DOSES AND ROUTES OF ADMINISTRATION FOR UTEROTONIC AGENTS TO PREVENT POSTPARTUM HAEMORRHAGE

by

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Abstract

Background: Postpartum haemorrhage (PPH) is the most common cause of maternal mortality and serious morbidity after childbirth, worldwide. Inadequate uterine tone after the birth of the baby can lead to excessive bleeding from the open vessels on the placental bed. Therefore, the administration of drugs that increase uterine contractility is recommended for all births. However, there is still uncertainty about the best route and dose of administration for each of the available uterotonic drugs.

Objectives: To perform two network meta-analyses, one to specify the route of administration, and one to specify the dose, that maximise the effectiveness of each of the available uterotonic drugs without increasing the risk for side effects. A ranking of the available options will be generated for all primary and secondary outcomes.

Selection criteria: *Population:* Randomised controlled trials involving women in the third stage of labour after a vaginal or caesarean delivery in hospital or community settings. *Interventions:* Systemically administered uterotonic drugs of any route and dose for PPH prevention. *Comparison:* Any other uterotonic drug, or a different route or dose of a given drug, or placebo, or no treatment. *Outcomes (primary):* PPH ≥500 mL and PPH ≥1000 mL.

Data collection and analysis: Data will be extracted from the eligible studies and entered on an electronic database. Risk of bias and trustworthiness assessments will be performed. Direct, indirect and network meta-analyses will be conducted, and results will be summarised as risk ratio with 95% confidence intervals (CI) for dichotomous outcomes and as mean difference with 95% CI for continuous outcomes. The certainty of generated evidence will be assessed according to the GRADE approach. Results with relative and absolute treatments effects will be summarised in Summary of Findings tables. Cumulative

probabilities will be calculated and the surface under the cumulative ranking curve (SUCRA) will be used to create a ranking of the available drugs.

Main results: One hundred eighty-one studies involving 122,867 randomised women were included in the Routes-NMA. Results suggest that carbetocin IV(B), ergometrine plus oxytocin combination IM, oxytocin IV(B+I), and oxytocin IV(B) are probably more effective in preventing PPH and related morbidity outcomes, when compared with oxytocin IM. Intramuscularly administered oxytocin and carbetocin have a favourable side effects profile.

One hundred eighty-two studies with 132,593 randomised participants were included in the Doses-NMA. Carbetocin 100 mcg, ergometrine >200 mcg, and ergometrine plus oxytocin combination 500 mcg plus 5 IU rank among the best options for preventing excessive bleeding, use of additional uterotonics, and administration of a blood transfusion. However, when comparing these uterotonics against oxytocin 10 IU the generated evidence varies from very low to moderate certainty without statistically significant results, and thus findings are inconclusive. Carbetocin 100 mcg is associated with a favourable side effects profile.

Authors' conclusions: Although carbetocin IV(B), ergometrine plus oxytocin combination IM, oxytocin IV(B+I), and oxytocin IV(B) are among the top uterotonics for PPH prevention, these uterotonics also increase the risk for side effects. In terms of which dose of administration maximises effectiveness results are unclear.

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Foreword

‘Διαιτήμασί τε χρήσομαι ἐπ᾽ ὠφελείῃ καμνόντων κατὰ δύναμιν καὶ κρίσιν ἐμήν, ἐπὶ δηλήσει δὲ καὶ ἀδικίῃ εἴρξειν.’

‘I will use those dietary regimens which will benefit my patients according to my greatest ability and judgement, and I will do no harm or injustice to them.’

According to the Hippocratic Oath, a doctor should use his/her knowledge and available medicines for the greatest benefit of the one in need. Women in labour, even in the Western world, may face serious threat to their lives, mainly because of excessive bleeding after childbirth. Therefore, the attending personnel should be adequately skilled and experienced to provide every mother with the best possible care. Given that excessive bleeding is most commonly caused by the inability of the uterine muscle to contract, drugs that increase the tone of the uterus should be given to all mothers for prophylaxis. However, there are several such drugs, known as uterotonics, each with different properties, in terms of effectiveness and side-effects. This project aims to answer which route and dose of administration maximises the effectiveness of each of the available uterotonics and is associated with a favourable side-effect profile, so that every obstetrician can keep his/her oath.

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Glossary of Terms

AMTSL	Active management of the third stage of labour
CI	Confidence intervals
ELCS	Elective caesarean section
EMCS	Emergency caesarean section
HIC	High income countries
ICC	Intra-cluster correlation coefficient
IM	Intramuscularly
IV(B)	Intravenous bolus
IV(I)	Intravenous infusion
IV(B+I)	Intravenous bolus and infusion
LIC	Low income countries
LMIC	Lower-middle income countries
MD	Mean difference
NMA	Network meta-analysis
PO	Per os, orally
PPH	Postpartum haemorrhage
PR	Per rectum, rectally
RCT	Randomised controlled trial
RoB	Risk of bias
RR	Risk ratio
SL	Sublingually
SoF Table	Summary of Findings Table
SUCRA	Surface under the cumulative ranking curve
UMIC	Upper-middle income countries
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Background

In 2020, eight hundred women died every day due to pregnancy- and childbirth-related causes.[1] Traditionally, most (19.7%, with 95% uncertainty interval 12.9 to 28.9) of these deaths are attributed to postpartum haemorrhage (PPH).[2] The World Health Organization (WHO) defines primary PPH as blood loss of at least 500 mL within the first 24 hours after childbirth, whereas secondary PPH can occur even up to 12 weeks postpartum.[3] Although several causes can lead to excessive bleeding after childbirth, uterine atony is the commonest *(Figure 1).*[2] Therefore, WHO recommends the administration of drugs that increase uterine contractility, as part of the active management of the third stage of labour (AMTSL), and prevent excessive blood loss from the open vessels on the placental bed. There are six classes of such drugs, known as uterotonics, each with a different effectiveness and side-effects profile, as described below in *Table 1.*[3,4]

