# Appendix J: Network meta-analyses results and input data for clinical evidence review of blood glucose lowering treatments

## Review question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?

## J.1 MODEL FIT STATISTICS FOR ALL TREATMENT PHASES

**Table 1: Model fit statistics used to select fixed or random effect models for all treatment phases**

| Treatment phase | Outcome | Model | Total model DIC | Total model DIC (FE – RE) | Total residual deviance | SD | Preferred model i.e. FE or RE |
|---|---|---|---|---|---|---|---|
| Initial therapy | HbA1c at 3 months | FE | 1093.910 | 1276.283 | 1518.0 | - | RE preferred |
| | | RE | -182.373 | | 172.1 | 0.2638 | |
| | HbA1c at 6 months | FE | 61.353 | 148.141 | 347.7 | - | RE preferred |
| | | RE | -86.788 | | 150.1 | 0.2495 | |
| | HbA1c at 12 months | FE | -5.799 | 3.165 | 54.62 | - | RE preferred |
| | | RE | -8.964 | | 44.75 | 0.1599 | |
| | HbA1c at 24 months | FE | -12.784 | 0.065 | 13.95 | - | FE preferred |
| | | RE | -12.849 | | 12.99 | 0.6734 | |
| | Weight at 12 months | FE | 82.276 | 5.779 | 34.03 | - | RE preferred |
| | | RE | 76.497 | | 24.56 | 1.86 | |
| | Weight at 24 months | FE | 27.270 | -1.368 | 11.0 | - | FE preferred |
| | | RE | 28.638 | | 11.69 | 2.578 | |
| | Dropouts due to AE | FE | 845.527 | 1.345 | 201.2 | - | FE preferred |
| | | RE | 844.182 | | 186.7 | 0.2486 | |
| | Total dropouts | FE | 1011.650 | 3.96 | 204.4 | - | RE preferred |
| | | RE | 1007.690 | | 183.1 | 0.1563 | |

| Treatment phase | Outcome | Model | Total model DIC | Total model DIC (FE – RE) | Total residual deviance | SD | Preferred model i.e. FE or RE |
|---|---|---|---|---|---|---|---|
| | Nausea | FE | 333.490 | -1.387 | 72.25 | - | FE preferred |
| | | RE | 334.877 | | 68.91 | 0.2362 | |
| | Hypoglycaemia | FE | 517.555 | 4.744 | 116.6 | - | RE preferred |
| | | RE | 512.811 | | 102.4 | 0.3108 | |
| | | | | | | | |
| First intensification | HbA1c at 3 months | FE | -29.368 | 45.52 | 104.9 | - | RE preferred |
| | | RE | -74.888 | | 47.4 | 0.2282 | |
| | HbA1c at 6 months | FE | -60.715 | 10.322 | 66.51 | - | RE preferred |
| | | RE | -71.037 | | 47.35 | 0.1456 | |
| | HbA1c at 12 months | FE | -21.882 | 32.024 | 75.2 | - | RE preferred |
| | | RE | -53.906 | | 35.37 | 0.3003 | |
| | HbA1c at 24 months | FE | -26.986 | -0.96 | 14.66 | - | FE preferred |
| | | RE | -26.026 | | 14.0 | 0.3692 | |
| | Weight at 12 months | FE | 45.463 | 0.424 | 23.36 | - | FE preferred |
| | | RE | 45.039 | | 20.4 | 0.9493 | |
| | Weight at 24 months | FE | 21.415 | 1.098 | 20.88 | - | FE preferred |
| | | RE | 20.317 | | 18.08 | 1.734 | |
| | Dropouts due to AE | FE | 386.464 | 19.463 | 92.93 | - | RE preferred |
| | | RE | 367.001 | | 62.51 | 0.5504 | |
| | Total dropouts | FE | 475.666 | 24.678 | 103.2 | - | RE preferred |
| | | RE | 450.988 | | 66.1 | 0.3173 | |
| | Nausea | FE | 152.038 | 2.256 | 32.22 | - | FE preferred |
| | | RE | 149.782 | | 26.39 | 0.4245 | |
| | Hypoglycaemia | FE | 350.153 | 38.594 | 94.51 | - | RE preferred |
| | | RE | 311.559 | | 47.75 | 0.6769 | |
| | | | | | | | |
| Second intensification | HbA1c up to 12 months | FE | 11.17 | -2.424 | 123.30 | - | FE preferred |
| | | RE | -13.594 | | 87.01 | 0.3235 | |

| Treatment phase | Outcome | Model | Total model DIC | Total model DIC (FE – RE) | Total residual deviance | SD | Preferred model i.e. FE or RE |
|---|---|---|---|---|---|---|---|
| | Weight up to 12 months | FE | 114.792 | -0.253 | 64.49 | - | FE preferred |
| | | RE | 115.045 | | 61.15 | 0.3884 | |
| | Dropouts due to AE | FE | 266.069 | -1.431 | 63.34 | - | FE preferred |
| | | RE | 267.5 | | 62.62 | 0.567 | |
| | Total dropouts | FE | 333.284 | -0.216 | 65.34 | - | FE preferred |
| | | RE | 333.5 | | 62.75 | 0.391 | |
| | Nausea | FE | 75.473 | 17.146 | 27.23 | - | RE preferred |
| | | RE | 58.327 | | 9.227 | 1.472 | |
| | Hypoglycaemia | FE | 639.403 | 32.771 | 124.1 | - | RE preferred |
| | | RE | 606.632 | | 79.94 | 0.3487 | |

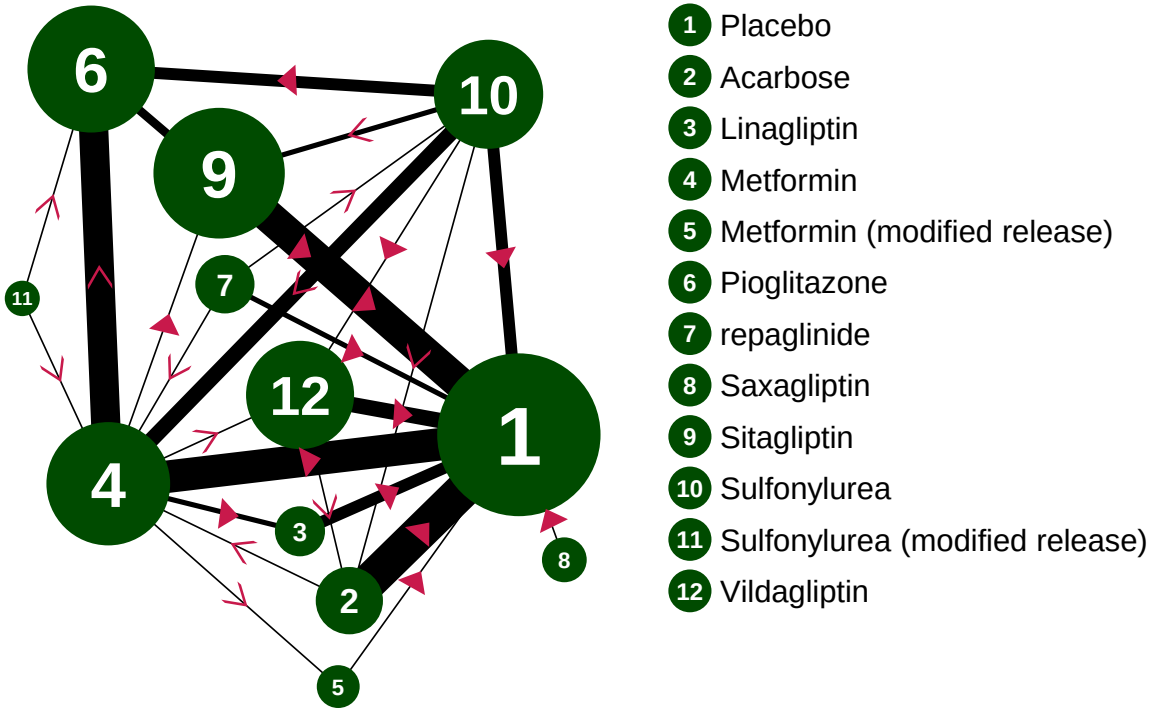
AE Adverse events, DIC Deviance information criterion, FE Fixed effect model, RE Random effect model, SD Standard deviation of random-effects term (tau)

# J.2 FULL DATASET

## J.2.1 RESULTS FOR INITIAL THERAPY

### J.2.1.1 Change in HbA1c at 3, 6, 12 and 24 months

**Change in HbA1c at 3 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 1: INITIAL THERAPY: HbA1c AT 3 MONTHS – evidence network**

**Table 2: INITIAL THERAPY: HbA1c AT 3 MONTHS – input data**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Foley & (2009) | | | | | | | | | | -1.48 (0.85) | | -1.13 (0.68) |
| Kato et al. (2009) | | | | -0.80 (0.91) | | -1.10 (1.16) | | | | | | |
| Derosa et al. (2009) | | | | -0.50 (0.76) | | -0.40 (0.83) | | | | | | |
| Bosi et al. (2009) | | | | -1.29 (0.87) | | | | | | | | -1.18 (0.86) |
| Erdem et al. (2008) | | | | -0.59 (0.95) | | -0.74 (0.80) | | | | | | |
| Gao et al. (2008) | | | | -0.30 (0.58) | -0.30 (0.70) | | | | | | | |
| Pan et al. (2008) | | -1.29 (0.66) | | | | | | | | | | -1.35 (0.65) |
| Formoso et al. (2008) | | | | -2.20 (0.04) | | | | | | -1.40 (0.03) | | |
| Goldstein et al. (2007) | 0.25 (0.64) | | | -0.84 (0.61) | | | | | -0.70 (0.65) | | | |
| Scott et al. (2007) | 0.23 (0.73) | | | | | | | | -0.38 (0.77) | -0.76 (0.78) | | |
| Jain et al. (2006) | | | | | | -2.04 (1.19) | | | | -2.45 (1.19) | | |
| Yoon et al. (2011) | | | | -0.80 (0.55) | | | | | | -1.05 (0.48) | | |
| Haak et al. (2012) | -0.15 (0.62) | | -0.65 (0.70) | -1.16 (0.58) | | | | | | | | |
| Haak et al. (2012) | 0.45 (0.57) | | -0.20 (0.60) | -0.42 (0.55) | | | | | | | | |
| Pan et al. (2012) | -0.32 (0.66) | | | | | | | -0.89 (0.67) | | | | |
| Shihara et al. (2011) | | | | | | -0.50 (0.65) | | | | -0.90 (0.57) | | |
| Aschner et al. (2006) | 0.20 (0.70) | | | | | | | | -0.57 (0.58) | | | |
| Bautista et al. (2003) | -0.70 (0.30) | | | | | | | | | -2.30 (0.30) | | |
| Uehara et al. (2001) | -0.80 (1.93) | | | -0.70 (0.99) | | | | | | | | |
| Delgado et al. (2002) | 0.00 (2.10) | -0.10 (0.99) | | | | | | | | | | |
| Barzilai et al. (2011) | 0.26 (0.50) | | | | | | | | -0.33 (0.52) | | | |
| Nonaka et al. (2008) | 0.41 (0.66) | | | | | | | | -0.65 (0.66) | | | |
| Hanefeld et al. (2007) | 0.12 (0.75) | | | | | | | | -0.40 (0.74) | | | |
| Kawamori et al. (2012) | 0.63 (0.72) | | -0.24 (0.76) | | | | | | | | | |
| Iwamoto et al. (2010) | 0.28 (0.52) | | | | | | | | -0.60 (0.51) | | | |
| Kikuchi et al. (2009) | 0.28 (0.85) | | | | | | | | | | | -0.71 (0.77) |
| Mohan et al. (2009) | 0.24 (0.70) | | | | | | | | -0.70 (0.75) | | | |
| Pi-Sunyer et al. (2007) | -0.42 (0.72) | | | | | | | | | | | -0.88 (0.64) |
| Pratley et al. (2006) | 0.00 (1.06) | | | | | | | | | | | -0.60 (0.84) |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ristic et al. (2005) | -0.13 (0.74) | | | | | | | | | | | -0.42 (0.76) |
| Scherbaum et al. (2008) | 0.02 (0.46) | | | | | | | | | | | -0.25 (0.30) |
| Herz et al. (2003) | -0.20 (0.41) | | | | | -0.85 (0.54) | | | | | | |
| Abbatecola et al. (2006) | | | | | | | -0.48 (0.57) | | | -0.26 (0.91) | | |
| Jovanovic et al. (2000) | 1.25 (2.15) | | | | | | -0.70 (1.78) | | | | | |
| Schernthaner et al. (2004) | | | | -1.25 (0.68) | | -1.00 (0.69) | | | | | | |
| Fujioka et al. (2005) | 0.19 (0.62) | | | | -0.60 (0.72) | | | | | | | |
| Campbell et al. (1994) | | | | -2.31 (1.32) | | | | | | -2.90 (1.49) | | |
| Aronoff et al. (2000) | 0.70 (0.89) | | | | | -0.15 (1.00) | | | | | | |
| Yamanouchi et al. (2005) | | | | -1.80 (0.57) | | -1.40 (0.57) | | | | -2.10 (0.46) | | |
| Raz et al. (2006) | 0.17 (0.80) | | | | | | | | -0.42 (0.64) | | | |
| Tessier et al. (1999) | | | | -0.80 (1.10) | | | | | | -1.00 (1.15) | | |
| Damsbo et al. (1998) | -3.30 (2.90) | | | -2.80 (1.24) | | | | | | | | |
| DeFronzo & (1995) | 0.15 (0.24) | | | -1.30 (0.60) | | | | | | | | |
| Mather et al. (2001) | -0.30 (1.28) | | | -0.30 (0.73) | | | | | | | | |
| Braun D,Schonherr (1996) | -0.90 (1.27) | -2.00 (1.27) | | | | | | | | | | |
| Buchanan et al. (1988) | 1.60 (2.56) | 1.10 (2.29) | | | | | | | | | | |
| Chiassonet al. (1994) | 0.10 (1.24) | -0.45 (1.40) | | | | | | | | | | |
| Coniff et al. (1995) | 0.31 (1.02) | -0.44 (1.04) | | | | | | | | | | |
| Fischer et al. (1998) | 0.38 (0.77) | -0.46 (0.77) | | | | | | | | | | |
| Hoffmann & (1994) | -0.06 (0.25) | -0.74 (0.28) | | | | | | | | -0.75 (0.24) | | |
| Hoffmann & (1997) | 0.10 (0.60) | -0.90 (0.61) | | -0.75 (0.57) | | | | | | | | |
| Hotta et al. (1993) | 0.20 (1.70) | -1.00 (1.29) | | | | | | | | | | |
| Santeusanio et al. (1993) | 0.30 (0.70) | -0.68 (0.68) | | | | | | | | | | |
| Scott et al. (1999) | 0.25 (1.20) | -0.14 (0.90) | | | | | | | | | | |
| Birkeland et al. (1994) | 0.05 (0.68) | | | | | | | | | -0.95 (0.79) | | |
| Charbonnel et al. (2005) | | | | | | -1.08 (0.73) | | | | -1.45 (0.75) | | |
| Moses et al. (2001) | -0.21 (1.50) | | | | | | -1.21 (1.17) | | | | | |
| Kikuchi et al. (2012) | 0.21 (1.10) | | | | | -0.91 (1.01) | | | | | | |

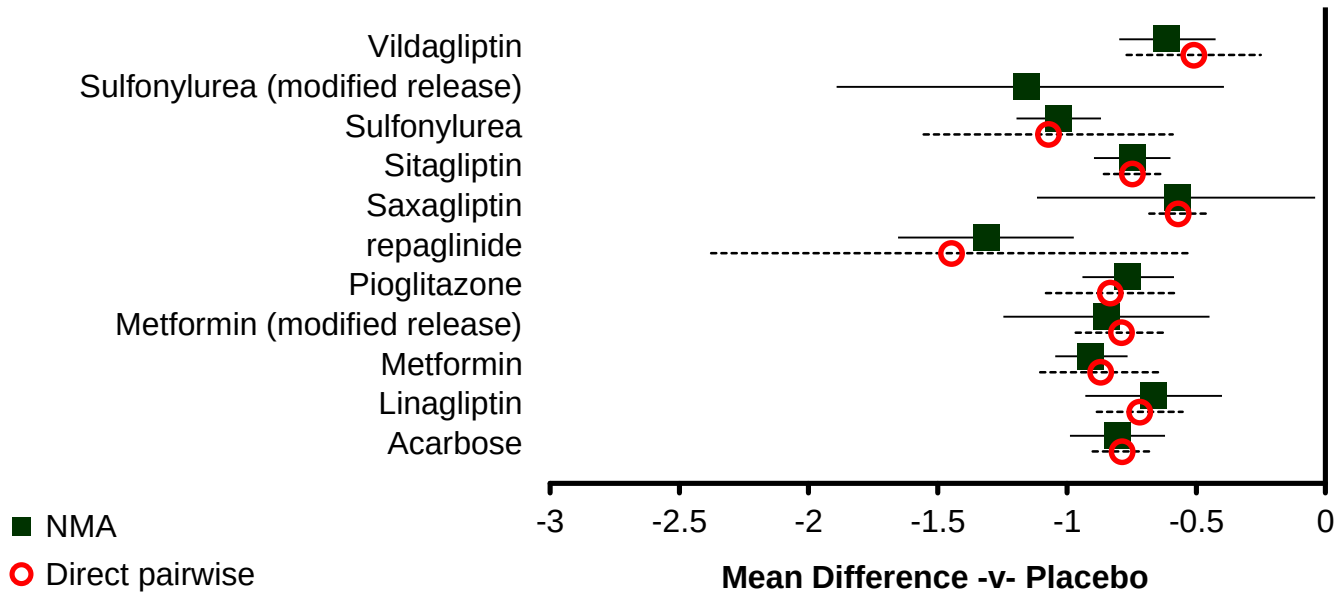
| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ferrannini et al. (2013) | 0.10 (0.92) | | | -0.70 (1.00) | | | | | | | | |
| Fonseca et al. (2013) | 0.26 (0.80) | | | -0.42 (0.83) | | | | | | | | |
| Arjona et al. (2013) | | | | | | | | | -0.56 (0.81) | -0.56 (0.83) | | |
| Barnett et al. (2012) | 0.24 (1.07) | | -0.57 (0.76) | | | | | | | | | |
| Genovese et al. (2013) | | | | -0.20 (0.47) | | -0.40 (0.58) | | | | | | |
| Taslimi et al. (2013) | | | | -1.40 (0.98) | | -0.90 (1.16) | | | | | | |
| Roden et al. (2013) | -0.02 (0.50) | | | | | | | | -0.63 (0.50) | | | |
| Erem et al. (2014) | | | | -0.95 (0.77) | | -1.13 (1.10) | | | | | -1.33 (1.11) | |
| Fang et al. (2014) | | | | -1.60 (1.50) | | | -1.80 (1.50) | | | | | |
| Esteghamati et al. (2014) | | | | -0.83 (1.02) | | -0.72 (1.30) | | | | | | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 3: INITIAL THERAPY: HbA1c AT 3 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | -0.79 (-0.90, -0.67) | -0.72 (-0.88, -0.55) | -0.87 (-1.10, -0.64) | -0.79 (-0.97, -0.61) | -0.83 (-1.08, -0.58) | -1.45 (-2.38, -0.52) | -0.57 (-0.68, -0.46) | -0.75 (-0.86, -0.64) | -1.07 (-1.55, -0.59) | - | -0.51 (-0.77, -0.25) |
| Acarbose | -0.80 (-0.99, -0.62) | | - | 0.15 (-0.14, 0.44) | - | - | - | - | - | -0.01 (-0.15, 0.13) | - | -0.06 (-0.17, 0.05) |
| Linagliptin | -0.67 (-0.93, -0.40) | 0.14 (-0.18, 0.46) | | -0.36 (-0.65, -0.08) | - | - | - | - | - | - | - | - |
| Metformin | -0.91 (-1.05, -0.77) | -0.10 (-0.32, 0.11) | -0.24 (-0.51, 0.03) | | 0.00 (-0.21, 0.21) | 0.11 (-0.06, 0.27) | -0.20 (-1.01, 0.61) | - | 0.14 (0.03, 0.25) | -0.08 (-0.77, 0.61) | -0.38 (-0.99, 0.23) | 0.11 (-0.03, 0.25) |
| Metformin (modified release) | -0.85 (-1.25, -0.45) | -0.04 (-0.48, 0.39) | -0.18 (-0.65, 0.28) | 0.06 (-0.34, 0.46) | | - | - | - | - | - | - | - |
| Pioglitazone | -0.76 (-0.94, -0.59) | 0.04 (-0.20, 0.29) | -0.10 (-0.40, 0.20) | 0.14 (-0.02, 0.31) | 0.09 (-0.34, 0.51) | | - | - | - | -0.45 (-0.57, -0.32) | -0.20 (-0.90, 0.50) | - |
| repaglinide | -1.31 (-1.65, -0.97) | -0.51 (-0.89, -0.13) | -0.65 (-1.07, -0.23) | -0.40 (-0.76, -0.05) | -0.46 (-0.99, 0.06) | -0.55 (-0.91, -0.18) | | - | - | 0.22 (-0.02, 0.45) | - | - |
| Saxagliptin | -0.57 (-1.12, -0.04) | 0.23 (-0.34, 0.80) | 0.09 (-0.51, 0.68) | 0.34 (-0.22, 0.88) | 0.28 (-0.40, 0.95) | 0.19 (-0.38, 0.75) | 0.74 (0.10, 1.37) | | - | - | - | - |
| Sitagliptin | -0.75 (-0.90, -0.60) | 0.06 (-0.18, 0.29) | -0.08 (-0.38, 0.21) | 0.16 (-0.03, 0.35) | 0.10 (-0.32, 0.52) | 0.02 (-0.20, 0.23) | 0.56 (0.20, 0.93) | -0.18 (-0.73, 0.39) | | -0.19 (-0.56, 0.18) | - | - |
| Sulfonylurea | -1.03 (-1.20, -0.87) | -0.23 (-0.46, 0.01) | -0.37 (-0.66, -0.07) | -0.12 (-0.30, 0.05) | -0.18 (-0.61, 0.24) | -0.27 (-0.45, -0.08) | 0.28 (-0.07, 0.63) | -0.46 (-1.02, 0.11) | -0.28 (-0.48, -0.09) | | - | 0.35 (0.24, 0.46) |
| Sulfonylurea (modified release) | -1.16 (-1.89, -0.39) | -0.35 (-1.11, 0.43) | -0.49 (-1.27, 0.30) | -0.25 (-0.98, 0.51) | -0.31 (-1.14, 0.55) | -0.39 (-1.13, 0.37) | 0.16 (-0.65, 0.98) | -0.58 (-1.50, 0.35) | -0.41 (-1.16, 0.37) | -0.12 (-0.86, 0.64) | | - |
| Vildagliptin | -0.61 (-0.80, -0.42) | 0.19 (-0.05, 0.44) | 0.05 (-0.26, 0.37) | 0.30 (0.08, 0.51) | 0.23 (-0.20, 0.67) | 0.15 (-0.09, 0.40) | 0.70 (0.32, 1.09) | -0.04 (-0.61, 0.53) | 0.14 (-0.10, 0.37) | 0.42 (0.19, 0.65) | 0.54 (-0.25, 1.30) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 2: INITIAL THERAPY: HbA1c AT 3 MONTHS – relative effect of all options versus reference treatment**

**Table 4: INITIAL THERAPY: HbA1c AT 3 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 12 (12, 12) |
| Acarbose | 0.000 | 6 (3, 10) |
| Linagliptin | 0.000 | 9 (4, 11) |
| Metformin | 0.000 | 4 (3, 7) |
| Metformin (modified release) | 0.020 | 5 (2, 11) |
| Pioglitazone | 0.000 | 7 (4, 10) |
| repaglinide | 0.611 | 1 (1, 3) |
| Saxagliptin | 0.005 | 10 (2, 11) |
| Sitagliptin | 0.000 | 7 (4, 10) |
| Sulfonylurea | 0.020 | 3 (2, 5) |
| Sulfonylurea (modified release) | 0.344 | 2 (1, 11) |
| Vildagliptin | 0.000 | 10 (6, 11) |

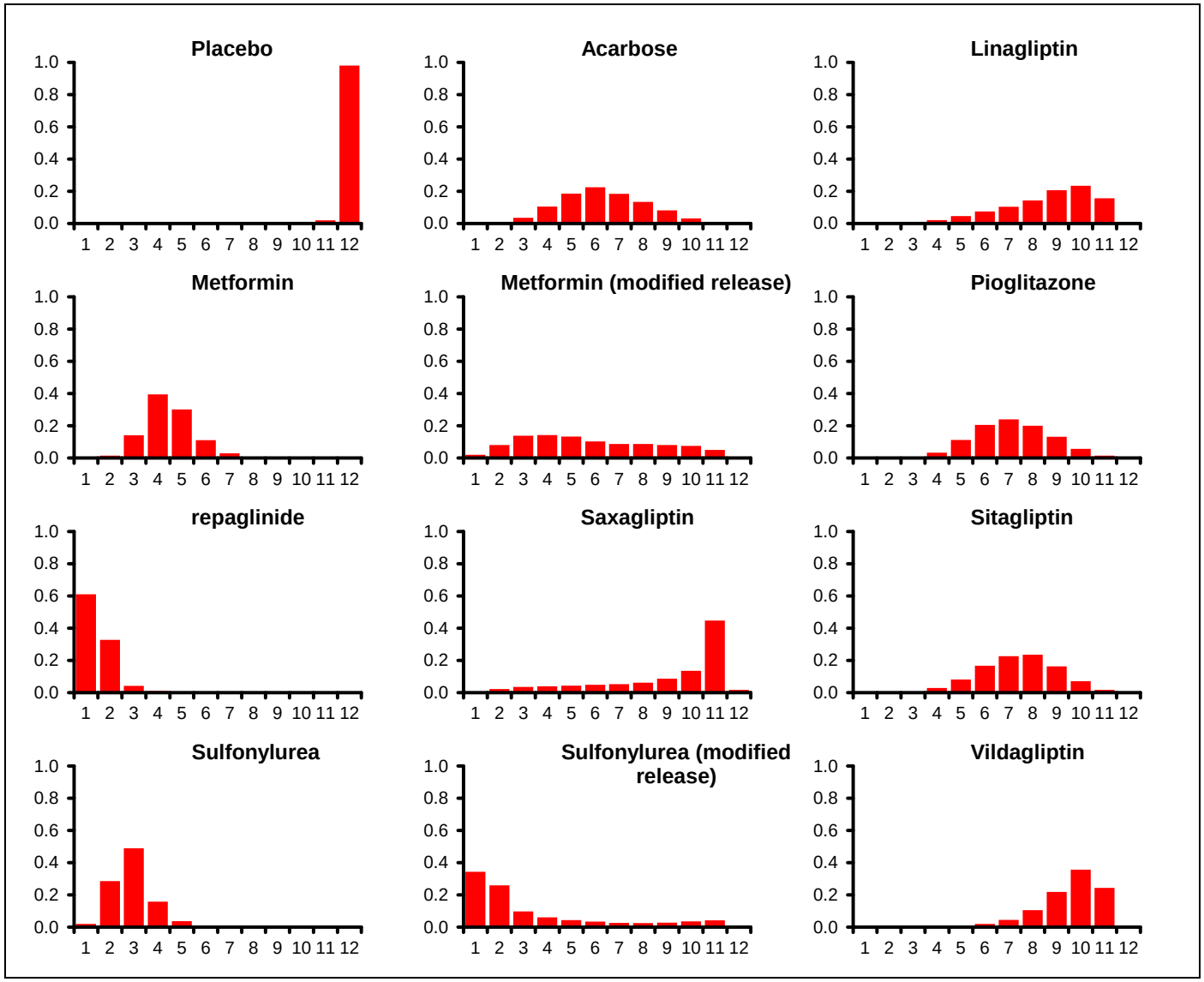



**Figure 3: INITIAL THERAPY: HbA1c AT 3 MONTHS – rank probability histograms**

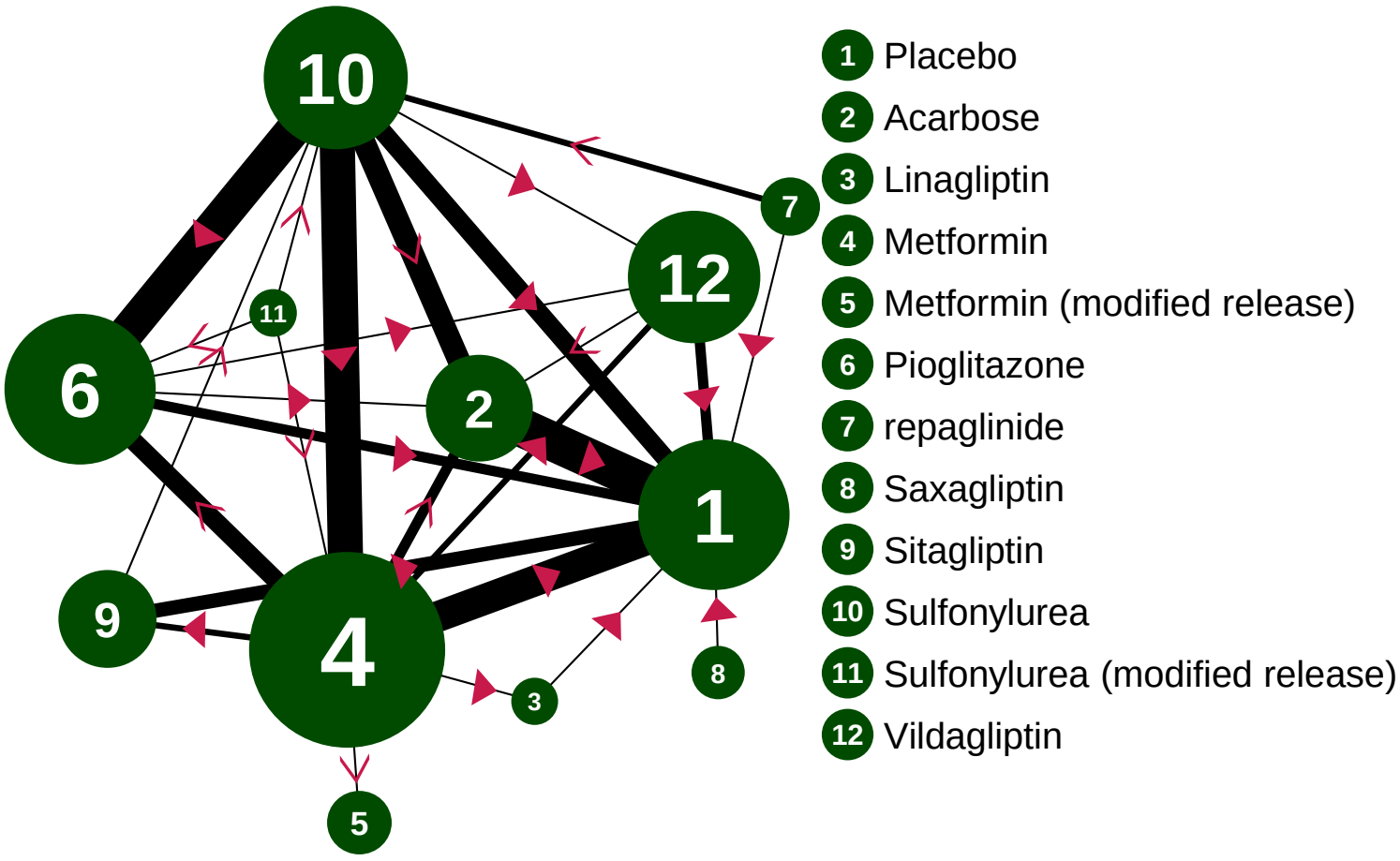
**Table 5: INITIAL THERAPY: HbA1c AT 3 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 172.1<br>(compared to 173 datapoints) | -331.422 | -480.472 | 149.05 | -182.373 | 0.262 (95%CI: 0.219, 0.316) |

**Table 6: INITIAL THERAPY: HbA1c AT 3 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

**Change in HbA1c at 6 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 4: INITIAL THERAPY: HbA1c AT 6 MONTHS – evidence network**

**Table 7: INITIAL THERAPY: HbA1c AT 6 MONTHS – input data**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Esposito et al. (2011) | | | | -0.90 (0.50) | | -0.90 (0.50) | | | | | | |
| Foley & (2009) | | | | | | | | | | -1.63 (1.12) | | -1.18 (1.13) |
| Schweizer et al. (2009) | | | | -0.75 (0.90) | | | | | | | | -0.64 (0.91) |
| Bosi et al. (2009) | | | | -1.40 (1.01) | | | | | | | | -1.10 (1.02) |
| Pan et al. (2008) | | -1.30 (1.37) | | | | | | | | | | -1.40 (1.97) |
| Goldstein et al. (2007) | 0.17 (1.15) | | | -0.97 (1.10) | | | | | -0.66 (1.16) | | | |
| Teramoto et al. (2007) | | | | | | -0.80 (1.14) | | | | -1.43 (1.09) | | |
| Jain et al. (2006) | | | | | | -2.22 (1.19) | | | | -2.34 (1.19) | | |
| Yoon et al. (2011) | | | | -0.95 (0.69) | | | | | | -1.07 (0.60) | | |
| Haak et al. (2012) | 0.10 (0.81) | | -0.50 (1.16) | -0.85 (1.18) | | | | | | | | |
| Pan et al. (2012) | -0.42 (1.02) | | | | | | | -0.95 (1.04) | | | | |
| Shihara et al. (2011) | | | | | | -0.86 (0.98) | | | | -0.98 (0.72) | | |
| Derosa et al. (2011) | -0.30 (0.41) | -1.10 (0.55) | | | | | | | | | | |
| Aschner et al. (2010) | | | | -0.57 (0.53) | | | | | -0.43 (0.54) | | | |
| Aschner et al. (2006) | 0.18 (0.96) | | | | | | | | -0.61 (1.00) | | | |
| Schwartz et al. (2006) | | | | -1.05 (2.72) | -0.82 (2.67) | | | | | | | |
| Barzilai et al. (2011) | 0.20 (0.97) | | | | | | | | -0.50 (1.03) | | | |
| Dejager et al. (2007) | -0.30 (0.97) | | | | | | | | | | | -0.83 (0.98) |
| Pi-Sunyer et al. (2007) | 0.00 (0.96) | | | | | | | | | | | -0.67 (0.94) |
| Rosenstock et al. (2007) | | | | | | -1.40 (1.25) | | | | | | -1.10 (1.22) |
| Scherbaum et al. (2008) | -0.05 (0.47) | | | | | | | | | | | -0.33 (0.41) |
| Abbatecola et al. (2006) | | | | | | | -0.55 (0.78) | | | -0.30 (1.49) | | |
| Horton et al. (2000) | 0.50 (0.99) | | | -0.80 (0.99) | | | | | | | | |
| Jovanovic et al. (2000) | 1.30 (3.01) | | | | | | -0.68 (1.78) | | | | | |
| Schernthaner et al. (2004) | | | | -1.70 (0.88) | | -1.55 (0.97) | | | | | | |
| Schernthaner et al. (2004) | | | | | | | | | | -1.20 (1.00) | -1.30 (1.10) | |
| Goke (2002) | | -0.48 (1.62) | | | | -1.16 (1.60) | | | | | | |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Campbell et al. (1994) | | | | -2.61 (1.58) | | | | | | -2.85 (1.75) | | |
| Aronoff et al. (2000) | 0.70 (1.51) | | | | | -0.32 (1.54) | | | | | | |
| Scherbaum et al. (2002) | -0.34 (0.98) | | | | | -0.98 (1.39) | | | | | | |
| Watanabe et al. (2005) | | | | | | -0.80 (0.27) | | | | -0.90 (0.42) | | |
| Ebeling et al. (2001) | -0.20 (0.78) | | | | | -1.10 (1.23) | | | | -1.20 (0.75) | | |
| Lawrence et al. (2004) | | | | -1.12 (0.84) | | -0.81 (0.63) | | | | -1.21 (0.82) | | |
| Yamanouchi et al. (2005) | | | | -1.90 (0.61) | | -2.20 (0.70) | | | | -2.00 (0.66) | | |
| Collier et al. (1989) | | | | -4.70 (2.05) | | | | | | -4.70 (1.23) | | |
| Tessier et al. (1999) | | | | -1.00 (1.42) | | | | | | -1.00 (1.58) | | |
| Hermann et al. (1994) | | | | -0.90 (0.87) | | | | | | -1.30 (0.87) | | |
| DeFronzo & (1995) | 0.40 (1.20) | | | -1.40 (1.19) | | | | | | | | |
| H+¤llsten et al. (2002) | -0.20 (0.34) | | | -0.70 (0.66) | | | | | | | | |
| Lee & (1998) | 0.20 (0.90) | | | -0.90 (0.90) | | | | | | | | |
| Del et al. (2003) | 0.48 (1.58) | | | -1.02 (1.38) | | | | | | | | |
| Braun D,Schonherr (1996) | -1.00 (2.13) | -2.50 (1.74) | | | | | | | | | | |
| Chan et al. (1998) | -0.27 (1.10) | -0.70 (1.21) | | | | | | | | | | |
| Chiasson et al. (1994) | -0.15 (0.93) | -0.90 (1.40) | | | | | | | | | | |
| Coniff et al. (1995) | 0.04 (1.02) | -0.54 (1.05) | | | | | | | | -0.99 (1.04) | | |
| Fischer et al. (1998) | 0.57 (1.07) | -0.42 (1.05) | | | | | | | | | | |
| Hoffmann & (1994) | 0.16 (0.39) | -0.98 (0.45) | | | | | | | | -0.76 (0.39) | | |
| Hoffmann & (1997) | 0.30 (0.83) | -1.10 (0.83) | | -0.90 (0.81) | | | | | | | | |
| Hotta et al. (1993) | -0.42 (1.30) | -1.38 (1.75) | | | | | | | | | | |
| Kovacevic et al. (1997) | 0.20 (1.40) | -0.70 (0.76) | | | | | | | | -1.60 (1.03) | | |
| Rosenthal & (2002) | | 0.00 (1.29) | | | | | | | | 0.00 (1.57) | | |
| Salman et al. (2001) | | -1.80 (1.33) | | | | | | | | -2.20 (0.74) | | |
| Birkeland et al. (1994) | 0.05 (0.92) | | | | | | | | | -0.68 (1.07) | | |
| Charbonnel et al. (2005) | | | | | | -1.58 (0.99) | | | | -1.83 (1.03) | | |
| Nakamura et al. (2004) | | | | | | -1.10 (1.16) | | | | -1.10 (1.25) | | |
| Tosi et al. (2003) | | | | -0.50 (1.10) | | | | | | -0.50 (1.30) | | |
| Saleem et al. (2011) | | | | | | | -0.60 (1.48) | | | -0.40 (1.48) | | |

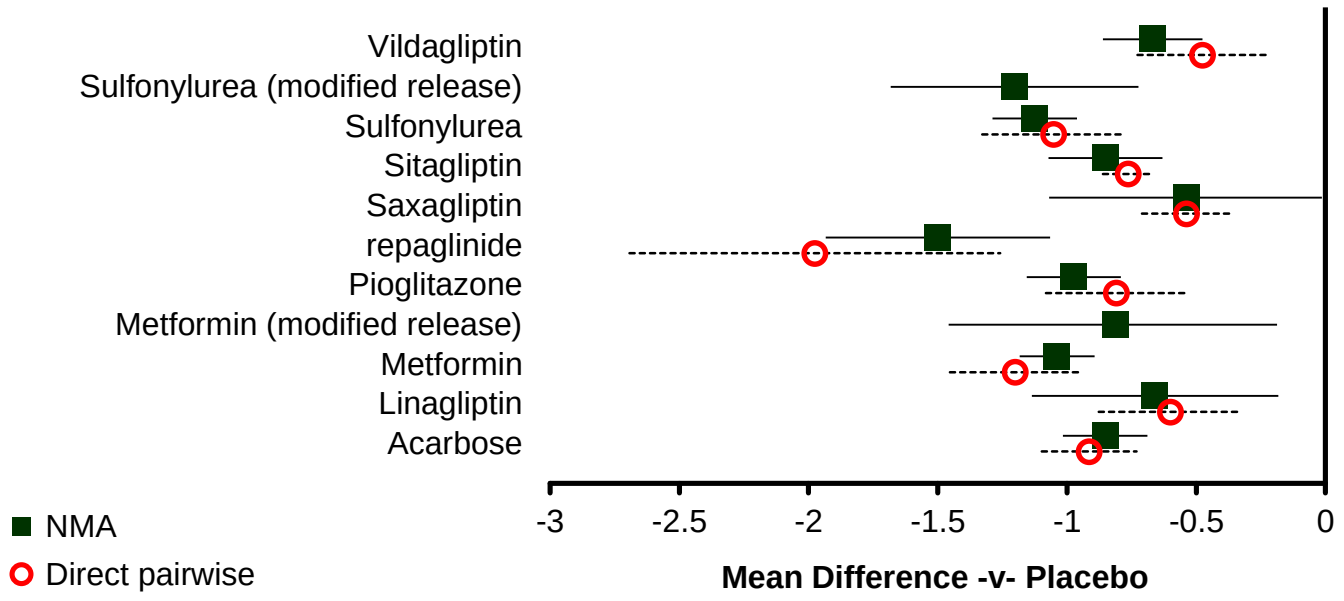
| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arjona et al. (2013) | | | | | | | | | -0.67 (0.81) | -0.55 (0.83) | | |
| Wang et al. (2013) | | -1.62 (0.68) | | -1.70 (0.63) | | | | | | -1.94 (0.76) | | |
| Roden et al. (2013) | 0.08 (0.85) | | | | | | | | -0.66 (0.76) | | | |
| Yang et al. (2014) | | -1.17 (0.68) | | -1.19 (0.76) | | | | | | | | |
| Erem et al. (2014) | | | | -1.20 (0.87) | | -1.18 (1.40) | | | | | -1.34 (1.39) | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 8: INITIAL THERAPY: HbA1c AT 6 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | -0.91 (-1.10, -0.73) | -0.60 (-0.88, -0.32) | -1.20 (-1.45, -0.95) | - | -0.81 (-1.08, -0.54) | -1.98 (-2.69, -1.26) | -0.54 (-0.71, -0.37) | -0.76 (-0.86, -0.67) | -1.05 (-1.33, -0.78) | - | -0.48 (-0.73, -0.23) |
| Acarbose | -0.85 (-1.02, -0.69) | | - | -0.01 (-0.11, 0.09) | - | -0.68 (-1.07, -0.29) | - | - | - | -0.30 (-0.68, 0.07) | - | -0.10 (-0.36, 0.16) |
| Linagliptin | -0.66 (-1.14, -0.18) | 0.19 (-0.30, 0.69) | | -0.35 (-0.59, -0.11) | - | - | - | - | - | - | - | - |
| Metformin | -1.04 (-1.18, -0.89) | -0.19 (-0.37, 0.00) | -0.38 (-0.85, 0.09) | | 0.23 (-0.24, 0.69) | 0.03 (-0.15, 0.21) | - | - | 0.20 (0.04, 0.36) | -0.14 (-0.26, -0.02) | -0.14 (-0.88, 0.60) | 0.21 (0.03, 0.40) |
| Metformin (modified release) | -0.81 (-1.46, -0.19) | 0.04 (-0.61, 0.68) | -0.15 (-0.94, 0.62) | 0.22 (-0.40, 0.84) | | - | - | - | - | - | - | - |
| Pioglitazone | -0.97 (-1.16, -0.79) | -0.12 (-0.33, 0.09) | -0.32 (-0.81, 0.18) | 0.06 (-0.11, 0.24) | -0.16 (-0.79, 0.49) | | - | - | - | -0.16 (-0.29, -0.04) | -0.16 (-1.05, 0.73) | 0.30 (0.02, 0.58) |
| repaglinide | -1.50 (-1.93, -1.07) | -0.65 (-1.09, -0.21) | -0.84 (-1.47, -0.21) | -0.46 (-0.90, -0.03) | -0.69 (-1.44, 0.07) | -0.52 (-0.97, -0.09) | | - | - | 0.23 (-0.08, 0.54) | - | - |
| Saxagliptin | -0.54 (-1.07, -0.01) | 0.31 (-0.24, 0.87) | 0.12 (-0.60, 0.83) | 0.50 (-0.05, 1.04) | 0.27 (-0.53, 1.10) | 0.44 (-0.12, 0.99) | 0.96 (0.29, 1.63) | | - | - | - | - |
| Sitagliptin | -0.85 (-1.07, -0.63) | 0.00 (-0.26, 0.26) | -0.19 (-0.71, 0.32) | 0.19 (-0.04, 0.42) | -0.04 (-0.69, 0.63) | 0.12 (-0.14, 0.39) | 0.65 (0.18, 1.12) | -0.31 (-0.88, 0.26) | | 0.12 (-0.07, 0.31) | - | - |
| Sulfonylurea | -1.12 (-1.29, -0.96) | -0.27 (-0.46, -0.09) | -0.46 (-0.95, 0.02) | -0.09 (-0.25, 0.07) | -0.31 (-0.94, 0.33) | -0.15 (-0.31, 0.02) | 0.38 (-0.04, 0.79) | -0.58 (-1.14, -0.04) | -0.27 (-0.51, -0.03) | | -0.10 (-0.35, 0.15) | 0.45 (0.29, 0.61) |
| Sulfonylurea (modified release) | -1.20 (-1.68, -0.72) | -0.35 (-0.84, 0.13) | -0.54 (-1.21, 0.12) | -0.16 (-0.64, 0.31) | -0.39 (-1.16, 0.39) | -0.23 (-0.71, 0.25) | 0.30 (-0.33, 0.91) | -0.66 (-1.38, 0.05) | -0.35 (-0.87, 0.16) | -0.08 (-0.54, 0.38) | | - |
| Vildagliptin | -0.67 (-0.86, -0.48) | 0.19 (-0.04, 0.41) | -0.01 (-0.51, 0.49) | 0.37 (0.17, 0.57) | 0.14 (-0.49, 0.80) | 0.31 (0.08, 0.54) | 0.83 (0.38, 1.29) | -0.13 (-0.69, 0.44) | 0.18 (-0.09, 0.46) | 0.46 (0.24, 0.67) | 0.54 (0.04, 1.04) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 5: INITIAL THERAPY: HbA1c AT 6 MONTHS – relative effect of all options versus reference treatment**

**Table 9: INITIAL THERAPY: HbA1c AT 6 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 12 (11, 12) |
| Acarbose | 0.000 | 7 (5, 9) |
| Linagliptin | 0.002 | 9 (3, 11) |
| Metformin | 0.002 | 4 (2, 6) |
| Metformin (modified release) | 0.027 | 8 (1, 11) |
| Pioglitazone | 0.000 | 5 (3, 8) |
| repaglinide | 0.797 | 1 (1, 3) |
| Saxagliptin | 0.002 | 10 (4, 11) |
| Sitagliptin | 0.000 | 7 (4, 10) |
| Sulfonylurea | 0.010 | 3 (2, 5) |
| Sulfonylurea (modified release) | 0.160 | 2 (1, 8) |
| Vildagliptin | 0.000 | 9 (7, 11) |

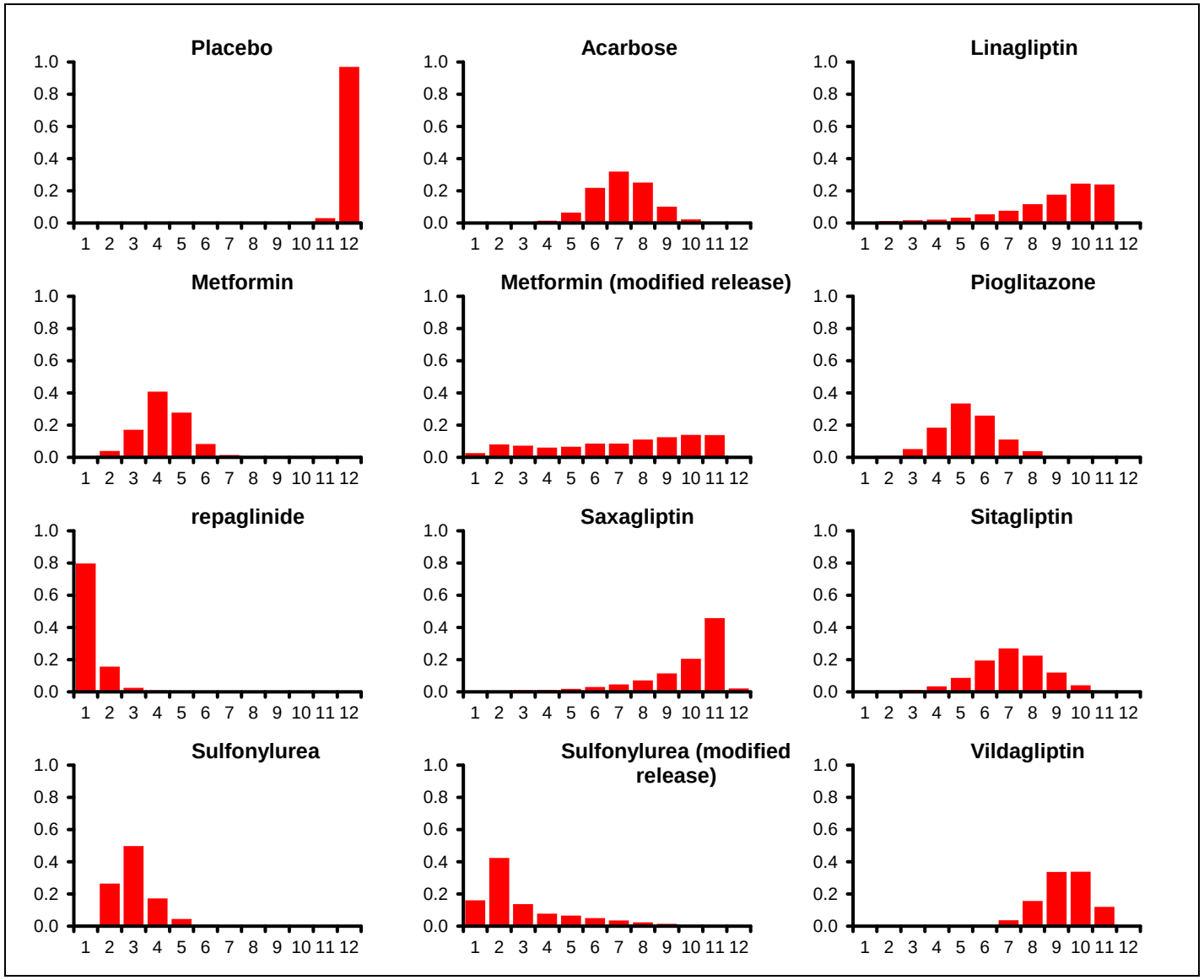



**Figure 6: INITIAL THERAPY: HbA1c AT 6 MONTHS – rank probability histograms**

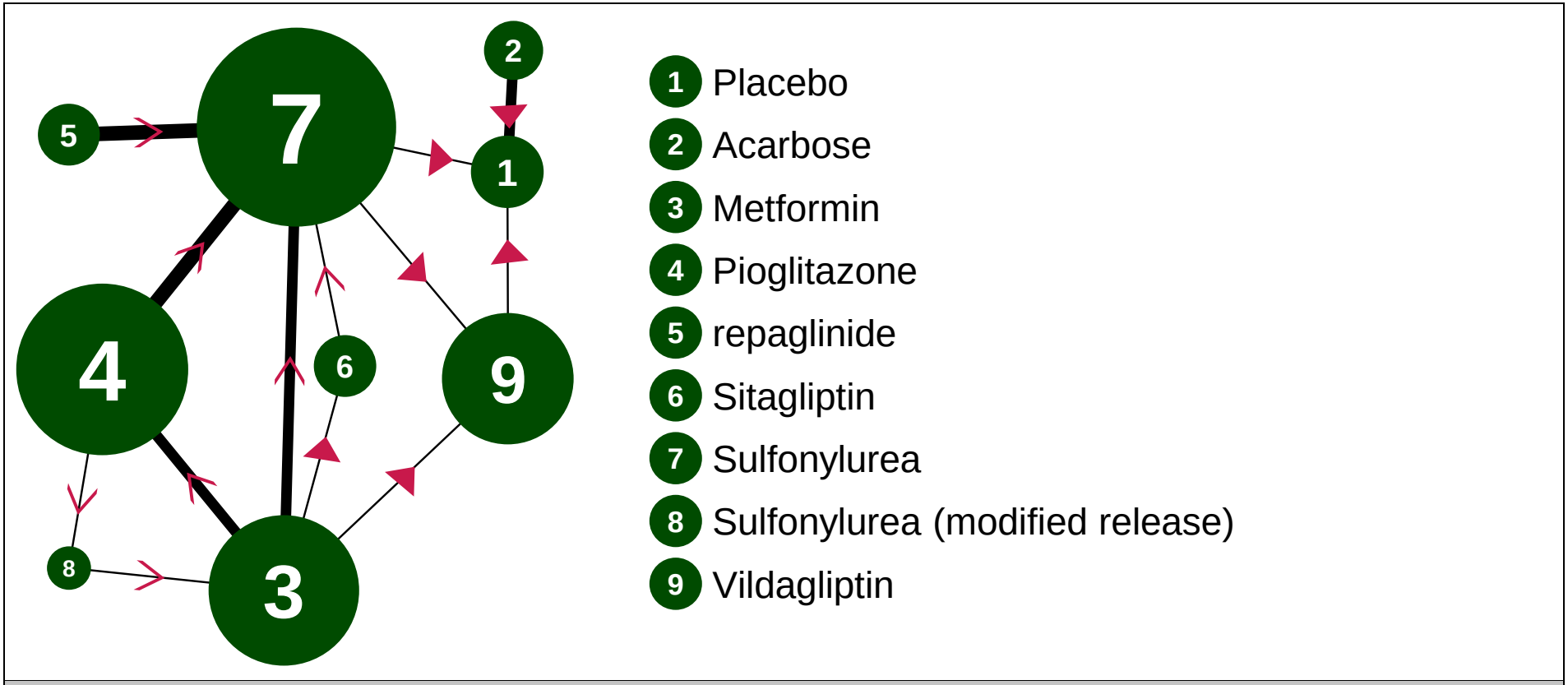
**Table 10: INITIAL THERAPY: HbA1c AT 6 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 150.1<br>(compared to 152 datapoints) | -209.086 | -331.383 | 122.297 | -86.788 | 0.248 (95%CI: 0.193, 0.315) |

**Table 11: INITIAL THERAPY: HbA1c AT 6 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

**Change in HbA1c at 12 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 7: INITIAL THERAPY: HbA1c AT 12 MONTHS – evidence network**

**Table 12: INITIAL THERAPY: HbA1c AT 12 MONTHS – input data**

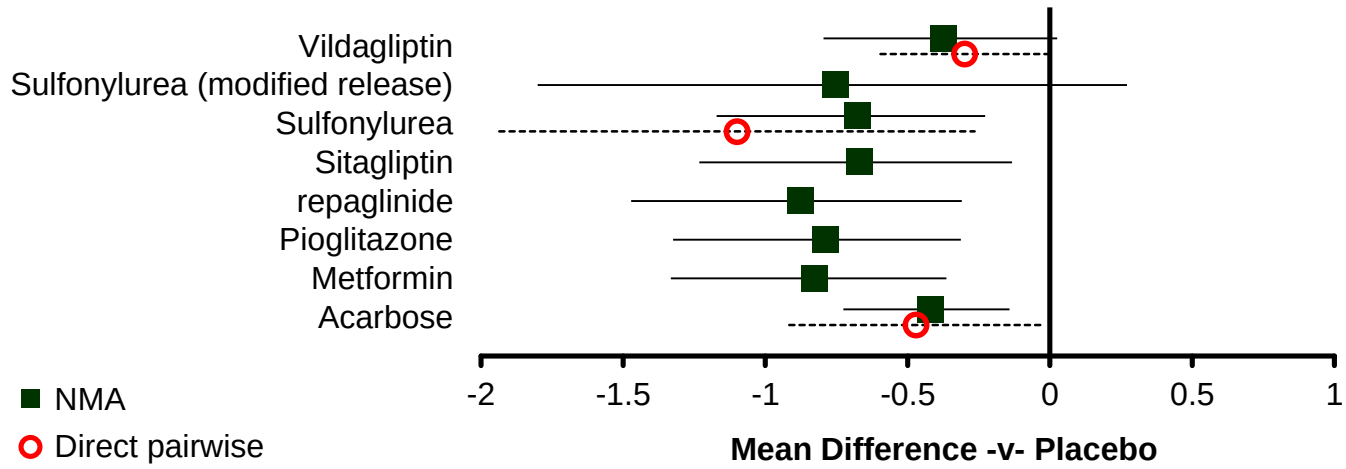
| | Placebo | Acarbose | Metformin | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Foley & (2009) | | | | | | | -1.49 (2.14) | | -1.20 (1.86) |
| Goldstein et al. (2007) | | | -1.16 (1.15) | | | -0.80 (1.05) | | | |
| Schweizer et al. (2007) | | | -1.40 (1.58) | | | | | | -1.00 (2.26) |
| Jain et al. (2006) | | | | -2.07 (1.19) | | | -2.02 (1.58) | | |
| Kirkman et al. (2006) | -0.10 (0.81) | -0.19 (0.92) | | | | | | | |
| Yoon et al. (2011) | | | -0.92 (0.96) | | | | -0.89 (0.76) | | |
| Derosa et al. (2003) | | | | | -1.20 (1.28) | | -1.10 (1.42) | | |
| Scherbaum et al. (2008) | 0.10 (1.22) | | | | | | | | -0.20 (1.25) |
| Abbatecola et al. (2006) | | | | | -0.75 (1.12) | | -0.50 (1.84) | | |
| Marbury et al. (1999) | | | | | -1.30 (1.41) | | -1.10 (1.47) | | |
| Schernthaner et al. (2004) | | | -1.50 (0.97) | -1.41 (0.97) | | | | | |
| Campbell et al. (1994) | | | -2.82 (2.15) | | | | -2.03 (2.68) | | |
| Yamanouchi et al. (2005) | | | -2.10 (1.15) | -2.30 (1.21) | | | -2.10 (1.08) | | |
| Chiasson et al. (1994) | 0.40 (1.09) | -0.50 (1.54) | | | | | | | |
| Birkeland et al. (1994) | 0.45 (1.30) | | | | | | -0.65 (1.51) | | |
| Charbonnel et al. (2005) | | | | -1.50 (1.42) | | | -1.40 (1.48) | | |
| Nakamura et al. (2004) | | | | -1.70 (1.55) | | | -1.50 (1.68) | | |
| Josse et al. (2003) | 0.30 (0.99) | -0.30 (0.96) | | | | | | | |
| Saleem et al. (2011) | | | | | -1.10 (2.20) | | -0.80 (2.07) | | |
| Arjona et al. (2013) | | | | | | -0.80 (0.59) | -0.60 (1.22) | | |
| Erem et al. (2014) | | | -1.22 (1.20) | -1.57 (1.73) | | | | -1.28 (1.67) | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 13: INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Metformin | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | | -0.47 (-0.92, -0.03) | - | - | - | - | -1.10 (-1.94, -0.26) | - | -0.30 (-0.60, 0.00) |
| Acarbose | -0.42 (-0.73, -0.14) | | - | - | - | - | - | - | - |
| Metformin | -0.83 (-1.33, -0.36) | -0.41 (-0.98, 0.16) | | 0.07 (-0.04, 0.18) | - | 0.36 (0.12, 0.61) | 0.04 (-0.16, 0.24) | -0.06 (-0.98, 0.86) | 0.40 (0.12, 0.68) |
| Pioglitazone | -0.79 (-1.33, -0.31) | -0.37 (-0.97, 0.20) | 0.04 (-0.22, 0.27) | | - | - | 0.09 (-0.04, 0.22) | 0.29 (-0.79, 1.37) | - |
| repaglinide | -0.87 (-1.47, -0.31) | -0.45 (-1.11, 0.20) | -0.05 (-0.46, 0.36) | -0.08 (-0.49, 0.34) | | - | 0.19 (-0.09, 0.48) | - | - |
| Sitagliptin | -0.67 (-1.23, -0.13) | -0.25 (-0.87, 0.37) | 0.16 (-0.15, 0.47) | 0.12 (-0.21, 0.49) | 0.20 (-0.26, 0.69) | | 0.20 (-0.02, 0.42) | - | - |
| Sulfonylurea | -0.68 (-1.17, -0.23) | -0.26 (-0.82, 0.29) | 0.15 (-0.08, 0.38) | 0.11 (-0.10, 0.35) | 0.20 (-0.15, 0.54) | 0.00 (-0.33, 0.30) | | - | 0.29 (0.01, 0.57) |
| Sulfonylurea (modified release) | -0.75 (-1.80, 0.27) | -0.33 (-1.42, 0.74) | 0.08 (-0.85, 1.00) | 0.04 (-0.91, 0.98) | 0.13 (-0.88, 1.13) | -0.08 (-1.07, 0.89) | -0.07 (-1.02, 0.86) | | - |
| Vildagliptin | -0.37 (-0.80, 0.03) | 0.05 (-0.45, 0.56) | 0.46 (0.13, 0.79) | 0.41 (0.07, 0.81) | 0.50 (0.04, 0.98) | 0.30 (-0.13, 0.71) | 0.30 (-0.01, 0.63) | 0.37 (-0.59, 1.37) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 8: INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment**

**Table 14: INITIAL THERAPY: HbA1c AT 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 9 (8, 9) |
| Acarbose | 0.023 | 7 (2, 8) |
| Metformin | 0.159 | 3 (1, 5) |
| Pioglitazone | 0.086 | 3 (1, 6) |
| repaglinide | 0.364 | 2 (1, 6) |
| Sitagliptin | 0.030 | 5 (1, 8) |
| Sulfonylurea | 0.002 | 5 (3, 7) |
| Sulfonylurea (modified release) | 0.335 | 4 (1, 9) |
| Vildagliptin | 0.001 | 7 (5, 8) |

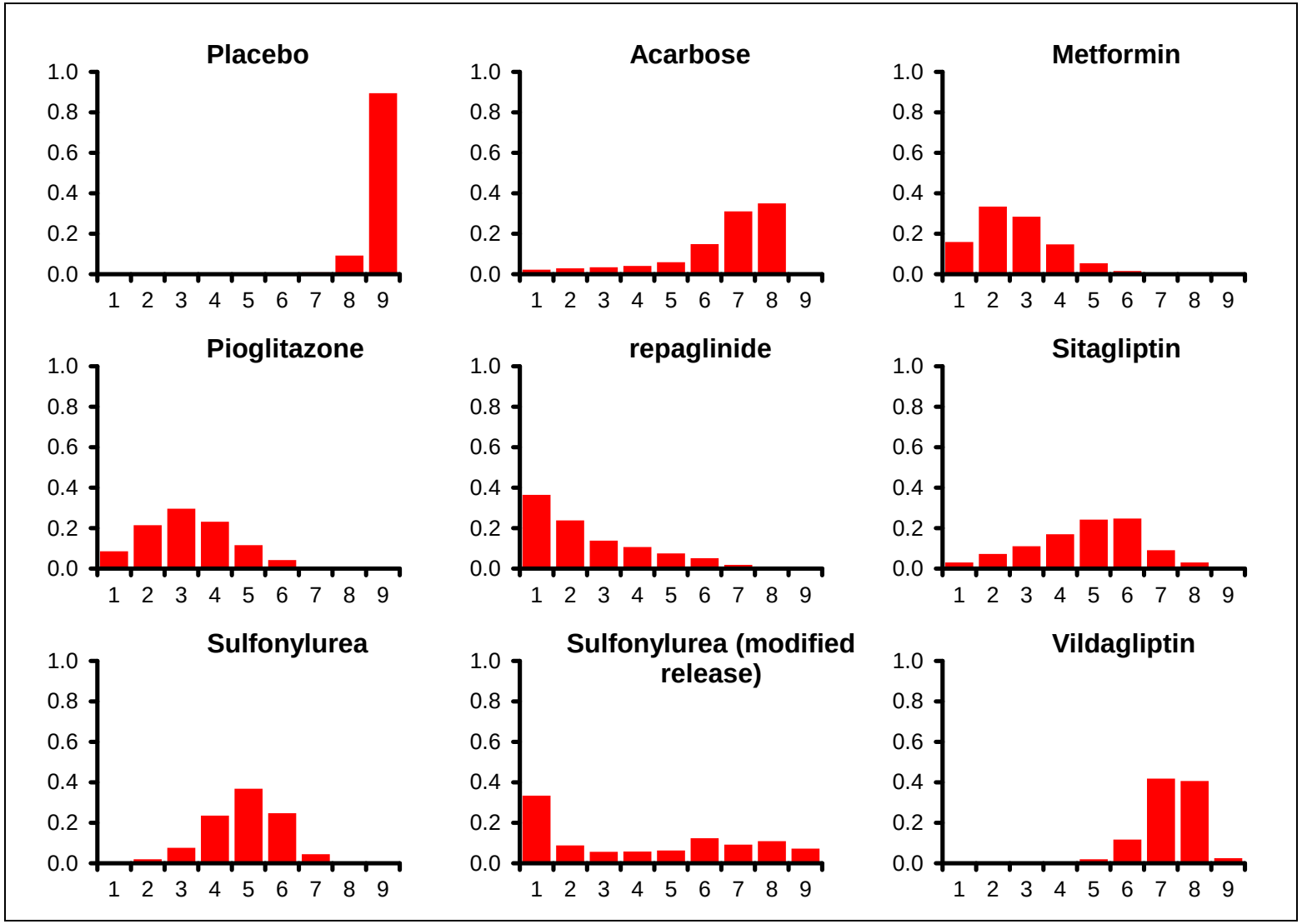



**Figure 9: INITIAL THERAPY: HbA1c AT 12 MONTHS – rank probability histograms**

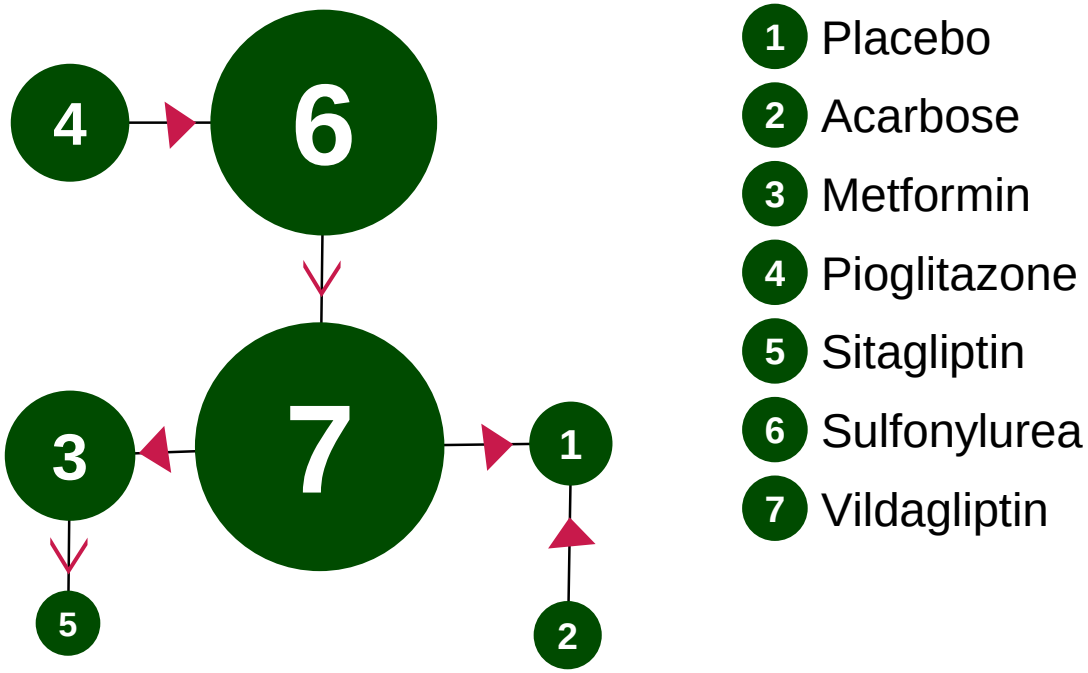
**Table 15: INITIAL THERAPY: HbA1c AT 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 44.75<br>(compared to 46 datapoints) | -44.572 | -80.181 | 35.608 | -8.964 | 0.155 (95%CI: 0.021, 0.328) |

**Table 16: INITIAL THERAPY: HbA1c AT 12 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

**Change in HbA1c at 24 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 10: INITIAL THERAPY: HbA1c AT 24 MONTHS – evidence network**

**Table 17: INITIAL THERAPY: HbA1c AT 24 MONTHS – input data**

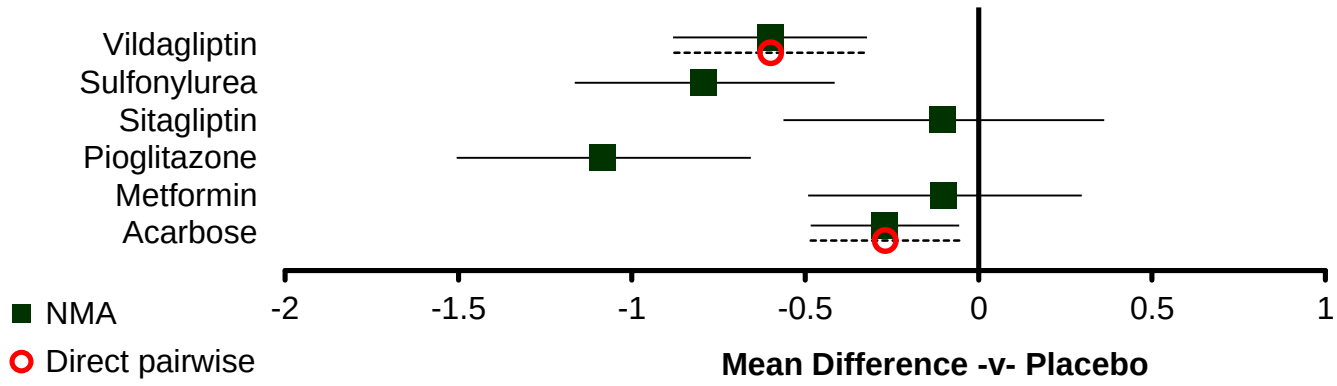
| | Placebo | Acarbose | Metformin | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|
| Foley & (2009) | | | | | | -0.89 (1.76) | -0.70 (1.78) |
| Goldstein et al. (2007) | | | -1.22 (0.90) | | -1.20 (0.72) | | |
| Schweizer et al. (2007) | | | -1.00 (1.26) | | | | -1.50 (1.75) |
| Kirkman et al. (2006) | -0.06 (0.63) | -0.33 (0.59) | | | | | |
| Scherbaum et al. (2008) | 0.50 (0.78) | | | | | | -0.10 (0.82) |
| Charbonnel et al. (2005) | | | | -1.25 (1.15) | | -0.96 (1.22) | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 18: INITIAL THERAPY: HbA1c AT 24 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Metformin | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|
| Placebo | | -0.27 (-0.48, -0.06) | - | - | - | - | -0.60 (-0.88, -0.32) |
| Acarbose | -0.27 (-0.48, -0.06) | | - | - | - | - | - |
| Metformin | -0.10 (-0.49, 0.30) | 0.17 (-0.28, 0.62) | | - | 0.02 (-0.23, 0.26) | - | -0.50 (-0.78, -0.22) |
| Pioglitazone | -1.08 (-1.51, -0.66) | -0.81 (-1.28, -0.33) | -0.98 (-1.40, -0.56) | | - | 0.29 (0.09, 0.49) | - |
| Sitagliptin | -0.10 (-0.56, 0.36) | 0.17 (-0.34, 0.68) | 0.00 (-0.25, 0.25) | 0.98 (0.49, 1.47) | | - | - |
| Sulfonylurea | -0.79 (-1.17, -0.42) | -0.52 (-0.95, -0.09) | -0.69 (-1.06, -0.32) | 0.29 (0.09, 0.49) | -0.69 (-1.13, -0.25) | | 0.19 (-0.05, 0.43) |
| Vildagliptin | -0.60 (-0.88, -0.32) | -0.33 (-0.68, 0.02) | -0.50 (-0.78, -0.22) | 0.48 (0.16, 0.80) | -0.50 (-0.87, -0.13) | 0.19 (-0.05, 0.44) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 11: INITIAL THERAPY: HbA1c AT 24 MONTHS – relative effect of all options versus reference treatment**

**Table 19: INITIAL THERAPY: HbA1c AT 24 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 7 (5, 7) |
| Acarbose | 0.000 | 4 (3, 6) |
| Metformin | 0.000 | 6 (4, 7) |
| Pioglitazone | 0.996 | 1 (1, 1) |
| Sitagliptin | 0.000 | 6 (4, 7) |
| Sulfonylurea | 0.002 | 2 (2, 3) |
| Vildagliptin | 0.001 | 3 (2, 4) |

