List of Appendices

Appendix 1 | Appraisal of randomized clinical trials using the Cochrane risk-of-bias tool[13]							
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Mathiesen,[29] 2012	Low	Unclear	Low	Low	Low	Unclear	High
Renard,[30] 2011	Unclear	Unclear	Low	Low	Low	Unclear	High
Zachariah,[31] 2011	Unclear	Unclear	Low	Low	Low	Low	Unclear
Bolli,[35] 2009	Unclear	Unclear	Low	Low	High	Unclear	High
Heller,[32] 2009	Low	Low	Low	Low	Low	Unclear	High
Le Floch,[33] 2009	Low	Low	Low	Low	Low	Low	High
Bartley,[34] 2008	Low	High	Low	Low	High	Unclear	High
Chatterjee,[36] 2007	Unclear	Low	Low	Low	Low	Unclear	Unclear
Pesic,[37] 2007	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
Philippo,[38] 2007[a]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Pieber,[39] 2007	Low	Unclear	Low	Low	Low	Unclear	High
Radman,[40] 2007	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
Ashwell,[41] 2006	Low	Unclear	Low	Low	Low	Unclear	Unclear
Kolendorf,[42] 2006	Unclear	Unclear	Low	Low	Low	Unclear	High
De Leeuw,[43] 2005	Unclear	Unclear	Low	Unclear	Low	Unclear	High
Fulcher,[44] 2005	Unclear	Unclear	Low	Low	High	Unclear	Unclear
Pieber,[45] 2005	Low	Unclear	Low	Low	Unclear	Unclear	High
Home,[46] 2004	Unclear	Low	Low	Low	Low	Unclear	High
Porcellati,[47] 2004	Low	Low	Low	Low	Low	Unclear	Low
Russell-Jones,[48] 2004	Low	High	Low	Low	High	Low	Unclear
Standl,[49] 2004	Unclear	Unclear	Low	Low	High	Unclear	High
Rossetti,[50] 2003	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
Vague,[51] 2003	Low	Unclear	Low	Low	Low	Unclear	High
Pieber,[52] 2000	Unclear	Unclear	Low	Low	Low	Unclear	High
Raskin,[53] 2000	Low	High	Low	Low	Low	Unclear	High
Ratner,[54] 2000 (CR: Hershon,[66] 2004)	Unclear	Unclear	Low	Low	High	Unclear	High
Rosenstock,[55] 2000	Unclear	Unclear	Low	Low	Low	Unclear	Unclear

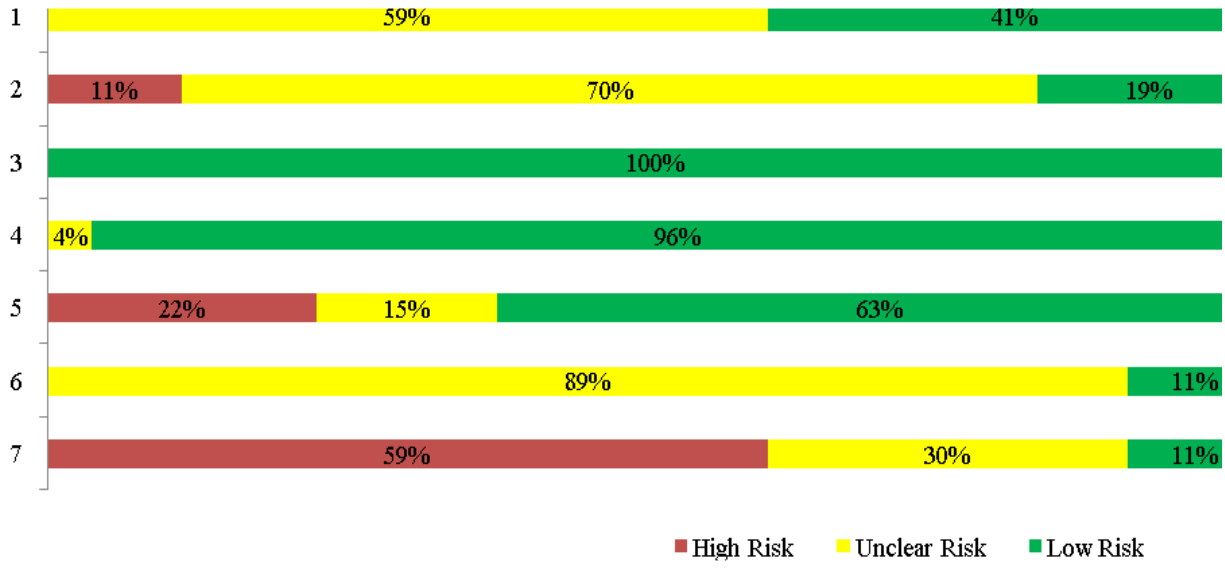
Items:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other bias

CR - companion report. High - high risk. Low - low risk. Unclear - unclear risk.

[a]Unpublished data.

Appendix 2 | Aggregate of Cochrane risk-of-bias results[13]



Items:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other bias

Appendix 3 | Appraisal of reporting of adverse drug reactions, according to McHarm tool[15]															
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Mathiesen,[29] 2012	Y	N	N	Y	N	N	N	N	N	N	Y	Y	Y	Y	N
Renard,[30] 2011	Y	N	Y	Y	N	N	N	N	N	N	Y	Y	Y	N	N
Zachariah,[31] 2011	N	N	N	N	Y	N	N	N	Y	N	N	Y	N	N	N
Heller,[32] 2009	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	Y	Y
Le Floch,[33] 2009	N	N	Y	N	N	Y	N	N	Y	N	Y	N	N	Y	N
Bartley,[34] 2008	Y	N	N	Y	N	N	N	N	N	N	N	Y	Y	N	N
Chatterjee,[36] 2007	Y	N	Y	N	Y	N	Y	N	U	N	U	U	U	N	Y
Philippo,[38] 2007[a]	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
Pieber,[39] 2007	Y	N	Y	N	N	N	N	N	Y	N	U	Y	Y	Y	U
Ashwell,[41] 2006	Y	N	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	Y
Kolendorf,[42] 2006	Y	N	Y	Y	N	Y	N	N	N	N	Y	Y	Y	Y	Y
De Leeuw,[43] 2005	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	N	Y
Fulcher,[44] 2005	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	Y	N
Pieber,[45] 2005	Y	N	N	Y	N	N	N	N	N	N	Y	Y	Y	Y	N
Home,[46] 2004	Y	N	N	N	N	N	N	N	N	N	N	Y	N	N	N
Porcellati,[47] 2004	U	N	N	N	N	N	N	N	Y	N	U	Y	Y	U	N
Russell-Jones,[48] 2004	Y	Y	N	N	N	N	N	N	Y	N	Y	Y	Y	Y	N
Standl,[49] 2004	Y	N	N	N	Y	Y	N	N	Y	N	N	Y	Y	N	N
Vague,[51] 2003	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	N
Raskin,[53] 2000	Y	N	Y	Y	N	N	N	N	Y	N	U	Y	Y	Y	N
Ratner,[54] 2000 (CR: Hershon,[66] 2004)	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N

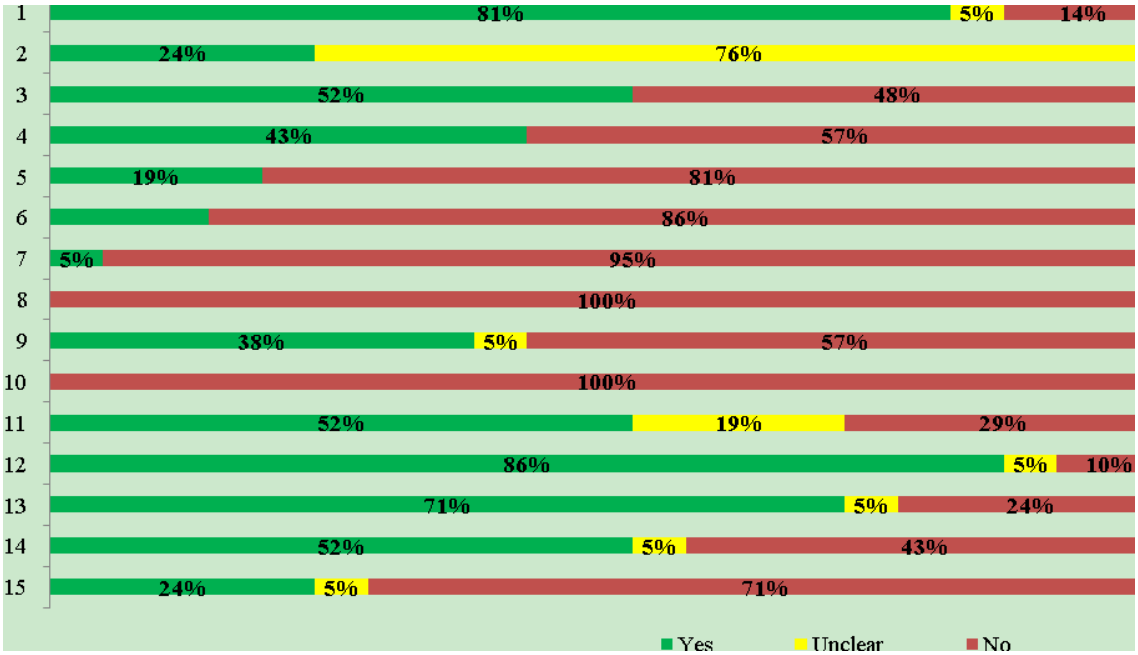
Items:

1. Were harms pre-defined?
2. Were serious events defined?
3. Were severe events defined?
4. Were the numbers of deaths in each study specified?
5. Was the mode of hard collection specified as active?
6. Was the mode of harms collected as passive?
7. Did the study specify who collected the harms?
8. Did the study specify training of background of who ascertained the harms?
9. Did the study specify the timing and frequency of collection of harms?
10. Did the authors use standard scales or checklists for harms?
11. Did the authors specify if the harms reported encompass all the events collected or a selected sample?
12. Was the number of participants that withdrew or were lost to follow up specified for each study group?
13. Was the total number of participants affected by harms specified for each study arm?
14. Did the author(s) specify the number for each type of harmful event for each study group?
15. Did the author(s) specify the type of analyses undertaken for harms data?

N – no. U – unclear. Y - yes.

[a]Unpublished data.

Appendix 4 | Aggregate of appraisal of reporting of adverse drug reactions, according to McHarm tool[15]



Items:

1. Were harms pre-defined?
2. Were serious events defined?
3. Were severe events defined?
4. Were the numbers of deaths in each study specified?
5. Was the mode of hard collection specified as active?
6. Was the mode of harms collected as passive?
7. Did the study specify who collected the harms?
8. Did the study specify training of background of who ascertained the harms?
9. Did the study specify the timing and frequency of collection of harms?
10. Did the authors use standard scales or checklists for harms?
11. Did the authors specify if the harms reported encompass all the events collected or a selected sample?
12. Was the number of participants that withdrew or were lost to follow up specified for each study group?
13. Was the total number of participants affected by harms specified for each study arm?
14. Did the author(s) specify the number for each type of harmful event for each study group?
15. Did the author(s) specify the type of analyses undertaken for harms data?

Appendix 5 | Appraisal of the cohort study using the Newcastle Ottawa scale[14]

Study	1	2	3	4	5	6	7
Currie,[56] 2007	Truly representative	Same community as exposed cohort	Secure record	Yes	No confounders controlled for	Record linkage/ questionnaire	No statement

Items:

1. Representativeness of the exposed cohort
2. Selection of the non exposed cohort
3. Ascertainment of exposure
4. Demonstration that outcome of interest was not present at start of study
5. Comparability of cohorts on the basis of the design or analysis
6. Assessment of outcome
7. Adequacy of follow up of cohorts

Appendix 6 | Appraisal of cost-effectiveness studies using the Drummond tool[12]										
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Pfohl,[57] 2012	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Valentine,[58]	Y	Y	N	Y	Y	Y	NA	Y	Y	Y
Valentine,[59] 2011	Y	Y	Y	Y	C	Y	Y	Y	Y	Y
Cameron,[7] 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Greiner,[60] 2009[a]	Y	Y	C	C	C	C	Y	Y	C	C
Gschwend,[61] 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tunis,[62] 2009	Y	Y	Y	Y	C	Y	Y	Y	Y	Y
Grima,[63] 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
McEwan,[64] 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	C
Valentine,[65] 2006	Y	Y	Y	Y	C	Y	C	Y	Y	Y

Items:

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was the effectiveness of the programme or services established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
10. Did the presentation and discussion of study results include all issues of concern to users?

C - can't tell. NA - not applicable. N – no. Y - yes.

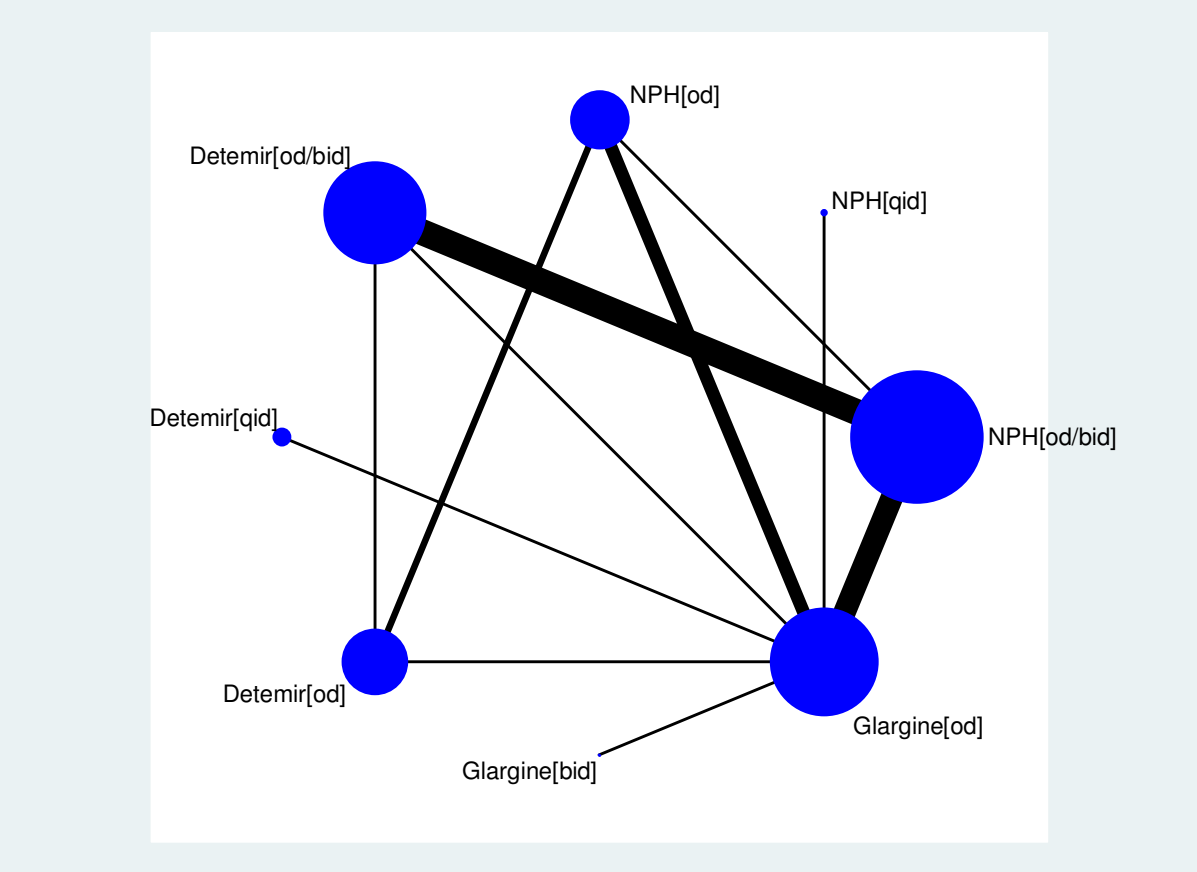
[a]Unpublished data.