Figure 1: Maternal mortality statistics

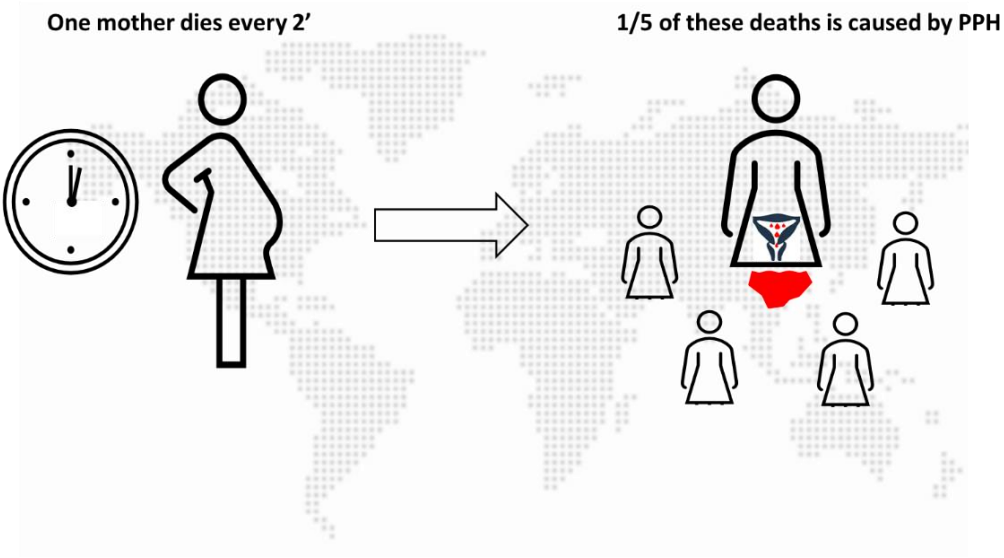


Table 1: Available uterotonics

Drug Profile	Oxytocin	Carbetocin	Ergometrine	Misoprostol	Injectable prostaglandins		Combination drugs	
					Carboprost	Sulprostone	Ergometrine Plus Oxytocin	Misoprostol Plus Oxytocin
Form	Synthetic form of the naturally occurring hormone	Long-acting synthetic analogue of oxytocin	Ergot alkaloids	PGE1 analogue	15-methyl-PGF2a	PGE2 analogue	Fixed-dose available	No fixed-dose available
Recommended doses	10 IU	100 mcg	200 mcg	400 or 600 mcg	Not for PPH prophylaxis	Not for PPH prophylaxis	Fixed-dose combination 500 mcg plus 5 IU	See single drugs
Routes of administration	IM, IV	IM, IV	IM, IV	PO, (PR, SL)	IM	IM	IM, IV	See single drugs
Onset of action	IM: 3-7 mins IV: 0 mins	2 mins	2-3 mins	9-15 mins	15-60 mins to peak [plasma]	15-60 mins to peak [plasma]	2-3 mins	See single drugs
Half-life	1-6 mins	40 mins	30-120 mins	20-40 mins	8 mins	8 mins	See single drugs	See single drugs
Contraindications	Not specific	Not specific	hyperTN	Asthma	Not for PPH prophylaxis	Not for PPH prophylaxis	See single drugs	See single drugs
Common side effects	GIS disorders, hypoTN, headache	GIS disorders, headache	hyperTN	GIS disorders, fever	GIS disorders	GIS disorders	See single drugs	See single drugs
Storage	Protection from light, 2-8 °C	Heat-stable available	Protection from light, 2-8 °C	Protection from humidity	2-8 °C	2-8 °C	See single drugs	See single drugs

Footnotes: **GIS:** gastrointestinal system, **hyperTN:** hypertension, **hypoTN:** hypotension, **PPH:** postpartum haemorrhage, **[plasma]:** plasma concentration

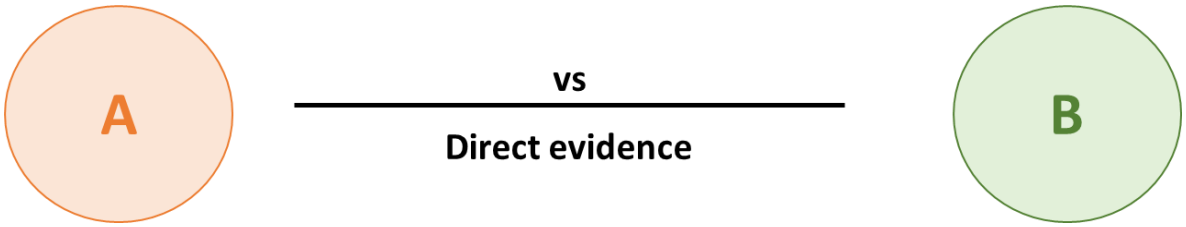
Based on the information provided in *Table 1,* and the hundreds of available randomised and non-randomised studies comparing the available uterotonics, it is practically impossible for any care provider to decide which uterotonic drug works best. For this reason, a research team from the University of Birmingham has tried to create a meaningful ranking of all the available uterotonic drugs, based on what is called a 'Network meta-analysis' (NMA). This project is registered with the Cochrane Library, and thus it is updated when new evidence is made available to the scientific society. In the latest update, in 2018, authors found that carbetocin and combination uterotonic drugs are more effective than oxytocin, which is considered the drug of choice. They also found that carbetocin and oxytocin are associated with relatively few and self-limiting side-effects.[5] However, this NMA was not

able to specify the best route and dose of administration for each of the available drugs, a question of highest importance according to WHO.[3]