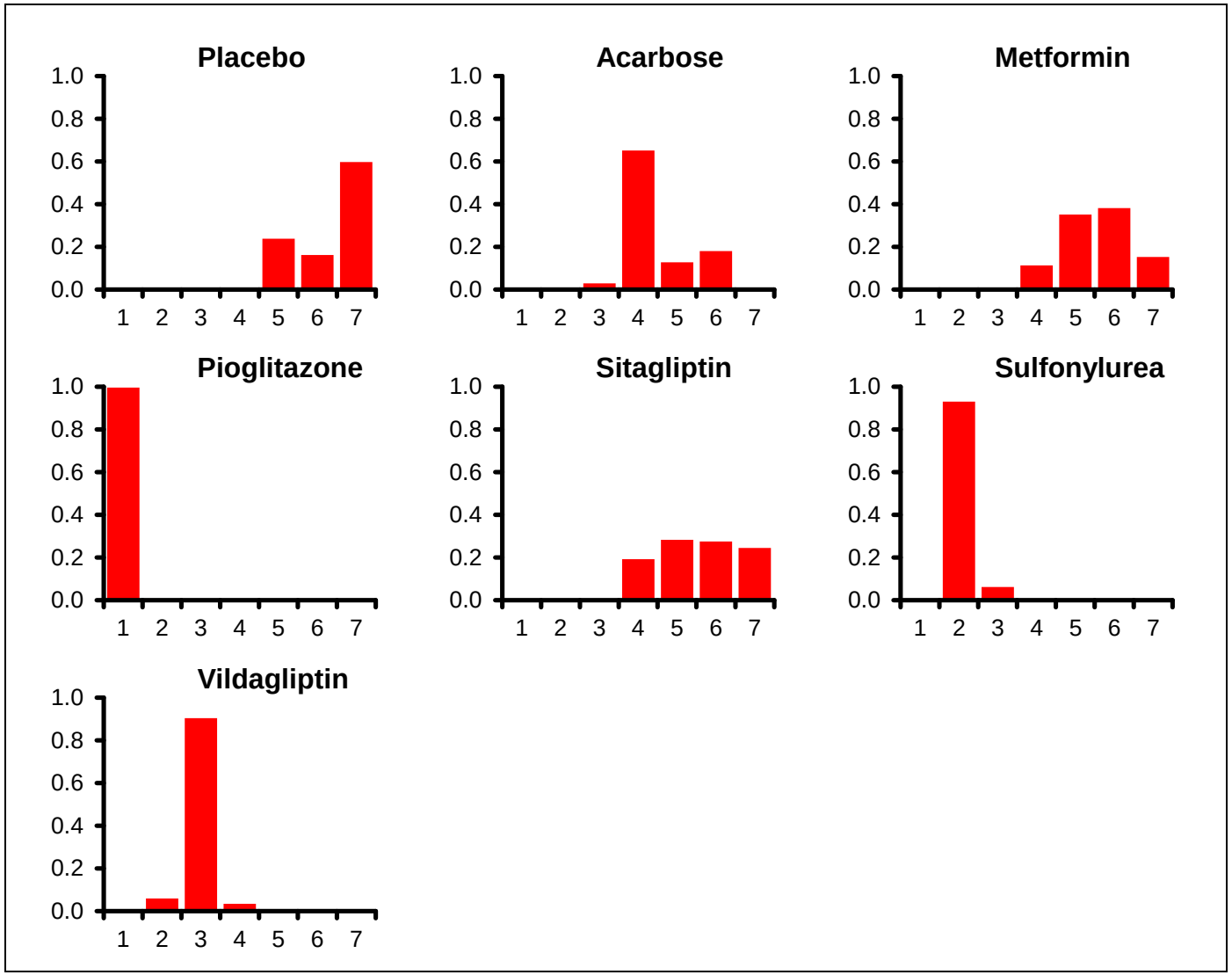



**Figure 12: INITIAL THERAPY: HbA1c AT 24 MONTHS – rank probability histograms**

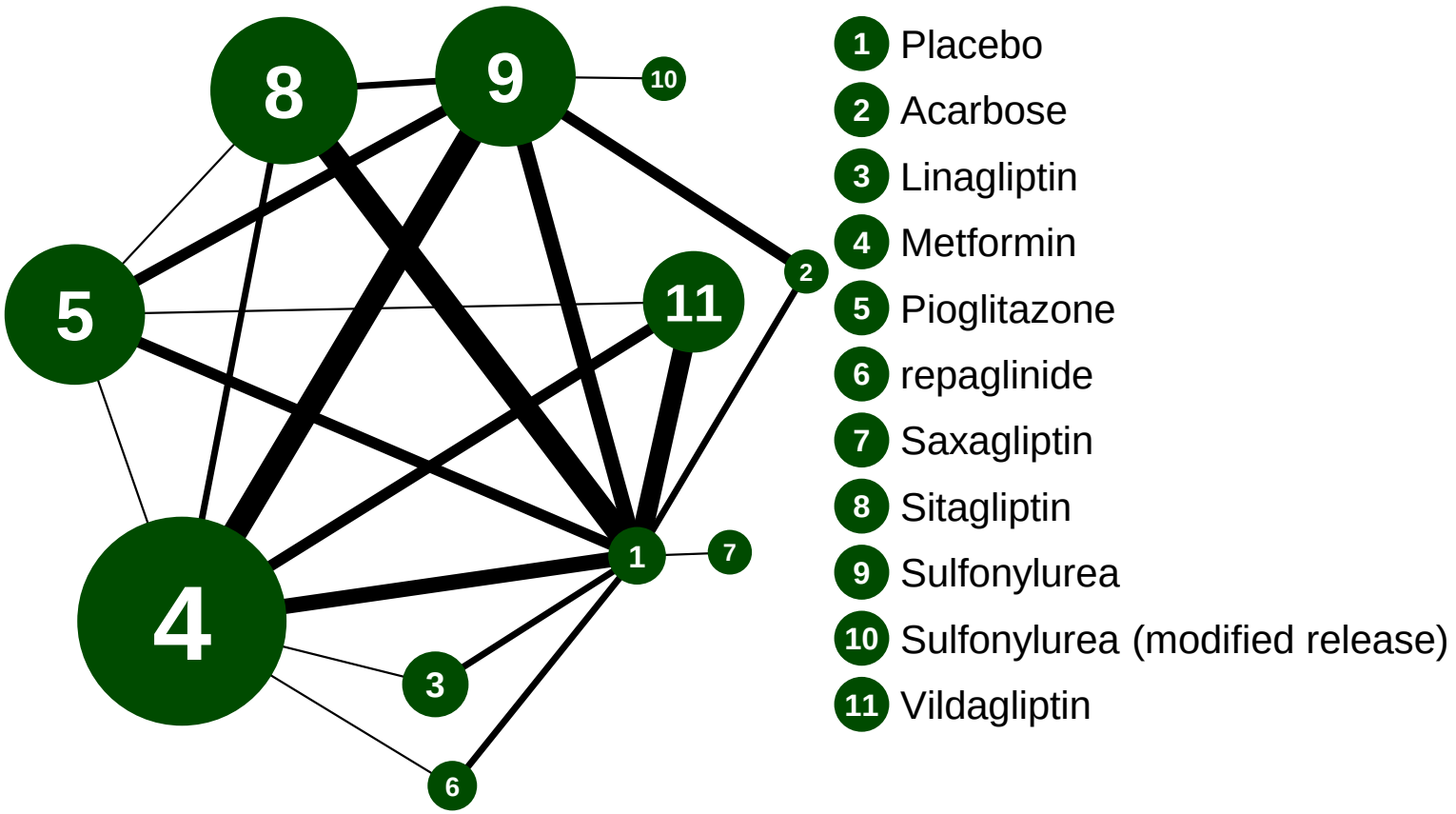
**Table 20: INITIAL THERAPY: HbA1c AT 24 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 13.95<br>(compared to 13 datapoints) | -24.809 | -36.833 | 12.024 | -12.784 | |

**Table 21: INITIAL THERAPY: HbA1c AT 24 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.1.2 Hypoglycaemia at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 13: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network**

**Table 22: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data**

| | Placebo | Acarbose | Linagliptin | Metformin | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dichotomous proportion data | | | | | | | | | | | |
| Schweizer et al. (2009) - 0.46yr | | | | 2/165 | | | | | | | 0/167 |
| Goldstein et al. (2007) - 1.99yr | | | | 7/364 | | | | 2/179 | | | |
| Schweizer et al. (2007) - 1.99yr | | | | 0/158 | | | | | | | 1/304 |
| Scott et al. (2007) - 0.23yr | 3/125 | | | | | | | 12/495 | 21/123 | | |
| Yoon et al. (2011) - 0.92yr | | | | 4/114 | | | | | 23/118 | | |
| Haak et al. (2012) - 0.46yr | 1/72 | | 0/142 | 7/291 | | | | | | | |
| Pan et al. (2012) - 0.46yr | 2/284 | | | | | | 5/284 | | | | |
| Shihara et al. (2011) - 0.50yr | | | | | 5/96 | | | | 7/95 | | |
| Aschner et al. (2006) - 0.46yr | 2/253 | | | | | | | 2/238 | | | |
| Hanefeld et al. (2007) - 0.23yr | 0/111 | | | | | | | 5/441 | | | |
| Dejager et al. (2007) - 0.46yr | 0/157 | | | | | | | | | | 3/468 |
| Iwamoto et al. (2010) - 0.23yr | 2/73 | | | | | | | 7/222 | | | |
| Kikuchi et al. (2009) - 0.23yr | 1/72 | | | | | | | | | | 5/219 |
| Rosenstock et al. (2007) - 0.46yr | | | | | 1/161 | | | | | | 1/153 |
| Pratley et al. (2006) - 0.23yr | 0/28 | | | | | | | | | | 1/70 |
| Ristic et al. (2005) - 0.23yr | 3/56 | | | | | | | | | | 14/220 |
| Scherbaum et al. (2008) - 2.07yr | 2/150 | | | | | | | | | | 0/156 |
| Herz et al. (2003) - 0.31yr | 11/96 | | | | 21/191 | | | | | | |
| Horton et al. (2000) - 0.46yr | 3/104 | | | 11/104 | | | | | | | |
| Jovanovic et al. (2000) - 0.46yr | 8/75 | | | | | 89/286 | | | | | |
| Schernthaner et al. (2004) - 0.52yr | | | | | | | | | 15/156 | 7/133 | |
| Aronoff et al. (2000) - 0.50yr | 0/79 | | | | 4/329 | | | | | | |
| Raz et al. (2006) - 0.34yr | 0/110 | | | | | | | 3/205 | | | |
| Collier et al. (1989) - 0.46yr | | | | 0/12 | | | | | 2/12 | | |

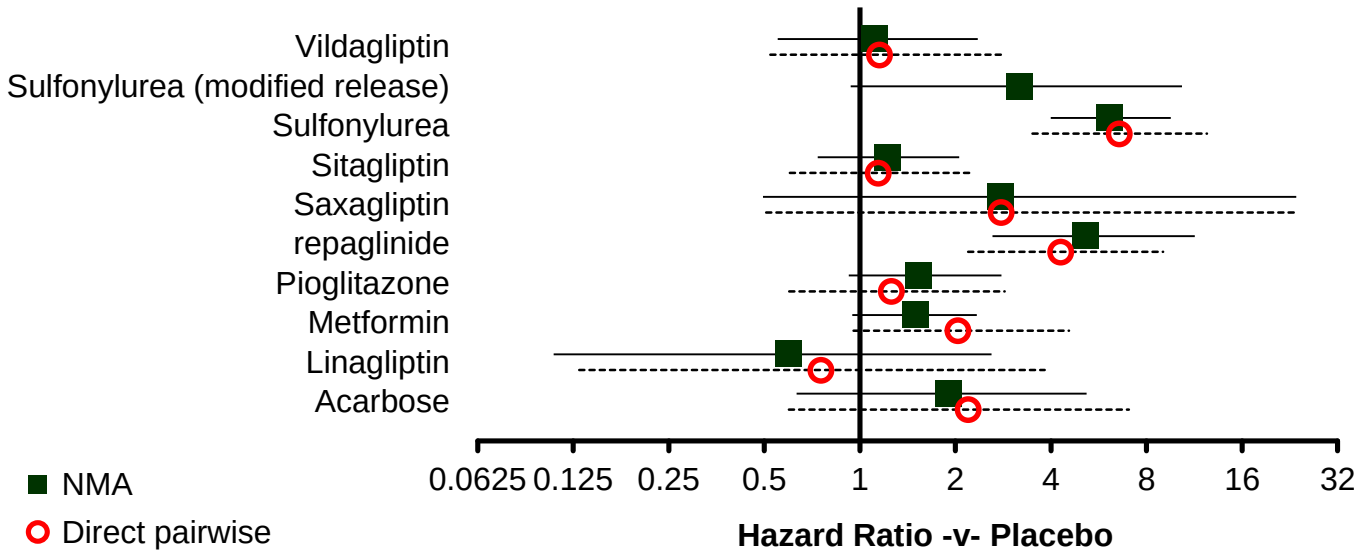
| | Placebo | Acarbose | Linagliptin | Metformin | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tessier et al. (1999) - 0.46yr | | | | 3/18 | | | | | 8/18 | | |
| Hermann et al. (1994) - 0.46yr | | | | 8/38 | | | | | 12/34 | | |
| Chiasson & (2001) - 0.69yr | 7/83 | | | 8/83 | | | | | | | |
| Coniff et al. (1995) - 0.46yr | 4/72 | 6/74 | | | | | | | 11/71 | | |
| Hoffmann & (1994) - 0.46yr | 0/30 | 0/28 | | | | | | | 2/27 | | |
| Johnston et al. (1998) - 1.07yr | 8/101 | | | | | | | | 48/104 | | |
| Salman et al. (2001) - 0.46yr | | 0/27 | | | | | | | 3/30 | | |
| Viberti et al. (2002) - 3.99yr | | | | 168/1454 | | | | | 557/1441 | | |
| Charbonnel et al. (2005) - 1.00yr | | | | | 22/624 | | | | 63/626 | | |
| Moses et al. (2001) - 0.31yr | 4/134 | | | | | 44/260 | | | | | |
| Ferrannini et al. (2013) - 0.23yr | 1/82 | | | 1/80 | | | | | | | |
| Arjona et al. (2013) - 1.03yr | | | | | | | | 13/210 | 36/212 | | |
| Alba et al. (2013) - 0.23yr | 0/53 | | | | 2/54 | | | 0/52 | | | |
| Count data | | | | | | | | | | | |
| Bosi et al. (2009) - 0.46yr | | | | 2/45276 | | | | | | | 2/45780 |
| Jain et al. (2006) - 1.07yr | | | | | 24/75460 | | | | 176/74284 | | |
| Bruce et al. (2006) - 0.38yr | | | | 0/2030 | | | | | 13/2240 | | |
| Aschner et al. (2010) - 0.46yr | | | | 23/81396 | | | | 17/83580 | | | |
| Barnett et al. (2012) - 0.34yr | 0/8820 | | 2/18144 | | | | | | | | |
| Genovese et al. (2013) - 0.31yr | | | | 0/3080 | 4/2968 | | | | | | |
| Fang et al. (2014) - 0.29yr | | | | 0/2100 | | 10/4147.5 | | | | | |

*Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 23: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Acarbose | 1.91 (0.63, 5.18) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin | 0.60 (0.11, 2.60) | 0.31 (0.04, 1.89) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin | 1.50 (0.95, 2.33) | 0.78 (0.29, 2.32) | 2.50 (0.59, 13.91) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Pioglitazone | 1.54 (0.92, 2.79) | 0.81 (0.29, 2.62) | 2.60 (0.58, 15.21) | 1.02 (0.62, 1.93) | | N/A | N/A | N/A | N/A | N/A | N/A |
| repaglinide | 5.16 (2.62, 11.36) | 2.72 (0.82, 10.42) | 8.75 (1.71, 55.99) | 3.45 (1.58, 8.33) | 3.36 (1.38, 8.31) | | N/A | N/A | N/A | N/A | N/A |
| Saxagliptin | 2.78 (0.50, 23.69) | 1.48 (0.20, 16.13) | 4.84 (0.45, 73.85) | 1.86 (0.31, 16.44) | 1.81 (0.29, 16.34) | 0.54 (0.08, 5.13) | | N/A | N/A | N/A | N/A |
| Sitagliptin | 1.23 (0.74, 2.06) | 0.65 (0.23, 1.98) | 2.05 (0.46, 11.93) | 0.82 (0.50, 1.35) | 0.80 (0.41, 1.43) | 0.24 (0.09, 0.55) | 0.44 (0.05, 2.71) | | N/A | N/A | N/A |
| Sulfonylurea | 6.13 (3.99, 9.55) | 3.21 (1.26, 9.16) | 10.28 (2.37, 57.94) | 4.08 (2.86, 6.10) | 4.00 (2.38, 6.08) | 1.19 (0.49, 2.60) | 2.20 (0.25, 13.25) | 4.98 (3.15, 8.02) | | N/A | N/A |
| Sulfonylurea (modified release) | 3.19 (0.94, 10.35) | 1.68 (0.38, 7.60) | 5.31 (0.80, 41.45) | 2.11 (0.64, 6.93) | 2.07 (0.57, 6.59) | 0.61 (0.14, 2.33) | 1.11 (0.10, 9.55) | 2.58 (0.75, 8.67) | 0.52 (0.16, 1.56) | | N/A |
| Vildagliptin | 1.12 (0.55, 2.35) | 0.59 (0.18, 2.10) | 1.88 (0.38, 11.61) | 0.75 (0.35, 1.65) | 0.72 (0.30, 1.72) | 0.22 (0.07, 0.59) | 0.40 (0.04, 2.74) | 0.91 (0.40, 2.16) | 0.18 (0.08, 0.41) | 0.36 (0.09, 1.44) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 14: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 24: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.100 | 3 (1, 5) |
| Acarbose | 0.032 | 7 (1, 10) |
| Linagliptin | 0.663 | 1 (1, 8) |
| Metformin | 0.002 | 6 (3, 8) |
| Pioglitazone | 0.005 | 6 (2, 8) |
| repaglinide | 0.000 | 10 (8, 11) |
| Saxagliptin | 0.052 | 8 (1, 11) |
| Sitagliptin | 0.033 | 4 (1, 7) |
| Sulfonylurea | 0.000 | 10 (9, 11) |
| Sulfonylurea (modified release) | 0.008 | 8 (3, 11) |
| Vildagliptin | 0.106 | 3 (1, 8) |

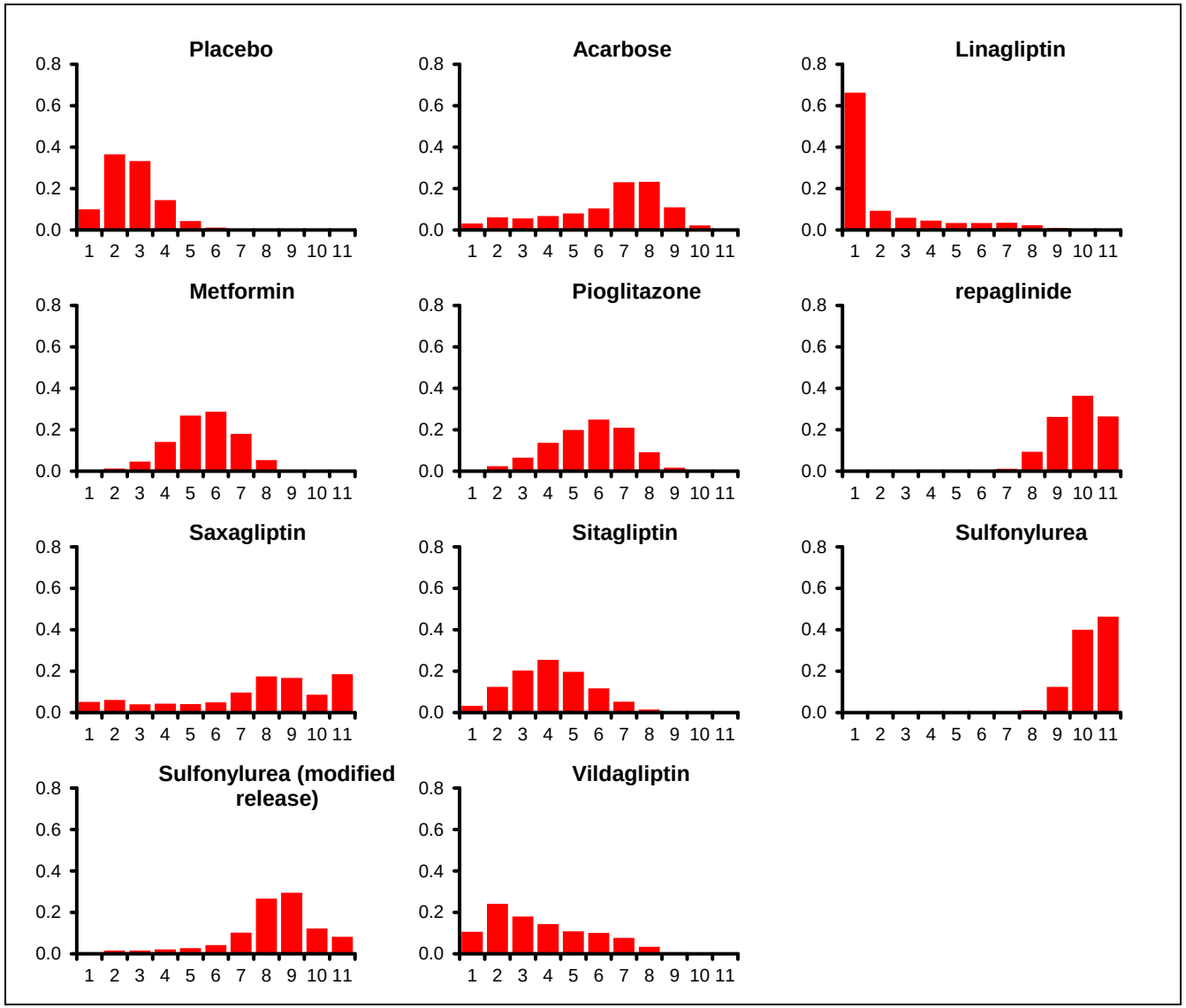



**Figure 15: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms**

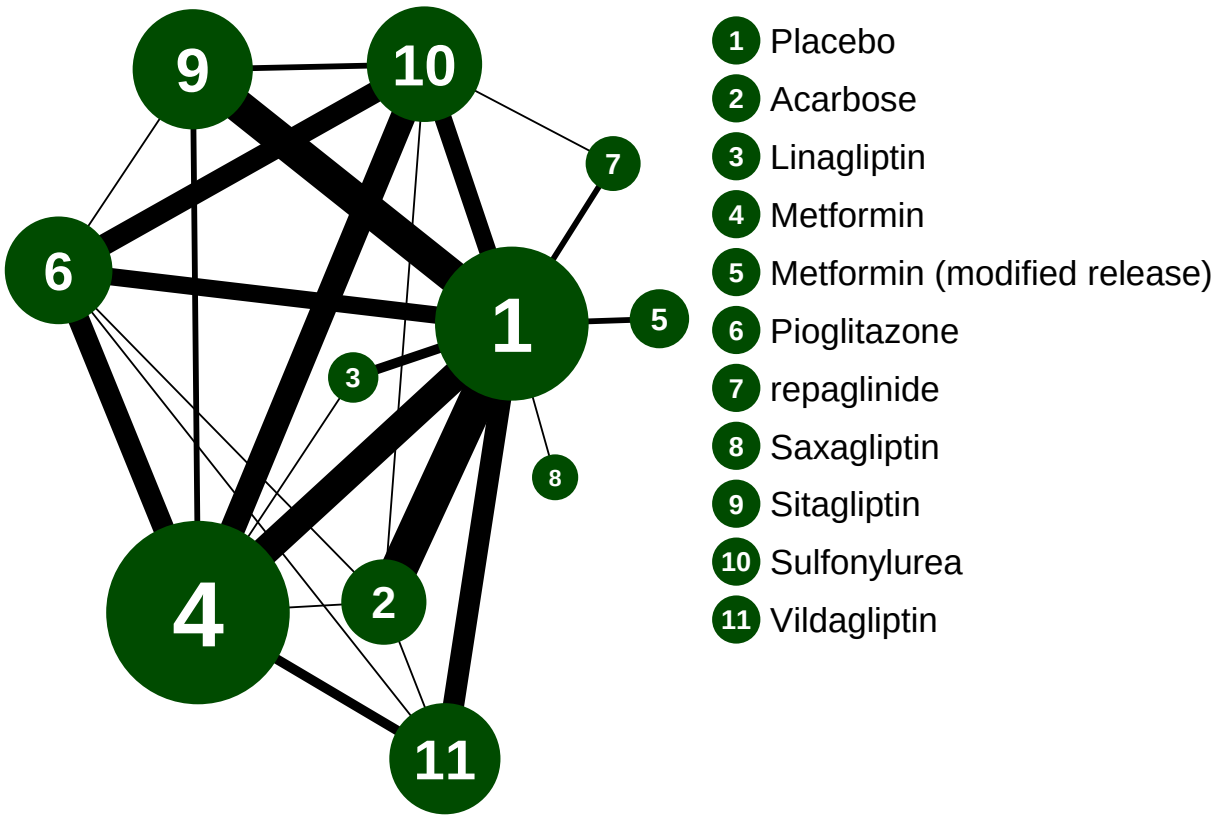
**Table 25: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 102.4<br>(compared to 112 datapoints) | 382.848 | 329.618 | 53.23 | 512.811 | 0.305 (95%CI: 0.072, 0.582) |

**Table 26: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes**

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

### J.2.1.3 Dropouts due to adverse events at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 16: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – evidence network**

**Table 27: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – input data**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Santilli et al. (2010) - 0.38yr | 2/27 | 2/27 | | | | | | | | | |
| Derosa et al. (2009) - 1.25yr | | | | 5/67 | | 3/69 | | | | | |
| Schweizer et al. (2009) - 0.46yr | | | | 13/166 | | | | | | | 6/169 |
| Bosi et al. (2009) - 0.46yr | | | | 13/294 | | | | | | | 7/300 |
| Pan et al. (2008) - 0.46yr | | 7/220 | | | | | | | | | 11/441 |
| Goldstein et al. (2007) - 1.99yr | | | | 25/364 | | | | | 14/179 | | |
| Schweizer et al. (2007) - 1.99yr | | | | 3/158 | | | | | | | 5/304 |
| Teramoto et al. (2007) - 0.46yr | | | | | | 1/46 | | | | 3/46 | |
| Scott et al. (2007) - 0.23yr | 1/125 | | | | | | | | 9/495 | 7/123 | |
| Jain et al. (2006) - 1.07yr | | | | | | 14/251 | | | | 25/251 | |
| Kirkman et al. (2006) - 5.00yr | 5/119 | 13/120 | | | | | | | | | |
| Bruce et al. (2006) - 0.38yr | | | | 0/15 | | | | | | 1/17 | |
| Yoon et al. (2011) - 0.92yr | | | | 9/114 | | | | | | 10/118 | |
| Haak et al. (2012) - 0.46yr | 3/72 | | 6/142 | 10/291 | | | | | | | |
| Pan et al. (2012) - 0.46yr | 3/284 | | | | | | | 3/284 | | | |
| Derosa et al. (2011) - 0.54yr | 1/87 | 8/88 | | | | | | | | | |
| Aschner et al. (2010) - 0.46yr | | | | 19/522 | | | | | 9/528 | | |
| Aschner et al. (2006) - 0.46yr | 5/253 | | | | | | | | 5/238 | | |
| Derosa et al. (2003) - 1.15yr | | | | | | | 0/66 | | | 2/66 | |
| Barzilai et al. (2011) - 0.46yr | 3/104 | | | | | | | | 5/102 | | |
| Nonaka et al. (2008) - 0.23yr | 3/76 | | | | | | | | 0/76 | | |
| Hanefeld et al. (2007) - 0.23yr | 4/111 | | | | | | | | 9/444 | | |
| Dejager et al. (2007) - 0.46yr | 6/160 | | | | | | | | | | 11/472 |
| Kawamori et al. (2012) - 0.23yr | 6/80 | | 3/159 | | | | | | | | |
| Iwamoto et al. (2010) - 0.23yr | 0/73 | | | | | | | | 2/222 | | |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kikuchi et al. (2009) - 0.23yr | 1/72 | | | | | | | | | | 3/219 |
| Mohan et al. (2009) - 0.34yr | 4/178 | | | | | | | | 6/352 | | |
| Pi-Sunyer et al. (2007) - 0.46yr | 3/92 | | | | | | | | | | 2/262 |
| Rosenstock et al. (2007) - 0.46yr | | | | | | 9/161 | | | | | 4/154 |
| Pratley et al. (2006) - 0.23yr | 0/28 | | | | | | | | | | 2/72 |
| Ristic et al. (2005) - 0.23yr | 3/56 | | | | | | | | | | 11/220 |
| Scherbaum et al. (2008) - 2.07yr | 10/150 | | | | | | | | | | 18/156 |
| Herz et al. (2003) - 0.31yr | 1/99 | | | | | 4/198 | | | | | |
| Horton et al. (2000) - 0.46yr | 9/172 | | | 12/178 | | | | | | | |
| Jovanovic et al. (2000) - 0.46yr | 12/75 | | | | | | 21/286 | | | | |
| Schernthaner et al. (2004) - 1.00yr | | | | 39/597 | | 42/597 | | | | | |
| Fujioka et al. (2005) - 0.46yr | 2/79 | | | | 8/161 | | | | | | |
| Fujioka et al. (2005) - 0.31yr | 1/117 | | | | 17/625 | | | | | | |
| Goke (2002) - 0.50yr | | 5/136 | | | | 1/129 | | | | | |
| Aronoff et al. (2000) - 0.50yr | 2/79 | | | | | 13/329 | | | | | |
| Scherbaum et al. (2002) - 0.50yr | 2/84 | | | | | 2/167 | | | | | |
| Watanabe et al. (2005) - 0.50yr | | | | | | 2/15 | | | | 1/15 | |
| Lawrence et al. (2004) - 0.46yr | | | | 1/21 | | 1/21 | | | | 2/22 | |
| Pavo et al. (2003) - 0.61yr | | | | 0/100 | | 2/105 | | | | | |
| Yamanouchi et al. (2005) - 1.00yr | | | | 0/39 | | 2/38 | | | | 0/37 | |
| Raz et al. (2006) - 0.34yr | 4/110 | | | | | | | | 1/205 | | |
| Tessier et al. (1999) - 0.46yr | | | | 1/20 | | | | | | 1/19 | |
| Hermann et al. (1994) - 0.54yr | | | | 3/34 | | | | | | 9/38 | |
| DeFronzo & (1995) - 0.56yr | 2/146 | | | 14/143 | | | | | | | |
| H+¤llsten et al. (2002) - 0.50yr | 0/14 | | | 1/16 | | | | | | | |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Del et al. (2003) - 0.56yr | 6/144 | | | 16/284 | | | | | | | |
| Chiasson & (2001) - 0.69yr | 2/83 | | | 5/83 | | | | | | | |
| Coniff et al. (1995) - 0.31yr | 3/73 | 27/145 | | | | | | | | | |
| Fischer et al. (1998) - 0.46yr | 0/97 | 11/398 | | | | | | | | | |
| Hotta et al. (1993) - 0.46yr | 0/18 | 1/19 | | | | | | | | | |
| Johnston et al. (1998) - 1.07yr | 6/101 | | | | | | | | | 6/104 | |
| Kovacevic et al. (1997) - 0.46yr | 3/34 | 0/34 | | | | | | | | 0/34 | |
| Santeusanio et al. (1993) - 0.31yr | 1/29 | 6/55 | | | | | | | | | |
| Scott et al. (1999) - 0.31yr | 4/52 | 4/53 | | | | | | | | | |
| Segal et al. (1997) - 0.46yr | 1/65 | | | | | | | | | 2/69 | |
| Viberti et al. (2002) - 3.99yr | | | | 178/1454 | | | | | | 215/1441 | |
| Birkeland et al. (1994) - 5.33yr | 4/16 | | | | | | | | | 2/30 | |
| Charbonnel et al. (2005) - 1.99yr | | | | | | 33/270 | | | | 25/297 | |
| Moses et al. (2001) - 0.31yr | 2/138 | | | | | | 9/270 | | | | |
| Josse et al. (2003) - 1.00yr | 3/99 | 10/93 | | | | | | | | | |
| Kikuchi et al. (2012) - 0.54yr | 1/54 | | | | | 14/159 | | | | | |
| Ferrannini et al. (2013) - 0.23yr | 0/82 | | | 3/80 | | | | | | | |
| Fonseca et al. (2013) - 0.23yr | 1/69 | | | 1/69 | | | | | | | |
| Arjona et al. (2013) - 1.03yr | | | | | | | | | 16/211 | 18/212 | |
| Barnett et al. (2012) - 0.34yr | 0/76 | | 1/151 | | | | | | | | |
| Genovese et al. (2013) - 0.31yr | | | | 2/29 | | 4/29 | | | | | |
| Alba et al. (2013) - 0.23yr | 2/53 | | | | | 0/54 | | | 3/52 | | |
| Yang et al. (2014) - 0.46yr | | 9/393 | | 11/395 | | | | | | | |

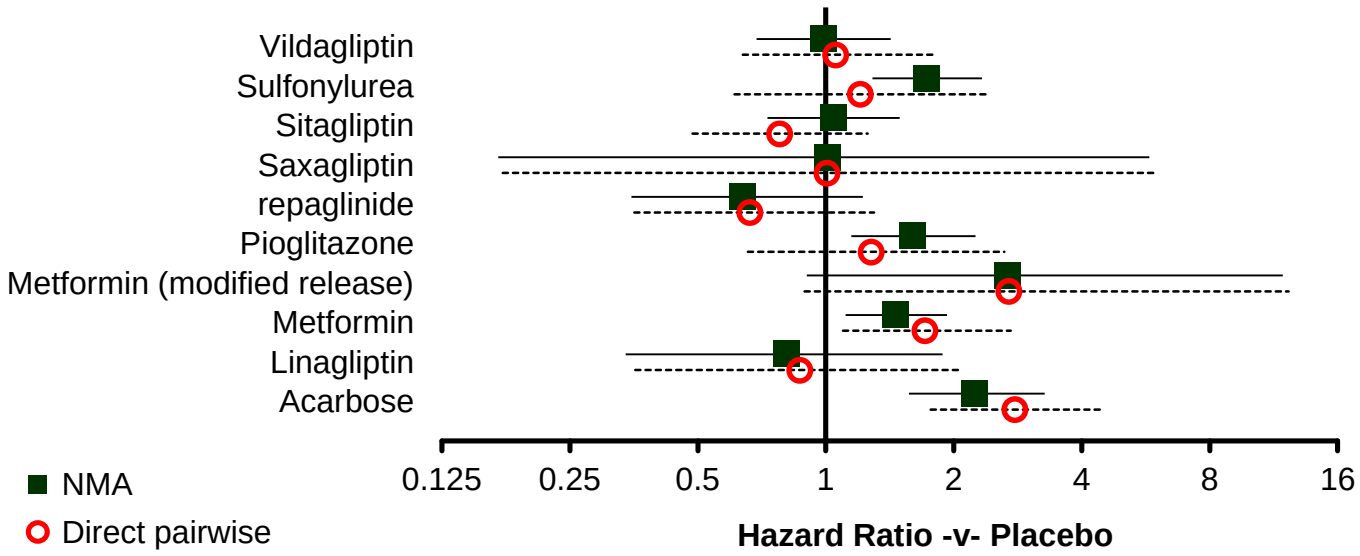
*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 28: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Acarbose | 2.24 (1.57, 3.27) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin | 0.81 (0.34, 1.88) | 0.36 (0.14, 0.90) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin | 1.46 (1.11, 1.93) | 0.65 (0.43, 0.97) | 1.80 (0.77, 4.35) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin (modified release) | 2.67 (0.90, 11.88) | 1.20 (0.38, 5.60) | 3.34 (0.81, 18.41) | 1.84 (0.60, 8.32) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Pioglitazone | 1.61 (1.15, 2.25) | 0.72 (0.45, 1.12) | 1.98 (0.83, 4.93) | 1.10 (0.85, 1.44) | 0.60 (0.13, 1.88) | | N/A | N/A | N/A | N/A | N/A |
| repaglinide | 0.64 (0.35, 1.22) | 0.28 (0.14, 0.60) | 0.79 (0.28, 2.34) | 0.44 (0.23, 0.88) | 0.24 (0.05, 0.86) | 0.40 (0.20, 0.81) | | N/A | N/A | N/A | N/A |
| Saxagliptin | 1.01 (0.17, 5.77) | 0.45 (0.07, 2.66) | 1.25 (0.17, 8.91) | 0.70 (0.11, 4.04) | 0.37 (0.04, 2.97) | 0.63 (0.10, 3.71) | 1.58 (0.24, 9.89) | | N/A | N/A | N/A |
| Sitagliptin | 1.04 (0.73, 1.49) | 0.46 (0.29, 0.75) | 1.28 (0.53, 3.24) | 0.72 (0.51, 0.99) | 0.39 (0.09, 1.23) | 0.65 (0.44, 0.97) | 1.63 (0.79, 3.27) | 1.03 (0.18, 6.42) | | N/A | N/A |
| Sulfonylurea | 1.73 (1.29, 2.33) | 0.77 (0.50, 1.18) | 2.13 (0.90, 5.23) | 1.18 (1.00, 1.40) | 0.64 (0.14, 2.00) | 1.07 (0.82, 1.40) | 2.70 (1.35, 5.27) | 1.71 (0.29, | 1.65 (1.18, 2.34) | | N/A |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Saxagliptin | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 10.45) | | | |
| Vildagliptin | 0.99 (0.69, 1.42) | 0.44 (0.28, 0.69) | 1.21 (0.49, 3.12) | 0.68 (0.47, 0.98) | 0.37 (0.08, 1.16) | 0.61 (0.41, 0.94) | 1.54 (0.74, 3.14) | 0.98 (0.17, 6.05) | 0.95 (0.59, 1.51) | 0.57 (0.38, 0.85) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 17: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 29: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.004 | 4 (2, 6) |
| Acarbose | 0.000 | 10 (8, 11) |
| Linagliptin | 0.231 | 3 (1, 9) |
| Metformin | 0.000 | 7 (5, 9) |
| Metformin (modified release) | 0.003 | 11 (3, 11) |
| Pioglitazone | 0.000 | 8 (6, 10) |
| repaglinide | 0.462 | 2 (1, 6) |
| Saxagliptin | 0.261 | 4 (1, 11) |
| Sitagliptin | 0.013 | 5 (2, 7) |
| Sulfonylurea | 0.000 | 9 (7, 10) |
| Vildagliptin | 0.026 | 4 (1, 7) |

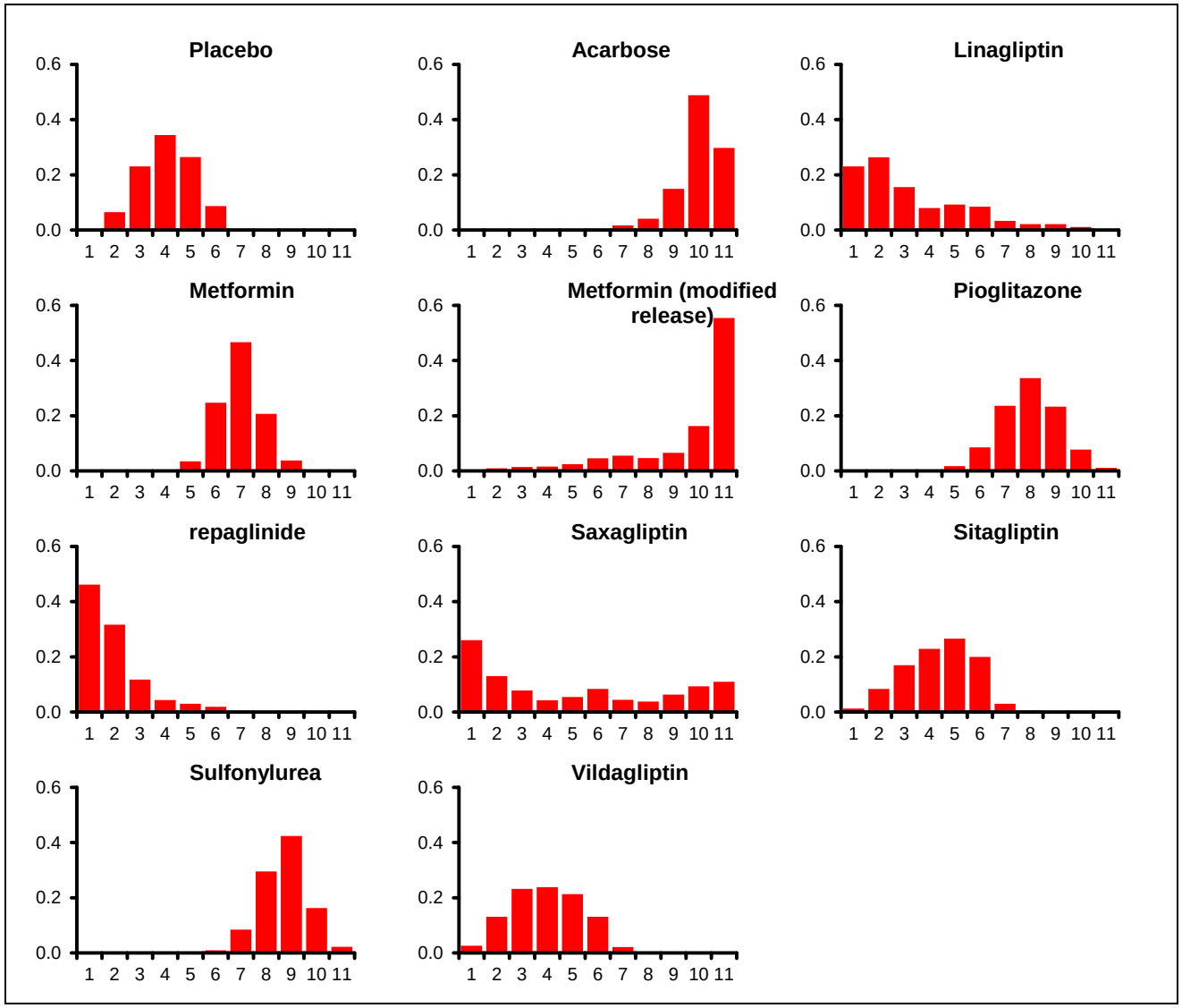



**Figure 18: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rank probability histograms**

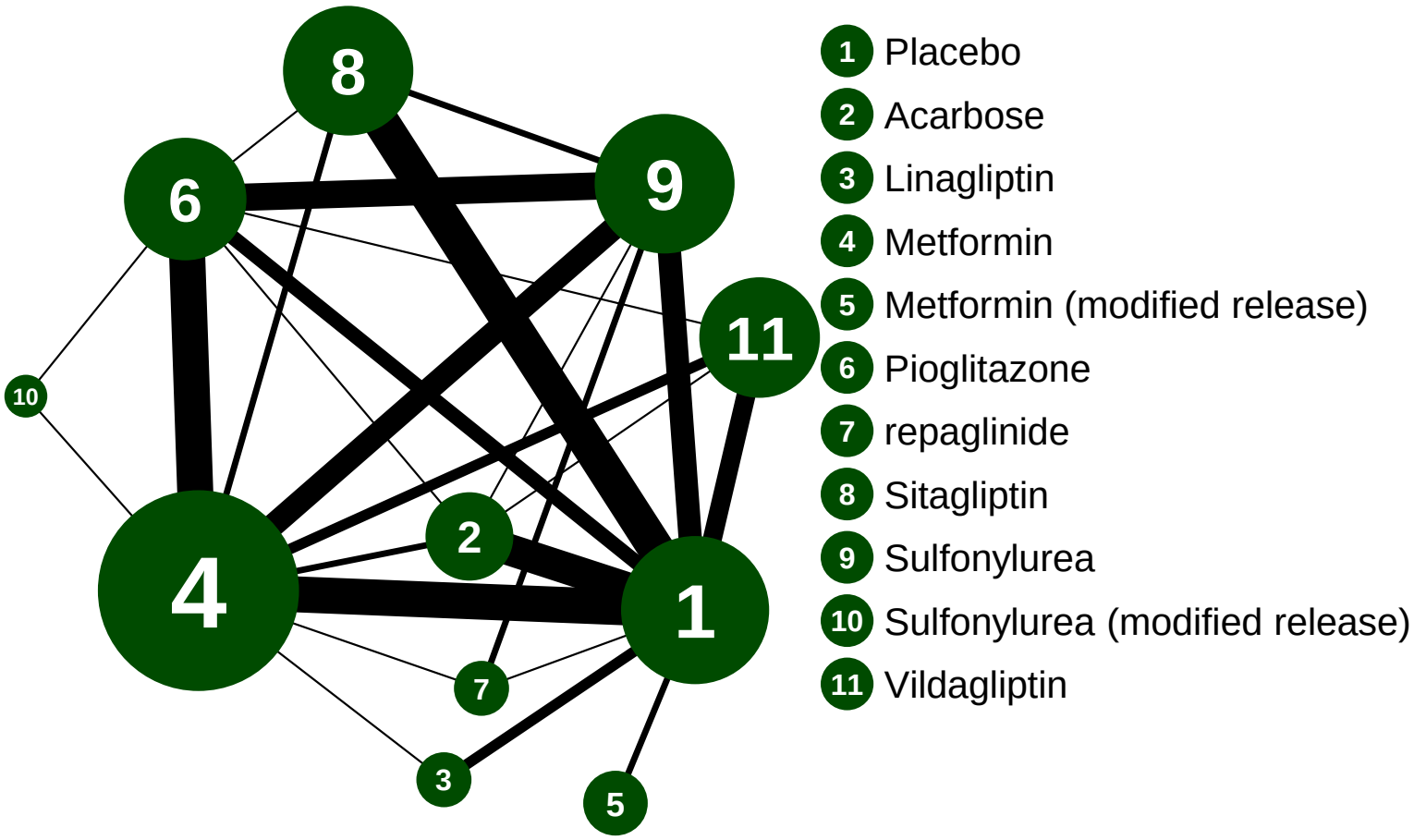
**Table 30: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 201.2<br>(compared to 186 datapoints) | 764.01 | 682.494 | 81.517 | 845.527 | |

**Table 31: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.1.4 Total dropouts at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 19: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – evidence network**

**Table 32: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – input data**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Esposito et al. (2011) - 0.46yr | | | | 4/55 | | 4/55 | | | | | |
| Santilli et al. (2010) - 0.38yr | 4/27 | 2/27 | | | | | | | | | |
| Schweizer et al. (2009) - 0.46yr | | | | 26/166 | | | | | | | 27/169 |
| Bosi et al. (2009) - 0.46yr | | | | 49/294 | | | | | | | 55/300 |
| Erdem et al. (2008) - 0.23yr | | | | 4/27 | | 5/26 | | | | | |
| Pan et al. (2008) - 0.46yr | | 28/220 | | | | | | | | | 42/441 |
| Goldstein et al. (2007) - 1.03yr | | | | 102/364 | | | | 57/179 | | | |
| Schweizer et al. (2007) - 1.99yr | | | | 112/254 | | | | | | | 266/526 |
| Teramoto et al. (2007) - 0.46yr | | | | | | 7/46 | | | 5/46 | | |
| Scott et al. (2007) - 0.23yr | 17/125 | | | | | | | 52/495 | 23/123 | | |
| Jain et al. (2006) - 1.07yr | | | | | | 117/251 | | | 123/251 | | |
| Kirkman et al. (2006) - 5.00yr | 51/119 | 64/120 | | | | | | | | | |
| Bruce et al. (2006) - 0.38yr | | | | 1/15 | | | | | 2/17 | | |
| Yoon et al. (2011) - 0.92yr | | | | 43/114 | | | | | 36/118 | | |
| Haak et al. (2012) - 0.46yr | 18/72 | | 21/142 | 38/291 | | | | | | | |
| Shihara et al. (2011) - 0.50yr | | | | | | 5/96 | | | 9/95 | | |
| Derosa et al. (2011) - 0.54yr | 5/92 | 8/96 | | | | | | | | | |
| Aschner et al. (2010) - 0.46yr | | | | 75/522 | | | | 61/528 | | | |
| Aschner et al. (2006) - 0.46yr | 37/253 | | | | | | | 29/238 | | | |
| Derosa et al. (2003) - 1.15yr | | | | | | | 4/66 | | 4/66 | | |
| Bautista et al. (2003) - 0.31yr | 7/22 | | | | | | | | 7/48 | | |
| Uehara et al. (2001) - 0.23yr | 2/13 | | | 2/13 | | | | | | | |
| Barzilai et al. (2011) - 0.46yr | 47/104 | | | | | | | 32/102 | | | |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nonaka et al. (2008) - 0.23yr | 9/76 | | | | | | | 3/76 | | | |
| Hanefeld et al. (2007) - 0.23yr | 30/111 | | | | | | | 50/444 | | | |
| Dejager et al. (2007) - 0.46yr | 41/160 | | | | | | | | | | 80/472 |
| Kawamori et al. (2012) - 0.23yr | 6/80 | | 3/159 | | | | | | | | |
| Iwamoto et al. (2010) - 0.23yr | 5/73 | | | | | | | 6/222 | | | |
| Kikuchi et al. (2009) - 0.23yr | 6/72 | | | | | | | | | | 6/219 |
| Mohan et al. (2009) - 0.34yr | 45/178 | | | | | | | 46/352 | | | |
| Pi-Sunyer et al. (2007) - 0.46yr | 29/92 | | | | | | | | | | 52/262 |
| Rosenstock et al. (2007) - 0.46yr | | | | | | 28/161 | | | | | 18/154 |
| Pratley et al. (2006) - 0.23yr | 2/28 | | | | | | | | | | 7/72 |
| Madsbad et al. (2004) - 0.23yr | 5/29 | | | | | | | | 1/27 | | |
| Scherbaum et al. (2008) - 2.07yr | 100/150 | | | | | | | | | | 98/156 |
| Herz et al. (2003) - 0.31yr | 11/99 | | | | | 14/198 | | | | | |
| Abbatecola et al. (2006) - 1.00yr | | | | | | | 12/77 | | 16/79 | | |
| Horton et al. (2000) - 0.46yr | 66/172 | | | 45/178 | | | | | | | |
| Schernthaner et al. (2004) - 1.00yr | | | | 96/597 | | 98/597 | | | | | |
| Fujioka et al. (2005) - 0.46yr | 41/79 | | | | 54/161 | | | | | | |
| Fujioka et al. (2005) - 0.46yr | 28/117 | | | | 91/625 | | | | | | |
| Goke (2002) - 0.50yr | | 39/136 | | | | 19/129 | | | | | |
| Scherbaum et al. (2002) - 0.50yr | 19/78 | | | | | 30/155 | | | | | |
| Watanabe et al. (2005) - 0.50yr | | | | | | 2/15 | | | 1/15 | | |
| Lawrence et al. (2004) - 0.46yr | | | | 1/21 | | 1/21 | | | 2/22 | | |
| Pavo et al. (2003) - 0.61yr | | | | 9/100 | | 5/105 | | | | | |
| Yamanouchi et al. (2005) - 1.00yr | | | | 2/39 | | 3/38 | | | 3/37 | | |
| Raz et al. (2006) - 0.34yr | 19/110 | | | | | | | 17/205 | | | |

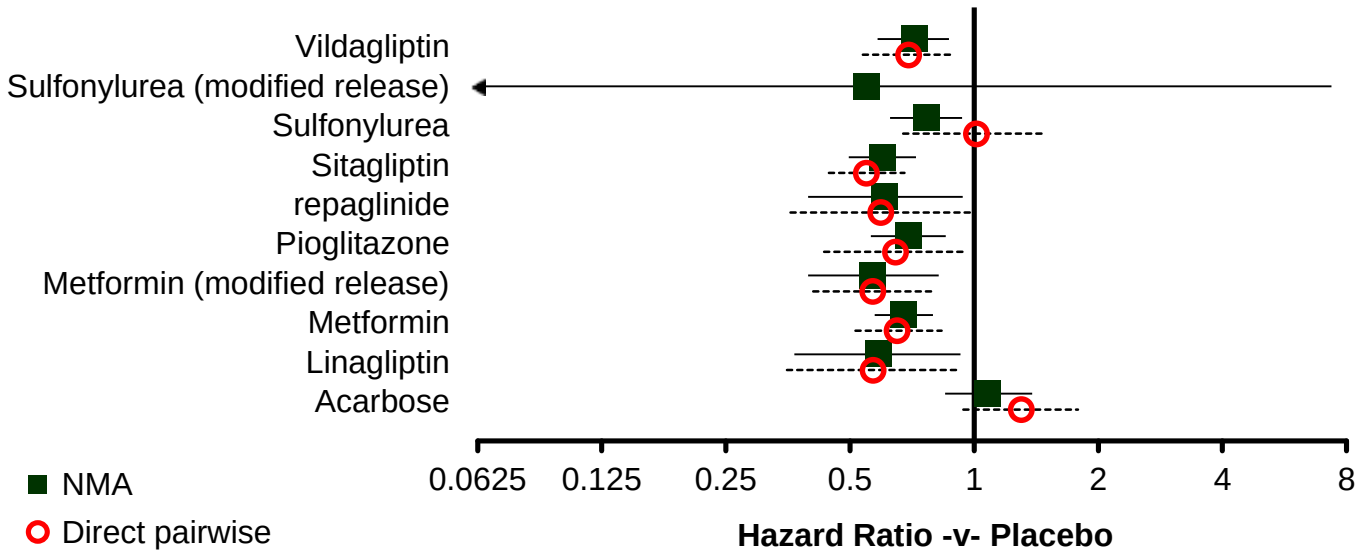
| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tessier et al. (1999) - 0.46yr | | | | 2/20 | | | | | 1/19 | | |
| DeFronzo & (1995) - 0.56yr | 41/146 | | | 31/143 | | | | | | | |
| H+¤llsten et al. (2002) - 0.50yr | 0/14 | | | 3/16 | | | | | | | |
| Lee & (1998) - 0.46yr | 8/24 | | | 8/24 | | | | | | | |
| Del et al. (2003) - 0.56yr | 36/144 | | | 45/284 | | | | | | | |
| Chan et al. (1998) - 0.46yr | 6/63 | 11/63 | | | | | | | | | |
| Fischer et al. (1998) - 0.46yr | 11/97 | 32/398 | | | | | | | | | |
| Hoffmann & (1997) - 0.46yr | 1/32 | 3/31 | | 1/31 | | | | | | | |
| Johnston et al. (1998) - 1.07yr | 9/101 | | | | | | | | 12/104 | | |
| Kovacevic I,Profozic V,Skrabalo Z,Cabrijan T,Zjacic-Rotkvic V,Goldoni (1997) - 0.46yr | 3/34 | 1/34 | | | | | | | 1/34 | | |
| Segal et al. (1997) - 0.46yr | 6/64 | | | | | | | | 11/61 | | |
| Viberti et al. (2002) - 3.99yr | | | | 551/1454 | | | | | 634/1441 | | |
| Charbonnel et al. (2005) - 1.99yr | | | | | | 477/624 | | | 499/626 | | |
| Moses et al. (2001) - 0.31yr | 41/138 | | | | | | 51/270 | | | | |
| Josse et al. (2003) - 1.00yr | 5/99 | 13/93 | | | | | | | | | |
| Kikuchi et al. (2012) - 0.54yr | 11/54 | | | | | 22/159 | | | | | |
| Ferrannini et al. (2013) - 0.23yr | 6/82 | | | 6/80 | | | | | | | |
| Arjona et al. (2013) - 1.03yr | | | | | | | | 47/211 | 42/212 | | |
| Barnett et al. (2012) - 0.34yr | 12/76 | | 14/151 | | | | | | | | |
| Genovese et al. (2013) - 0.31yr | | | | 3/29 | | 5/29 | | | | | |
| Alba et al. (2013) - 0.23yr | 5/53 | | | | | 2/54 | | 6/52 | | | |
| Yang et al. (2014) - 0.46yr | | 42/393 | | 48/395 | | | | | | | |
| Erem et al. (2014) - 1.00yr | | | | 1/20 | | 1/20 | | | | 1/20 | |
| Fang et al. (2014) - 0.29yr | | | | 0/20 | | | 1/40 | | | | |
| Esteghamati et al. (2014) - 0.23yr | | | | 2/43 | | 5/55 | | | | | |

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.* | | | | | | | | | | | |

**Table 33: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Acarbose | 1.08 (0.85, 1.38) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin | 0.59 (0.37, 0.93) | 0.54 (0.32, 0.90) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin | 0.67 (0.57, 0.79) | 0.62 (0.48, 0.81) | 1.15 (0.73, 1.86) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin (modified release) | 0.57 (0.40, 0.82) | 0.53 (0.34, 0.81) | 0.97 (0.54, 1.75) | 0.84 (0.57, 1.26) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Pioglitazone | 0.69 (0.56, 0.85) | 0.64 (0.48, 0.85) | 1.19 (0.72, 1.96) | 1.03 (0.84, 1.25) | 1.22 (0.80, 1.86) | | N/A | N/A | N/A | N/A | N/A |
| repaglinide | 0.61 (0.40, 0.94) | 0.56 (0.34, 0.92) | 1.04 (0.55, 1.94) | 0.90 (0.58, 1.41) | 1.06 (0.61, 1.87) | 0.87 (0.55, 1.39) | | N/A | N/A | N/A | N/A |
| Sitagliptin | 0.60 (0.50, 0.72) | 0.55 (0.41, 0.74) | 1.03 (0.63, 1.68) | 0.89 (0.72, 1.09) | 1.06 (0.70, 1.58) | 0.87 (0.67, 1.10) | 0.99 (0.62, 1.57) | | N/A | N/A | N/A |
| Sulfonylurea | 0.77 (0.62, 0.93) | 0.71 (0.53, 0.94) | 1.31 (0.80, 2.16) | 1.14 (0.93, 1.37) | 1.34 (0.88, 2.04) | 1.10 (0.91, 1.34) | 1.26 (0.81, 1.96) | 1.27 (1.02, 1.61) | | N/A | N/A |
| Sulfonylurea (modified release) | 0.55 (0.01, 7.35) | 0.51 (0.01, 6.74) | 0.93 (0.02, 12.93) | 0.81 (0.02, 10.86) | 0.97 (0.02, 13.39) | 0.79 (0.02, 10.54) | 0.90 (0.02, 12.57) | 0.91 (0.02, 12.32) | 0.72 (0.02, 9.68) | | N/A |
| Vildagliptin | 0.72 (0.58, 0.87) | 0.66 (0.49, 0.87) | 1.22 (0.75, 2.01) | 1.07 (0.86, 1.29) | 1.26 (0.83, 1.89) | 1.04 (0.79, 1.32) | 1.18 (0.74, 1.87) | 1.19 (0.93, 1.53) | 0.94 (0.72, 1.19) | 1.30 (0.10, 49.34) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 20: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 34: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 10 (9, 11) |
| Acarbose | 0.000 | 11 (9, 11) |
| Linagliptin | 0.167 | 3 (1, 9) |
| Metformin | 0.003 | 5 (3, 8) |
| Metformin (modified release) | 0.173 | 3 (1, 9) |
| Pioglitazone | 0.004 | 6 (2, 9) |
| repaglinide | 0.125 | 4 (1, 9) |
| Sitagliptin | 0.061 | 3 (1, 7) |
| Sulfonylurea | 0.000 | 8 (5, 9) |
| Sulfonylurea (modified release) | 0.465 | 2 (1, 11) |
| Vildagliptin | 0.003 | 7 (3, 9) |

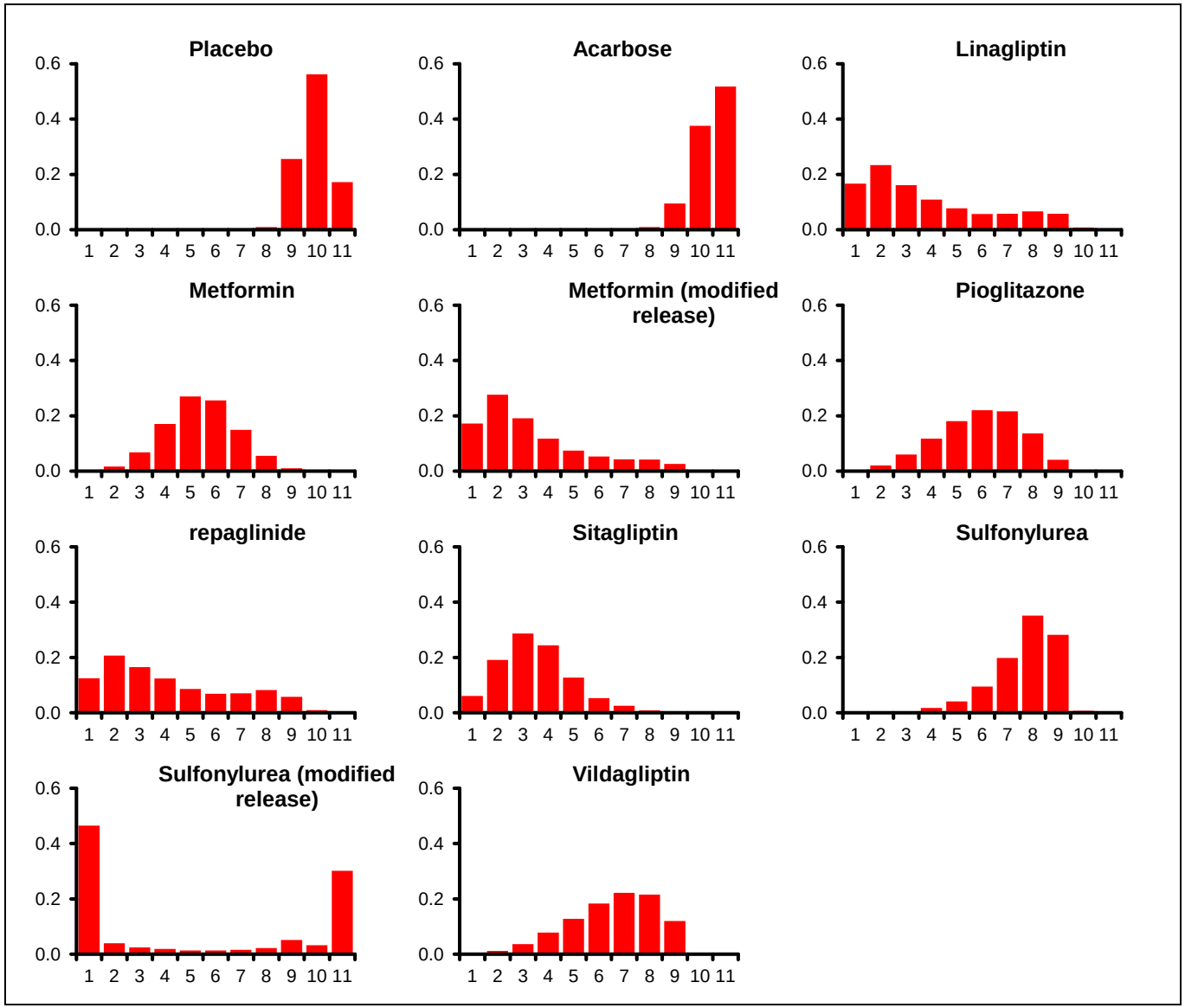



**Figure 21: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – rank probability histograms**

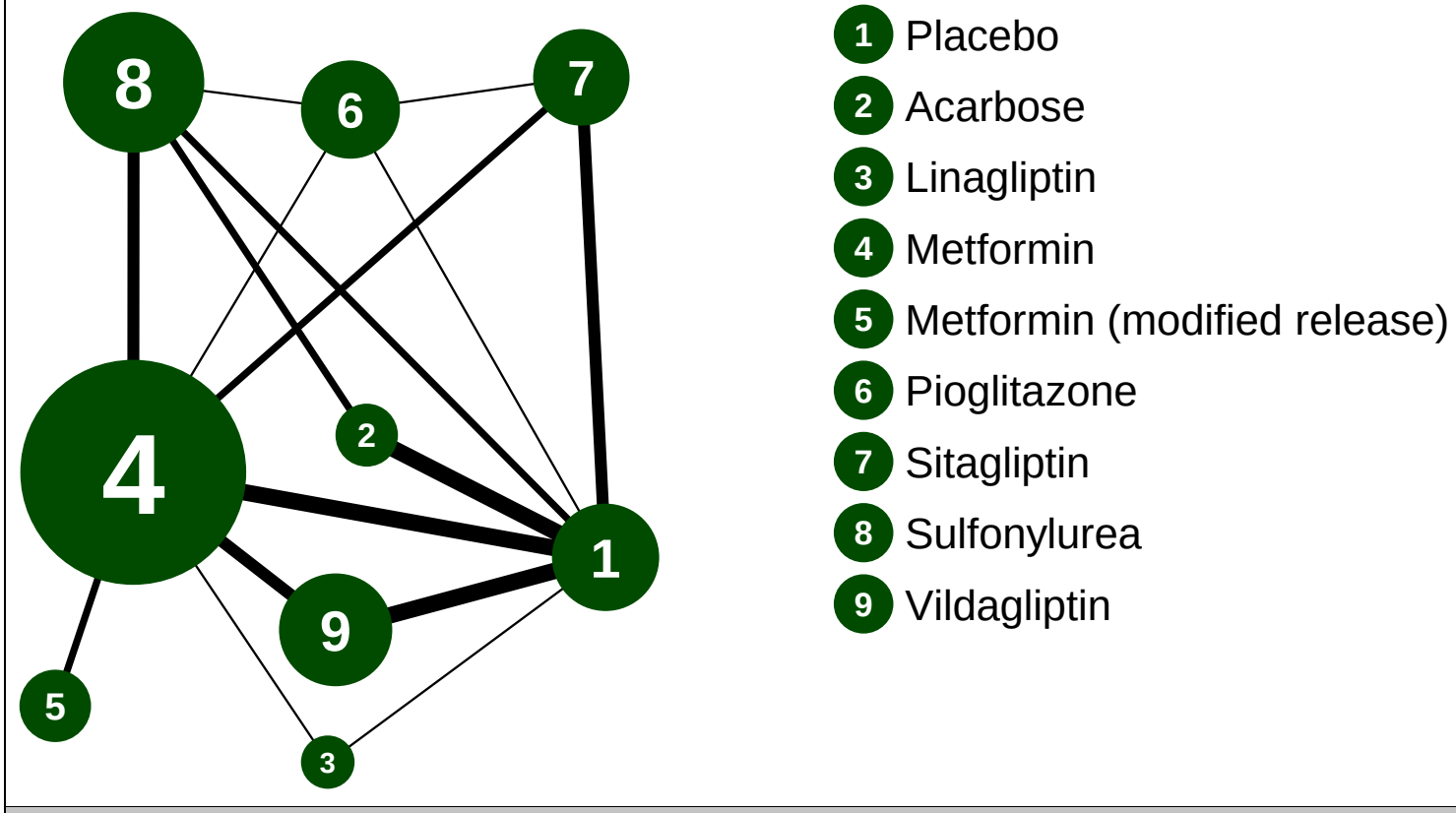
**Table 35: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 183.1<br>(compared to 177 datapoints) | 908.143 | 808.597 | 99.546 | 1007.69 | 0.158 (95%CI: 0.023, 0.286) |

**Table 36: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

### J.2.1.5 Nausea at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 22: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – evidence network**

**Table 37: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – input data**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Schweizer et al. (2009) - 0.46yr | | | | 9/165 | | | | | 5/167 |
| Bosi et al. (2009) - 0.46yr | | | | 17/292 | | | | | 7/297 |
| Gao et al. (2008) - 0.23yr | | | | 1/71 | 0/69 | | | | |
| Goldstein et al. (2007) - 1.99yr | | | | 25/364 | | | 2/179 | | |
| Schweizer et al. (2007) - 1.99yr | | | | 15/158 | | | | | 9/304 |
| Haak et al. (2012) - 0.46yr | 0/72 | | 1/142 | 5/291 | | | | | |
| Aschner et al. (2010) - 0.46yr | | | | 16/522 | | | 6/528 | | |
| Aschner et al. (2006) - 0.46yr | 3/253 | | | | | | 5/238 | | |
| Schwartz et al. (2006) - 0.46yr | | | | 19/174 | 45/532 | | | | |
| Dejager et al. (2007) - 0.46yr | 6/157 | | | | | | | | 9/468 |
| Pi-Sunyer et al. (2007) - 0.46yr | 0/92 | | | | | | | | 1/91 |
| Pratley et al. (2006) - 0.23yr | 1/28 | | | | | | | | 1/70 |
| Ristic et al. (2005) - 0.23yr | 3/56 | | | | | | | | 5/220 |
| Horton et al. (2000) - 0.46yr | 4/104 | | | 10/104 | | | | | |
| Schernthaner et al. (2004) - 1.00yr | | | | 25/597 | | 14/597 | | | |
| Raz et al. (2006) - 0.34yr | 0/110 | | | | | | 2/205 | | |
| Collier A,Watson HH,Patrick AW,Ludlam (1989) - 0.46yr | | | | 3/12 | | | | 0/12 | |
| Hermann et al. (1994) - 0.46yr | | | | 9/38 | | | | 3/34 | |
| Chiasson & (2001) - 0.69yr | 2/83 | | | 14/83 | | | | | |
| Braun D,Schonherr (1996) - 0.46yr | 1/44 | 0/42 | | | | | | | |
| Coniff et al. (1995) - 0.46yr | 2/72 | 6/74 | | | | | | 7/71 | |
| Coniff et al. (1995) - 0.31yr | 0/73 | 10/145 | | | | | | | |
| Johnston et al. (1998) - 1.07yr | 5/101 | | | | | | | 6/104 | |
| Salman S,Salman F,Satman I,Yilmaz Y,Ozer E,Sengul (2001) - 0.46yr | | 1/27 | | | | | | 0/30 | |
| Viberti et al. (2002) - 3.99yr | | | | 170/1454 | | | | 99/1441 | |

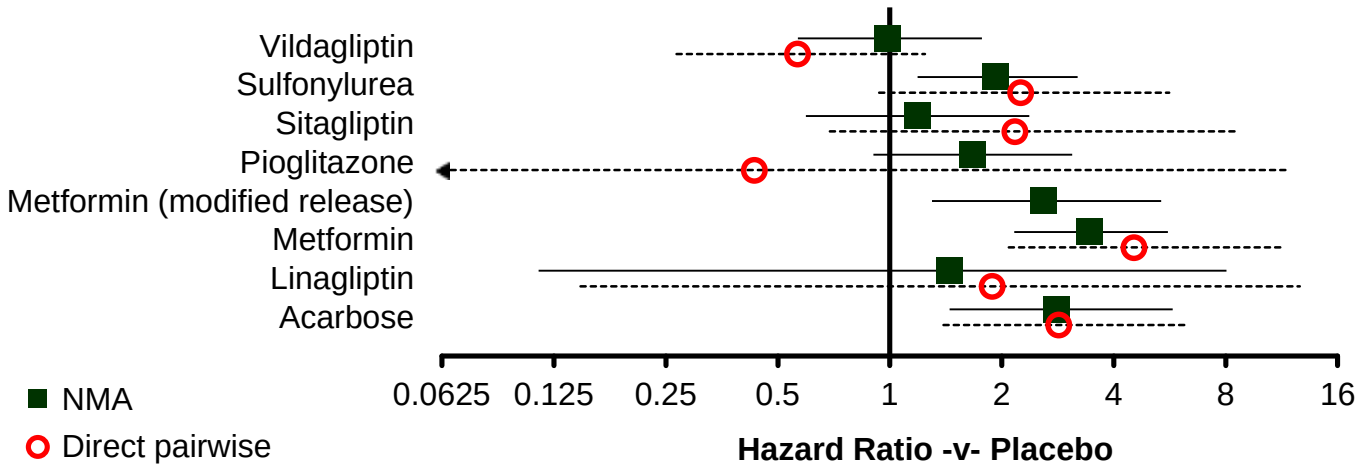
| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Charbonnel et al. (2005) - 1.00yr | | | | | | 27/620 | | 32/618 | |
| Josse et al. (2003) - 1.00yr | 3/99 | 10/93 | | | | | | | |
| Ferrannini et al. (2013) - 0.23yr | 0/82 | | | 3/80 | | | | | |
| Alba et al. (2013) - 0.23yr | 0/53 | | | | | 0/54 | 1/52 | | |

*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 38: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Metformin (modified release) | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Acarbose | 2.82 (1.45, 5.76) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin | 1.45 (0.11, 8.04) | 0.51 (0.04, 3.09) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin | 3.44 (2.16, 5.59) | 1.21 (0.57, 2.56) | 2.36 (0.46, 30.19) | | N/A | N/A | N/A | N/A | N/A |
| Metformin (modified release) | 2.59 (1.30, 5.37) | 0.92 (0.37, 2.30) | 1.80 (0.32, 23.48) | 0.75 (0.45, 1.30) | | N/A | N/A | N/A | N/A |
| Pioglitazone | 1.67 (0.90, 3.09) | 0.59 (0.25, 1.36) | 1.14 (0.21, 15.01) | 0.48 (0.32, 0.74) | 0.64 (0.32, 1.24) | | N/A | N/A | N/A |
| Sitagliptin | 1.19 (0.59, 2.37) | 0.42 (0.16, 1.04) | 0.83 (0.14, 10.96) | 0.35 (0.18, 0.63) | 0.46 (0.20, 1.01) | 0.71 (0.34, 1.48) | | N/A | N/A |
| Sulfonylurea | 1.93 (1.19, 3.20) | 0.68 (0.32, 1.43) | 1.33 (0.25, 16.90) | 0.56 (0.44, 0.70) | 0.74 (0.41, 1.30) | 1.16 (0.77, 1.75) | 1.61 (0.86, 3.12) | | N/A |
| Vildagliptin | 0.99 (0.57, 1.77) | 0.35 (0.15, 0.80) | 0.69 (0.12, 8.88) | 0.29 (0.17, 0.47) | 0.38 (0.18, 0.78) | 0.59 (0.31, 1.13) | 0.83 (0.39, 1.80) | 0.51 (0.30, 0.88) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 23: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 39: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.256 | 2 (1, 4) |
| Acarbose | 0.000 | 8 (4, 9) |
| Linagliptin | 0.306 | 4 (1, 9) |
| Metformin | 0.000 | 8 (7, 9) |
| Metformin (modified release) | 0.000 | 7 (4, 9) |
| Pioglitazone | 0.006 | 5 (2, 7) |
| Sitagliptin | 0.139 | 3 (1, 6) |
| Sulfonylurea | 0.000 | 6 (4, 7) |
| Vildagliptin | 0.292 | 2 (1, 4) |