Appendix 7 | Patient characteristics					
Study	**% female**	**Mean age, years (SD) [range]**	**Mean BMI (SD) [range]**	**Mean A1C (SD) [range]**	**Mean duration of T1DM, years (SD) [range]**
RANDOMIZED CLINICAL TRIALS					
Mathiesen,[32] 2012	100.0	30.1 (8.0)	24.8 (4.1)	7.0 (4.4)	12.3 (8.0)
Renard,[33] 2011	39.1	47.4 (9.2)	25.0 (3.5)	7.1 (0.7)	17.8 (9.2)
Zachariah,[34] 2011	39.1	38.8 (2.1)	28.0 (3.6)	8.2 (0.2)	20.0 (2.1)
Heller,[35] 2009	44.0	42.0 (11.4)	26.5 (4.0)	8.1 (1.1)	17.2 (11.4)
Le Floch,[36] 2009	47.5	41.5 (10.0)	25.0 (4.0)	8.5 (0.9)	16.5 (10.0)
Bartley,[37] 2008	45.3	35.0 [18.0-75.0]	24.7 [15.4-34.7]	8.3 [5.0-11.6]	13.0 [1.0-50.4]
Bolli,[38] 2008	44.6	36.3 (9.0)	23.5 (2.0)	7.9 (0.7)	13.9 (9.0)
Chatterjee,[39] 2007	41.7	42.9 (11.8)	27.0 (4.2)	8.5 (1.2)	18.2 (11.8)
Pesic,[40] 2007	45.8	28.3 (2.1)	23.1 (10.5)	NR	13.1 (2.1)
Philippo,[41] 2007[a]	43.1	40.3 (NR)	NR	8.5 (0.9)	NA
Pieber,[42] 2007	48.8	40.5 [18.0-79.0]	25.6 [16.8-35.1]	8.9 [7.6-11.9]	16.5 [1.0-57.0]
Radman,[43] 2007	42.9	36.7 (8.2)	24.4 (2.7)	8.3 (1.4)	12.1 (8.2)
Ashwell,[44] 2006	40.0	43.4 (12.1)	26.7 (4.5)	8.0 (0.9)	26.9 (12.1)
Kolendorf,[45] 2006	46.2	39.2 (10.2)	25.3 (3.5)	7.9 (0.7)	16.6 (10.2)
De Leeuw,[46] 2005	59.0	40.3 (9.9)	24.5 (3.1)	8.1 (1.1)	14.4 (9.9)
Fulcher,[47] 2005	61.0	40.5 (10.1)	26.6 (3.8)	9.5 (1.2)	17.5 (10.1)
Peiber,[48] 2005	21.0	40.1 (10.1)	25.2 (3.4)	8.1 (1.3)	14.6 (10.1)
Home,[49] 2004	46.1	40.2 (10.6)	25.2 (2.4)	8.6 (1.2)	16.6 (10.6)
Porcellati,[50] 2004	44.6	35.0 (0.3)	23.1 (0.1)	7.2 (0.2)	14.0 (0.3)
Russell-Jones,[51] 2004	35.9	40.5 (10.7)	25.2 (3.4)	8.4 (1.2)	16.9 (10.7)
Standl,[52] 2004	36.0	41.6 (9.8)	25.7 (3.2)	7.7 (1.2)	16.1 (9.8)
Rossetti,[53] 2003	47.0	32.4 (2.2)	23.1 (0.9)	6.9 (0.2)	13.6 (2.2)
Vague,[54] 2003	47.2	40.4 (10.3)	24.6 (3.3)	8.2 (1.1)	17.2 (10.3)
Pieber,[55] 2000	39.1	36.3 [18.0-70.0]	24.0 [18.6-30.3]	8.0 (0.1)	11.0 [1.0-48.0]
Raskin,[56] 2000	48.5	39.2 (11.7)	25.6 (3.7)	NR	18.6 (11.7)
Ratner,[57] 2000	49.4	38.5 (10.9)	25.8 (4.3)	7.7 (1.2)	17.4 (10.9)

Rosenstock,[58] 2000	48.1	37.5 (10.7)	24.3 (2.6)	7.9 (1.1)	16.3 (10.7)
COHORT STUDY					
Currie,[59] 2007	46.6	37.8 (NR)	25.6 (NR)	NR	NR
COST-EFFECTIVENESS STUDIES					
Pfohl,[60] 2012	47.4	34.9 (10.0)	NR	8.8 (2.3)	13.4 (NR)
Valentine,[61] 2012	NR	NR	NR	NR	NR
Valentine,[62] 2011	45.3	35.0 (12.0)	24.7 (3.7)	8.3 (1.2)	13.0 (NR)
Cameron,[7] 2009	NR	NR	NR	NR	NR
Greiner,[63] 2009[a]	NR	NR	NR	NR	NR
Gschwend,[64] 2009	45.3	35.0 (12.0)	24.7 (3.7)	8.3 (1.2)	13.0 (NR)
Tunis,[65] 2009	46.0	27.0 (NR)	23.8 (NR)	8.9 (NR)	9.0 (NR)
Grima,[66] 2007	NR	27.0 (NR)	NR	8.5 (NR)	NR
McEwan,[67] 2007	46.0	27.0 (NR)	NR	8.8 (NR)	NR
Valentine,[68] 2006	48.7	40.2 (NR)	25.2 (NR)	8.38(NR)	16.3 (NR)

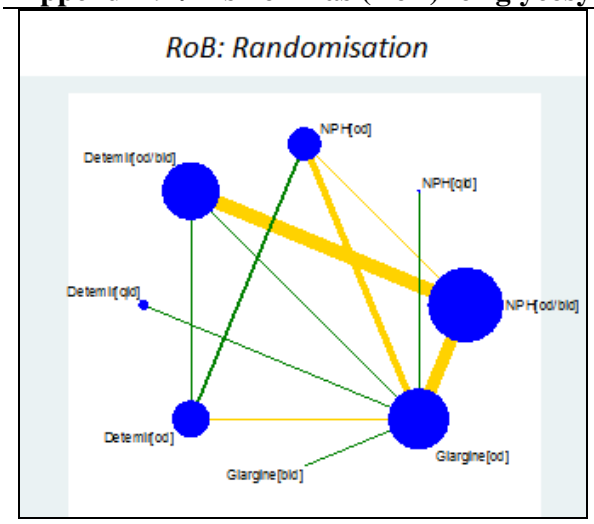
A1C - glycosylated hemoglobin (%). BMI - body mass index (kg/m^2). NR - not reported; SD - standard deviation. T1DM - type 1 diabetes mellitus.
[a]Unpublished data.

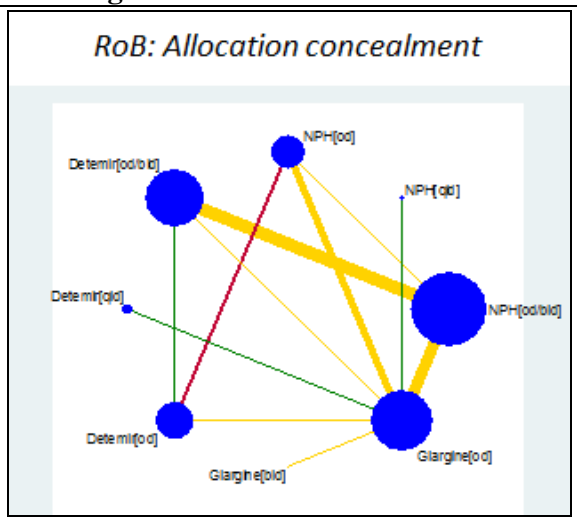
Appendix 8 | Network geometry for glycosylated hemoglobin*

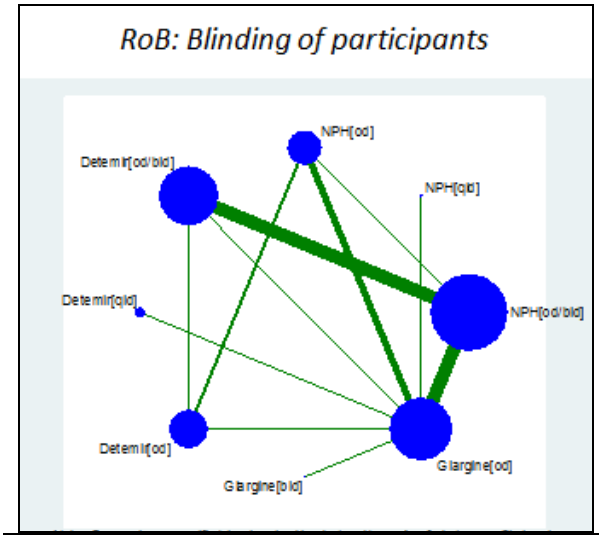


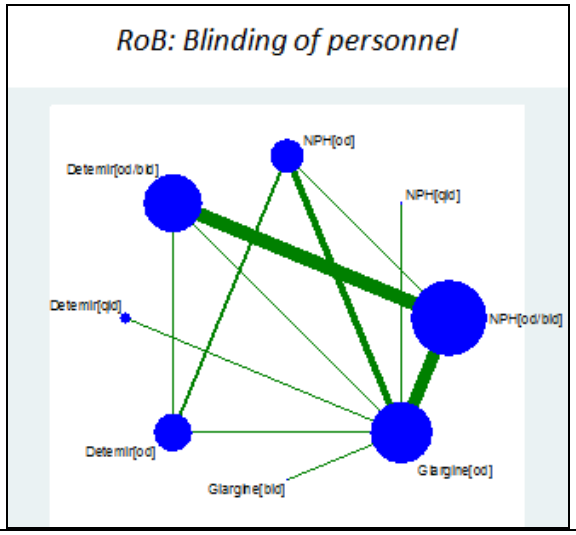
* 26 randomized clinical trials including 6,776 patients contributing to network meta-analysis for glycosylated hemoglobin. Size of the node and line indicates the number of studies included in each comparison.
Abbreviations: bid - twice daily; od - once daily; qid - four times daily.

Appendix 9 | Risk of Bias (RoB) for glycosylated hemoglobin*



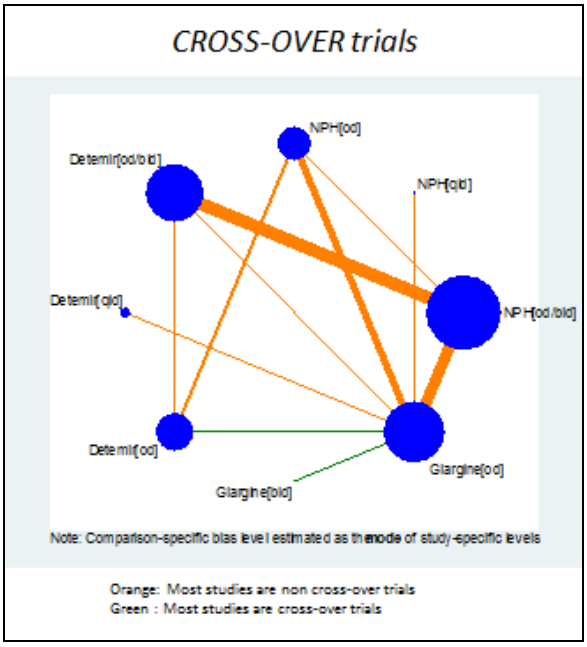


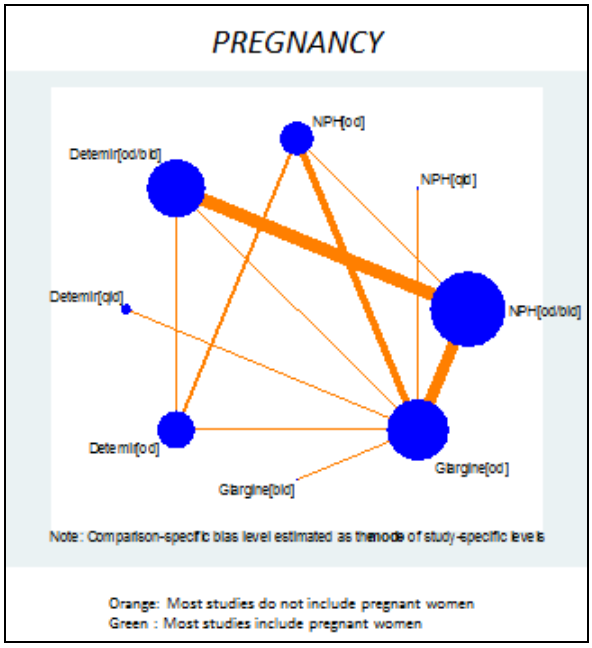


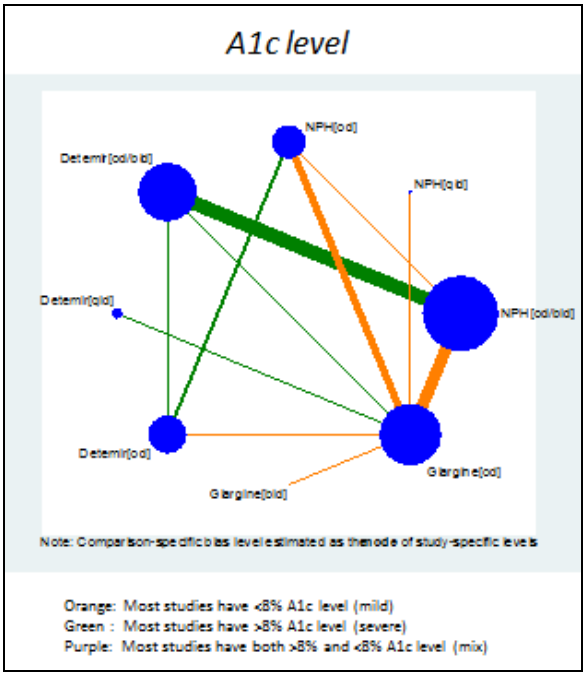


* 26 randomized clinical trials including 6,776 patients contributing to network meta-analysis for glycosylated hemoglobin. Size of the node and line indicates the number of studies included in each comparison.
Abbreviations: bid - twice daily; od - once daily; qid - four times daily.
Note: Comparison-specific bias level estimated as the node of study-specific levels. Green= low bias level; yellow= unclear bias level; red = high bias level.

