglobin A, glycosylatedexplode all trees
29. ((blood in All Text and glucos*in All Text) or hyperglycaemi* in All Text or hyperglycemi*in All Text or (haemoglobin* in All Text and Ain All Text) or (hemoglobin* in All Text and Ain All Text))
30. (HbA1C in All Text or (Hbin All Text and A in All Text) or (HbA in All Text and 1c in All Text) or HbA in All Text or A1Cs in All Text)
31. (glycosylated in All Text near/6 haemoglobin*in All Text)
32. (glycosylated in All Text near/6 hemoglobin*in All Text)
33. (glucos* in All Text near/3 management*in All Text)
34. (#26 or #27 or #28or #29 or #30 or #31 or #32or #33)
35. (#25 or #34)
36. (intensi* in All Text near/3 control*in All Text)
37. (intensi* in All Text near/3 therap*in All Text)
38. (intensi* in All Text near/3 treatment*in All Text)
39. (intensi* in All Text near/3 intervention*in All Text)
40. (intensi* in All Text near/3 management*in All Text)

41. (conventional* in All Text near/3 control*in All Text)
42. (conventional* in All Text near/3 therap*in All Text)
43. (conventional* in All Text near/3 treatment*in All Text)
44. (conventional* in All Text near/3 intervention*in All Text)
45. (conventional in All Text near/3 management*in All Text)
46. (regular in All Text near/3 control*in All Text)
47. (regular in All Text near/3 therap*in All Text)
48. (regular in All Text near/3 treatment*in All Text)
49. (regular in All Text near/3 intervention*in All Text)
50. (regular in All Text near/3 management*in All Text)
51. (usual in All Text near/3 control*in All Text)
52. (usual in All Text near/3 therap*in All Text)
53. (usual in All Text near/3 treatmentin All Text)
54. (usual in All Text near/3 intervention*in All Text)
55. (usual in All Text near/3 management*in All Text)
56. (routin* in All Text near/3 control*in All Text)
57. (routin* in All Text near/3 therap*in All Text)
58. (routin* in All Text near/3 treatment*in All Text)
59. (routin* in All Text near/3 intervention*in All Text)
60. (routin* in All Text near/3 management*in All Text)
61. (tight in All Text near/3 control*in All Text)
62. (tight in All Text near/3 therap*in All Text)
63. (tight in All Text near/3 treatment*in All Text)
64. (tight in All Text near/3 intervention*in All Text)
65. (tight in All Text near/3 management*in All Text)
66. (#36 or #37 or #38or #39 or #40 or #41 or #42or #43 or #44 or #45 or #46or #47 or #48 or #49 or #50or #51 or #52 or #53 or #54or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65)
67. (#35 and #66)

MEDLINE
1. exp Blood Glucose/
2. exp Hyperglycemia/
3. exp Hemoglobin A, Glycosylated/
4. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti.
5. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
6. (glycosylated adj6 h?emoglobin$).ab,ti.
7. (glucos$ adj3 management$).ab,ti.
8. or/1-7
9. exp Diabetes Mellitus, Type 2/
10. exp Diabetes Complications/
11. (MODY or NIDDM or T2DM).tw,ot.
12. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend).tw,ot.
13. ((typ$ 2 or typ$ II) adj3 diabet$).tw,ot.
14. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
15. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ab,ti.
16. or/9-15
17. exp Diabetes Insipidus/
18. diabet$ insipidus.tw,ot.

19. 17 or 18
20. 16 not 19
21. 8 or 20
22. ((intensi$ or conventional$ or regular or tight or usual or routin$ or or standard) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti.
23. 21 and 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomi?ed.ab,ti.
27. placebo$.ab,ti.
28. drug therapy.fs.
29. randomly.ab,ti.
30. trial$.ab,ti.
31. group$.ab,ti.
32. or/24-31
33. Meta-analysis.pt.
34. exp Technology Assessment, Biomedical/
35. exp Meta-analysis/
36. exp Meta-analysis as topic/
37. hta.tw,ot.
38. (health technology adj6 assessment$).tw,ot.
39. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
40. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systemat$)).tw,ot.
41. or/33-40
42. (comment or editorial or historical-article).pt.
43. 41 not 42
44. 32 or 43
45. 23 and 44
46. (animals not (animals and humans)).sh.
47. 45 not 46