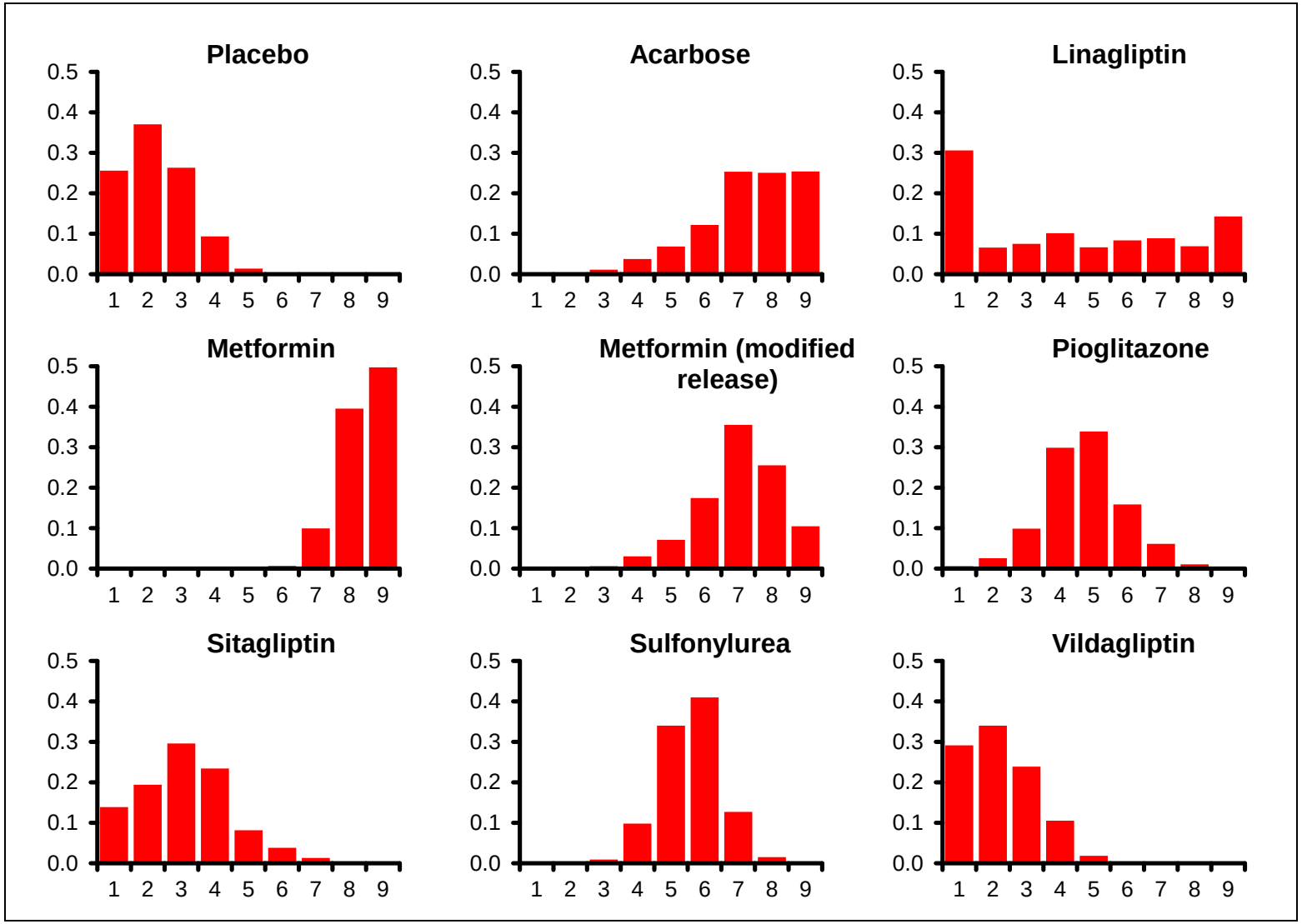



**Figure 24: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – rank probability histograms**

**Table 40: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – model fit statistics**

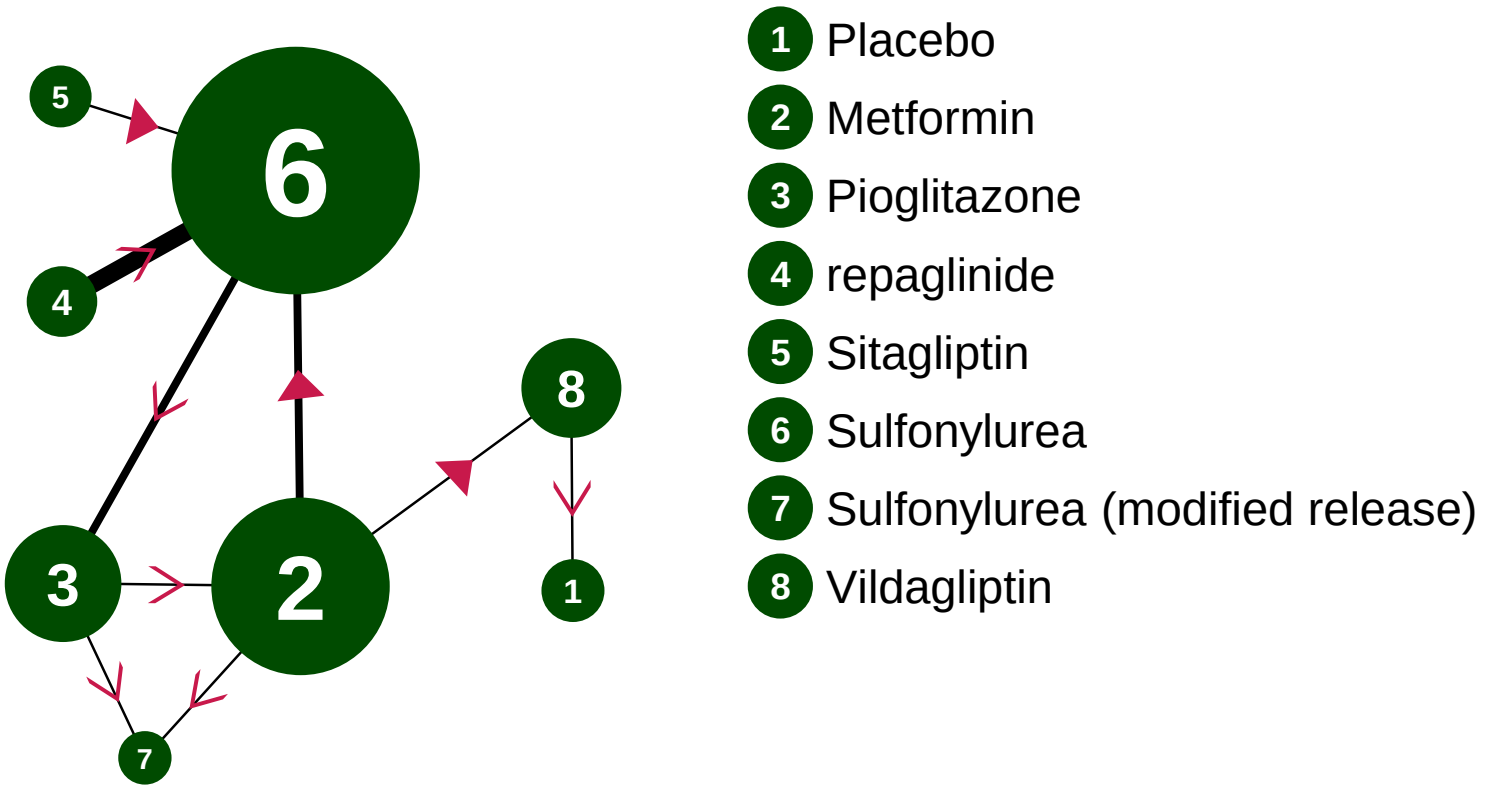
| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 72.25<br>(compared to 71 datapoints) | 297.292 | 261.094 | 36.198 | 333.49 | |

**Table 41: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.1.6 Change in body weight at 12 and 24 months

**Change in body weight at 12 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 25: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – evidence network**

**Table 42: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – input data**

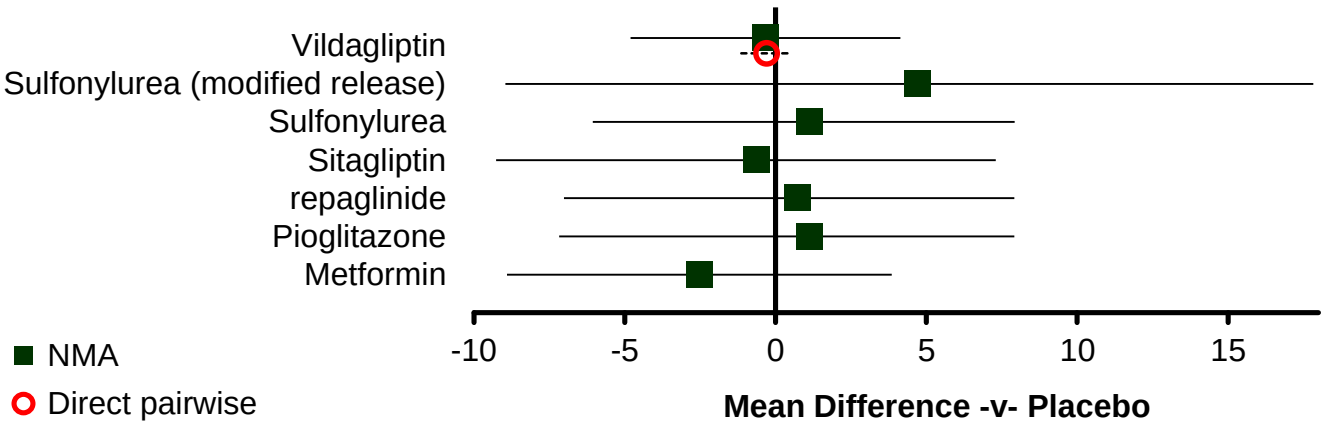
| | Placebo | Metformin | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|
| Schweizer et al. (2007) | | -1.90 (4.78) | | | | | | 0.30 (4.59) |
| Jain et al. (2006) | | | 3.66 (6.14) | | | 1.95 (5.35) | | |
| Derosa et al. (2003) | | | | 0.10 (5.25) | | -0.50 (5.62) | | |
| Scherbaum et al. (2008) | -0.20 (3.67) | | | | | | | -0.50 (3.75) |
| Marbury et al. (1999) | | | | 2.45 (4.02) | | 3.64 (4.81) | | |
| Campbell et al. (1994) | | -1.97 (3.43) | | | | 2.62 (4.41) | | |
| Viberti et al. (2002) | | -2.27 (16.47) | | | | 1.30 (17.71) | | |
| Charbonnel et al. (2005) | | | 1.70 (16.67) | | | 3.30 (15.04) | | |
| Shah et al. (2011) | | | | -1.80 (9.13) | | 0.20 (16.39) | | |
| Saleem et al. (2011) | | | | 0.20 (9.11) | | -1.00 (16.41) | | |
| Arjona et al. (2013) | | | | | -0.60 (3.49) | 1.15 (3.57) | | |
| Erem et al. (2014) | | -4.10 (13.10) | -5.13 (14.10) | | | | 0.94 (23.23) | |

*Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 43: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Metformin | Pioglitazone | repaglinide | Sitagliptin | Sulfonylurea | Sulfonylurea (modified release) | Vildagliptin |
|---|---|---|---|---|---|---|---|---|
| Placebo | | - | - | - | - | - | - | -0.30 (-1.14, 0.54) |
| Metformin | -2.52 (-8.90, 3.85) | | -1.03 (-9.68, 7.62) | - | - | 3.81 (2.72, 4.90) | 5.04 (-6.95, 17.03) | 2.20 (1.49, 2.91) |
| Pioglitazone | 1.14 (-7.17, 7.92) | 3.64 (-1.22, 7.14) | | - | - | -0.14 (-3.38, 3.10) | 6.07 (-6.15, 18.29) | - |
| repaglinide | 0.74 (-7.01, 7.91) | 3.26 (-1.07, 7.10) | -0.36 (-4.07, 4.13) | | - | 0.27 (-1.06, 1.60) | - | - |
| Sitagliptin | -0.63 (-9.26, 7.30) | 1.89 (-3.83, 7.10) | -1.76 (-6.68, 4.09) | -1.39 (-6.49, 3.82) | | 1.75 (0.92, 2.58) | - | - |
| Sulfonylurea | 1.13 (-6.06, 7.92) | 3.64 (0.32, 6.55) | 0.02 (-2.65, 3.54) | 0.38 (-2.22, 3.07) | 1.75 (-2.68, 6.17) | | - | - |
| Sulfonylurea (modified release) | 4.72 (-8.96, 17.83) | 7.18 (-5.01, 18.96) | 3.68 (-8.44, 15.60) | 3.95 (-8.53, 16.18) | 5.32 (-7.62, 17.97) | 3.56 (-8.64, 15.48) | | - |
| Vildagliptin | -0.32 (-4.80, 4.13) | 2.21 (-2.18, 6.59) | -1.46 (-6.76, 5.29) | -1.06 (-6.73, 5.18) | 0.31 (-6.45, 7.50) | -1.44 (-6.56, 4.12) | -5.02 (-17.48, 7.97) | |

*Values given are mean differences in body-weight in kilograms.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 26: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – relative effect of all options versus reference treatment**

**Table 44: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.103 | 4 (1, 8) |
| Metformin | 0.576 | 1 (1, 4) |
| Pioglitazone | 0.018 | 6 (2, 8) |
| repaglinide | 0.018 | 5 (2, 8) |
| Sitagliptin | 0.141 | 3 (1, 8) |
| Sulfonylurea | 0.001 | 6 (3, 8) |
| Sulfonylurea (modified release) | 0.101 | 8 (1, 8) |
| Vildagliptin | 0.043 | 4 (1, 8) |

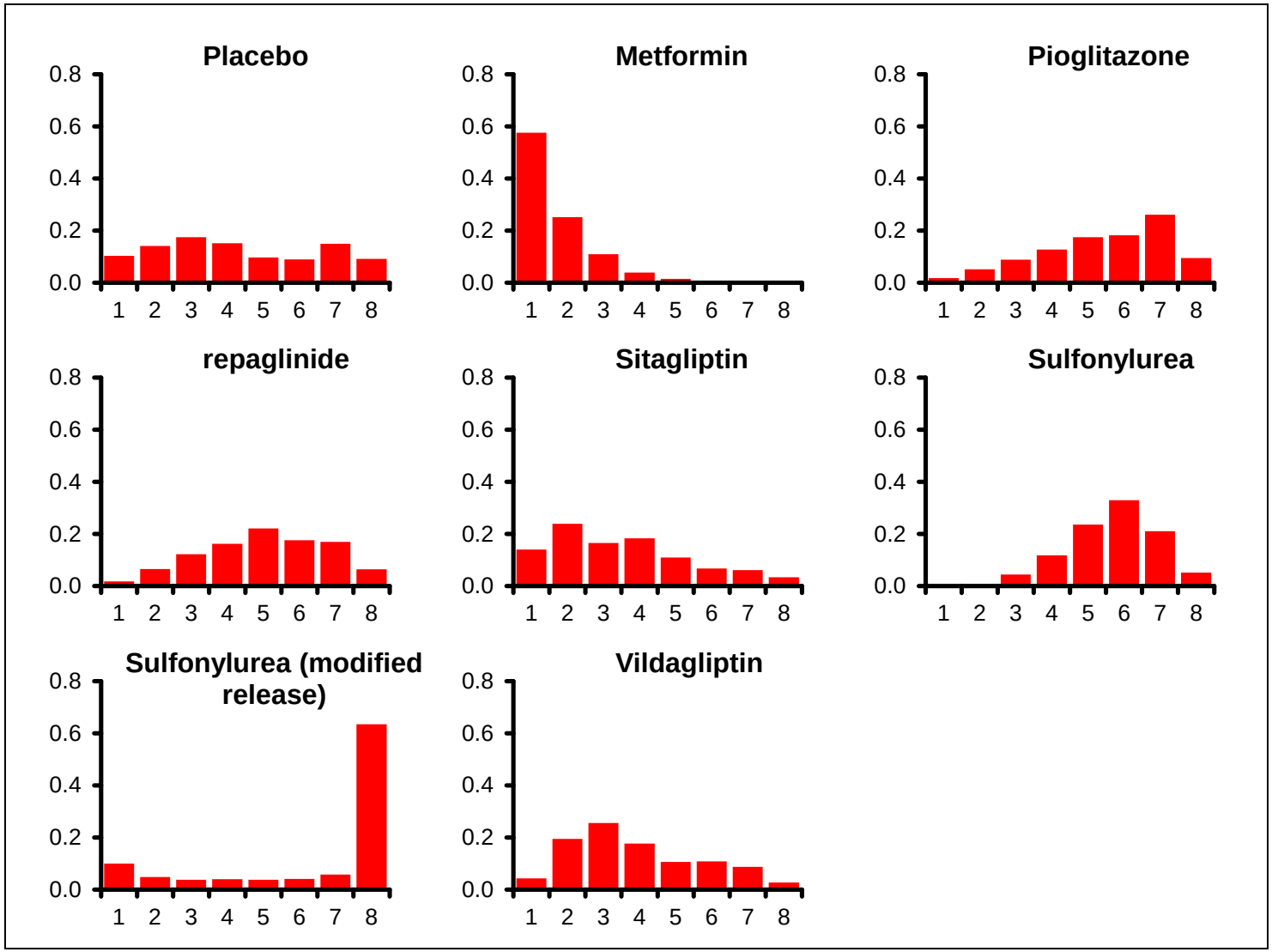



**Figure 27: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – rank probability histograms**

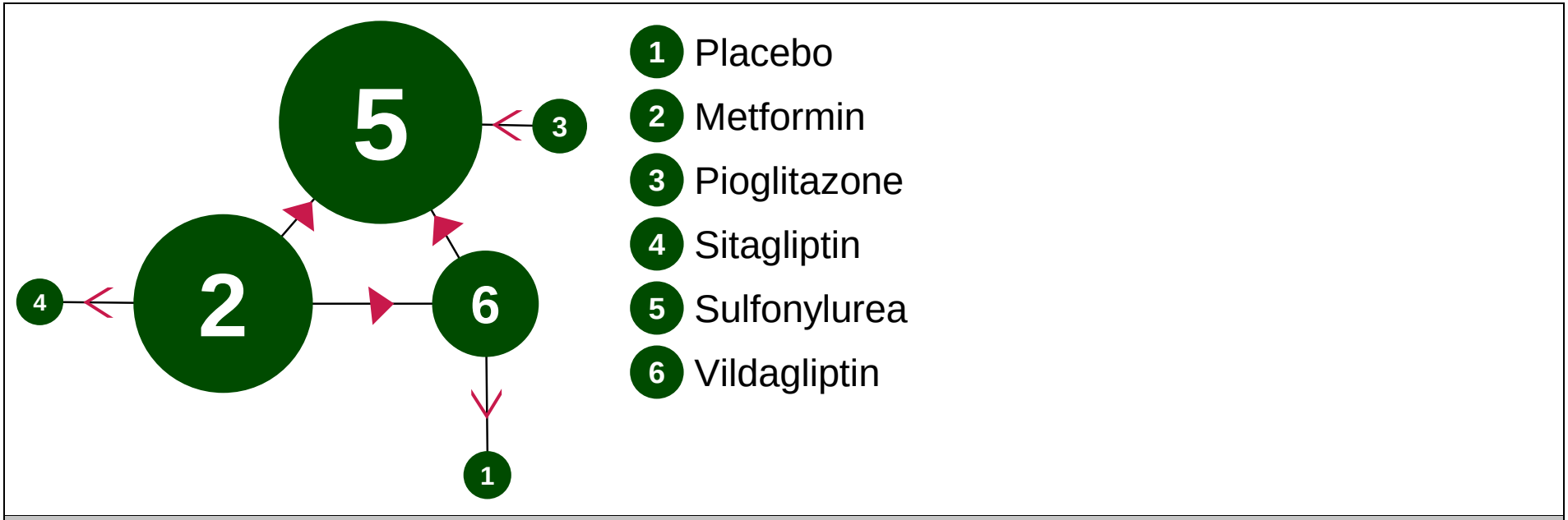
**Table 45: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 24.56<br>(compared to 25 datapoints) | 53.79 | 31.083 | 22.707 | 76.497 | 1.630 (95%CI: 0.463, 4.596) |

**Table 46: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=10)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

**Change in body weight at 24 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 28: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – evidence network**

**Table 47: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – input data**

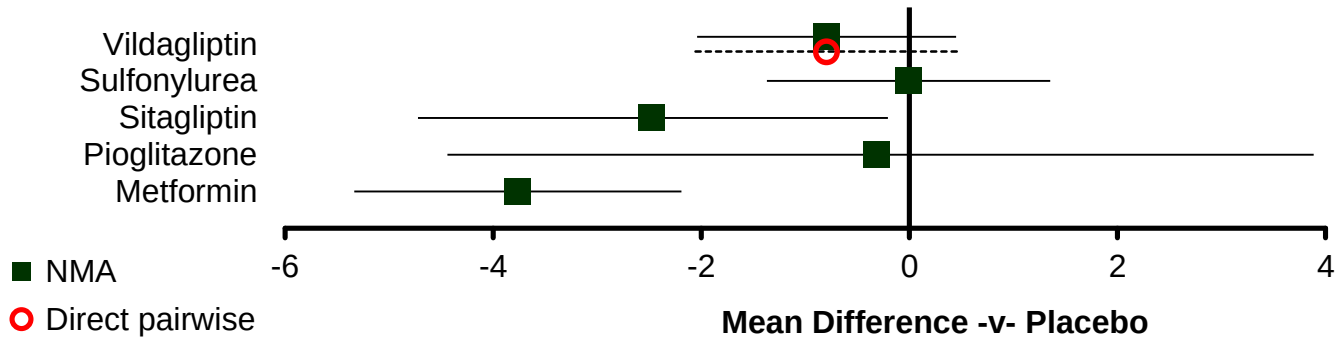
| | Placebo | Metformin | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|
| Foley & (2009) | | | | | 1.60 (4.01) | 0.80 (4.04) |
| Goldstein et al. (2007) | | -0.80 (4.31) | | 0.50 (4.33) | | |
| Schweizer et al. (2007) | | -2.50 (6.28) | | | | 0.50 (6.99) |
| Scherbaum et al. (2008) | -0.30 (3.17) | | | | | -1.10 (4.12) |
| Viberti et al. (2002) | | -2.43 (16.47) | | | 1.30 (17.70) | |
| Charbonnel et al. (2005) | | | 3.90 (17.52) | | 4.20 (15.88) | |

*Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 48: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Metformin | Pioglitazone | Sitagliptin | Sulfonylurea | Vildagliptin |
|---|---|---|---|---|---|---|
| Placebo | | - | - | - | - | -0.80<br>(-2.05, 0.45) |
| Metformin | -3.76<br>(-5.34, -2.19) | | - | 1.30<br>(-0.33, 2.93) | 3.73<br>(2.49, 4.98) | 3.00<br>(1.75, 4.25) |
| Pioglitazone | -0.31<br>(-4.44, 3.89) | 3.44<br>(-0.59, 7.54) | | - | 0.30<br>(-3.66, 4.26) | - |
| Sitagliptin | -2.47<br>(-4.72, -0.21) | 1.30<br>(-0.34, 2.92) | -2.16<br>(-6.57, 2.22) | | - | - |
| Sulfonylurea | 0.00<br>(-1.37, 1.36) | 3.76<br>(2.85, 4.68) | 0.31<br>(-3.67, 4.23) | 2.47<br>(0.59, 4.32) | | -0.80<br>(-1.35, -0.25) |
| Vildagliptin | -0.79<br>(-2.04, 0.45) | 2.97<br>(2.06, 3.90) | -0.48<br>(-4.50, 3.47) | 1.68<br>(-0.19, 3.55) | -0.79<br>(-1.32, -0.26) | |

*Values given are mean differences in body-weight in kilograms.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 29: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – relative effect of all options versus reference treatment**

**Table 49: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 5 (3, 6) |
| Metformin | 0.893 | 1 (1, 2) |
| Pioglitazone | 0.047 | 4 (1, 6) |
| Sitagliptin | 0.060 | 2 (1, 4) |
| Sulfonylurea | 0.000 | 5 (4, 6) |
| Vildagliptin | 0.000 | 3 (3, 5) |

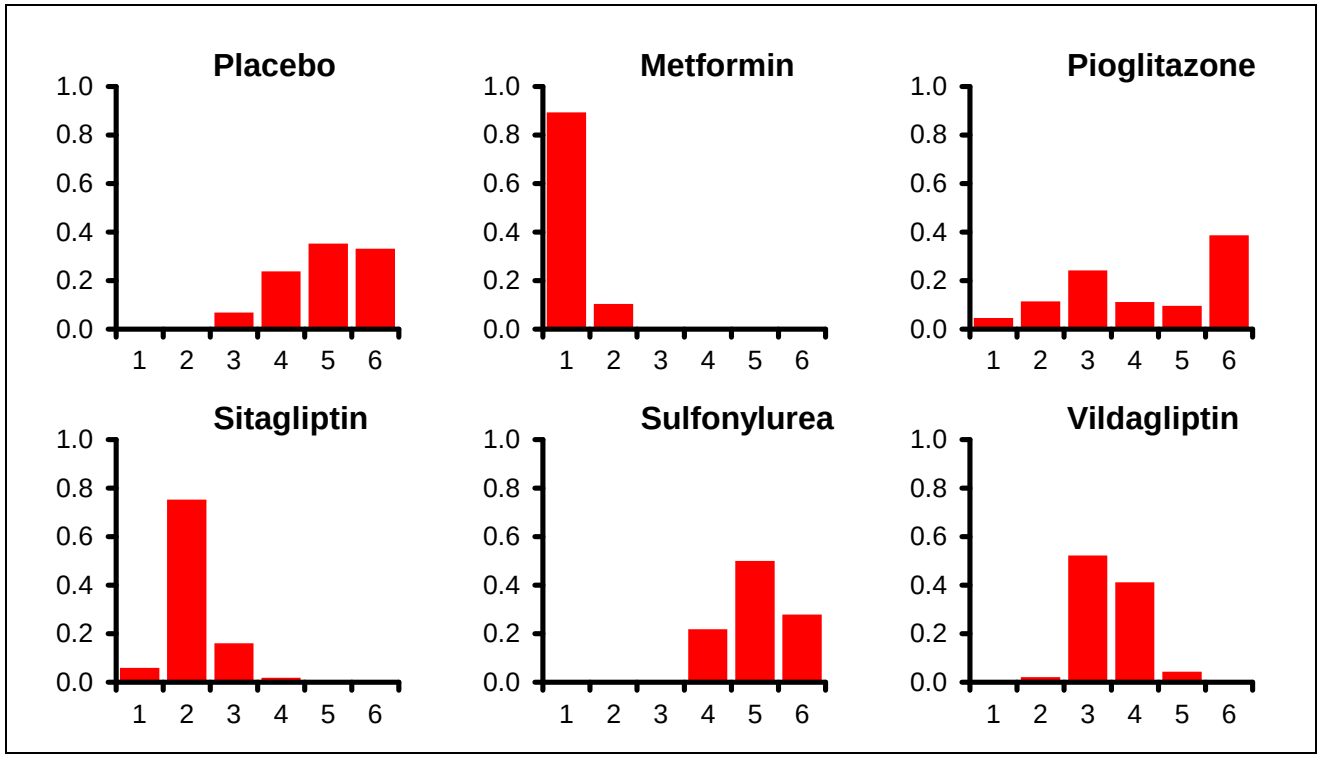



**Figure 30: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – rank probability histograms**

**Table 50: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC |
|---|---|---|---|---|
| 11<br>(compared to 12 datapoints) | 16.272 | 5.273 | 10.999 | 27.27 |

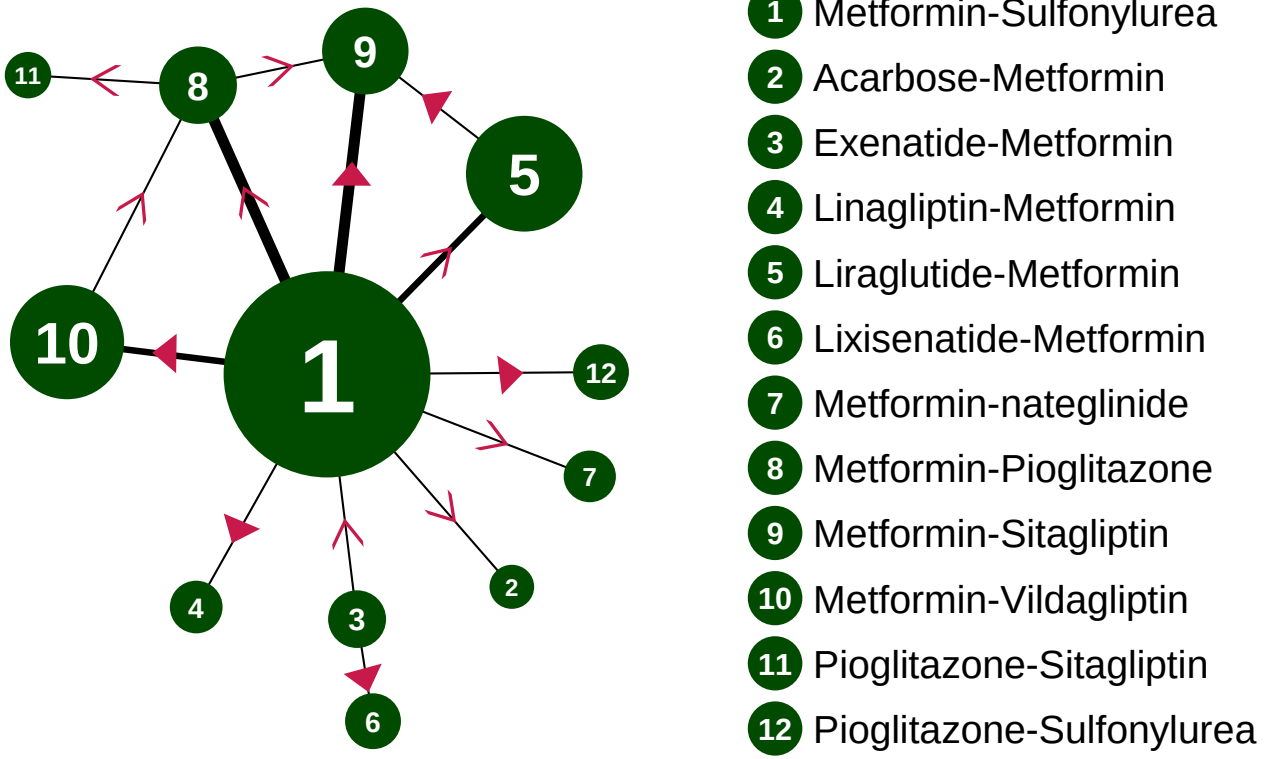
**Table 51: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

## J.2.2 RESULTS FOR FIRST INTENSIFICATION OF TREATMENT

### J.2.2.1 Change in HbA1c at 3, 6, 12 and 24 months

**Change in HbA1c at 3 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 31: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – evidence network**

**Table 52: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – input data**

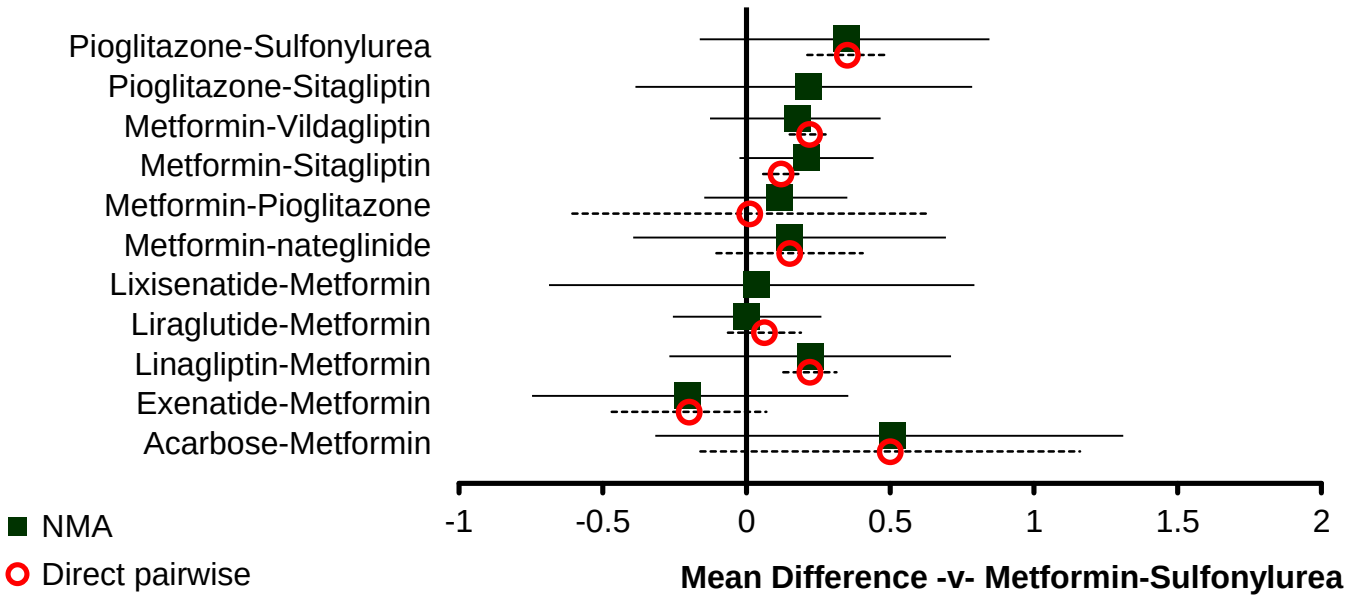
| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wang et al. (2011) | -1.20 (1.44) | -0.70 (0.80) | | | | | | | | | | |
| Derosa et al. (2011) | -0.40 (0.75) | | -0.60 (0.66) | | | | | | | | | |
| Derosa et al. (2011) | -0.40 (1.08) | | | | | | | -0.20 (1.05) | | | | |
| Yang et al. (2011) | -1.39 (1.16) | | | | -1.32 (1.14) | | | | | | | |
| Filozof & (2010) | -1.15 (0.91) | | | | | | | | | -0.98 (0.90) | | |
| Derosa et al. (2010) | | | | | | | | -0.40 (0.72) | | | -0.30 (0.82) | |
| Derosa et al. (2009) | -0.50 (0.98) | | | | | | | -1.20 (1.22) | | | | |
| Ferrannini et al. (2009) | -0.77 (1.08) | | | | | | | | | -0.53 (0.85) | | |
| Bolli et al. (2008) | | | | | | | | -0.91 (0.84) | | -0.91 (0.86) | | |
| Nauck et al. (2007) | -0.68 (0.62) | | | | | | | | -0.57 (0.53) | | | |
| Arechavaleta et al. (2010) | -0.54 (0.94) | | | | | | | | -0.43 (0.59) | | | |
| Nauck et al. (2009) | -1.00 (1.37) | | | | -0.95 (1.07) | | | | | | | |
| Matthews et al. (2005) | -1.45 (0.53) | | | | | | | -0.98 (0.71) | | | | |
| Srivastava et al. (2012) | -0.77 (0.51) | | | | | | | | -0.50 (0.42) | | | |
| Pratley et al. (2010) | | | | | -1.33 (1.04) | | | | -1.00 (1.03) | | | |
| Gerich et al. (2005) | -1.90 (1.28) | | | | | | -1.75 (1.34) | | | | | |
| Hanefeld et al. (2004) | -1.60 (0.89) | | | | | | | | | | | -1.25 (0.89) |
| Gallwitz et al. (2012) | -0.80 (0.54) | | | -0.58 (0.52) | | | | | | | | |
| Chawla et al. (2013) | | | | | | | | -0.75 (0.35) | -0.66 (0.21) | | | |
| Rosenstock et al. (2013) | | | -1.02 (0.85) | | | -0.78 (0.85) | | | | | | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 53: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | 0.50 (-0.16, 1.16) | -0.20 (-0.47, 0.07) | 0.22 (0.13, 0.31) | 0.06 (-0.06, 0.19) | - | 0.15 (-0.10, 0.40) | 0.01 (-0.61, 0.63) | 0.12 (0.06, 0.18) | 0.22 (0.15, 0.29) | - | 0.35 (0.21, 0.49) |
| Acarbose-Metformin | 0.51 (-0.32, 1.31) | | - | - | - | - | - | - | - | - | - | - |
| Exenatide-Metformin | -0.20 (-0.75, 0.35) | -0.71 (-1.69, 0.27) | | - | - | 0.24 (0.11, 0.37) | - | - | - | - | - | - |
| Linagliptin-Metformin | 0.22 (-0.27, 0.71) | -0.29 (-1.23, 0.68) | 0.43 (-0.32, 1.16) | | - | - | - | - | - | - | - | - |
| Liraglutide-Metformin | 0.00 (-0.26, 0.26) | -0.51 (-1.34, 0.36) | 0.21 (-0.41, 0.80) | -0.22 (-0.77, 0.33) | | - | - | - | 0.33 (0.17, 0.50) | - | - | - |
| Lixisenatide-Metformin | 0.04 (-0.69, 0.79) | -0.47 (-1.56, 0.63) | 0.24 (-0.25, 0.74) | -0.19 (-1.06, 0.71) | 0.03 (-0.74, 0.84) | | - | - | - | - | - | - |
| Metformin-nateglinide | 0.15 (-0.39, 0.69) | -0.36 (-1.32, 0.63) | 0.36 (-0.42, 1.13) | -0.07 (-0.81, 0.66) | 0.15 (-0.46, 0.75) | 0.11 (-0.82, 1.02) | | - | - | - | - | - |
| Metformin-Pioglitazone | 0.12 (-0.15, 0.35) | -0.39 (-1.23, 0.46) | 0.32 (-0.31, 0.90) | -0.10 (-0.67, 0.43) | 0.12 (-0.25, 0.44) | 0.08 (-0.74, 0.83) | -0.03 (-0.64, 0.55) | | 0.09 (-0.07, 0.25) | 0.00 (-0.14, 0.14) | 0.10 (-0.15, 0.35) | - |
| Metformin-Sitagliptin | 0.21 (-0.02, 0.44) | -0.30 (-1.13, 0.55) | 0.42 (-0.20, 1.00) | -0.01 (-0.56, 0.53) | 0.21 (-0.09, 0.50) | 0.17 (-0.61, 0.94) | 0.06 (-0.52, 0.65) | 0.09 (-0.20, 0.41) | | - | - | - |
| Metformin-Vildagliptin | 0.18 (-0.13, 0.47) | -0.33 (-1.19, 0.54) | 0.38 (-0.26, 0.99) | -0.04 (-0.62, 0.52) | 0.18 (-0.22, 0.56) | 0.14 (-0.68, 0.92) | 0.03 (-0.59, 0.64) | 0.06 (-0.26, 0.41) | -0.03 (-0.40, 0.33) | | - | - |
| Pioglitazone-Sitagliptin | 0.22 (-0.39, 0.78) | -0.30 (-1.29, 0.71) | 0.42 (-0.41, 1.21) | 0.00 (-0.78, 0.73) | 0.21 (-0.44, 0.83) | 0.18 (-0.79, 1.10) | 0.07 (-0.75, 0.84) | 0.10 (-0.44, 0.63) | 0.01 (-0.63, 0.60) | 0.04 (-0.59, 0.65) | | - |
| Pioglitazone-Sulfonylurea | 0.35 (-0.16, 0.85) | -0.16 (-1.10, 0.79) | 0.55 (-0.20, 1.28) | 0.13 (-0.57, 0.83) | 0.35 (-0.21, 0.90) | 0.31 (-0.59, 1.19) | 0.20 (-0.54, 0.94) | 0.23 (-0.31, 0.80) | 0.14 (-0.42, 0.69) | 0.17 (-0.41, 0.75) | 0.13 (-0.61, 0.91) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 32: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – relative effect of all options versus reference treatment**

**Table 54: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.030 | 4 (1, 7) |
| Acarbose-Metformin | 0.036 | 11 (1, 12) |
| Exenatide-Metformin | 0.512 | 1 (1, 9) |
| Linagliptin-Metformin | 0.038 | 8 (1, 12) |
| Liraglutide-Metformin | 0.094 | 4 (1, 9) |
| Lixisenatide-Metformin | 0.103 | 5 (1, 12) |

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-nateglinide | 0.082 | 7 (1, 12) |
| Metformin-Pioglitazone | 0.014 | 6 (2, 10) |
| Metformin-Sitagliptin | 0.001 | 8 (4, 11) |
| Metformin-Vildagliptin | 0.012 | 7 (2, 11) |
| Pioglitazone-Sitagliptin | 0.064 | 8 (1, 12) |
| Pioglitazone-Sulfonylurea | 0.014 | 10 (2, 12) |

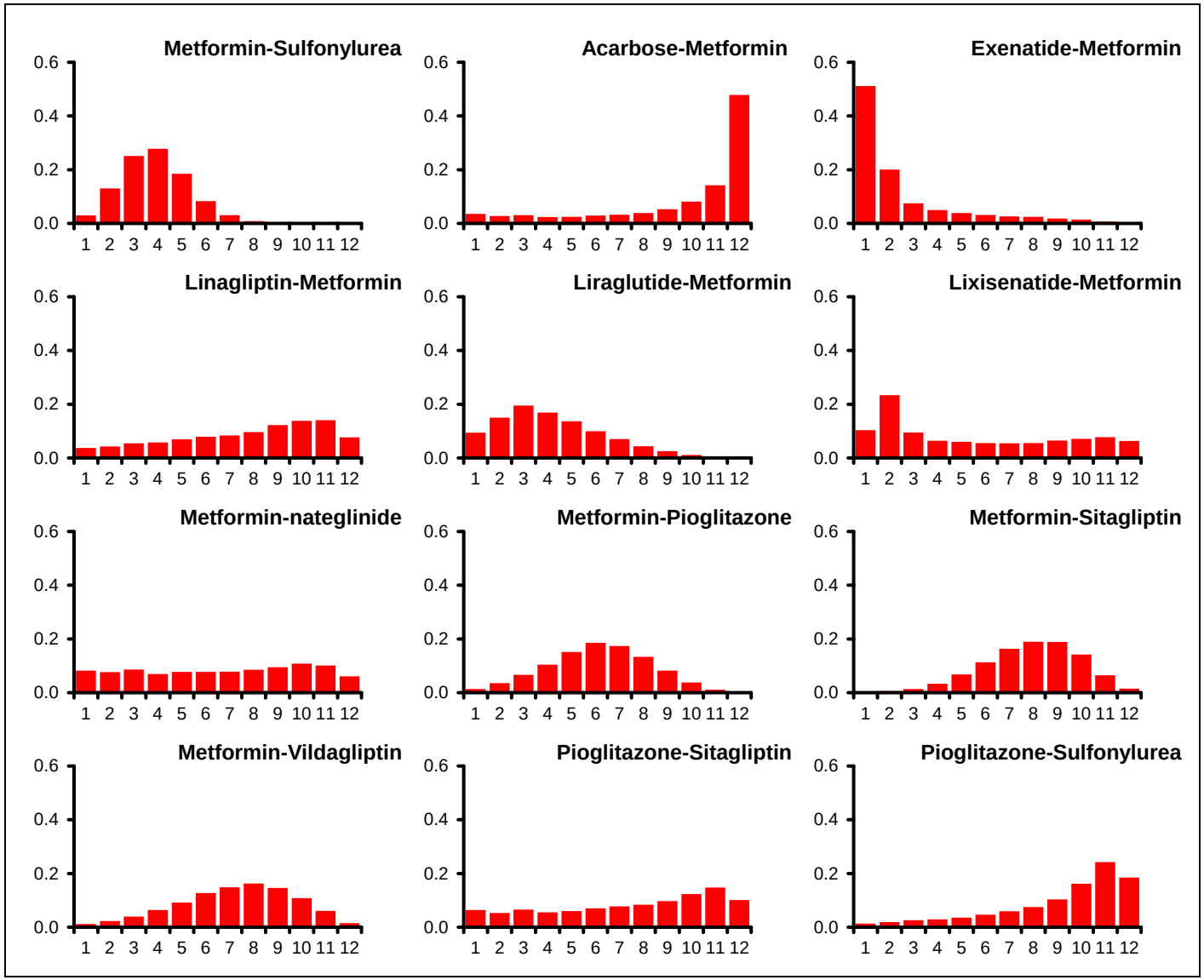



**Figure 33: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – rank probability histograms**

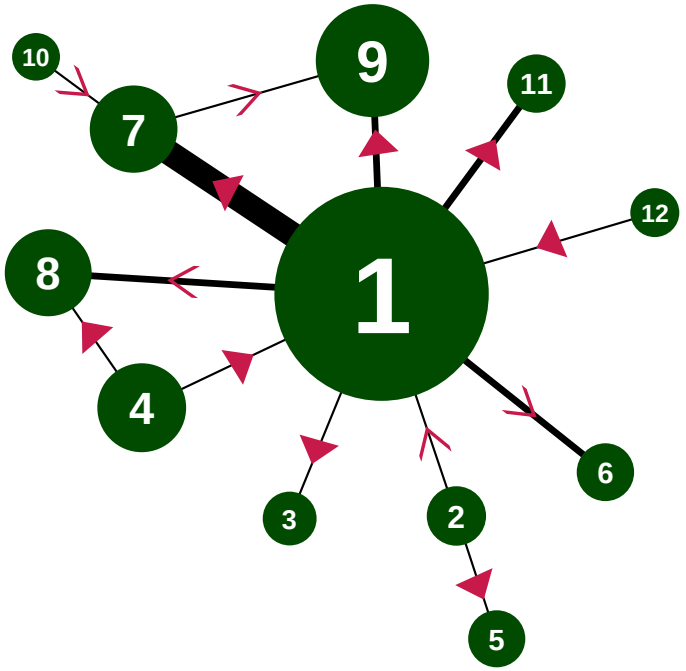
**Table 55: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 47.4<br>(compared to 45 datapoints) | -117.793 | -160.698 | 42.905 | -74.888 | 0.219 (95%CI: 0.127, 0.383) |

**Table 56: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

**Change in HbA1c at 6 months**




1 Metformin-Sulfonylurea
2 Exenatide-Metformin
3 Linagliptin-Metformin
4 Liraglutide-Metformin
5 Lixisenatide-Metformin
6 Metformin-nateglinide
7 Metformin-Pioglitazone
8 Metformin-Sitagliptin
9 Metformin-Vildagliptin
10 Pioglitazone-Sitagliptin
11 Pioglitazone-Sulfonylurea
12 Sitagliptin-Sulfonylurea

*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 34: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – evidence network**

**Table 57: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – input data**

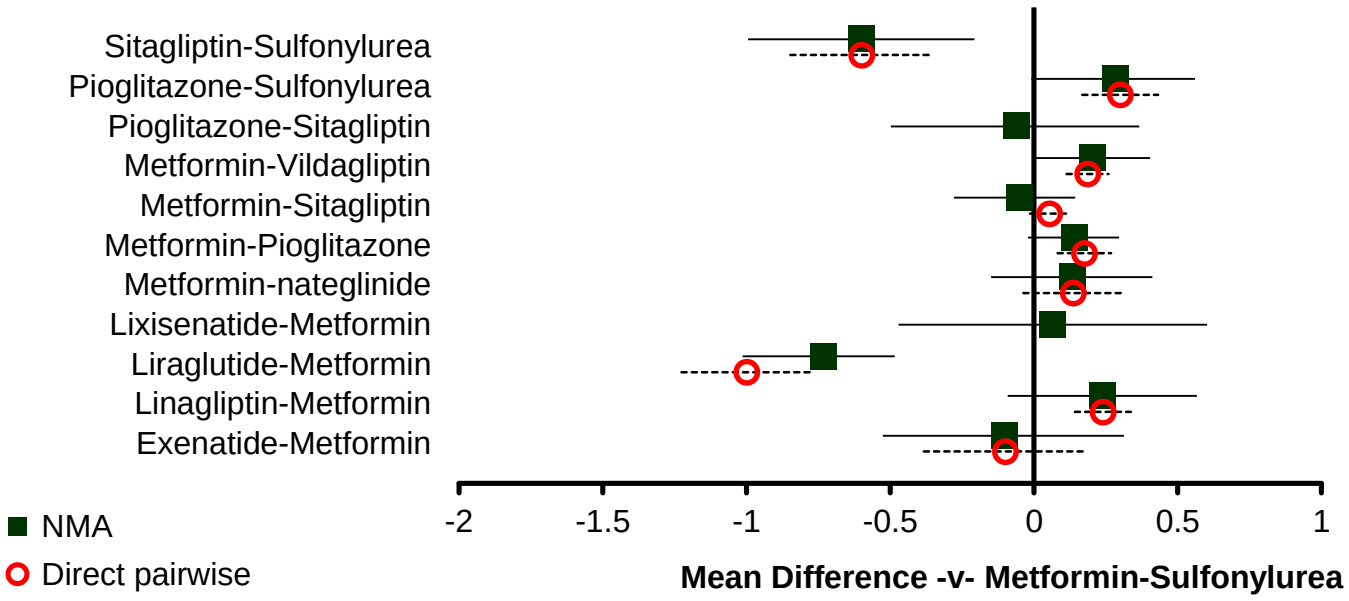
| | Metformin-Sulfonylurea | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea | Sitagliptin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Derosa et al. (2011) | -0.70 (0.78) | -0.80 (0.68) | | | | | | | | | | |
| Derosa et al. (2011) | -0.50 (1.15) | | | | | | -0.40 (1.07) | | | | | |
| Pfutzner et al. (2011) | -1.00 (0.90) | | | | | | -0.80 (0.90) | | | | | |
| Filozof & (2010) | -1.19 (0.93) | | | | | | | | -1.01 (0.98) | | | |
| Derosa et al. (2010) | | | | | | | -0.60 (0.75) | | | -0.80 (0.84) | | |
| Papathanassiou et al. (2009) | -0.56 (0.57) | | | | | | -0.60 (0.85) | | | | | |
| Ferrannini et al. (2009) | -0.74 (1.15) | | | | | | | | -0.55 (0.92) | | | |
| Bolli et al. (2008) | | | | | | | -1.01 (0.92) | | -0.91 (1.04) | | | |
| Hermansen et al. (2007) | 0.30 (0.87) | | | | | | | | | | | -0.30 (0.95) |
| Nauck et al. (2007) | -0.75 (0.65) | | | | | | | -0.70 (0.55) | | | | |
| Ristic et al. (2006) | -0.57 (0.87) | | | | | -0.41 (0.91) | | | | | | |
| Arechavaleta et al. (2010) | -0.52 (0.92) | | | | | | | -0.46 (0.92) | | | | |
| Nauck et al. (2009) | 0.10 (1.56) | | | -0.90 (1.55) | | | | | | | | |
| Matthews et al. (2005) | -1.39 (0.88) | | | | | | -1.15 (0.89) | | | | | |
| Pratley et al. (2010) | | | | -1.37 (0.99) | | | | -0.90 (0.98) | | | | |
| Umpierrez et al. (2006) | -1.30 (0.75) | | | | | | -1.23 (0.76) | | | | | |
| van der et al. (2009) | -0.80 (0.68) | | | | | | | | | | -0.60 (1.15) | |
| Gerich et al. (2005) | -2.00 (1.40) | | | | | -1.90 (1.46) | | | | | | |
| Hanefeld et al. (2004) | -1.70 (0.89) | | | | | | | | | | -1.39 (0.89) | |
| Gallwitz et al. (2012) | -0.82 (0.55) | | -0.58 (0.55) | | | | | | | | | |
| Rosenstock et al. (2013) | | -0.96 (0.89) | | | -0.79 (0.89) | | | | | | | |
| Maffioli et al. (2013) | -0.80 (1.77) | | | | | | -0.60 (1.48) | | | | | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 58: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea | Sitagliptin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | -0.10 (-0.38, 0.18) | 0.24 (0.14, 0.34) | -1.00 (-1.23, -0.77) | - | 0.14 (-0.04, 0.31) | 0.18 (0.08, 0.27) | 0.05 (-0.01, 0.12) | 0.19 (0.11, 0.26) | - | 0.30 (0.17, 0.43) | -0.60 (-0.85, -0.35) |
| Exenatide-Metformin | -0.10 (-0.53, 0.31) | | - | - | 0.17 (0.03, 0.31) | - | - | - | - | - | - | - |
| Linagliptin-Metformin | 0.24 (-0.09, 0.57) | 0.34 (-0.19, 0.88) | | - | - | - | - | - | - | - | - | - |
| Liraglutide-Metformin | -0.73 (-1.01, -0.48) | -0.63 (-1.14, -0.15) | -0.97 (-1.42, -0.58) | | - | - | - | 0.47 (0.31, 0.63) | - | - | - | - |
| Lixisenatide-Metformin | 0.07 (-0.47, 0.60) | 0.17 (-0.18, 0.51) | -0.17 (-0.81, 0.46) | 0.80 (0.22, 1.41) | | - | - | - | - | - | - | - |
| Metformin-nateglinide | 0.13 (-0.15, 0.41) | 0.24 (-0.27, 0.75) | -0.11 (-0.54, 0.32) | 0.86 (0.50, 1.27) | 0.07 (-0.53, 0.67) | | - | - | - | - | - | - |
| Metformin-Pioglitazone | 0.14 (-0.02, 0.30) | 0.25 (-0.20, 0.69) | -0.10 (-0.47, 0.26) | 0.87 (0.59, 1.19) | 0.08 (-0.48, 0.63) | 0.01 (-0.32, 0.33) | | - | 0.10 (-0.06, 0.26) | -0.20 (-0.45, 0.05) | - | - |
| Metformin-Sitagliptin | -0.05 (-0.28, 0.14) | 0.05 (-0.43, 0.51) | -0.29 (-0.70, 0.08) | 0.68 (0.44, 0.93) | -0.12 (-0.71, 0.45) | -0.18 (-0.55, 0.16) | -0.19 (-0.46, 0.06) | | - | - | - | - |
| Metformin-Vildagliptin | 0.20 (0.00, 0.40) | 0.31 (-0.16, 0.77) | -0.04 (-0.42, 0.35) | 0.93 (0.63, 1.28) | 0.14 (-0.44, 0.71) | 0.07 (-0.28, 0.42) | 0.06 (-0.16, 0.29) | 0.25 (-0.02, 0.56) | | - | - | - |
| Pioglitazone-Sitagliptin | -0.06 (-0.50, 0.37) | 0.04 (-0.57, 0.65) | -0.30 (-0.86, 0.24) | 0.67 (0.18, 1.19) | -0.13 (-0.82, 0.57) | -0.20 (-0.71, 0.32) | -0.20 (-0.60, 0.20) | -0.01 (-0.48, 0.48) | -0.26 (-0.73, 0.19) | | - | - |
| Pioglitazone-Sulfonylurea | 0.28 (-0.01, 0.56) | 0.39 (-0.12, 0.90) | 0.04 (-0.40, 0.48) | 1.01 (0.64, 1.41) | 0.22 (-0.39, 0.82) | 0.15 (-0.26, 0.54) | 0.14 (-0.18, 0.47) | 0.33 (-0.01, 0.69) | 0.08 (-0.27, 0.42) | 0.34 (-0.17, 0.86) | | - |
| Sitagliptin-Sulfonylurea | -0.60 (-0.99, -0.21) | -0.50 (-1.08, 0.08) | -0.84 (-1.36, -0.32) | 0.13 (-0.32, 0.62) | -0.67 (-1.34, 0.01) | -0.73 (-1.21, -0.25) | -0.74 (-1.16, -0.31) | -0.55 (-0.98, -0.09) | -0.80 (-1.24, -0.36) | -0.54 (-1.12, 0.05) | -0.88 (-1.36, -0.39) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 35: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – relative effect of all options versus reference treatment**

**Table 59: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 6 (4, 8) |
| Exenatide-Metformin | 0.003 | 4 (2, 10) |
| Linagliptin-Metformin | 0.000 | 10 (4, 12) |
| Liraglutide-Metformin | 0.712 | 1 (1, 2) |
| Lixisenatide-Metformin | 0.003 | 7 (3, 12) |
| Metformin-nateglinide | 0.000 | 8 (3, 12) |

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Pioglitazone | 0.000 | 9 (5, 11) |
| Metformin-Sitagliptin | 0.000 | 5 (3, 9) |
| Metformin-Vildagliptin | 0.000 | 10 (6, 12) |
| Pioglitazone-Sitagliptin | 0.003 | 5 (2, 12) |
| Pioglitazone-Sulfonylurea | 0.000 | 11 (6, 12) |
| Sitagliptin-Sulfonylurea | 0.278 | 2 (1, 4) |

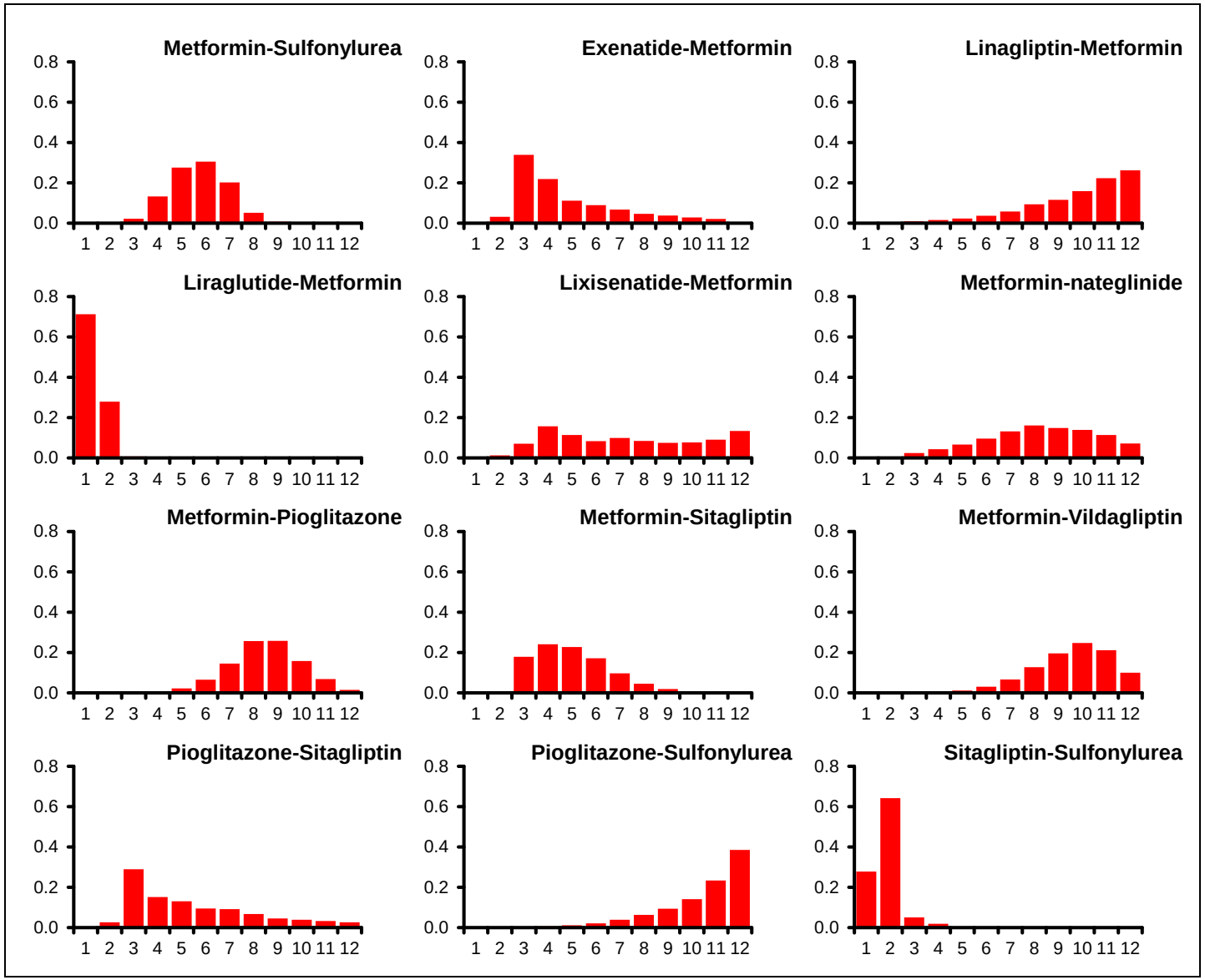



**Figure 36: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – rank probability histograms**

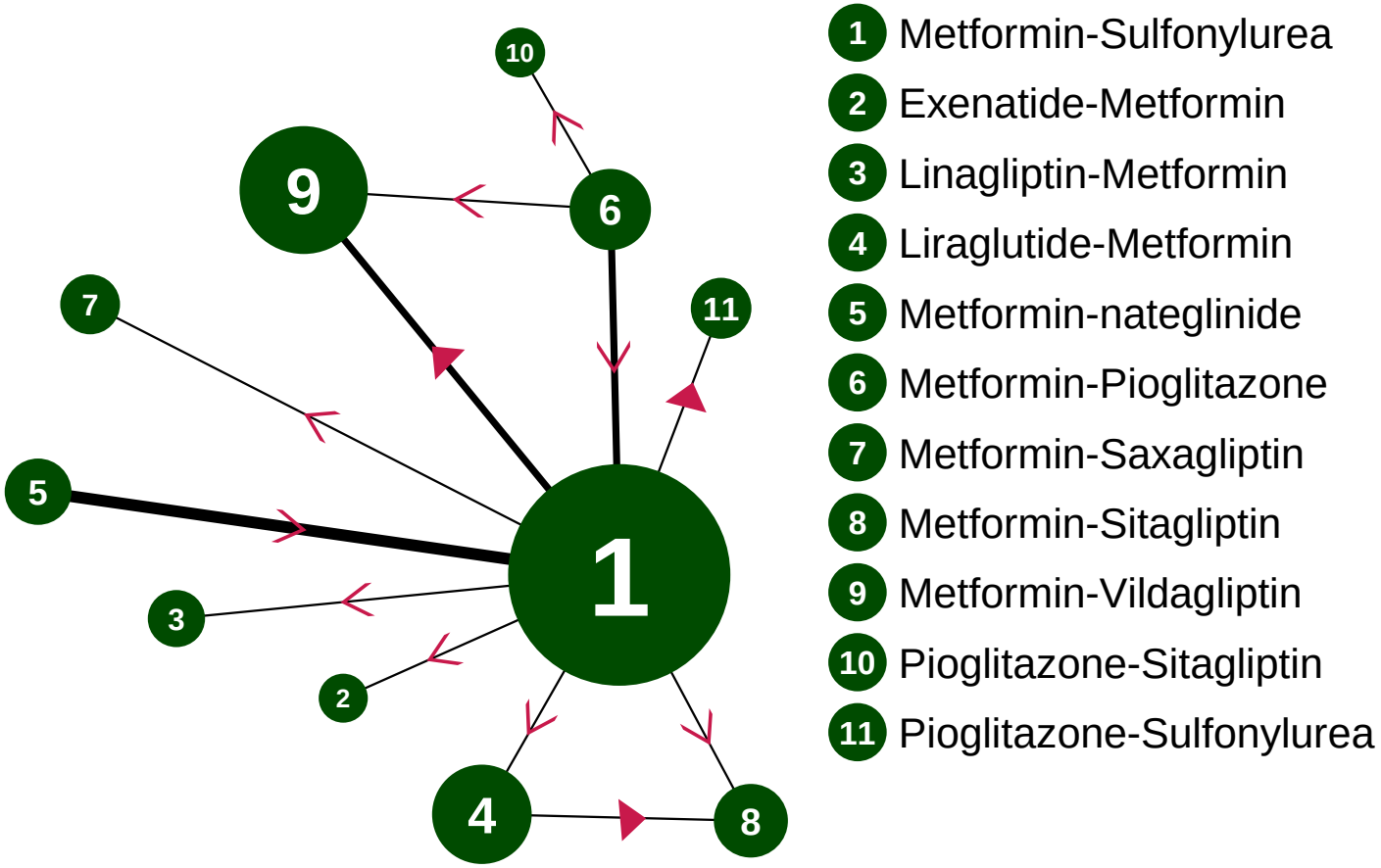
**Table 60: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 47.35<br>(compared to 47 datapoints) | -112.895 | -154.753 | 41.858 | -71.037 | 0.140 (95%CI: 0.056, 0.265) |

**Table 61: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

**Change in HbA1c at 12 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 37: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – evidence network**

**Table 62: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – input data**

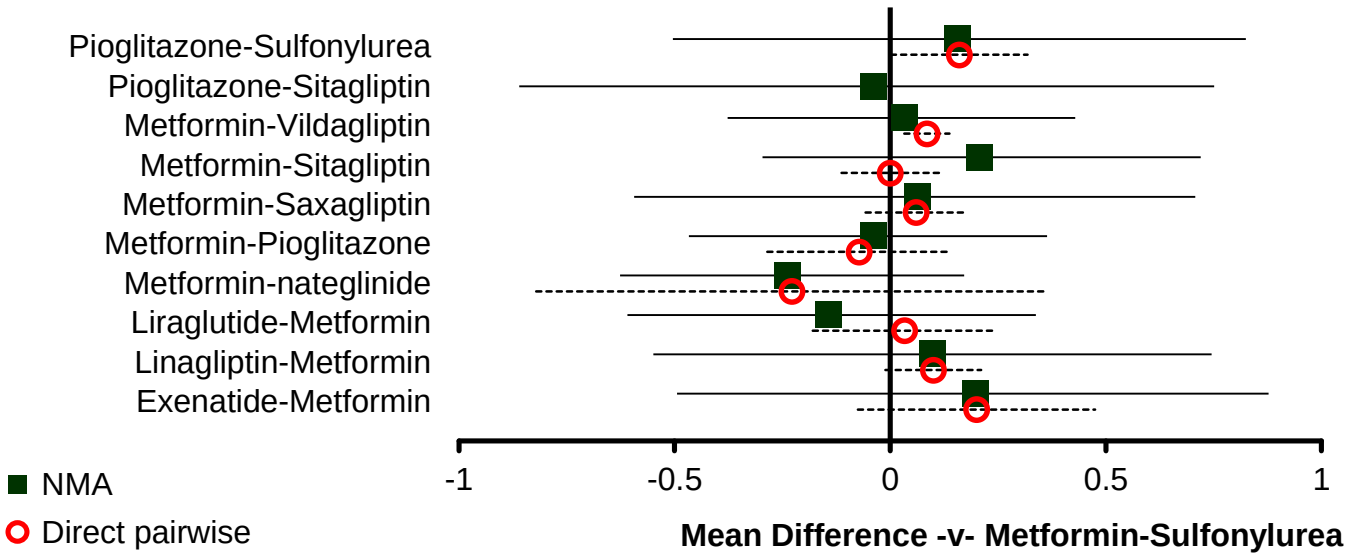
| | Metformin-Sulfonylurea | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Goke et al. (2010) | -0.80 (0.86) | | | | | | -0.74 (0.57) | | | | |
| Derosa et al. (2011) | -1.40 (0.75) | -1.20 (0.65) | | | | | | | | | |
| Derosa et al. (2011) | -0.80 (1.12) | | | | | -1.00 (1.03) | | | | | |
| Filozof & (2010) | -0.85 (1.19) | | | | | | | | -0.81 (1.18) | | |
| Derosa et al. (2010) | | | | | | -1.40 (0.75) | | | | -1.40 (0.84) | |
| Ferrannini et al. (2009) | -0.53 (0.65) | | | | | | | | -0.44 (0.67) | | |
| Bolli et al. (2008) | | | | | | -0.60 (1.45) | | | -0.60 (0.96) | | |
| Derosa et al. (2007) | -0.90 (1.04) | | | | -1.70 (0.93) | | | | | | |
| Nauck et al. (2007) | -0.67 (0.83) | | | | | | | -0.67 (0.80) | | | |
| Ristic et al. (2006) | -0.20 (1.22) | | | | -0.12 (1.07) | | | | | | |
| Nauck et al. (2009) | -0.70 (1.52) | | | -0.67 (1.32) | | | | | | | |
| Matthews et al. (2005) | -1.01 (1.59) | | | | | -0.99 (1.60) | | | | | |
| Pratley et al. (2010) | | | | -1.40 (1.06) | | | | -0.88 (1.06) | | | |
| Gerich et al. (2005) | -1.80 (1.44) | | | | -1.75 (1.50) | | | | | | |
| Hanefeld et al. (2004) | -1.36 (1.02) | | | | | | | | | | -1.20 (1.02) |
| Gallwitz et al. (2012) | -0.77 (0.62) | | -0.67 (0.64) | | | | | | | | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 63: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | 0.20 (-0.08, 0.48) | 0.10 (-0.01, 0.21) | 0.03 (-0.18, 0.25) | -0.23 (-0.82, 0.36) | -0.07 (-0.29, 0.14) | 0.06 (-0.06, 0.18) | 0.00 (-0.11, 0.11) | 0.09 (0.03, 0.14) | - | 0.16 (0.00, 0.32) |
| Exenatide-Metformin | 0.20 (-0.49, 0.88) | | - | - | - | - | - | - | - | - | - |
| Linagliptin-Metformin | 0.10 (-0.55, 0.74) | -0.10 (-1.03, 0.85) | | - | - | - | - | - | - | - | - |
| Liraglutide-Metformin | -0.14 (-0.61, 0.34) | -0.34 (-1.17, 0.52) | -0.25 (-1.04, 0.56) | | - | - | - | 0.52 (0.35, 0.69) | - | - | - |
| Metformin-nateglinide | -0.24 (-0.63, 0.17) | -0.43 (-1.23, 0.38) | -0.34 (-1.08, 0.44) | -0.09 (-0.71, 0.53) | | - | - | - | - | - | - |
| Metformin-Pioglitazone | -0.04 (-0.47, 0.36) | -0.24 (-1.05, 0.56) | -0.14 (-0.91, 0.61) | 0.10 (-0.54, 0.72) | 0.19 (-0.40, 0.76) | | - | - | 0.00 (-0.20, 0.20) | 0.00 (-0.27, 0.27) | - |
| Metformin-Saxagliptin | 0.06 (-0.59, 0.71) | -0.14 (-1.08, 0.81) | -0.04 (-0.95, 0.88) | 0.21 (-0.60, 0.99) | 0.30 (-0.48, 1.06) | 0.10 (-0.67, 0.89) | | - | - | - | - |
| Metformin-Sitagliptin | 0.21 (-0.30, 0.72) | 0.01 (-0.85, 0.88) | 0.11 (-0.71, 0.94) | 0.35 (-0.13, 0.83) | 0.44 (-0.21, 1.09) | 0.25 (-0.39, 0.93) | 0.14 (-0.66, 0.97) | | - | - | - |
| Metformin-Vildagliptin | 0.03 (-0.38, 0.43) | -0.16 (-0.96, 0.63) | -0.07 (-0.82, 0.69) | 0.18 (-0.46, 0.79) | 0.27 (-0.31, 0.83) | 0.08 (-0.40, 0.56) | -0.03 (-0.80, 0.73) | -0.17 (-0.83, 0.46) | | - | - |
| Pioglitazone-Sitagliptin | -0.04 (-0.86, 0.75) | -0.24 (-1.31, 0.81) | -0.14 (-1.17, 0.87) | 0.10 (-0.85, 1.02) | 0.20 (-0.72, 1.07) | 0.00 (-0.69, 0.68) | -0.10 (-1.16, 0.92) | -0.25 (-1.22, 0.67) | -0.08 (-0.93, 0.75) | | - |
| Pioglitazone-Sulfonylurea | 0.16 (-0.50, 0.82) | -0.04 (-1.00, 0.91) | 0.06 (-0.87, 0.98) | 0.30 (-0.51, 1.12) | 0.40 (-0.40, 1.15) | 0.20 (-0.57, 0.99) | 0.10 (-0.84, 1.02) | -0.05 (-0.88, 0.78) | 0.12 (-0.64, 0.90) | 0.20 (-0.81, 1.25) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 38: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment**

**Table 64: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.001 | 6 (3, 9) |
| Exenatide-Metformin | 0.044 | 9 (1, 11) |
| Linagliptin-Metformin | 0.061 | 7 (1, 11) |
| Liraglutide-Metformin | 0.179 | 3 (1, 9) |
| Metformin-nateglinide | 0.327 | 2 (1, 8) |
| Metformin-Pioglitazone | 0.039 | 5 (1, 10) |
| Metformin-Saxagliptin | 0.081 | 7 (1, 11) |
| Metformin-Sitagliptin | 0.007 | 9 (2, 11) |
| Metformin-Vildagliptin | 0.025 | 6 (2, 11) |
| Pioglitazone-Sitagliptin | 0.191 | 5 (1, 11) |
| Pioglitazone-Sulfonylurea | 0.047 | 8 (1, 11) |