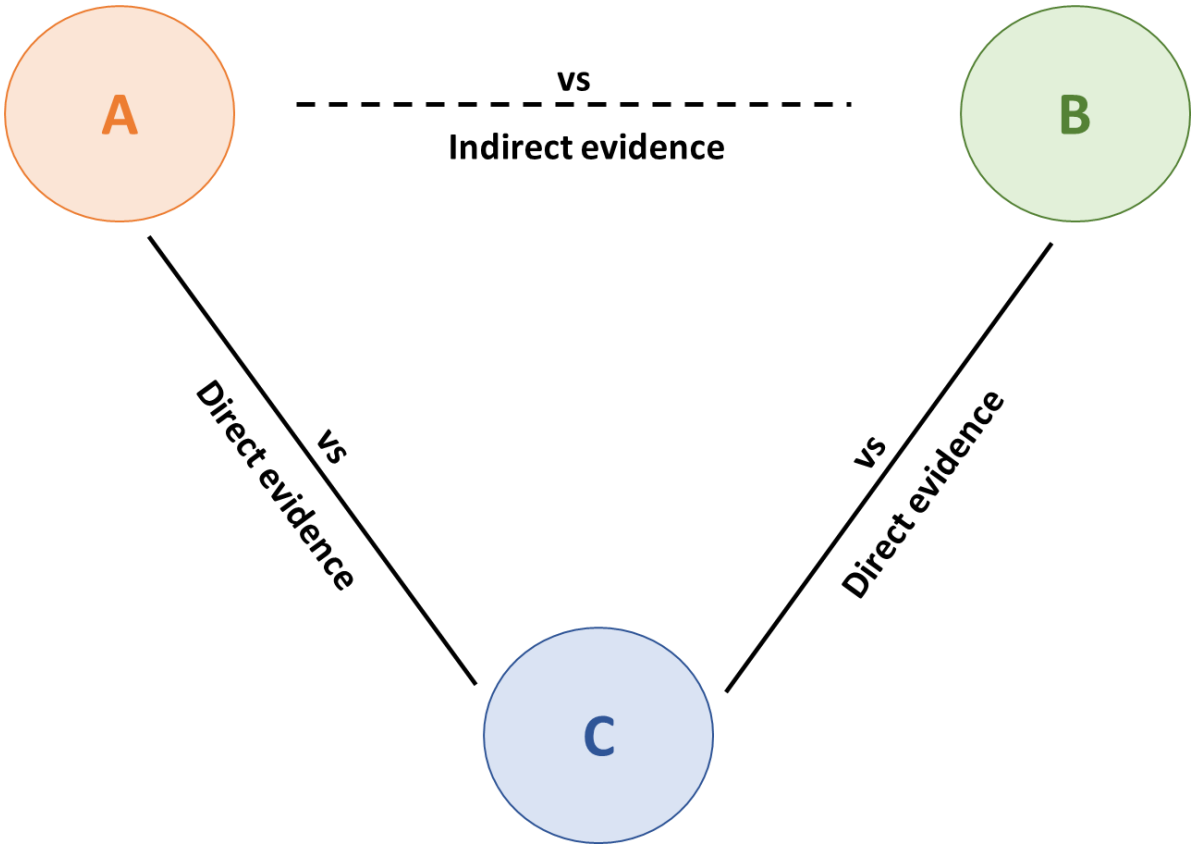
The project presented in this *Thesis* is an extension of the existing Cochrane review on uterotonics for PPH prevention. The aim is to perform two NMAs (one comparing available routes and one comparing available doses of the uterotonic drugs) to create a ranking showing which route and dose works best for each of the agents. Given that readers might not be familiar with *'Network meta-analysis',* some of the basic principles will be presented in the upcoming section.

Basic principles of NMA

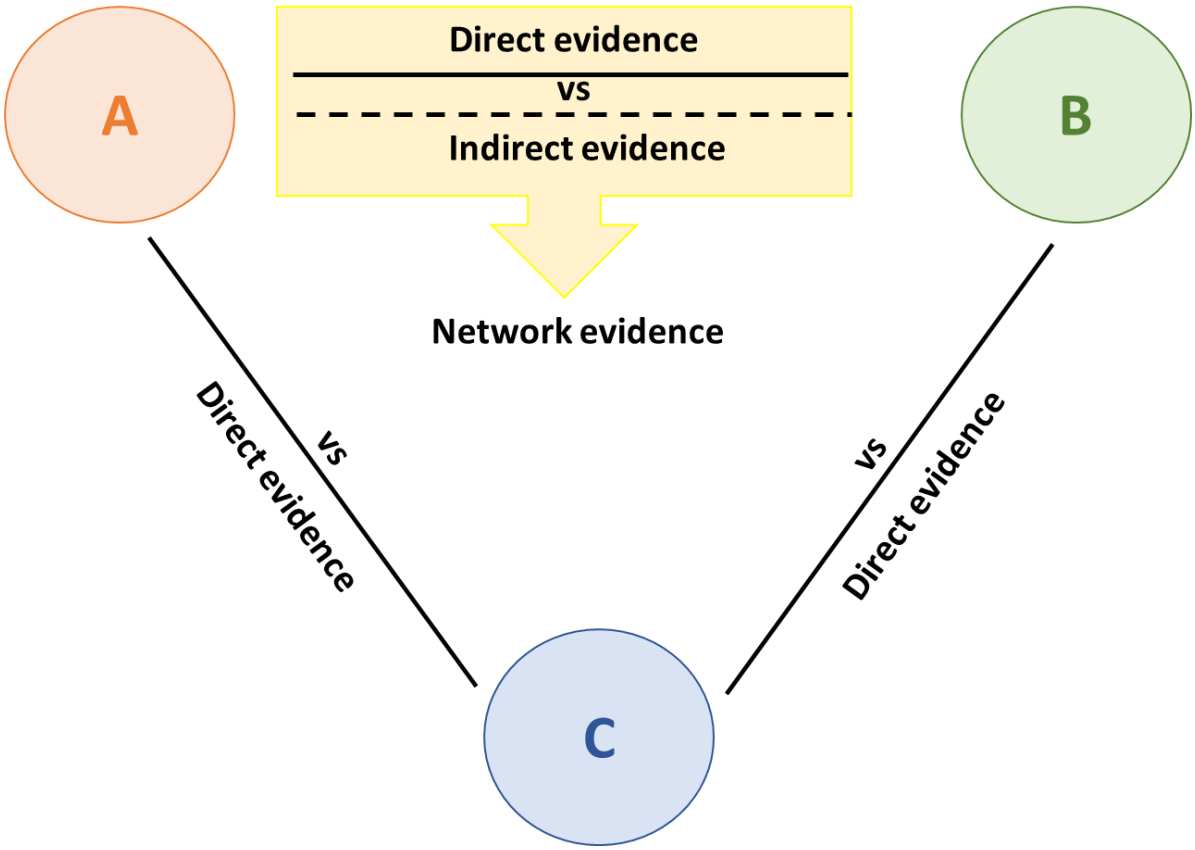
When one drug A is compared in head-to-head trials with a drug B, direct evidence is generated.[6]



When one drug A is not compared in head-to-head trials with a drug B, but evidence on their relative treatment effects is derived through a common comparator, drug C for instance, then indirect evidence is generated.[6]



Simply explained, when both direct and indirect evidence is available for a given comparison, e.g., drug A against drug B, then network evidence is also generated.[6]



For every **pairwise comparison** contributing to the network:

(a) **Indirectness should be low.** If indirectness is high, i.e., most weight of the effect estimate is provided by studies not answering directly the research question, the transitivity assumption is unlikely to hold (see below).

(b) **Heterogeneity should be low.** High levels of heterogeneity suggest that an effect modifier might be underlying and warrants further investigation with subgroup analyses. If heterogeneity remains high, even within the subgroups, the meta-analysis should not be performed.[6,7]

For a **NMA** to hold two conditions need to be fulfilled:

(a) **The transitivity assumption:** each randomised participant would have been equally likely randomised to receive any of the competing interventions across the entire network.

(b) **Consistency of the network:** Direct and indirect estimates for each treatment comparison within the network should agree.[6,7]

Rationale of the project

As previously discussed, there is still uncertainty regarding the dose and route of administration that maximises the effectiveness of each of the available uterotonics for PPH prevention. That is because the existing Cochrane review is grouping together all doses and routes for each of the available uterotonics.[5]

This project will extend the existing NMA by breaking down each drug to its different doses and routes of administration, and by adding evidence from all previously excluded studies which were comparing various doses and routes of a specific drug.