EMBASE
1. exp Diabetes Mellitus, Type 2/
2. exp Insulin Resistance/
3. impaired glucose toleranc$.ab,ti,ot.
4. glucose intoleranc$.ab,ti,ot.
5. insulin$ resistanc$.ab,ti,ot.
6. (obes$ adj diabet$).ab,ti,ot.
7. (MODY or NIDDM or TDM2).ab,ti,ot.
8. (non insulin$ depend$ or noninsulin depend$ or noninsulin?depend$ or non insulin?depend$).ab,ti,ot.
9. ((typ$ 2 or typ$ II) adj diabet$).ab,ti,ot.
10. (diabet$ adj (typ$ 2 or typ$ II)).ab,ti,ot.
11. ((keto?resist$ or non?keto$) adj diabet$).ab,ti,ot.
12. ((adult$ or matur$ or late or slow or stabl$) adj diabet$).ab,ti,ot.
13. (insulin$ defic$ adj relativ$).ab,ti,ot.
14. pluri?metabolic$ syndrom$.ab,ti,ot.

15. or/1-14
16. exp Diabetes Insipidus/
17. diabet$ insipidus.ab,ti,ot.
18. 16 or 17
19. 15 not 18
20. exp Glucose Blood Level/
21. exp Hyperglycemia/
22. exp Glycosylated Hemoglobin/
23. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti,ot.
24. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.
25. (glycosylated adj6 h?emoglobin$).ab,ti,ot.
26. (glucos$ adj3 management$).ab,ti,ot.
27. or/20-25
28. 19 or 27
29. ((intensiv$ or conventional$ or regular or tight or usual or routin$) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti,ot.
30. 28 and 29
31. Randomized Controlled Trial/
32. exp Controlled Clinical Trial/
33. randomi?ed.ab,ti.
34. placebo$.ab,ti.
35. exp Drug Therapy/
36. randomly.ab,ti.
37. trial$.ab,ti.
38. group$.ab,ti.
39. or/31-38
40. exp meta analysis/
41. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
42. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.
43. exp Literature/
44. exp Biomedical Technology Assessment/
45. hta.tw,ot.
46. (health technology adj6 assessment$).tw,ot.
47. or/40-46
48. (comment or editorial or historical-article).pt.
49. 47 not 48
50. 39 or 49
51. 30 and 50
52. limit 51 to human

Science Citation Index Expanded
1. TS=(blood glucos* or glyc?emic* control or hyperglyc?emi* or h?emoglobin* A)
2. 2. TS=(HbA1C or Hb A or HbA 1c or HbA or A1Cs)
3. 3. TS=(glycosylated SAME h?emoglobin*)
4. 4. TS=(glucos* SAME management*)
5. 5. #4 OR #3 OR #2 OR #1
6. 6. TS=(MODY or NIDDM or T2DM)

7. 7. TS=(non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*)
8. 8. TS=(diabet* SAME (typ* 2 or typ* II))
9. 9. TS=(diabet* SAME (keto*resist* or non*keto*))
10. 10. TS=((onset SAME (late or adult* or matur* or slow or stabl*)) and diabet*)
11. 11. #10 OR #9 OR #8 OR #7 OR #6
12. 12. #11 NOT TS=(diabet* insipidus)
13. 13. #12 OR #5
14. 14. TS=((intensi* or tight or conventional* or regular or usual or routin* or standard) SAME (control* or therap* or treatment* or intervention* or management*))
15. 15. #14 AND #13
16. 16. TS=(random* OR blind* OR placebo* OR group*)
17. 17. TS=(animal* NOT (animal* AND human*))
18. 18. #16 NOT #17
19. 19. #18 AND #15

LILAC

1. (Blood Glucose or Hyperglycemia or hemoglobin A, glycosylated or Diabetes mellitus) [Subject descriptor]
2. and
3. 2. (control$ or management) [Palavras]
4. and
5. 3. (random$ or placebo$ or trial or group$) [Palavras]