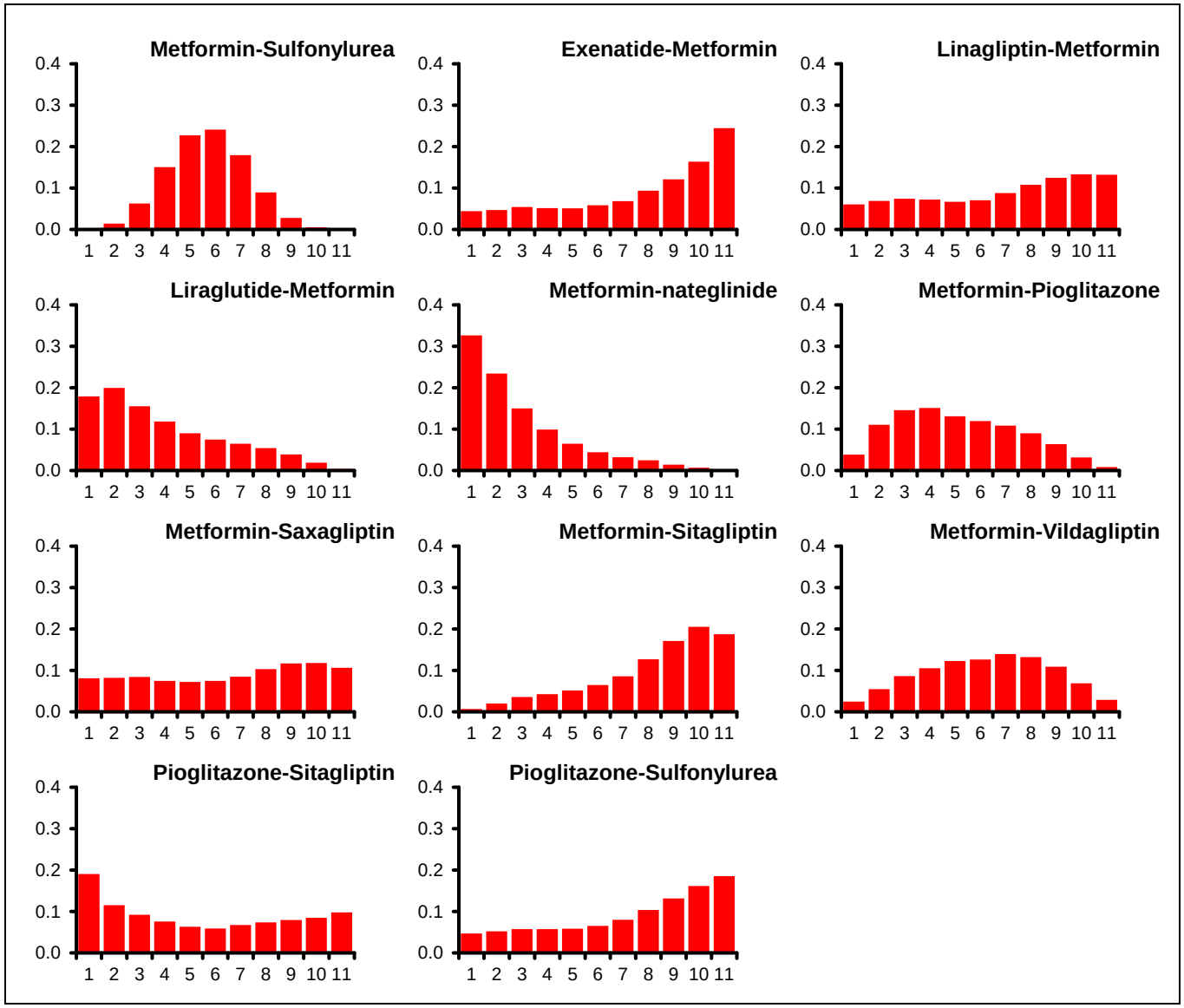



**Figure 39: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rank probability histograms**

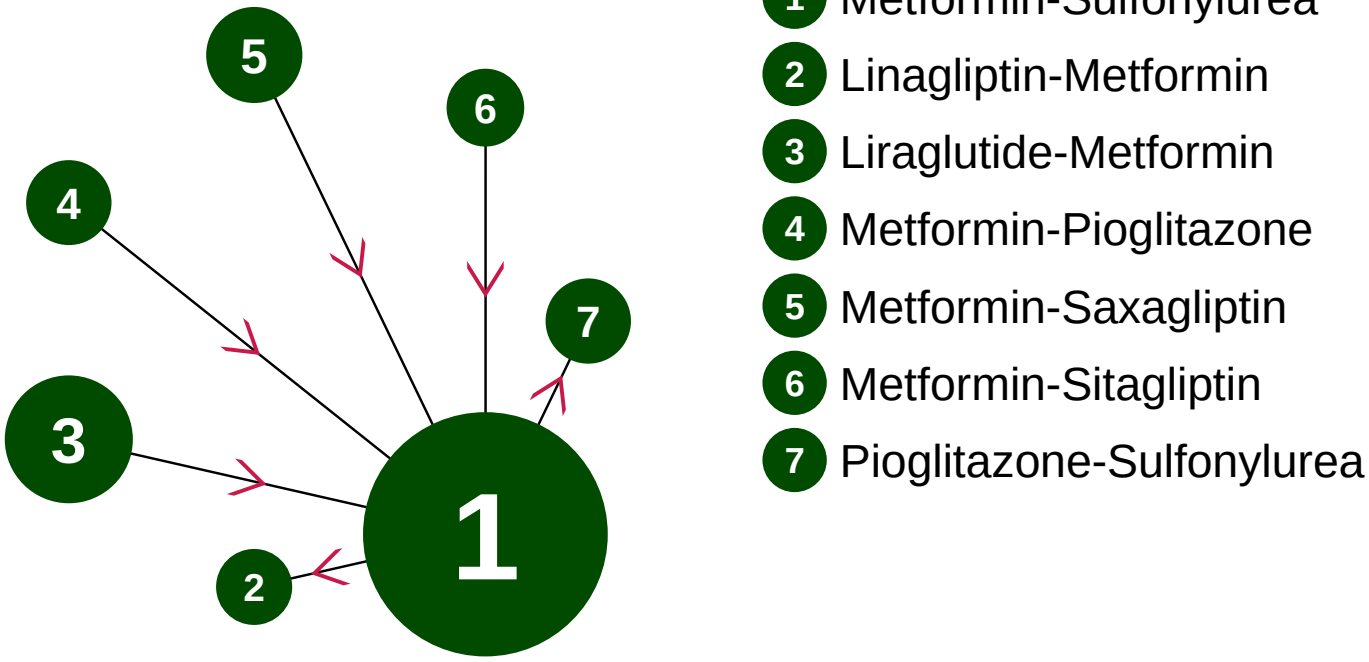
**Table 65: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 35.37<br>(compared to 35 datapoints) | -87.735 | -121.564 | 33.829 | -53.906 | 0.283 (95%CI: 0.154, 0.548) |

**Table 66: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

**Change in HbA1c at 24 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 40: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – evidence network**

**Table 67: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – input data**

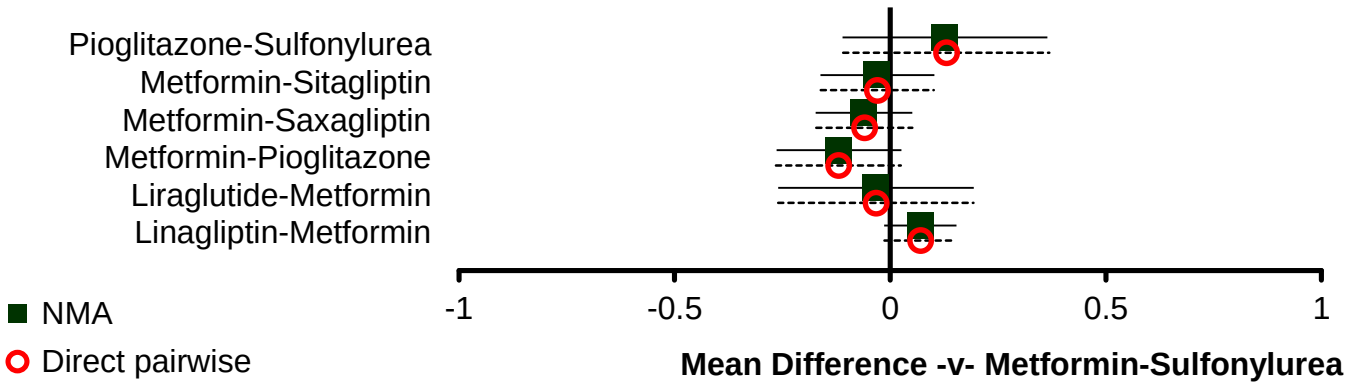
| | Metformin-Sulfonylurea | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|
| Goke et al. (2010) | -0.35 (0.83) | | | | -0.41 (0.83) | | |
| Nauck et al. (2007) | -0.51 (0.73) | | | | | -0.54 (0.76) | |
| Nauck et al. (2009) | -0.50 (1.56) | | -0.53 (1.55) | | | | |
| Matthews et al. (2005) | -0.77 (0.76) | | | -0.89 (1.07) | | | |
| Hanefeld et al. (2004) | -1.16 (1.79) | | | | | | -1.03 (1.25) |
| Gallwitz et al. (2012) | -0.63 (0.49) | -0.56 (0.46) | | | | | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 68: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | 0.07 (-0.01, 0.15) | -0.03 (-0.26, 0.19) | -0.12 (-0.26, 0.02) | -0.06 (-0.17, 0.05) | -0.03 (-0.16, 0.10) | 0.13 (-0.11, 0.37) |
| Linagliptin-Metformin | 0.07 (-0.01, 0.15) | | - | - | - | - | - |
| Liraglutide-Metformin | -0.03 (-0.26, 0.19) | -0.10 (-0.34, 0.14) | | - | - | - | - |
| Metformin-Pioglitazone | -0.12 (-0.26, 0.03) | -0.19 (-0.36, -0.02) | -0.09 (-0.35, 0.18) | | - | - | - |
| Metformin-Saxagliptin | -0.06 (-0.17, 0.05) | -0.13 (-0.27, 0.01) | -0.03 (-0.28, 0.22) | 0.06 (-0.12, 0.24) | | - | - |
| Metformin-Sitagliptin | -0.03 (-0.16, 0.10) | -0.10 (-0.25, 0.06) | 0.00 (-0.26, 0.27) | 0.09 (-0.10, 0.28) | 0.03 (-0.14, 0.20) | | - |
| Pioglitazone-Sulfonylurea | 0.13 (-0.11, 0.36) | 0.06 (-0.20, 0.31) | 0.16 (-0.17, 0.49) | 0.25 (-0.03, 0.53) | 0.19 (-0.07, 0.45) | 0.16 (-0.11, 0.43) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 41: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – relative effect of all options versus reference treatment**

**Table 69: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.001 | 4 (3, 6) |
| Linagliptin-Metformin | 0.000 | 6 (4, 7) |
| Liraglutide-Metformin | 0.201 | 3 (1, 7) |
| Metformin-Pioglitazone | 0.538 | 1 (1, 5) |
| Metformin-Saxagliptin | 0.155 | 3 (1, 6) |
| Metformin-Sitagliptin | 0.088 | 3 (1, 7) |
| Pioglitazone-Sulfonylurea | 0.018 | 7 (2, 7) |

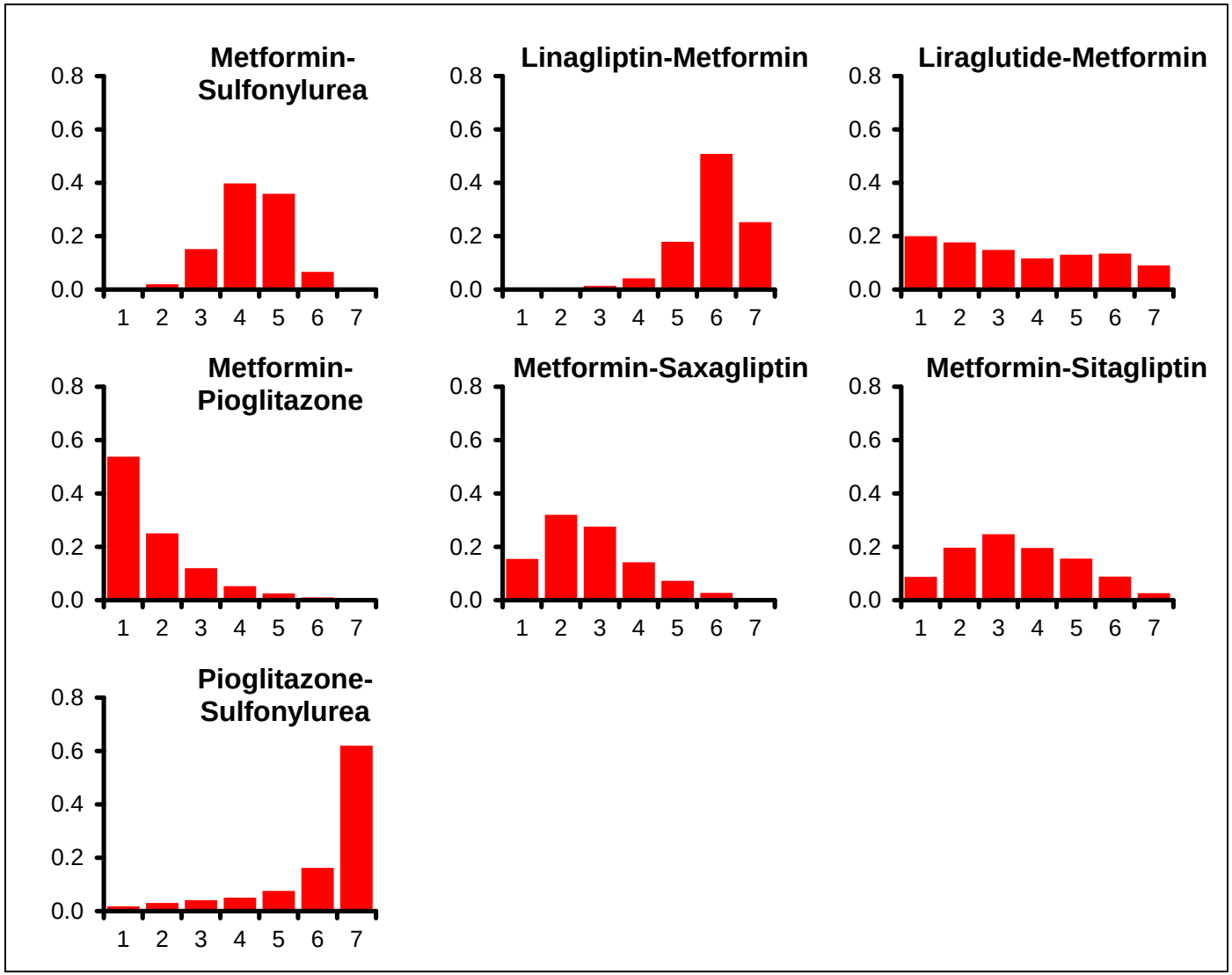



**Figure 42: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – rank probability histograms**

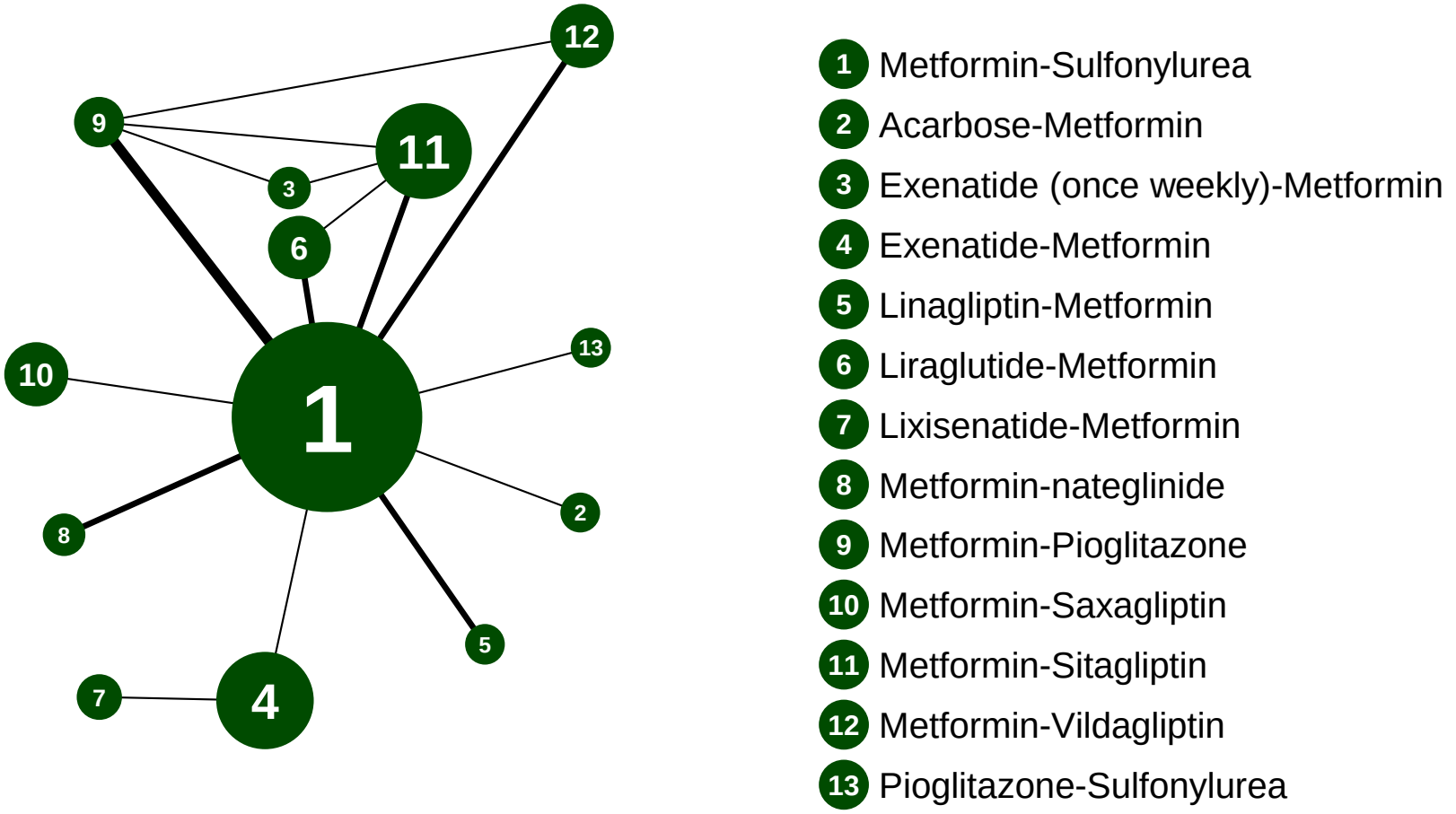
**Table 70: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 14.66<br>(compared to 14 datapoints) | -38.976 | -50.966 | 11.99 | -26.986 | |

**Table 71: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 10000 burn-ins; 10000 recorded iterations

### J.2.2.2 Hypoglycaemia at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 43: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network**

**Table 72: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data**

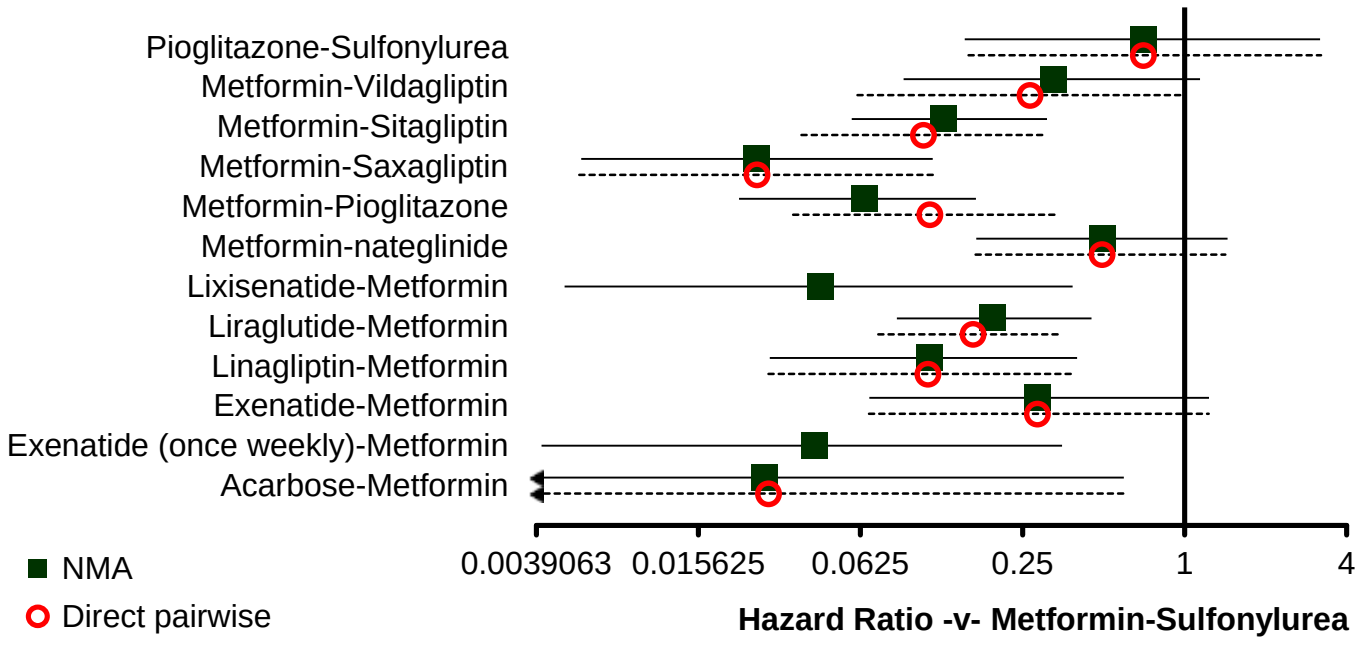
| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dichotomous proportion data | | | | | | | | | | | | | |
| Wang et al. (2011) - 0.31yr | 6/26 | 0/29 | | | | | | | | | | | |
| Forst et al. (2010) - 0.23yr | 3/65 | | | | 0/131 | | | | | | | | |
| Jeon & (2011) - 0.61yr | 10/51 | | | | | | | | | | | 1/51 | |
| Matthews et al. (2005) - 1.99yr | 36/313 | | | | | | | | 7/317 | | | | |
| Umpierrez et al. (2006) - 0.50yr | 32/96 | | | | | | | | 1/107 | | | | |
| Gerich et al. (2005) - 1.99yr | 35/198 | | | | | | | 17/208 | | | | | |
| Hanefeld et al. (2004) - 1.99yr | 50/320 | | | | | | | | | | | | 36/319 |
| Gallwitz et al. (2012) - 1.99yr | 114/271 | | | | 14/233 | | | | | | | | |
| Count data | | | | | | | | | | | | | |
| Gallwitz et al. (2012) - 2.99yr | 7162/491400 | | | 1946/467376 | | | | | | | | | |
| Goke et al. (2010) - 1.99yr | 896/210028 | | | | | | | | | 24/215852 | | | |
| Pfutzner et al. (2011) - 0.46yr | 5/22764 | | | | | | | | 2/23352 | | | | |
| Yang et al. (2011) - 0.31yr | 84/24976 | | | | | 32/70728 | | | | | | | |
| Bergenstal et al. (2010) - 0.50yr | | | 2/26117 | | | | | | 1/26936 | | 9/28210 | | |
| Filozof & (2010) - 1.00yr | 11/164892 | | | | | | | | | | | 6/167440 | |
| Bolli et al. (2008) - 0.46yr | | | | | | | | | 0/44100 | | | 3/46788 | |
| Nauck et al. (2007) - 1.99yr | 805/312676 | | | | | | | | | | 57/306852 | | |
| Ristic et al. (2006) - 0.46yr | 188/19992 | | | | | | | 110/21252 | | | | | |
| Arechavaleta et al. (2010) - 0.57yr | 460/103441 | | | | | | | | | | 73/103441 | | |
| Pratley et al. (2010) - 1.00yr | | | | | | 94/133042 | | | | | 25/67340 | | |
| Rosenstock et al. (2013) - 0.46yr | | | | 48/49308 | | | 8/49980 | | | | | | |
| Brady et al. (2014) - 0.27yr | 127/4410 | | | | | 32/3871 | | | | | | | |

*Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 73: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acarbose-Metformin | 0.03 (0.00, 0.59) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide (once weekly)-Metformin | 0.04 (0.00, 0.34) | 1.63 (0.03, 1082.00) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin | 0.29 (0.07, 1.22) | 10.54 (0.35, 6309.00) | 6.79 (0.51, 103.90) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin-Metformin | 0.11 (0.03, 0.40) | 4.08 (0.14, 2354.00) | 2.65 (0.22, 37.79) | 0.39 (0.05, 2.76) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin | 0.19 (0.09, 0.45) | 7.06 (0.29, 3790.00) | 4.57 (0.53, 51.80) | 0.68 (0.13, 3.74) | 1.75 (0.38, 8.75) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Lixisenatide-Metformin | 0.04 (0.01, 0.39) | 1.71 (0.04, 1220.00) | 1.08 (0.05, 25.64) | 0.16 (0.03, 0.80) | 0.40 (0.03, 5.13) | 0.23 (0.02, 2.24) | | N/A | N/A | N/A | N/A | N/A |
| Metformin-nateglinide | 0.49 (0.17, 1.45) | 18.09 (0.71, 9590.00) | 11.68 (1.09, 148.90) | 1.71 (0.28, 10.51) | 4.42 (0.83, 25.26) | 2.55 (0.65, 9.66) | 11.04 (0.96, 124.20) | | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone | 0.06 (0.02, 0.17) | 2.35 (0.09, 1305.00) | 1.52 (0.17, 15.52) | 0.23 (0.04, 1.28) | 0.58 (0.11, 2.94) | 0.33 (0.09, 1.11) | 1.45 (0.13, 15.27) | 0.13 (0.03, 0.54) | | N/A | N/A | N/A |
| Metformin-Saxagliptin | 0.03 (0.01, 0.11) | 0.96 (0.03, 549.70) | 0.61 (0.05, 9.44) | 0.09 (0.01, 0.70) | 0.23 (0.03, 1.79) | 0.13 (0.02, 0.72) | 0.58 (0.04, 8.20) | 0.05 (0.01, 0.33) | 0.40 (0.07, 2.64) | | N/A | N/A |
| Metformin-Sitagliptin | 0.13 (0.06, 0.31) | 4.67 (0.20, 2622.00) | 3.01 (0.42, 30.54) | 0.44 (0.09, 2.54) | 1.14 (0.26, 5.96) | 0.66 (0.27, 1.75) | 2.85 (0.29, 30.98) | 0.26 (0.07, 1.06) | 1.96 (0.66, 7.44) | 4.94 (0.93, 28.98) | | N/A |
| Metformin-Vildagliptin | 0.33 (0.09, 1.16) | 12.01 (0.43, 6413.00) | 7.74 (0.68, 108.20) | 1.14 (0.17, 7.83) | 2.94 (0.46, 18.69) | 1.68 (0.36, 7.49) | 7.30 (0.59, 88.79) | 0.66 (0.13, 3.46) | 5.04 (1.15, 24.72) | 12.66 (1.79, 89.45) | 2.55 (0.54, 10.82) | |
| Pioglitazone-Sulfonylurea | 0.70 (0.15, 3.14) | 26.13 (0.82, 15940.00) | 16.88 (1.22, 260.10) | 2.45 (0.29, 20.50) | 6.29 (0.85, 48.11) | 3.64 (0.62, 19.71) | 15.65 (1.09, 229.10) | 1.43 (0.22, 9.35) | 10.89 (1.88, 68.21) | 27.58 (3.22, 230.50) | 5.55 (0.92, 29.34) | 2.16 (0.30, 15.60) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 44: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 74: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 13 (11, 13) |
| Acarbose-Metformin | 0.401 | 2 (1, 11) |
| Exenatide (once weekly)-Metformin | 0.167 | 3 (1, 10) |
| Exenatide-Metformin | 0.000 | 9 (5, 13) |
| Linagliptin-Metformin | 0.009 | 6 (2, 10) |
| Liraglutide-Metformin | 0.000 | 8 (5, 11) |
| Lixisenatide-Metformin | 0.140 | 3 (1, 9) |
| Metformin-nateglinide | 0.000 | 11 (7, 13) |
| Metformin-Pioglitazone | 0.016 | 4 (2, 7) |
| Metformin-Saxagliptin | 0.267 | 2 (1, 6) |
| Metformin-Sitagliptin | 0.000 | 6 (4, 9) |
| Metformin-Vildagliptin | 0.000 | 10 (5, 13) |
| Pioglitazone-Sulfonylurea | 0.000 | 12 (7, 13) |

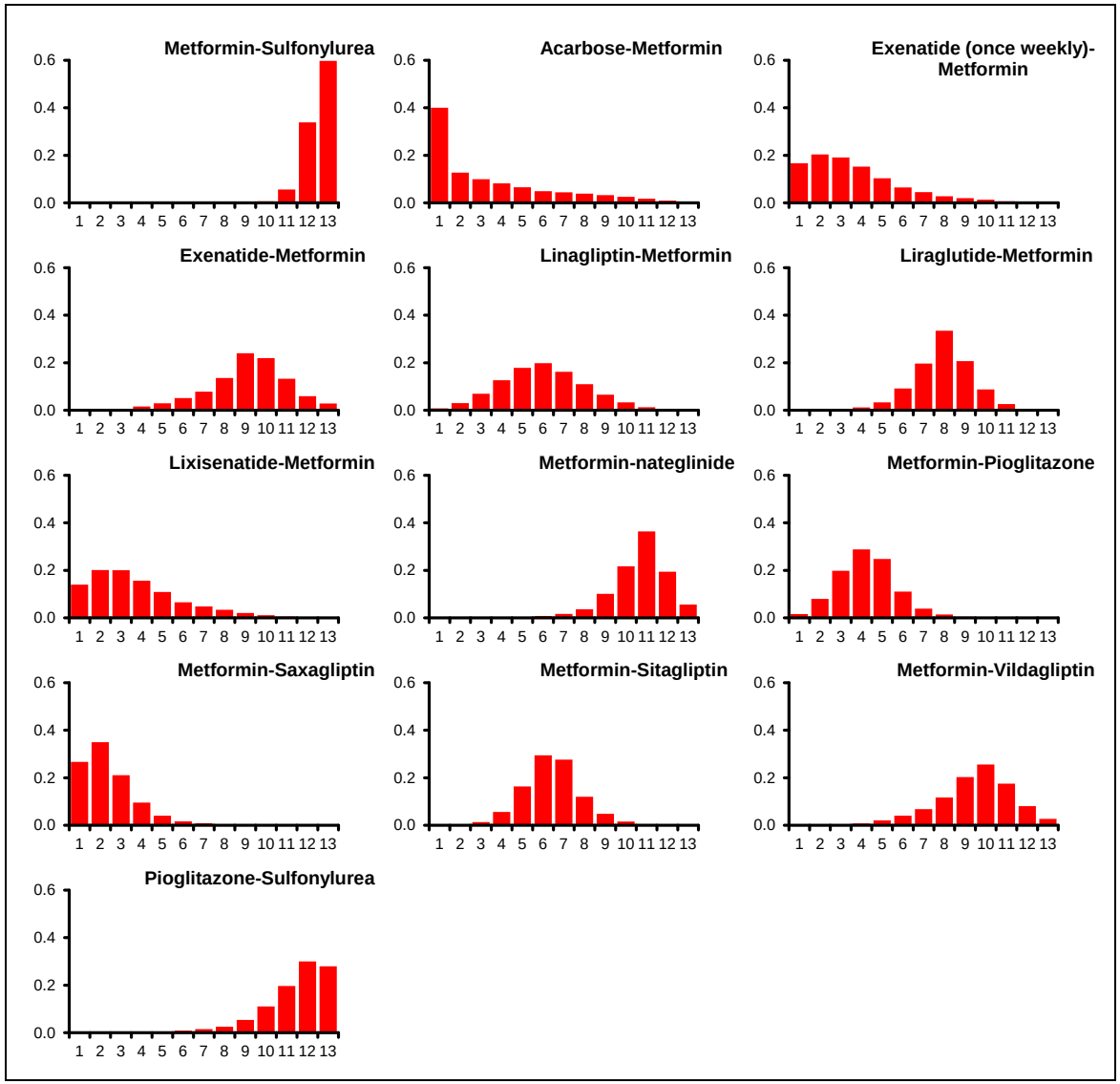



**Figure 45: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms**

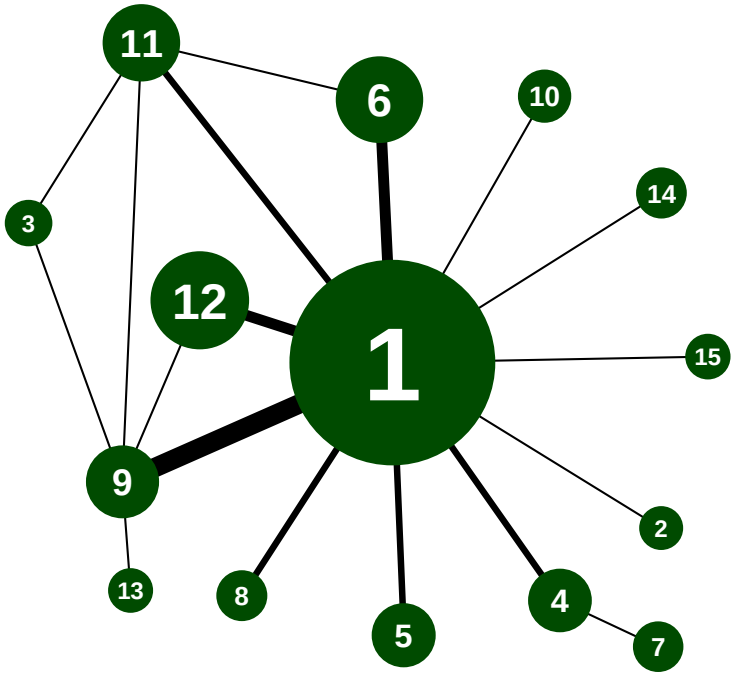
**Table 75: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 47.75<br>(compared to 47 datapoints) | 80.655 | 66.7 | 13.955 | 311.559 | 0.636 (95%CI: 0.327, 1.272) |

**Table 76: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes**

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.2.3 Dropouts due to adverse events at study endpoint




1 Metformin-Sulfonylurea
2 Acarbose-Metformin
3 Exenatide (once weekly)-Metformin
4 Exenatide-Metformin
5 Linagliptin-Metformin
6 Liraglutide-Metformin
7 Lixisenatide-Metformin
8 Metformin-nateglinide
9 Metformin-Pioglitazone
10 Metformin-Saxagliptin
11 Metformin-Sitagliptin
12 Metformin-Vildagliptin
13 Pioglitazone-Sitagliptin
14 Pioglitazone-Sulfonylurea
15 Sitagliptin-Sulfonylurea

*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 46: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – evidence network**

**Table 77: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – input data**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea | Sitagliptin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gallwitz et al. (2012) - 2.99yr | 17/514 | | | 49/515 | | | | | | | | | | | |
| Wang et al. (2011) - 0.31yr | 1/26 | 0/29 | | | | | | | | | | | | | |
| Goke et al. (2010) - 1.99yr | 36/430 | | | | | | | | | 32/428 | | | | | |
| Derosa et al. (2011) - 1.00yr | 4/54 | | | 4/57 | | | | | | | | | | | |
| Derosa et al. (2011) - 1.00yr | 3/99 | | | | | | | | 2/102 | | | | | | |
| Pfutzner et al. (2011) - 0.46yr | 7/150 | | | | | | | | 13/155 | | | | | | |
| Yang et al. (2011) - 0.31yr | 3/231 | | | | | 61/698 | | | | | | | | | |
| Forst et al. (2010) - 0.23yr | 3/65 | | | | 8/131 | | | | | | | | | | |
| Bergenstal et al. (2010) - 0.50yr | | | 11/160 | | | | | | 6/165 | | 5/166 | | | | |
| Filozof & (2010) - 1.00yr | 22/494 | | | | | | | | | | | 33/513 | | | |
| Derosa et al. (2010) - 1.00yr | | | | | | | | | 7/76 | | | | 4/75 | | |
| Ferrannini et al. (2009) - 1.99yr | 160/1556 | | | | | | | | | | | 123/1562 | | | |
| Bolli et al. (2008) - 0.46yr | | | | | | | | | 9/281 | | | 8/295 | | | |
| Hermansen et al. (2007) - 0.46yr | 2/113 | | | | | | | | | | | | | | 4/106 |
| Nauck et al. (2007) - 1.99yr | 38/584 | | | | | | | | | | 32/588 | | | | |
| Ristic et al. (2006) - 1.00yr | 2/101 | | | | | | | 1/112 | | | | | | | |
| Jeon & (2011) - 0.61yr | 1/51 | | | | | | | | | | | 3/51 | | | |
| Arechavaleta et al. (2010) - 0.57yr | 4/518 | | | | | | | | | | 18/516 | | | | |
| Nauck et al. (2009) - 0.50yr | 8/244 | | | | | 63/725 | | | | | | | | | |
| Matthews et al. (2005) - 1.99yr | 19/313 | | | | | | | | 22/317 | | | | | | |
| Pratley et al. (2010) - 1.00yr | | | | | | 44/446 | | | | | 7/219 | | | | |
| Umpierrez et al. (2006) - 0.50yr | 1/101 | | | | | | | | 4/109 | | | | | | |
| Gerich et al. (2005) - 1.99yr | 28/209 | | | | | | | 27/219 | | | | | | | |

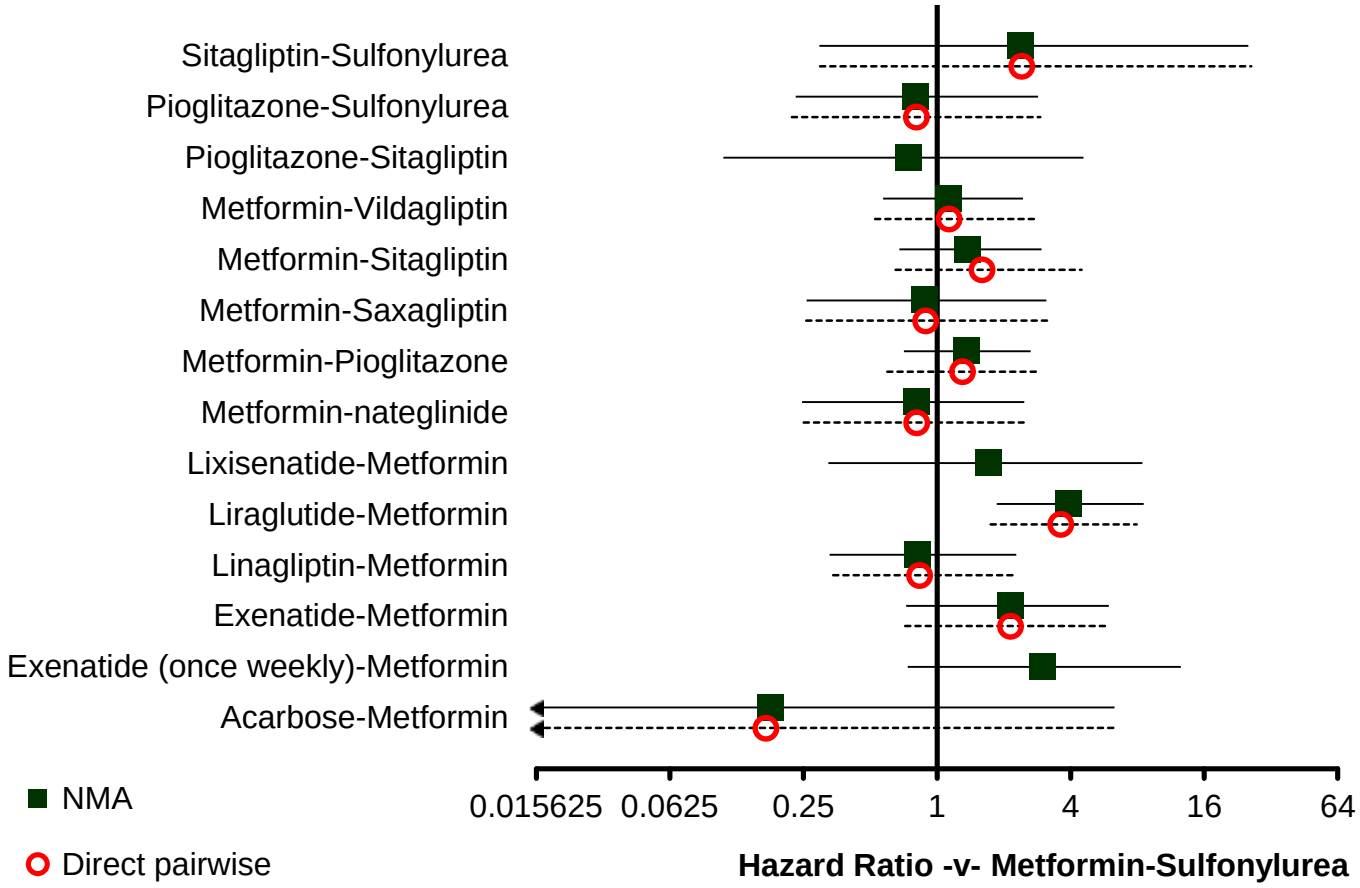
| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea | Sitagliptin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hanefeld et al. (2004) - 1.99yr | 32/320 | | | | | | | | | | | | | 26/319 | |
| Gallwitz et al. (2012) - 1.99yr | 90/775 | | | | 61/776 | | | | | | | | | | |
| Rosenstock et al. (2013) - 0.46yr | | | | 41/316 | | | 33/318 | | | | | | | | |
| Maffioli et al. (2013) - 0.50yr | 2/84 | | | | | | | | 1/86 | | | | | | |
| Brady et al. (2014) - 0.27yr | 1/52 | | | | | 1/47 | | | | | | | | | |

*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 78: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acarbose-Metformin | 0.18 (0.00, 6.32) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide (once weekly)-Metformin | 2.98 (0.74, 12.56) | 17.71 (0.35, 7799) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin | 2.16 (0.72, 5.94) | 12.17 (0.29, 5470) | 0.72 (0.12, 4.03) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin-Metformin | 0.82 (0.33, 2.27) | 4.79 (0.11, 1946) | 0.28 (0.05, 1.54) | 0.38 (0.10, 1.72) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin | 3.93 (1.86, 8.53) | 22.59 (0.57, 9350) | 1.32 (0.28, 6.10) | 1.83 (0.52, 7.01) | 4.79 (1.36, 15.97) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Lixisenatide-Metformin | 1.70 (0.32, 8.43) | 9.83 (0.19, 4753) | 0.57 (0.06, 4.80) | 0.79 (0.23, 2.74) | 2.07 (0.29, 12.80) | 0.43 (0.07, 2.47) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-nateglinide | 0.81 (0.25, 2.47) | 4.71 (0.10, 1962) | 0.27 (0.04, 1.59) | 0.38 (0.08, 1.76) | 0.98 (0.21, 4.09) | 0.21 (0.05, 0.77) | 0.47 (0.06, 3.53) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone | 1.36 (0.71, 2.64) | 7.76 (0.21, 3243) | 0.46 (0.11, 1.80) | 0.63 (0.19, 2.31) | 1.66 (0.50, 5.11) | 0.35 (0.13, 0.93) | 0.80 (0.14, 4.79) | 1.69 (0.46, 6.63) | | N/A | N/A | N/A | N/A | N/A |
| Metformin-Saxagliptin | 0.88 (0.26, 3.11) | 5.13 (0.11, 2229) | 0.30 (0.04, 1.89) | 0.41 (0.09, 2.24) | 1.08 (0.21, 5.08) | 0.22 (0.05, 0.96) | 0.52 (0.07, 4.22) | 1.10 (0.20, 6.27) | 0.65 (0.16, 2.68) | | N/A | N/A | N/A | N/A |
| Metformin-Sitagliptin | 1.38 (0.68, 2.96) | 7.87 (0.21, 3237) | 0.46 (0.12, 1.87) | 0.64 (0.19, 2.47) | 1.68 (0.50, 5.53) | 0.35 (0.15, 0.85) | 0.81 (0.14, 5.14) | 1.71 (0.47, 7.00) | 1.02 (0.42, 2.52) | 1.56 (0.37, 6.74) | | N/A | N/A | N/A |
| Metformin-Vildagliptin | 1.13 (0.57, 2.44) | 6.53 (0.17, 2634) | 0.38 (0.08, 1.82) | 0.53 (0.16, 2.02) | 1.38 (0.42, 4.57) | 0.29 (0.11, 0.85) | 0.66 (0.12, 4.30) | 1.40 (0.38, 5.86) | 0.83 (0.36, 2.03) | 1.28 (0.31, 5.63) | 0.82 (0.30, 2.32) | | N/A | N/A |
| Pioglitazone-Sitagliptin | 0.74 (0.11, 4.57) | 4.42 (0.07, 2148) | 0.25 (0.03, 2.21) | 0.34 (0.04, 2.92) | 0.90 (0.11, 6.81) | 0.19 (0.02, 1.36) | 0.44 (0.04, 5.12) | 0.92 (0.10, 8.35) | 0.55 (0.09, 2.93) | 0.84 (0.09, 7.57) | 0.53 (0.07, 3.66) | 0.66 (0.09, 4.23) | | N/A |
| Pioglitazone-Sulfonylurea | 0.80 (0.23, 2.85) | 4.63 (0.10, 1982) | 0.27 (0.04, 1.77) | 0.37 (0.08, 2.03) | 0.98 (0.19, 4.75) | 0.20 (0.05, 0.89) | 0.48 (0.06, 3.87) | 1.00 (0.19, 5.67) | 0.60 (0.14, 2.42) | 0.91 (0.16, 5.34) | 0.58 (0.13, 2.45) | 0.71 (0.16, 2.95) | 1.09 (0.12, 10.74) | |
| Sitagliptin-Sulfonylurea | 2.39 (0.30, 25.28) | 14.73 (0.21, 8124) | 0.81 (0.06, 12.44) | 1.12 (0.11, 15.10) | 2.88 (0.29, 36.84) | 0.61 (0.07, 7.27) | 1.43 (0.10, 25.49) | 2.98 (0.28, 42.18) | 1.77 (0.20, 20.25) | 2.72 (0.24, 38.38) | 1.73 (0.19, 20.38) | 2.10 (0.23, 24.98) | 3.27 (0.21, 65.77) | 2.98 (0.26, 42.47) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 47: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 79: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 6 (3, 9) |
| Acarbose-Metformin | 0.638 | 1 (1, 15) |
| Exenatide (once weekly)-Metformin | 0.001 | 13 (4, 15) |
| Exenatide-Metformin | 0.001 | 12 (4, 15) |
| Linagliptin-Metformin | 0.036 | 5 (1, 12) |
| Liraglutide-Metformin | 0.000 | 14 (11, 15) |
| Lixisenatide-Metformin | 0.017 | 11 (2, 15) |
| Metformin-nateglinide | 0.054 | 5 (1, 13) |
| Metformin-Pioglitazone | 0.000 | 9 (4, 13) |
| Metformin-Saxagliptin | 0.043 | 5 (1, 13) |
| Metformin-Sitagliptin | 0.001 | 9 (3, 13) |
| Metformin-Vildagliptin | 0.003 | 7 (3, 13) |
| Pioglitazone-Sitagliptin | 0.124 | 4 (1, 14) |
| Pioglitazone-Sulfonylurea | 0.060 | 5 (1, 13) |
| Sitagliptin-Sulfonylurea | 0.020 | 12 (2, 15) |

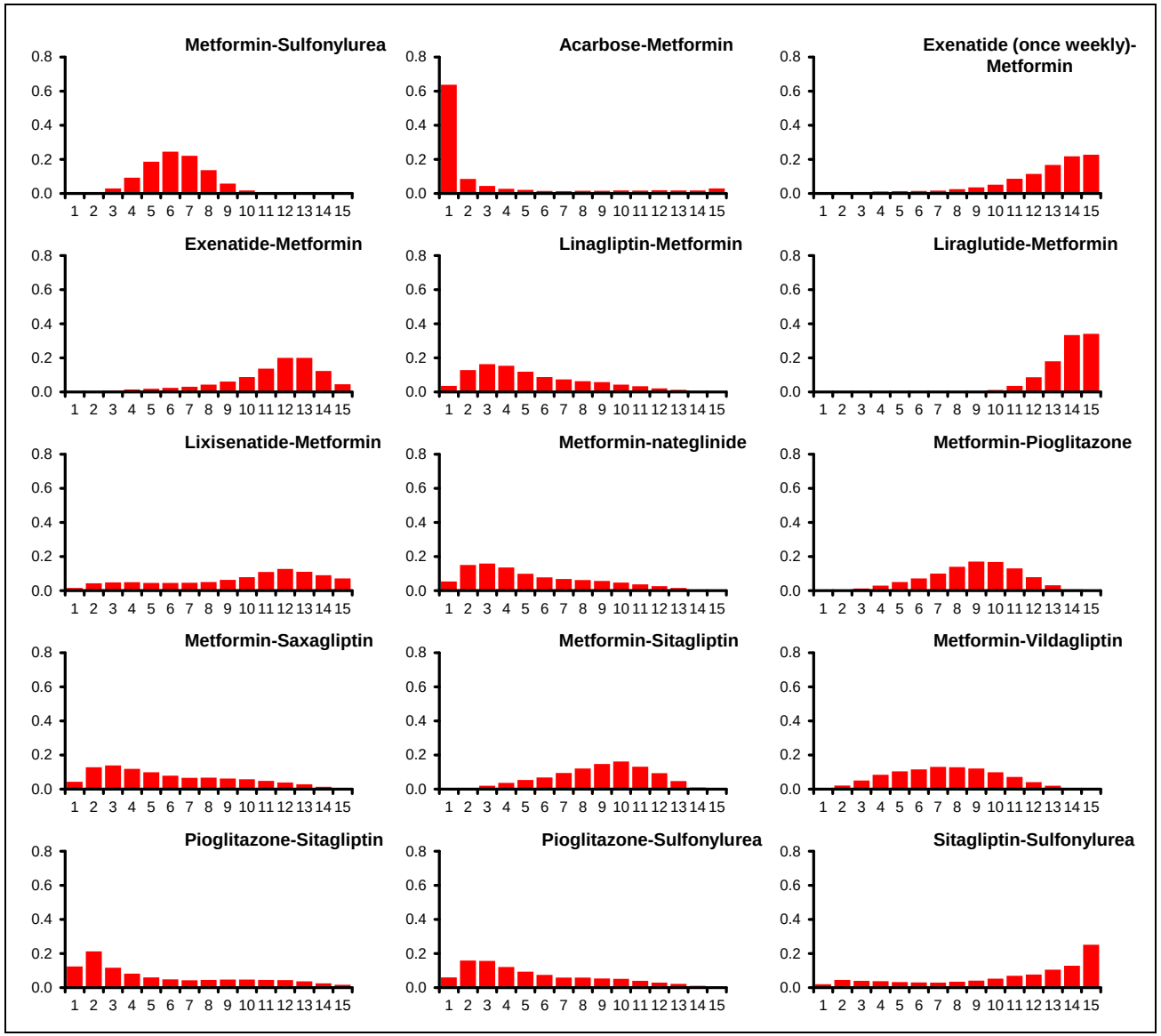



**Figure 48: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rank probability histograms**

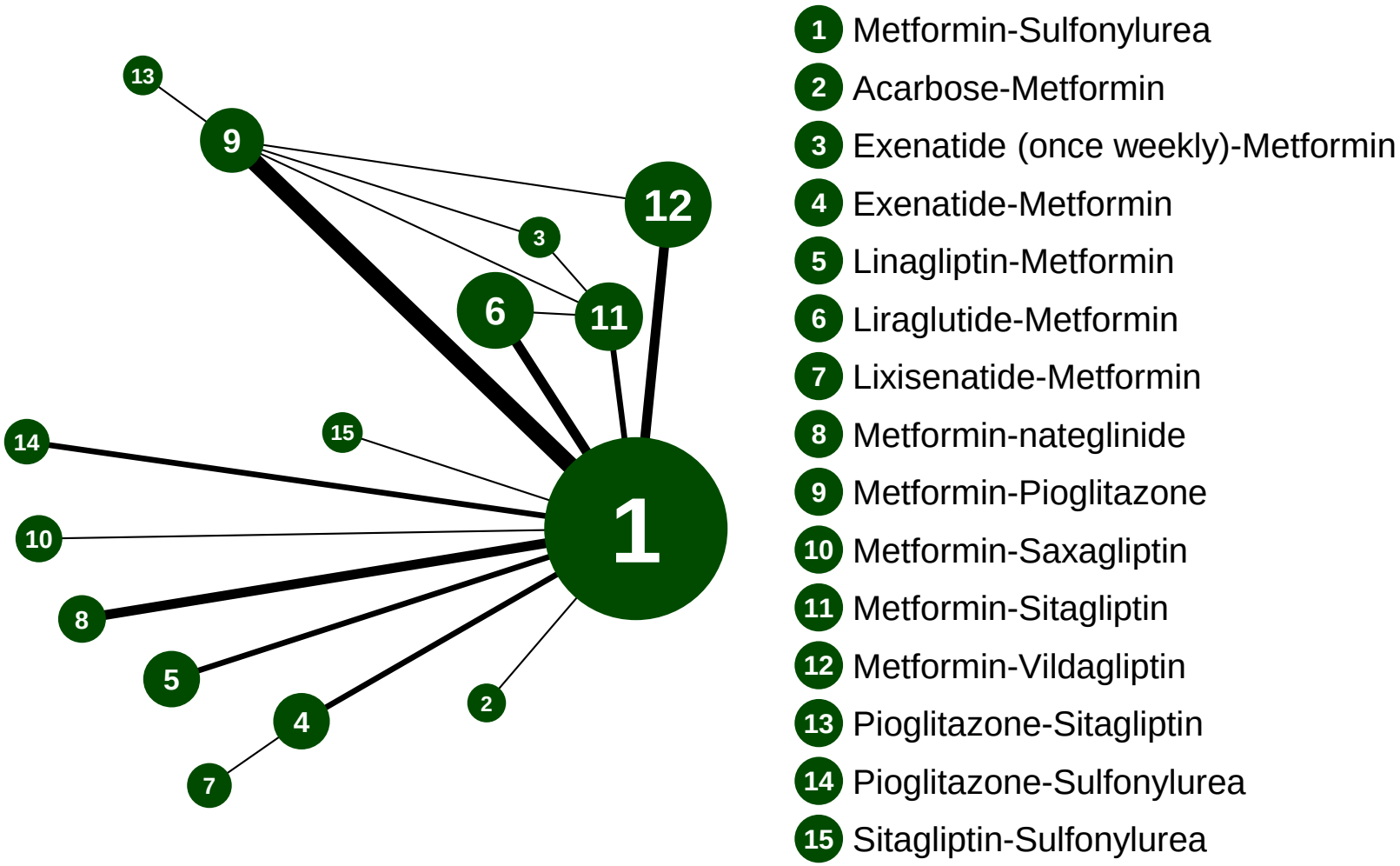
**Table 80: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 62.51<br>(compared to 63 datapoints) | 314.769 | 262.537 | 52.232 | 367.001 | 0.534 (95%CI: 0.283, 0.913) |

**Table 81: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.2.4 Total dropouts at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 49: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – evidence network**

**Table 82: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – input data**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea | Sitagliptin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gallwitz et al. (2012) - 2.99yr | 128/514 | | | 174/515 | | | | | | | | | | | |
| Wang et al. (2011) - 0.31yr | 3/26 | 1/29 | | | | | | | | | | | | | |
| Goke et al. (2010) - 1.99yr | 283/430 | | | | | | | | | 263/428 | | | | | |
| Derosa et al. (2011) - 1.00yr | 5/54 | | | 5/57 | | | | | | | | | | | |
| Derosa et al. (2011) - 1.00yr | 4/99 | | | | | | | | 3/102 | | | | | | |
| Pfutzner et al. (2011) - 0.46yr | 29/150 | | | | | | | | 32/155 | | | | | | |
| Yang et al. (2011) - 0.31yr | 16/231 | | | | | 133/698 | | | | | | | | | |
| Forst et al. (2010) - 0.23yr | 4/65 | | | | 23/131 | | | | | | | | | | |
| Bergenstal et al. (2010) - 0.50yr | | | 33/160 | | | | | | 34/165 | | 22/166 | | | | |
| Filozof & (2010) - 1.00yr | 82/494 | | | | | | | | | | | 106/513 | | | |
| Derosa et al. (2010) - 1.00yr | | | | | | | | | 8/76 | | | | 6/75 | | |
| Ferrannini et al. (2009) - 1.99yr | 604/1556 | | | | | | | | | | | 569/1562 | | | |
| Bolli et al. (2008) - 0.46yr | | | | | | | | | 37/281 | | | 33/295 | | | |
| Derosa et al. (2007) - 1.00yr | 10/124 | | | | | | | 5/124 | | | | | | | |
| Hermansen et al. (2007) - 0.46yr | 21/113 | | | | | | | | | | | | | | 23/106 |
| Nauck et al. (2007) - 1.99yr | 320/584 | | | | | | | | | | 333/588 | | | | |
| Ristic et al. (2006) - 1.00yr | 3/101 | | | | | | | 4/112 | | | | | | | |
| Jeon & (2011) - 0.61yr | 1/51 | | | | | | | | | | | 3/51 | | | |
| Arechavaleta et al. (2010) - 0.57yr | 51/519 | | | | | | | | | | 48/516 | | | | |
| Nauck et al. (2009) - 1.99yr | 131/244 | | | | | 339/725 | | | | | | | | | |
| Matthews et al. (2005) - 1.99yr | 75/313 | | | | | | | | 84/317 | | | | | | |
| Pratley et al. (2010) - 1.00yr | | | | | | 161/446 | | | | | 68/219 | | | | |
| Umpierrez et al. (2006) - 0.50yr | 13/101 | | | | | | | | 16/109 | | | | | | |

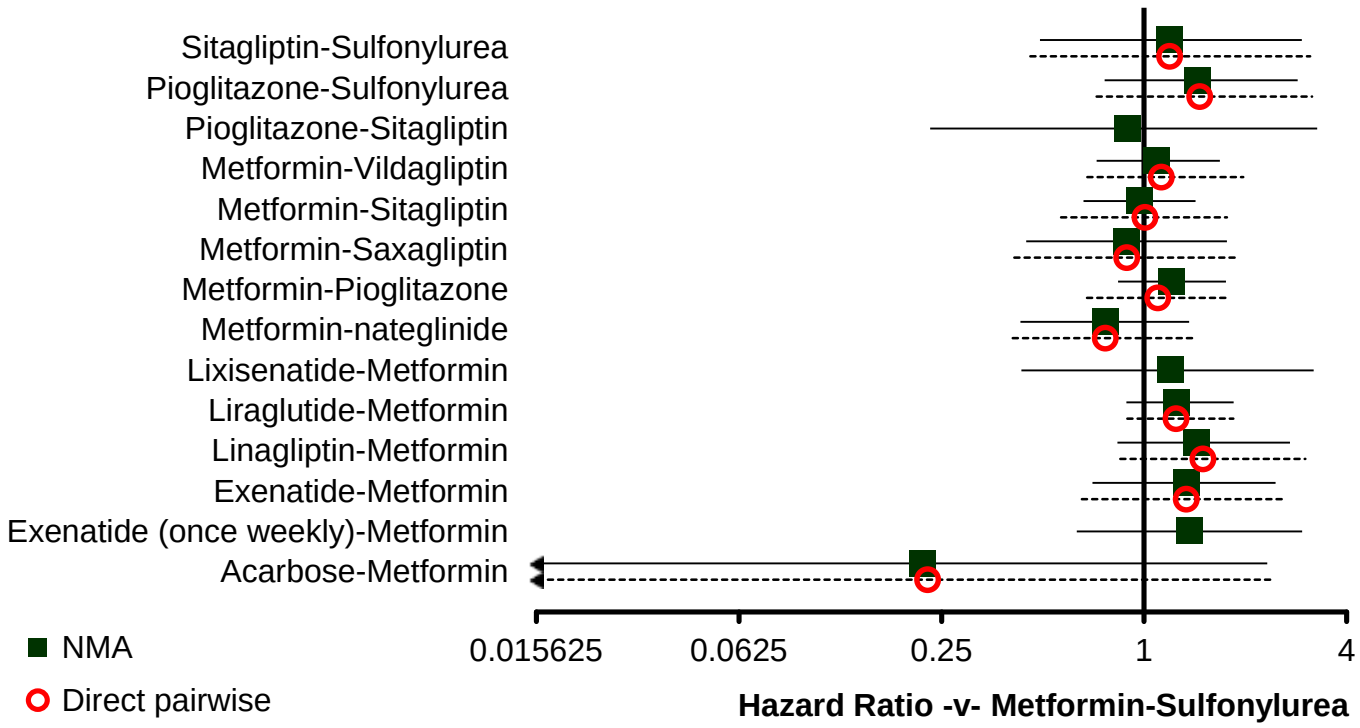
| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea | Sitagliptin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| van der et al. (2009) - 0.46yr | 2/39 | | | | | | | | | | | | | 5/39 | |
| Gerich et al. (2005) - 1.99yr | 87/209 | | | | | | | 78/219 | | | | | | | |
| Hanefeld et al. (2004) - 1.99yr | 70/320 | | | | | | | | | | | | | 88/319 | |
| Gallwitz et al. (2012) - 1.99yr | 171/775 | | | | 189/776 | | | | | | | | | | |
| Rosenstock et al. (2013) - 0.46yr | | | | 45/316 | | | 41/318 | | | | | | | | |
| Maffioli et al. (2013) - 0.50yr | 2/84 | | | | | | | | 3/86 | | | | | | |
| Brady et al. (2014) - 0.27yr | 14/52 | | | | | 15/47 | | | | | | | | | |

***Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.***

**Table 83: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acarbose-Metformin | 0.22 (0.01, 2.32) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide (once weekly)-Metformin | 1.37 (0.63, 2.95) | 6.23 (0.52, 197.60) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin | 1.34 (0.70, 2.46) | 6.08 (0.53, 194.50) | 0.98 (0.36, 2.60) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin-Metformin | 1.43 (0.83, 2.71) | 6.59 (0.59, 201.30) | 1.06 (0.42, 2.89) | 1.07 (0.48, 2.69) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin | 1.25 (0.88, 1.85) | 5.74 (0.53, 174.80) | 0.92 (0.41, 2.13) | 0.94 (0.47, 2.02) | 0.88 (0.43, 1.69) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Lixisenatide-Metformin | 1.20 (0.43, 3.19) | 5.48 (0.42, 184.60) | 0.88 (0.24, 3.09) | 0.90 (0.41, 1.92) | 0.84 (0.25, 2.50) | 0.96 (0.32, 2.64) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-nateglinide | 0.77 (0.43, 1.36) | 3.49 (0.31, 106.20) | 0.56 (0.22, 1.46) | 0.57 (0.25, 1.37) | 0.54 (0.23, 1.16) | 0.61 (0.30, 1.19) | 0.64 (0.21, 2.06) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone | 1.20 (0.84, 1.75) | 5.47 (0.50, 167.00) | 0.88 (0.42, 1.87) | 0.90 (0.44, 1.88) | 0.84 (0.40, 1.63) | 0.96 (0.57, 1.57) | 1.00 (0.36, 2.99) | 1.57 (0.80, 3.13) | | N/A | N/A | N/A | N/A | N/A |
| Metformin-Saxagliptin | 0.89 (0.45, 1.76) | 4.07 (0.35, 128.70) | 0.65 (0.23, 1.82) | 0.66 (0.27, 1.72) | 0.62 (0.24, 1.45) | 0.71 (0.32, 1.52) | 0.74 (0.23, 2.53) | 1.16 (0.47, 2.87) | 0.74 (0.34, 1.60) | | N/A | N/A | N/A | N/A |
| Metformin-Sitagliptin | 0.97 (0.66, 1.42) | 4.41 (0.40, 132.50) | 0.71 (0.33, 1.51) | 0.72 (0.35, 1.54) | 0.68 (0.32, 1.31) | 0.77 (0.49, 1.18) | 0.80 (0.29, 2.42) | 1.26 (0.63, 2.52) | 0.80 (0.50, 1.30) | 1.09 (0.50, 2.39) | | N/A | N/A | N/A |
| Metformin-Vildagliptin | 1.09 (0.72, 1.68) | 5.01 (0.46, 150.60) | 0.80 (0.35, 1.90) | 0.81 (0.39, 1.77) | 0.76 (0.36, 1.51) | 0.87 (0.50, 1.49) | 0.90 (0.32, 2.81) | 1.42 (0.71, 2.95) | 0.90 (0.56, 1.51) | 1.22 (0.56, 2.79) | 1.13 (0.65, 2.00) | | N/A | N/A |
| Pioglitazone-Sitagliptin | 0.90 (0.23, 3.27) | 4.12 (0.27, 149.10) | 0.65 (0.14, 2.76) | 0.67 (0.15, 2.85) | 0.62 (0.14, 2.54) | 0.71 (0.17, 2.70) | 0.75 (0.14, 3.87) | 1.16 (0.26, 4.86) | 0.74 (0.20, 2.58) | 1.01 (0.22, 4.35) | 0.92 (0.23, 3.49) | 0.82 (0.20, 3.11) | | N/A |
| Pioglitazone-Sulfonylurea | 1.44 (0.76, 2.86) | 6.64 (0.56, 208.90) | 1.06 (0.39, 2.96) | 1.08 (0.45, 2.78) | 1.01 (0.41, 2.38) | 1.15 (0.54, 2.46) | 1.21 (0.38, 4.16) | 1.88 (0.79, 4.64) | 1.20 (0.56, 2.59) | 1.62 (0.65, 4.29) | 1.49 (0.71, 3.25) | 1.33 (0.61, 2.91) | 1.62 (0.38, 7.53) | |
| Sitagliptin-Sulfonylurea | 1.19 (0.49, 2.94) | 5.49 (0.42, 180.60) | 0.87 (0.27, 2.87) | 0.89 (0.31, 2.69) | 0.83 (0.27, 2.35) | 0.95 (0.36, 2.47) | 1.00 (0.26, 3.89) | 1.55 (0.53, 4.51) | 0.99 (0.38, 2.63) | 1.34 (0.45, 4.15) | 1.23 (0.47, 3.29) | 1.10 (0.41, 2.88) | 1.34 (0.28, 6.89) | 0.83 (0.27, 2.46) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 50: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 84: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 6 (3, 10) |
| Acarbose-Metformin | 0.754 | 1 (1, 15) |
| Exenatide (once weekly)-Metformin | 0.006 | 11 (2, 15) |
| Exenatide-Metformin | 0.001 | 11 (3, 15) |
| Linagliptin-Metformin | 0.001 | 12 (4, 15) |
| Liraglutide-Metformin | 0.000 | 10 (5, 14) |
| Lixisenatide-Metformin | 0.022 | 10 (2, 15) |
| Metformin-nateglinide | 0.059 | 3 (1, 12) |
| Metformin-Pioglitazone | 0.000 | 10 (4, 14) |
| Metformin-Saxagliptin | 0.034 | 5 (1, 14) |
| Metformin-Sitagliptin | 0.006 | 6 (2, 12) |
| Metformin-Vildagliptin | 0.002 | 8 (3, 14) |
| Pioglitazone-Sitagliptin | 0.096 | 5 (1, 15) |
| Pioglitazone-Sulfonylurea | 0.001 | 12 (3, 15) |
| Sitagliptin-Sulfonylurea | 0.018 | 9 (2, 15) |

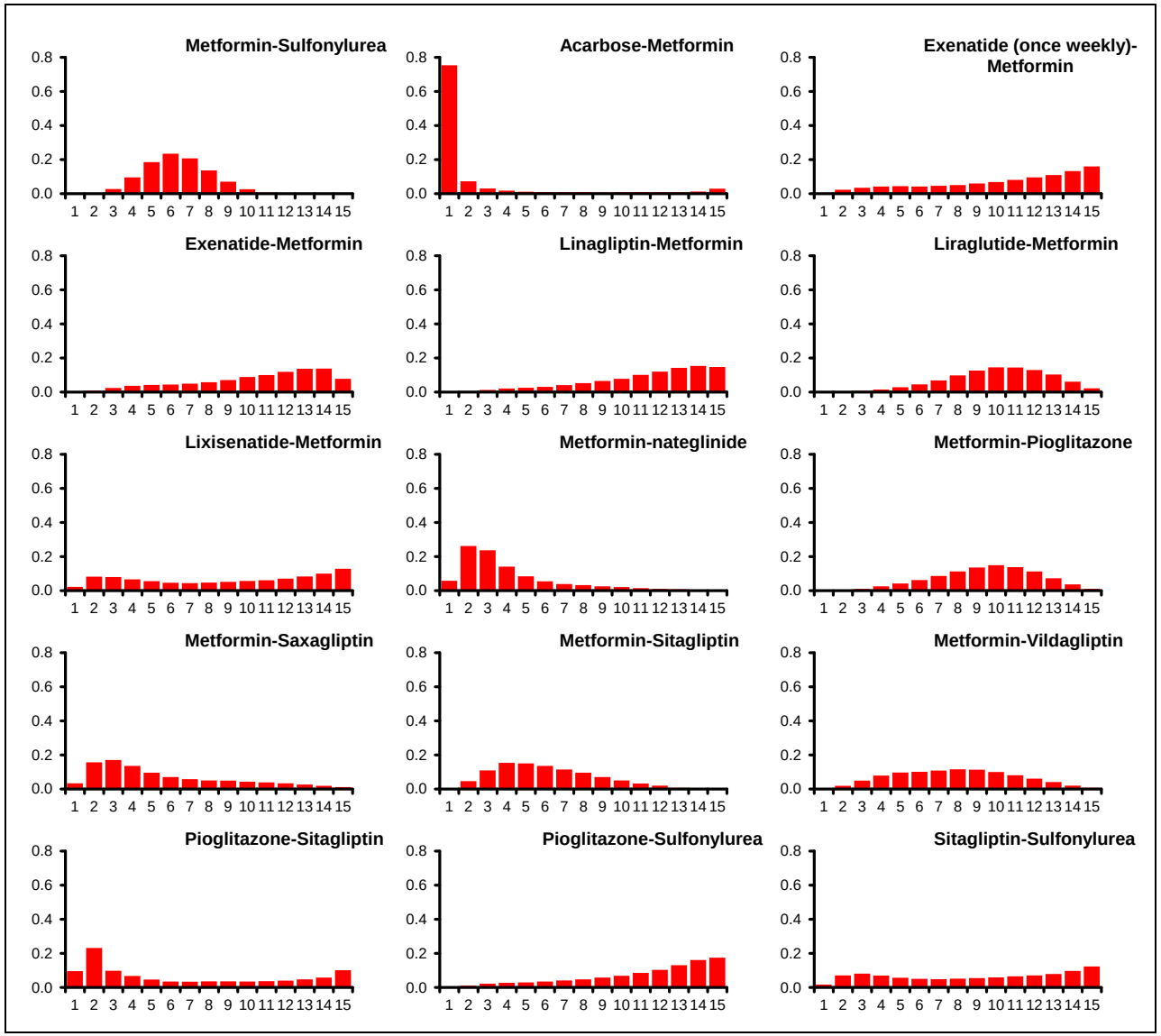



**Figure 51: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rank probability histograms**

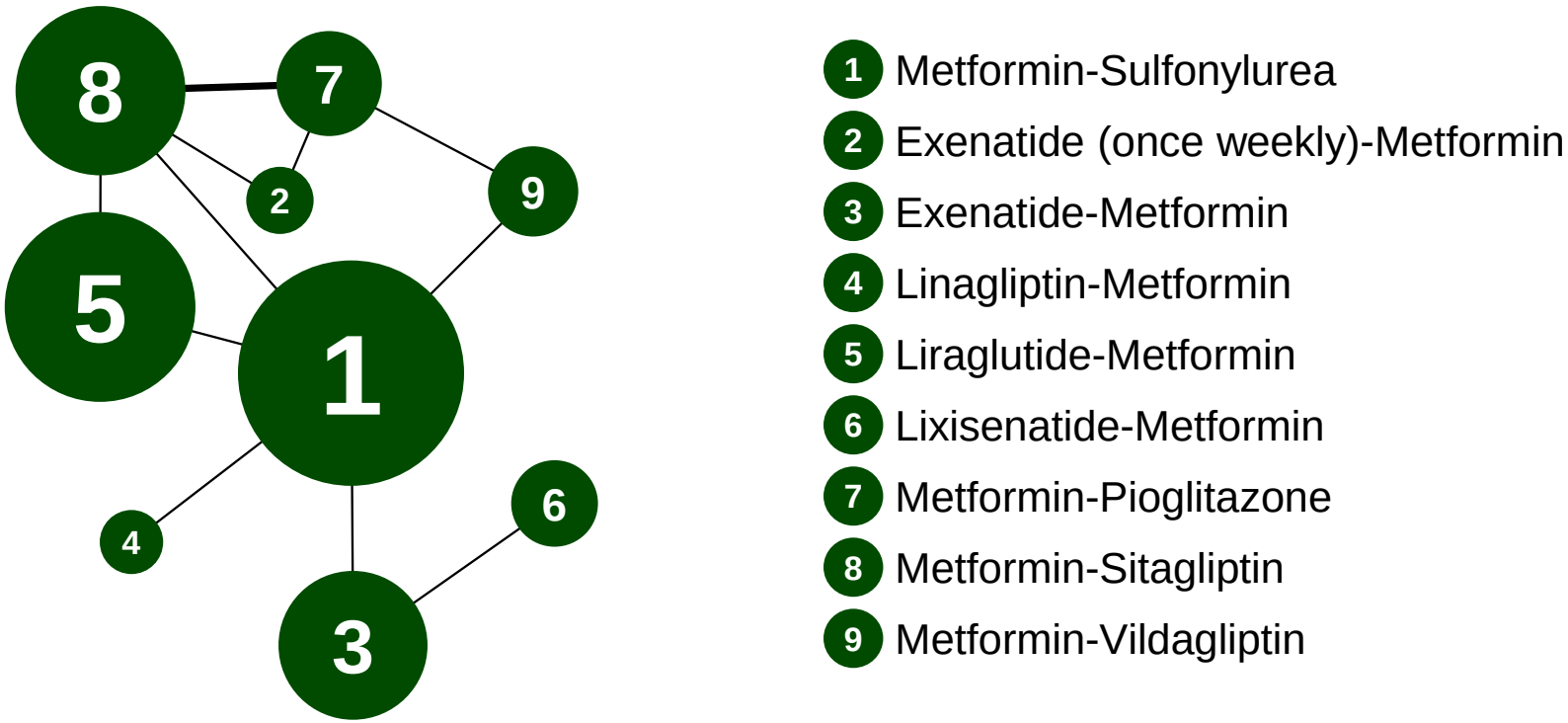
**Table 85: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 66.1<br>(compared to 67 datapoints) | 394.825 | 338.662 | 56.163 | 450.988 | 0.309 (95%CI: 0.170, 0.514) |

**Table 86: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 100000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.2.5 Nausea at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 52: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – evidence network**

**Table 87: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – input data**

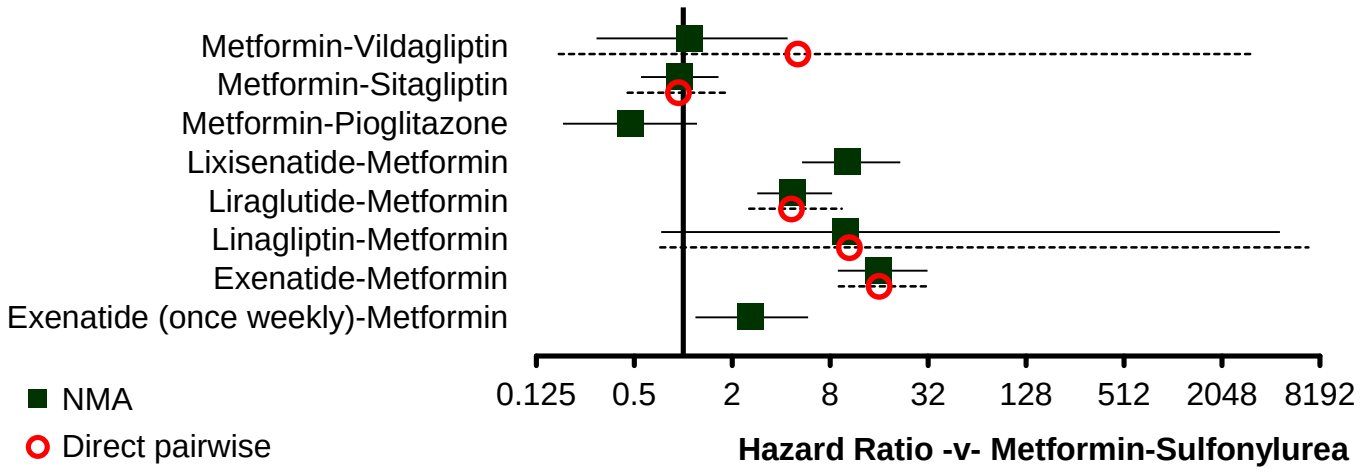
| | Metformin-Sulfonylurea | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Gallwitz et al. (2012) - 2.99yr | 11/508 | | 147/511 | | | | | | |
| Forst et al. (2010) - 0.23yr | 0/65 | | | 4/131 | | | | | |
| Bergenstal et al. (2010) - 0.50yr | | 38/160 | | | | | 8/165 | 16/166 | |
| Bolli et al. (2008) - 1.00yr | | | | | | | 5/280 | | 10/295 |
| Nauck et al. (2007) - 1.00yr | 16/584 | | | | | | | 15/588 | |
| Jeon & (2011) - 0.61yr | 0/51 | | | | | | | | 1/51 |
| Nauck et al. (2009) - 1.99yr | 10/244 | | | | 124/725 | | | | |
| Pratley et al. (2010) - 1.00yr | | | | | 108/439 | | | 12/219 | |
| Chawla et al. (2013) - 0.31yr | | | | | | | 0/25 | 1/25 | |
| Rosenstock et al. (2013) - 0.46yr | | | 111/316 | | | 78/318 | | | |