Objectives of the project

Primary

1) To perform a NMA to identify **the most effective route** for each of the available uterotonics for PPH prevention with the least side-effects, and to generate a ranking of all options for the primary and secondary outcomes.
2) To perform a NMA to identify **the most effective dose** for each of the available uterotonics for PPH prevention with the least side-effects, and to generate a ranking of all options for the primary and secondary outcomes.

Secondary

To provide relative treatment effect rankings for our two primary outcomes (PPH ≥500 mL, PPH ≥1000 mL) within the following population subgroups: women delivering vaginally, women having a caesarean section, women at high risk for PPH, women at low risk for PPH, women delivering in hospital settings, and women delivering in community settings.

CHAPTER 2: METHODS

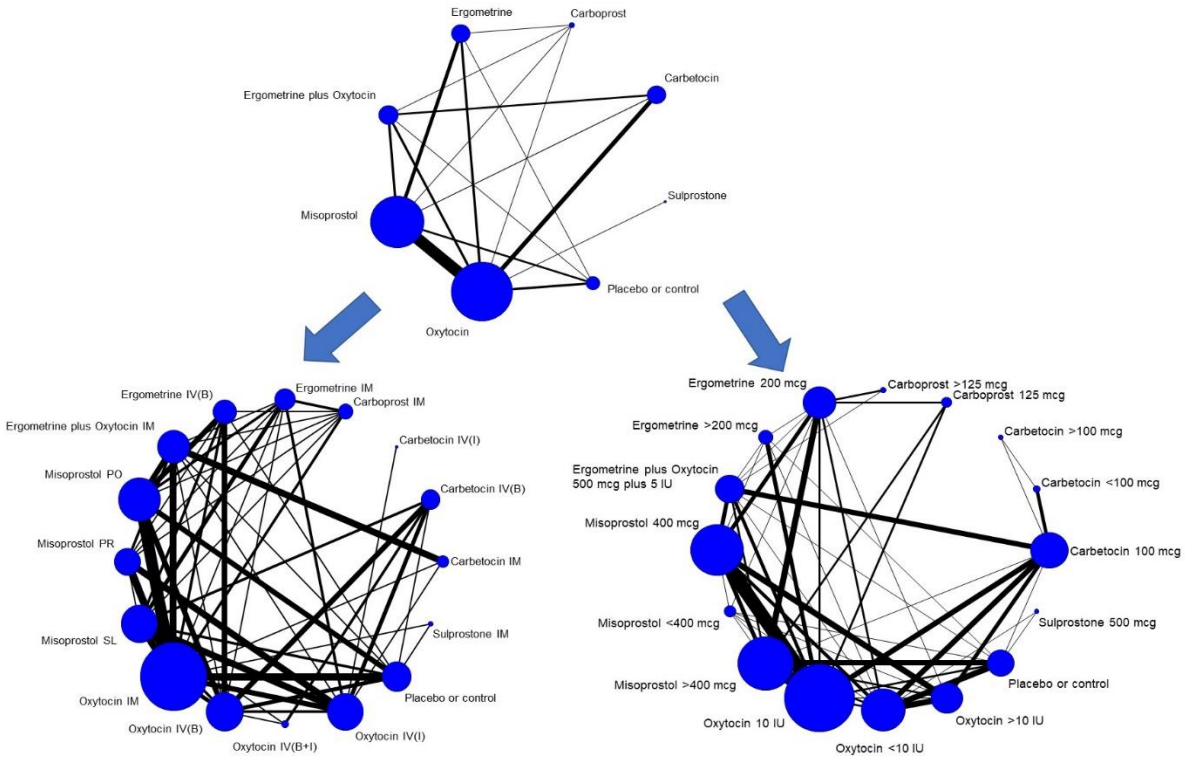
Study design

Two systematic reviews and network meta-analyses will be conducted to identify the dose and route of administration that maximise the effectiveness of each of the available uterotonic agents without increasing the risk for side effects, the *Doses-NMA* and the *Routes-NMA* respectively. For the *Doses-NMA* each of the uterotonic agents will be further classified according to the doses tested in the available studies, whereas for the *Routes-NMA* the classification will be based on the available data for different routes of administration, as shown in *Table 2* and *Figure 2.*

Table 2: Available uterotonic drugs included in the Routes-NMA and the Doses-NMA.

	Doses-NMA	Routes-NMA	WHO recommendations
Single drugs			
Oxytocin (Gold standard)	<10 IU, 10 IU, >10 IU	IM, IV(B), IV(B+I), IV(I)	10 IU IM/IV is recommended for all births
Carbetocin	<100 mcg, 100 mcg, >100 mcg	IM, IV(B), IV(I)	100 mcg IM/IV where its cost is comparable to other effective uterotonics
Carboprost	125 mcg, >125 mcg	IM	Not recommended for PPH prevention
Ergometrine	<200 mcg, 200 mcg, >200 mcg	IM, IV(B)	200 mcg IM/IV when hypertensive disorders can be excluded before its administration
Misoprostol	<400 mcg, 400 mcg, >400 mcg	PO, PR, SL	400 or 600 mcg PO is recommended for all births
Sulprostone	500 mcg	IM	Not recommended for PPH prevention
Combination drugs			
Ergometrine plus Oxytocin	500 mcg plus 5 IU	IM	When hypertensive disorders can be excluded before its administration
Misoprostol plus Oxytocin	Not included in the NMA	Not included in the NMA	No specific recommendation
Footnotes			
IM: intramuscularly, **IV(B):** intravenous bolus, **IV(B+I):** intravenous bolus and infusion, **IV(I):** intravenous infusion, **PO:** orally, **PR:** rectally, **SL:** sublingually.			

Figure 2: Available uterotonic drugs included in the Routes-NMA and the Doses-NMA



For widely used **single drugs**, the lowest recommended dose will be used as a cut-off for the *Doses-NMA* (i.e., carbetocin 100 mcg, ergometrine 200 mcg, misoprostol 400 mcg, and oxytocin 10 IU). For non-recommended **single drugs**, the lowest available dose will be also used as cut-off for the *Doses-NMA* (i.e., Carboprost 125 mcg and Sulprostone 500 mcg).

Studies testing **combination drugs**, i.e, ergometrine plus oxytocin and misoprostol plus oxytocin, will be eligible for inclusion in the systematic reviews, but only the fixed-dose ergometrine plus oxytocin combination, known under the brand name Syntometrine®, and Syntometrine-like® regimens will contribute data to the meta-analyses.