CINAHL

1. MM "Blood Glucose"
2. MM "Glycemic Control"
3. MM "Hyperglycemia+"
4. MM "Hemoglobin A, Glycosylated"
5. TI (blood glucos* OR hyperglyc?emi* OR h?emoglobin A) or AB (blood glucos* OR hyperglyc?emi* OR h?emoglobin A)
6. TI (HbA1C or Hb A or HbA 1c or HbA or A1Cs) or AB (HbA1C or Hb A or HbA 1c or HbA or A1Cs)
7. TI glycosylated N6 h?emoglobin* or AB glycosylated N6 h?emoglobin*
8. TI glucos* N3 management* or AB glucos* N3 management*
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. MM "Diabetes Mellitus, Non-Insulin-Dependent"
11. TX Diabetes Complications
12. TX MODY or NIDDM or T2DM
13. TX non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend
14. TX diabet* AND (typ* 2 or typ* II)
15. TX diabet* AND (keto*resist* or non*keto*)
16. TI (onset AND (late or adult* or matur* or slow or stabl*)) and TI diabet*
17. AB (onset N3 (late or adult* or matur* or slow or stabl*)) and AB diabet*
18. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19. MM "Diabetes Insipidus"
20. TX diabet* insipidus
21. #19 or #20

22. #18 NOT #21
23. #9 or #22
24. TI (control* AND (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (control* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
25. TI (therap* AND (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (therap* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
26. TI (treatment* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (treatment* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
27. TI (intervention* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (intervention* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
28. TI (management* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard)) or AB (management* N3 (intensi* or tight or conventional* or regular or usual or routin* or standard))
29. #24 or #25 or #26 or #27 or #28
30. #23 and #29
31. TX random* OR blind* OR placebo* OR group*
32. TX animal* NOT (animal* AND human*)
33. #31 NOT #32
34. #30 and #33

Appendix 2. Description of bias assessment

Risk of bias components based on the Cochrane risk of bias tool classification:

Sequence generation
- Low risk of bias, if the allocation sequence was generated by a computer or a random number table or similar.
- Uncertain risk of bias, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- High risk of bias, if a system involving dates, names, or admittance number was used for the allocation of patients (quasi-randomised). Such trials were not found, but would have been excluded.

Allocation concealment
- Low risk of bias, if the allocation of patients involved a central independent unit, on-site locked computer, or consecutively numbered sealed envelopes.
- Uncertain risk of bias, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- High risk of bias, if the allocation sequence was known to the investigators, who assigned participants or if the study was quasi-randomised. Such trials were not found, but would have been excluded.

Blinding
It was not possible to blind the health-care provider and patients in the treatment groups. Blinding was therefore considered adequate if the outcome assessors were blinded, although we were aware of the fact that even such trials may be subject to bias.
- Low risk of bias, if the outcome assessors were blinded and the method of blinding was described.
- Uncertain risk of bias, if the outcome assessors were blinded and the method of blinding was not described.
- High risk of bias, if the outcome assessors were not blinded.

Incomplete data outcomes
- Low risk of bias, if it was clearly described if there were any post-randomisation drop-outs or withdrawals and the reason for these drop-outs was described.
- Uncertain risk of bias, if it was not clear whether there were any drop-outs or withdrawals or if the reasons for these drop-outs were not clear.
- High risk of bias, if the reasons for missing data were likely to be related to true outcomes; (1) 'as-treated' analysis were performed, (2) potentially inappropriate application of simple imputation, (3) potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting
- Low risk of bias, if all the pre-defined (primary and secondary) outcomes mentioned in the trial´s protocol or in the design article were reported and the reporting had been done in the pre-specified way.

- Uncertain risk of bias, if there was insufficient information to assess whether the risk of selective outcome reporting was present.
- High risk of bias, if not all the pre-specified outcomes were reported or if the primary outcomes were changed or if some of the important outcomes were incompletely reported.

Other Bias

Sponsor bias
- Low risk of bias, if the trial was unfunded or was not funded by an instrument or equipment or drug manufacturer.
- Uncertain risk of bias, if the source of funding was not clear.
- High risk of bias, if the trial was funded by an instrument or equipment or drug manufacturer.