Appendix 10 | Sub-group analysis for glycosylated hemoglobin

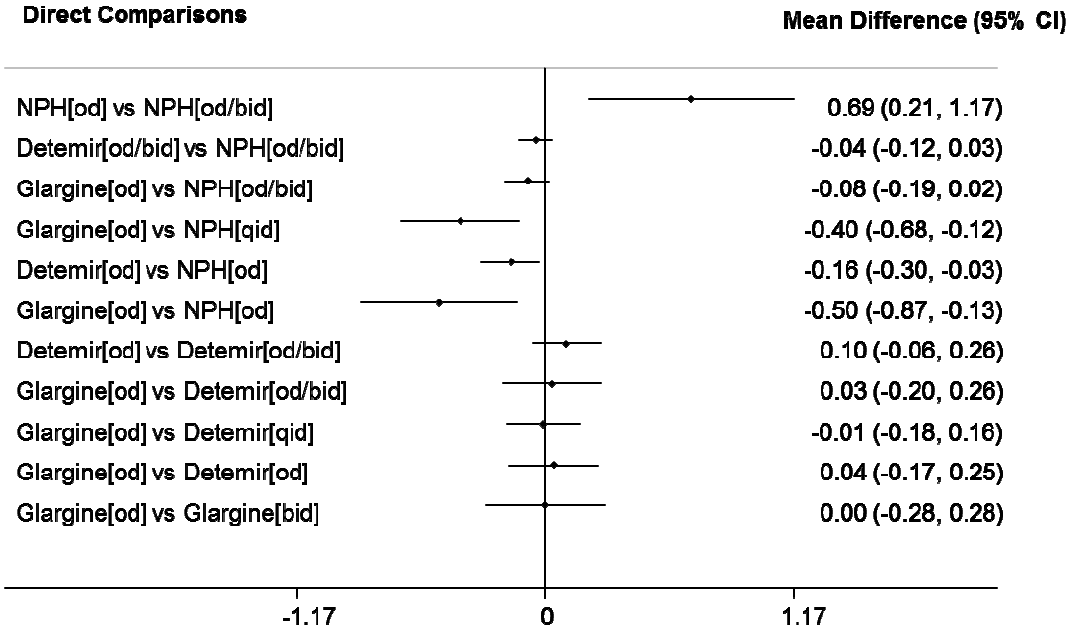






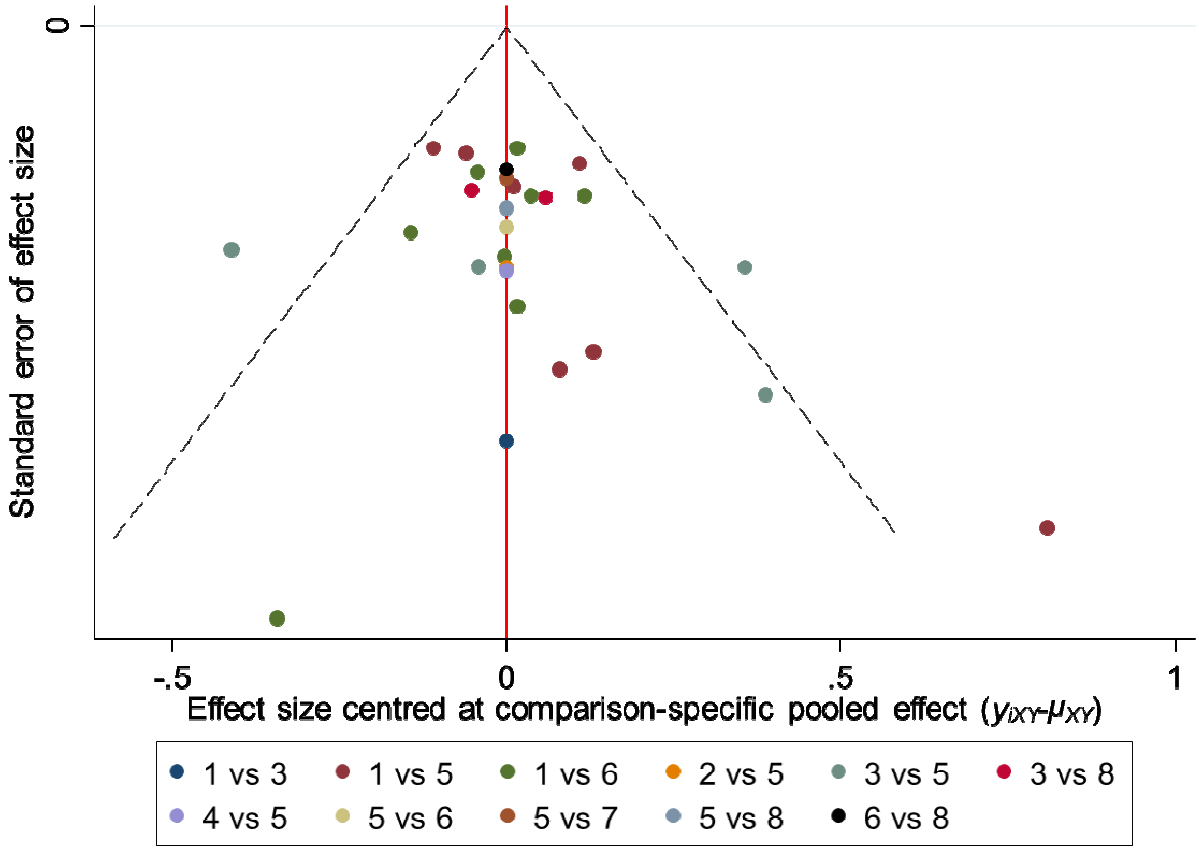
Size of the node and line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.
Note: Comparison-specific bias level estimated as the node of study-specific levels.

Appendix 11 | Random effects pairwise meta-analysis for glycosylated hemoglobin*



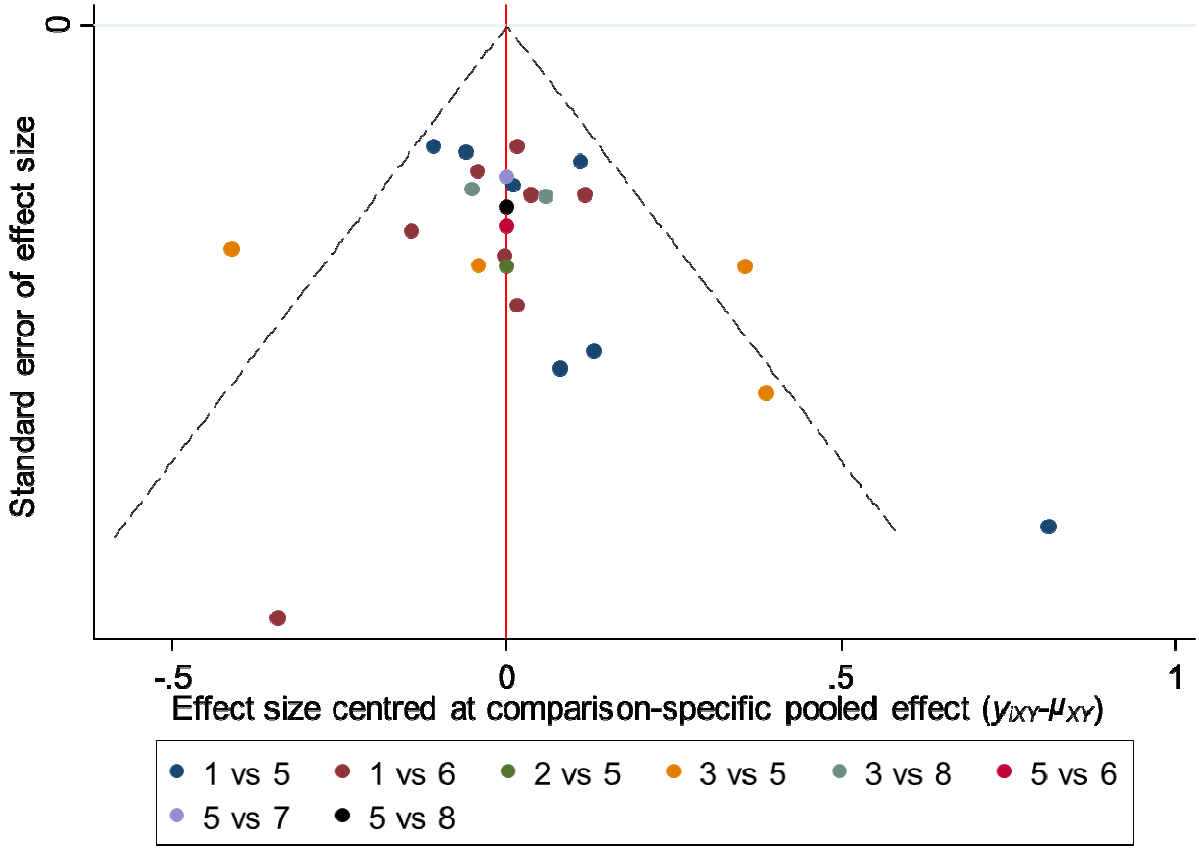
* 26 randomized clinical trials including 6,776 patients contributing to random effects pairwise meta-analysis, assuming that each comparison has a different amount of heterogeneity, for glycosylated hemoglobin. The heterogeneity has been estimated using the restricted Maximum Likelihood method.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 12 | Comparison adjusted funnel plot for glycosylated hemoglobin*



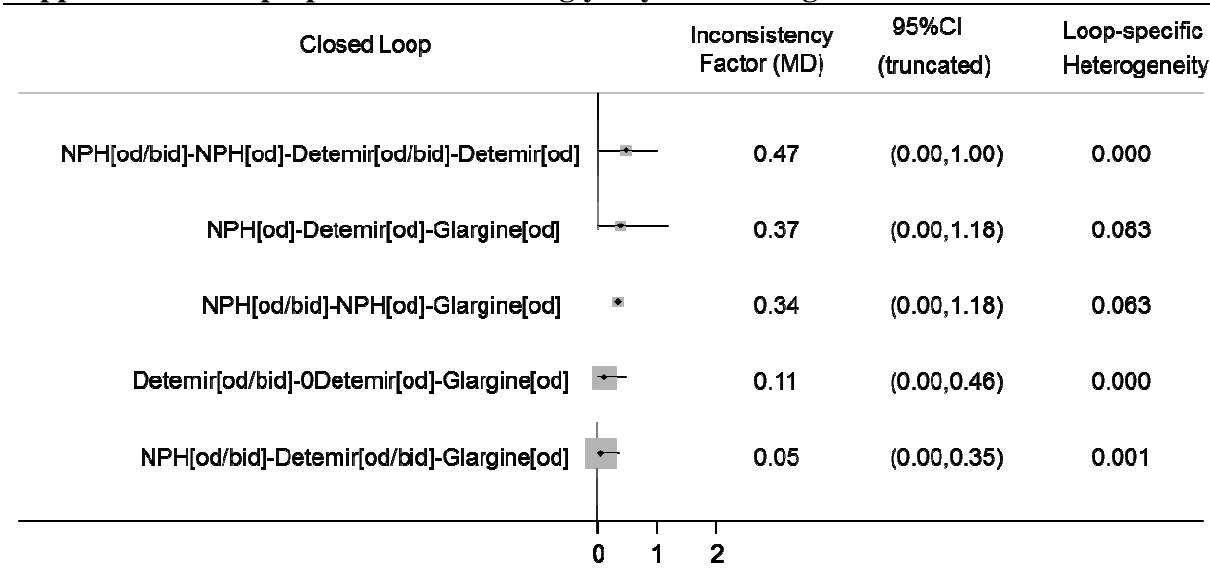
* 26 randomized clinical trials including 6,776 patients contributing to the funnel plot.