Search strategy

Since this project aims to expand the existing Cochrane review on uterotonic agents for prevention of PPH, Cochrane's information specialist will be contacted to perform the literature search. However, given that the validity of the search is limited to one year,

according to Cochrane's guidance, and the project might take longer for its completion, additional literature searches will be performed before proceeding to the analysis stage, irrespectively of Cochrane's support. Literature searches will include the following databases: CENTRAL, MEDLINE, Embase, CINAHL, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The reference lists of the retrieved study records will be also searched. For the terms used in the non-Cochrane literature searches please refer to

Based on the above, larger scale randomised trials assessing different routes and doses of administration need to be conducted. Additionally, there is an urgent need for studies testing uterotonics that are not commonly used either because of licensing reasons, financial constraints, or theoretically expected side effects. In any case, future studies should focus not only on reporting blood loss related outcomes and side effects, but also on women's views and acceptability of the interventions.

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APPENDIX 1: Additional information Routes-NMA & Doses-NMA.

Study selection

All study records retrieved from the literature search will be screened against this project's PICO selection criteria, based on the existing relevant Cochrane review and the available core outcome set for PPH prevention, and as shown in *Figure 3****Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε.***

Figure 3: PICO selection criteria

Population:	Randomised women in the third stage of labour after a vaginal or caesarean birth in the hospital or community setting.
Intervention:	Systemically administered uterotonic agents of any dosage, route or regimen in the third stage of labour for preventing PPH.
Comparison:	Any other uterotonic agent, or a different dose or route of administration of a specific uterotonic agent, or placebo, or no treatment.
Outcomes:	Primary: PPH ≥500 mL and PPH ≥1000 mL. Secondary: maternal death, intensive care unit admission, shock, use of additional uterotonics, blood transfusion, mean blood loss, change in haemoglobin before and after delivery, breastfeeding at discharge, side-effects (nausea, vomiting, hypertension, headache, fever, shivering, abdominal pain, diarrhoea), maternal sense of wellbeing and maternal satisfaction.

Study records meeting the above listed criteria will be further considered for inclusion, whereas records not fulfilling these criteria will be permanently excluded. Records that are eligible for inclusion but are written in any language other than English and an English translation is not available by the time the dataset is complete will be listed as 'awaiting classification'. Similarly, records for which no full-text report is available, and records for

which further clarifications from the primary study authors are required, will be also listed as 'awaiting classification'. Finally, records corresponding to study protocols meeting the PICO selection criteria and for which published results have not been identified will be listed as 'ongoing studies'.

Data extraction

Data will be extracted from all study records meeting the PICO selection criteria using an electronic data collection form on Microsoft Access. The data to be extracted are:

1. **Study characteristics:** Study ID based on the primary reference for a given study (i.e., first author's surname and year of publication), the country where the study was conducted, the study period, the language in which the full-text study report is available, and the level of randomisation (i.e., direct comparison randomised trials and cluster randomised trials).

2. **Population:** Setting (hospital or community), mode of birth (vaginal or caesarean birth), prior risk of PPH (low, high, mixed, or not stated), gestational age at randomisation, participants' parity, and any exclusion criteria.

3. **Intervention/Comparison:** Drug type: (a) single drugs (i.e., carbetocin, carboprost, ergometrine, misoprostol, oxytocin, sulprostone), (b) combination drugs (i.e., ergometrine plus oxytocin and misoprostol plus oxytocin), (c) placebo or no treatment. Dose and route (orally, intramuscularly, intravenously by a bolus injection, and/or a continuous infusion, rectally, sublingually) of administration.

4. **Outcomes:** For binary outcomes: the number of events and the total number of randomised women in each arm. For continuous outcomes: means, standard deviations, and the total number of randomised women in each arm.

5. **Risk of bias and trustworthiness assessment information:** See sections *'Risk of Bias assessment'* and *'Trustworthiness assessment'.*

6. **Contact information:** Contact details, date of first and last contact, questions asked, additional data provided if any.

Risk of Bias assessment

The risk of bias assessment will be performed according to Cochrane's guidance as outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[6] Therefore, for each eligible study we will extract information to assess for:

1. **Bias arising from the randomisation process**: Sequence generation and methods of allocation concealment.

2. **Bias due to deviations from intended interventions:** Blinding of participants and personnel, intention to treat analysis.

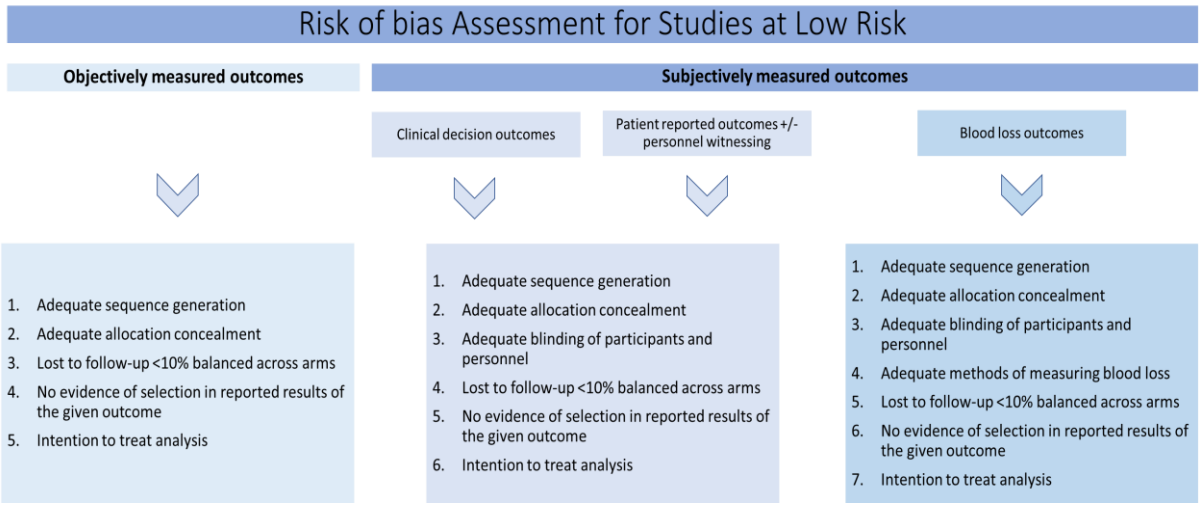
3. **Bias in the measurement of the outcome:** Methods of measuring blood loss.

4. **Bias due to missing outcome data:** Lost to follow-up cases.

5. **Bias in selection of the reported result:** Protocol registration records.