Academic bias
- Low risk of bias, if the author of the trial had not conducted previous trials addressing the same interventions.
- Uncertain risk of bias, if it was not clear if the author had conducted previous trials addressing the same interventions.
- High risk of bias, if the author of the trial had conducted previous trials addressing the same interventions.

Besides investigating each bias domain, we also evaluated the overall risk of bias. When sequence generation, allocation concealment, and blinding were judged adequately, the trial was classified as a trial with low-risk of bias.

Appendix 3. Definitions or Reporting in Trials

Trial	Type 2 diabetes	Cardiovascular Mortality	Non-fatal myocardial infarction	Severe hypoglycaemmia
ACCORD[a], 2008[4;67-74]	American Diabetes Association criteria	Unexpected death and death due to myocardial infarction, congestive heart failure, after invasive cardiovascular interventions, arrhythmia, stroke, cardiovascular causes after non-cardiovascular surgery, other cardiovascular diseases (eg, pulmonary emboli or abdominal aortic rupture) and presumed cardiovascular death (every component described in details in study protocol p 87-88)	Prolonged ischemic symptoms > 20 minutes and or raised cardiac enzymes (Troponin T or I and/or serum creatine kinase-MB), included Q-wave myocardial infarction, non Q-wave myocardial infarction, silent myocardial infarction, probable non Q-wave myocardial infarction, myocardial infarction after coronary bypass graft surgery, myocardial infarction after cardiovascular invasive interventions and myocardial infarction after non-cardiovascular surgery	Severe hypoglycaemia is defined as hypoglycaemia with documented blood glucose < 2.8 mmol/L (50 mg/dL) or symptoms that promptly resolve with oral carbohydrate, intravenous glucose, or glucagon that require the assistance of medical or paramedical personnel
ADVANCE[b], 2008[75-78;123]	Type 2 diabetes	Death from cardiovascular causes	Non-fatal myocardial infarction	Patients with transient dysfunction of the central nervous system who were unable to treat themselves (requiring help from another person) were considered to have severe hypoglycaemia
Bagg et al, 2001[79-82]	1) Age at diagnosis > 35 years; 2) no episodes of ketoacidosis in the past; 3) insulin independence for more than 12 months or fasting plasma C-peptide > 0.21 pmol/L if duration of disease less than 12	ND[c]	Non-fatal myocardial infarction	Severe hypoglycaemia was defined as the presence of impaired consciousness requiring the help of another person, coma or seizure, and the presence of low blood glucose

	months			
Becker et al, 2003[83;84]	World Health Organisation criteria	ND	ND	ND
IDA[d], 2009[92;93]	All patients had previously known diabetes accepted as type 2 if the patient was > 35 years of age at onset of disease and without any demand of insulin during at least two years thereafter	ND	ND	Severe hypoglycaemic episodes
Jaber et al, 1996[94]	Type 2 diabetes	ND	ND	ND
Kumamoto, 2000[7;95;96]	All of the patients were diagnosed as being affected with type 2 diabetes mellitus by their characteristics of no history of ketoacidosis, negative islet cell antibody and daily urinary C-peptide excretion more than 20 pg	Sudden death (probably myocardial infarction) and death due to cerebral vascular disease	Non-fatal myocardial infarction	Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the patient required the assistance of another person and which was associated with a blood glucose level < 50 mg/dL and a prompt recovery after intravenous glucose loading
Lu et al, 2010[86]	Type 2 diabetes	ND	ND	ND
REMBO[e], 2008[85]	Type 2 diabetes	Stroke, heart failure	ND	ND
Service et al, 1983[87]	Participants were stratified as having type 1 or type 2 diabetes by basal and postprandial C-peptide values of less than 1 (type 1 diabetes mellitus) and more than 1	ND	ND	ND