Appendix 13 | Comparison adjusted funnel plot for glycosylated hemoglobin*



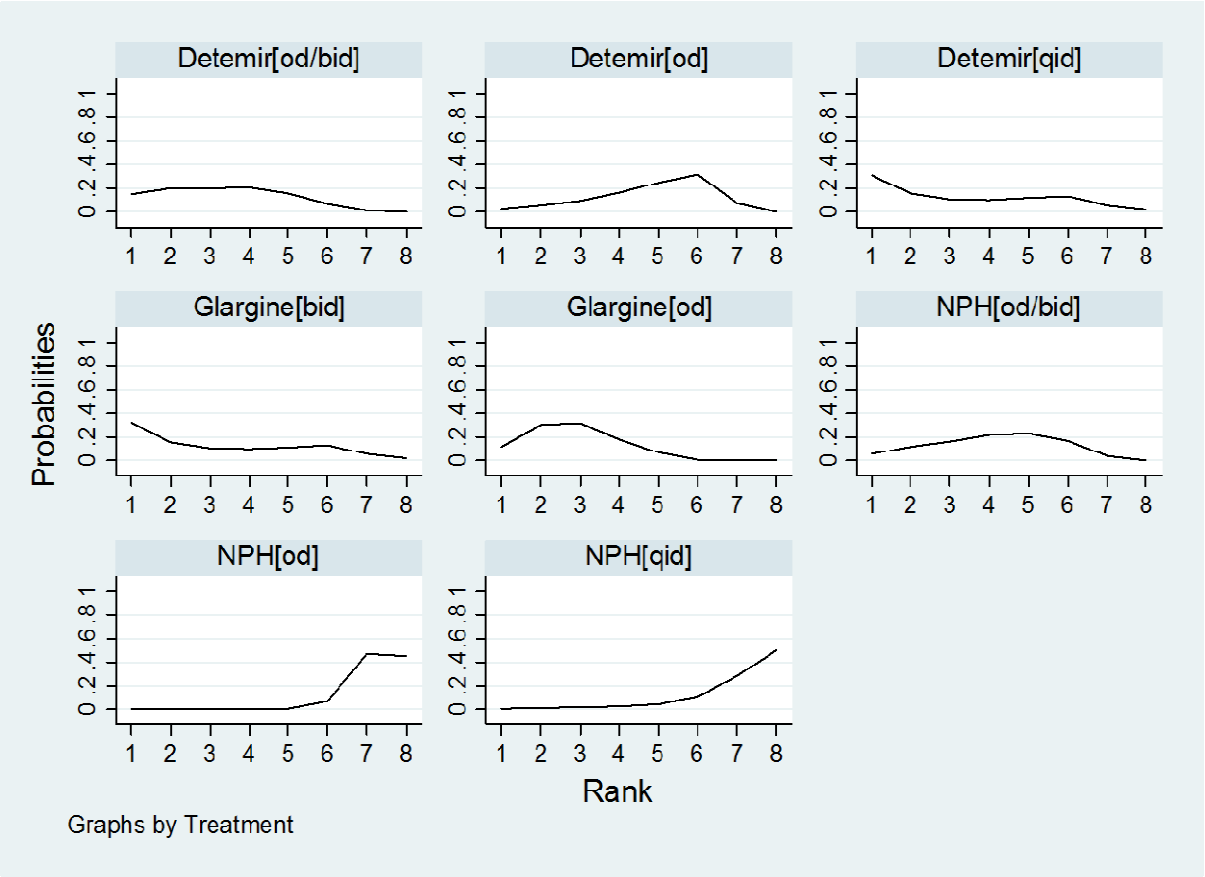
* 26 randomized clinical trials including 6,776 patients contributing to the funnel plot. Restricting only to general comparisons: NPH vs. Glargine; NPH vs. Detemir; Detemir vs. Glargine

Appendix 14 | Loop-Specific Method for glycosylated hemoglobin*



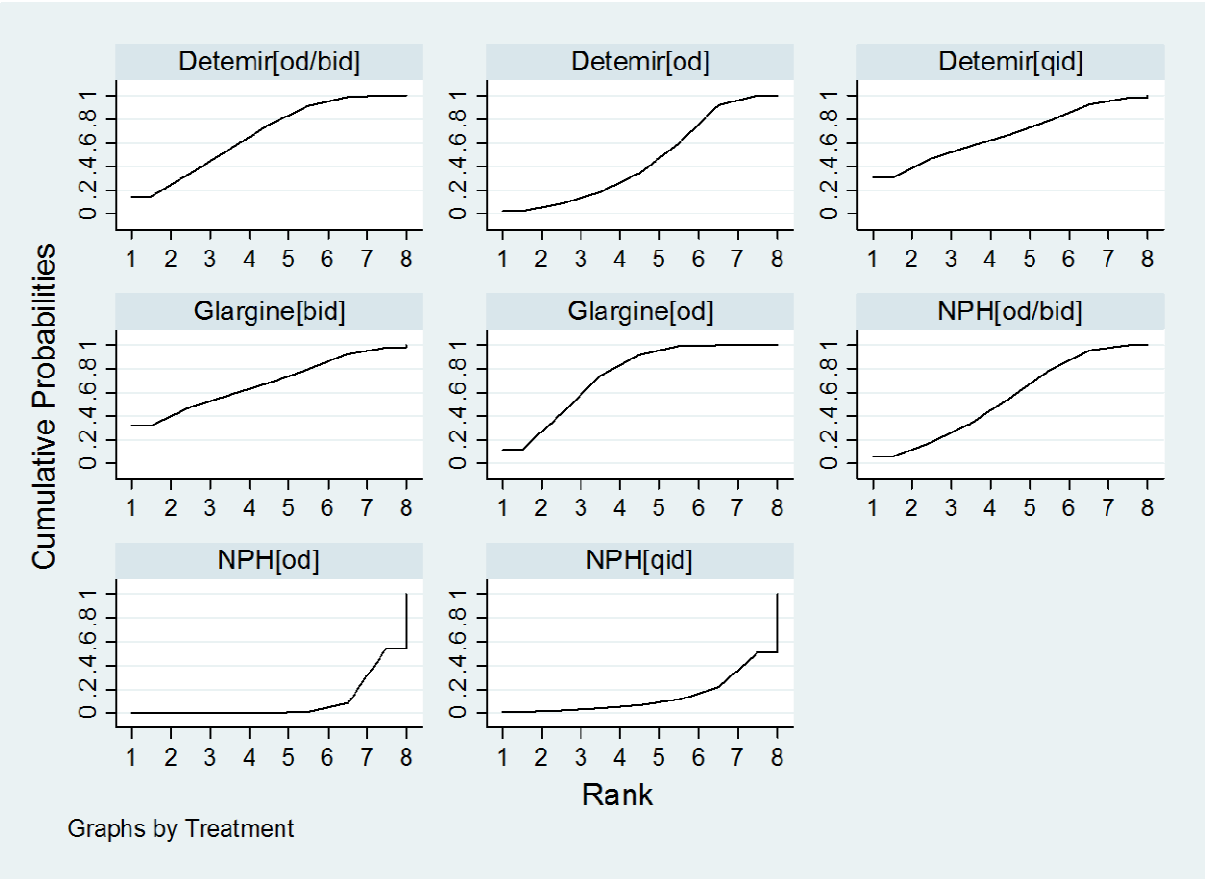
* 26 randomized clinical trials including 6,776 patients contributing to the loop-specific method.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 15 | Treatment Ranking: Probabilities of being the best for glycosylated hemoglobin*



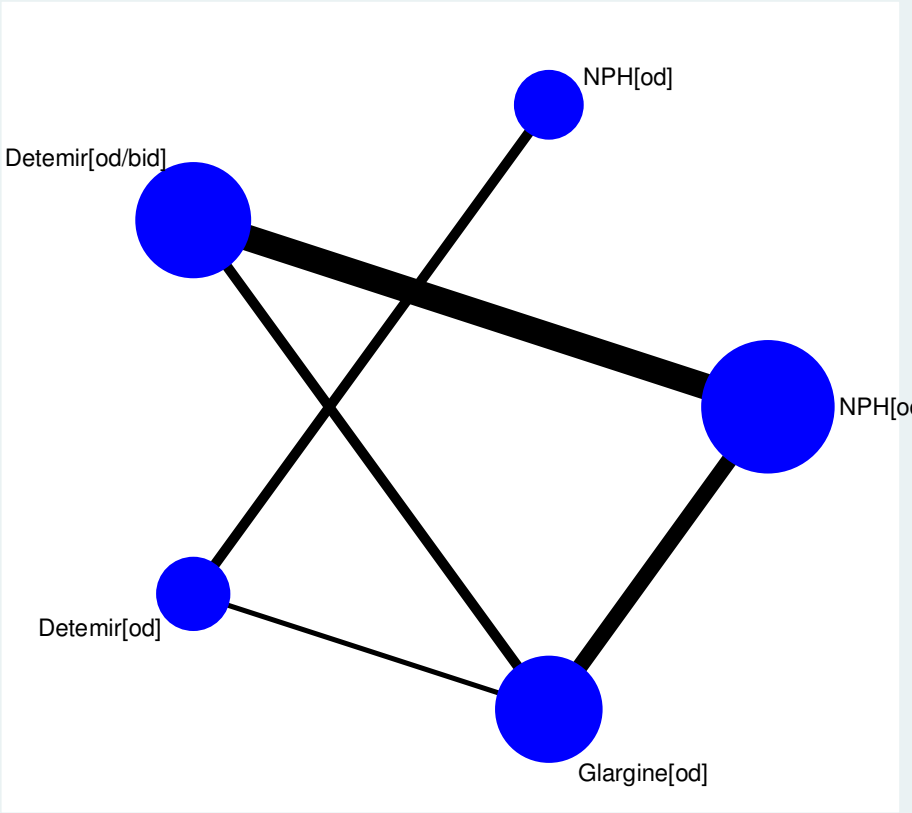
*26 randomized clinical trials including 6,776 patients contributing to the treatment ranking analysis showing the probabilities of being the best for glycosylated hemoglobin.
**Bid - twice daily. Od - once daily. SUCRA - surface under the cumulative ranking curve. Qid - four times daily.

Appendix 16 | Surface under the cumulative ranking curve for glycosylated hemoglobin*



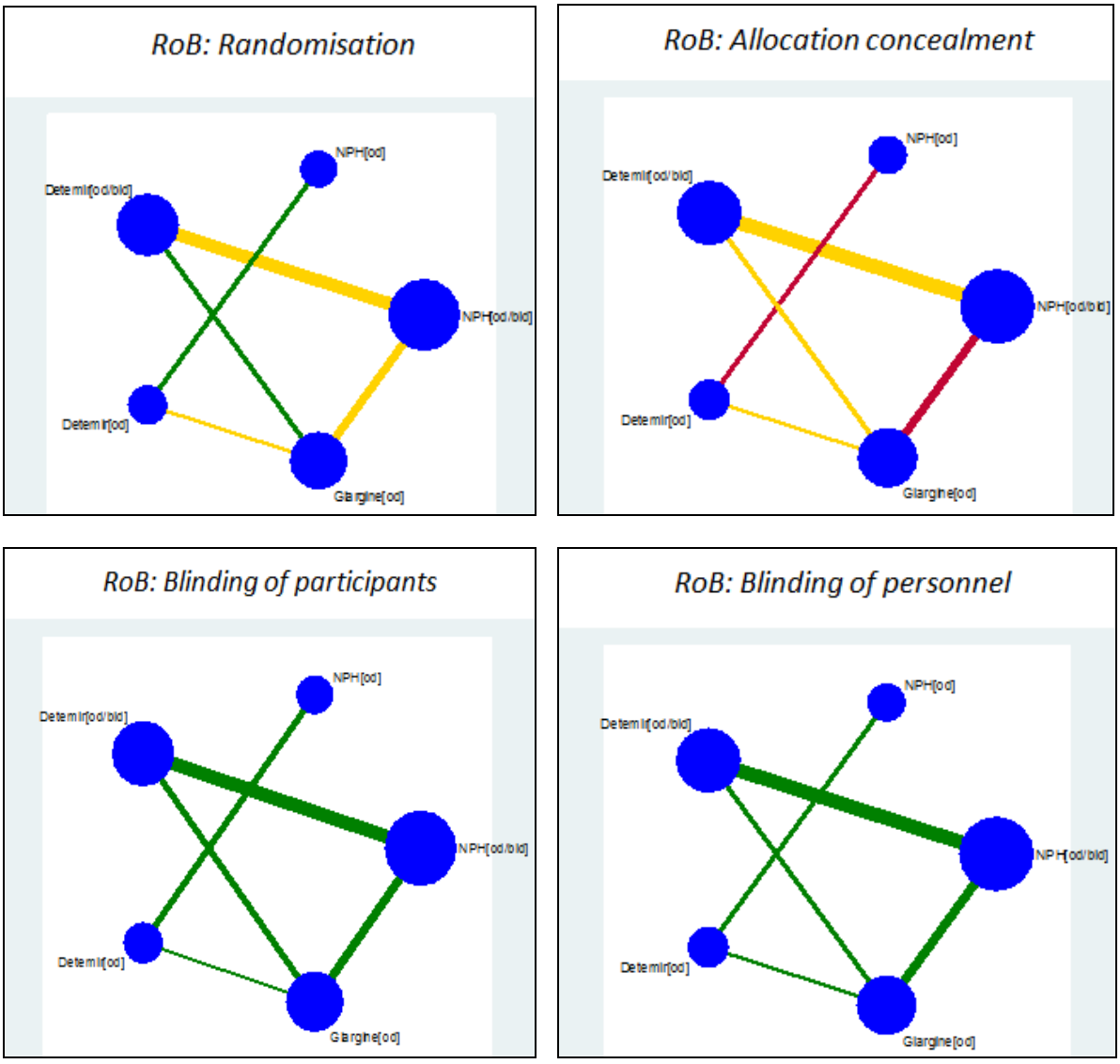
*26 randomized clinical trials including 6,776 patients contributing to the treatment ranking analysis using SUCRA approach.
**Bid - twice daily. Od - once daily. SUCRA - surface under the cumulative ranking curve. Qid - four times daily. The SUCRA allows identifying which treatment is the most effective overall and can be interpreted as 1 = treatment is certain to be the best and 0 = treatment is certain to be the worst.

Appendix 17 | Network geometry for body weight*



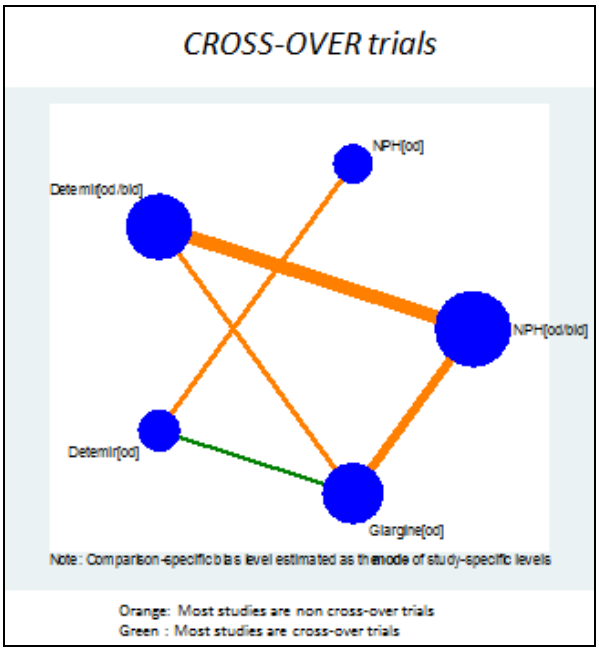
*13 randomized clinical trials including 3,396 patients contributing to network meta-analysis. Size of the node and line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.