*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 88: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Exenatide (once weekly)-Metformin | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide (once weekly)-Metformin | 2.62 (1.19, 5.85) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin | 15.89 (8.94, 31.69) | 6.12 (2.24, 17.41) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Linagliptin-Metformin | 9.91 (0.73, 4659.00) | 3.84 (0.24, 1885.00) | 0.62 (0.04, 308.60) | | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin | 4.73 (2.85, 8.21) | 1.81 (0.84, 3.92) | 0.30 (0.13, 0.66) | 0.47 (0.00, 6.95) | | N/A | N/A | N/A | N/A |
| Lixisenatide-Metformin | 10.34 (5.37, 21.63) | 3.98 (1.38, 11.62) | 0.65 (0.49, 0.87) | 1.05 (0.00, 16.01) | 2.19 (0.93, 5.42) | | N/A | N/A | N/A |
| Metformin-Pioglitazone | 0.48 (0.18, 1.22) | 0.18 (0.08, 0.37) | 0.03 (0.01, 0.09) | 0.05 (0.00, 0.81) | 0.10 (0.04, 0.25) | 0.05 (0.01, 0.14) | | N/A | N/A |
| Metformin-Sitagliptin | 0.95 (0.55, 1.65) | 0.36 (0.20, 0.64) | 0.06 (0.03, 0.13) | 0.10 (0.00, 1.41) | 0.20 (0.12, 0.32) | 0.09 (0.04, 0.22) | 1.97 (0.92, 4.54) | | N/A |
| Metformin-Vildagliptin | 1.10 (0.29, 4.39) | 0.42 (0.12, 1.55) | 0.07 (0.02, 0.30) | 0.11 (0.00, 2.28) | 0.23 (0.06, 0.93) | 0.11 (0.02, 0.48) | 2.30 (0.84, 7.21) | 1.16 (0.33, 4.32) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 53: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 89: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.048 | 3 (1, 4) |
| Exenatide (once weekly)-Metformin | 0.000 | 5 (4, 6) |
| Exenatide-Metformin | 0.000 | 9 (8, 9) |
| Linagliptin-Metformin | 0.014 | 7 (2, 9) |
| Liraglutide-Metformin | 0.000 | 6 (5, 7) |
| Lixisenatide-Metformin | 0.000 | 7 (6, 8) |
| Metformin-Pioglitazone | 0.863 | 1 (1, 3) |
| Metformin-Sitagliptin | 0.023 | 3 (2, 4) |
| Metformin-Vildagliptin | 0.053 | 4 (1, 6) |

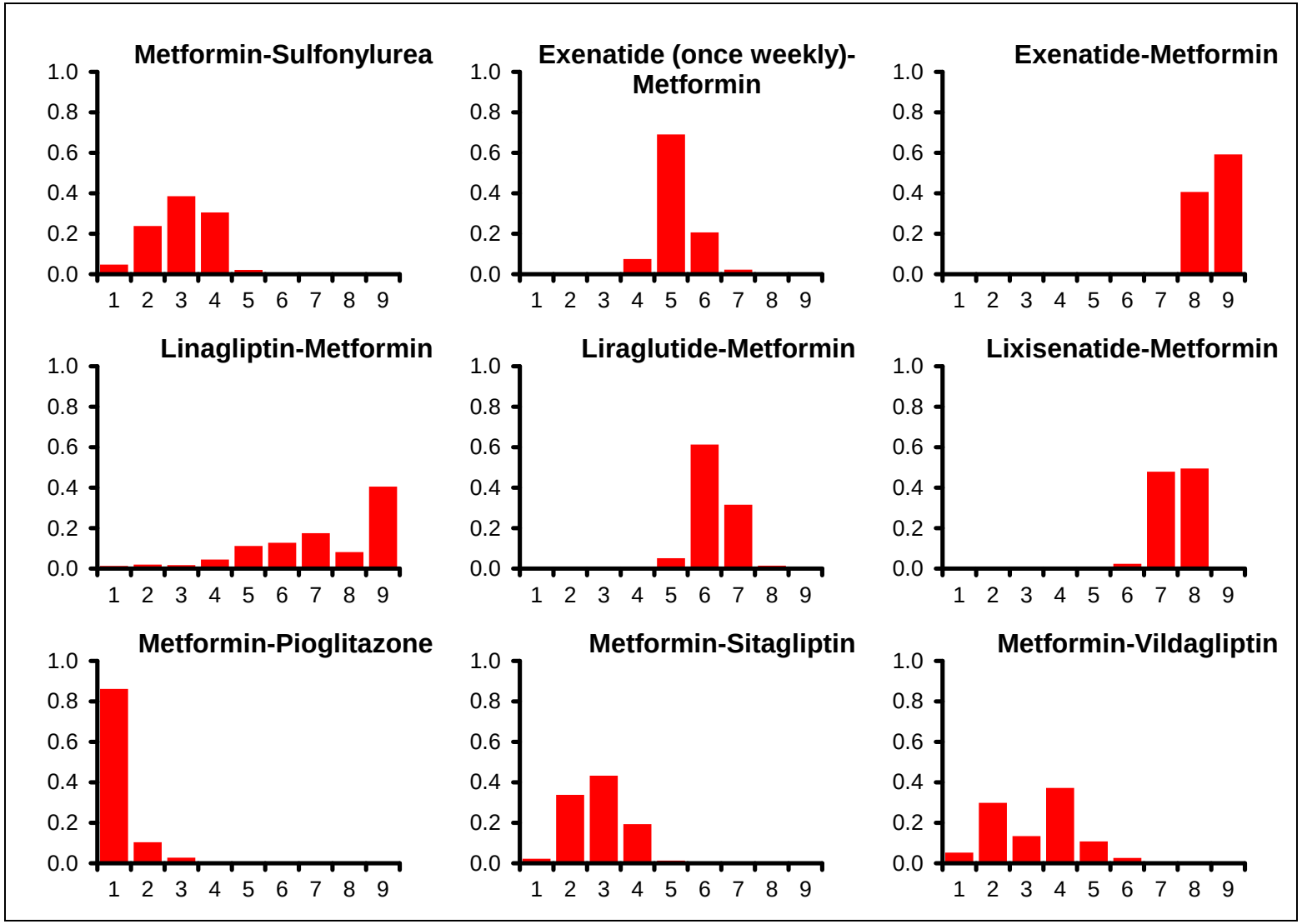



**Figure 54: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rank probability histograms**

**Table 90: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – model fit statistics**

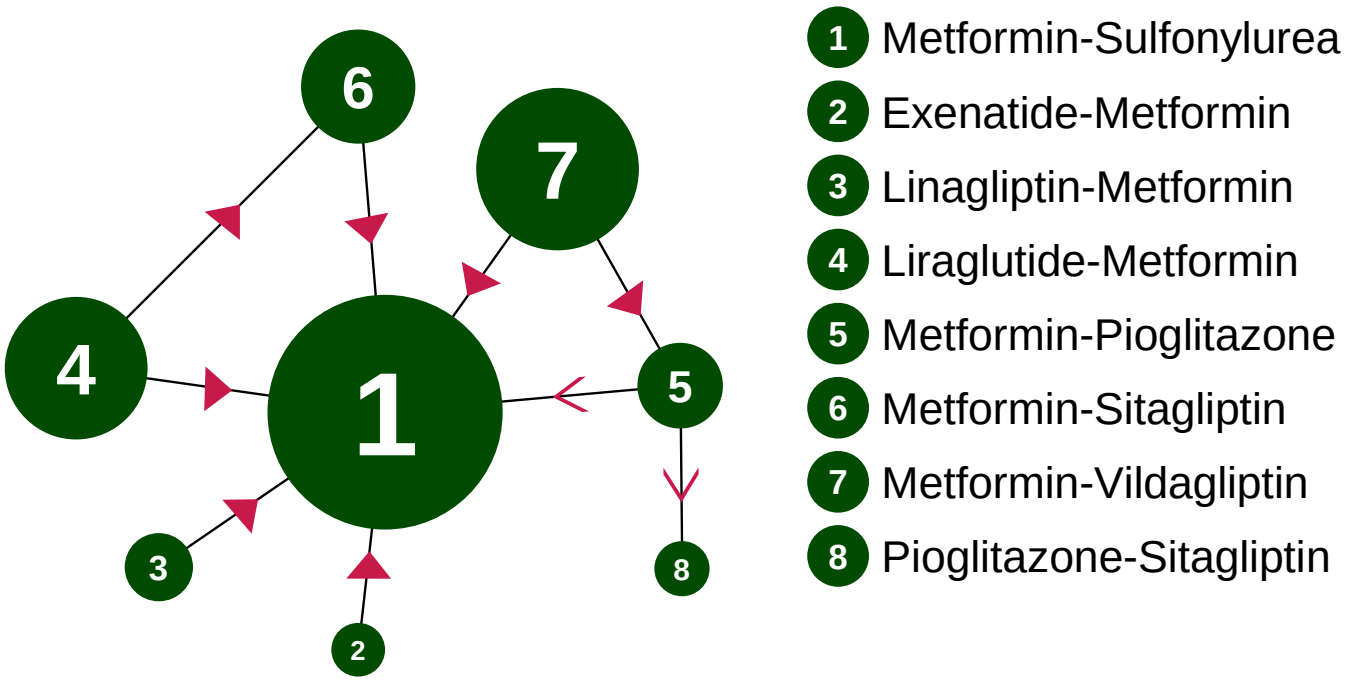
| Residual deviance | Dbar | Dhat | pD | DIC |
|---|---|---|---|---|
| 32.22<br>(compared to 25 datapoints) | 134.512 | 116.986 | 17.526 | 152.038 |

**Table 91: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.2.6 Change in body weight at 12 and 24 months

**Change in body weight at 12 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 55: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – evidence network**

**Table 92: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – input data**

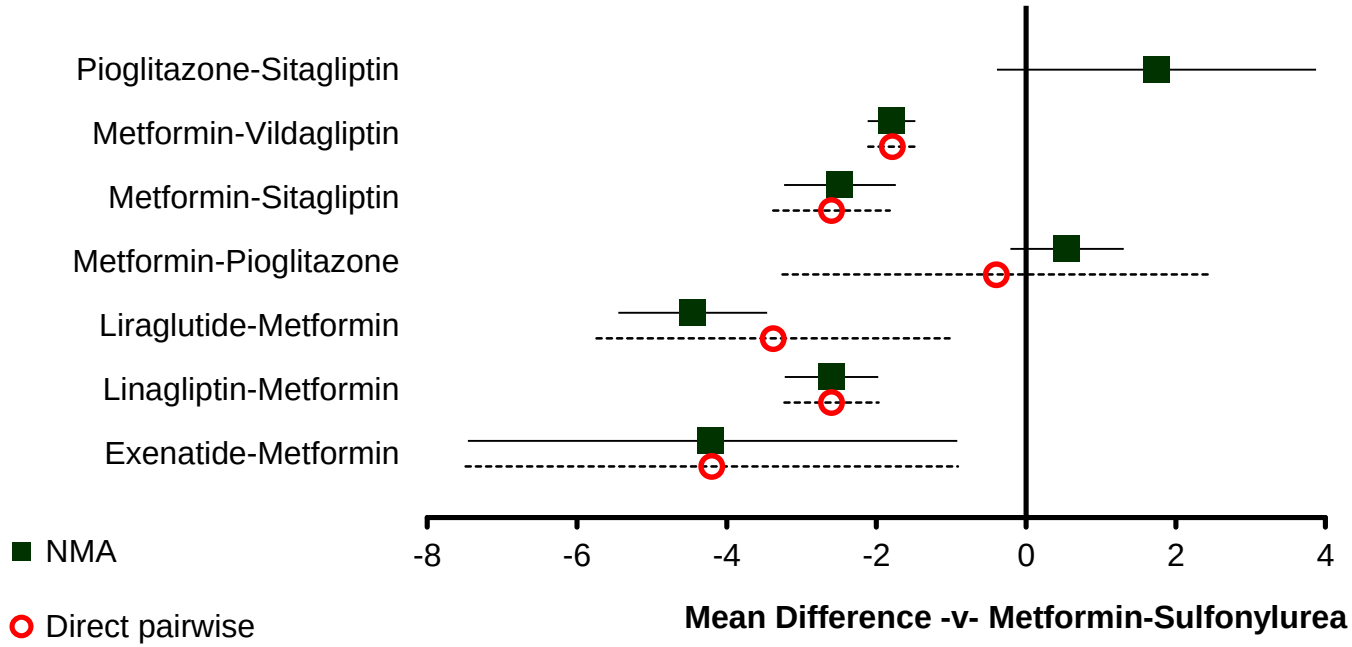
| | Metformin-Sulfonylurea | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin |
|---|---|---|---|---|---|---|---|---|
| Derosa et al. (2011) | -0.90 (8.89) | -5.10 (7.91) | | | | | | |
| Derosa et al. (2011) | 1.20 (9.93) | | | | 0.80 (10.36) | | | |
| Derosa et al. (2010) | | | | | -2.80 (5.45) | | | -1.60 (6.46) |
| Ferrannini et al. (2009) | 1.56 (3.93) | | | | | | -0.23 (3.68) | |
| Bolli et al. (2008) | | | | | 2.60 (5.02) | | 0.20 (3.44) | |
| Nauck et al. (2007) | 1.10 (6.78) | | | | | -1.50 (6.80) | | |
| Nauck et al. (2009) | 1.94 (16.23) | | | -1.44 (16.35) | | | | |
| Pratley et al. (2010) | | | | -3.23 (4.61) | | -1.16 (4.61) | | |
| Gallwitz et al. (2012) | 0.95 (3.29) | | -1.65 (3.82) | | | | | |

*Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 93: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Exenatide-Metformin | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-Pioglitazone | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin |
|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | -4.20 (-7.49, -0.91) | -2.60 (-3.23, -1.97) | -3.38 (-5.74, -1.02) | -0.40 (-3.25, 2.45) | -2.60 (-3.38, -1.82) | -1.79 (-2.11, -1.47) | - |
| Exenatide-Metformin | -4.22 (-7.46, -0.92) | | - | - | - | - | - | - |
| Linagliptin-Metformin | -2.60 (-3.22, -1.98) | 1.61 (-1.74, 4.90) | | - | - | - | - | - |
| Liraglutide-Metformin | -4.45 (-5.45, -3.46) | -0.24 (-3.69, 3.18) | -1.85 (-3.02, -0.68) | | - | 2.07 (1.32, 2.81) | - | - |
| Metformin-Pioglitazone | 0.55 (-0.21, 1.31) | 4.77 (1.39, 8.10) | 3.15 (2.18, 4.14) | 5.00 (3.76, 6.25) | | - | -2.40 (-3.11, -1.69) | 1.20 (-0.80, 3.20) |
| Metformin-Sitagliptin | -2.49 (-3.24, -1.74) | 1.73 (-1.66, 5.08) | 0.11 (-0.87, 1.09) | 1.97 (1.25, 2.68) | -3.04 (-4.11, -1.96) | | - | - |
| Metformin-Vildagliptin | -1.80 (-2.12, -1.48) | 2.42 (-0.88, 5.67) | 0.80 (0.11, 1.51) | 2.65 (1.61, 3.70) | -2.35 (-3.04, -1.65) | 0.69 (-0.13, 1.51) | | - |
| Pioglitazone-Sitagliptin | 1.75 (-0.39, 3.87) | 5.98 (2.07, 9.85) | 4.36 (2.13, 6.55) | 6.21 (3.85, 8.56) | 1.20 (-0.77, 3.18) | 4.25 (1.98, 6.48) | 3.55 (1.44, 5.65) | |

*Values given are mean differences in body-weight in kilograms.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 56: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – relative effect of all options versus reference treatment**

**Table 94: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 6 (6, 7) |
| Exenatide-Metformin | 0.445 | 2 (1, 5) |
| Linagliptin-Metformin | 0.000 | 3 (2, 4) |
| Liraglutide-Metformin | 0.555 | 1 (1, 2) |
| Metformin-Pioglitazone | 0.000 | 7 (6, 8) |
| Metformin-Sitagliptin | 0.000 | 4 (2, 5) |
| Metformin-Vildagliptin | 0.000 | 5 (4, 5) |
| Pioglitazone-Sitagliptin | 0.000 | 8 (6, 8) |

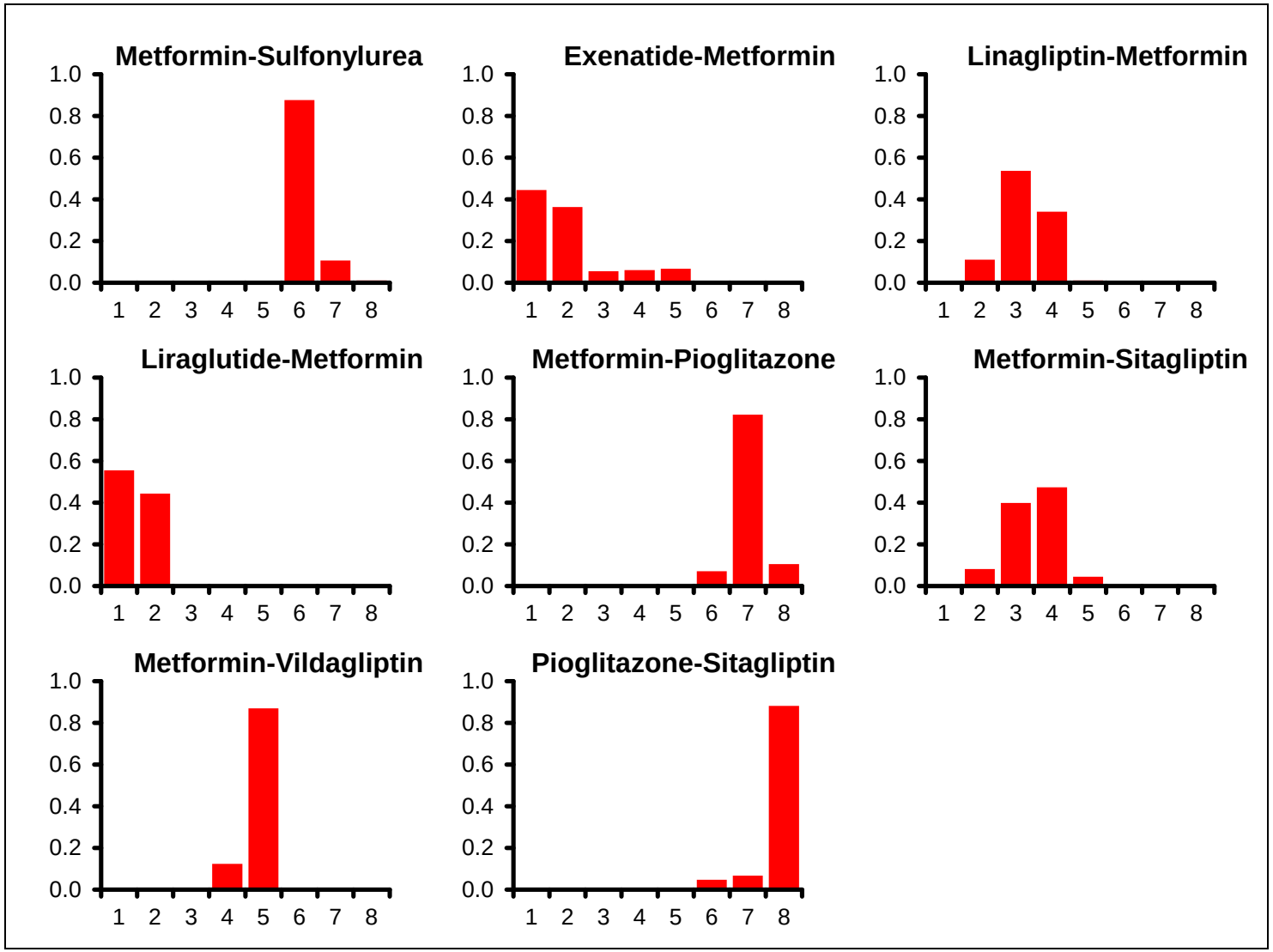



**Figure 57: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – rank probability histograms**

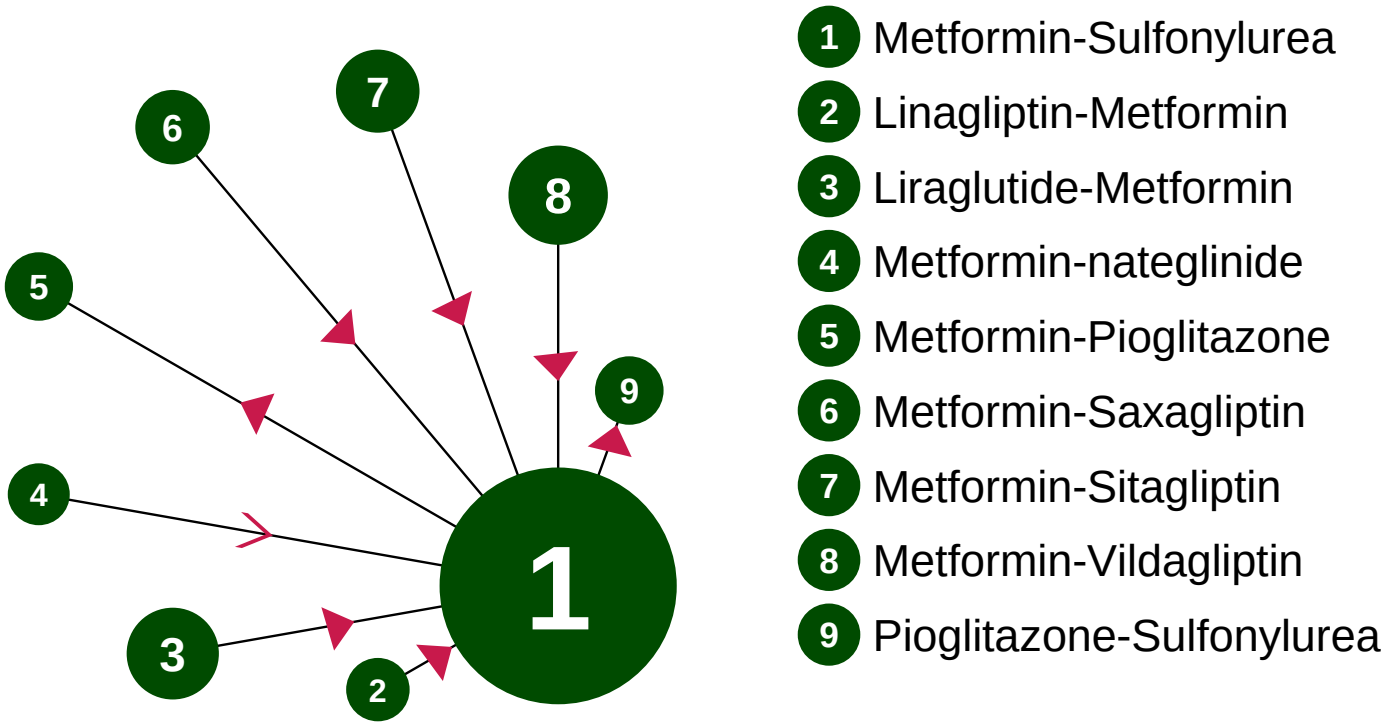
**Table 95: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 23.36<br>(compared to 21 datapoints) | 29.421 | 13.38 | 16.041 | 45.463 | |

**Table 96: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

**Change in body weight at 24 months**




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 58: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – evidence network**

**Table 97: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – input data**

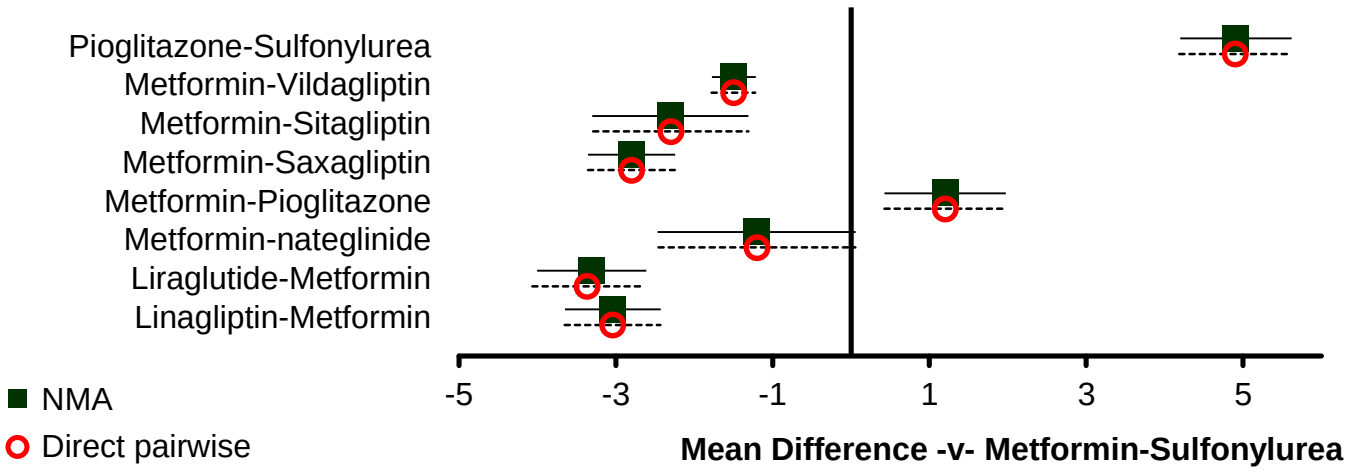
| | Metformin-Sulfonylurea | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|
| Goke et al. (2010) | 1.30 (4.13) | | | | | -1.50 (4.12) | | | |
| Ferrannini et al. (2009) | 1.20 (2.97) | | | | | | | -0.30 (2.92) | |
| Nauck et al. (2007) | 0.70 (8.44) | | | | | | -1.60 (8.57) | | |
| Nauck et al. (2009) | 0.70 (4.68) | | -2.67 (5.19) | | | | | | |
| Matthews et al. (2005) | 1.10 (4.60) | | | | 2.30 (5.30) | | | | |
| Gerich et al. (2005) | 0.80 (7.04) | | | -0.40 (5.77) | | | | | |
| Hanefeld et al. (2004) | -1.70 (4.50) | | | | | | | | 3.20 (4.70) |
| Gallwitz et al. (2012) | 0.98 (3.79) | -2.06 (3.21) | | | | | | | |

*Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 98: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Linagliptin-Metformin | Liraglutide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | -3.04 (-3.65, -2.43) | -3.37 (-4.06, -2.67) | -1.20 (-2.45, 0.05) | 1.20 (0.43, 1.97) | -2.80 (-3.35, -2.25) | -2.30 (-3.29, -1.31) | -1.50 (-1.78, -1.22) | 4.90 (4.19, 5.61) |
| Linagliptin-Metformin | -3.04 (-3.65, -2.43) | | - | - | - | - | - | - | - |
| Liraglutide-Metformin | -3.31 (-4.00, -2.61) | -0.26 (-1.18, 0.66) | | - | - | - | - | - | - |
| Metformin-nateglinide | -1.20 (-2.47, 0.06) | 1.84 (0.42, 3.25) | 2.11 (0.66, 3.56) | | - | - | - | - | - |
| Metformin-Pioglitazone | 1.20 (0.43, 1.98) | 4.24 (3.26, 5.23) | 4.51 (3.48, 5.55) | 2.41 (0.93, 3.89) | | - | - | - | - |
| Metformin-Saxagliptin | -2.80 (-3.35, -2.25) | 0.24 (-0.59, 1.07) | 0.51 (-0.38, 1.40) | -1.60 (-2.98, -0.22) | -4.00 (-4.96, -3.05) | | - | - | - |
| Metformin-Sitagliptin | -2.30 (-3.30, -1.31) | 0.74 (-0.44, 1.89) | 1.00 (-0.22, 2.22) | -1.10 (-2.71, 0.50) | -3.51 (-4.77, -2.24) | 0.50 (-0.66, 1.63) | | - | - |
| Metformin-Vildagliptin | -1.50 (-1.77, -1.22) | 1.55 (0.87, 2.21) | 1.81 (1.06, 2.57) | -0.30 (-1.58, 1.01) | -2.70 (-3.52, -1.87) | 1.30 (0.68, 1.92) | 0.81 (-0.23, 1.85) | | - |
| Pioglitazone-Sulfonylurea | 4.91 (4.20, 5.62) | 7.95 (7.02, 8.88) | 8.21 (7.23, 9.20) | 6.11 (4.64, 7.57) | 3.70 (2.66, 4.75) | 7.70 (6.82, 8.60) | 7.21 (5.98, 8.44) | 6.40 (5.65, 7.16) | |

*Values given are mean differences in body-weight in kilograms.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 59: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – relative effect of all options versus reference treatment**

**Table 99: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 7 (6, 7) |
| Linagliptin-Metformin | 0.249 | 2 (1, 4) |
| Liraglutide-Metformin | 0.652 | 1 (1, 3) |
| Metformin-nateglinide | 0.001 | 6 (4, 7) |
| Metformin-Pioglitazone | 0.000 | 8 (8, 8) |
| Metformin-Saxagliptin | 0.068 | 3 (1, 4) |
| Metformin-Sitagliptin | 0.030 | 4 (1, 5) |
| Metformin-Vildagliptin | 0.000 | 5 (4, 6) |
| Pioglitazone-Sulfonylurea | 0.000 | 9 (9, 9) |

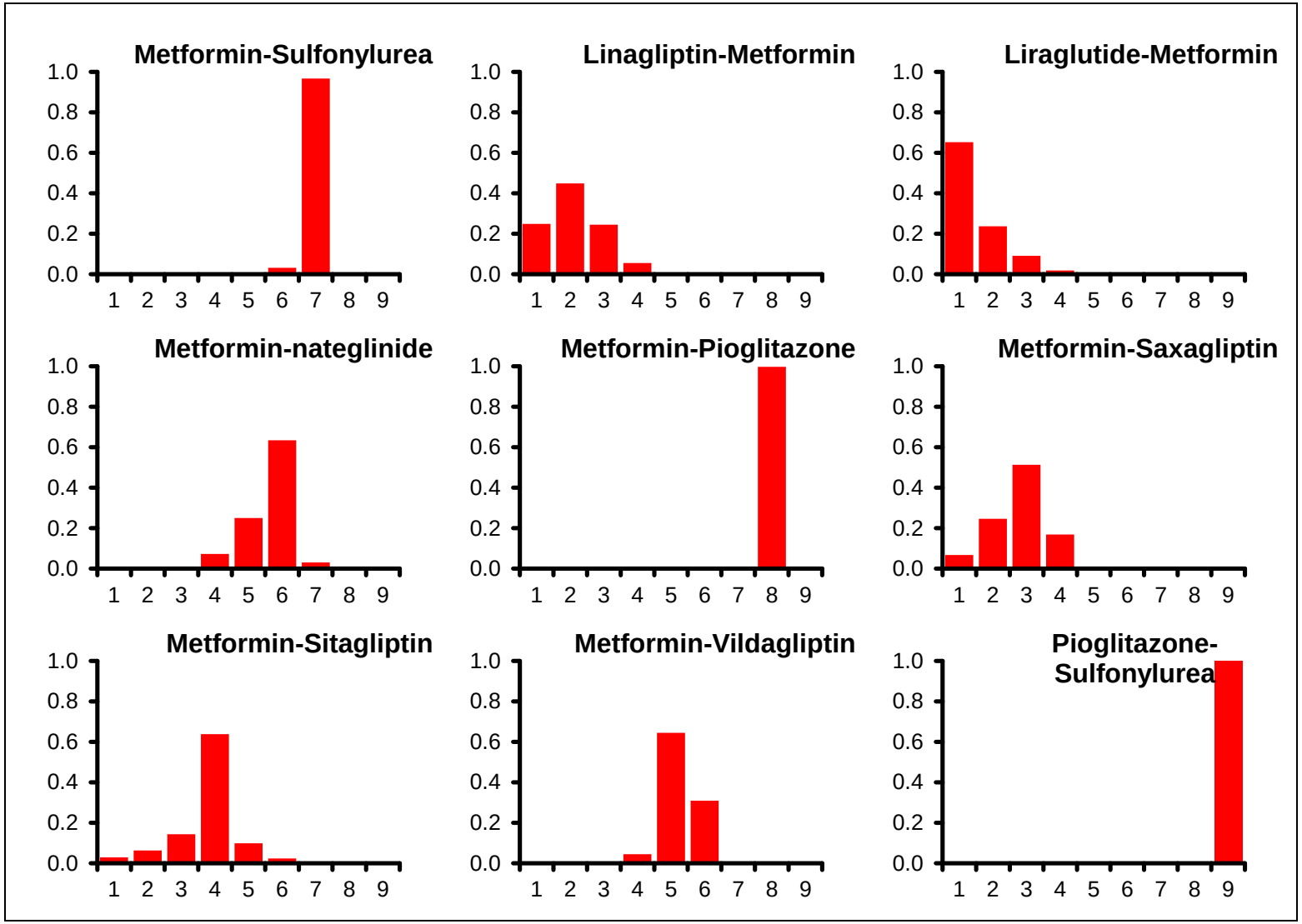



**Figure 60: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – rank probability histograms**

**Table 100: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – model fit statistics**

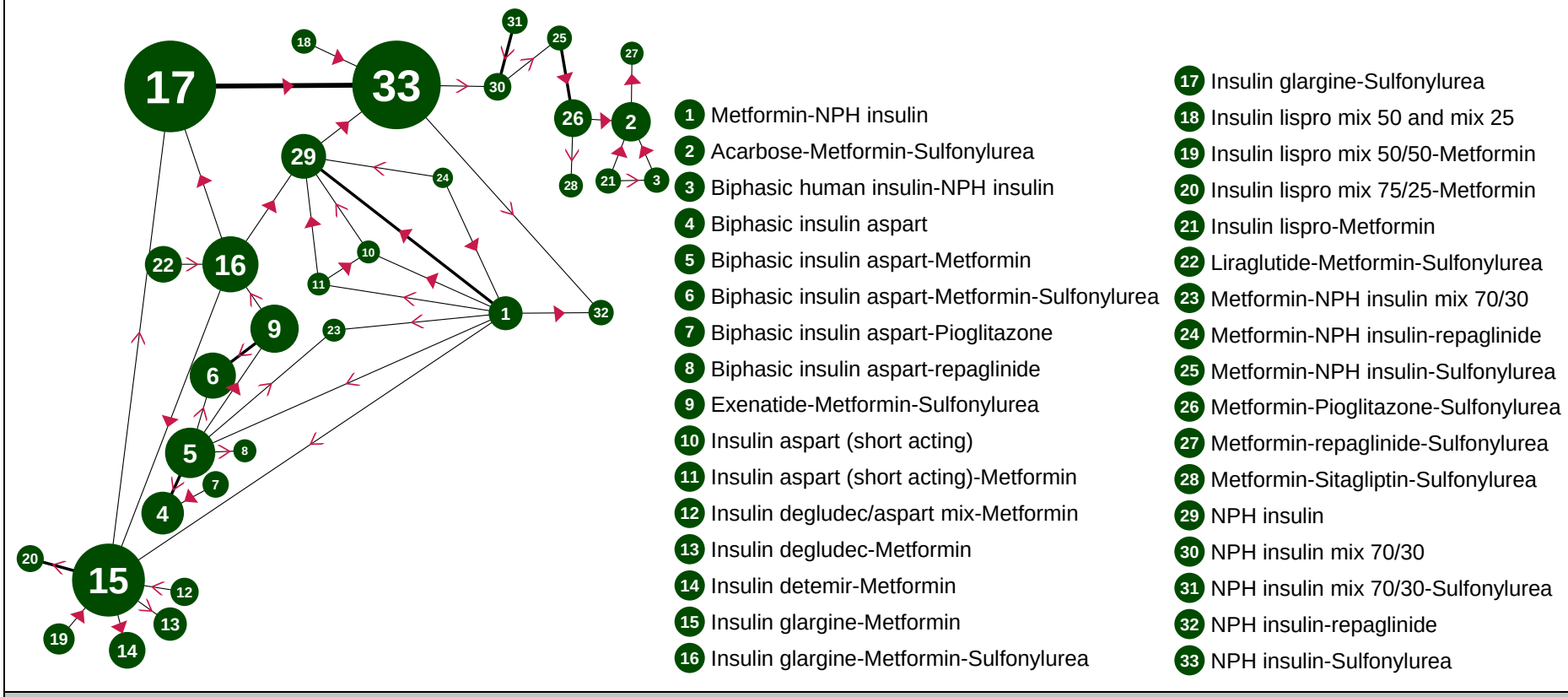
| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 20.88<br>(compared to 18 datapoints) | 5.351 | -10.713 | 16.064 | 21.415 | |

**Table 101: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

## J.2.3 RESULTS FOR SECOND INTENSIFICATION OF TREATMENT

### J.2.3.1 Change in HbA1c up to 12 months




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 61: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – evidence network**

**Table 102: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – input data**

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic human insulin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Insulin lispro mix 75/25-Metformin | Insulin lispro-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zinman et al. (2011) | | | | | | | | | | | | | -1.37 (1.10) | | -1.50 (1.10) | | | | | | | | | | | | | | | | | | |
| Heise et al. (2011) | | | | | | | | | | | | -1.40 (1.22) | | | -1.30 (1.10) | | | | | | | | | | | | | | | | | | |
| Gram et al. (2011) | -1.40 (1.04) | | | | | | | | | -0.70 (1.04) | -1.30 (1.04) | | | | | | | | | | | | | | | | | | -0.50 (1.29) | | | | |
| Derosa et al. (2010) | | -0.90 (0.52) | | | | | | | | | | | | | | | | | | | | | | | | -1.40 (0.43) | | | | | | | |
| Lund et al. (2009) | | | | | -1.42 (0.65) | | | -1.23 (0.70) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hartemann-Heurtier et al. (2009) | | | | | | | | | | | | | | | | | | | | | | | | | -1.60 (0.50) | -1.20 (0.70) | | | | | | | |
| Russell-Jones et al. (2009) | | | | | | | | | | | | | | | | -1.09 (1.37) | | | | | | -1.33 (1.36) | | | | | | | | | | | |
| Milicevic et al. (2009) | | | | | | | | | | | | | | | | | | -1.30 (2.00) | | | | | | | | | | | | | | | -0.50 (1.60) |
| Derosa et al. (2009) | | -1.40 (0.79) | | | | | | | | | | | | | | | | | | | | | | | | | -1.10 (0.69) | | | | | | |
| Bergenstal et al. (2009) | | | | | -2.76 (1.79) | -2.34 (1.51) | | | -1.75 (1.57) | | | | | | | | | | | | | | | | | | | | | | | | |
| Civera et al. (2008) | -0.70 (1.20) | | | | | | | | | | | | | | | | | | | | | | | -2.40 (1.10) | | | | | -1.40 (1.60) | | | | |
| Ushakova et al. (2007) | | | | -2.90 (1.50) | -3.00 (1.60) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic human insulin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Insulin lispro mix 75/25-Metformin | Insulin lispro-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Robbins et al. (2007) | | | | | | | | | | | | | | | -0.30 (0.95) | | | | -0.70 (0.90) | | | | | | | | | | | | | | |
| Pan et al. (2007) | | | | | | | | | | | | | | | | | -1.12 (1.04) | | | | | | | | | | | | | | | | -0.92 (1.05) |
| Nauck et al. (2007) | | | | | | -0.89 (0.94) | | | -1.04 (1.11) | | | | | | | | | | | | | | | | | | | | | | | | |
| Eliaschewitz et al. (2006) | | | | | | | | | | | | | | | | | -1.38 (1.32) | | | | | | | | | | | | | | | | -1.44 (1.33) |
| Yki-Jarvinen et al. (2006) | -2.10 (0.87) | | | | | | | | | | | | | | -1.99 (0.87) | | | | | | | | | | | | | | | | | | |
| Raz et al. (2005) | | | | -0.50 (1.29) | | | -1.20 (1.25) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Malone et al. (2005) | | | | | | | | | | | | | | | -0.89 (0.93) | | | | | -0.45 (0.93) | | | | | | | | | | | | | |
| Janka et al. (2005) | | | | | | | | | | | | | | | | -1.64 (0.92) | | | | | | | | | | | | | -1.31 (0.94) | | | | |
| Malone et al. (2004) | | | | | | | | | | | | | | | -0.77 (1.45) | | | | | -1.40 (1.13) | | | | | | | | | | | | | |
| Olsson & (2002) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | -1.30 (0.74) | | | -1.50 (1.23) |
| Kokic et al. (2010) | | -1.30 (1.64) | -2.20 (1.82) | | | | | | | | | | | | | | | | | | -2.60 (1.75) | | | | | | | | | | | | |
| Heine et al. (2005) | | | | | | | | | -0.72 (0.76) | | | | | | | -0.64 (0.76) | | | | | | | | | | | | | | | | | |
| Aljabri et al. (2004) | | | | | | | | | | | | | | | | | | | | | | | | | -2.30 (1.50) | -1.90 (1.50) | | | | | | | |
| Stehouwer et al. (2003) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | -1.10 (1.24) | | | | -0.50 (1.30) |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic human insulin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Insulin lispro mix 75/25-Metformin | Insulin lispro-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kilo et al. (2003) | -1.25 (1.40) | | | | -1.20 (1.62) | | | | | | | | | | | | | | | | | | -1.10 (1.21) | | | | | | | | | | |
| Goudswaard et al. (2004) | | | | | | | | | | | | | | | | | | | | | | | | | -0.80 (1.30) | | | | | -1.20 (1.20) | | | |
| Furlong et al. (2002) | -0.30 (1.31) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 0.50 (1.27) | |
| Furlong et al. (2003) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | -0.90 (1.77) | -1.00 (1.66) |
| Kvapil et al. (2006) | | | | -1.55 (2.00) | -1.80 (1.81) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fritsche et al. (2003) | | | | | | | | | | | | | | | | | -1.10 (1.09) | | | | | | | | | | | | | | | | -0.84 (1.09) |
| Riddle et al. (1992) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | -0.80 (0.63) | -1.30 (0.33) | | |
| Riddle & (1998) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | -2.10 (1.17) | -2.10 (1.13) | | |
| Liu et al. (2013) | | | | | | | | | | | | | | | | | | | | | | | | | | -0.94 (0.92) | | -0.71 (0.93) | | | | | |
| Meneghini et al. (2013) | | | | | | | | | | | | | | -0.48 (0.80) | -0.73 (0.66) | | | | | | | | | | | | | | | | | | |
| Park et al. (2014) | | | | | | | | | | | | | | | -0.80 (0.85) | -1.40 (0.79) | -0.70 (1.17) | | | | | | | | | | | | | | | | |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 103: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effectiveness of all pairwise combinations – part A**

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic human insulin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-NPH insulin | | - | - | - | 0.05 (-0.56, 0.66) | - | - | - | - | 0.70 (0.28, 1.12) | 0.10 (-0.33, 0.53) | - | - | - | 0.11 (-0.22, 0.44) | - | - |
| Acarbose-Metformin-Sulfonylurea | 2.37 (1.12, 3.68) | | -0.90 (-1.44, -0.36) | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic human insulin-NPH insulin | 1.47 (0.10, 2.89) | -0.90 (-1.44, -0.36) | | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart | -0.20 (-0.75, 0.34) | -2.57 (-3.99, -1.23) | -1.68 (-3.19, -0.22) | | -0.16 (-0.49, 0.17) | - | -0.70 (-1.06, -0.34) | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Metformin | -0.37 (-0.80, 0.08) | -2.73 (-4.10, -1.44) | -1.84 (-3.31, -0.42) | -0.16 (-0.49, 0.17) | | 0.42 (-0.04, 0.88) | - | 0.19 (-0.07, 0.45) | 1.01 (0.53, 1.49) | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.15 (-0.27, 0.57) | -2.22 (-3.57, -0.94) | -1.33 (-2.77, 0.08) | 0.35 (-0.14, 0.86) | 0.51 (0.14, 0.89) | | - | - | -0.04 (-0.21, 0.12) | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Pioglitazone | -0.90 (-1.56, -0.25) | -3.27 (-4.72, -1.89) | -2.38 (-3.92, -0.88) | -0.70 (-1.06, -0.33) | -0.54 (-1.03, -0.05) | -1.05 (-1.68, -0.43) | | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-repaglinide | -0.18 (-0.69, 0.34) | -2.55 (-3.93, -1.22) | -1.66 (-3.15, -0.21) | 0.03 (-0.39, 0.45) | 0.19 (-0.07, 0.45) | -0.33 (-0.78, 0.14) | 0.73 (0.18, 1.29) | | - | - | - | - | - | - | - | - | - |
| Exenatide-Metformin-Sulfonylurea | 0.09 (-0.31, 0.49) | -2.28 (-3.61, -1.01) | -1.39 (-2.82, 0.01) | 0.29 (-0.21, 0.79) | 0.45 (0.08, 0.82) | -0.06 (-0.23, 0.10) | 0.99 (0.38, 1.62) | 0.27 (-0.19, 0.72) | | - | - | - | - | - | - | 0.08 (-0.25, 0.41) | - |
| Insulin aspart (short acting) | 0.50 (0.10, 0.89) | -1.87 (-3.22, -0.59) | -0.98 (-2.43, 0.43) | 0.70 (0.05, 1.35) | 0.87 (0.30, 1.42) | 0.35 (-0.19, 0.89) | 1.40 (0.66, 2.14) | 0.68 (0.05, 1.30) | 0.41 (-0.11, 0.93) | | -0.60 (-1.02, -0.18) | - | - | - | - | - | - |
| Insulin aspart (short acting)-Metformin | -0.10 (-0.51, 0.30) | -2.48 (-3.82, -1.18) | -1.58 (-3.02, -0.16) | 0.10 (-0.56, 0.76) | 0.27 (-0.31, 0.83) | -0.25 (-0.79, 0.28) | 0.80 (0.05, 1.55) | 0.08 (-0.55, 0.70) | -0.19 (-0.71, 0.33) | -0.60 (-1.02, -0.18) | | - | - | - | - | - | - |
| Insulin degludec/aspart mix-Metformin | 0.28 (-0.18, 0.72) | -2.10 (-3.47, -0.80) | -1.20 (-2.67, 0.21) | 0.48 (-0.19, 1.16) | 0.64 (0.05, 1.22) | 0.13 (-0.44, 0.68) | 1.18 (0.42, 1.95) | 0.45 (-0.20, 1.10) | 0.19 (-0.36, 0.73) | -0.22 (-0.80, 0.34) | 0.38 (-0.20, 0.95) | | - | - | 0.10 (-0.25, 0.45) | - | - |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic human insulin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Insulin degludec-Metformin | 0.47 (0.05, 0.89) | -1.90 (-3.26, -0.61) | -1.00 (-2.47, 0.42) | 0.68 (0.02, 1.33) | 0.84 (0.26, 1.40) | 0.32 (-0.22, 0.87) | 1.38 (0.63, 2.13) | 0.65 (0.01, 1.28) | 0.38 (-0.14, 0.91) | -0.03 (-0.57, 0.53) | 0.57 (0.02, 1.13) | 0.20 (-0.27, 0.67) | | - | -0.13 (-0.45, 0.18) | - | - |
| Insulin detemir-Metformin | 0.59 (0.28, 0.89) | -1.78 (-3.11, -0.53) | -0.89 (-2.32, 0.50) | 0.79 (0.20, 1.38) | 0.96 (0.46, 1.44) | 0.44 (-0.02, 0.90) | 1.49 (0.80, 2.19) | 0.77 (0.20, 1.33) | 0.50 (0.07, 0.94) | 0.09 (-0.39, 0.57) | 0.69 (0.21, 1.17) | 0.32 (-0.05, 0.69) | 0.12 (-0.23, 0.47) | | -0.25 (-0.39, -0.11) | - | - |
| Insulin glargine-Metformin | 0.34 (0.06, 0.61) | -2.03 (-3.35, -0.78) | -1.13 (-2.56, 0.24) | 0.55 (-0.03, 1.12) | 0.71 (0.22, 1.18) | 0.19 (-0.25, 0.63) | 1.25 (0.57, 1.93) | 0.52 (-0.03, 1.07) | 0.25 (-0.16, 0.66) | -0.16 (-0.61, 0.30) | 0.44 (-0.01, 0.90) | 0.07 (-0.28, 0.41) | -0.13 (-0.45, 0.19) | -0.25 (-0.39, -0.11) | | -0.60 (-1.00, -0.20) | 0.10 (-0.39, 0.59) |
| Insulin glargine-Metformin-Sulfonylurea | 0.05 (-0.27, 0.36) | -2.33 (-3.62, -1.08) | -1.43 (-2.83, -0.06) | 0.25 (-0.28, 0.78) | 0.41 (-0.01, 0.84) | -0.10 (-0.44, 0.24) | 0.95 (0.29, 1.59) | 0.22 (-0.28, 0.72) | -0.04 (-0.35, 0.27) | -0.45 (-0.89, -0.01) | 0.15 (-0.29, 0.59) | -0.23 (-0.69, 0.24) | -0.43 (-0.88, 0.02) | -0.54 (-0.88, -0.20) | -0.29 (-0.60, 0.02) | | 0.70 (0.22, 1.18) |
| Insulin glargine-Sulfonylurea | 0.71 (0.34, 1.08) | -1.66 (-2.92, -0.45) | -0.76 (-2.13, 0.58) | 0.91 (0.31, 1.52) | 1.08 (0.57, 1.58) | 0.56 (0.10, 1.01) | 1.62 (0.91, 2.32) | 0.89 (0.31, 1.46) | 0.62 (0.19, 1.05) | 0.21 (-0.28, 0.70) | 0.81 (0.32, 1.31) | 0.44 (-0.07, 0.94) | 0.24 (-0.25, 0.72) | 0.12 (-0.27, 0.51) | 0.37 (0.00, 0.74) | 0.66 (0.35, 0.98) | |
| Insulin lispro mix 50 and mix 25 | 0.08 (-0.63, 0.80) | -2.29 (-3.68, -0.95) | -1.39 (-2.89, 0.07) | 0.29 (-0.57, 1.15) | 0.45 (-0.33, 1.25) | -0.06 (-0.83, 0.69) | 0.99 (0.06, 1.92) | 0.26 (-0.57, 1.10) | 0.00 (-0.75, 0.73) | -0.41 (-1.19, 0.37) | 0.19 (-0.60, 0.97) | -0.19 (-0.98, 0.60) | -0.39 (-1.17, 0.39) | -0.51 (-1.22, 0.22) | -0.26 (-0.97, 0.46) | 0.04 (-0.65, 0.72) | -0.62 (-1.25, -0.01) |
| Insulin lispro mix 50/50-Metformin | -0.06 (-0.40, 0.28) | -2.43 (-3.76, -1.16) | -1.53 (-2.98, -0.15) | 0.15 (-0.47, 0.75) | 0.31 (-0.21, 0.82) | -0.21 (-0.69, 0.27) | 0.85 (0.14, 1.56) | 0.12 (-0.47, 0.70) | -0.15 (-0.61, 0.31) | -0.56 (-1.05, -0.06) | 0.04 (-0.46, 0.54) | -0.33 (-0.73, 0.07) | -0.53 (-0.91, -0.15) | -0.65 (-0.89, -0.40) | -0.40 (-0.60, -0.20) | -0.10 (-0.48, 0.26) | -0.77 (-1.19, -0.35) |
| Insulin lispro mix 75/25-Metformin | 0.40 (-0.01, 0.80) | -1.97 (-3.31, -0.69) | -1.07 (-2.52, 0.33) | 0.60 (-0.05, 1.25) | 0.76 (0.20, 1.32) | 0.25 (-0.28, 0.78) | 1.31 (0.56, 2.05) | 0.58 (-0.04, 1.19) | 0.31 (-0.19, 0.82) | -0.10 (-0.63, 0.44) | 0.50 (-0.05, 1.05) | 0.12 (-0.33, 0.59) | -0.07 (-0.51, 0.36) | -0.19 (-0.52, 0.13) | 0.06 (-0.24, 0.36) | 0.35 (-0.08, 0.78) | -0.31 (-0.78, 0.16) |
| Insulin lispro-Metformin | 1.07 (-0.29, 2.48) | -1.30 (-1.83, -0.78) | -0.40 (-0.96, 0.16) | 1.27 (-0.18, 2.77) | 1.44 (0.03, 2.90) | 0.92 (-0.47, 2.36) | 1.97 (0.48, 3.51) | 1.25 (-0.18, 2.73) | 0.99 (-0.40, 2.40) | 0.57 (-0.82, 2.01) | 1.18 (-0.23, 2.61) | 0.80 (-0.60, 2.27) | 0.60 (-0.80, 2.06) | 0.48 (-0.88, 1.90) | 0.73 (-0.64, 2.14) | 1.03 (-0.32, 2.41) | 0.36 (-0.96, 1.71) |
| Liraglutide-Metformin-Sulfonylurea | -0.19 (-0.59, 0.20) | -2.57 (-3.89, -1.30) | -1.67 (-3.11, -0.28) | 0.01 (-0.58, 0.60) | 0.17 (-0.32, 0.66) | -0.34 (-0.77, 0.08) | 0.71 (0.01, 1.40) | -0.01 (-0.58, 0.54) | -0.28 (-0.68, 0.12) | -0.69 (-1.19, -0.19) | -0.09 (-0.60, 0.41) | -0.47 (-0.99, 0.06) | -0.67 (-1.17, -0.16) | -0.78 (-1.20, -0.36) | -0.53 (-0.93, -0.14) | -0.24 (-0.49, 0.01) | -0.90 (-1.31, -0.51) |
| Metformin-NPH insulin mix 70/30 | -0.02 (-0.52, 0.48) | -2.40 (-3.81, -1.05) | -1.50 (-3.01, -0.04) | 0.18 (-0.44, 0.80) | 0.34 (-0.18, 0.87) | -0.17 (-0.74, 0.40) | 0.88 (0.17, 1.59) | 0.15 (-0.43, 0.73) | -0.11 (-0.67, 0.45) | -0.52 (-1.15, 0.10) | 0.08 (-0.55, 0.71) | -0.30 (-0.95, 0.35) | -0.49 (-1.14, 0.15) | -0.61 (-1.18, -0.05) | -0.36 (-0.92, 0.19) | -0.07 (-0.62, 0.48) | -0.73 (-1.33, -0.14) |
| Metformin-NPH insulin-repaglinide | -1.28 (-2.12, -0.45) | -3.65 (-5.19, -2.16) | -2.75 (-4.39, -1.17) | -1.08 (-2.05, -0.10) | -0.92 (-1.83, 0.00) | -1.43 (-2.33, -0.52) | -0.38 (-1.42, 0.67) | -1.10 (-2.06, -0.15) | -1.37 (-2.26, -0.47) | -1.78 (-2.69, -0.89) | -1.18 (-2.09, -0.28) | -1.56 (-2.49, -0.63) | -1.76 (-2.67, -0.85) | -1.87 (-2.74, -1.00) | -1.62 (-2.48, -0.76) | -1.33 (-2.17, -0.47) | -1.99 (-2.87, -1.12) |
| Metformin-NPH | 1.47 | -0.90 | 0.00 | 1.67 | 1.83 | 1.32 | 2.38 | 1.65 | 1.38 | 0.97 | 1.57 | 1.19 | 1.00 | 0.88 | 1.13 | 1.42 | 0.76 |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic human insulin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| insulin-Sulfonylurea | (0.28, 2.73) | (-1.31, -0.49) | (-0.68, 0.67) | (0.38, 3.02) | (0.59, 3.13) | (0.10, 2.61) | (1.04, 3.76) | (0.37, 2.97) | (0.16, 2.65) | (-0.26, 2.25) | (0.33, 2.85) | (-0.04, 2.50) | (-0.24, 2.29) | (-0.31, 2.14) | (-0.06, 2.38) | (0.24, 2.65) | (-0.38, 1.95) |
| Metformin-Pioglitazone-Sulfonylurea | 1.87 (0.62, 3.18) | -0.50 (-0.61, -0.39) | 0.40 (-0.15, 0.94) | 2.07 (0.73, 3.49) | 2.23 (0.94, 3.60) | 1.72 (0.44, 3.07) | 2.77 (1.40, 4.21) | 2.05 (0.72, 3.43) | 1.78 (0.52, 3.11) | 1.37 (0.10, 2.72) | 1.98 (0.68, 3.31) | 1.60 (0.30, 2.96) | 1.40 (0.12, 2.76) | 1.28 (0.03, 2.60) | 1.53 (0.28, 2.84) | 1.83 (0.59, 3.12) | 1.16 (-0.05, 2.41) |
| Metformin-repaglinide-Sulfonylurea | 2.67 (1.39, 4.02) | 0.30 (0.00, 0.60) | 1.20 (0.58, 1.81) | 2.87 (1.49, 4.32) | 3.03 (1.70, 4.44) | 2.52 (1.21, 3.90) | 3.57 (2.16, 5.05) | 2.85 (1.48, 4.26) | 2.58 (1.27, 3.95) | 2.17 (0.86, 3.55) | 2.77 (1.45, 4.15) | 2.40 (1.07, 3.80) | 2.20 (0.88, 3.59) | 2.08 (0.79, 3.44) | 2.33 (1.04, 3.67) | 2.62 (1.36, 3.95) | 1.96 (0.71, 3.25) |
| Metformin-Sitagliptin-Sulfonylurea | 2.10 (0.80, 3.45) | -0.27 (-0.62, 0.08) | 0.63 (-0.02, 1.27) | 2.30 (0.91, 3.74) | 2.47 (1.12, 3.86) | 1.95 (0.63, 3.33) | 3.00 (1.58, 4.48) | 2.28 (0.91, 3.70) | 2.01 (0.69, 3.37) | 1.60 (0.27, 2.98) | 2.21 (0.86, 3.58) | 1.83 (0.49, 3.22) | 1.63 (0.29, 3.02) | 1.51 (0.21, 2.86) | 1.76 (0.46, 3.11) | 2.06 (0.77, 3.39) | 1.39 (0.13, 2.69) |
| NPH insulin | 0.39 (0.09, 0.71) | -1.98 (-3.27, -0.74) | -1.08 (-2.48, 0.28) | 0.60 (0.05, 1.15) | 0.76 (0.32, 1.20) | 0.25 (-0.13, 0.62) | 1.30 (0.64, 1.96) | 0.57 (0.05, 1.09) | 0.31 (-0.04, 0.66) | -0.10 (-0.52, 0.32) | 0.50 (0.08, 0.92) | 0.12 (-0.35, 0.60) | -0.07 (-0.53, 0.37) | -0.19 (-0.54, 0.15) | 0.06 (-0.27, 0.37) | 0.35 (0.17, 0.53) | -0.31 (-0.62, -0.01) |
| NPH insulin mix 70/30 | 1.08 (0.04, 2.14) | -1.30 (-2.04, -0.55) | -0.40 (-1.31, 0.52) | 1.28 (0.13, 2.46) | 1.44 (0.33, 2.56) | 0.93 (-0.15, 2.03) | 1.98 (0.78, 3.22) | 1.26 (0.12, 2.40) | 0.99 (-0.08, 2.08) | 0.58 (-0.50, 1.68) | 1.18 (0.09, 2.29) | 0.81 (-0.29, 1.92) | 0.60 (-0.49, 1.72) | 0.49 (-0.56, 1.57) | 0.74 (-0.31, 1.80) | 1.03 (0.00, 2.08) | 0.37 (-0.62, 1.36) |
| NPH insulin mix 70/30-Sulfonylurea | 0.85 (-0.23, 1.95) | -1.52 (-2.33, -0.72) | -0.62 (-1.59, 0.34) | 1.06 (-0.14, 2.27) | 1.22 (0.08, 2.37) | 0.70 (-0.41, 1.85) | 1.76 (0.51, 3.02) | 1.03 (-0.15, 2.21) | 0.77 (-0.34, 1.90) | 0.35 (-0.76, 1.50) | 0.95 (-0.18, 2.09) | 0.58 (-0.56, 1.74) | 0.38 (-0.75, 1.53) | 0.26 (-0.83, 1.37) | 0.51 (-0.57, 1.62) | 0.81 (-0.27, 1.89) | 0.14 (-0.88, 1.18) |
| NPH insulin-repaglinide | 0.87 (0.40, 1.33) | -1.51 (-2.87, -0.21) | -0.61 (-2.06, 0.82) | 1.07 (0.37, 1.78) | 1.23 (0.61, 1.85) | 0.72 (0.11, 1.32) | 1.77 (0.98, 2.57) | 1.04 (0.37, 1.71) | 0.78 (0.19, 1.36) | 0.37 (-0.22, 0.96) | 0.97 (0.37, 1.57) | 0.59 (-0.03, 1.22) | 0.39 (-0.20, 1.01) | 0.28 (-0.25, 0.81) | 0.53 (0.01, 1.05) | 0.82 (0.30, 1.34) | 0.16 (-0.35, 0.67) |
| NPH insulin-Sulfonylurea | 0.88 (0.51, 1.25) | -1.49 (-2.74, -0.28) | -0.59 (-1.95, 0.74) | 1.09 (0.49, 1.69) | 1.25 (0.74, 1.75) | 0.74 (0.28, 1.18) | 1.79 (1.08, 2.49) | 1.06 (0.48, 1.63) | 0.80 (0.37, 1.22) | 0.39 (-0.10, 0.87) | 0.99 (0.50, 1.48) | 0.61 (0.11, 1.12) | 0.41 (-0.07, 0.90) | 0.29 (-0.09, 0.69) | 0.54 (0.18, 0.92) | 0.84 (0.53, 1.15) | 0.17 (0.06, 0.29) |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*

***Continued***

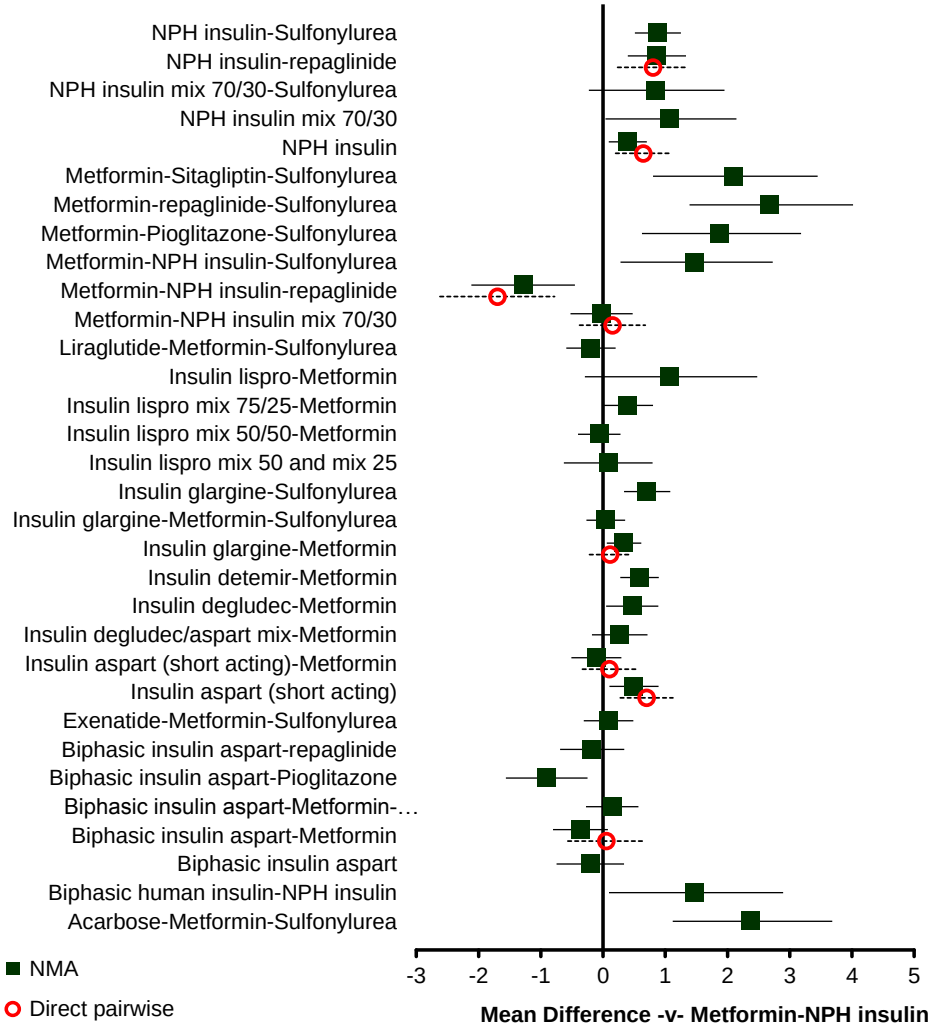
**Table 104: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effectiveness of all pairwise combinations – Part B**

| | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Insulin lispro mix 75/25-Metformin | Insulin lispro-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-NPH insulin | - | - | - | - | - | 0.15 (-0.38, 0.68) | -1.70 (-2.62, -0.78) | - | - | - | - | 0.64 (0.20, 1.09) | - | - | 0.80 (0.23, 1.37) | - |
| Acarbose-Metformin-Sulfonylurea | - | - | - | -1.30 (-1.83, -0.77) | - | - | - | - | -0.50 (-0.61, -0.39) | 0.30 (0.01, 0.59) | - | - | - | - | - | - |
| Biphasic human insulin-NPH insulin | - | - | - | -0.40 (-0.96, 0.16) | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Metformin | - | - | - | - | - | 0.10 (-0.48, 0.68) | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Metformin-Sulfonylurea | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Pioglitazone | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-repaglinide | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Exenatide-Metformin-Sulfonylurea | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin aspart (short acting) | - | - | - | - | - | - | - | - | - | - | - | 0.20 (-0.27, 0.67) | - | - | - | - |
| Insulin aspart (short acting)-Metformin | - | - | - | - | - | - | - | - | - | - | - | 0.80 (0.32, 1.28) | - | - | - | - |
| Insulin degludec/aspart mix-Metformin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin degludec-Metformin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin detemir-Metformin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin glargine-Metformin | - | -0.40 (-0.60, -0.20) | 0.06 (-0.24, 0.35) | - | - | - | - | - | - | - | - | - | - | - | - | - |

| | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Insulin lispro mix 75/25-Metformin | Insulin lispro-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Insulin glargine-Metformin-Sulfonylurea | - | - | - | - | -0.24 (-0.49, 0.01) | - | - | - | - | - | - | 0.33 (0.14, 0.52) | - | - | - | - |
| Insulin glargine-Sulfonylurea | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.17 (0.05, 0.28) |
| Insulin lispro mix 50 and mix 25 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.80 (0.19, 1.41) |
| Insulin lispro mix 50/50-Metformin | -0.14 (-0.88, 0.60) | | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin lispro mix 75/25-Metformin | 0.31 (-0.45, 1.09) | 0.46 (0.10, 0.82) | | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin lispro-Metformin | 0.99 (-0.44, 2.48) | 1.13 (-0.24, 2.55) | 0.67 (-0.72, 2.11) | | - | - | - | - | - | - | - | - | - | - | - | - |
| Liraglutide-Metformin-Sulfonylurea | -0.28 (-1.01, 0.45) | -0.13 (-0.58, 0.31) | -0.59 (-1.08, -0.10) | -1.27 (-2.69, 0.11) | | - | - | - | - | - | - | - | - | - | - | - |
| Metformin-NPH insulin mix 70/30 | -0.11 (-0.95, 0.74) | 0.04 (-0.56, 0.63) | -0.42 (-1.05, 0.21) | -1.10 (-2.59, 0.36) | 0.17 (-0.43, 0.77) | | - | - | - | - | - | - | - | - | - | - |
| Metformin-NPH insulin-repaglinide | -1.37 (-2.43, -0.30) | -1.22 (-2.11, -0.34) | -1.68 (-2.59, -0.77) | -2.35 (-3.97, -0.77) | -1.09 (-1.97, -0.20) | -1.26 (-2.22, -0.29) | | - | - | - | - | 1.00 (-0.07, 2.07) | - | - | - | - |
| Metformin-NPH insulin-Sulfonylurea | 1.39 (0.10, 2.71) | 1.53 (0.32, 2.80) | 1.07 (-0.14, 2.35) | 0.39 (-0.27, 1.06) | 1.66 (0.46, 2.93) | 1.49 (0.21, 2.83) | 2.75 (1.30, 4.23) | | 0.40 (0.01, 0.79) | - | - | - | -0.40 (-1.01, 0.21) | - | - | - |
| Metformin-Pioglitazone-Sulfonylurea | 1.79 (0.45, 3.18) | 1.93 (0.67, 3.26) | 1.47 (0.19, 2.81) | 0.80 (0.26, 1.34) | 2.06 (0.81, 3.39) | 1.90 (0.55, 3.31) | 3.15 (1.67, 4.69) | 0.40 (0.01, 0.79) | | - | 0.23 (-0.10, 0.56) | - | - | - | - | - |

| | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Insulin lispro mix 75/25-Metformin | Insulin lispro-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-repaglinide-Sulfonylurea | 2.59 (1.22, 4.02) | 2.73 (1.44, 4.10) | 2.27 (0.95, 3.65) | 1.60 (1.00, 2.20) | 2.86 (1.56, 4.23) | 2.70 (1.32, 4.15) | 3.95 (2.44, 5.53) | 1.20 (0.70, 1.70) | 0.80 (0.49, 1.12) | | - | - | - | - | - | - |
| Metformin-Sitagliptin-Sulfonylurea | 2.02 (0.64, 3.44) | 2.16 (0.84, 3.52) | 1.70 (0.38, 3.07) | 1.03 (0.39, 1.67) | 2.29 (0.99, 3.66) | 2.13 (0.74, 3.57) | 3.38 (1.86, 4.95) | 0.63 (0.12, 1.14) | 0.23 (-0.10, 0.56) | -0.57 (-1.03, -0.12) | | - | - | - | - | - |
| NPH insulin | 0.31 (-0.36, 0.99) | 0.45 (0.08, 0.84) | 0.00 (-0.44, 0.43) | -0.68 (-2.07, 0.67) | 0.59 (0.29, 0.89) | 0.42 (-0.13, 0.97) | 1.68 (0.84, 2.52) | -1.08 (-2.30, 0.10) | -1.48 (-2.77, -0.24) | -2.27 (-3.59, -1.00) | -1.71 (-3.04, -0.42) | | - | - | - | 0.60 (0.22, 0.98) |
| NPH insulin mix 70/30 | 0.99 (-0.16, 2.16) | 1.14 (0.07, 2.22) | 0.68 (-0.41, 1.79) | 0.00 (-0.90, 0.92) | 1.27 (0.22, 2.35) | 1.10 (-0.04, 2.26) | 2.36 (1.04, 3.69) | -0.39 (-1.00, 0.22) | -0.80 (-1.53, -0.06) | -1.60 (-2.40, -0.80) | -1.03 (-1.84, -0.22) | 0.68 (-0.34, 1.72) | | -0.22 (-0.52, 0.07) | - | -0.20 (-1.19, 0.79) |
| NPH insulin mix 70/30-Sulfonylurea | 0.77 (-0.42, 1.97) | 0.91 (-0.19, 2.03) | 0.46 (-0.66, 1.60) | -0.23 (-1.18, 0.74) | 1.05 (-0.05, 2.17) | 0.88 (-0.30, 2.08) | 2.14 (0.79, 3.50) | -0.62 (-1.30, 0.06) | -1.02 (-1.82, -0.23) | -1.82 (-2.68, -0.98) | -1.25 (-2.12, -0.39) | 0.46 (-0.60, 1.54) | -0.22 (-0.52, 0.07) | | - | - |
| NPH insulin-repaglinide | 0.78 (-0.02, 1.57) | 0.93 (0.37, 1.49) | 0.47 (-0.12, 1.06) | -0.21 (-1.65, 1.20) | 1.06 (0.49, 1.64) | 0.89 (0.22, 1.57) | 2.15 (1.22, 3.10) | -0.61 (-1.91, 0.63) | -1.01 (-2.37, 0.29) | -1.81 (-3.20, -0.47) | -1.24 (-2.63, 0.11) | 0.47 (-0.04, 0.98) | -0.21 (-1.32, 0.88) | 0.01 (-1.13, 1.15) | | -0.10 (-0.85, 0.65) |
| NPH insulin-Sulfonylurea | 0.80 (0.19, 1.41) | 0.94 (0.53, 1.37) | 0.49 (0.01, 0.96) | -0.19 (-1.53, 1.14) | 1.08 (0.69, 1.47) | 0.91 (0.31, 1.50) | 2.17 (1.30, 3.04) | -0.59 (-1.78, 0.56) | -0.99 (-2.24, 0.22) | -1.79 (-3.07, -0.54) | -1.22 (-2.51, 0.04) | 0.49 (0.19, 0.78) | -0.20 (-1.18, 0.78) | 0.03 (-1.01, 1.05) | 0.02 (-0.49, 0.52) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 62: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effect of all options versus reference treatment**