The risk of bias assessment will be performed on an outcome-level instead of a study-level. The same study might be at high risk of bias for a given outcome, whereas for another outcome it might be at low risk, as shown in *Figure 4.*

Figure 4: Risk of Bias assessment for low-risk studies



Trustworthiness assessment

The Cochrane Pregnancy and Childbirth Group has introduced the trustworthiness assessment of randomised studies after the identification of fraudulent studies.[9-11] Four domains are assessed, namely research governance, baseline characteristics, feasibility, and results. The reasons to judge a study as 'high risk' after the trustworthiness assessment are listed below:

1. Research governance

- No prospective trial registration for studies published after 2010.[6,12,13]
- Primary study authors refuse to engage in communication with systematic review authors or refuse to share the protocol of their study and/or the ethics approval letter of the local institutional review board, or refuse to share the IPD data.

2. Baseline characteristics

- Baseline characteristics of randomised study participants are identical or too similar.[6,11]

3. Feasibility

- Zero or close to zero lost to follow-up cases.

- Very fast recruitment, especially if the population of interest is very rare and the recruitment site is not a referral centre.

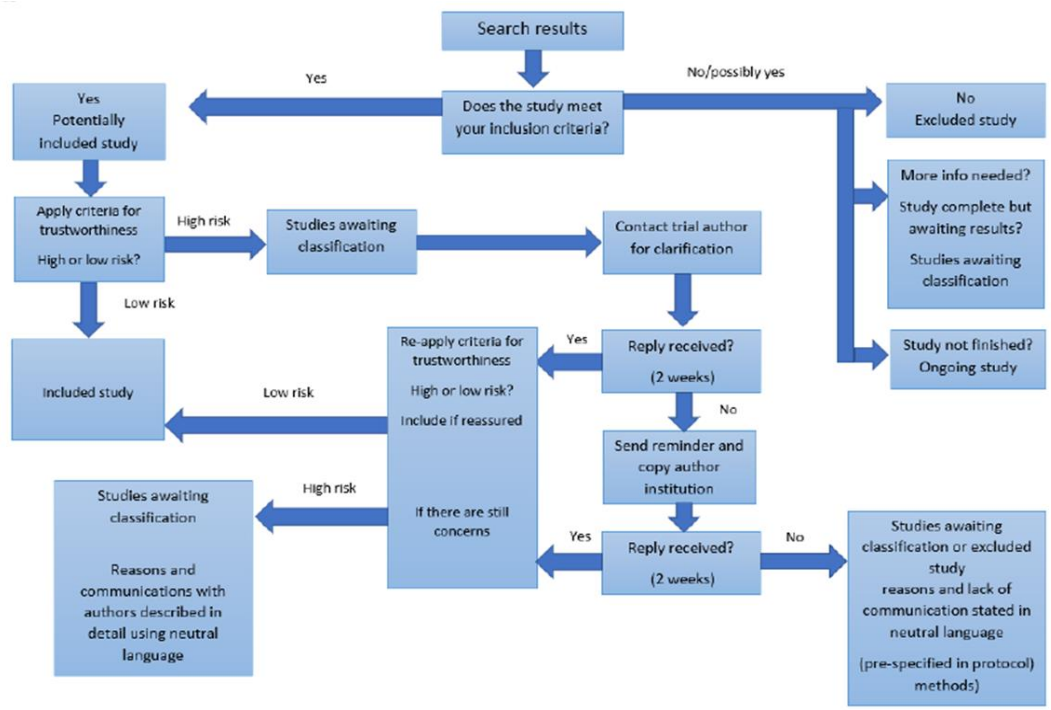
4. Results

- Implausible results.
- Unexpectedly even numbers of women ‘randomised’ including a mismatch between the numbers and the methods.

The assessment process is illustrated in

Figure 5.

Figure 5: Cochrane's tool for assessing the trustworthiness of a study



Data analysis

Pairwise meta-analyses using a random-effects model for every available treatment comparison will be performed.[6,14,15] Network meta-analyses within a frequentist framework using multivariate meta-analysis estimated by restricted maximum likelihood will be also performed.[16-17] The Stata® statistical software release 17 will be used for all analyses.[18]

For dichotomous outcomes, relative treatment effects will be summarised as risk ratios (RR) with 95% confidence intervals (CI). For continuous outcomes, mean difference (MD) with 95% CI will be used.[6] In order to create a ranking of relative treatment effects, cumulative probabilities will be calculated and the surface under the cumulative ranking curve (SUCRA) will be used to obtain treatment hierarchies.[6,19-21]

As previously discussed, indirectness across all contributing pairwise comparisons will be assessed. In case most weight is provided by studies where indirectness is noted, the respective pairwise comparisons will not contribute to the NMA. That is because high levels of indirectness will question the transitivity assumption, and thus the validity of the respective NMA. Through the same prism, high levels of statistical heterogeneity, quantified with the I^2 statistic, will be further assessed using subgroup analyses to identify the distribution of potential effect modifiers. If heterogeneity remains high, even within the subgroups, the respective direct comparison will be excluded from the NMA.[22-24] In terms of consistency, also known as coherence of the network, the 'design-by-treatment' interaction model will be also used to evaluate the validity of the network.[7,25]

Unit of analysis issues

The number of clusters, the available outcome data irrespectively of the unit of randomisation, and an estimation of the Intra-cluster Correlation Co-efficient (ICC) will be used.[6]

Subgroup and sensitivity analyses

The following **subgroup analyses** will be performed for the two primary outcomes (PPH ≥500 mL, PPH ≥1000 mL):

1. According to prior risk of PPH: women at high risk, women at low risk.
2. According to the mode of birth: women delivering vaginally, women having a caesarean section.
3. According to study setting: women delivering in a hospital setting, women delivering in community settings.

The following **sensitivity analyses** will be performed for the two primary outcomes (PPH ≥500 mL, PPH ≥1000 mL):

1. Excluding 'high' risk of bias studies.
2. Excluding studies assessed as 'high' risk of bias for the 'funding source' domain, i.e., excluding industry-funded studies.
3. Excluding studies assessed as 'high' risk of bias for the 'blood loss measurement' domain, i.e., studies reporting subjective methods of measuring blood loss.
4. Excluding studies at 'high' risk for incomplete outcome.
5. Excluding studies involving <400 participants.[26,27]

GRADE assessment

For the outcomes reported in the Summary of Findings (SoF) tables, i.e., PPH ≥500 mL, PPH ≥1000 mL, additional uterotonics, blood transfusion, vomiting, hypertension, and fever, the grade of the generated evidence will be assessed.[28,29] This process will be performed in three stages:

1. **Grade assessment of the <u>direct evidence</u> according to relevant WHO standard operating procedures and guidance by the GRADE working group:**

    a. **Study design limitations:** Based on the RoB assessment, as described in section *'Risk of Bias assessment'.* When most weight of the summary effect estimate is provided by studies without design limitations-studies type A, the certainty of the evidence will not be downgraded. When most weight is provided by studies with some design limitations-studies type B, the certainty of the generated evidence will be downgraded only once. However, when studies with severe design limitations-studies type C contribute the most weight to the summary effect estimate, the certainty of the generated evidence will be downgraded twice.[30,31]

    b. **Indirectness:** In the presence of indirect PICO the certainty of the evidence will be downgraded once. However, if studies with indirect PICO contribute most weight to the effect estimate, as previously discussed, the pairwise comparison will be totally excluded.[30,32]

    c. **Heterogeneity:** When I^2 ≥60% and no imprecision due to wide confidence intervals is present, the generated evidence will be downgraded once. When I^2

≥60% and imprecision due to wide confidence intervals is present with single study estimates pointing towards: (a) opposite directions, the generated evidence will not be downgraded for heterogeneity, (b) the same direction, the generated evidence will be downgraded once for heterogeneity and at least once for imprecision.[29,33,34]

d. **Imprecision:** When CIs are wide and include the line of no effect (0 for continuous and 1 for binary outcomes, respectively) the generated evidence will be downgraded once. The generated evidence will be also downgraded once if the total sample size is small (<300 participants for binary and <400 participants for continuous outcomes). In case of small number of events (<30 for binary outcomes) with adequate sample size the generated evidence will be downgraded once.[29,34]

e. **Publication bias:** Visual assessment of the funnel plot when at least 10 studies are plotted. In case of funnel plot asymmetry and high level of suspicion for publication bias (e.g., statistically significant results favouring a given intervention with high levels of heterogeneity), contour enhanced funnel plots will be created. If results tend to appear in the statistically significant areas and missing from the non-statistically significant ones, the generated evidence will be downgraded once.[29,35,36]

2. **GRADE assessment of the indirect evidence according to guidance by the GRADE working group:** For a given comparison, the dominant first order loop will be used for the assessment. The least favourable grade assessment of the generated direct evidence

from the two most contributing arms will be used as the level of certainty for the generated indirect evidence.[37,38]

3. **GRADE assessment of the network evidence according to guidance by the GRADE working group:** For a given comparison, the grade assessment of the respective direct and indirect evidence will be evaluated. The most favourable of the two grade assessments (direct and indirect) will be used as the grade assessment for the certainty of the network evidence, when results are coherent. In case of incoherence, the certainty of the generated network evidence will be further downgraded once. [37,38]

Reporting of results

For each of the **GRADE outcomes** of this project (PPH ≥500 mL, PPH ≥1000 mL, additional uterotonics, blood transfusion, vomiting, hypertension, and fever), a SoF Table will be created, presenting the relative and absolute treatment effects for all available uterotonic drugs compared against the reference uterotonic drug for the specific NMA (oxytocin IM and oxytocin 10 IU for the *Routes-NMA* and the *Doses-NMA*, respectively). Network diagrams with grading of the certainty of the direct evidence, forestplots presenting direct, indirect and network estimates, and rankograms with SUCRAs will be also presented.

For each of the **additional outcomes** (maternal death, maternal morbidity-ICU admissions, maternal morbidity-shock, mean blood loss, change in haemoglobin measurements before and after delivery, breastfeeding at discharge, abdominal pain, diarrhoea, headache, nausea, shivering, maternal sense of well-being and maternal satisfaction), network diagrams, forestplots presenting direct, indirect and network estimates, and rankograms with SUCRAs will be presented. The certainty of the evidence will not be graded and no SoF tables will be created.

For **subgroup and sensitivity analyses** network diagrams, forestplots presenting direct, indirect and network estimates, and rankograms with SUCRAs will be presented. The certainty of the evidence will not be graded and no SoF tables will be created.

CHAPTER 3: RESULTS FOR THE ROUTE NMA

Study characteristics

The study flow diagram is available in

Based on the above, larger scale randomised trials assessing different routes and doses of administration need to be conducted. Additionally, there is an urgent need for studies testing uterotonics that are not commonly used either because of licensing reasons, financial constraints, or theoretically expected side effects. In any case, future studies should focus not only on reporting blood loss related outcomes and side effects, but also on women's views and acceptability of the interventions.

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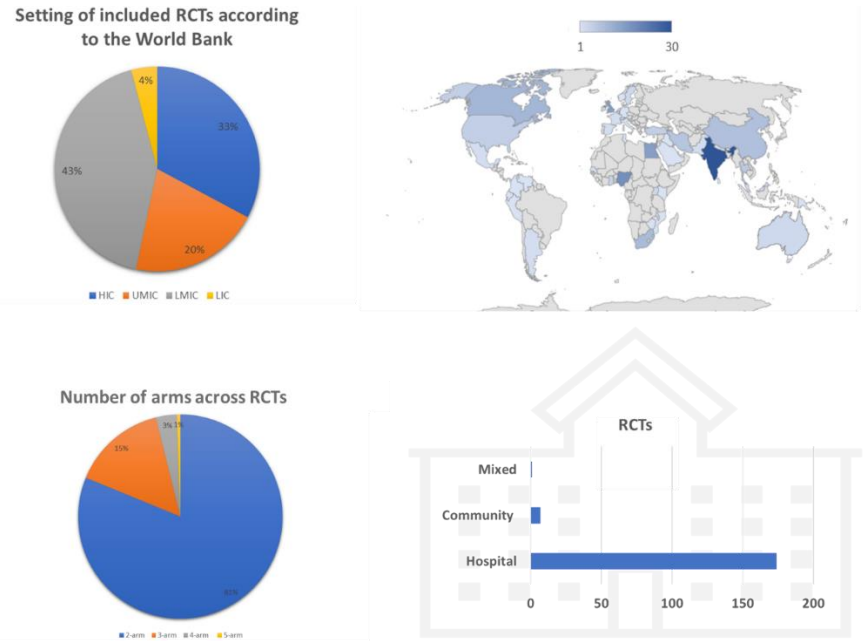
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APPENDIX 1: Additional information Routes-NMA & Doses-NMA. One hundred eighty-one studies, involving 122,867 randomised women, contributed data to the Route-NMA. Most studies (81%) included two arms, twenty-seven (15%) had three arms, six (3%) had 4 arms, and only one (1%) had 5 arms. Most studies (95%) were conducted in a hospital setting, seven (4%) were conducted in a community setting, and only one (1%) took place in a mixed setting. According to the World Bank classification, most studies (43%) were conducted in lower-middle income countries (LMIC), one third was conducted in high income countries (HIC), one fifth in upper-middle income countries (UMIC), and only 4% in low-income countries (LIC). India was the country where most studies were conducted. All information listed above is summarised in *Figure 6.*