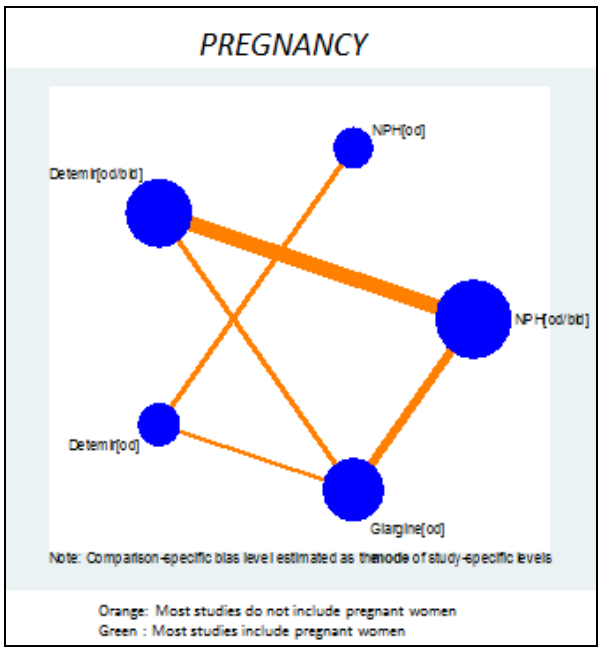
Appendix 18 | Risk of Bias (RoB) for body weight*



*13 randomized clinical trials including 3,396 patients contributing to network meta-analysis. Size of the node and line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.
Note: Comparison-specific bias level estimated as the node of study-specific levels. Green= low bias level; yellow= unclear bias level; red = high bias level.

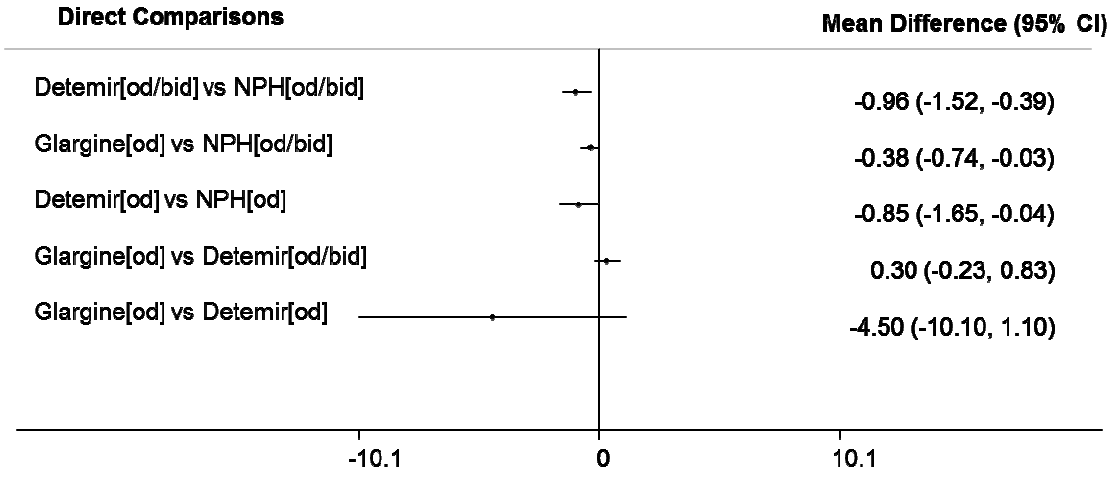
Appendix 19 | Sub-group analysis for body weight





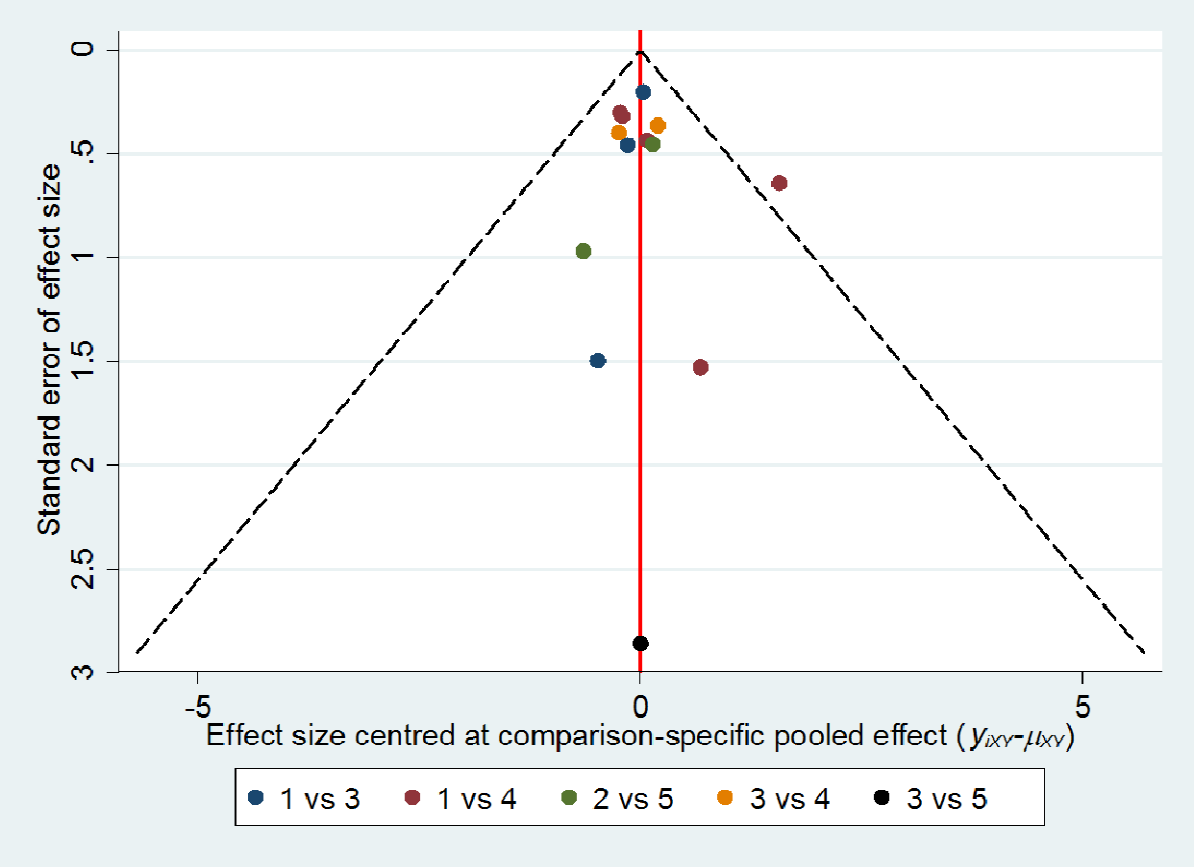
Size of the node and line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.
Note: Comparison-specific bias level estimated as the node of study-specific levels.

Appendix 20 | Random Effects Pairwise Meta-analysis for body weight*



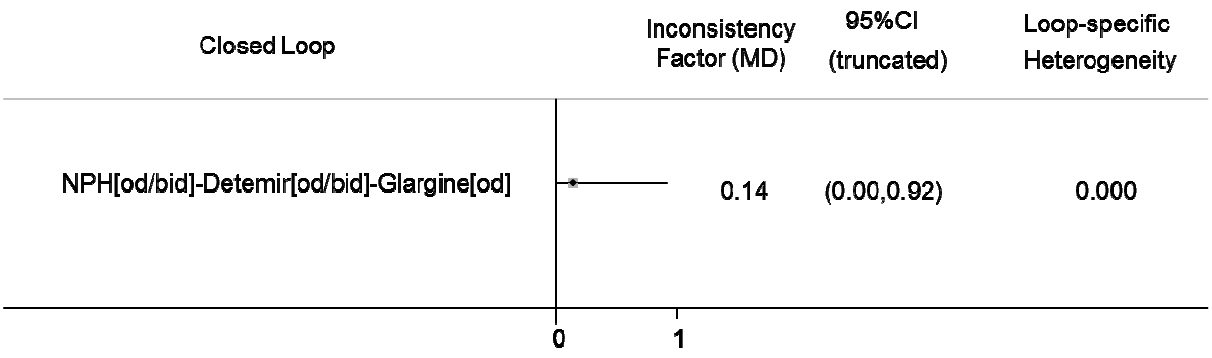
*13 randomized clinical trials including 3,396 patients contributing to the random effects pairwise meta-analysis, assuming that each comparison has a different amount of heterogeneity. The heterogeneity has been estimated using the restricted Maximum Likelihood method.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 21 | Comparison adjusted funnel plot for body weight*



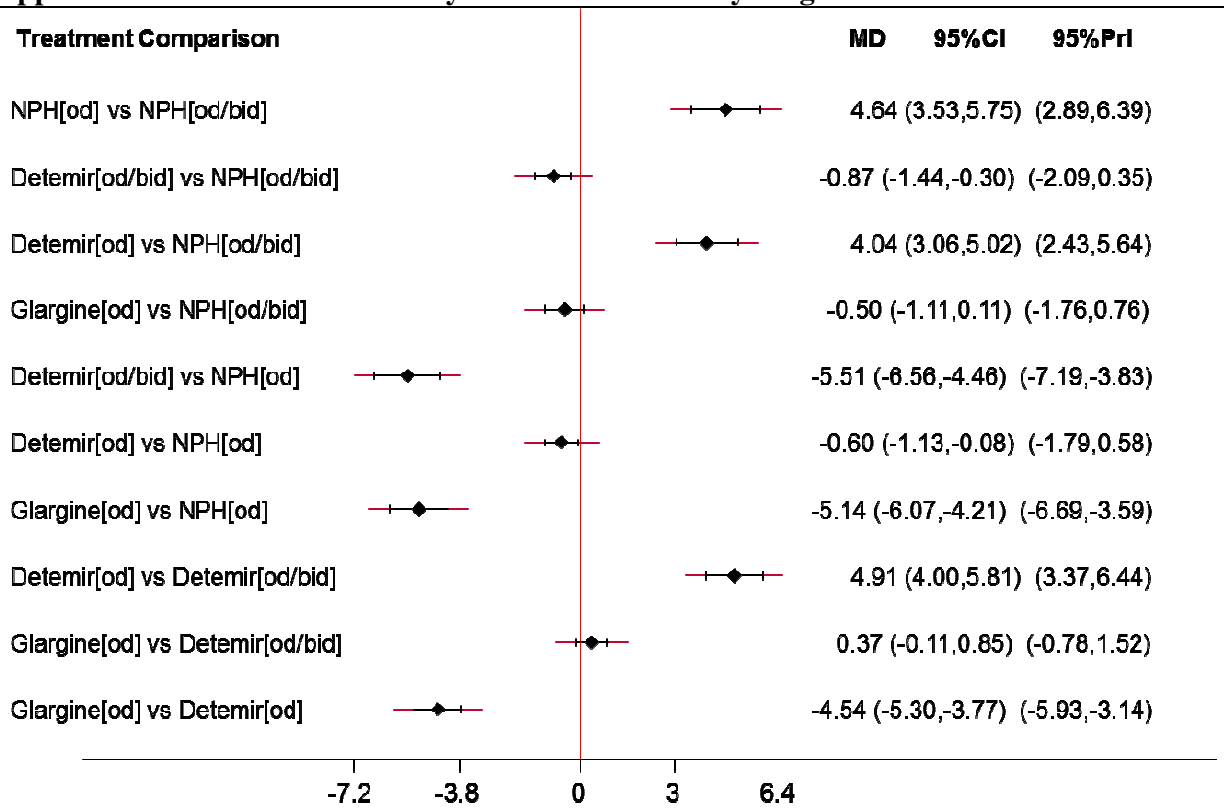
*13 randomized clinical trials including 3,396 patients contributing to the comparison adjusted funnel plot for body weight.

Appendix 22 | Loop-Specific method for body weight*



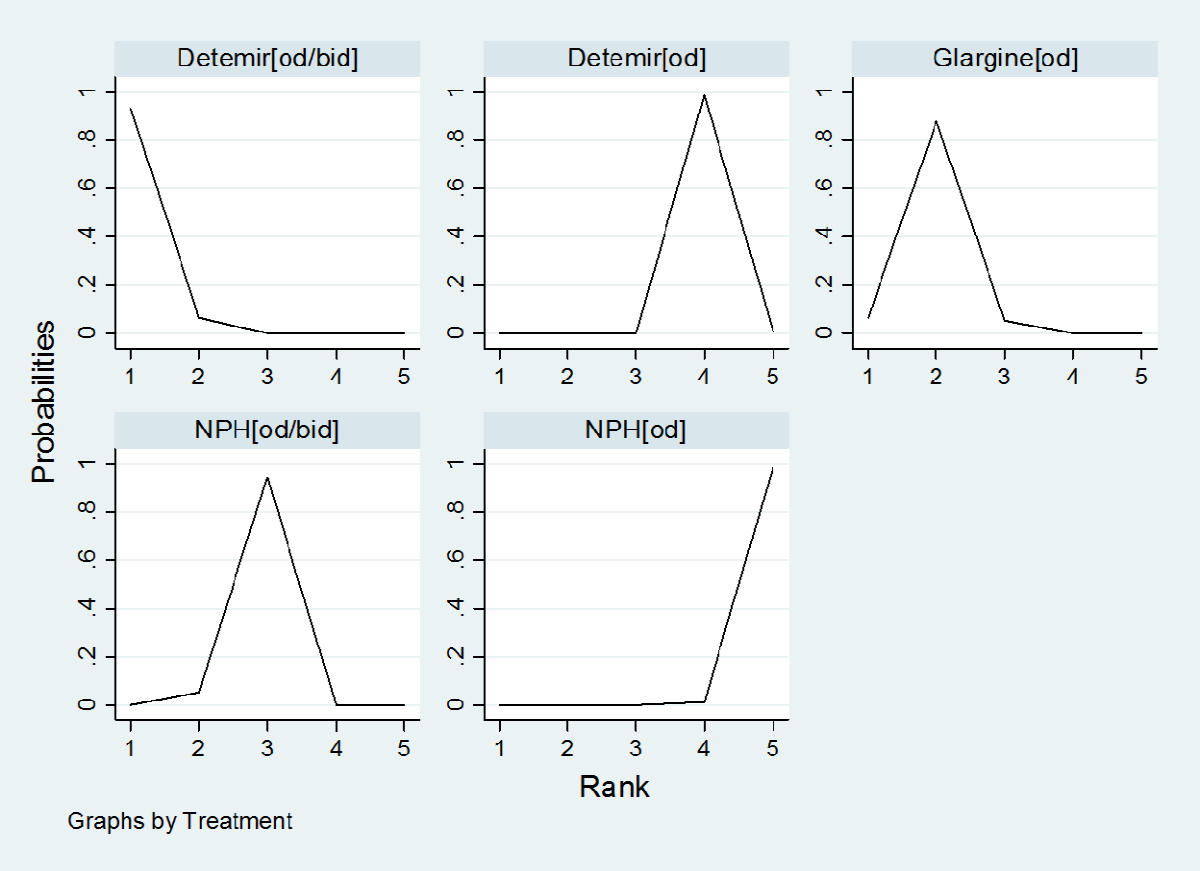
*13 randomized clinical trials including 3,396 patients contributing to the loop-specific method for body weight.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 23 | Network Meta-analysis estimates for body weight*