**Table 105: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.000 | 10 (5, 15) |
| Acarbose-Metformin-Sulfonylurea | 0.000 | 32 (31, 32) |
| Biphasic human insulin-NPH insulin | 0.000 | 28 (14, 30) |
| Biphasic insulin aspart | 0.000 | 6 (3, 16) |
| Biphasic insulin aspart-Metformin | 0.000 | 4 (3, 9) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.000 | 13 (7, 21) |
| Biphasic insulin aspart-Pioglitazone | 0.236 | 2 (1, 3) |
| Biphasic insulin aspart-repaglinide | 0.000 | 6 (3, 16) |
| Exenatide-Metformin-Sulfonylurea | 0.000 | 12 (6, 18) |
| Insulin aspart (short acting) | 0.000 | 20 (12, 27) |
| Insulin aspart (short acting)-Metformin | 0.000 | 8 (3, 16) |
| Insulin degludec/aspart mix-Metformin | 0.000 | 15 (7, 23) |
| Insulin degludec-Metformin | 0.000 | 19 (12, 26) |
| Insulin detemir-Metformin | 0.000 | 21 (17, 27) |
| Insulin glargine-Metformin | 0.000 | 17 (12, 21) |
| Insulin glargine-Metformin-Sulfonylurea | 0.000 | 11 (6, 16) |
| Insulin glargine-Sulfonylurea | 0.000 | 22 (18, 28) |
| Insulin lispro mix 50 and mix 25 | 0.001 | 12 (3, 23) |
| Insulin lispro mix 50/50-Metformin | 0.000 | 8 (3, 15) |
| Insulin lispro mix 75/25-Metformin | 0.000 | 18 (10, 25) |
| Insulin lispro-Metformin | 0.001 | 26 (5, 28) |
| Liraglutide-Metformin-Sulfonylurea | 0.000 | 6 (3, 12) |
| Metformin-NPH insulin mix 70/30 | 0.000 | 9 (3, 20) |
| Metformin-NPH insulin-repaglinide | 0.761 | 1 (1, 3) |
| Metformin-NPH insulin-Sulfonylurea | 0.000 | 28 (19, 29) |
| Metformin-Pioglitazone-Sulfonylurea | 0.000 | 30 (26, 31) |
| Metformin-repaglinide-Sulfonylurea | 0.000 | 33 (32, 33) |

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sitagliptin-Sulfonylurea | 0.000 | 31 (29, 32) |
| NPH insulin | 0.000 | 18 (13, 23) |
| NPH insulin mix 70/30 | 0.000 | 26 (13, 29) |
| NPH insulin mix 70/30-Sulfonylurea | 0.000 | 24 (6, 27) |
| NPH insulin-repaglinide | 0.000 | 24 (18, 31) |
| NPH insulin-Sulfonylurea | 0.000 | 24 (22, 30) |

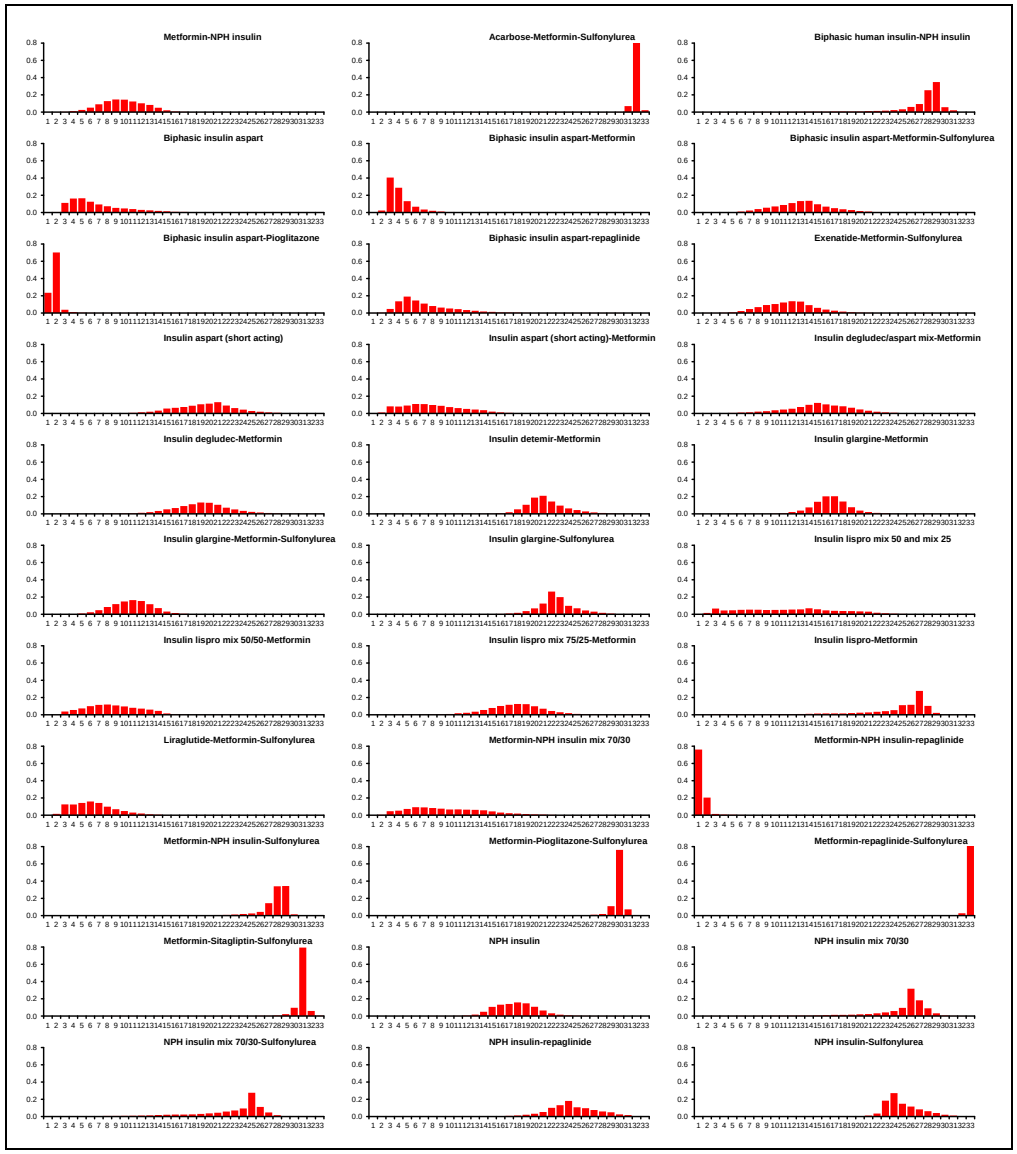



**Figure 63: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rank probability histograms**

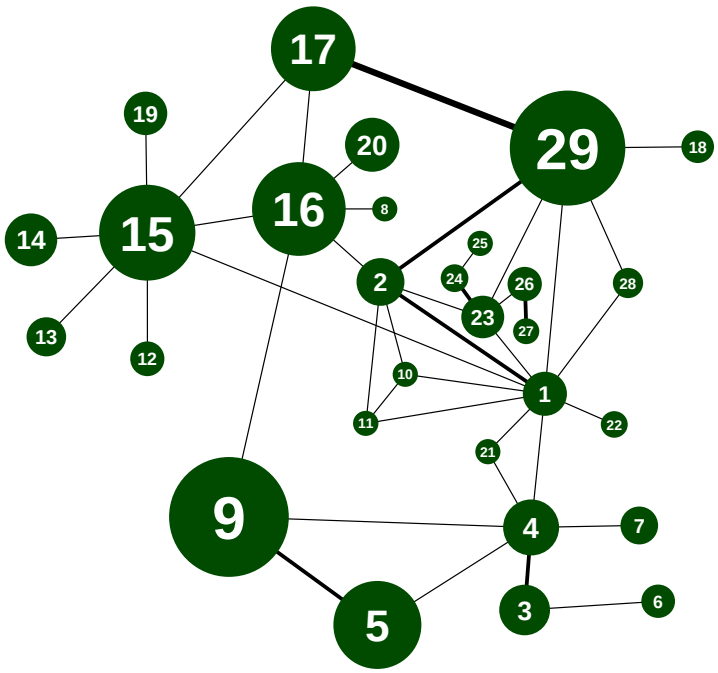
**Table 106: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 123.3<br>(compared to 85 datapoints) | -57.69 | -126.5 | 68.86 | 11.17 | |

**Table 107: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

### J.2.3.2 Hypoglycaemia at study endpoint




1 Metformin-NPH insulin
2 _NPH insulin
3 Biphasic insulin aspart
4 Biphasic insulin aspart-Metformin
5 Biphasic insulin aspart-Metformin-Sulfonylurea
6 Biphasic insulin aspart-Pioglitazone
7 Biphasic insulin aspart-repaglinide
8 Exenatide (once weekly)-Metformin-Sulfonylurea
9 Exenatide-Metformin-Sulfonylurea
10 Insulin aspart (short acting)
11 Insulin aspart (short acting)-Metformin
12 Insulin degludec/aspart mix-Metformin
13 Insulin degludec-Metformin
14 Insulin detemir-Metformin
15 Insulin glargine-Metformin
16 Insulin glargine-Metformin-Sulfonylurea
17 Insulin glargine-Sulfonylurea
18 Insulin lispro mix 50 and mix 25
19 Insulin lispro mix 50/50-Metformin
20 Liraglutide-Metformin-Sulfonylurea
21 Metformin-NPH insulin mix 70/30
22 Metformin-NPH insulin-repaglinide
23 Metformin-NPH insulin-Sulfonylurea
24 Metformin-Pioglitazone-Sulfonylurea
25 Metformin-Sitagliptin-Sulfonylurea
26 NPH insulin mix 70/30
27 NPH insulin mix 70/30-Sulfonylurea
28 NPH insulin-repaglinide
29 NPH insulin-Sulfonylurea

*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 64: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network**

## Table 108: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

| | Metformin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/ aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/ 50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/ 30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/ 30 | NPH insulin mix 70/ 30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dichotomous proportion data | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Gram et al. (2011) - 1.99yr | 33/ 45 | | | | | | | | 43/ 48 | 36/ 45 | | | | | | | | | | | | | | | 35/ 46 | | | | |
| Diamant et al. (2010) - 1.61yr | | | | | | | 25/ 69 | | | | | | | | 37/ 66 | | | | | | | | | | | | | | |
| Hartemann-Heurtier et al. (2009) - 0.46yr | | | | | | | | | | | | | | | | | | | | | | 10/ 13 | 6/ 14 | | | | | | |
| Bergenstal et al. (2009) - 0.46yr | | | 76/ 124 | 69/ 124 | | | | 36/ 124 | | | | | | | | | | | | | | | | | | | | | |
| Janka et al. (2005) - 0.46yr | | | | | | | | | | | | | | | 109/ 177 | | | | | | | | | | 127/ 187 | | | | |
| Kilo et al. (2003) - 0.23yr | 13/ 47 | | 20/ 46 | | | | | | | | | | | | | | | | | 15/ 47 | | | | | | | | | |
| Fritsche et al. (2003) - 0.46yr | | | | | | | | | | | | | | | | 330/ 463 | | | | | | | | | | | | | 173/ 232 |
| Riddle & (1998) - 0.46yr | | | | | | | | | | | | | | | | | | | | | | | | | | 27/ 73 | 37/ 72 | | |
| Liu et al. (2013) - 0.46yr | | | | | | | | | | | | | | | | | | | | | | | 5/ 59 | 6/ 60 | | | | | |
| Count data | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zinman et al. (2011) - 0.31yr | | | | | | | | | | | | 23/ 19264 | | 12/ 6608 | | | | | | | | | | | | | | | |
| Heise et al. (2011) - 0.31yr | | | | | | | | | | | 61/ 12656 | | | 12/ 6440 | | | | | | | | | | | | | | | |
| Lund et al. (2009) - 1.00yr | | | 1238/ 19477 | | | 1418/ 17310 | | | | | | | | | | | | | | | | | | | | | | | |
| Russell-Jones et al. (2009) - 0.50yr | | | | | | | | | | | | | | | 202/ 41041 | | | | 109/ 39767 | | | | | | | | | | |

| | Metformin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/ aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/ 50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/ 30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/ 30 | NPH insulin mix 70/ 30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Milicevic et al. (2009) - 0.46yr | | | | | | | | | | | | | | | | | 124/ 10080 | | | | | | | | | | | | 31/ 10248 |
| Civera et al. (2008) - 0.46yr | 6/ 2016 | | | | | | | | | | | | | | | | | | | | 10/ 2016 | | | | | | | | |
| Ushakova et al. (2007) - 0.31yr | | 23/ 11424 | 21/ 10920 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Robbins et al. (2007) - 0.46yr | | | | | | | | | | | | | | 247/ 24696 | | | | 586/ 25116 | | | | | | | | | | | |
| Pan et al. (2007) - 0.46yr | | | | | | | | | | | | | | | | 682/ 36960 | | | | | | | | | | | | | 1019/ 37464 |
| Nauck et al. (2007) - 1.00yr | | | | 1315/ 85722 | | | | 1059/ 82264 | | | | | | | | | | | | | | | | | | | | | |
| Eliaschewitz et al. (2006) - 0.46yr | | | | | | | | | | | | | | | | 517/ 37716 | | | | | | | | | | | | | 819/ 41496 |
| Yki-Jarvinen et al. (2006) - 0.69yr | 268/ 12222 | | | | | | | | | | | | | 226/ 15246 | | | | | | | | | | | | | | | |
| Raz et al. (2005) - 0.34yr | | 221/ 11718 | | | 134/ 11277 | | | | | | | | | | | | | | | | | | | | | | | | |
| Heine et al. (2005) - 0.50yr | | | | | | | | 928/ 46410 | | | | | | | 799/ 46319 | | | | | | | | | | | | | | |
| Aljabri et al. (2004) - 0.31yr | | | | | | | | | | | | | | | | | | | | | | 79/ 3220 | 34/ 3416 | | | | | | |
| Stehouwer et al. (2003) - 0.69yr | | | | | | | | | | | | | | | | | | | | | | | | | 355/ 22176 | | | | 253/ 21672 |
| Goudswaard et al. (2004) - 1.00yr | | | | | | | | | | | | | | | | | | | | | | 89/ 12012 | | | | 133/ 11284 | | | |
| Furlong et al. (2002) - 0.25yr | 64/ 3609 | | | | | | | | | | | | | | | | | | | | | | | | | | | 38/ 3381 | |
| Furlong et al. (2003) - 0.25yr | | | | | | | | | | | | | | | | | | | | | | | | | | | | 94/ 3458 | 115/ 3549 |

| | Metformin-NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/ aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/ 50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/ 30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/ 30 | NPH insulin mix 70/ 30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kvapil et al. (2006) - 0.31yr | | 62/ 11648 | 64/ 11480 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Riddle et al. (1992) - 0.31yr | | | | | | | | | | | | | | | | | | | | | | | | | | 69/ 1120 | 97/ 1232 | | |
| Yki-JaŸˆrvinen et al. (1999) - 1.00yr | 25/ 7826 | | | | | | | | | | | | | | | | | | | | | 73/ 8554 | | | 94/ 8736 | | | | 68/ 8372 |
| Meneghini et al. (2013) - 0.50yr | | | | | | | | | | | | | 329/ 37644 | 457/ 37824 | | | | | | | | | | | | | | | |
| Park et al. (2014) - 0.54yr | | | | | | | | | | | | | | 64/ 5698 | 83/ 5940 | 95/ 5978 | | | | | | | | | | | | | |

*Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 109: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

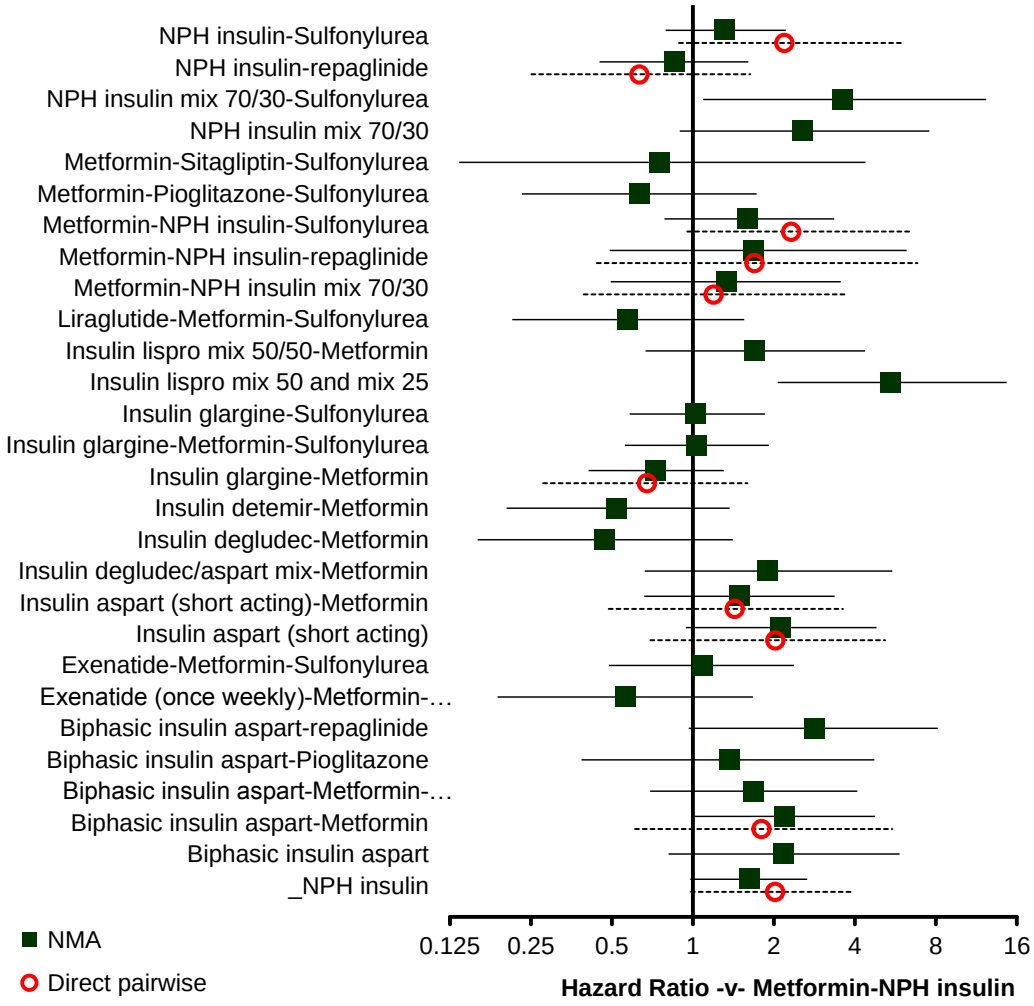
| | Metformin-NPH insulin | _NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-NPH insulin | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| _NPH insulin | 1.62 (0.98, 2.66) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart | 2.17 (0.81, 5.87) | 1.34 (0.48, 3.79) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin | 2.19 (1.00, 4.75) | 1.35 (0.58, 3.11) | 1.00 (0.55, 1.85) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 1.68 (0.69, 4.08) | 1.04 (0.42, 2.57) | 0.77 (0.31, 1.96) | 0.77 (0.38, 1.57) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Pioglitazone | 1.37 (0.39, 4.72) | 0.85 (0.23, 3.04) | 0.63 (0.29, 1.35) | 0.63 (0.24, 1.65) | 0.81 (0.24, 2.67) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-repaglinide | 2.83 (0.96, 8.13) | 1.74 (0.57, 5.33) | 1.29 (0.50, 3.37) | 1.29 (0.61, 2.71) | 1.68 (0.60, 4.60) | 2.07 (0.59, 6.99) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide (once weekly)-Metformin-Sulfonylurea | 0.56 (0.19, 1.67) | 0.35 (0.12, 0.99) | 0.26 (0.07, 0.98) | 0.26 (0.08, 0.86) | 0.33 (0.10, 1.13) | 0.41 (0.09, 1.92) | 0.20 (0.05, 0.82) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

| | Metformin-NPH insulin | _NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exenatide-Metformin-Sulfonylurea | 1.09 (0.49, 2.38) | 0.68 (0.30, 1.46) | 0.50 (0.20, 1.22) | 0.50 (0.26, 0.96) | 0.65 (0.37, 1.10) | 0.80 (0.24, 2.59) | 0.39 (0.14, 1.04) | 1.94 (0.62, 5.76) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin aspart (short acting) | 2.12 (0.94, 4.81) | 1.31 (0.58, 2.94) | 0.97 (0.28, 3.41) | 0.97 (0.32, 2.88) | 1.27 (0.40, 3.95) | 1.55 (0.35, 6.70) | 0.75 (0.20, 2.79) | 3.77 (1.03, 13.77) | 1.95 (0.67, 5.72) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin aspart (short acting)-Metformin | 1.50 (0.66, 3.37) | 0.92 (0.41, 2.06) | 0.69 (0.19, 2.40) | 0.68 (0.23, 2.05) | 0.89 (0.28, 2.86) | 1.10 (0.25, 4.75) | 0.53 (0.14, 1.96) | 2.65 (0.73, 9.71) | 1.37 (0.48, 4.08) | 0.70 (0.29, 1.73) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin degludec/aspart mix-Metformin | 1.90 (0.66, 5.51) | 1.17 (0.39, 3.54) | 0.87 (0.21, 3.54) | 0.87 (0.25, 3.08) | 1.13 (0.31, 4.12) | 1.40 (0.28, 7.04) | 0.68 (0.16, 2.92) | 3.37 (0.83, 14.00) | 1.75 (0.53, 6.09) | 0.89 (0.25, 3.31) | 1.27 (0.35, 4.71) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin degludec-Metformin | 0.47 (0.16, 1.41) | 0.29 (0.09, 0.90) | 0.22 (0.05, 0.92) | 0.21 (0.06, 0.79) | 0.28 (0.07, 1.06) | 0.35 (0.07, 1.76) | 0.17 (0.04, 0.74) | 0.83 (0.20, 3.59) | 0.43 (0.13, 1.55) | 0.22 (0.06, 0.85) | 0.31 (0.08, 1.18) | 0.25 (0.07, 0.88) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin detemir-Metformin | 0.52 (0.20, 1.37) | 0.32 (0.12, 0.88) | 0.24 (0.06, 0.90) | 0.24 (0.07, 0.79) | 0.31 (0.09, 1.06) | 0.38 (0.08, 1.77) | 0.19 (0.05, 0.74) | 0.93 (0.24, 3.52) | 0.48 (0.16, 1.56) | 0.24 (0.07, 0.84) | 0.35 (0.10, 1.17) | 0.28 (0.09, 0.87) | 1.11 (0.34, 3.64) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin | 0.73 (0.41, 1.30) | 0.45 (0.23, 0.86) | 0.33 (0.11, 0.99) | 0.33 (0.14, 0.82) | 0.43 (0.16, 1.13) | 0.53 (0.14, 2.04) | 0.26 (0.08, 0.83) | 1.29 (0.43, 3.98) | 0.66 (0.29, 1.60) | 0.34 (0.13, 0.90) | 0.49 (0.19, 1.25) | 0.38 (0.16, 0.92) | 1.55 (0.61, 3.83) | 1.39 (0.65, 2.91) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin-Sulfonylurea | 1.03 (0.56, 1.92) | 0.64 (0.36, 1.12) | 0.47 (0.17, 1.29) | 0.47 (0.21, 1.05) | 0.61 (0.28, 1.37) | 0.75 (0.22, 2.70) | 0.37 (0.12, 1.08) | 1.84 (0.75, 4.53) | 0.94 (0.50, 1.87) | 0.49 (0.19, 1.26) | 0.69 (0.27, 1.78) | 0.54 (0.18, 1.60) | 2.20 (0.70, 6.75) | 1.98 (0.72, 5.29) | 1.43 (0.74, 2.71) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Sulfonylurea | 1.02 (0.58, 1.85) | 0.63 (0.37, 1.11) | 0.47 (0.16, 1.37) | 0.47 (0.20, 1.13) | 0.61 (0.24, 1.57) | 0.74 (0.20, 2.86) | 0.36 (0.12, 1.17) | 1.82 (0.63, 5.48) | 0.94 (0.42, 2.22) | 0.48 (0.19, 1.23) | 0.68 (0.28, 1.75) | 0.54 (0.18, 1.59) | 2.19 (0.72, 6.69) | 1.96 (0.74, 5.27) | 1.41 (0.76, 2.68) | 0.99 (0.55, 1.84) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

| | Metformin-NPH insulin | _NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Insulin lispro mix 50 and mix 25 | 5.41 (2.07, 14.65) | 3.34 (1.30, 8.71) | 2.49 (0.66, 9.61) | 2.47 (0.76, 8.34) | 3.21 (0.95, 11.31) | 3.94 (0.86, 18.99) | 1.92 (0.48, 7.95) | 9.65 (2.54, 38.08) | 4.95 (1.60, 16.24) | 2.56 (0.77, 8.67) | 3.61 (1.10, 12.00) | 2.84 (0.72, 11.39) | 11.55 (2.84, 46.67) | 10.31 (2.83, 37.85) | 7.44 (2.66, 21.65) | 5.24 (1.89, 14.64) | 5.29 (2.13, 13.18) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin lispro mix 50/50-Metformin | 1.70 (0.67, 4.37) | 1.05 (0.39, 2.85) | 0.78 (0.21, 2.92) | 0.77 (0.24, 2.50) | 1.01 (0.30, 3.44) | 1.24 (0.27, 5.86) | 0.60 (0.15, 2.43) | 3.02 (0.80, 11.51) | 1.55 (0.52, 5.00) | 0.80 (0.24, 2.70) | 1.13 (0.34, 3.76) | 0.89 (0.28, 2.84) | 3.62 (1.12, 11.65) | 3.26 (1.12, 9.43) | 2.34 (1.10, 4.95) | 1.65 (0.61, 4.41) | 1.66 (0.61, 4.36) | 0.31 (0.08, 1.12) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin-Sulfonylurea | 0.57 (0.21, 1.55) | 0.35 (0.14, 0.92) | 0.26 (0.07, 0.93) | 0.26 (0.09, 0.79) | 0.34 (0.11, 1.05) | 0.42 (0.10, 1.83) | 0.20 (0.05, 0.77) | 1.01 (0.32, 3.39) | 0.52 (0.19, 1.48) | 0.27 (0.08, 0.93) | 0.38 (0.11, 1.30) | 0.30 (0.08, 1.14) | 1.22 (0.31, 4.84) | 1.10 (0.31, 3.86) | 0.79 (0.29, 2.17) | 0.55 (0.26, 1.20) | 0.56 (0.21, 1.50) | 0.11 (0.03, 0.38) | 0.34 (0.10, 1.18) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-NPH insulin mix 70/30 | 1.34 (0.49, 3.54) | 0.83 (0.28, 2.39) | 0.62 (0.20, 1.89) | 0.61 (0.23, 1.56) | 0.80 (0.26, 2.43) | 0.98 (0.25, 3.79) | 0.47 (0.14, 1.56) | 2.38 (0.58, 9.39) | 1.23 (0.42, 3.58) | 0.63 (0.18, 2.17) | 0.89 (0.25, 3.15) | 0.70 (0.17, 2.88) | 2.84 (0.66, 12.13) | 2.57 (0.66, 9.64) | 1.84 (0.60, 5.48) | 1.30 (0.44, 3.71) | 1.31 (0.43, 3.81) | 0.25 (0.06, 0.95) | 0.79 (0.20, 2.96) | 2.34 (0.63, 8.55) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-NPH insulin-repaglinide | 1.69 (0.49, 6.23) | 1.05 (0.28, 4.27) | 0.78 (0.16, 3.97) | 0.77 (0.18, 3.49) | 1.01 (0.22, 4.85) | 1.24 (0.22, 7.54) | 0.60 (0.12, 3.26) | 2.99 (0.58, 16.38) | 1.56 (0.36, 7.14) | 0.80 (0.18, 3.72) | 1.13 (0.26, 5.32) | 0.89 (0.17, 4.75) | 3.61 (0.70, 19.97) | 3.23 (0.68, 16.32) | 2.33 (0.58, 9.83) | 1.64 (0.41, 6.94) | 1.65 (0.42, 6.88) | 0.31 (0.06, 1.59) | 1.00 (0.21, 5.05) | 2.97 (0.60, 15.29) | 1.27 (0.26, 6.59) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-NPH insulin-Sulfonylurea | 1.60 (0.78, 3.35) | 0.99 (0.49, 2.03) | 0.74 (0.23, 2.44) | 0.73 (0.27, 2.06) | 0.96 (0.33, 2.83) | 1.17 (0.30, 4.92) | 0.57 (0.17, 2.03) | 2.85 (0.85, 9.83) | 1.47 (0.56, 4.13) | 0.76 (0.28, 2.15) | 1.08 (0.39, 3.03) | 0.84 (0.25, 2.90) | 3.43 (0.97, 12.04) | 3.06 (0.99, 9.61) | 2.21 (0.95, 5.26) | 1.55 (0.68, 3.63) | 1.56 (0.73, 3.43) | 0.30 (0.10, 0.87) | 0.94 (0.30, 2.98) | 2.79 (0.90, 8.94) | 1.20 (0.37, 4.05) | 0.95 (0.21, 4.02) | | N/A | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone-Sulfonylurea | 0.63 (0.23, 1.72) | 0.39 (0.15, 1.06) | 0.29 (0.07, 1.16) | 0.29 (0.09, 0.99) | 0.38 (0.11, 1.37) | 0.46 (0.10, 2.22) | 0.22 (0.06, 0.95) | 1.13 (0.28, 4.66) | 0.58 (0.18, 2.00) | 0.30 (0.09, 1.04) | 0.42 (0.13, 1.47) | 0.33 (0.08, 1.37) | 1.36 (0.32, 5.64) | 1.22 (0.32, 4.60) | 0.87 (0.29, 2.65) | 0.61 (0.21, 1.86) | 0.62 (0.22, 1.74) | 0.12 (0.03, 0.42) | 0.37 (0.10, 1.41) | 1.11 (0.29, 4.27) | 0.47 (0.12, 1.92) | 0.37 (0.07, 1.85) | 0.40 (0.20, 0.78) | | N/A | N/A | N/A | N/A |
| Metformin-Sitagliptin-Sulfonylurea | 0.75 (0.14, 4.38) | 0.47 (0.08, 2.69) | 0.34 (0.05, 2.57) | 0.34 (0.05, 2.32) | 0.45 (0.07, 3.13) | 0.55 (0.07, 4.63) | 0.27 (0.04, 2.02) | 1.34 (0.19, 10.21) | 0.69 (0.11, 4.60) | 0.35 (0.05, 2.39) | 0.50 (0.08, 3.34) | 0.40 (0.05, 2.99) | 1.62 (0.21, 12.43) | 1.45 (0.21, 10.24) | 1.04 (0.17, 6.46) | 0.73 (0.13, 4.49) | 0.74 (0.13, 4.36) | 0.14 (0.02, 0.96) | 0.44 (0.06, 3.19) | 1.32 (0.19, 9.63) | 0.56 (0.08, 4.16) | 0.44 (0.05, 3.81) | 0.47 (0.10, 2.37) | 1.18 (0.29, 5.04) | | N/A | N/A | N/A |
| NPH insulin mix 70/30 | 2.56 (0.89, 7.55) | 1.58 (0.56, 4.57) | 1.18 (0.29, 5.01) | 1.17 (0.33, 4.32) | 1.53 (0.41, 6.02) | 1.87 (0.38, 9.64) | 0.91 (0.21, 4.02) | 4.54 (1.11, 19.95) | 2.35 (0.69, 8.71) | 1.21 (0.34, 4.42) | 1.71 (0.49, 6.26) | 1.35 (0.32, 5.76) | 5.44 (1.26, 24.21) | 4.90 (1.24, 19.46) | 3.53 (1.12, 11.51) | 2.47 (0.83, 7.89) | 2.49 (0.85, 7.58) | 0.47 (0.12, 1.80) | 1.51 (0.39, 6.02) | 4.47 (1.14, 18.28) | 1.92 (0.46, 8.09) | 1.52 (0.29, 7.88) | 1.60 (0.74, 3.45) | 4.05 (1.44, 11.52) | 3.41 (0.58, 19.24) | | N/A | N/A |

| | Metformin-NPH insulin | _NPH insulin | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NPH insulin mix 70/30-Sulfonylurea | 3.59 (1.09, 12.30) | 2.23 (0.68, 7.41) | 1.65 (0.36, 7.70) | 1.64 (0.40, 6.85) | 2.14 (0.51, 9.35) | 2.61 (0.48, 14.89) | 1.27 (0.27, 6.32) | 6.35 (1.39, 31.26) | 3.29 (0.85, 13.79) | 1.69 (0.42, 7.02) | 2.40 (0.61, 9.96) | 1.88 (0.39, 9.09) | 7.65 (1.58, 38.55) | 6.82 (1.56, 30.95) | 4.92 (1.37, 18.45) | 3.48 (0.99, 12.69) | 3.49 (1.03, 12.08) | 0.66 (0.15, 2.86) | 2.11 (0.48, 9.51) | 6.26 (1.44, 28.66) | 2.69 (0.58, 12.63) | 2.12 (0.36, 12.21) | 2.24 (0.87, 5.89) | 5.66 (1.77, 18.57) | 4.76 (0.74, 30.21) | 1.40 (0.78, 2.51) | | N/A |
| NPH insulin-repaglinide | 0.86 (0.45, 1.61) | 0.53 (0.26, 1.07) | 0.39 (0.12, 1.24) | 0.39 (0.15, 1.03) | 0.51 (0.18, 1.43) | 0.62 (0.16, 2.50) | 0.30 (0.09, 1.03) | 1.52 (0.46, 5.07) | 0.78 (0.31, 2.05) | 0.40 (0.15, 1.08) | 0.57 (0.21, 1.54) | 0.45 (0.14, 1.46) | 1.82 (0.53, 6.16) | 1.64 (0.54, 4.89) | 1.18 (0.52, 2.59) | 0.83 (0.37, 1.82) | 0.84 (0.40, 1.67) | 0.16 (0.06, 0.45) | 0.50 (0.17, 1.48) | 1.48 (0.50, 4.54) | 0.64 (0.20, 2.04) | 0.51 (0.12, 2.02) | 0.53 (0.22, 1.26) | 1.35 (0.43, 4.07) | 1.13 (0.18, 6.80) | 0.33 (0.10, 1.06) | 0.24 (0.06, 0.86) | |
| NPH insulin-Sulfonylurea | 1.31 (0.79, 2.22) | 0.81 (0.51, 1.30) | 0.60 (0.21, 1.74) | 0.60 (0.26, 1.43) | 0.78 (0.31, 1.97) | 0.96 (0.26, 3.61) | 0.47 (0.15, 1.48) | 2.34 (0.80, 6.93) | 1.20 (0.55, 2.80) | 0.62 (0.26, 1.52) | 0.87 (0.37, 2.15) | 0.69 (0.23, 2.04) | 2.80 (0.91, 8.51) | 2.51 (0.93, 6.77) | 1.81 (0.96, 3.44) | 1.27 (0.70, 2.35) | 1.28 (0.87, 1.87) | 0.24 (0.11, 0.55) | 0.77 (0.29, 2.08) | 2.29 (0.86, 6.13) | 0.98 (0.34, 2.94) | 0.77 (0.19, 3.01) | 0.82 (0.40, 1.64) | 2.07 (0.77, 5.64) | 1.74 (0.30, 9.66) | 0.51 (0.18, 1.43) | 0.37 (0.11, 1.19) | 1.53 (0.83, 2.89) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 65: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 110: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.000 | 10 (5, 17) |
| _NPH insulin | 0.000 | 19 (12, 25) |
| Biphasic insulin aspart | 0.000 | 23 (9, 28) |
| Biphasic insulin aspart-Metformin | 0.000 | 23 (13, 27) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.000 | 19 (8, 27) |
| Biphasic insulin aspart-Pioglitazone | 0.015 | 16 (2, 27) |
| Biphasic insulin aspart-repaglinide | 0.000 | 26 (12, 29) |
| Exenatide (once weekly)-Metformin-Sulfonylurea | 0.156 | 4 (1, 17) |
| Exenatide-Metformin-Sulfonylurea | 0.001 | 12 (4, 21) |
| Insulin aspart (short acting) | 0.000 | 22 (10, 28) |
| Insulin aspart (short acting)-Metformin | 0.001 | 17 (5, 27) |
| Insulin degludec/aspart mix-Metformin | 0.000 | 21 (7, 28) |
| Insulin degludec-Metformin | 0.284 | 3 (1, 16) |
| Insulin detemir-Metformin | 0.157 | 3 (1, 15) |
| Insulin glargine-Metformin | 0.001 | 6 (3, 14) |
| Insulin glargine-Metformin-Sulfonylurea | 0.000 | 11 (5, 19) |
| Insulin glargine-Sulfonylurea | 0.000 | 11 (5, 19) |
| Insulin lispro mix 50 and mix 25 | 0.000 | 29 (22, 29) |
| Insulin lispro mix 50/50-Metformin | 0.000 | 19 (7, 28) |
| Liraglutide-Metformin-Sulfonylurea | 0.120 | 4 (1, 16) |
| Metformin-NPH insulin mix 70/30 | 0.005 | 15 (3, 26) |
| Metformin-NPH insulin-repaglinide | 0.009 | 19 (3, 29) |
| Metformin-NPH insulin-Sulfonylurea | 0.000 | 18 (8, 26) |
| Metformin-Pioglitazone-Sulfonylurea | 0.075 | 5 (1, 18) |
| Metformin-Sitagliptin-Sulfonylurea | 0.164 | 7 (1, 27) |
| NPH insulin mix 70/30 | 0.000 | 24 (10, 28) |
| NPH insulin mix 70/30-Sulfonylurea | 0.000 | 27 (14, 29) |
| NPH insulin-repaglinide | 0.009 | 8 (2, 19) |
| NPH insulin-Sulfonylurea | 0.000 | 15 (9, 22) |

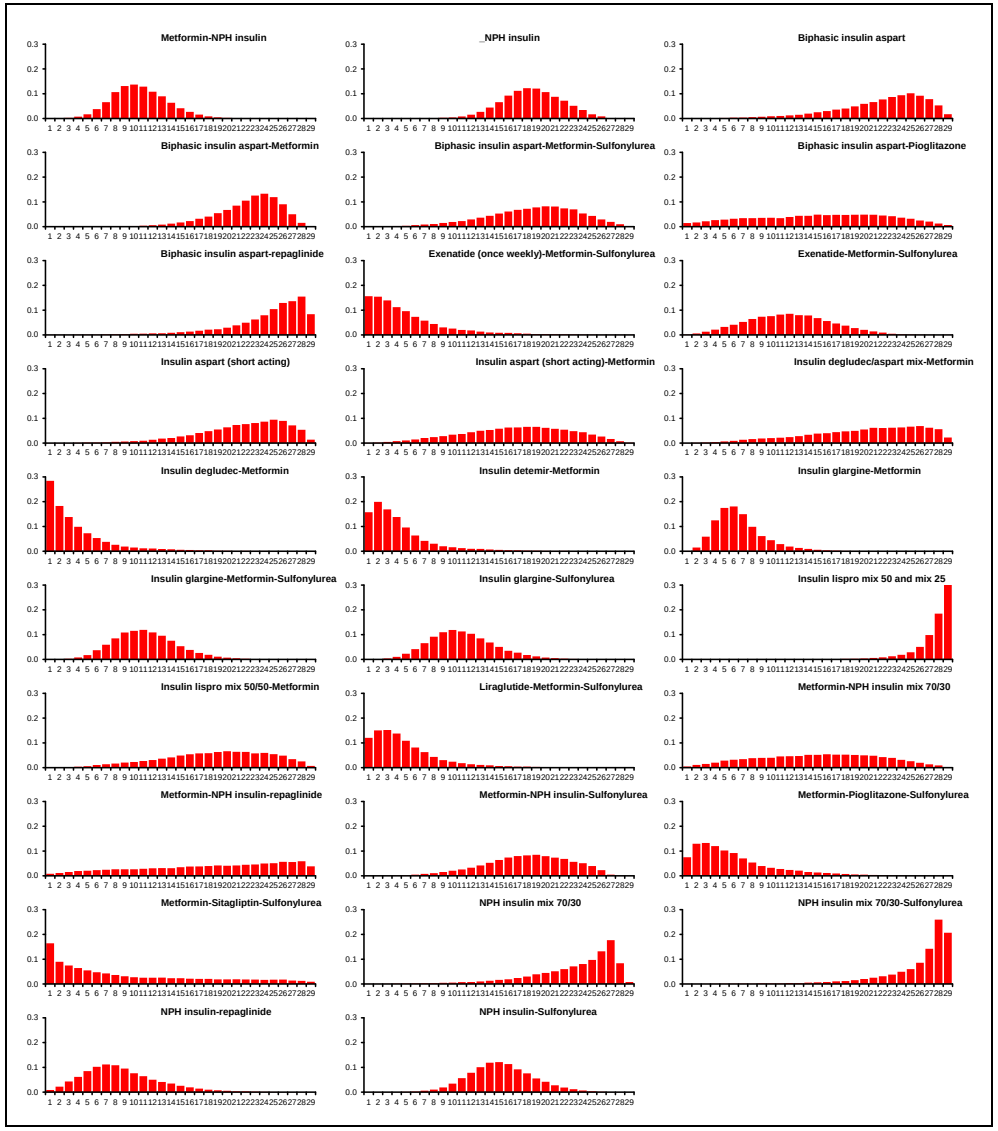



**Figure 66: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms**

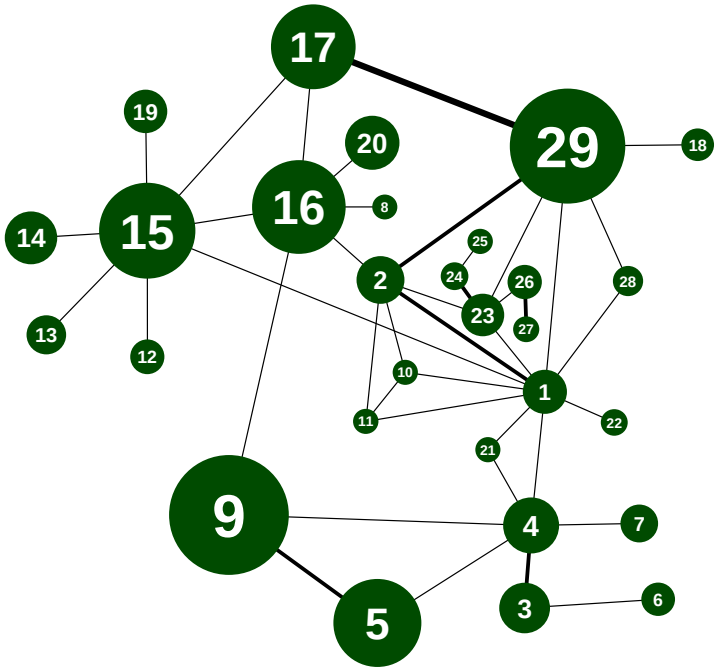
**Table 111: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 79.94<br>(compared to 77 datapoints) | 125.496 | 104.158 | 21.338 | 606.632 | 0.335 (95%CI: 0.183, 0.590) |

**Table 112: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes**

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

### J.2.3.3 Dropouts due to adverse events at study endpoint




1 Metformin-NPH insulin
2 _NPH insulin
3 Biphasic insulin aspart
4 Biphasic insulin aspart-Metformin
5 Biphasic insulin aspart-Metformin-Sulfonylurea
6 Biphasic insulin aspart-Pioglitazone
7 Biphasic insulin aspart-repaglinide
8 Exenatide (once weekly)-Metformin-Sulfonylurea
9 Exenatide-Metformin-Sulfonylurea
10 Insulin aspart (short acting)
11 Insulin aspart (short acting)-Metformin
12 Insulin degludec/aspart mix-Metformin
13 Insulin degludec-Metformin
14 Insulin detemir-Metformin
15 Insulin glargine-Metformin
16 Insulin glargine-Metformin-Sulfonylurea
17 Insulin glargine-Sulfonylurea
18 Insulin lispro mix 50 and mix 25
19 Insulin lispro mix 50/50-Metformin
20 Liraglutide-Metformin-Sulfonylurea
21 Metformin-NPH insulin mix 70/30
22 Metformin-NPH insulin-repaglinide
23 Metformin-NPH insulin-Sulfonylurea
24 Metformin-Pioglitazone-Sulfonylurea
25 Metformin-Sitagliptin-Sulfonylurea
26 NPH insulin mix 70/30
27 NPH insulin mix 70/30-Sulfonylurea
28 NPH insulin-repaglinide
29 NPH insulin-Sulfonylurea

*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 67: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – evidence network**

## Table 113: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – input data

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zinman et al. (2011) - 0.31yr | | | | | | | | | | | | 1/183 | | 1/62 | | | | | | | | | | | | | |
| Heise et al. (2011) - 0.31yr | | | | | | | | | | | 1/118 | | | 0/60 | | | | | | | | | | | | | |
| Gram et al. (2011) - 1.99yr | 5/45 | | | | | | | | 3/48 | 2/45 | | | | | | | | | | | | | | | | 0/46 | |
| Derosa et al. (2010) - 0.73yr | | 16/175 | | | | | | | | | | | | | | | | | | | | | 16/175 | | | | |
| Lund et al. (2009) - 1.00yr | | | | 0/52 | | | 2/49 | | | | | | | | | | | | | | | | | | | | |
| Hartemann-Heurtier et al. (2009) - 0.46yr | | | | | | | | | | | | | | | | | | | | | | 1/14 | 1/14 | | | | |
| Russell-Jones et al. (2009) - 0.50yr | | | | | | | | | | | | | | | 5/232 | | | | 11/230 | | | | | | | | |
| Milicevic et al. (2009) - 0.46yr | | | | | | | | | | | | | | | | | 1/68 | | | | | | | | | | 5/67 |
| Derosa et al. (2009) - 0.29yr | | 2/52 | | | | | | | | | | | | | | | | | | | | | | 1/51 | | | |
| Bergenstal et al. (2009) - 0.46yr | | | | 6/124 | 1/124 | | | 9/124 | | | | | | | | | | | | | | | | | | | |
| Civera et al. (2008) - 0.46yr | 0/12 | | | | | | | | | | | | | | | | | | | | 1/12 | | | | | 0/13 | |
| Ushakova et al. (2007) - 0.31yr | | | | | | | | | | | | | | 1/158 | | | | 5/157 | | | | | | | | | |
| Robbins et al. (2007) - 0.46yr | | | | | 0/248 | | | 20/253 | | | | | | | | | | | | | | | | | | | |
| Nauck et al. (2007) - 1.00yr | | | | | | | | | | | | | | | | 2/231 | | | | | | | | | | | 0/250 |
| Eliaschewitz et al. (2006) - 0.46yr | 1/49 | | | | | | | | | | | | | 1/61 | | | | | | | | | | | | | |
| Yki-Jarvinen et al. (2006) - 0.69yr | | | 2/97 | | | 1/93 | | | | | | | | | | | | | | | | | | | | | |
| Raz et al. (2005) - 0.34yr | | | | | | | | | | | | | | | 1/177 | | | | | | | | | | | 6/187 | |
| Janka et al. (2005) - 0.46yr | | | 1/107 | 2/108 | | | | | | | | | | | | | | | | | | | | | | | |
| Heine et al. (2005) - 0.50yr | | | | | | | | | | | | | | | | 9/463 | | | | | | | | | | | 7/232 |
| Kilo et al. (2003) - 0.23yr | | | | | | | | | | | | | | | | | | | | | | | 2/59 | | 1/60 | | |
| Kvapil et al. (2006) - 0.31yr | | | 1/100 | 1/100 | | | | | | | | | | | | | | | | | | | | | | | |
| Fritsche A,Schweitzer MA,Haring (2003) - 0.46yr | | | | | | | | 27/282 | | | | | | | 2/267 | | | | | | | | | | | | |
| Yki-JaÝˆrvinen et al. (1999) - 1.00yr | 0/47 | | | 2/46 | | | | | | | | | | | | | | | | 0/47 | | | | | | | |
| Liu et al. (2013) - 0.46yr | 4/24 | | | | | | | | | | | | | | | | | | | | | 1/24 | | | | 0/24 | 1/24 |
| Meneghini et al. (2013) - 0.50yr | | | | | | | | | | | | | 5/228 | 3/229 | | | | | | | | | | | | | |

*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

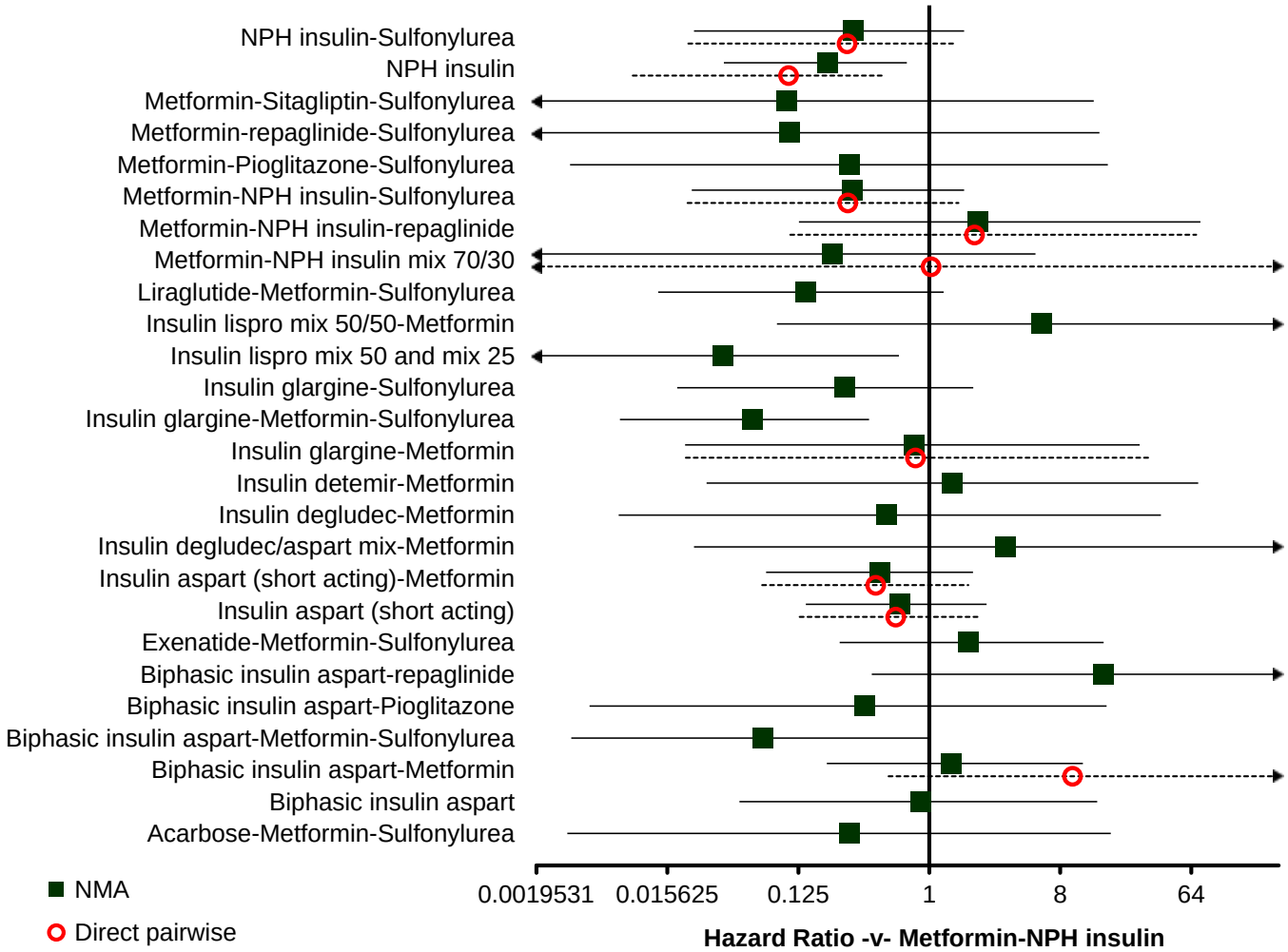
**Table 114: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-NPH insulin | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Acarbose-Metformin-Sulfonylurea | 0.28 (0.00, 17.84) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart | 0.88 (0.05, 14.37) | 3.17 (0.02, 581.50) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin | 1.42 (0.20, 11.47) | 5.15 (0.05, 641.50) | 1.59 (0.24, 13.55) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.07 (0.00, 0.99) | 0.25 (0.00, 42.12) | 0.08 (0.00, 1.34) | 0.05 (0.00, 0.30) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Pioglitazone | 0.36 (0.00, 16.68) | 1.27 (0.00, 428.60) | 0.43 (0.01, 5.35) | 0.25 (0.01, 6.47) | 5.08 (0.07, 283.30) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-repaglinide | 15.94 (0.40, 10090.00) | 65.49 (0.22, 121200.00) | 17.79 (0.48, 11140.00) | 10.20 (0.56, 5283.00) | 224.90 (6.17, 147300.00) | 49.42 (0.48, 52500.00) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin-Sulfonylurea | 1.86 (0.24, 15.90) | 6.76 (0.07, 853.40) | 2.10 (0.25, 22.13) | 1.31 (0.50, 3.63) | 24.41 (5.91, 278.20) | 5.21 (0.18, 320.50) | 0.13 (0.00, 2.89) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin aspart (short acting) | 0.63 (0.14, 2.48) | 2.22 (0.03, 221.80) | 0.71 (0.03, 16.27) | 0.44 (0.04, 4.63) | 8.80 (0.44, 231.00) | 1.76 (0.03, 168.70) | 0.04 (0.00, 1.98) | 0.33 (0.03, 3.66) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin aspart (short acting)-Metformin | 0.46 (0.07, 2.00) | 1.59 (0.02, 172.50) | 0.51 (0.02, 12.49) | 0.32 (0.02, 3.60) | 6.37 (0.28, 179.70) | 1.26 (0.02, 123.00) | 0.03 (0.00, 1.49) | 0.24 (0.02, 2.78) | 0.72 (0.11, 4.04) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Insulin degludec/aspart mix-Metformin | 3.37 (0.02, 3135.00) | 12.91 (0.02, 42000.00) | 4.11 (0.01, 6011.00) | 2.44 (0.01, 2658.00) | 50.76 (0.17, 79410.00) | 10.75 (0.02, 27400.00) | 0.19 (0.00, 450.20) | 1.86 (0.01, 2128.00) | 5.52 (0.03, 6023.00) | 7.86 (0.04, 8307.00) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin degludec-Metformin | 0.51 (0.01, 39.48) | 1.83 (0.00, 869.10) | 0.58 (0.00, 106.20) | 0.36 (0.00, 43.06) | 7.35 (0.05, 1391.00) | 1.49 (0.00, 657.80) | 0.03 (0.00, 10.14) | 0.27 (0.00, 32.77) | 0.81 (0.01, 80.38) | 1.16 (0.01, 120.00) | 0.16 (0.00, 9.91) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin detemir-Metformin | 1.44 (0.03, 71.34) | 5.07 (0.02, 1750.00) | 1.62 (0.01, 202.70) | 1.01 (0.01, 79.68) | 20.52 (0.18, 2735.00) | 4.14 (0.02, 1413.00) | 0.08 (0.00, 19.81) | 0.76 (0.01, 61.10) | 2.31 (0.04, 147.20) | 3.27 (0.05, 224.60) | 0.46 (0.00, 16.57) | 2.84 (0.15, 43.66) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin | 0.79 (0.02, 28.18) | 2.84 (0.01, 818.20) | 0.91 (0.01, 86.46) | 0.56 (0.01, 32.89) | 11.45 (0.13, 1131.00) | 2.25 (0.01, 608.10) | 0.04 (0.00, 8.74) | 0.43 (0.01, 24.60) | 1.27 (0.03, 59.71) | 1.79 (0.03, 92.05) | 0.27 (0.00, 6.00) | 1.62 (0.12, 13.84) | 0.57 (0.11, 2.42) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin-Sulfonylurea | 0.06 (0.01, 0.38) | 0.21 (0.00, 24.66) | 0.07 (0.00, 1.03) | 0.04 (0.00, 0.23) | 0.84 (0.06, 13.39) | 0.17 (0.00, 12.75) | 0.00 (0.00, 0.13) | 0.03 (0.00, 0.14) | 0.10 (0.01, 0.92) | 0.13 (0.01, 1.52) | 0.02 (0.00, 3.66) | 0.12 (0.00, 12.12) | 0.04 (0.00, 3.11) | 0.07 (0.00, 4.54) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Sulfonylurea | 0.26 (0.02, 2.01) | 0.88 (0.01, 96.82) | 0.29 (0.01, 10.11) | 0.18 (0.01, 3.13) | 3.55 (0.09, 138.10) | 0.70 (0.01, 82.69) | 0.01 (0.00, 1.16) | 0.14 (0.01, 2.45) | 0.41 (0.02, 5.25) | 0.57 (0.03, 8.41) | 0.07 (0.00, 16.38) | 0.49 (0.00, 57.24) | 0.17 (0.00, 15.25) | 0.31 (0.00, 21.04) | 4.24 (0.19, 75.58) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin lispro mix 50 and mix 25 | 0.04 (0.00, 0.62) | 0.12 (0.00, 21.53) | 0.04 (0.00, 2.36) | 0.03 (0.00, 0.83) | 0.51 (0.00, 31.88) | 0.10 (0.00, 18.35) | 0.00 (0.00, 0.27) | 0.02 (0.00, 0.64) | 0.06 (0.00, 1.46) | 0.08 (0.00, 2.29) | 0.01 (0.00, 3.28) | 0.07 (0.00, 12.41) | 0.02 (0.00, 3.34) | 0.04 (0.00, 4.60) | 0.62 (0.01, 19.69) | 0.16 (0.00, 1.49) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin lispro mix 50/50-Metformin | 5.99 (0.09, 734.90) | 22.52 (0.06, 13500.00) | 7.07 (0.04, 1811.00) | 4.26 (0.04, 755.00) | 90.38 (0.58, 23120.00) | 18.18 (0.06, 10880.00) | 0.34 (0.00, 169.80) | 3.28 (0.03, 601.30) | 9.72 (0.12, 1496.00) | 13.61 (0.16, 2155.00) | 1.90 (0.00, 178.00) | 11.69 (0.44, 566.20) | 4.06 (0.29, 144.60) | 6.92 (0.94, 211.90) | 102.20 (0.99, 18920.00) | 24.77 (0.20, 5727.00) | 177.20 (1.03, 85900.00) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin-Sulfonylurea | 0.14 (0.01, 1.26) | 0.51 (0.00, 68.62) | 0.16 (0.01, 3.13) | 0.10 (0.01, 0.80) | 2.01 (0.12, 38.90) | 0.40 (0.01, 34.33) | 0.01 (0.00, 0.37) | 0.08 (0.01, 0.51) | 0.23 (0.02, 2.80) | 0.32 (0.02, 4.62) | 0.04 (0.00, 9.50) | 0.28 (0.00, 33.15) | 0.10 (0.00, 8.30) | 0.18 (0.00, 12.21) | 2.33 (0.85, 7.58) | 0.57 (0.03, 16.22) | 3.93 (0.10, 336.60) | 0.02 (0.00, 2.67) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-NPH insulin mix 70/30 | 0.22 (0.00, 5.40) | 0.64 (0.00, 189.40) | 0.23 (0.00, 10.83) | 0.15 (0.00, 3.37) | 2.92 (0.01, 156.40) | 0.54 (0.00, 96.10) | 0.01 (0.00, 1.22) | 0.11 (0.00, 2.83) | 0.33 (0.00, 12.22) | 0.46 (0.00, 18.67) | 0.05 (0.00, 24.47) | 0.36 (0.00, 86.23) | 0.13 (0.00, 23.60) | 0.24 (0.00, 34.54) | 3.55 (0.01, 118.80) | 0.80 (0.00, 51.20) | 5.42 (0.01, 947.60) | 0.03 (0.00, 7.56) | 1.45 (0.00, 59.76) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-NPH insulin-repaglinide | 2.18 (0.13, 73.91) | 8.33 (0.05, 1983.00) | 2.58 (0.05, 217.40) | 1.58 (0.05, 78.91) | 32.43 (0.65, 2798.00) | 6.54 (0.05, 1556.00) | 0.13 (0.00, 20.91) | 1.19 (0.03, 63.03) | 3.55 (0.15, 150.60) | 5.02 (0.19, 236.10) | 0.63 (0.00, 294.20) | 4.44 (0.02, 1021.00) | 1.59 (0.01, 275.60) | 2.89 (0.03, 421.00) | 37.56 (1.26, 1868.00) | 8.98 (0.25, 655.00) | 63.61 (1.03, 11130.00) | 0.38 (0.00, 83.31) | 15.89 (0.45, 920.00) | 11.94 (0.13, 10590.00) | | N/A | N/A | N/A | N/A | N/A |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin mix 70/30 | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-NPH insulin-Sulfonylurea | 0.30 (0.02, 1.74) | 1.00 (0.02, 43.28) | 0.32 (0.01, 9.58) | 0.20 (0.01, 2.85) | 3.99 (0.11, 133.60) | 0.78 (0.01, 86.95) | 0.02 (0.00, 1.11) | 0.15 (0.01, 2.26) | 0.46 (0.03, 4.67) | 0.64 (0.04, 7.85) | 0.08 (0.00, 16.43) | 0.54 (0.00, 56.65) | 0.19 (0.00, 14.12) | 0.34 (0.01, 20.94) | 4.79 (0.23, 70.81) | 1.12 (0.06, 20.46) | 7.46 (0.24, 491.90) | 0.05 (0.00, 4.66) | 2.01 (0.08, 36.34) | 1.39 (0.02, 753.40) | 0.12 (0.00, 3.77) | | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone-Sulfonylurea | 0.28 (0.00, 17.02) | 1.00 (0.50, 2.00) | 0.31 (0.00, 47.45) | 0.19 (0.00, 17.87) | 4.01 (0.02, 587.00) | 0.80 (0.00, 305.90) | 0.02 (0.00, 4.32) | 0.15 (0.00, 13.96) | 0.45 (0.00, 34.58) | 0.62 (0.01, 53.08) | 0.08 (0.00, 51.06) | 0.55 (0.00, 196.00) | 0.20 (0.00, 54.12) | 0.36 (0.00, 80.29) | 4.72 (0.04, 424.90) | 1.14 (0.01, 116.10) | 8.04 (0.05, 1778.00) | 0.04 (0.00, 16.77) | 1.98 (0.02, 204.80) | 1.55 (0.01, 1745.00) | 0.12 (0.00, 18.97) | 1.01 (0.02, 41.25) | | N/A | N/A | N/A |
| Metformin-repaglinide-Sulfonylurea | 0.11 (0.00, 14.91) | 0.42 (0.01, 5.44) | 0.12 (0.00, 37.31) | 0.07 (0.00, 15.59) | 1.55 (0.00, 483.70) | 0.31 (0.00, 225.10) | 0.01 (0.00, 3.21) | 0.06 (0.00, 11.90) | 0.17 (0.00, 29.91) | 0.24 (0.00, 46.48) | 0.03 (0.00, 36.81) | 0.21 (0.00, 142.90) | 0.07 (0.00, 40.84) | 0.13 (0.00, 58.95) | 1.81 (0.01, 366.90) | 0.44 (0.00, 90.19) | 3.10 (0.01, 1365.00) | 0.02 (0.00, 11.59) | 0.76 (0.00, 177.10) | 0.62 (0.00, 1092.00) | 0.05 (0.00, 14.15) | 0.40 (0.00, 37.54) | 0.42 (0.01, 6.12) | | N/A | N/A |
| Metformin-Sitagliptin-Sulfonylurea | 0.10 (0.00, 13.61) | 0.40 (0.01, 5.89) | 0.12 (0.00, 34.71) | 0.07 (0.00, 14.81) | 1.52 (0.00, 454.70) | 0.29 (0.00, 198.80) | 0.01 (0.00, 3.01) | 0.05 (0.00, 11.60) | 0.17 (0.00, 28.45) | 0.23 (0.00, 41.72) | 0.03 (0.00, 31.03) | 0.20 (0.00, 126.40) | 0.07 (0.00, 36.10) | 0.13 (0.00, 57.94) | 1.79 (0.01, 335.20) | 0.43 (0.00, 88.11) | 3.06 (0.01, 1317.00) | 0.02 (0.00, 10.34) | 0.73 (0.00, 161.10) | 0.59 (0.00, 994.00) | 0.04 (0.00, 14.41) | 0.38 (0.00, 35.10) | 0.40 (0.01, 5.30) | 0.95 (0.01, 73.01) | | N/A |
| NPH insulin | 0.20 (0.04, 0.70) | 0.67 (0.01, 67.47) | 0.22 (0.01, 3.97) | 0.14 (0.02, 0.99) | 2.65 (0.19, 55.24) | 0.53 (0.01, 45.94) | 0.01 (0.00, 0.47) | 0.10 (0.01, 0.75) | 0.31 (0.04, 1.87) | 0.43 (0.06, 3.25) | 0.06 (0.00, 9.91) | 0.38 (0.00, 32.40) | 0.13 (0.00, 8.58) | 0.24 (0.01, 12.11) | 3.08 (0.68, 19.04) | 0.75 (0.06, 12.49) | 5.14 (0.23, 317.60) | 0.03 (0.00, 2.71) | 1.32 (0.20, 10.79) | 0.90 (0.03, 418.30) | 0.09 (0.00, 1.92) | 0.67 (0.07, 9.83) | 0.67 (0.01, 64.60) | 1.76 (0.01, 466.50) | 1.82 (0.01, 503.70) | |
| NPH insulin-Sulfonylurea | 0.30 (0.02, 1.74) | 0.98 (0.01, 103.90) | 0.32 (0.01, 9.92) | 0.20 (0.01, 2.94) | 4.02 (0.12, 136.60) | 0.78 (0.01, 90.54) | 0.02 (0.00, 1.14) | 0.15 (0.01, 2.27) | 0.46 (0.03, 4.74) | 0.64 (0.04, 7.94) | 0.08 (0.00, 16.99) | 0.55 (0.00, 59.57) | 0.19 (0.00, 15.77) | 0.36 (0.01, 21.56) | 4.78 (0.24, 69.90) | 1.13 (0.42, 2.86) | 7.02 (0.95, 214.70) | 0.05 (0.00, 4.84) | 1.98 (0.08, 36.58) | 1.39 (0.02, 708.30) | 0.13 (0.00, 3.85) | 1.00 (0.07, 16.14) | 0.99 (0.01, 99.28) | 2.58 (0.01, 695.00) | 2.62 (0.01, 756.90) | 1.53 (0.10, 14.13) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 68: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 115: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.000 | 19 (12, 24) |
| Acarbose-Metformin-Sulfonylurea | 0.004 | 12 (2, 26) |
| Biphasic insulin aspart | 0.000 | 18 (5, 26) |
| Biphasic insulin aspart-Metformin | 0.000 | 20 (10, 25) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.114 | 5 (1, 17) |
| Biphasic insulin aspart-Pioglitazone | 0.050 | 13 (1, 26) |
| Biphasic insulin aspart-repaglinide | 0.000 | 26 (14, 27) |
| Exenatide-Metformin-Sulfonylurea | 0.000 | 22 (12, 26) |
| Insulin aspart (short acting) | 0.000 | 16 (6, 24) |
| Insulin aspart (short acting)-Metformin | 0.003 | 14 (4, 23) |
| Insulin degludec/aspart mix-Metformin | 0.008 | 23 (3, 27) |
| Insulin degludec-Metformin | 0.036 | 14 (1, 26) |
| Insulin detemir-Metformin | 0.003 | 20 (4, 26) |
| Insulin glargine-Metformin | 0.004 | 17 (3, 24) |
| Insulin glargine-Metformin-Sulfonylurea | 0.082 | 4 (1, 12) |
| Insulin glargine-Sulfonylurea | 0.003 | 11 (2, 22) |
| Insulin lispro mix 50 and mix 25 | 0.268 | 3 (1, 15) |
| Insulin lispro mix 50/50-Metformin | 0.000 | 25 (8, 27) |
| Liraglutide-Metformin-Sulfonylurea | 0.006 | 8 (2, 19) |
| Metformin-NPH insulin mix 70/30 | 0.119 | 10 (1, 25) |
| Metformin-NPH insulin-repaglinide | 0.002 | 22 (7, 27) |
| Metformin-NPH insulin-Sulfonylurea | 0.005 | 12 (3, 21) |
| Metformin-Pioglitazone-Sulfonylurea | 0.003 | 12 (3, 26) |
| Metformin-repaglinide-Sulfonylurea | 0.146 | 7 (1, 26) |
| Metformin-Sitagliptin-Sulfonylurea | 0.143 | 6 (1, 25) |
| NPH insulin | 0.001 | 9 (3, 17) |

| | Probability best | Median rank (95%CI) |
|---|---|---|
| NPH insulin-Sulfonylurea | 0.000 | 12 (3, 22) |

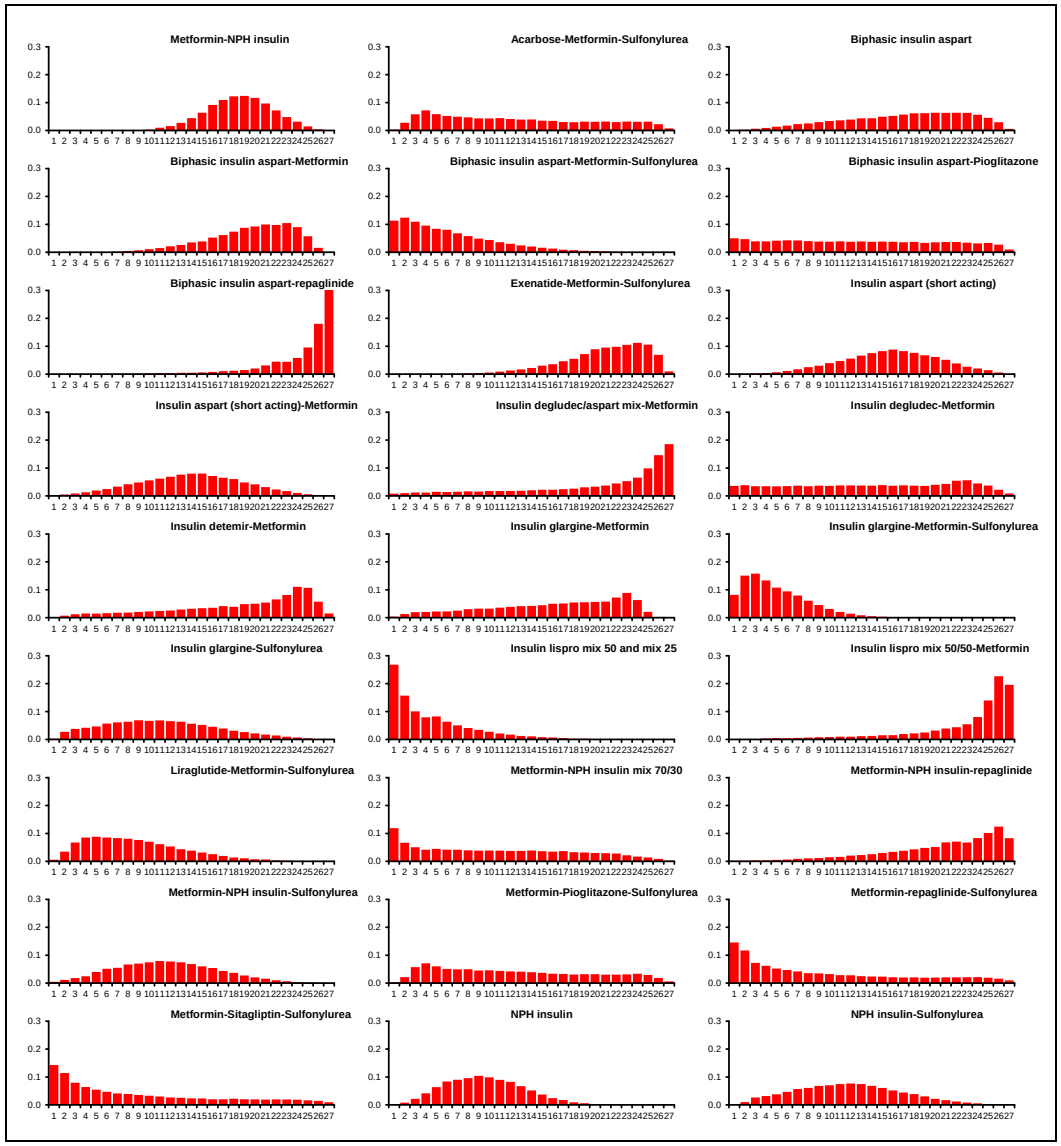



**Figure 69: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rank probability histograms**

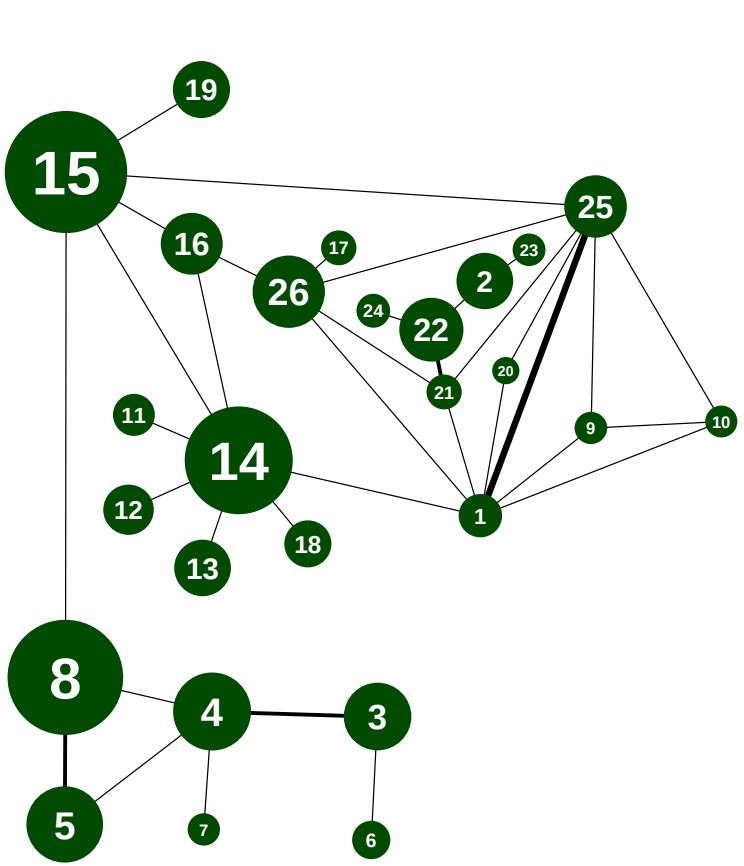
**Table 116: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 63.34<br>(compared to 61 datapoints) | 218.857 | 171.644 | 47.212 | 266.069 | |