	(type 2 diabetes mellitus) ng/ml			
UGDP[†], 1978[88-91]	The results of the glucose tolerance test provided the primary basis for the diagnosis of diabetes for patients admitted to the study. A sum of four glucose values from glucose tolerance test had to be equal or greater than 500 mg/100 mL	Death due to: Sudden death; defined as a death occurring within three hours of the onset of symptoms in an otherwise clinically stable patient and in a manner consistent with a cardiovascular event. Myocardial infarction; this diagnosis was made from electrocardiogram changes and changes in serum enzymes observed during the terminal course of illness, or if the events leading to death were clinically compatible with the diagnosis and autopsy findings provided evidence that an myocardial infarction was the principal cause of death. Other heart disease, included deaths due to congestive heart failure, valvular heart disease, atherosclerotic heart disease and hypertensive heart disease. Extracardiac vascular disease: cerebral vascular disease, pulmonary embolism and peripheral vascular	Patients hospitalised with a diagnosis of non-fatal myocardial infarction or changes from a less severe finding for Q/QS and T patterns on the baseline electrocardiogram to a more severe finding for these abnormalities on a follow-up electrocardiogram	ND
UKPDS[g],	Main criterion	Fatal myocardial	World Health Organisation	Hypoglycaemia

1998[1;8;97-102]	for type 2 diabetes mellitus was fasting plasma glucose > 6 mmol/L on two mornings 1-3 weeks apart	infarction, fatal stroke, death from peripheral vascular disease and sudden death	clinical criteria with associated electrocardiogram/enzyme changes or new pathological Q wave (ICD[h] 9 Code 410)	requiring third-party help or medical intervention
VA CSDM[i], 1995[103-109]	Fasting plasma C-peptide > 0.21 pmol/L	Cardiovascular death is classified as sudden death, coronary heart disease, cerebrovascular attack, or other cardiovascular causes (pulmonary embolism, cardiomyopathy, etc)	Myocardial infarctions are classified by the CER-Lab using the Minnesota code. Patients with suspected acute myocardial infarction, treated with thrombolytic therapy or with acute coronary angioplasty (within 24 hour of the onset of symptoms), who do not meet the electrocardiogram criteria, also are counted	Coma, seizure, or impaired consciousness requiring assistance
VADT[j], 2009[6;110;111]	Fasting plasma C-peptide > 0.21 pgrams per cc	In appendix listed as death caused by: Myocardial infarction, congestive heart failure, coronary revascularisation, stroke, cerebral revascularisation, complications of occlusions, peripheral revascularisation, sudden death and pulmonary embolism	Q wave in 2 consecutive leads or a new R-wave in V1 of at least 50% accompanied with motion abnormality in MUGA[k] scan or echocardiography; or ST depression over 1 mm or new T-wave in 2 consecutive leads with injury changes in creatine phosphokinase over 2 times and elevated creatine kinase-MB or troponins	Defined with as a serious adverse event ,i.e., life threatening, death, hospitalisation, disability or incapacity, cancer or other important event requiring medical intervention/treatment

[a]ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, [b]ADVANCE: Action in Diabetes and Vascular disease – PreterAx and DiamicroN MR Controlled Evaluation, [c]ND:Not defined, [d]IDA:Insulin Diabetes Angioplasty, [e]REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, [f]UGDP: University Group Diabetes Program, [g]UKPDS: United Kingdom Prospective Diabetes Study, [h]ICD: International Classification of Diseases, [i]VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, [j]VADT: Veterans Affairs Diabetes Trial, [k]MUGA scan: multiple-gated acquisition scan