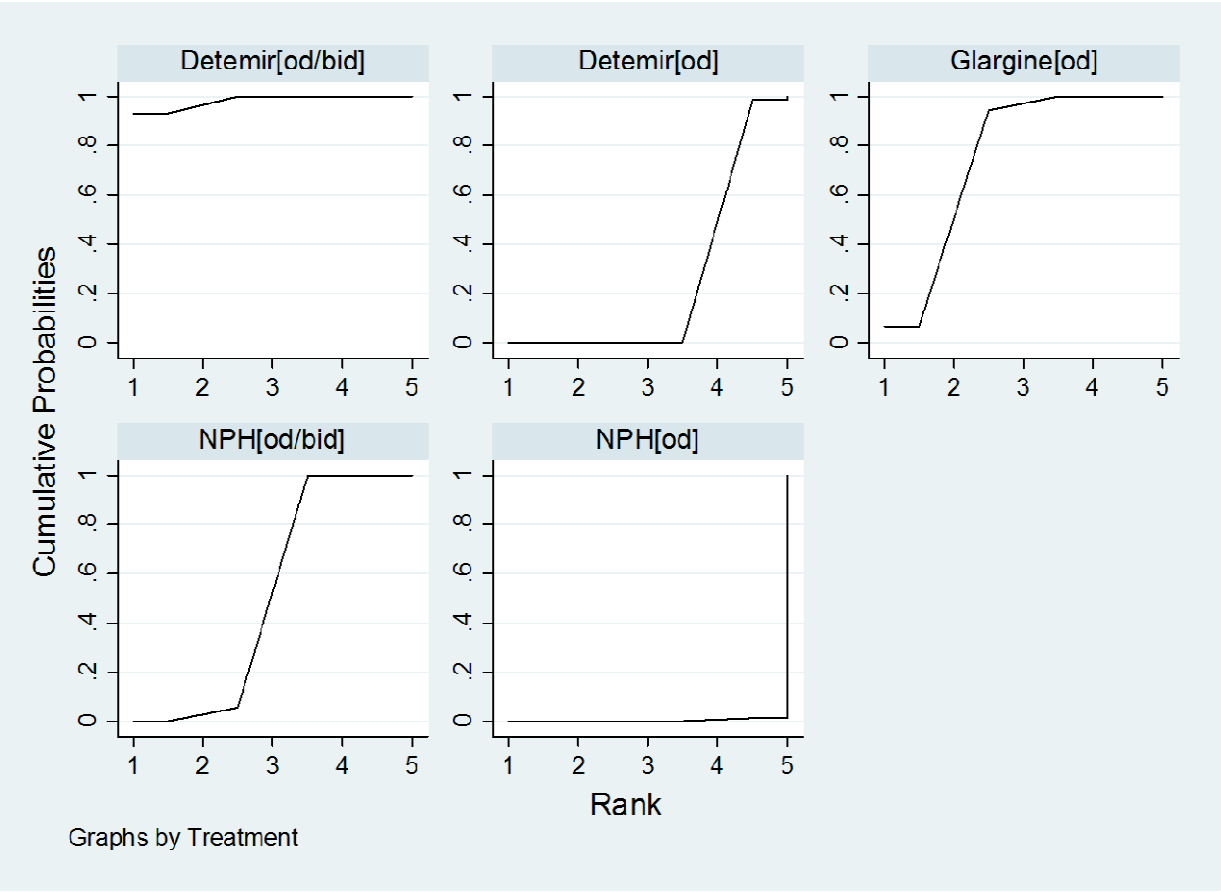
*13 randomized clinical trials including 3,396 patients contributing to the network meta-analysis estimates.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 24 | Treatment Ranking: Probabilities of being the best for body weight*



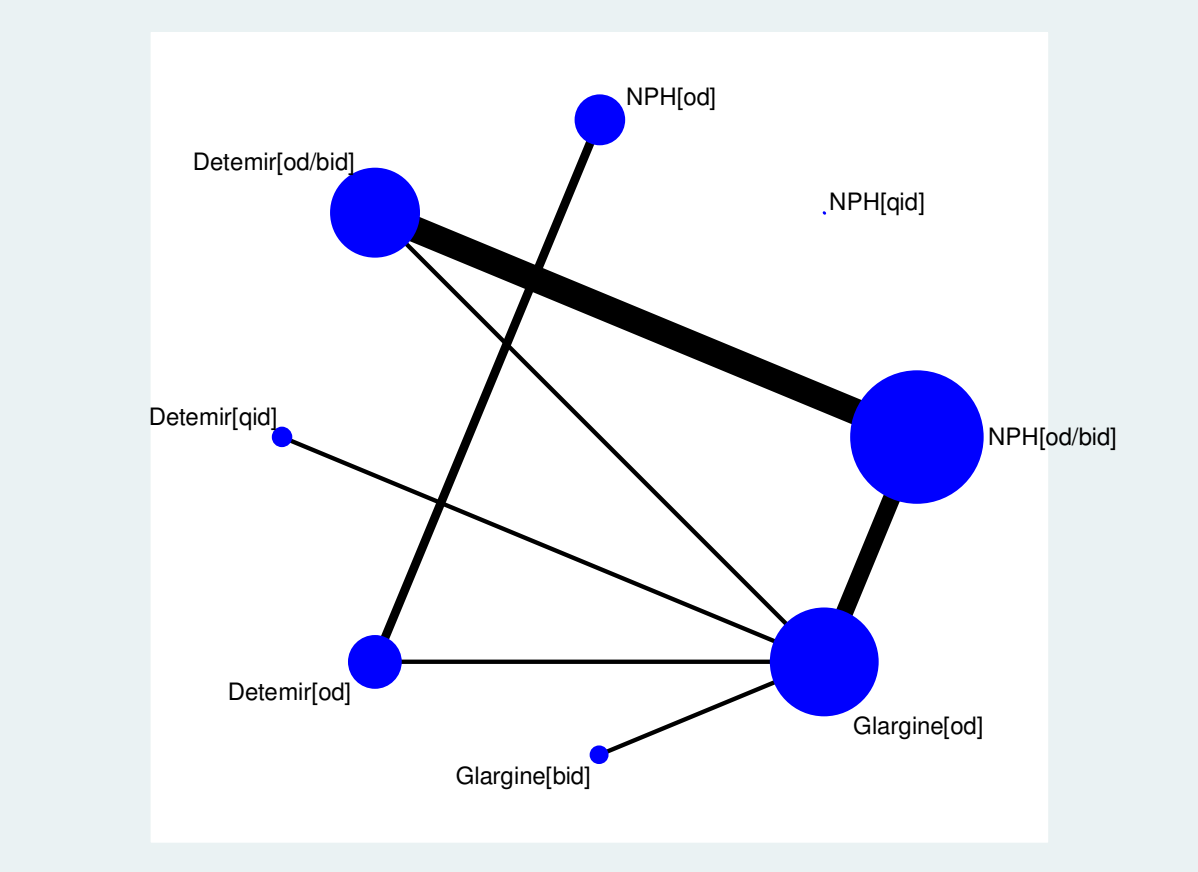
*13 randomized clinical trials including 3,396 patients contributing to the treatment ranking analysis showing the probabilities of being the best.
**Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 25 | Surface under the cumulative ranking curve for body weight*



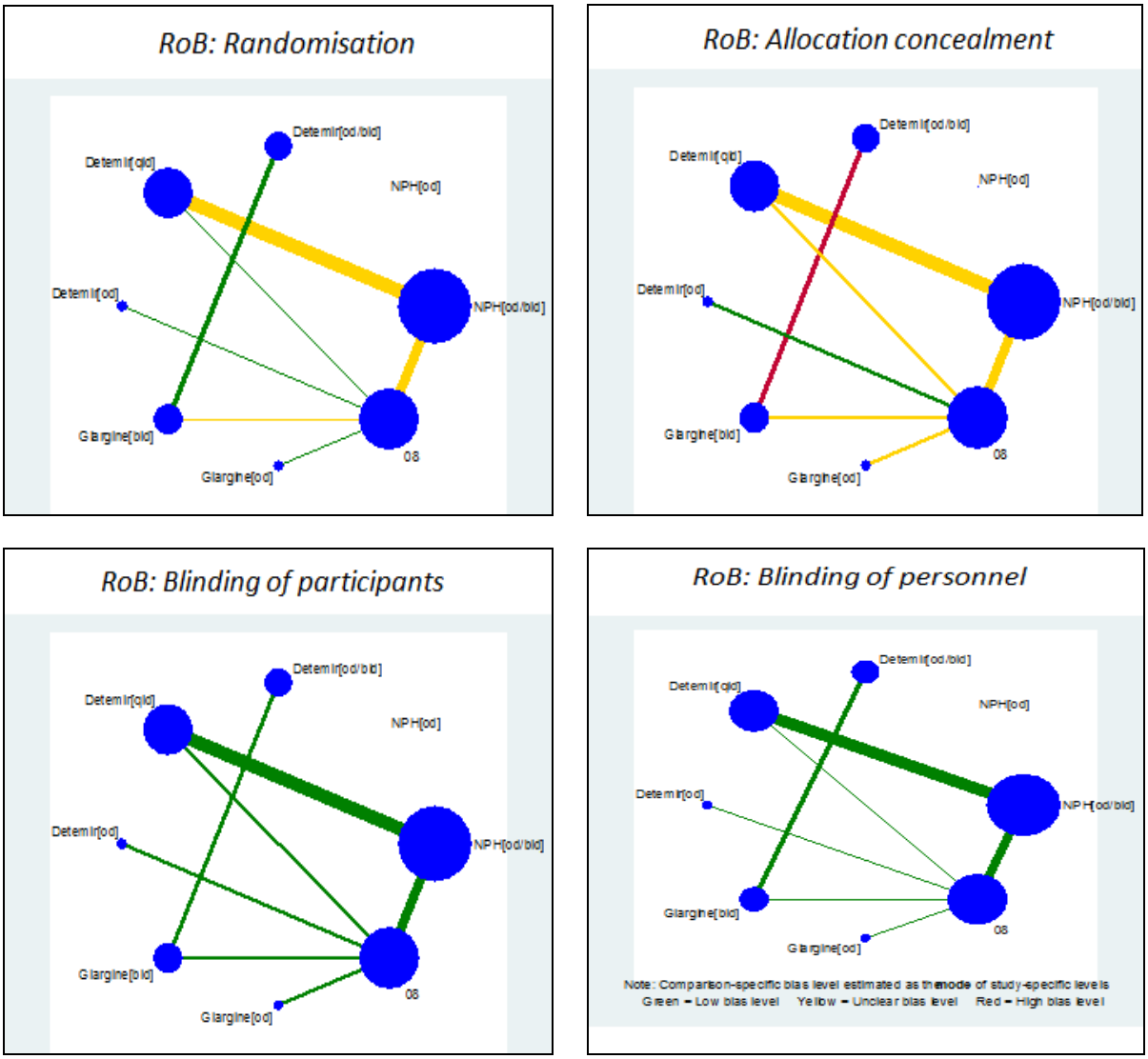
*13 randomized clinical trials including 3,396 patients contributing to the treatment ranking analysis using SUCRA approach.
**Bid - twice daily; Od - once daily; Qid - four times daily. SUCRA - surface under the cumulative ranking curve.The SUCRA allows identifying which treatment is the most effective overall and can be interpreted as 1 = treatment is certain to be the best and 0 = treatment is certain to be the worst.

Appendix 26 | Network geometry for severe hypoglycemia*



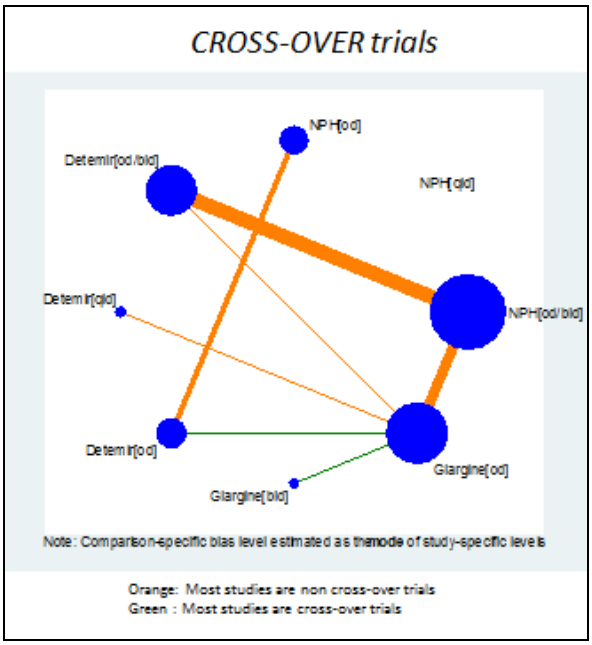
*16 RCTs including 5697 patients contributing to network meta-analysis. Size of the node thickness of the line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.

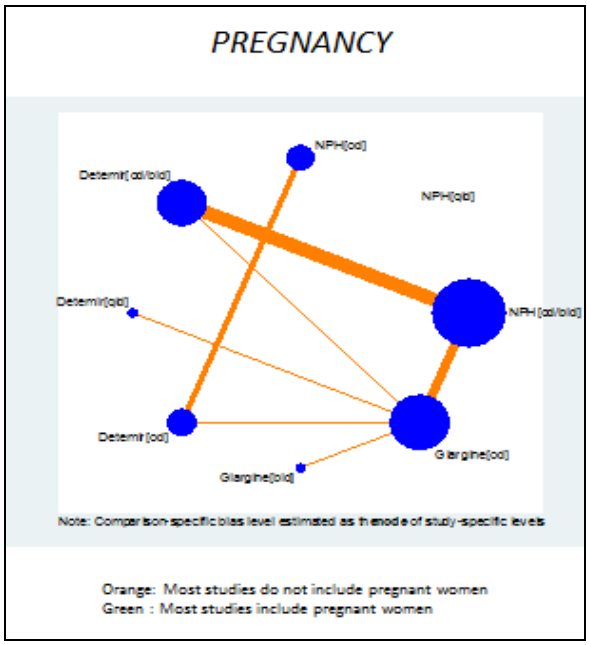
Appendix 27 | Risk of Bias (RoB) for hypoglycemia*



*16 RCTs including 5697 patients contributing to network meta-analysis. Size of the node thickness of the line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.
Note: Comparison-specific bias level estimated as the node of study-specific levels. Green= low bias level; yellow= unclear bias level; red = high bias level.