**Table 117: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

### J.2.3.4 Total dropouts at study endpoint




1 Metformin-NPH insulin
2 Acarbose-Metformin-Sulfonylurea
3 Biphasic insulin aspart
4 Biphasic insulin aspart-Metformin
5 Biphasic insulin aspart-Metformin-Sulfonylurea
6 Biphasic insulin aspart-Pioglitazone
7 Biphasic insulin aspart-repaglinide
8 Exenatide-Metformin-Sulfonylurea
9 Insulin aspart (short acting)
10 Insulin aspart (short acting)-Metformin
11 Insulin degludec/aspart mix-Metformin
12 Insulin degludec-Metformin
13 Insulin detemir-Metformin
14 Insulin glargine-Metformin
15 Insulin glargine-Metformin-Sulfonylurea
16 Insulin glargine-Sulfonylurea
17 Insulin lispro mix 50 and mix 25
18 Insulin lispro mix 50/50-Metformin
19 Liraglutide-Metformin-Sulfonylurea
20 Metformin-NPH insulin-repaglinide
21 Metformin-NPH insulin-Sulfonylurea
22 Metformin-Pioglitazone-Sulfonylurea
23 Metformin-repaglinide-Sulfonylurea
24 Metformin-Sitagliptin-Sulfonylurea
25 NPH insulin
26 NPH insulin-Sulfonylurea

*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 70: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – evidence network**

**Table 118: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – input data**

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zinman et al. (2011) - 0.31yr | | | | | | | | | | | | 22/183 | | 6/62 | | | | | | | | | | | | |
| Heise et al. (2011) - 0.31yr | | | | | | | | | | | 10/118 | | | 5/60 | | | | | | | | | | | | |
| Gram et al. (2011) - 1.99yr | 8/45 | | | | | | | | 15/48 | 7/45 | | | | | | | | | | | | | | | 6/46 | |
| Derosa et al. (2010) - 0.73yr | | 39/175 | | | | | | | | | | | | | | | | | | | | 37/175 | | | | |
| Lund et al. (2009) - 1.00yr | | | | 1/52 | | | 3/49 | | | | | | | | | | | | | | | | | | | |
| Hartemann-Heurtier et al. (2009) - 0.46yr | | | | | | | | | | | | | | | | | | | | | 1/14 | 1/14 | | | | |
| Russell-Jones et al. (2009) - 0.50yr | | | | | | | | | | | | | | | 13/232 | | | | 23/230 | | | | | | | |
| Milicevic et al. (2009) - 0.46yr | | | | | | | | | | | | | | | | | 16/68 | | | | | | | | | 12/67 |
| Derosa et al. (2009) - 0.29yr | | 3/52 | | | | | | | | | | | | | | | | | | | | | 1/51 | | | |
| Bergenstal et al. (2009) - 0.46yr | | | | 24/124 | 20/124 | | | 37/124 | | | | | | | | | | | | | | | | | | |
| Civera et al. (2008) - 0.46yr | 0/12 | | | | | | | | | | | | | | | | | | | 1/12 | | | | | 1/13 | |
| Ushakova et al. (2007) - 0.31yr | | | | | | | | | | | | | | 22/158 | | | | 15/157 | | | | | | | | |
| Robbins et al. (2007) - 0.46yr | | | | | 25/248 | | | 54/253 | | | | | | | | | | | | | | | | | | |
| Nauck et al. (2007) - 1.00yr | | | | | | | | | | | | | | | | 13/231 | | | | | | | | | | 6/250 |
| Eliaschewitz et al. (2006) - 0.46yr | 1/49 | | | | | | | | | | | | | 1/61 | | | | | | | | | | | | |
| Yki-Jarvinen et al. (2006) - 0.69yr | | | 8/97 | | | 7/93 | | | | | | | | | | | | | | | | | | | | |
| Raz et al. (2005) - 0.34yr | | | | | | | | | | | | | | | 7/177 | | | | | | | | | | 28/187 | |
| Janka et al. (2005) - 0.46yr | | | | | | | | | | | | | | | | | | | | | 3/31 | 1/31 | | | | |
| Heine et al. (2005) - 0.50yr | | | 6/107 | 11/108 | | | | | | | | | | | | | | | | | | | | | | |
| Aljabri et al. (2004) - 0.31yr | | | | | | | | | | | | | | | | | | | | | | 8/60 | | 6/60 | | |
| Kvapil et al. (2006) - 0.31yr | | | 4/104 | 5/100 | | | | | | | | | | | | | | | | | | | | | | |
| Yki-JaÝˆrvinen et al. (1999) - 1.00yr | | | | | | | | 54/282 | | | | | | | 25/267 | | | | | | | | | | | |
| Liu et al. (2013) - 0.46yr | 5/24 | | | | | | | | | | | | | | | | | | | | 1/24 | | | | 0/24 | 2/24 |
| Meneghini et al. (2013) - 0.50yr | | | | | | | | | | | | | 38/228 | 41/229 | | | | | | | | | | | | |
| Park et al. (2014) - 0.54yr | | | | | | | | | | | | | | 7/33 | 8/32 | 7/34 | | | | | | | | | | |

*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms*

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart- | Biphasic insulin aspart- | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin determir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin- | Metformin-NPH insulin- | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide- | Metformin-Sitagliptin- | NPH insulin | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *have been pooled here, whereas each arm is entered separately into the NMAs.* | | | | | | | | | | | | | | | | | | | | | | | | | | |

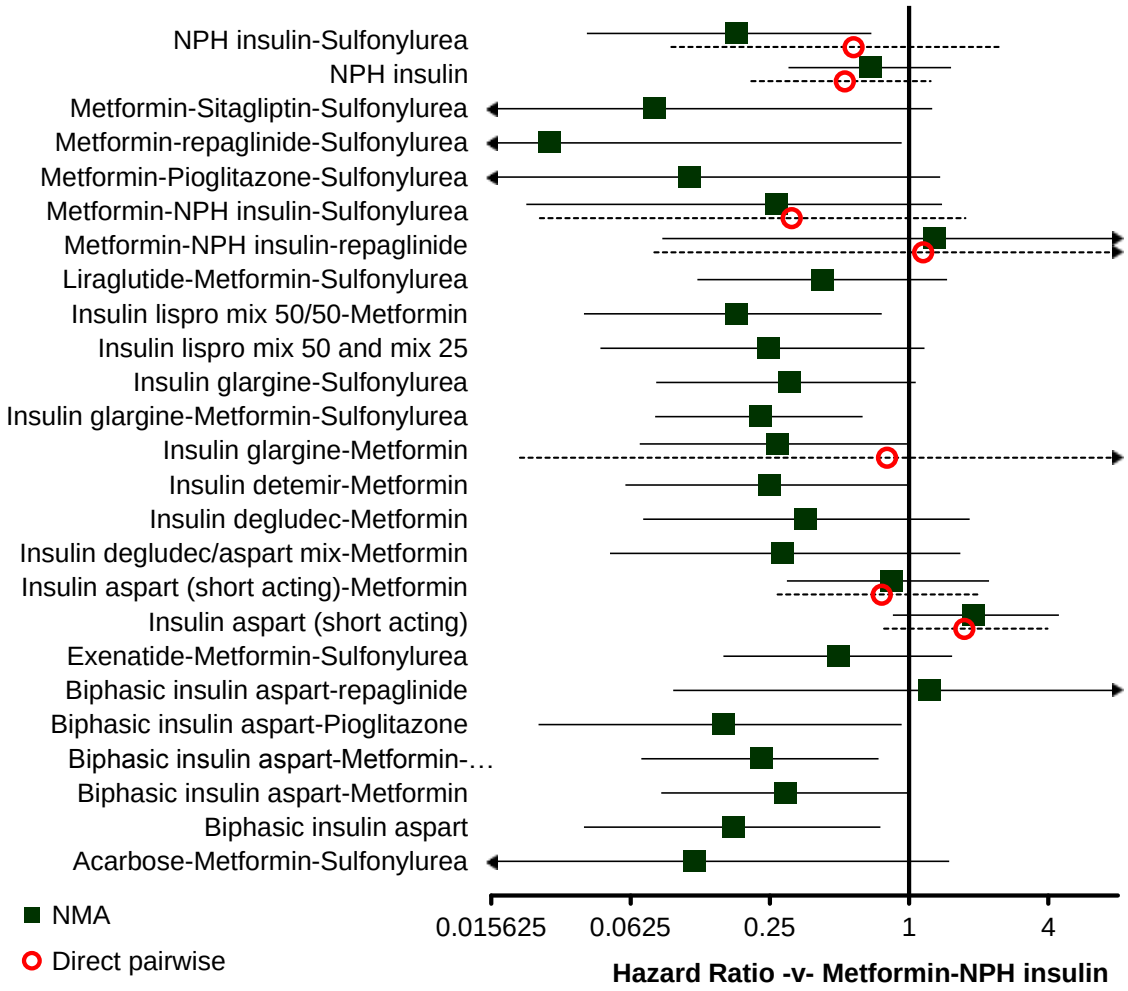
**Table 119: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin determir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acarbose-Metformin-Sulfonylurea | 0.12 (0.01, 1.49) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart | 0.17 (0.04, 0.75) | 1.48 (0.09, 43.68) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin | 0.29 (0.08, 0.99) | 2.49 (0.16, 65.37) | 1.67 (0.75, 3.83) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.23 (0.07, 0.74) | 1.94 (0.13, 50.37) | 1.31 (0.51, 3.52) | 0.78 (0.46, 1.37) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Pioglitazone | 0.16 (0.02, 0.93) | 1.35 (0.06, 45.69) | 0.90 (0.31, 2.55) | 0.54 (0.14, 1.98) | 0.69 (0.16, 2.83) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-repaglinide | 1.23 (0.10, 47.17) | 11.43 (0.30, 1153.00) | 7.11 (0.65, 246.30) | 4.16 (0.45, 138.70) | 5.30 (0.53, 178.30) | 7.97 (0.56, 311.10) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide- | 0.50 | 4.24 | 2.83 | 1.69 | 2.16 | 3.14 | 0.41 | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | (0.16, 1.53) | (0.28, 105.30) | (1.12, 7.49) | (1.05, 2.83) | (1.52, 3.12) | (0.79, 13.23) | (0.01, 4.09) | | | | | | | | | | | | | | | | | | |
| Insulin aspart (short acting) | 1.91 (0.85, 4.44) | 16.32 (1.15, 404.50) | 10.96 (2.40, 51.78) | 6.57 (1.85, 24.73) | 8.37 (2.40, 30.13) | 12.15 (1.94, 80.82) | 1.55 (0.04, 20.83) | 3.86 (1.17, 13.08) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin aspart (short acting)-Metformin | 0.84 (0.30, 2.22) | 7.11 (0.48, 187.60) | 4.80 (0.94, 24.91) | 2.87 (0.69, 12.03) | 3.65 (0.91, 14.58) | 5.31 (0.78, 38.04) | 0.67 (0.02, 9.93) | 1.69 (0.44, 6.40) | 0.44 (0.16, 1.07) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin degludec/aspart mix-Metformin | 0.29 (0.05, 1.67) | 2.44 (0.12, 79.60) | 1.64 (0.26, 11.08) | 0.98 (0.19, 5.47) | 1.25 (0.25, 6.61) | 1.82 (0.22, 15.73) | 0.23 (0.01, 4.08) | 0.58 (0.12, 2.96) | 0.15 (0.02, 0.93) | 0.34 (0.05, 2.36) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin degludec-Metformin | 0.36 (0.07, 1.83) | 3.06 (0.17, 95.42) | 2.05 (0.36, 12.63) | 1.23 (0.26, 6.03) | 1.56 (0.34, 7.35) | 2.29 (0.30, 18.41) | 0.28 (0.01, 4.53) | 0.72 (0.16, 3.24) | 0.19 (0.03, 1.04) | 0.43 (0.07, 2.67) | 1.25 (0.29, 5.38) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin detemir-Metformin | 0.25 (0.06, 0.98) | 2.12 (0.13, 59.42) | 1.42 (0.30, 6.89) | 0.85 (0.23, 3.26) | 1.08 (0.30, 3.90) | 1.58 (0.24, 10.57) | 0.20 (0.01, 2.80) | 0.50 (0.15, 1.71) | 0.13 (0.03, 0.57) | 0.30 (0.06, 1.48) | 0.87 (0.25, 2.81) | 0.70 (0.23, 1.84) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin | 0.27 (0.07, 0.98) | 2.29 (0.15, 62.92) | 1.54 (0.35, 7.02) | 0.92 (0.27, 3.24) | 1.17 (0.35, 3.90) | 1.70 (0.28, 10.86) | 0.22 (0.01, 2.89) | 0.54 (0.17, 1.71) | 0.14 (0.03, 0.57) | 0.32 (0.07, 1.50) | 0.95 (0.29, 2.74) | 0.76 (0.27, 1.79) | 1.08 (0.70, 1.69) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin-Sulfonylurea | 0.23 (0.08, 0.63) | 1.92 (0.14, 48.20) | 1.30 (0.46, 3.80) | 0.78 (0.39, 1.54) | 0.99 (0.54, 1.80) | 1.44 (0.33, 6.51) | 0.19 (0.01, 1.94) | 0.46 (0.28, 0.73) | 0.12 (0.04, 0.35) | 0.27 (0.08, 0.97) | 0.79 (0.17, 3.63) | 0.63 (0.15, 2.56) | 0.92 (0.30, 2.88) | 0.85 (0.30, 2.43) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin glargine-Sulfonylurea | 0.31 (0.08, 1.07) | 2.58 (0.17, 66.72) | 1.73 (0.40, 7.49) | 1.04 (0.31, 3.52) | 1.32 (0.42, 4.19) | 1.93 (0.33, 11.73) | 0.24 (0.01, 3.15) | 0.61 (0.20, 1.83) | 0.16 (0.04, 0.61) | 0.36 (0.08, 1.65) | 1.06 (0.23, 4.59) | 0.85 (0.21, 3.22) | 1.21 (0.41, 3.67) | 1.12 (0.42, 3.07) | 1.33 (0.49, 3.61) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin lispro mix 50 and mix 25 | 0.25 (0.05, 1.17) | 2.12 (0.11, 61.36) | 1.41 (0.23, 8.36) | 0.84 (0.17, 4.12) | 1.07 (0.22, 5.07) | 1.55 (0.20, 12.31) | 0.19 (0.00, 3.18) | 0.49 (0.10, 2.24) | 0.13 (0.02, 0.67) | 0.29 (0.05, 1.71) | 0.85 (0.13, 5.31) | 0.68 (0.11, 3.80) | 0.98 (0.20, 4.61) | 0.91 (0.20, 4.04) | 1.08 (0.25, 4.55) | 0.81 (0.25, 2.55) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Insulin lispro mix 50/50-Metformin | 0.18 (0.04, 0.76) | 1.52 (0.09, 42.71) | 1.02 (0.20, 5.28) | 0.61 (0.15, 2.52) | 0.78 (0.20, 3.05) | 1.13 (0.16, 7.93) | 0.14 (0.00, 2.11) | 0.36 (0.10, 1.34) | 0.09 (0.02, 0.44) | 0.22 (0.04, 1.12) | 0.63 (0.16, 2.20) | 0.51 (0.15, 1.50) | 0.72 (0.32, 1.59) | 0.66 (0.34, 1.28) | 0.79 (0.23, 2.68) | 0.59 (0.18, 1.93) | 0.73 (0.14, 3.75) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin-Sulfonylurea | 0.42 (0.12, 1.46) | 3.57 (0.23, 96.12) | 2.40 (0.69, 8.62) | 1.44 (0.55, 3.89) | 1.84 (0.74, 4.63) | 2.68 (0.54, 14.01) | 0.34 (0.01, 4.11) | 0.85 (0.37, 1.98) | 0.22 (0.06, 0.80) | 0.50 (0.12, 2.16) | 1.48 (0.27, 7.70) | 1.18 (0.24, 5.54) | 1.70 (0.46, 6.47) | 1.57 (0.45, 5.59) | 1.85 (0.94, 3.78) | 1.40 (0.41, 4.65) | 1.73 (0.36, 8.77) | 2.36 (0.59, 9.76) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Metformin-NPH insulin-repaglinide | 1.29 (0.09, | 11.04 (0.28, | 7.32 (0.37, | 4.37 (0.26, | 5.59 (0.33, | 8.09 (0.35, | 0.97 (0.01, | 2.59 (0.15, | 0.67 (0.04, | 1.52 (0.09, | 4.46 (0.20, | 3.53 (0.17, | 5.15 (0.27, | 4.73 (0.26, | 5.67 (0.35, | 4.20 (0.24, | 5.21 (0.26, | 7.15 (0.37, | 3.05 (0.17, | | N/A | N/A | N/A | N/A | N/A |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-Pioglitazone | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin aspart (short acting) | Insulin aspart (short acting)-Metformin | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13.88) | 521.40) | 108.60) | 57.97) | 70.88) | 148.30) | 32.26) | 32.13) | 7.73) | 19.28) | 75.32) | 58.74) | 75.44) | 67.60) | 66.93) | 58.50) | 84.64) | 109.70) | 39.14) | | | | | | |
| Metformin-NPH insulin-Sulfonylurea | 0.27 (0.02, 1.39) | 2.10 (0.36, 17.72) | 1.50 (0.10, 12.56) | 0.90 (0.06, 6.28) | 1.15 (0.09, 7.78) | 1.65 (0.09, 18.20) | 0.20 (0.00, 4.14) | 0.53 (0.04, 3.45) | 0.14 (0.01, 0.83) | 0.31 (0.02, 2.12) | 0.91 (0.05, 9.01) | 0.73 (0.04, 6.70) | 1.06 (0.07, 8.39) | 0.98 (0.07, 7.34) | 1.17 (0.09, 7.01) | 0.87 (0.06, 6.15) | 1.06 (0.07, 9.65) | 1.47 (0.09, 12.28) | 0.63 (0.04, 4.29) | 0.20 (0.01, 4.91) | | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone-Sulfonylurea | 0.11 (0.00, 1.36) | 0.94 (0.60, 1.48) | 0.64 (0.02, 10.63) | 0.38 (0.01, 5.64) | 0.49 (0.02, 6.94) | 0.71 (0.02, 14.40) | 0.08 (0.00, 3.11) | 0.22 (0.01, 3.18) | 0.06 (0.00, 0.77) | 0.13 (0.01, 1.93) | 0.39 (0.01, 7.26) | 0.31 (0.01, 5.26) | 0.44 (0.02, 6.97) | 0.41 (0.02, 6.13) | 0.49 (0.02, 6.45) | 0.37 (0.01, 5.44) | 0.45 (0.02, 8.04) | 0.62 (0.02, 10.31) | 0.26 (0.01, 3.87) | 0.09 (0.00, 3.34) | 0.45 (0.06, 2.50) | | N/A | N/A | N/A |
| Metformin-repaglinide-Sulfonylurea | 0.03 (0.00, 0.93) | 0.26 (0.01, 2.42) | 0.16 (0.00, 6.56) | 0.10 (0.00, 3.60) | 0.12 (0.00, 4.55) | 0.18 (0.00, 8.62) | 0.02 (0.00, 1.70) | 0.06 (0.00, 2.09) | 0.01 (0.00, 0.53) | 0.03 (0.00, 1.26) | 0.10 (0.00, 4.23) | 0.08 (0.00, 3.32) | 0.11 (0.00, 4.51) | 0.10 (0.00, 4.04) | 0.12 (0.00, 4.37) | 0.09 (0.00, 3.50) | 0.11 (0.00, 4.99) | 0.16 (0.00, 6.40) | 0.07 (0.00, 2.52) | 0.02 (0.00, 1.76) | 0.12 (0.00, 2.18) | 0.27 (0.01, 2.72) | | N/A | N/A |
| Metformin-Sitagliptin-Sulfonylurea | 0.08 (0.00, 1.26) | 0.68 (0.20, 2.20) | 0.45 (0.01, 9.46) | 0.27 (0.01, 5.07) | 0.35 (0.01, 6.24) | 0.50 (0.01, 12.71) | 0.06 (0.00, 2.55) | 0.16 (0.01, 2.87) | 0.04 (0.00, 0.71) | 0.09 (0.00, 1.73) | 0.28 (0.01, 6.66) | 0.22 (0.01, 4.78) | 0.32 (0.01, 6.28) | 0.29 (0.01, 5.59) | 0.35 (0.01, 5.97) | 0.26 (0.01, 4.91) | 0.32 (0.01, 7.13) | 0.44 (0.01, 8.91) | 0.19 (0.01, 3.43) | 0.06 (0.00, 2.76) | 0.32 (0.03, 2.42) | 0.72 (0.23, 2.14) | 2.66 (0.20, 95.87) | | N/A |
| NPH insulin | 0.68 (0.30, 1.52) | 5.74 (0.46, 136.50) | 3.89 (1.12, 14.40) | 2.33 (0.88, 6.44) | 2.94 (1.17, 7.75) | 4.32 (0.86, 23.30) | 0.55 (0.02, 6.49) | 1.36 (0.58, 3.36) | 0.36 (0.15, 0.84) | 0.81 (0.29, 2.40) | 2.39 (0.45, 12.21) | 1.90 (0.41, 8.76) | 2.74 (0.77, 10.07) | 2.52 (0.78, 8.67) | 2.97 (1.49, 6.45) | 2.24 (0.73, 7.21) | 2.75 (0.64, 13.32) | 3.80 (0.99, 15.18) | 1.61 (0.59, 4.49) | 0.53 (0.05, 8.06) | 2.55 (0.47, 31.07) | 6.05 (0.50, 136.90) | 24.10 (0.74, 2195.00) | 8.50 (0.55, 231.90) | |
| NPH insulin-Sulfonylurea | 0.18 (0.04, 0.69) | 1.52 (0.09, 41.03) | 1.02 (0.20, 5.02) | 0.61 (0.15, 2.43) | 0.78 (0.19, 2.97) | 1.13 (0.17, 7.65) | 0.14 (0.00, 2.06) | 0.36 (0.09, 1.31) | 0.09 (0.02, 0.40) | 0.21 (0.04, 1.03) | 0.62 (0.11, 3.28) | 0.50 (0.10, 2.31) | 0.72 (0.18, 2.74) | 0.66 (0.18, 2.36) | 0.79 (0.22, 2.62) | 0.59 (0.24, 1.37) | 0.73 (0.34, 1.55) | 0.99 (0.23, 4.19) | 0.42 (0.10, 1.67) | 0.14 (0.01, 2.59) | 0.68 (0.09, 9.52) | 1.61 (0.10, 42.15) | 6.42 (0.16, 638.00) | 2.22 (0.11, 69.53) | 0.26 (0.07, 0.92) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 0 favour metformin- NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 71: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 120: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.000 | 23 (17, 25) |
| Acarbose-Metformin-Sulfonylurea | 0.009 | 5 (2, 24) |
| Biphasic insulin aspart | 0.025 | 8 (2, 18) |
| Biphasic insulin aspart-Metformin | 0.000 | 14 (5, 20) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.003 | 10 (3, 18) |
| Biphasic insulin aspart-Pioglitazone | 0.081 | 7 (1, 21) |
| Biphasic insulin aspart-repaglinide | 0.005 | 24 (5, 26) |
| Exenatide-Metformin-Sulfonylurea | 0.000 | 19 (11, 24) |
| Insulin aspart (short acting) | 0.000 | 25 (22, 26) |
| Insulin aspart (short acting)-Metformin | 0.000 | 22 (11, 25) |
| Insulin degludec/aspart mix-Metformin | 0.014 | 13 (2, 24) |
| Insulin degludec-Metformin | 0.003 | 16 (4, 25) |
| Insulin detemir-Metformin | 0.003 | 11 (3, 21) |
| Insulin glargine-Metformin | 0.000 | 13 (4, 20) |
| Insulin glargine-Metformin-Sulfonylurea | 0.002 | 10 (4, 17) |
| Insulin glargine-Sulfonylurea | 0.001 | 14 (5, 22) |
| Insulin lispro mix 50 and mix 25 | 0.015 | 11 (2, 23) |
| Insulin lispro mix 50/50-Metformin | 0.038 | 8 (1, 18) |
| Liraglutide-Metformin-Sulfonylurea | 0.000 | 17 (7, 24) |
| Metformin-NPH insulin-repaglinide | 0.010 | 24 (3, 26) |
| Metformin-NPH insulin-Sulfonylurea | 0.005 | 12 (3, 24) |
| Metformin-Pioglitazone-Sulfonylurea | 0.013 | 4 (2, 23) |
| Metformin-repaglinide-Sulfonylurea | 0.610 | 1 (1, 21) |
| Metformin-Sitagliptin-Sulfonylurea | 0.130 | 3 (1, 22) |
| NPH insulin | 0.000 | 21 (14, 24) |
| NPH insulin-Sulfonylurea | 0.033 | 8 (1, 18) |

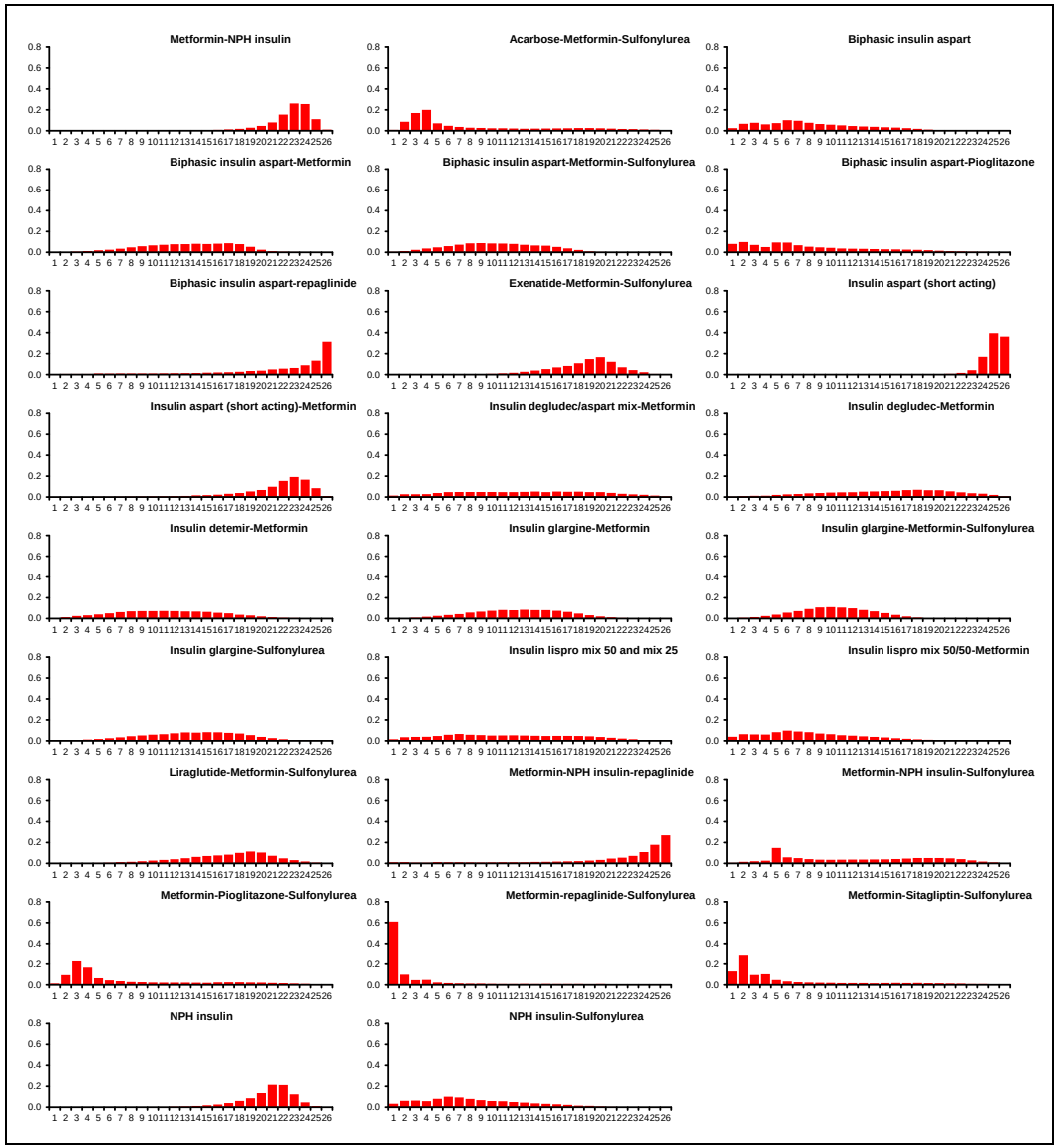



**Figure 72: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rank probability histograms**

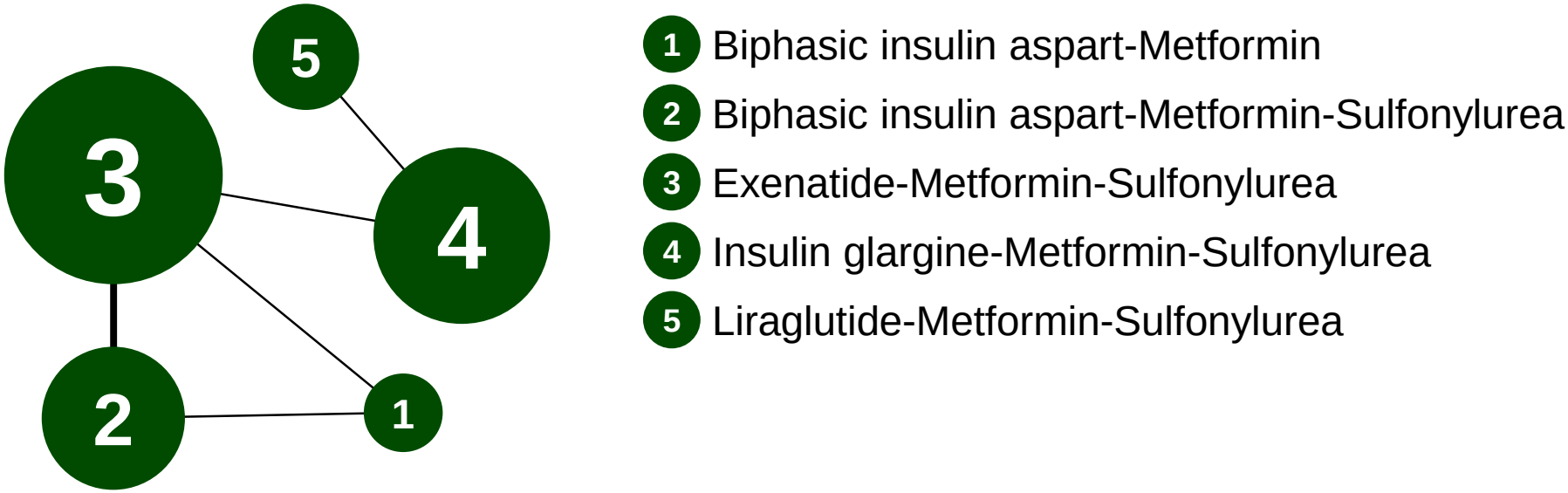
**Table 121: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 65.34<br>(compared to 60 datapoints) | 284.271 | 235.257 | 49.013 | 333.284 | |

**Table 122: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

### J.2.3.5 Nausea at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 73: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – evidence network**

**Table 123: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – input data**

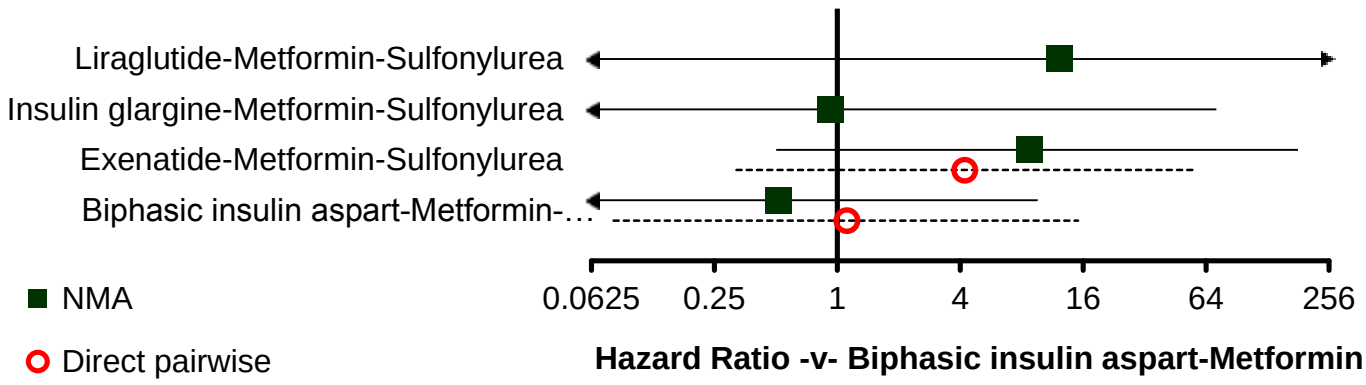
| | **Biphasic insulin aspart-Metformin** | **Biphasic insulin aspart-Metformin-Sulfonylurea** | **Exenatide-Metformin-Sulfonylurea** | **Insulin glargine-Metformin-Sulfonylurea** | **Liraglutide-Metformin-Sulfonylurea** |
|---|---|---|---|---|---|
| Russell-Jones et al. (2009) - 0.50yr | | | | 3/232 | 32/230 |
| Bergenstal et al. (2009) - 0.46yr | 10/124 | 11/124 | 36/124 | | |
| Nauck et al. (2007) - 1.00yr | | 1/248 | 84/253 | | |
| Heine et al. (2005) - 0.50yr | | | 161/282 | 23/267 | |

*Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 124: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin glargine-Metformin-Sulfonylurea | Liraglutide-Metformin-Sulfonylurea |
|---|---|---|---|---|---|
| Biphasic insulin aspart-Metformin | | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.52 (0.03, 9.60) | | N/A | N/A | N/A |
| Exenatide-Metformin-Sulfonylurea | 8.78 (0.50, 180.50) | 16.96 (1.81, 199.20) | | N/A | N/A |
| Insulin glargine-Metformin-Sulfonylurea | 0.93 (0.01, 72.03) | 1.79 (0.04, 100.60) | 0.11 (0.00, 2.41) | | N/A |
| Liraglutide-Metformin-Sulfonylurea | 12.36 (0.06, 2925.00) | 23.65 (0.16, 4448.00) | 1.38 (0.02, 143.10) | 13.16 (0.52, 355.20) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour Biphasic insulin aspart-metformin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 74: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 125: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Biphasic insulin aspart-Metformin | 0.222 | 2 (1, 5) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.460 | 2 (1, 4) |
| Exenatide-Metformin-Sulfonylurea | 0.000 | 4 (3, 5) |
| Insulin glargine-Metformin-Sulfonylurea | 0.292 | 2 (1, 4) |
| Liraglutide-Metformin-Sulfonylurea | 0.025 | 5 (1, 5) |

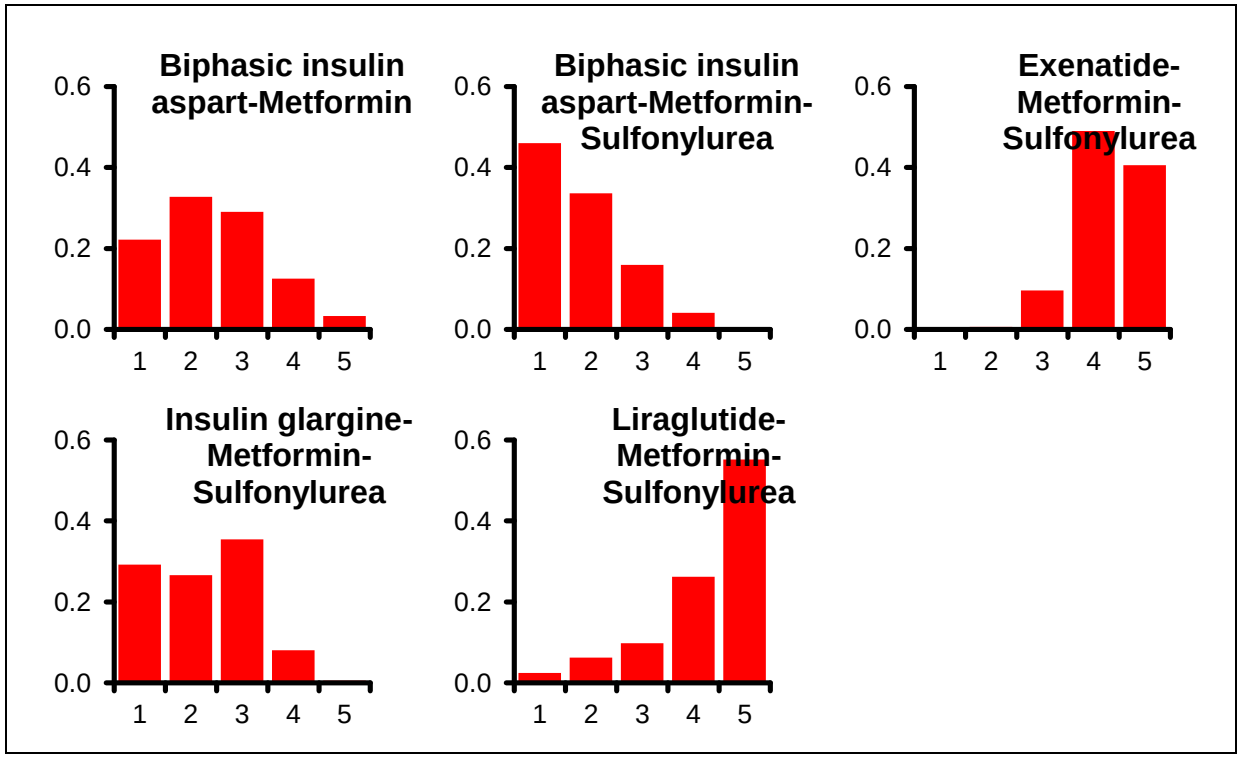



**Figure 75: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rank probability histograms**

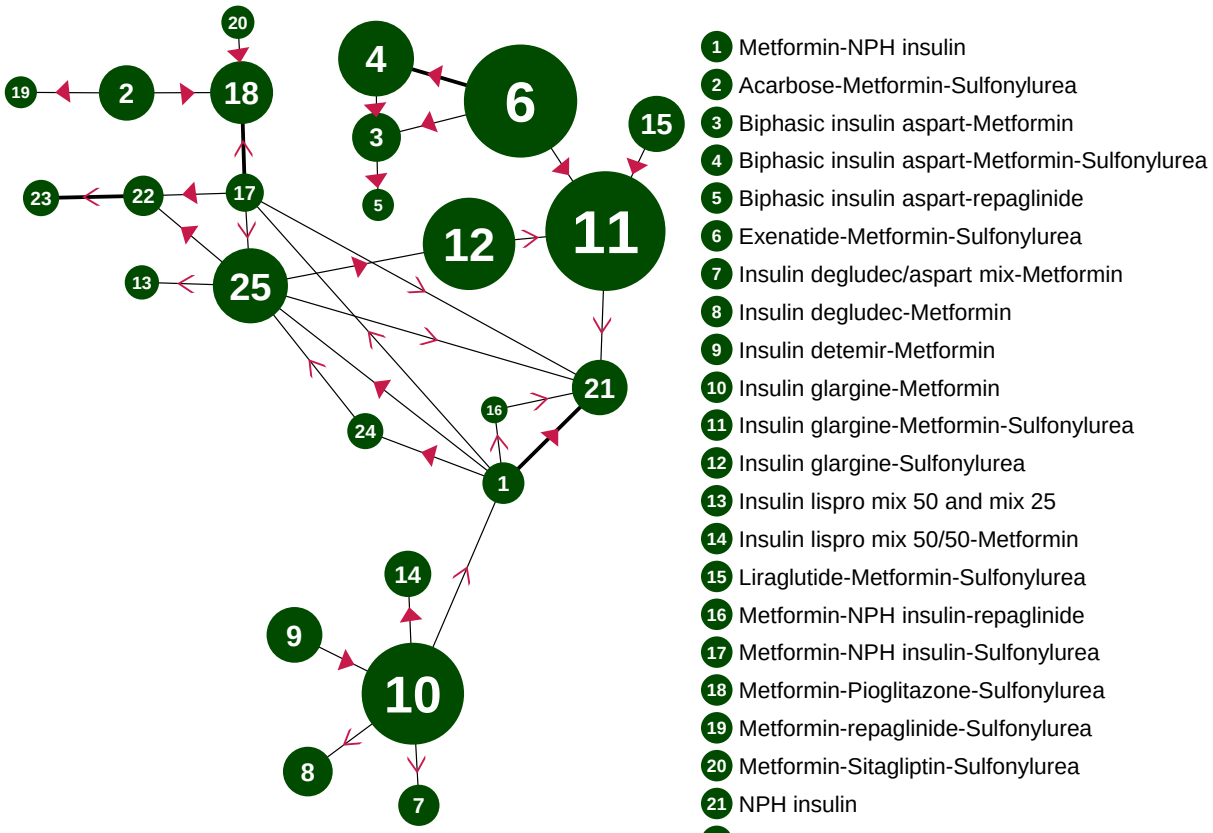
**Table 126: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 9.227<br>(compared to 9 datapoints) | 49.509 | 40.69 | 8.818 | 58.327 | 1.523 (95%CI: 0.694, 1.978) |

**Table 127: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – notes**

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.2.3.6 Change in body weight up to 12 months




1 Metformin-NPH insulin
2 Acarbose-Metformin-Sulfonylurea
3 Biphasic insulin aspart-Metformin
4 Biphasic insulin aspart-Metformin-Sulfonylurea
5 Biphasic insulin aspart-repaglinide
6 Exenatide-Metformin-Sulfonylurea
7 Insulin degludec/aspart mix-Metformin
8 Insulin degludec-Metformin
9 Insulin detemir-Metformin
10 Insulin glargine-Metformin
11 Insulin glargine-Metformin-Sulfonylurea
12 Insulin glargine-Sulfonylurea
13 Insulin lispro mix 50 and mix 25
14 Insulin lispro mix 50/50-Metformin
15 Liraglutide-Metformin-Sulfonylurea
16 Metformin-NPH insulin-repaglinide
17 Metformin-NPH insulin-Sulfonylurea
18 Metformin-Pioglitazone-Sulfonylurea
19 Metformin-repaglinide-Sulfonylurea
20 Metformin-Sitagliptin-Sulfonylurea
21 NPH insulin
22 NPH insulin mix 70/30
23 NPH insulin mix 70/30-Sulfonylurea
24 NPH insulin-repaglinide
25 NPH insulin-Sulfonylurea

*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 76: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – evidence network**

**Table 128: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – input data**

| | Metformin-NPH insulin | Acarbose-Metformin- | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin- | Biphasic insulin aspart-repaglinide | Exenatide-Metformin- | Insulin degludec/aspart | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin- | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin- | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone- | Metformin-repaglinide- | Metformin-Sitagliptin- | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zinman et al. (2011) | | | | | | | | 0.27 (2.36) | | -0.30 (2.40) | | | | | | | | | | | | | | | |
| Heise et al. (2011) | | | | | | | -0.05 (2.25) | | | -0.10 (3.20) | | | | | | | | | | | | | | | |
| Derosa et al. (2010) | | -0.60 (1.34) | | | | | | | | | | | | | | | | 0.90 (1.41) | | | | | | | |
| Lund et al. (2009) | | | 2.22 (3.89) | | 4.73 (3.99) | | | | | | | | | | | | | | | | | | | | |
| Hartemann-Heurtier et al. (2009) | | | | | | | | | | | | | | | | | 2.40 (1.70) | 3.70 (3.50) | | | | | | | |
| Russell-Jones et al. (2009) | | | | | | | | | | | 1.60 (5.03) | | | | -1.80 (5.00) | | | | | | | | | | |
| Milicevic et al. (2009) | | | | | | | | | | | | | 1.42 (3.52) | | | | | | | | | | | | 1.20 (2.50) |
| Derosa et al. (2009) | | -1.40 (1.32) | | | | | | | | | | | | | | | | | 1.70 (1.58) | | | | | | |
| Bergenstal et al. (2009) | | | 4.10 (5.40) | 2.80 (3.60) | | -1.90 (3.80) | | | | | | | | | | | | | | | | | | | |
| Civera et al. (2008) | 1.70 (2.60) | | | | | | | | | | | | | | | 2.90 (2.80) | | | | | 3.00 (2.80) | | | | |
| Robbins et al. (2007) | | | | | | | | | | -0.50 (2.80) | | | | 1.20 (3.20) | | | | | | | | | | | |
| Nauck et al. (2007) | | | | 2.90 (3.15) | | -2.50 (3.18) | | | | | | | | | | | | | | | | | | | |
| Yki-Jarvinen et al. (2006) | 2.60 (2.80) | | | | | | | | | 2.00 (2.34) | | | | | | | | | | | | | | | |
| Janka et al. (2005) | | | | | | | | | | | 1.40 (3.40) | | | | | | | | | | 2.10 (4.20) | | | | |
| Olsson & (2002) | | | | | | | | | | | | | | | | | | | | | | 5.80 (2.69) | | | 1.90 (2.83) |

| | Metformin-NPH insulin | Acarbose-Metformin- | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin- | Biphasic insulin aspart-repaglinide | Exenatide-Metformin- | Insulin degludec/aspart | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin- | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin- | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone- | Metformin-repaglinide- | Metformin-Sitagliptin- | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heine et al. (2005) | | | | | | -2.30 (3.65) | | | | | 1.80 (3.55) | | | | | | | | | | | | | | |
| Aljabri et al. (2004) | | | | | | | | | | | | | | | | | 2.50 (2.80) | 2.60 (4.30) | | | | | | | |
| Goudswaard et al. (2004) | | | | | | | | | | | | | | | | | 1.30 (3.90) | | | | | 4.20 (4.30) | | | |
| Furlong et al. (2002) | 0.90 (2.56) | | | | | | | | | | | | | | | | | | | | | | | 2.70 (2.50) | |
| Furlong et al. (2003) | | | | | | | | | | | | | | | | | | | | | | | | 3.40 (2.56) | 4.10 (3.12) |
| Fritsche A,Schweitzer MA,Haring (2003) | | | | | | | | | | | | 3.80 (4.08) | | | | | | | | | | | | | 2.90 (4.30) |
| Riddle et al. (1992) | | | | | | | | | | | | | | | | | | | | | | 3.30 (3.79) | 4.90 (3.32) | | |
| Riddle & (1998) | | | | | | | | | | | | | | | | | | | | | | 4.00 (3.76) | 4.30 (3.00) | | |
| Yki-JaÝˆrvinen et al. (1999) | 0.90 (5.23) | | | | | | | | | | | | | | | | 3.60 (3.84) | | | | 4.60 (4.90) | | | | 3.90 (3.28) |
| Liu et al. (2013) | | | | | | | | | | | | | | | | | | 1.34 (2.46) | | -0.26 (2.48) | | | | | |
| Meneghini et al. (2013) | | | | | | | | | -0.49 (3.30) | 1.00 (3.10) | | | | | | | | | | | | | | | |
| Park et al. (2014) | | | | | | | | | | | 1.38 (2.97) | 1.26 (2.60) | | | | | | | | | | | | | |

*Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

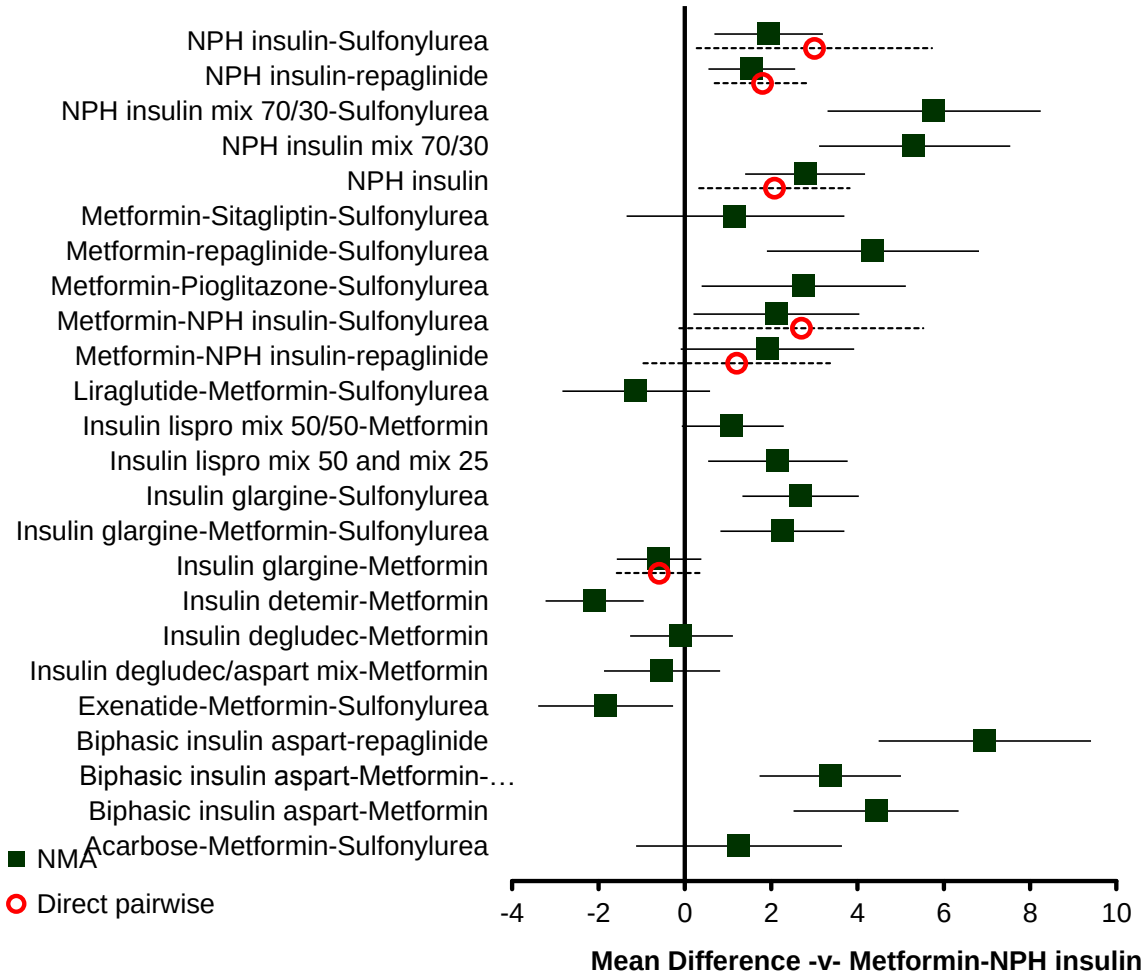
**Table 129: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acarbose-Metformin-Sulfonylurea | 1.26 (-1.13, 3.64) | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 1.50 (1.21, 1.79) | 3.10 (2.53, 3.67) | - | - | - | - | - |
| Biphasic insulin aspart-Metformin | 4.44 (2.52, 6.34) | 3.18 (0.50, 5.85) | | -1.30 (-2.44, -0.16) | 2.51 (0.97, 4.05) | -6.00 (-7.16, -4.84) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 3.38 (1.73, 5.01) | 2.12 (-0.36, 4.61) | -1.05 (-2.15, 0.03) | | - | -5.21 (-5.69, -4.74) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Biphasic insulin aspart-repaglinide | 6.95 (4.49, 9.41) | 5.70 (2.61, 8.79) | 2.51 (0.97, 4.06) | 3.57 (1.71, 5.46) | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Exenatide-Metformin-Sulfonylurea | -1.83 (-3.40, -0.27) | -3.09 (-5.53, -0.66) | -6.27 (-7.37, -5.19) | -5.21 (-5.69, -4.74) | -8.78 (-10.66, -6.90) | | - | - | - | - | 4.10 (3.49, 4.71) | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin degludec/aspart mix-Metformin | -0.54 (-1.87, 0.82) | -1.80 (-4.54, 0.95) | -4.97 (-7.31, -2.65) | -3.91 (-6.03, -1.82) | -7.48 (-10.27, -4.71) | 1.31 (-0.75, 3.35) | | - | - | -0.05 (-0.96, 0.86) | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin degludec-Metformin | -0.09 (-1.27, 1.11) | -1.35 (-4.00, 1.35) | -4.52 (-6.77, -2.27) | -3.47 (-5.49, -1.45) | -7.02 (-9.76, -4.32) | 1.75 (-0.22, 3.68) | 0.45 (-0.68, 1.57) | | - | -0.57 (-1.26, 0.12) | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin detemir-Metformin | -2.09 (-3.23, -0.95) | -3.35 (-5.99, -0.68) | -6.53 (-8.74, -4.29) | -5.48 (-7.48, -3.49) | -9.04 (-11.73, -6.33) | -0.25 (-2.21, 1.65) | -1.56 (-2.64, -0.48) | -2.00 (-2.90, -1.09) | | 1.49 (0.90, 2.08) | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Insulin glargine-Metformin | -0.60 (-1.58, 0.38) | -1.86 (-4.43, 0.74) | -5.04 (-7.18, -2.89) | -3.98 (-5.91, -2.09) | -7.55 (-10.18, -4.90) | 1.24 (-0.61, 3.08) | -0.06 (-0.98, 0.84) | -0.51 (-1.20, 0.17) | 1.49 (0.91, 2.08) | | - | - | - | 1.70 (1.04, 2.36) | - | - | - | - | - | - | - | - | - | - |
| Insulin glargine-Metformin-Sulfonylurea | 2.27 (0.82, 3.70) | 1.01 (-1.35, 3.39) | -2.17 (-3.41, -0.91) | -1.11 (-1.89, -0.34) | -4.68 (-6.66, -2.71) | 4.10 (3.49, 4.70) | 2.80 (0.83, 4.75) | 2.36 (0.50, 4.23) | 4.36 (2.54, 6.21) | 2.87 (1.12, 4.61) | | -0.12 (-1.47, 1.23) | - | - | -3.40 (-4.31, -2.49) | - | - | - | - | - | 0.70 (-0.08, 1.48) | - | - | - |
| Insulin glargine-Sulfonylurea | 2.69 (1.33, 4.03) | 1.43 (-0.82, 3.70) | -1.76 (-3.43, -0.07) | -0.70 (-2.08, 0.67) | -4.27 (-6.53, -2.01) | 4.52 (3.24, 5.80) | 3.22 (1.30, 5.12) | 2.77 (0.96, 4.57) | 4.77 (3.02, 6.56) | 3.28 (1.62, 4.97) | 0.41 (-0.71, 1.53) | | - | - | - | - | - | - | - | - | - | - | - | - |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Insulin lispro mix 50 and mix 25 | 2.16 (0.54, 3.77) | 0.90 (-1.52, 3.34) | -2.28 (-4.29, -0.26) | -1.22 (-2.98, 0.53) | -4.80 (-7.34, -2.26) | 3.99 (2.31, 5.66) | 2.70 (0.60, 4.81) | 2.24 (0.24, 4.25) | 4.25 (2.29, 6.24) | 2.75 (0.88, 4.65) | -0.11 (-1.68, 1.45) | -0.53 (-1.73, 0.68) | | - | - | - | - | - | - | - | - | - | - | - |
| Insulin lispro mix 50/50-Metformin | 1.10 (-0.07, 2.29) | -0.16 (-2.82, 2.53) | -3.34 (-5.59, -1.09) | -2.28 (-4.32, -0.26) | -5.85 (-8.57, -3.12) | 2.93 (0.95, 4.89) | 1.64 (0.53, 2.75) | 1.18 (0.23, 2.14) | 3.19 (2.31, 4.08) | 1.70 (1.04, 2.36) | -1.18 (-3.04, 0.70) | -1.58 (-3.39, 0.23) | -1.05 (-3.06, 0.94) | | - | - | - | - | - | - | - | - | - | - |
| Liraglutide-Metformin-Sulfonylurea | -1.13 (-2.84, 0.58) | -2.38 (-4.91, 0.15) | -5.56 (-7.12, -4.00) | -4.51 (-5.72, -3.31) | -8.07 (-10.24, -5.90) | 0.71 (-0.41, 1.81) | -0.59 (-2.76, 1.58) | -1.04 (-3.13, 1.05) | 0.96 (-1.11, 3.03) | -0.53 (-2.51, 1.45) | -3.40 (-4.31, -2.48) | -3.81 (-5.26, -2.37) | -3.29 (-5.10, -1.48) | -2.22 (-4.33, -0.14) | | - | - | - | - | - | - | - | - | - |
| Metformin-NPH insulin-repaglinide | 1.92 (-0.10, 3.92) | 0.66 (-2.32, 3.65) | -2.52 (-4.96, -0.07) | -1.47 (-3.71, 0.79) | -5.03 (-7.93, -2.13) | 3.75 (1.56, 5.96) | 2.46 (0.05, 4.85) | 2.00 (-0.34, 4.32) | 4.02 (1.71, 6.31) | 2.52 (0.29, 4.74) | -0.35 (-2.47, 1.76) | -0.77 (-2.93, 1.44) | -0.24 (-2.63, 2.19) | 0.83 (-1.49, 3.12) | 3.05 (0.72, 5.38) | | - | - | - | - | 0.10 (-2.10, 2.30) | - | - | - |
| Metformin-NPH insulin-Sulfonylurea | 2.12 (0.20, 4.04) | 0.86 (-0.56, 2.28) | -2.32 (-4.58, -0.03) | -1.27 (-3.28, 0.78) | -4.83 (-7.56, -2.10) | 3.95 (1.99, 5.94) | 2.66 (0.29, 5.00) | 2.21 (-0.07, 4.45) | 4.21 (1.98, 6.47) | 2.73 (0.55, 4.88) | -0.16 (-2.02, 1.75) | -0.56 (-2.32, 1.20) | -0.03 (-2.01, 1.95) | 1.02 (-1.25, 3.27) | 3.24 (1.17, 5.35) | 0.20 (-2.39, 2.84) | | 0.64 (-0.74, 2.02) | - | - | 1.00 (-1.51, 3.51) | 2.90 (0.88, 4.92) | - | - |
| Metformin-Pioglitazone-Sulfonylurea | 2.76 (0.39, 5.12) | 1.50 (1.21, 1.79) | -1.68 (-4.32, 0.99) | -0.62 (-3.09, 1.84) | -4.19 (-7.27, -1.11) | 4.59 (2.18, 7.02) | 3.30 (0.56, 6.03) | 2.85 (0.17, 5.49) | 4.85 (2.20, 7.48) | 3.36 (0.77, 5.92) | 0.49 (-1.86, 2.83) | 0.08 (-2.18, 2.32) | 0.61 (-1.83, 3.00) | 1.66 (-1.02, 4.31) | 3.88 (1.36, 6.41) | 0.83 (-2.13, 3.80) | 0.64 (-0.75, 2.03) | | - | -1.60 (-2.49, -0.71) | - | - | - | - |
| Metformin-repaglinide-Sulfonylurea | 4.36 (1.90, 6.81) | 3.10 (2.52, 3.67) | -0.08 (-2.81, 2.68) | 0.97 (-1.58, 3.53) | -2.59 (-5.73, 0.56) | 6.19 (3.70, 8.69) | 4.90 (2.07, 7.68) | 4.44 (1.69, 7.15) | 6.45 (3.72, 9.16) | 4.95 (2.28, 7.59) | 2.10 (-0.34, 4.52) | 1.67 (-0.67, 4.00) | 2.20 (-0.30, 4.70) | 3.26 (0.51, 5.98) | 5.49 (2.87, 8.08) | 2.44 (-0.61, 5.49) | 2.24 (0.72, 3.77) | 1.60 (0.96, 2.24) | | - | - | - | - | - |
| Metformin-Sitagliptin-Sulfonylurea | 1.15 (-1.35, 3.69) | -0.10 (-1.04, 0.84) | -3.29 (-6.06, -0.48) | -2.23 (-4.85, 0.37) | -5.80 (-9.00, -2.61) | 2.98 (0.43, 5.55) | 1.69 (-1.18, 4.55) | 1.24 (-1.57, 4.02) | 3.25 (0.47, 5.99) | 1.76 (-0.95, 4.45) | -1.12 (-3.62, 1.37) | -1.53 (-3.95, 0.85) | -1.01 (-3.58, 1.55) | 0.06 (-2.73, 2.84) | 2.27 (-0.37, 4.95) | -0.77 (-3.88, 2.31) | -0.97 (-2.60, 0.68) | -1.60 (-2.50, -0.71) | -3.20 (-4.30, -2.11) | | - | - | - | - |
| NPH insulin | 2.79 (1.40, 4.18) | 1.53 (-0.83, 3.89) | -1.65 (-3.09, -0.19) | -0.59 (-1.65, 0.47) | -4.15 (-6.27, -2.06) | 4.63 (3.66, 5.58) | 3.32 (1.40, 5.25) | 2.88 (1.06, 4.71) | 4.88 (3.09, 6.69) | 3.39 (1.70, 5.09) | 0.52 (-0.23, 1.26) | 0.11 (-1.09, 1.30) | 0.63 (-0.95, 2.22) | 1.69 (-0.13, 3.52) | 3.92 (2.74, 5.10) | 0.87 (-1.16, 2.91) | 0.68 (-1.20, 2.54) | 0.03 (-2.29, 2.38) | -1.57 (-3.96, 0.87) | 1.64 (-0.85, 4.14) | | - | - | - |
| NPH insulin mix 70/30 | 5.31 (3.11, 7.54) | 4.06 (1.81, 6.29) | 0.88 (-1.62, 3.42) | 1.94 (-0.36, 4.27) | -1.63 (-4.56, 1.36) | 7.15 (4.90, 9.43) | 5.86 (3.26, 8.44) | 5.40 (2.89, 7.89) | 7.42 (4.91, 9.91) | 5.92 (3.51, 8.34) | 3.04 (0.87, 5.23) | 2.63 (0.61, 4.66) | 3.16 (0.97, 5.37) | 4.23 (1.71, 6.74) | 6.44 (4.11, 8.81) | 3.39 (0.57, 6.18) | 3.20 (1.47, 4.93) | 2.56 (0.35, 4.76) | 0.96 (-1.37, 3.26) | 4.16 (1.78, 6.54) | 2.53 (0.36, 4.69) | | 0.47 (-0.63, 1.56) | - |
| NPH insulin mix 70/30-Sulfonylurea | 5.78 (3.30, 8.25) | 4.53 (2.02, 6.98) | 1.33 (-1.38, 4.09) | 2.39 (-0.18, 4.97) | -1.19 (-4.29, 2.01) | 7.60 (5.10, 10.12) | 6.32 (3.45, 9.12) | 5.86 (3.10, 8.61) | 7.88 (5.13, 10.59) | 6.38 (3.71, 9.03) | 3.49 (1.06, 5.96) | 3.09 (0.79, 5.39) | 3.61 (1.14, 6.11) | 4.68 (1.93, 7.41) | 6.89 (4.31, 9.50) | 3.85 (0.81, 6.88) | 3.66 (1.60, 5.69) | 3.03 (0.54, 5.48) | 1.43 (-1.18, 3.96) | 4.62 (1.99, 7.24) | 2.98 (0.54, 5.41) | 0.45 (-0.63, 1.55) | | - |

| | Metformin-NPH insulin | Acarbose-Metformin-Sulfonylurea | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Biphasic insulin aspart-repaglinide | Exenatide-Metformin-Sulfonylurea | Insulin degludec/aspart mix-Metformin | Insulin degludec-Metformin | Insulin detemir-Metformin | Insulin glargine-Metformin | Insulin glargine-Metformin-Sulfonylurea | Insulin glargine-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Insulin lispro mix 50/50-Metformin | Liraglutide-Metformin-Sulfonylurea | Metformin-NPH insulin-repaglinide | Metformin-NPH insulin-Sulfonylurea | Metformin-Pioglitazone-Sulfonylurea | Metformin-repaglinide-Sulfonylurea | Metformin-Sitagliptin-Sulfonylurea | NPH insulin | NPH insulin mix 70/30 | NPH insulin mix 70/30-Sulfonylurea | NPH insulin-repaglinide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NPH insulin-repaglinide | 1.55 (0.54, 2.56) | 0.29 (-2.07, 2.70) | -2.89 (-4.80, -0.96) | -1.83 (-3.46, -0.19) | -5.40 (-7.85, -2.95) | 3.38 (1.82, 4.96) | 2.09 (0.42, 3.77) | 1.64 (0.06, 3.19) | 3.64 (2.13, 5.17) | 2.15 (0.75, 3.56) | -0.72 (-2.16, 0.74) | -1.14 (-2.35, 0.10) | -0.61 (-2.10, 0.89) | 0.45 (-1.11, 2.01) | 2.68 (0.96, 4.39) | -0.36 (-2.55, 1.79) | -0.58 (-2.47, 1.34) | -1.21 (-3.57, 1.17) | -2.81 (-5.23, -0.34) | 0.39 (-2.11, 2.93) | -1.24 (-2.65, 0.20) | -3.77 (-5.93, -1.59) | -4.22 (-6.65, -1.77) | |
| NPH insulin-Sulfonylurea | 1.94 (0.69, 3.20) | 0.68 (-1.53, 2.88) | -2.50 (-4.22, -0.77) | -1.45 (-2.87, -0.03) | -5.02 (-7.31, -2.72) | 3.77 (2.45, 5.11) | 2.48 (0.63, 4.30) | 2.03 (0.29, 3.76) | 4.03 (2.35, 5.73) | 2.53 (0.94, 4.14) | -0.33 (-1.51, 0.84) | -0.74 (-1.38, -0.11) | -0.22 (-1.25, 0.81) | 0.84 (-0.91, 2.57) | 3.06 (1.57, 4.56) | 0.02 (-2.16, 2.17) | -0.19 (-1.86, 1.50) | -0.82 (-3.01, 1.37) | -2.42 (-4.72, -0.15) | 0.78 (-1.58, 3.13) | -0.86 (-2.08, 0.37) | -3.38 (-5.33, -1.42) | -3.83 (-6.07, -1.60) | 0.39 (-0.71, 1.47) |

*Values given are mean differences in body-weight in kilograms.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 77: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – relative effect of all options versus reference treatment**

**Table 130: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.000 | 7 (4, 9) |
| Acarbose-Metformin-Sulfonylurea | 0.001 | 10 (4, 18) |
| Biphasic insulin aspart-Metformin | 0.000 | 22 (19, 24) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.000 | 20 (14, 22) |
| Biphasic insulin aspart-repaglinide | 0.000 | 25 (22, 25) |
| Exenatide-Metformin-Sulfonylurea | 0.366 | 2 (1, 5) |
| Insulin degludec/aspart mix-Metformin | 0.001 | 5 (2, 9) |
| Insulin degludec-Metformin | 0.000 | 6 (3, 10) |
| Insulin detemir-Metformin | 0.589 | 1 (1, 3) |
| Insulin glargine-Metformin | 0.000 | 4 (2, 7) |
| Insulin glargine-Metformin-Sulfonylurea | 0.000 | 15 (9, 19) |
| Insulin glargine-Sulfonylurea | 0.000 | 17 (12, 20) |
| Insulin lispro mix 50 and mix 25 | 0.000 | 14 (8, 20) |
| Insulin lispro mix 50/50-Metformin | 0.000 | 10 (7, 17) |
| Liraglutide-Metformin-Sulfonylurea | 0.041 | 3 (1, 8) |
| Metformin-NPH insulin-repaglinide | 0.000 | 13 (7, 21) |
| Metformin-NPH insulin-Sulfonylurea | 0.000 | 14 (9, 20) |
| Metformin-Pioglitazone-Sulfonylurea | 0.000 | 18 (10, 21) |
| Metformin-repaglinide-Sulfonylurea | 0.000 | 22 (16, 24) |
| Metformin-Sitagliptin-Sulfonylurea | 0.003 | 10 (3, 18) |
| NPH insulin | 0.000 | 18 (12, 20) |
| NPH insulin mix 70/30 | 0.000 | 23 (20, 25) |
| NPH insulin mix 70/30-Sulfonylurea | 0.000 | 24 (21, 25) |
| NPH insulin-repaglinide | 0.000 | 11 (8, 17) |
| NPH insulin-Sulfonylurea | 0.000 | 13 (9, 17) |

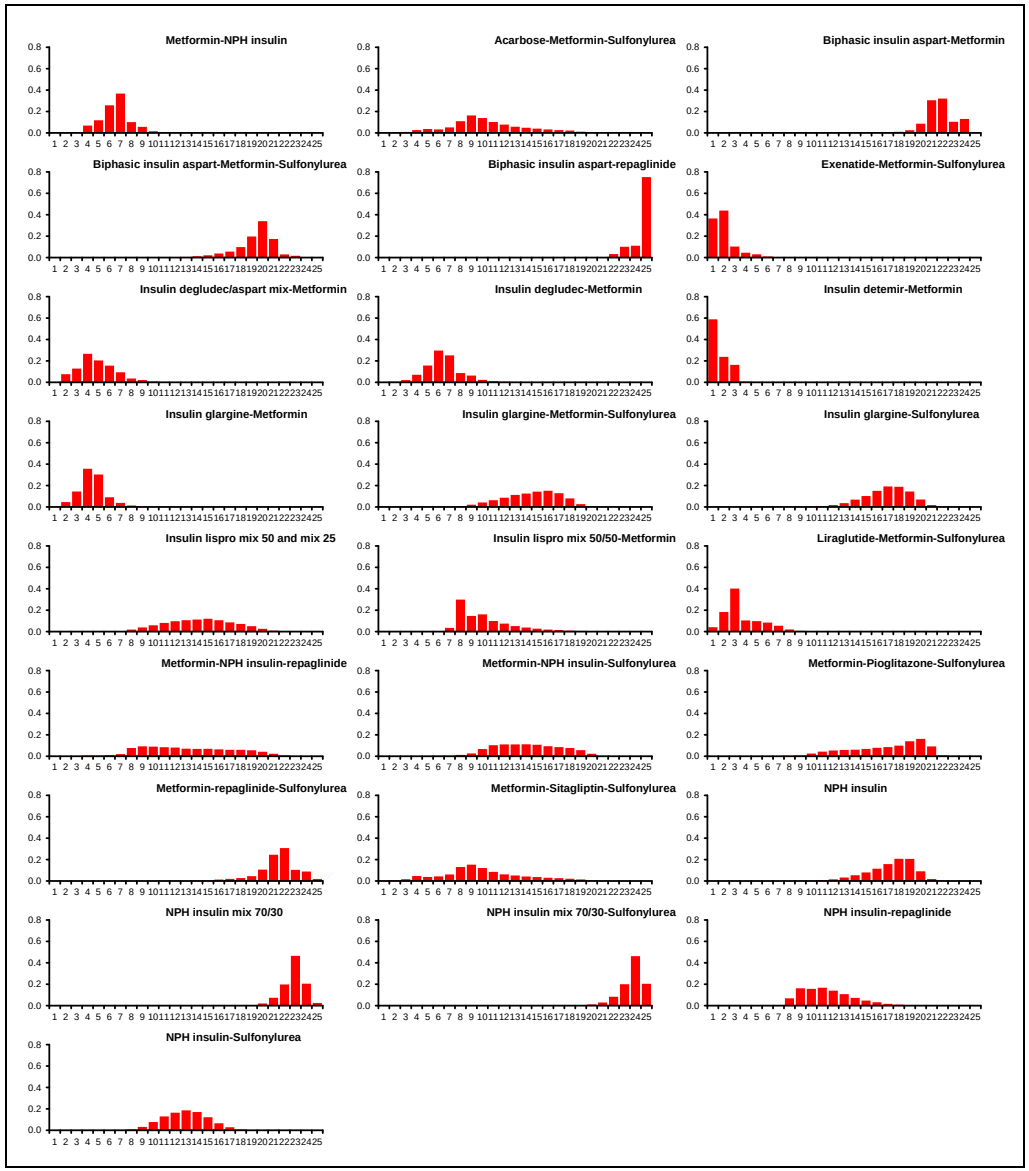



**Figure 78: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – rank probability histograms**

**Table 131: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | |
|---|---|---|---|---|---|
| 64.49<br>(compared to 62 datapoints) | 63.763 | 12.733 | 51.029 | 114.792 | |

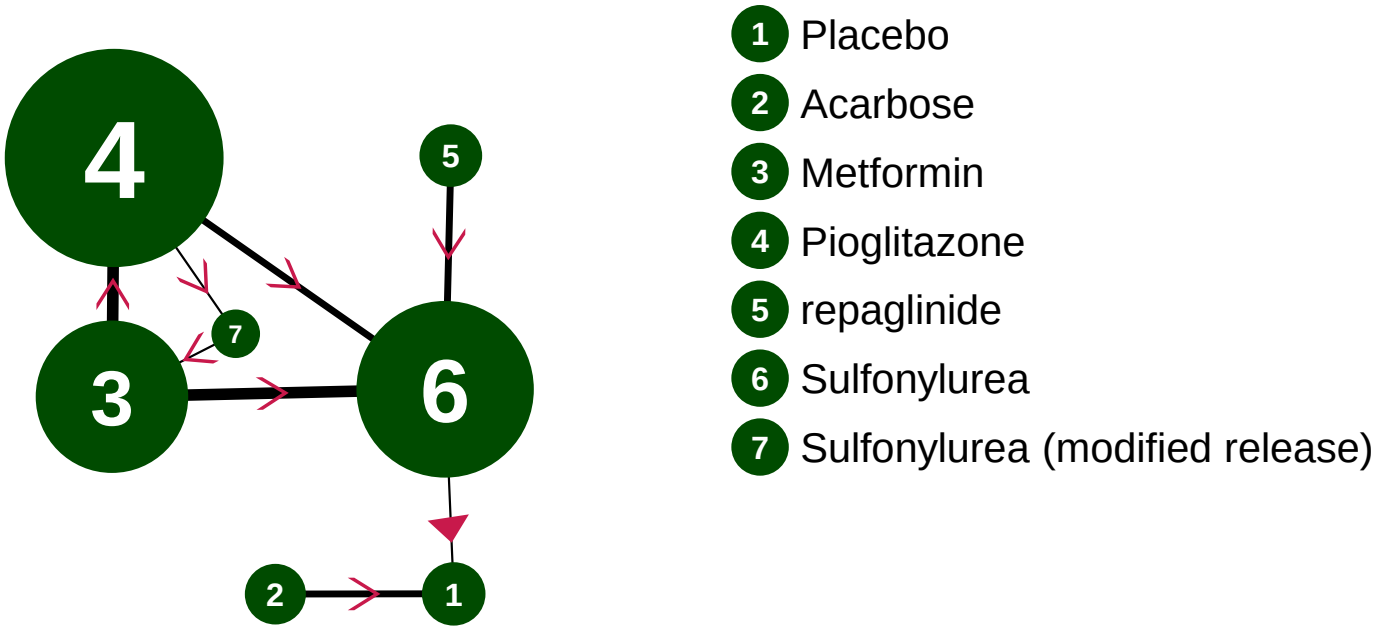
**Table 132: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – notes**

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

# J.3 SENSITIVITY ANALYSES

## J.3.1 RESULTS FOR INITIAL THERAPY – TRULY DRUG NAÏVE INDIVIDUALS

### J.3.1.1 Change in HbA1c at 12 months




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 79: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – evidence network**