Trial	Microvascular complications (composite outcome)	Retinopathy	Nephropathy
ACCORD[a], 2008[4;67-74]	Fatal or non-fatal renal failure (initiation of dialysis or end-stage renal disease, renal transplantation, or rise of serum creatinine > 291.7 µmol/L) or retinal photocoagulation or vitrectomy for diabetic retinopathy	Progression of diabetic retinopathy of at least 3 stages the Early Treatment of Diabetic Retinopathy Study scale	Composite nephropathy outcome: Doubling of serum creatinine or a 20 mL/min/1.73m^2 or decrease in estimated glomerular filtration rate, development of macroalbuminuria (albumin/creatinine ratio > 300 mg albumin per gram creatinine in random urine sample), development of renal failure (renal transplantation or initiation of dialysis or a rise in serum creatinine > 3.3 mg/dL in the absence of an acute reversible cause)
ADVANCE[b], 2008[75-78;123]	New or worsening nephropathy or retinopathy (development of proliferative retinopathy, macular edema or diabetes-related blindness, or the use of retinal photocoagulation therapy)	Progression of ≥2 steps in Early Treatment of Diabetic Retinopathy Study classification with laser coagulation therapy during follow-up as the final step in Early Treatment of Diabetic Retinopathy Study classification, including both incidence and progression of retinopathy	Development of macroalbuminuria, defined as a urinary albumin:creatinine ratio of more than 300 µg of albumin per milligram of creatinine (33.9 mg per millimole), or doubling of the serum creatinine level to at least 200 µmol/L, the need for renal-replacement therapy, or death due to renal disease
Bagg et al, 2001[79-82]	Not defined	Not defined	Macroalbuminuria
Becker et al, 2003[83;84]	Not defined	Not defined	Not defined
IDA[c], 2009[92;93]	Not defined	Not defined	Not defined
Jaber et al, 1996[94]	Not defined	Not defined	Not defined
Kumamoto, 2000[7;95;96]	Not defined	The degree of retinopathy for each patient was determined by the two eye examiners using the modified Early Treatment of Diabetic Retinopathy Study classification with a scale of 19 stages. The development and progression of retinopathy were	The patients with nephropathy were divided into three stages depending on their urinary albumin excretion: normoalbuminuria (< 30 mg/24 hour), microalbuminuria (30-300 mg/24 hour), or albuminuria (> 300 mg/24 hour). Reported for the primary prevention population as

		defined as a change of at least two steps up from stage 1 in the primary prevention population and as a change of two or more steps up from stages 2 to 5 in the secondary intervention population	participants developing nephropathy. Reported for the secondary intervention population as participants progressing to nephropathy
Lu et al, 2010[86]	Not defined	Not defined	World Health Organization 1999 criteria
REMBO[d], 2008[85]	Not defined	Not defined	Not defined
Service et al, 1983[87]	Not defined	Not defined	Not defined
UGDP[e], 1975[88-91]	Not defined	Mild retinal abnormalities: hard exudates, soft exudates, and/or haemorrhages or microaneurysms	Urine protein ≥ 1 gm/L.
UKPDS[†], 1998[1;8;97-102]	Retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure	Retinopathy was defined as one microaneurysm or more in one eye or worse retinopathy, and progression of retinopathy as a two-step change in Early Treatment of Diabetic Retinopathy Study grade	Two-fold plasma-creatinine increase (ICD 9: 250.3 and 585 to 586)
VA CSDM[g], 1995[103-109]	Not defined	Seven-field fundus photograph and ophthalmological examination The first two photographic end points is the presence of at least 3 counts of microaneurysms for the two eyes, and the second is the worsening of retinopathy as defined by a progression of two or more levels in the final Early Treatment of Diabetic Retinopathy Study	Overt nephropathy was defined as an albumin:creatinine ratio > 0.30

		scale	
VADT[h], 2009[6;110;111]	Retinopathy, nephropathy, and neuropathy	The 23-point Early Treatment Diabetic Retinopathy Study grading scale was used to define progression to new proliferative diabetic retinopathy. The progression of retinopathy was defined as a 2-point increase on the scale	Severe nephropathy was defined as a doubling of the serum creatinine level, a creatinine level of more than 3 mg per deciliter (265 µmol/L), or a glomerular filtration rate of less than 15 ml per minute

[a]ACCORD: Action to Control Cardiovascular Risk in Diabetes Study, [b]ADVANCE: Action in Diabetes and Vascular disease – PreterAx and DiamicroN MR Controlled Evaluation, [c]ND:Not defined, [d]IDA:Insulin Diabetes Angioplasty, [e]REMBO: Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure, [f]UGDP: University Group Diabetes Program, [g]UKPDS: United Kingdom Prospective Diabetes Study, [h]ICD: International Classification of Diseases, [i]VACSDM: Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, [j]VADT: Veterans Affairs Diabetes Trial,