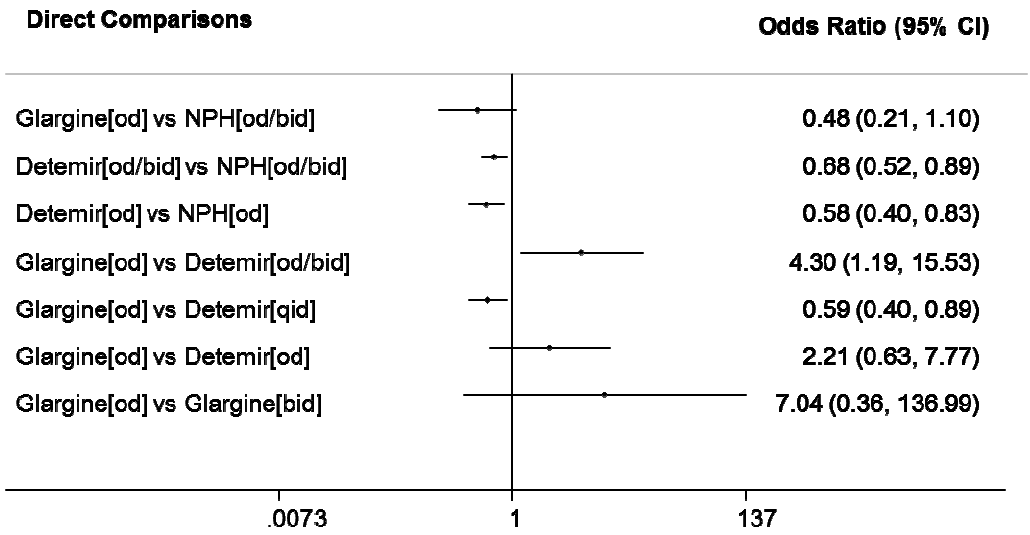
Appendix 28 | Sub-group analysis for hypoglycemia





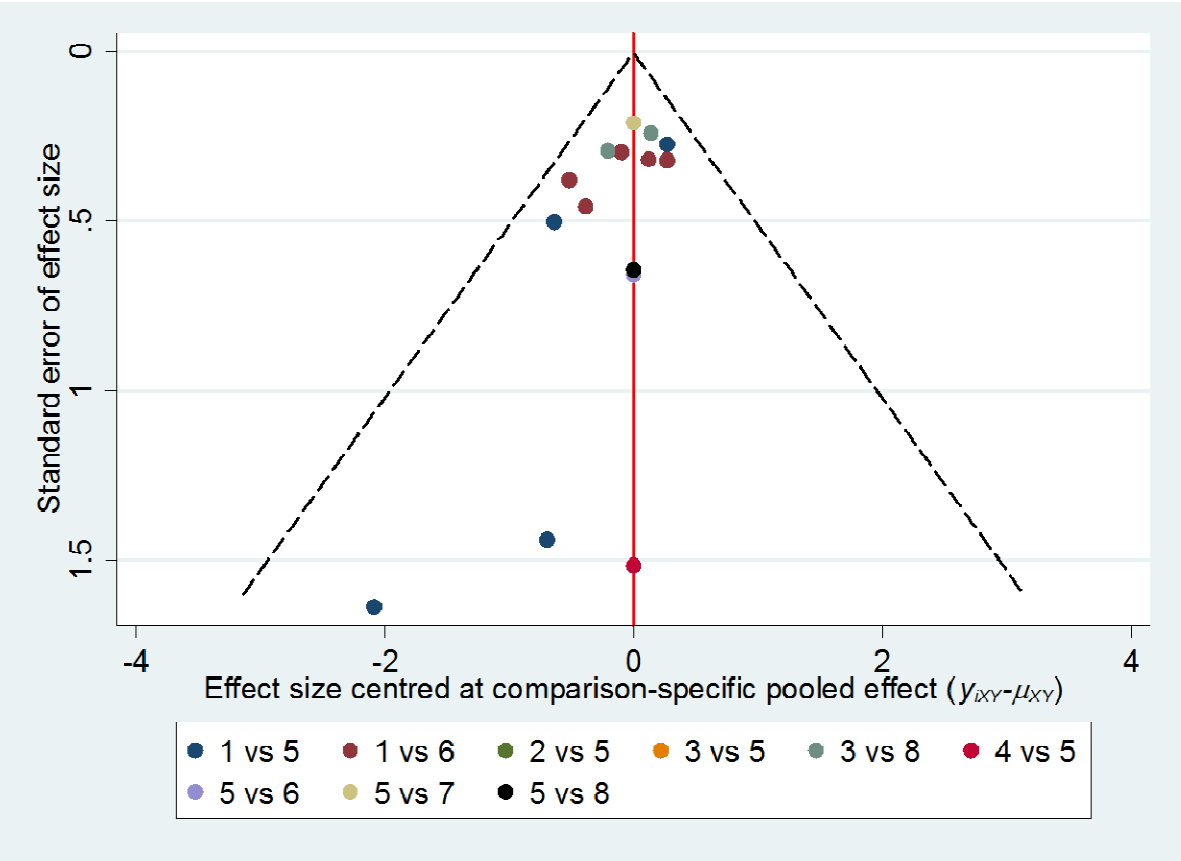
Size of the node and line indicates the number of studies included in each comparison.
** Bid - twice daily; Od - once daily; Qid - four times daily.
Note: Comparison-specific bias level estimated as the node of study-specific levels.

Appendix 29 | Random Effects Pairwise Meta-analysis for severe hypoglycemia*



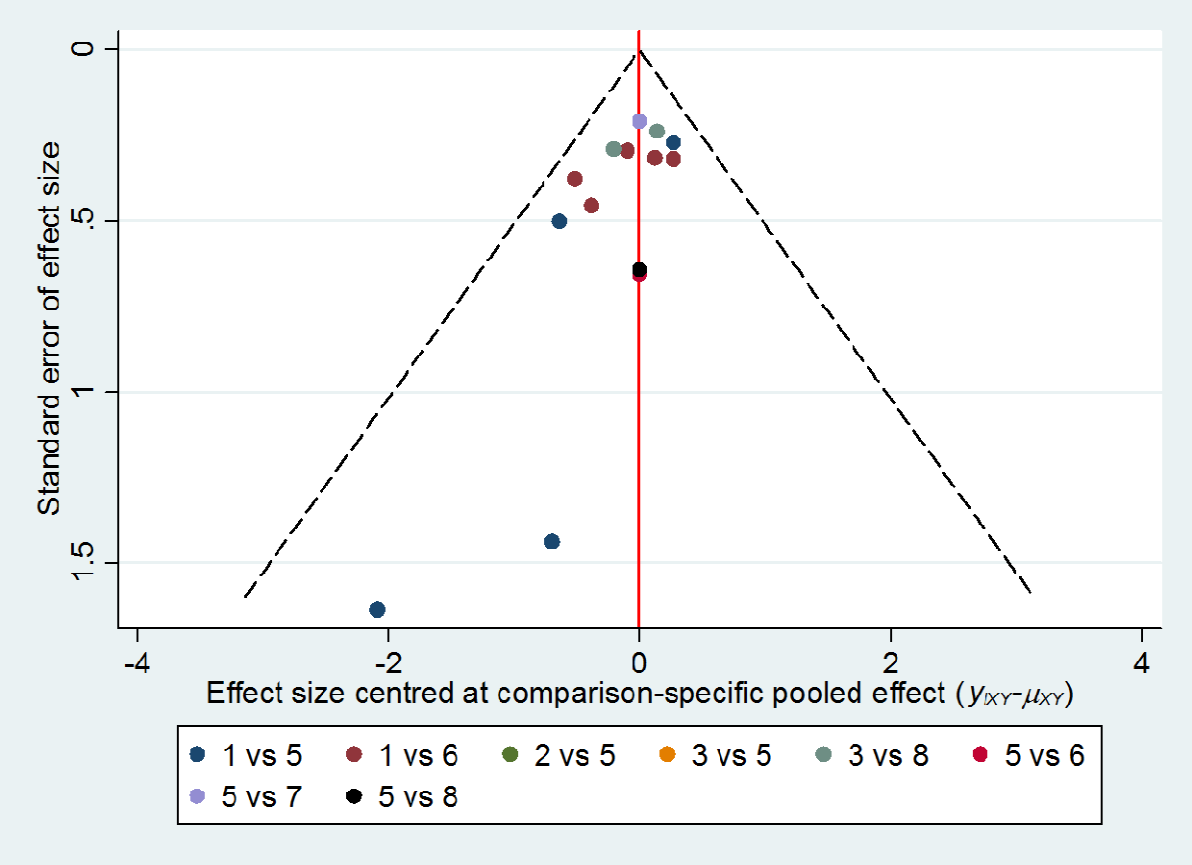
*16 RCTs including 5697 patients contributing to the random effects pairwise meta-analysis assuming that each comparison has a different amount of heterogeneity. The heterogeneity has been estimated using the restricted Maximum Likelihood method.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 30 | Comparison adjusted funnel plot for severe hypoglycemia*



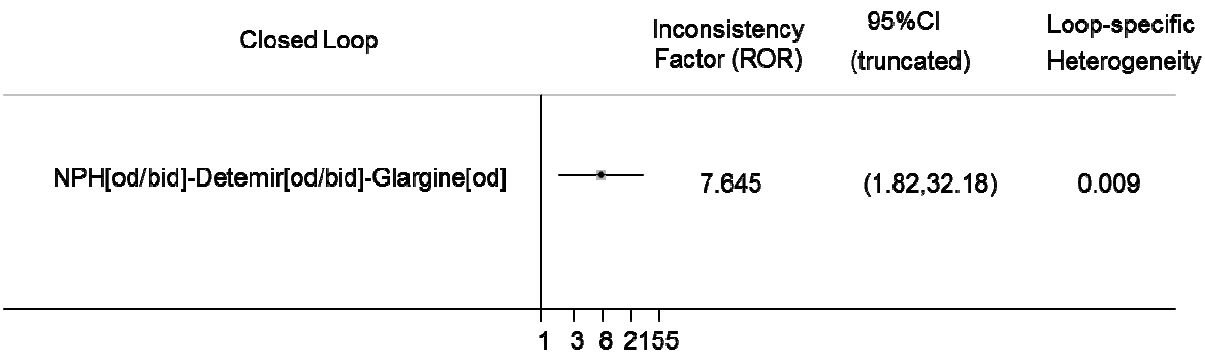
*16 RCTs including 5697 patients contributing to the comparison adjusted funnel plot.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 31 | Comparison adjusted funnel plot for severe hypoglycemia*



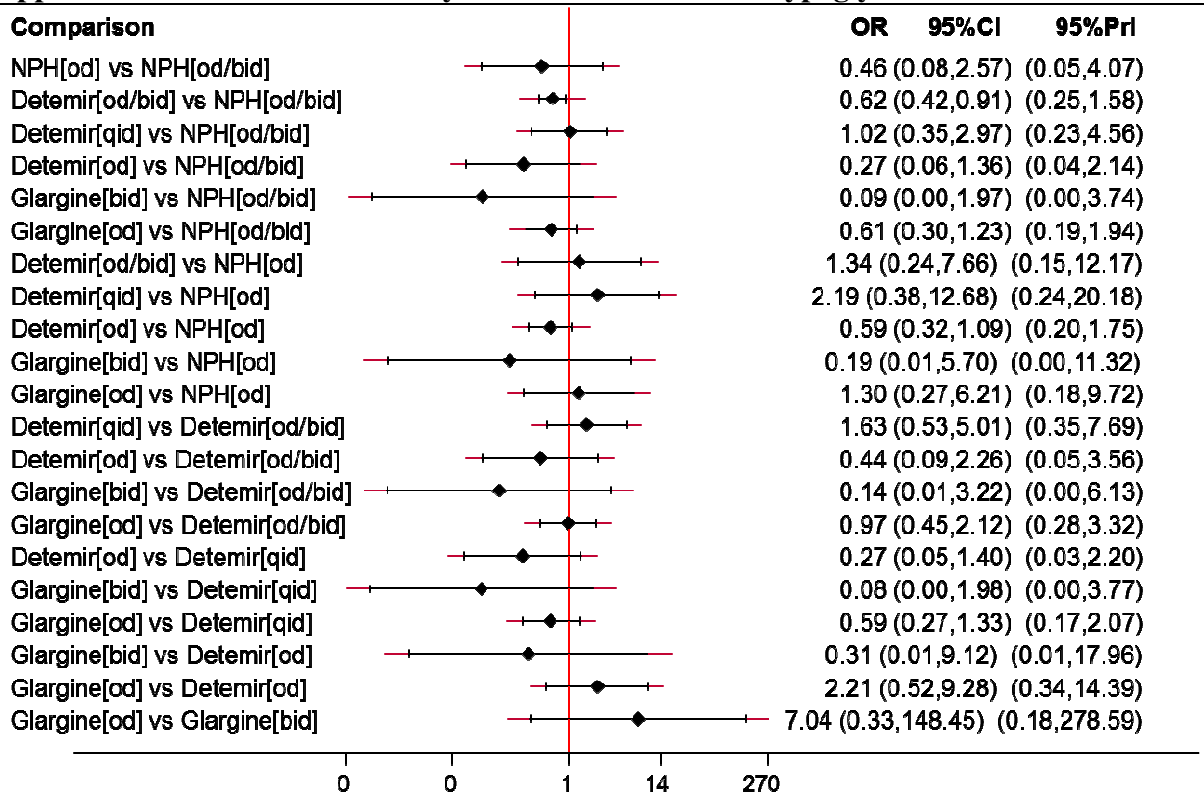
*16 RCTs including 5697 patients contributing to the comparison adjusted funnel plot, restricting only to general comparisons: NPH vs. Glargine; NPH vs. Detemir; Detemir vs. Glargine
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 32 | Loop-Specific method for severe hypoglycemia*



*16 RCTs including 5697 patients contributing to the loop-specific method for severe hypoglycemia.
** Bid - twice daily; Od - once daily; Qid - four times daily.