**Table 133: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – input data**

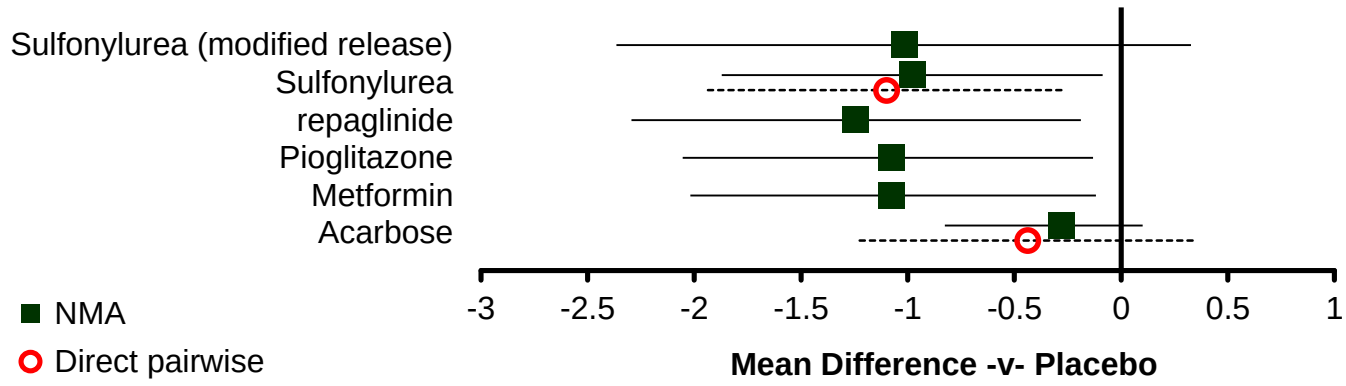
| | Placebo | Acarbose | Metformin | Pioglitazone | repaglinide | Sulfonylurea | Sulfonylurea (modified release) |
|---|---|---|---|---|---|---|---|
| Kirkman et al. (2006) | -0.10 (0.81) | -0.19 (0.92) | | | | | |
| Yoon et al. (2011) | | | -0.92 (0.96) | | | -0.89 (0.76) | |
| Abbatecola et al. (2006) | | | | | -0.75 (1.12) | -0.50 (1.84) | |
| Schernthaner et al. (2004) | | | -1.50 (0.97) | -1.41 (0.97) | | | |
| Campbell et al. (1994) | | | -2.82 (2.15) | | | -2.03 (2.68) | |
| Yamanouchi et al. (2005) | | | -2.10 (1.15) | -2.30 (1.21) | | -2.10 (1.08) | |
| Chiasson JL,Josse RG,Hunt JA,Palmason C,Rodger NW,Ross (1994) | 0.40 (1.09) | -0.50 (1.54) | | | | | |
| Birkeland et al. (1994) | 0.45 (1.30) | | | | | -0.65 (1.51) | |
| Charbonnel et al. (2005) | | | | -1.50 (1.42) | | -1.40 (1.48) | |
| Saleem et al. (2011) | | | | | -1.10 (2.20) | -0.80 (2.07) | |
| Erem et al. (2014) | | | -1.22 (1.20) | -1.57 (1.73) | | | -1.28 (1.67) |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 134: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Metformin | Pioglitazone | repaglinide | Sulfonylurea | Sulfonylurea (modified release) |
|---|---|---|---|---|---|---|---|
| Placebo | | -0.44 (-1.22, 0.35) | - | - | - | -1.10 (-1.94, -0.26) | - |
| Acarbose | -0.28 (-0.83, 0.10) | | - | - | - | - | - |
| Metformin | -1.07 (-2.02, -0.12) | -0.78 (-1.80, 0.31) | | 0.07 (-0.04, 0.18) | - | 0.04 (-0.16, 0.24) | -0.06 (-0.98, 0.86) |
| Pioglitazone | -1.08 (-2.06, -0.13) | -0.79 (-1.81, 0.29) | 0.01 (-0.38, 0.29) | | - | 0.11 (-0.04, 0.26) | 0.29 (-0.79, 1.37) |
| repaglinide | -1.24 (-2.29, -0.19) | -0.95 (-2.07, 0.24) | -0.17 (-0.80, 0.47) | -0.17 (-0.78, 0.51) | | 0.26 (-0.15, 0.68) | - |
| Sulfonylurea | -0.97 (-1.87, -0.09) | -0.68 (-1.65, 0.36) | 0.10 (-0.25, 0.45) | 0.09 (-0.21, 0.50) | 0.27 (-0.28, 0.81) | | - |
| Sulfonylurea (modified release) | -1.01 (-2.37, 0.33) | -0.72 (-2.12, 0.72) | 0.06 (-0.91, 1.03) | 0.06 (-0.90, 1.05) | 0.23 (-0.93, 1.38) | -0.04 (-1.05, 0.97) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 80: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment**

**Table 135: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.000 | 7 (5, 7) |
| Acarbose | 0.023 | 6 (2, 7) |
| Metformin | 0.101 | 3 (1, 5) |
| Pioglitazone | 0.094 | 3 (1, 5) |
| repaglinide | 0.490 | 2 (1, 5) |
| Sulfonylurea | 0.011 | 4 (2, 6) |
| Sulfonylurea (modified release) | 0.281 | 4 (1, 7) |

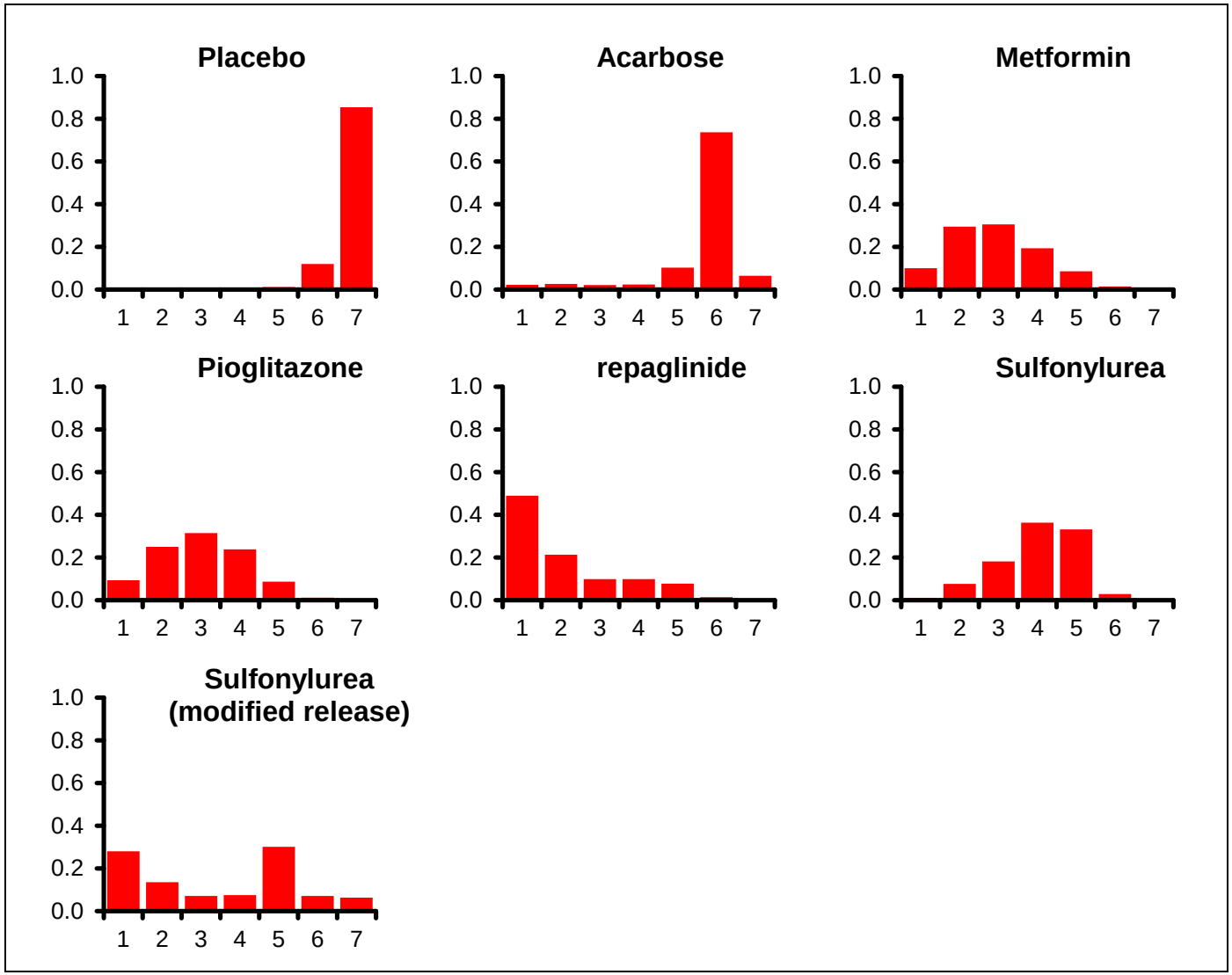



**Figure 81: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – rank probability histograms**

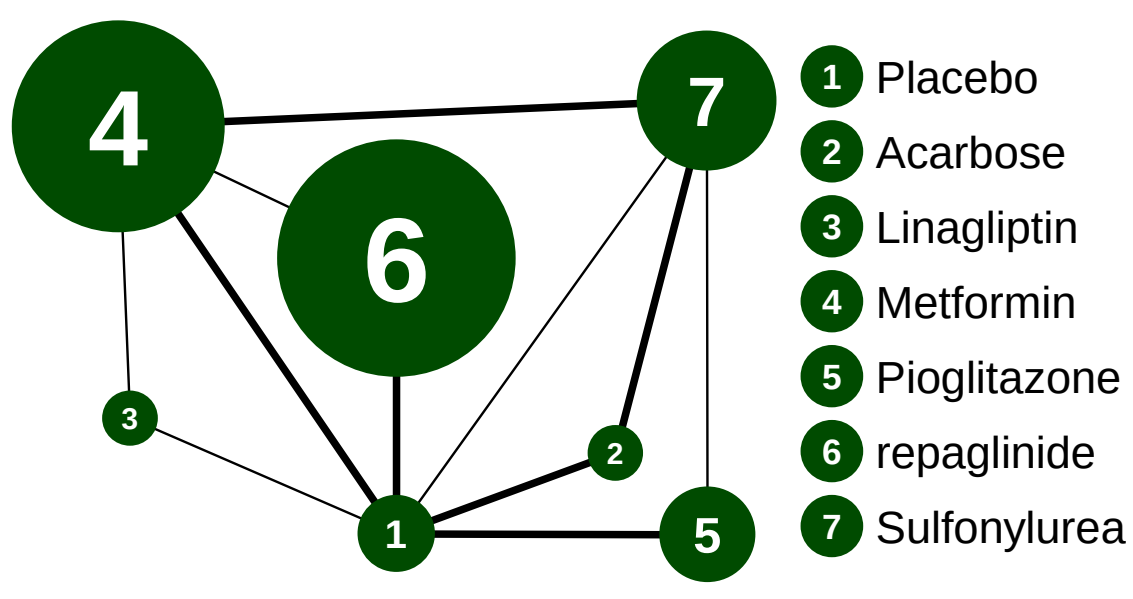
**Table 136: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 25.16<br>(compared to 25 datapoints) | -16.168 | -36.059 | 19.891 | 3.723 | 0.154 (95%CI: 0.008, 0.570) |

**Table 137: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

### J.3.1.2 Hypoglycaemia at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 82: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network**

**Table 138: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data**

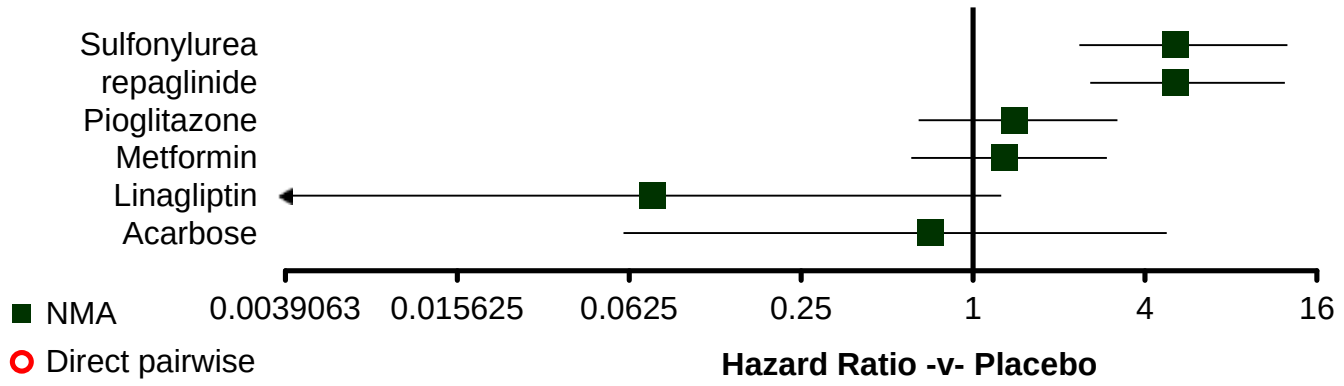
| | Placebo | Acarbose | Linagliptin | Metformin | Pioglitazone | repaglinide | Sulfonylurea |
|---|---|---|---|---|---|---|---|
| Dichotomous proportion data | | | | | | | |
| Yoon et al. (2011) - 0.92yr | | | | 4/114 | | | 23/118 |
| Haak et al. (2012) - 0.46yr | 1/72 | | 0/142 | 7/291 | | | |
| Derosa et al. (2011) - 0.54yr | 0/87 | 0/88 | | | | | |
| Herz et al. (2003) - 0.31yr | 11/96 | | | | 21/191 | | |
| Horton et al. (2000) - 0.46yr | 3/104 | | | 11/104 | | | |
| Jovanovic et al. (2000) - 0.46yr | 8/75 | | | | | 89/286 | |
| Aronoff et al. (2000) - 0.50yr | 0/79 | | | | 4/329 | | |
| Hoffmann & (1994) - 0.46yr | 0/30 | 0/28 | | | | | 2/27 |
| Salman et al. (2001) - 0.46yr | | 0/27 | | | | | 3/30 |
| Viberti et al. (2002) - 3.99yr | | | | 168/1454 | | | 557/1441 |
| Charbonnel et al. (2005) - 1.00yr | | | | | 22/624 | | 63/626 |
| Moses et al. (2001) - 0.31yr | 4/134 | | | | | 44/260 | |
| Count data | | | | | | | |
| Fang et al. (2014) - 0.29yr | | | | 0/2100 | | 10/4147.5 | |

*Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 139: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Placebo | Acarbose | Linagliptin | Metformin | Pioglitazone | repaglinide | Sulfonylurea |
|---|---|---|---|---|---|---|---|
| Placebo | | N/A | N/A | N/A | N/A | N/A | N/A |
| Acarbose | 0.71 (0.06, 4.76) | | N/A | N/A | N/A | N/A | N/A |
| Linagliptin | 0.08 (0.00, 1.25) | 0.10 (0.00, 3.99) | | N/A | N/A | N/A | N/A |
| Metformin | 1.30 (0.61, 2.94) | 1.82 (0.29, 21.87) | 16.86 (1.14, 8532.00) | | N/A | N/A | N/A |
| Pioglitazone | 1.40 (0.64, 3.20) | 1.98 (0.30, 25.17) | 18.50 (1.07, 9188.00) | 1.09 (0.44, 2.62) | | N/A | N/A |
| repaglinide | 5.11 (2.57, 12.34) | 7.46 (1.00, 97.67) | 70.06 (3.85, 36660.00) | 3.96 (1.49, 11.89) | 3.65 (1.30, 11.73) | | N/A |
| Sulfonylurea | 5.14 (2.36, 12.59) | 7.24 (1.26, 85.76) | 67.95 (4.34, 33440.00) | 3.98 (2.18, 7.86) | 3.67 (1.74, 8.51) | 1.01 (0.33, 2.90) | |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 83: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 140: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Placebo | 0.015 | 3 (2, 5) |
| Acarbose | 0.113 | 2 (1, 6) |
| Linagliptin | 0.866 | 1 (1, 3) |
| Metformin | 0.002 | 4 (2, 5) |
| Pioglitazone | 0.004 | 4 (2, 5) |
| repaglinide | 0.000 | 6 (5, 7) |
| Sulfonylurea | 0.000 | 7 (6, 7) |

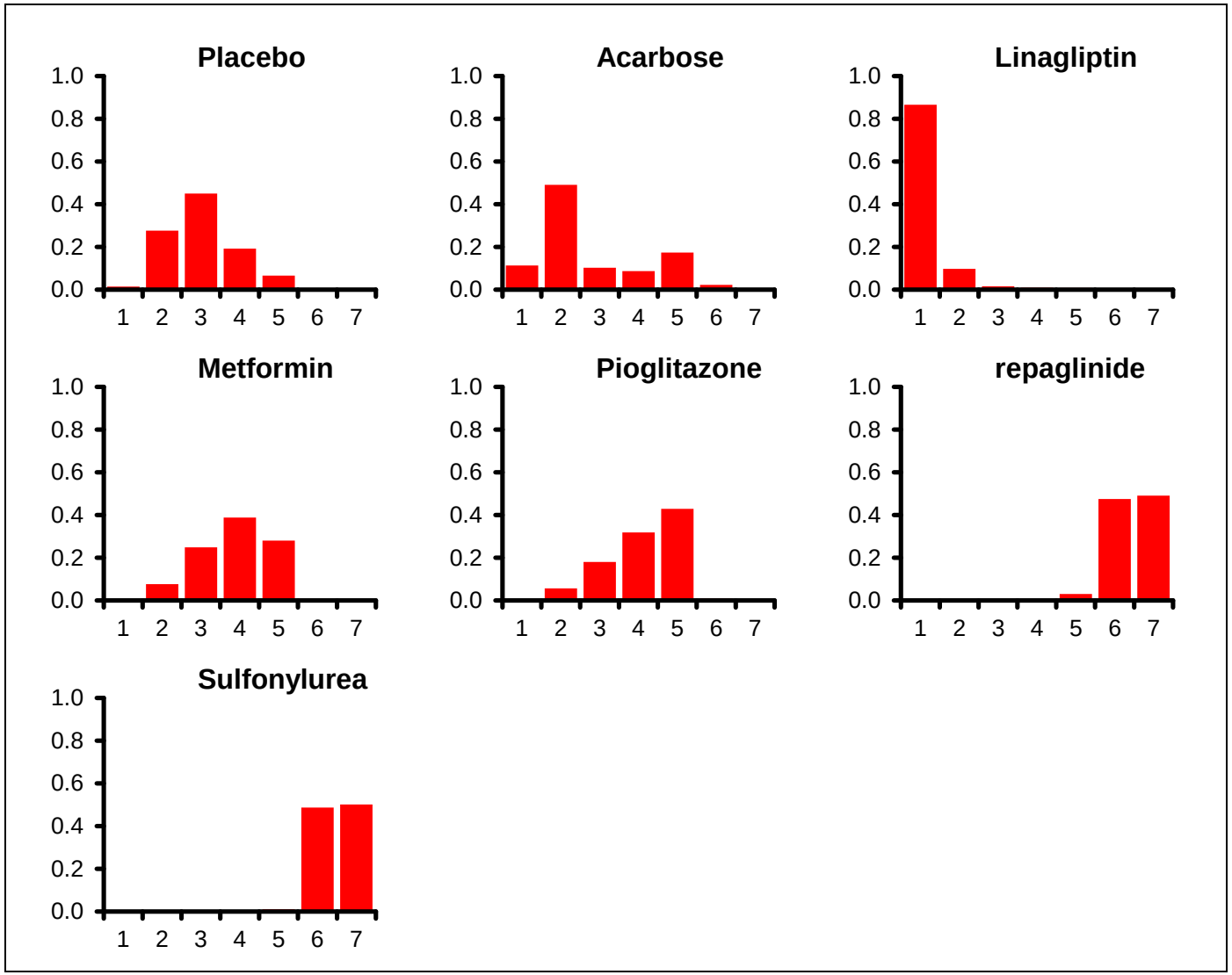



**Figure 84: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms**

**Table 141: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics**

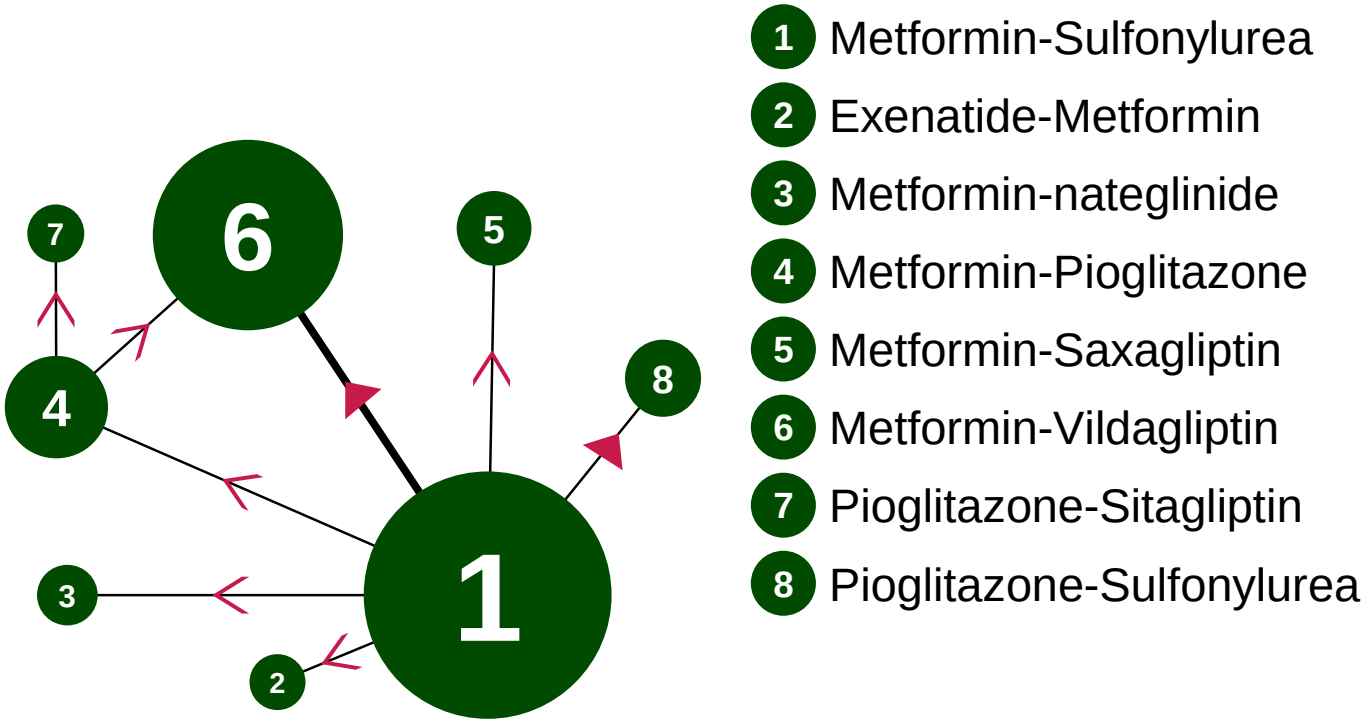
| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 28.2<br>(compared to 31 datapoints) | 129.942 | 109.874 | 20.068 | 158.983 | 0.280 (95%CI: 0.018, 0.919) |

**Table 142: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes**

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

## J.3.2 RESULTS FOR FIRST INTENSIFICATION – PEOPLE PREVIOUSLY ON 1 ORAL ANTIDIABETIC MEDICINE

### J.3.2.1 Change in HbA1c at 12 months




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 85: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – evidence network**

**Table 143: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – input data**

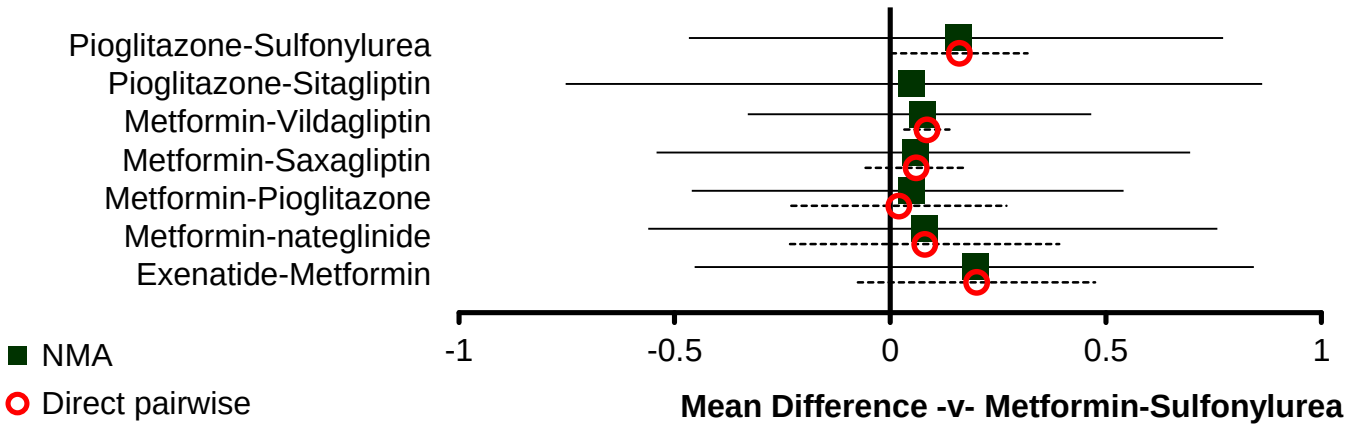
| | Metformin-Sulfonylurea | Exenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|
| Goke et al. (2010) | -0.80 (0.86) | | | | -0.74 (0.57) | | | |
| Derosa et al. (2011) | -1.40 (0.75) | -1.20 (0.65) | | | | | | |
| Filozof & (2010) | -0.85 (1.19) | | | | | -0.81 (1.18) | | |
| Derosa et al. (2010) | | | | -1.40 (0.75) | | | -1.40 (0.84) | |
| Ferrannini et al. (2009) | -0.53 (0.65) | | | | | -0.44 (0.67) | | |
| Bolli et al. (2008) | | | | -0.60 (1.45) | | -0.60 (0.96) | | |
| Ristic et al. (2006) | -0.20 (1.22) | | -0.12 (1.07) | | | | | |
| Matthews et al. (2005) | -1.01 (1.59) | | | -0.99 (1.60) | | | | |
| Hanefeld et al. (2004) | -1.36 (1.02) | | | | | | | -1.20 (1.02) |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 144: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Exenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Vildagliptin | Pioglitazone-Sitagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|
| Metformin-Sulfonylurea | | 0.20 (-0.08, 0.48) | 0.08 (-0.23, 0.39) | 0.02 (-0.23, 0.27) | 0.06 (-0.06, 0.18) | 0.09 (0.03, 0.14) | - | 0.16 (0.00, 0.32) |
| Exenatide-Metformin | 0.20 (-0.45, 0.84) | | - | - | - | - | - | - |
| Metformin-nateglinide | 0.08 (-0.56, 0.76) | -0.12 (-1.02, 0.86) | | - | - | - | - | - |
| Metformin-Pioglitazone | 0.05 (-0.46, 0.54) | -0.15 (-0.99, 0.66) | -0.03 (-0.89, 0.76) | | - | 0.00 (-0.20, 0.20) | 0.00 (-0.27, 0.27) | - |
| Metformin-Saxagliptin | 0.06 (-0.54, 0.70) | -0.14 (-1.01, 0.77) | -0.02 (-0.93, 0.88) | 0.01 (-0.74, 0.82) | | - | - | - |
| Metformin-Vildagliptin | 0.08 (-0.33, 0.47) | -0.13 (-0.90, 0.62) | -0.01 (-0.81, 0.74) | 0.02 (-0.48, 0.51) | 0.01 (-0.75, 0.72) | | - | - |
| Pioglitazone-Sitagliptin | 0.05 (-0.75, 0.86) | -0.15 (-1.18, 0.90) | -0.03 (-1.09, 1.01) | 0.00 (-0.63, 0.66) | -0.01 (-1.04, 1.02) | -0.02 (-0.81, 0.80) | | - |
| Pioglitazone-Sulfonylurea | 0.16 (-0.47, 0.77) | -0.04 (-0.97, 0.84) | 0.08 (-0.86, 0.95) | 0.11 (-0.70, 0.90) | 0.10 (-0.80, 0.96) | 0.09 (-0.67, 0.81) | 0.11 (-0.90, 1.11) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 86: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment**

**Table 145: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.163 | 3 (1, 6) |
| Exenatide-Metformin | 0.067 | 7 (1, 8) |
| Metformin-nateglinide | 0.206 | 5 (1, 8) |
| Metformin-Pioglitazone | 0.091 | 4 (1, 8) |
| Metformin-Saxagliptin | 0.126 | 4 (1, 8) |
| Metformin-Vildagliptin | 0.036 | 5 (1, 7) |
| Pioglitazone-Sitagliptin | 0.259 | 4 (1, 8) |
| Pioglitazone-Sulfonylurea | 0.053 | 6 (1, 8) |

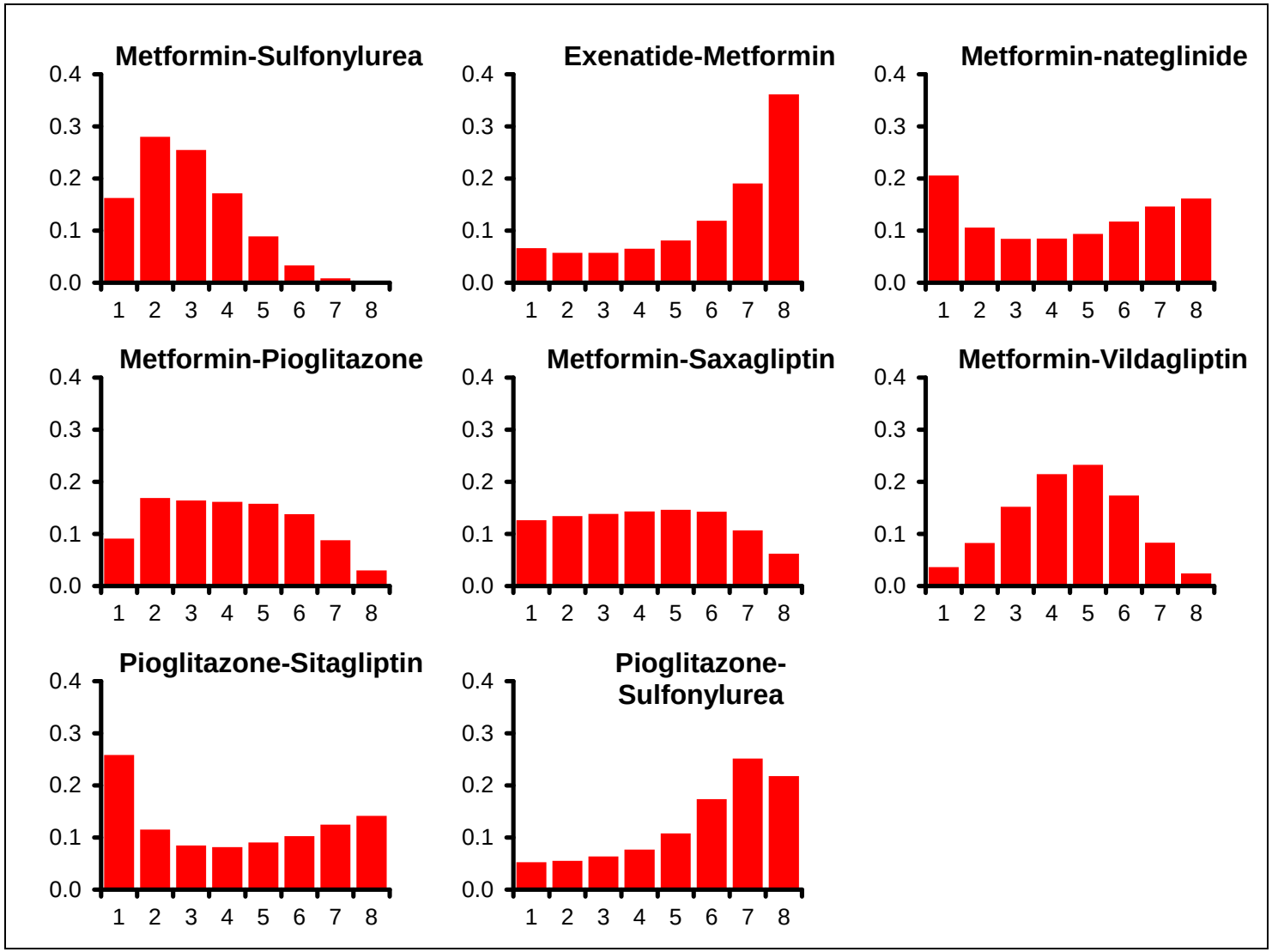



**Figure 87: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rank probability histograms**

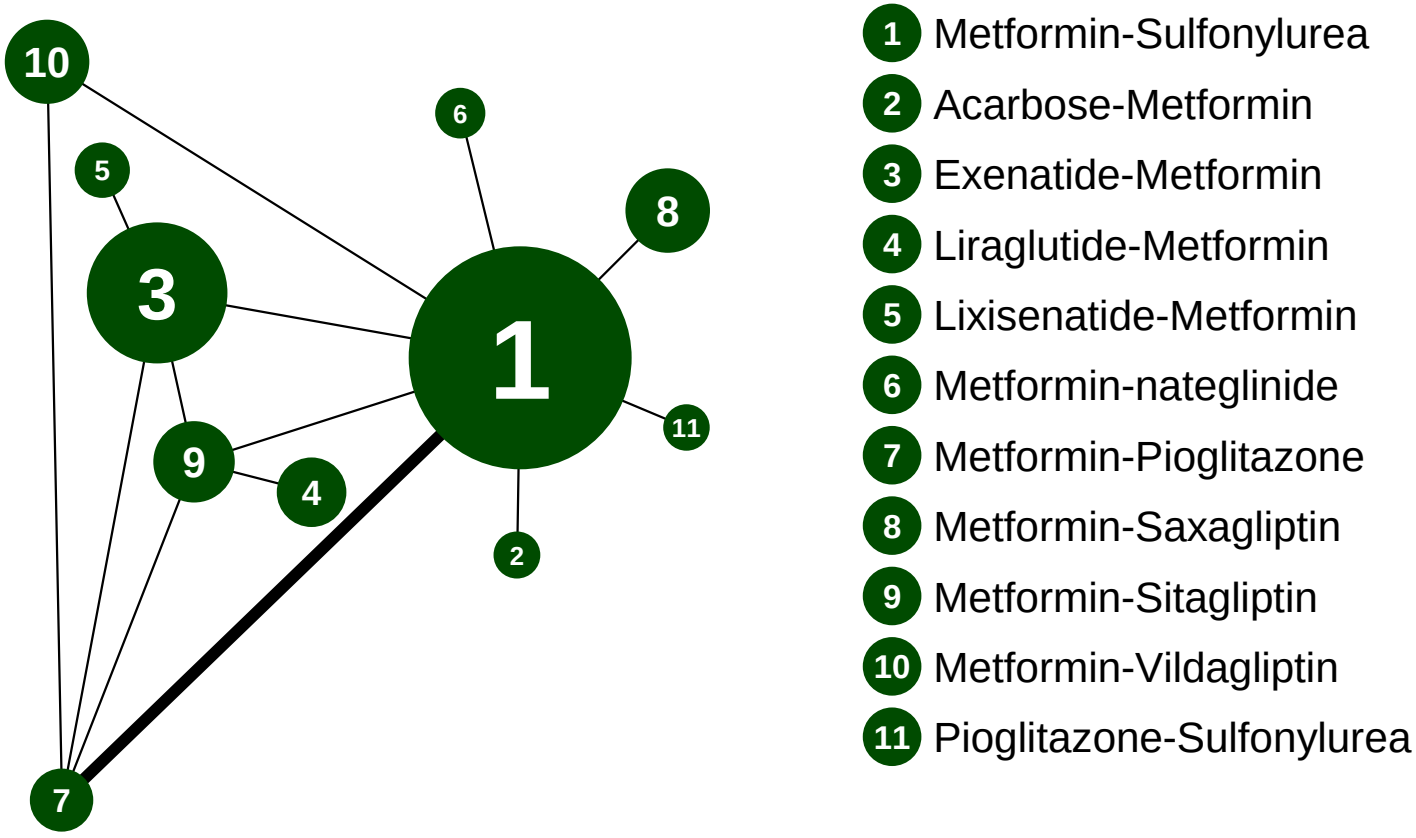
**Table 146: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 17.12<br>(compared to 18 datapoints) | -48.664 | -65.697 | 17.033 | -31.631 | 0.086 (95%CI: 0.003, 1.099) |

**Table 147: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.3.2.2 Hypoglycaemia at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 88: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network**

**Table 148: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data**

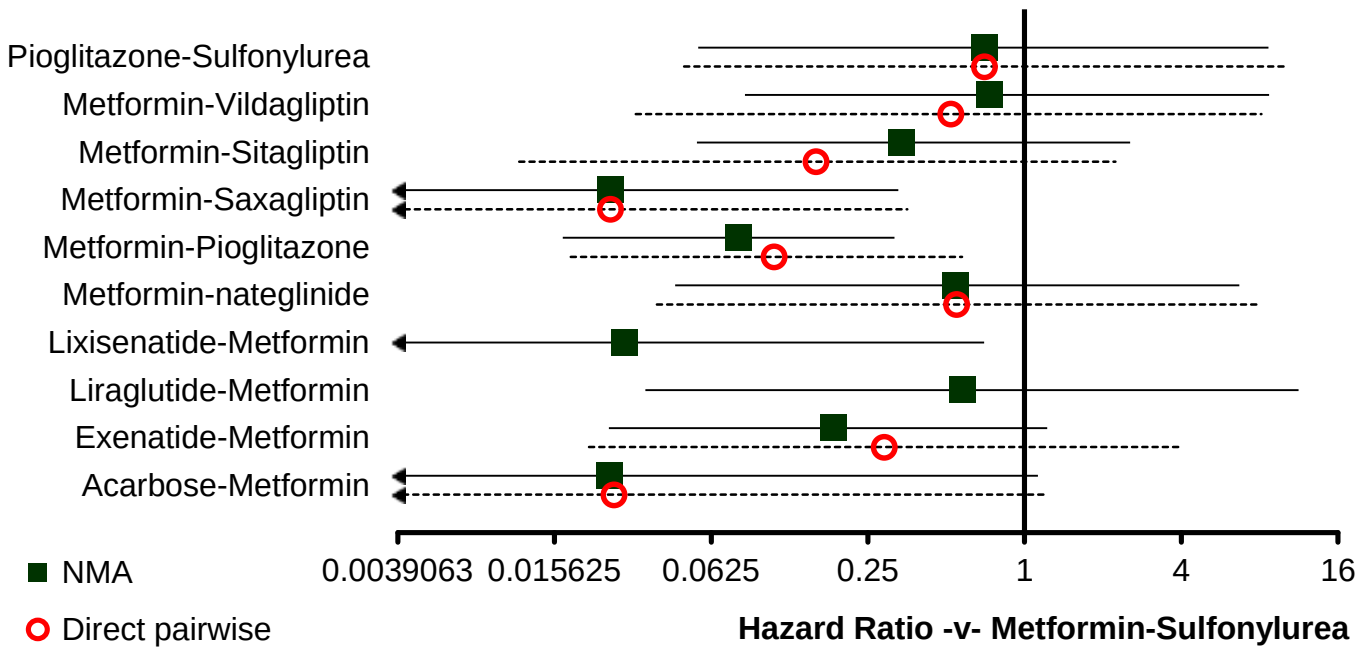
| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin | Pioglitazone-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dichotomous proportion data | | | | | | | | | | | |
| Wang et al. (2011) - 0.31yr | 6/26 | 0/29 | | | | | | | | | |
| Matthews et al. (2005) - 1.99yr | 36/313 | | | | | | 7/317 | | | | |
| Umpierrez et al. (2006) - 0.50yr | 32/96 | | | | | | 1/107 | | | | |
| Hanefeld et al. (2004) - 1.99yr | 50/320 | | | | | | | | | | 36/319 |
| Count data | | | | | | | | | | | |
| Gallwitz et al. (2012) - 2.99yr | 7162/491400 | | 1946/467376 | | | | | | | | |
| Goke et al. (2010) - 1.99yr | 896/210028 | | | | | | | 24/215852 | | | |
| Pfutzner et al. (2011) - 0.46yr | 5/22764 | | | | | | 2/23352 | | | | |
| Bergenstal et al. (2010) - 0.50yr | | | 2/26117 | | | | 1/26936 | | 9/28210 | | |
| Filozof & (2010) - 1.00yr | 11/164892 | | | | | | | | | 6/167440 | |
| Bolli et al. (2008) - 0.46yr | | | | | | | 0/44100 | | | 3/46788 | |
| Ristic et al. (2006) - 0.46yr | 188/19992 | | | | | 110/21252 | | | | | |
| Arechavaleta et al. (2010) - 0.57yr | 460/103441 | | | | | | | | 73/103441 | | |
| Pratley et al. (2010) - 1.00yr | | | | 94/133042 | | | | | 25/67340 | | |
| Rosenstock et al. (2013) - 0.46yr | | | 48/49308 | | 8/49980 | | | | | | |

*Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 149: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-Sulfonylurea | Acarbose-Metformin | Exenatide-Metformin | Liraglutide-Metformin | Lixisenatide-Metformin | Metformin-nateglinide | Metformin-Pioglitazone | Metformin-Saxagliptin | Metformin-Sitagliptin | Metformin-Vildagliptin |
|---|---|---|---|---|---|---|---|---|---|---|
| Acarbose-Metformin | 0.03 (0.00, 1.13) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin | 0.18 (0.03, 1.22) | 7.44 (0.10, 5579.00) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Liraglutide-Metformin | 0.58 (0.03, 11.29) | 25.12 (0.21, 26080.00) | 3.12 (0.15, 83.46) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Lixisenatide-Metformin | 0.03 (0.00, 0.70) | 1.20 (0.01, 1308.00) | 0.16 (0.01, 2.05) | 0.05 (0.00, 2.60) | | N/A | N/A | N/A | N/A | N/A |
| Metformin-nateglinide | 0.55 (0.05, 6.68) | 22.89 (0.24, 20240.00) | 2.97 (0.13, 73.54) | 0.95 (0.02, 40.53) | 18.72 (0.33, 1242.00) | | N/A | N/A | N/A | N/A |
| Metformin-Pioglitazone | 0.08 (0.02, 0.32) | 3.15 (0.05, 2189.00) | 0.43 (0.05, 3.72) | 0.14 (0.01, 2.54) | 2.75 (0.09, 81.50) | 0.15 (0.01, 2.37) | | N/A | N/A | N/A |
| Metformin-Saxagliptin | 0.03 (0.00, 0.33) | 1.06 (0.01, 1045.00) | 0.14 (0.01, 3.72) | 0.04 (0.00, 1.92) | 0.89 (0.01, 57.75) | 0.05 (0.00, 1.63) | 0.32 (0.02, 6.57) | | N/A | N/A |
| Metformin-Sitagliptin | 0.34 (0.06, 2.54) | 13.96 (0.21, 9787.00) | 1.82 (0.23, 19.95) | 0.58 (0.06, 5.28) | 11.69 (0.44, 407.80) | 0.61 (0.03, 14.57) | 4.22 (0.61, 42.01) | 13.19 (0.58, 335.00) | | N/A |
| Metformin-Vildagliptin | 0.73 (0.08, 8.69) | 31.17 (0.38, 28030.00) | 4.00 (0.24, 93.59) | 1.26 (0.03, 53.34) | 26.02 (0.57, 1549.00) | 1.34 (0.05, 44.44) | 9.21 (0.93, 148.20) | 29.05 (1.06, 975.20) | 2.18 (0.12, 43.23) | |
| Pioglitazone-Sulfonylurea | 0.70 (0.06, 8.64) | 29.12 (0.30, 27940.00) | 3.80 (0.17, 94.03) | 1.20 (0.02, 50.23) | 24.18 (0.44, 1479.00) | 1.27 (0.04, 44.92) | 8.78 (0.50, 174.70) | 27.31 (0.75, 892.90) | 2.08 (0.08, 46.40) | 0.95 (0.03, 25.71) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 89: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 150: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-Sulfonylurea | 0.000 | 10 (7, 11) |
| Acarbose-Metformin | 0.391 | 2 (1, 9) |
| Exenatide-Metformin | 0.002 | 5 (3, 9) |

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Liraglutide-Metformin | 0.005 | 8 (3, 11) |
| Lixisenatide-Metformin | 0.279 | 2 (1, 8) |
| Metformin-nateglinide | 0.004 | 8 (3, 11) |
| Metformin-Pioglitazone | 0.027 | 4 (1, 7) |
| Metformin-Saxagliptin | 0.287 | 2 (1, 7) |
| Metformin-Sitagliptin | 0.001 | 7 (4, 10) |
| Metformin-Vildagliptin | 0.001 | 9 (4, 11) |
| Pioglitazone-Sulfonylurea | 0.003 | 9 (3, 11) |

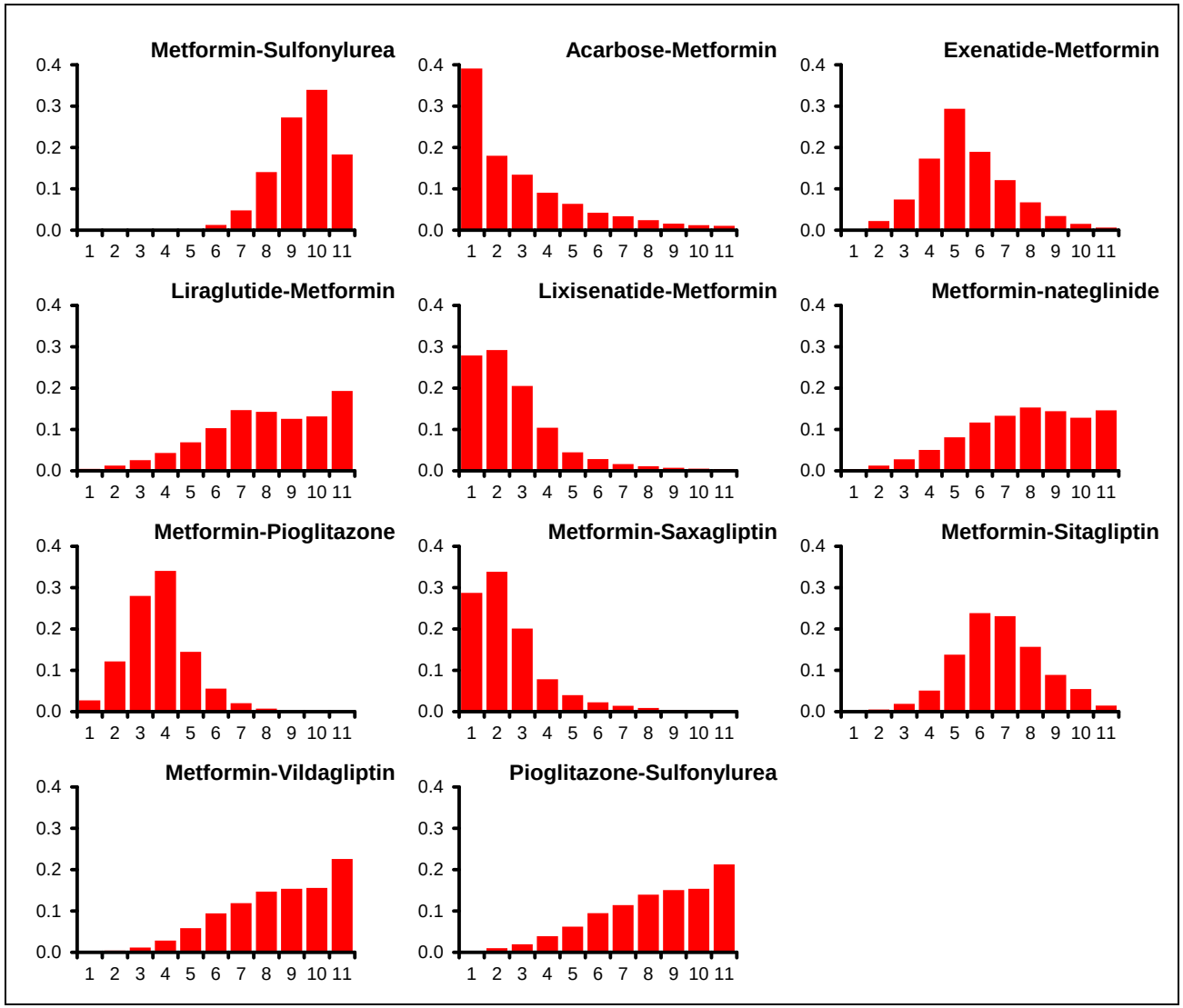



**Figure 90: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms**

**Table 151: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics**

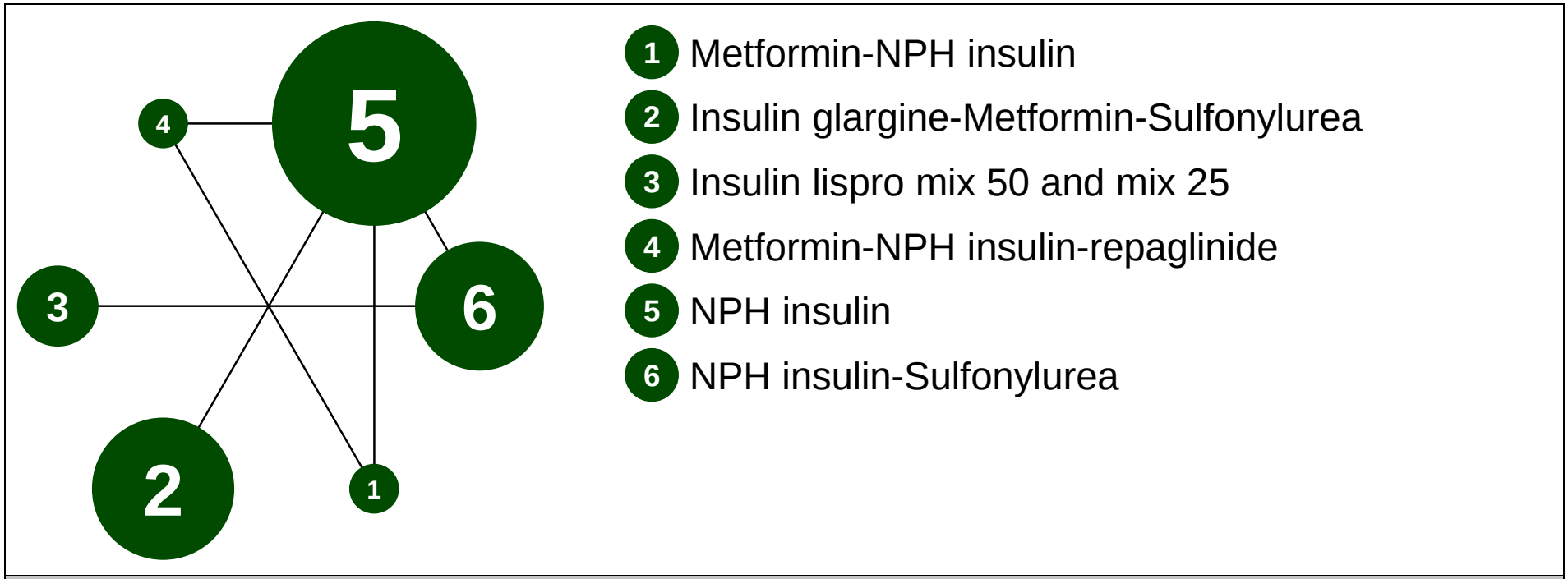
| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 30.32<br>(compared to 30 datapoints) | 40.088 | 32.724 | 7.364 | 146.372 | 1.120 (95%CI: 0.502, 1.912) |

**Table 152: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes**

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

## J.3.3 RESULTS FOR SECOND INTENSIFICATION – INDIVIDUALS PREVIOUSLY ON 2 NON-INSULIN BASED MEDICINES

### J.3.3.1 Change in HbA1c up to 12 months




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.*

**Figure 91: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – evidence network**

**Table 153: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – input data**

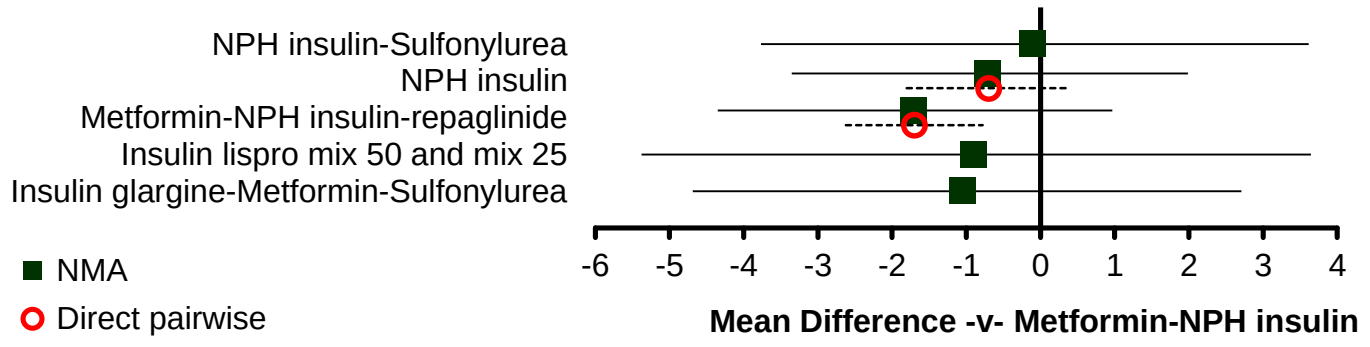
| | Metformin-NPH insulin | Insulin glargine-Metformin-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Metformin-NPH insulin-repaglinide | NPH insulin | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|
| Milicevic et al. (2009) | | | -1.30 (2.00) | | | -0.50 (1.60) |
| Civera et al. (2008) | -0.70 (1.20) | | | -2.40 (1.10) | -1.40 (1.60) | |
| Janka et al. (2005) | | -1.64 (0.92) | | | -1.31 (0.94) | |
| Stehouwer et al. (2003) | | | | | -1.10 (1.24) | -0.50 (1.30) |

*Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 154: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effectiveness of all pairwise combinations**

| | Metformin-NPH insulin | Insulin glargine-Metformin-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Metformin-NPH insulin-repaglinide | NPH insulin | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|
| Metformin-NPH insulin | | - | - | -1.70 (-2.62, -0.78) | -0.70 (-1.80, 0.40) | - |
| Insulin glargine-Metformin-Sulfonylurea | -1.05 (-4.69, 2.71) | | - | - | 0.33 (0.14, 0.52) | - |
| Insulin lispro mix 50 and mix 25 | -0.90 (-5.38, 3.65) | 0.14 (-4.29, 4.58) | | - | - | 0.80 (0.19, 1.41) |
| Metformin-NPH insulin-repaglinide | -1.71 (-4.35, 0.97) | -0.68 (-4.36, 3.07) | -0.81 (-5.34, 3.60) | | 1.00 (-0.07, 2.07) | - |
| NPH insulin | -0.70 (-3.35, 1.99) | 0.33 (-2.18, 2.89) | 0.20 (-3.47, 3.79) | 1.01 (-1.70, 3.70) | | 0.60 (0.22, 0.98) |
| NPH insulin-Sulfonylurea | -0.11 (-3.77, 3.61) | 0.94 (-2.60, 4.54) | 0.80 (-1.79, 3.35) | 1.61 (-2.08, 5.29) | 0.60 (-1.94, 3.15) | |

*Values given are mean differences in HbA1c in percentage-points.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.*




*Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.*

**Figure 92: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effect of all options versus reference treatment**

**Table 155: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.025 | 5 (1, 6) |
| Insulin glargine-Metformin-Sulfonylurea | 0.190 | 3 (1, 6) |
| Insulin lispro mix 50 and mix 25 | 0.212 | 3 (1, 6) |
| Metformin-NPH insulin-repaglinide | 0.530 | 1 (1, 5) |
| NPH insulin | 0.024 | 4 (2, 6) |
| NPH insulin-Sulfonylurea | 0.018 | 5 (2, 6) |

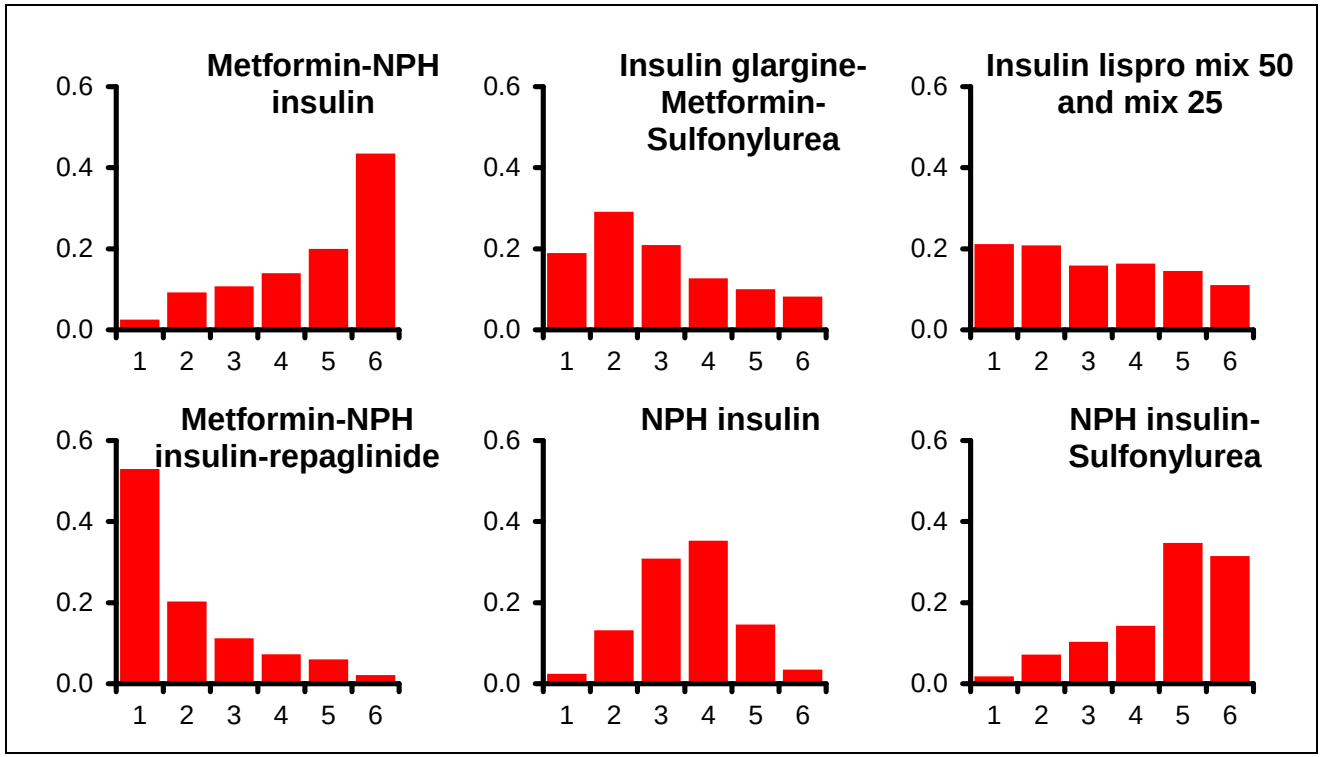



**Figure 93: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rank probability histograms**

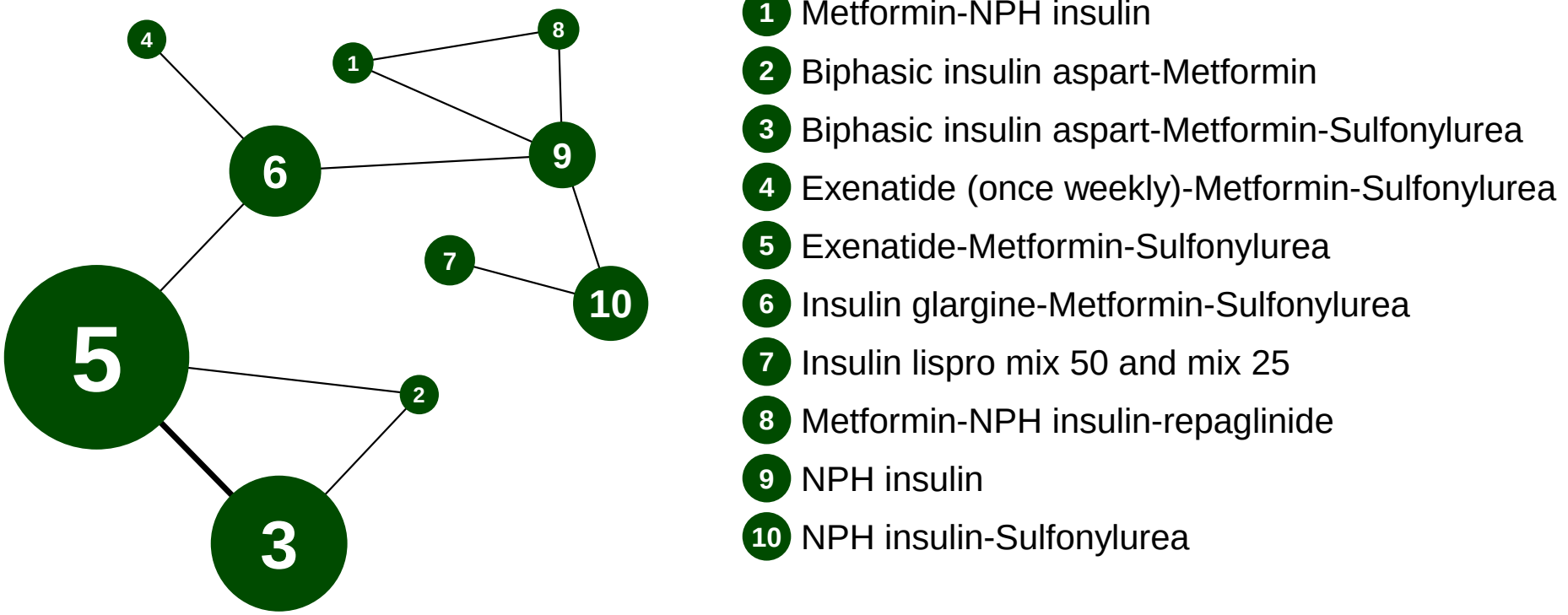
**Table 156: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 9.004<br>(compared to 9 datapoints) | -5.256 | -14.259 | 9.003 | 3.747 | 1.009 (95%CI: 0.058, 1.952) |

**Table 157: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – notes**

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

### J.3.3.2 Hypoglycaemia at study endpoint




*Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.*

**Figure 94: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network**

**Table 158: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data**

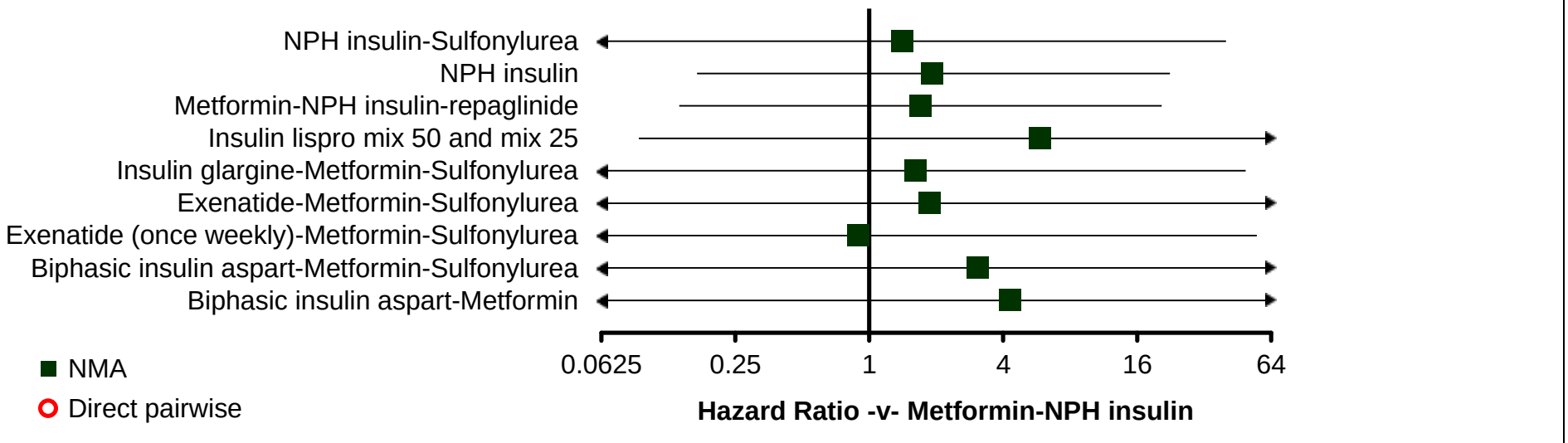
| | Metformin-NPH insulin | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Exenatide (once weekly)-Metformin | Exenatide-Metformin-Sulfonylurea | Insulin glargine-Metformin-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Metformin-NPH insulin-repaglinide | NPH insulin | NPH insulin-Sulfonylurea |
|---|---|---|---|---|---|---|---|---|---|---|
| Dichotomous proportion data | | | | | | | | | | |
| Diamant et al. (2010) - 1.61yr | | 76/124 | 69/124 | | 36/124 | | | | | |
| Bergenstal et al. (2009) - 0.46yr | | | | | | 109/177 | | | 127/187 | |
| Janka et al. (2005) - 0.46yr | | | | 25/69 | | 37/66 | | | | |
| Milicevic et al. (2009) - 0.46yr | | | | | | | 124/10080 | | | 31/10248 |
| Count data | | | | | | | | | | |
| Civera et al. (2008) - 0.46yr | 6/2016 | | | | | | | 10/2016 | 12/2184 | |
| Nauck et al. (2007) - 1.00yr | | | 1315/85722 | | 1059/82264 | | | | | |
| Heine et al. (2005) - 0.50yr | | | | | | | | | 355/22176 | 253/21672 |
| Stehouwer et al. (2003) - 0.69yr | | | | | 928/46410 | 799/46319 | | | | |

*Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.*

**Table 159: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations**

| | Metformin-NPH insulin | Biphasic insulin aspart-Metformin | Biphasic insulin aspart-Metformin-Sulfonylurea | Exenatide (once weekly)-Metformin-Sulfonylurea | Exenatide-Metformin-Sulfonylurea | Insulin glargine-Metformin-Sulfonylurea | Insulin lispro mix 50 and mix 25 | Metformin-NPH insulin-repaglinide | NPH insulin |
|---|---|---|---|---|---|---|---|---|---|
| Biphasic insulin aspart -Metformin | 4.30 (0.04, 469.00) | | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Biphasic insulin aspart -Metformin-Sulfonylurea | 3.07 (0.04, 251.00) | 0.71 (0.08, 6.66) | | N/A | N/A | N/A | N/A | N/A | N/A |
| Exenatide (once weekly) -Metformin-Sulfonylurea | 0.90 (0.01, 55.29) | 0.21 (0.00, 10.36) | 0.29 (0.01, 11.60) | | N/A | N/A | N/A | N/A | N/A |
| Exenatide-Metformin -Sulfonylurea | 1.87 (0.03, 112.70) | 0.44 (0.05, 3.93) | 0.62 (0.12, 3.15) | 2.11 (0.08, 59.03) | | N/A | N/A | N/A | N/A |
| Insulin glargine-Metformin -Sulfonylurea | 1.61 (0.06, 49.19) | 0.38 (0.02, 8.94) | 0.54 (0.03, 9.29) | 1.83 (0.18, 19.69) | 0.86 (0.09, 8.84) | | N/A | N/A | N/A |
| Insulin lispro mix 50 and mix 25 | 5.88 (0.09, 355.00) | 1.36 (0.01, 249.70) | 1.91 (0.01, 277.80) | 6.54 (0.06, 748.20) | 3.11 (0.03, 334.70) | 3.60 (0.07, 217.00) | | N/A | N/A |
| Metformin-NPH insulin -repaglinide | 1.71 (0.14, 20.65) | 0.40 (0.00, 43.22) | 0.55 (0.01, 47.13) | 1.93 (0.03, 119.60) | 0.90 (0.02, 56.23) | 1.06 (0.04, 30.98) | 0.29 (0.01, 17.27) | | N/A |
| NPH insulin | 1.92 (0.17, 22.48) | 0.45 (0.01, 23.17) | 0.64 (0.02, 25.86) | 2.16 (0.08, 59.49) | 1.02 (0.04, 28.41) | 1.19 (0.12, 11.80) | 0.33 (0.01, 9.74) | 1.12 (0.10, 12.84) | |
| NPH insulin-Sulfonylurea | 1.42 (0.05, 40.10) | 0.33 (0.00, 35.38) | 0.46 (0.01, 38.42) | 1.58 (0.03, 98.46) | 0.75 (0.01, 46.19) | 0.87 (0.03, 23.65) | 0.24 (0.02, 2.54) | 0.83 (0.03, 23.05) | 0.74 (0.07, 7.50) |

*Values given are hazard ratios.*
*The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.*




*Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.*

**Figure 95: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment**

**Table 160: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator**

| | Probability best | Median rank (95%CI) |
|---|---|---|
| Metformin-NPH insulin | 0.271 | 3 (1, 10) |
| Biphasic insulin aspart-Metformin | 0.030 | 9 (1, 10) |
| Biphasic insulin aspart-Metformin-Sulfonylurea | 0.032 | 8 (1, 10) |
| Exenatide (once weekly)-Metformin-Sulfonylurea | 0.340 | 2 (1, 10) |
| Exenatide-Metformin-Sulfonylurea | 0.058 | 5 (1, 9) |
| Insulin glargine-Metformin-Sulfonylurea | 0.022 | 5 (2, 9) |
| Insulin lispro mix 50 and mix 25 | 0.022 | 9 (2, 10) |
| Metformin-NPH insulin-repaglinide | 0.087 | 5 (1, 10) |
| NPH insulin | 0.011 | 6 (2, 9) |
| NPH insulin-Sulfonylurea | 0.127 | 4 (1, 9) |

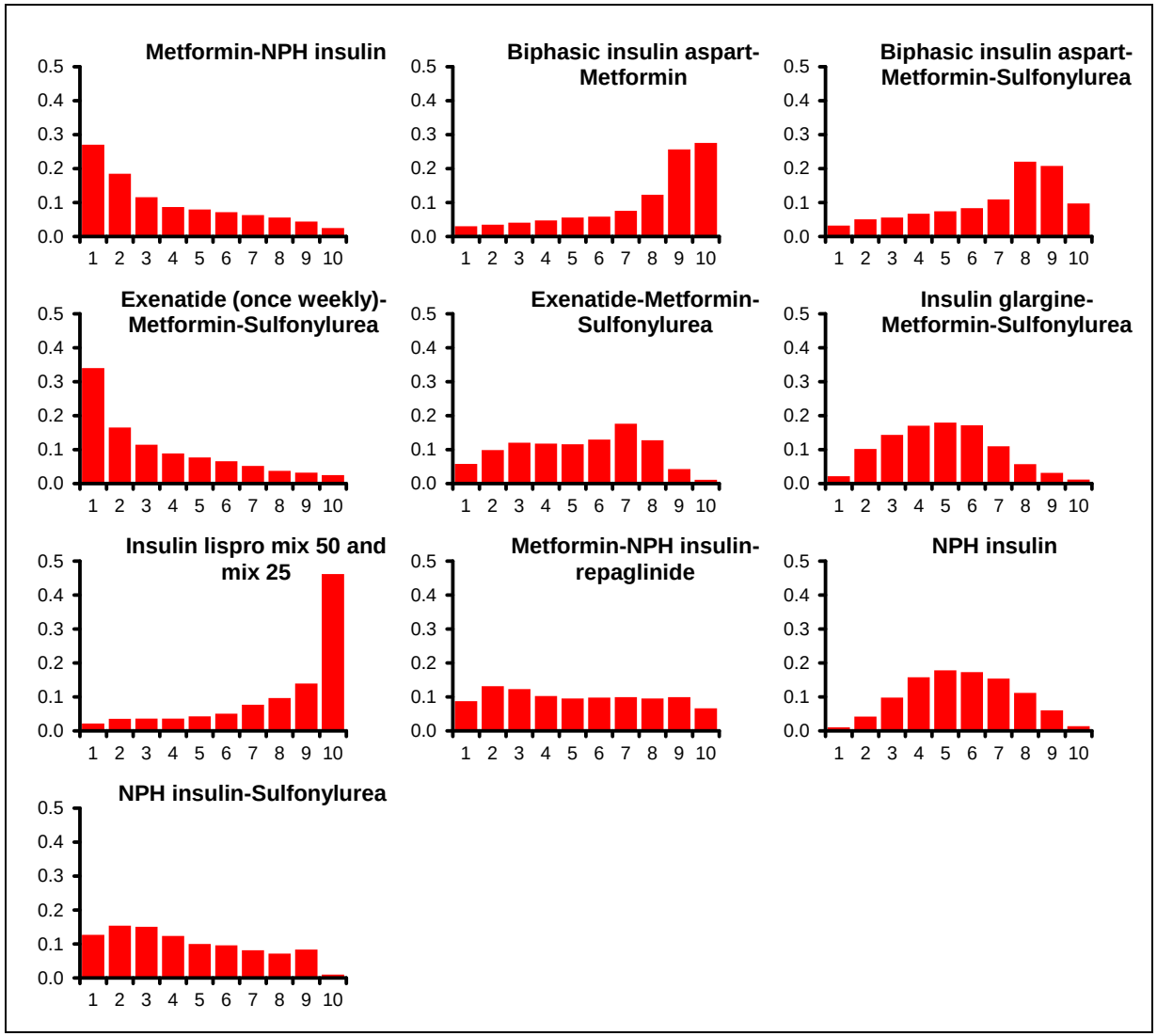



**Figure 96: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms**

**Table 161: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics**

| Residual deviance | Dbar | Dhat | pD | DIC | tau |
|---|---|---|---|---|---|
| 18.2<br>(compared to 18 datapoints) | 43.058 | 36.009 | 7.049 | 50.107 | 0.868 (95%CI: 0.203, 1.924) |

**Table 162: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes**

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)