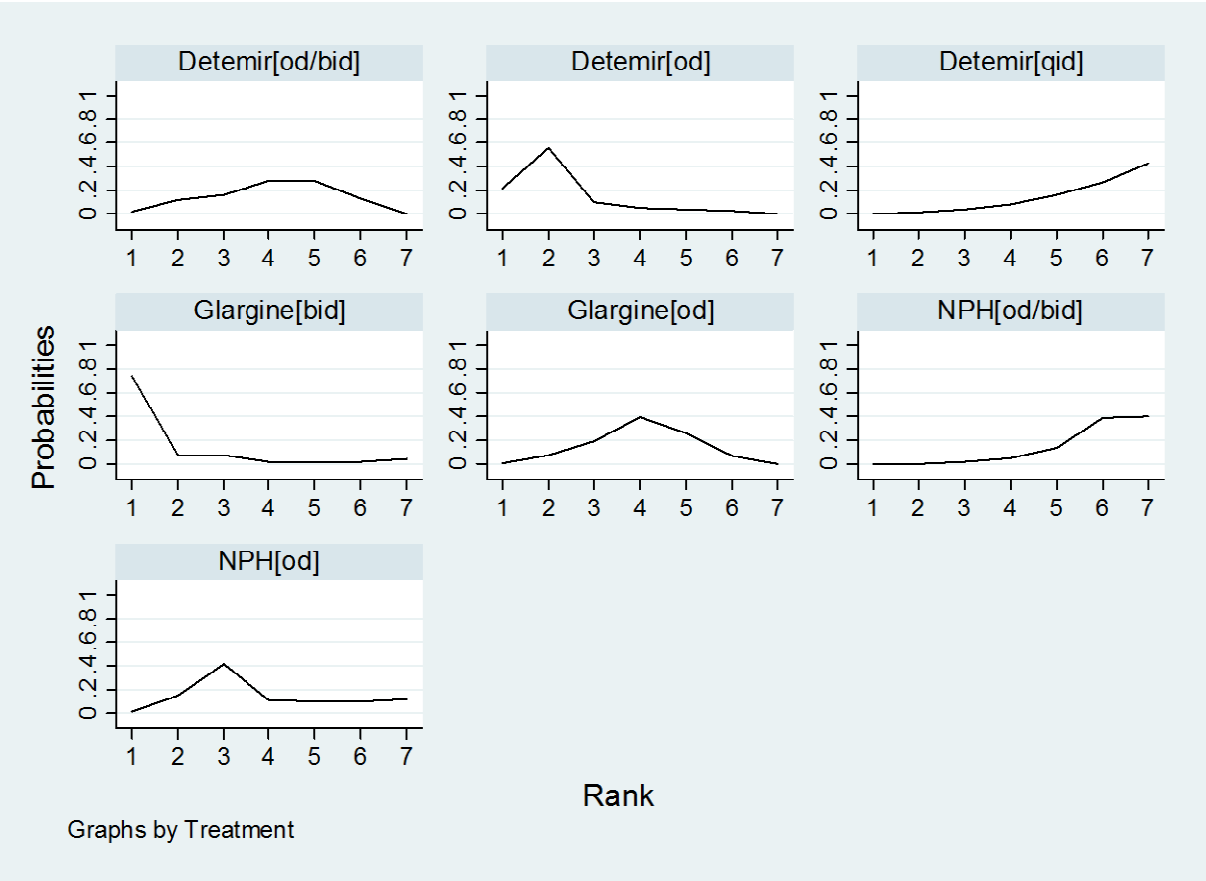
Appendix 33 | Network meta-analysis estimates for severe hypoglycemia*



*16 RCTs including 5697 patients contributing to the network meta-analysis estimates for severe hypoglycemia.

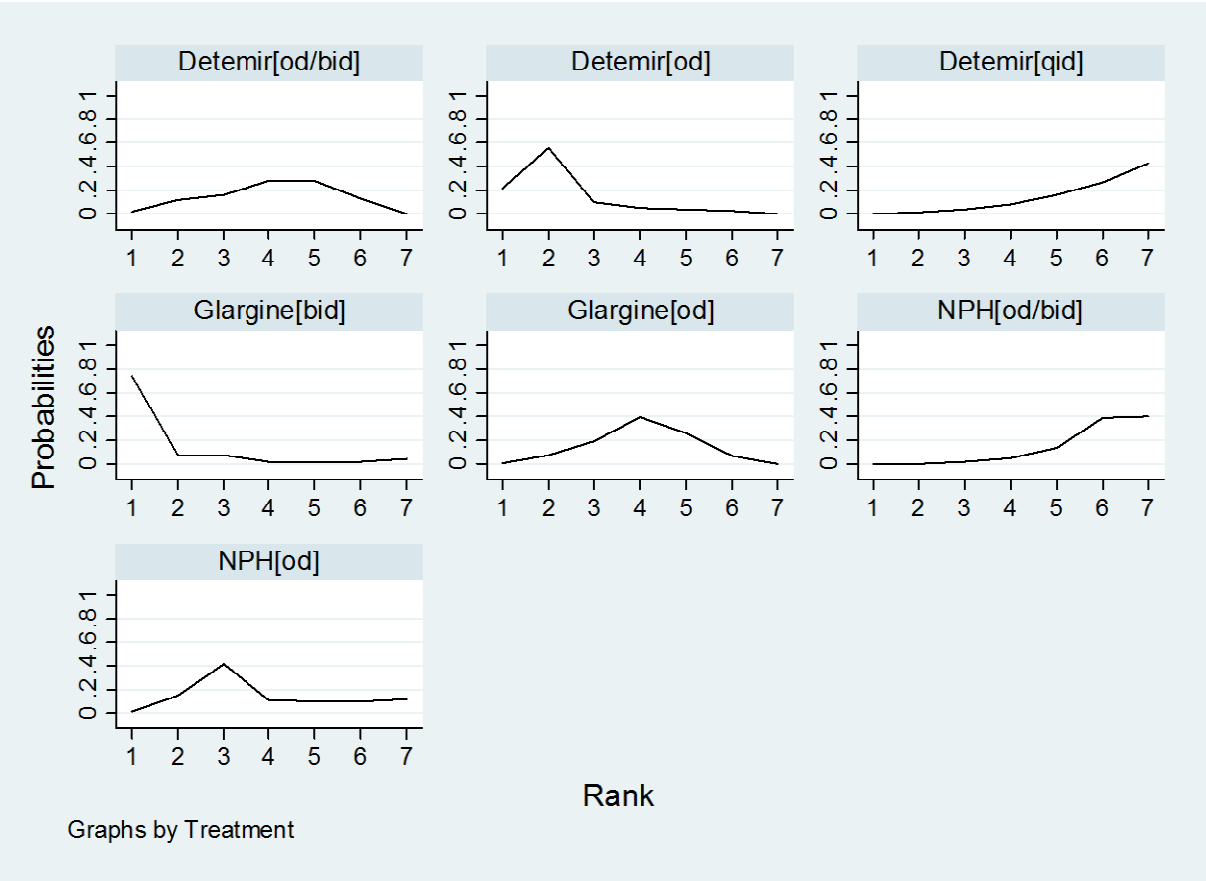
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 34 | Treatment Ranking: Probabilities of being the best for severe hypoglycemia*



*16 RCTs including 5697 patients contributing to the treatment ranking analysis showing the probabilities of being the best for severe hypoglycemia.
** Bid - twice daily; Od - once daily; Qid - four times daily.

Appendix 35 | Treatment Ranking: Probabilities of being the best for severe hypoglycemia*



*16 RCTs including 5697 patients contributing to the treatment ranking analysis using the SUCRA approach.
**Bid - twice daily; Od - once daily; Qid - four times daily. SUCRA - surface under the cumulative ranking curve.The SUCRA allows identifying which treatment is the most effective overall and can be interpreted as 1 = treatment is certain to be the best and 0 = treatment is certain to be the worst.

Appendix 36 | Definitions of severe hypoglycemia	
Study	**Definition of severe hypoglycemia**
Mathiesen,[29] 2012	"Major hypoglycemia was defined as an episode in which the subject was unable to treat herself"
Renard,[30] 2011	"Severe hypoglycemia was defined as an episode in which the patient's condition requires the indispensable assistance of a third person and is associated with blood glucose of < 1.98 mmol/L or a quick recovery after ingestion of sugar or intravenous glucose or glucagon administration"
Zachariah,[31] 2011	"Major hypoglycemia episodes: defined as patients unable to treat themselves"
Bolli,[35] 2009	"Severe hypoglycemia an event with symptoms consistent with hypoglycemia, during which the participant required the assistance of another person, or with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration."
Heller,[32] 2009	"Hypoglycemic episodes were defined as *major* (the patient could not treat the episode by himself/herself)"
Bartley,[34] 2008	Severe hypoglycemia unspecified
Chatterjee,[36] 2007	"Severe hypoglycemia was defined as a hypoglycemic episode requiring third-party assistance and/or intravenous glucose or intramuscular glucagon"
Pieber,[39] 2007	"Hypoglycemic episodes were recorded throughout the trial and were classified as severe if help from a third party was required"
Ashwell,[41] 2006	"Hypoglycemia was classified as anytime severe (requiring third party assistance)"
Kolendorf,[42] 2006	"Hypoglycemic episodes were classified as *severe* if help from others was required"
De Leeuw,[43] 2005	"Hypoglycemic episodes were classified as major [an episode with severe central nervous system (CNS) symptoms consistent with hypoglycemia, in which the subject was unable to treat himself/herself and which had one of the following characteristics: BG recorded as <2.8 mmol/l or symptom reversal achieved with food, glucose or glucagon]"
Fulcher,[44] 2005	"A severe event was one where symptoms consistent with hypoglycemia required the assistance of another person and was associated with a BG level <2.8 mmol/L or prompt recovery after oral carbohydrate, i.v. glucose or s.c. glucagon administration"
Home,[46] 2004	Hypoglycemic episodes were classified as major (requiring assistance from another person)"
Porcellati,[47] 2004	"Hypoglycemia was considered …severe when the episode required external help (any kind)"
Russell-Jones,[48] 2004	"A hypoglycemic episode was classified as *major* if the patient was unable to self treat"
Standl,[49] 2004	"Hypoglycemia was defined as major if third-party help was required"
Rossetti,[50] 2003	"Hypoglycemia was considered severe when the episode required any kind of external help. hypoglycemia was defined as any episode associated with measurement of blood glucose <4.0 mmol/l irrespective of symptoms, as previously reported"
Vague,[51] 2003	"Hypoglycemia episodes were classified as "major" if assistance to treat was required."
Pieber,[52] 2000	"Episodes of hypoglycemia(2.8 mmol/l) were recorded by the patients and were classified as severe (requiring assistance).Hypoglycemia was reported as a serious adverse event when it led to coma or to a car accident"
Raskin,[53]	"Severe hypoglycemia was defined as an event with symptoms consistent with

2000	hypoglycemia in which the subject required assistance from another person and which was accompanied by a blood glucose level <36.0 mg/dl (2.0 mmol/l) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration"
Ratner,[54] 2000 (CR: Hershon,[66] 2004)	"Any episode of hypoglycemia that met the criteria for a serious adverse event (e.g., death, a life-threatening episode, hospitalization, or medical intervention to prevent permanent impairment) was considered to be a treatment-related adverse event"

CR – companion report.

Appendix 37 | Randomized clinical trials included in our review versus previous reviews					
Study	**Monami[4]**	**Vardi[6]**	**Sanches[5]**	**Tran[67]**	**# patients**
Mathiesen,[29] 2012	No	No	No	No	340
Renard,[30] 2011	No	No	No	No	135
Zachariah,[31] 2011	No	No	No	No	23
Heller,[32] 2009	No	No	Yes	No	447
Le Floch,[33] 2009	No	No	No	No	512
Bartley,[34] 2008	Yes	No	Yes	No	497
Bolli,[35] 2009	No	No	Yes	No	175
Chatterjee,[36] 2007	Yes	Yes	No	No	60
Pesic,[37] 2007	No	No	No	No	48
Philippo,[38] 2007[a]	Yes	No	No	No	113
Pieber,[39] 2007	Yes	No	Yes	No	322
Radman,[40] 2007	Yes	No	No	No	56
Ashwell,[41] 2006	No	Yes	No	No	20
Kolendorf,[42] 2006	No	No	No	Yes	130
De Leeuw,[43] 2005	Yes	Yes	Yes	Yes	315
Fulcher,[44] 2005	No	Yes	Yes	Yes	125
Pieber,[45] 2005	No	No	Yes	Yes	400
Home,[46] 2004	Yes	Yes	Yes	Yes	408
Porcellati,[47] 2004	Yes	Yes	Yes	Yes	121
Russell-Jones,[48] 2004	Yes	Yes	Yes	Yes	749
Standl,[49] 2004	Yes	No	No	Yes	289
Rossetti,[50] 2003	No	Yes	No	Yes	51
Vague,[51] 2003	Yes	Yes	Yes	Yes	448
Pieber,[52] 2000	No	Yes	No	Yes	333
Raskin,[53] 2000	Yes	Yes	Yes	Yes	619
Ratner,[54] 2000 (CR: Hershon,[66] 2004)	Yes	Yes	Yes	Yes	534
Rosenstock,[55] 2000	No	Yes	Yes	Yes	256

Appendix 38 | Randomized clinical trials excluded in our review that were included in previous reviews

Study	Monami[4]	Vardi[6]	Sanches[5]	Tran[67]	Reason for exclusion
Hassan, 2008	Yes	No	No	No	Children
Robertson, 2007	Yes	Yes	No	No	Children
Home, 2005	Yes	Yes	Yes	Yes	Pre-mixed insulin therapy
Kawamura, 2005	No	No	No	Yes	Children
Kudva, 2005	No	No	No	Yes	No relevant comparator
Robertson, 2004	No	No	No	Yes	Children
Hermansen, 2004	No	Yes	Yes	Yes	Pre-mixed insulin therapy
Murphy, 2003	No	Yes	No	No	Children
Schober, 2002	Yes	No	No	Yes	Children
Hermansen, 2001	No	Yes	No	Yes	Pre-mixed insulin therapy
Schober, 2001	No	Yes	No	No	Children
Garg, 1998	No	No	No	Yes	Abstract not found, older than 10yrs
Tunbridge, 1989	No	Yes	No	No	No relevant intervention
Francis, 1986	No	Yes	No	No	No relevant comparator
NN304-1476	Yes	No	No	No	Japanese article, can't translate
NN304-1604	Yes	No	No	No	Children