Figure 6: Characteristics of studies included in the Routes-NMA



Participant characteristics across included studies

Participant characteristics are summarised in *Figure 7.* In most included studies (69%) women had a vaginal delivery, in 30% of cases participants delivered by a caesarean section, and in the remaining 1% of available studies the population was mixed, consisting of both vaginal and caesarean births. Among the fifty-four studies where women had a caesarean birth, 48% corresponded to elective caesarean sections (ELCS), 11% to emergency caesarean sections (EMCS), 37% to both ELCS and EMCS, whereas in the remaining 4% the type of caesarean section was not further specified. In one hundred twenty-six studies (70%) women had a singleton pregnancy, in only two studies (1%) the gestation was multiple, in 18% of contributing studies both singleton and multiple gestations were included, and in the remaining twenty studies (11%) the type of gestation was not further specified. In 39% of included studies participants were found to be at high risk for PPH, whereas in 25% of studies the respective risk was judged to be low. In one third of available studies both high and low risk for PPH cases were enrolled. In only 1% of contributing studies the risk for excessive bleeding after birth was not specified by authors neither was possible to assess.

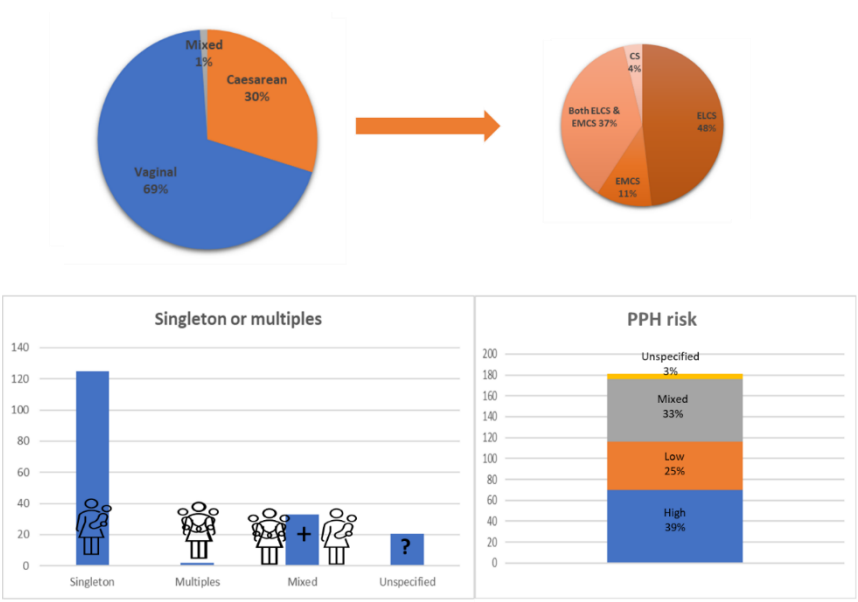


Figure 7: Participant characteristics for studies included in the Routes-NMA

Uterotonic interventions contributing to the analyses

One hundred eighty-one studies were available for the Routes-NMA and included four hundred four arms. From the total available arms 92% contributed data to the analyses as shown in *Table 3.* The remaining 8% of available arms were excluded for the following reasons: (a) the specific uterotonic intervention was excluded from the analysis (see *CHAPTER 2: METHODS*), (b) a non-uterotonic agent was tested, and (c) a non-pharmaceutical intervention was tested.

Table 3: Study arms for the Routes-NMA

Available studies included in total 404 arms				
Included		% of Included	Excluded	
Oxytocin IM	48	12.9	**Uterotonic interventions**	
Oxytocin IV(B)	41	11.1	Oxytocin IM+IV(I)	2
Oxytocin IV(I)	42	11.3	Oxytocin IV(I) given after 3rd stage	1
Oxytocin IV(B+I)	22	5.9	Oxytocin intraumbilically	1
Carbetocin IM	9	2.4	Intramyometrial Carboprost	1
Carbetocin IV(B)	26	7.0	Carboprost plus Oxytocin IM plus IV(B+I)	1
Carbetocin IV(I)	3	0.8	Ergometrine plus Oxytocin IV(B)	2
Carboprost IM	12	3.2	Ergometrine plus Oxytocin IV(B+I)	2
Ergometrine IM	12	3.2	Ergometrine plus Oxytocin IM plus IV(B)	1
Ergometrine IV(B)	17	4.6	Ergometrine plus Oxytocin IM plus IV(I)	2
Misoprostol PO	36	9.7	Misoprostol plus Oxytocin PO plus IV(B)	2
Misoprostol PR	22	5.9	Misoprostol plus Oxytocin PR plus IM	1
Misoprostol SL	29	7.8	Misoprostol plus Oxytocin PR plus IV(B)	1
Syntometrine and Syntometrine-like IM	27	7.3	Misoprostol plus Oxytocin PR plus IV(I)	4
Sulprostone IM	2	0.5	Misoprostol plus Oxytocin SL plus IM	1
Placebo or control	23	6.2	Misoprostol plus Oxytocin SL plus IM+IV(I)	1
Total	**371**	**100**	Misoprostol plus Oxytocin SL plus IV(B)	1
			Misoprostol plus Oxytocin SL plus IV(B+I)	1
			Misoprostol plus Oxytocin SL plus IV(I)	5
			Misoprostol plus Oxytocin SL+PR plus IM	1
			Non-uterotonic interventions	
			Acupuncture	1
			Tranexamic acid	1
			Total	**33**

Risk of bias

Nine domains were assessed for risk of bias and the respective summary is presented in *Figure 8*. For most domains of assessment at least 50% of included studies were found to be at 'low' risk of bias. For the domains of 'selective reporting' and 'funding source' most studies were judged to be at 'unclear' risk.

Selection bias:

One hundred thirty-seven studies (76%) reported adequate methods of random sequence generation in sufficient detail, whereas the remaining forty-four (24%) did not provide this information and were found to be at unclear risk of bias for this domain. In terms of allocation concealment, about half studies (55%) were judged to be at low risk of bias for this domain. In seventy-nine studies (44%), authors did not provide sufficient information on the methods used to conceal the allocation or the reported methods might have failed (e.g., small block randomisation), and these studies were assessed as 'unclear' risk for this domain. In only three studies (1%) investigators made no attempt to conceal the allocation of the randomised interventions, and thus these studies were judged to be at 'high' risk.

Performance bias:

In eighty-four studies (46%), randomised participants and attending personnel were adequately blinded to the allocated interventions, and thus these studies were found to be at 'low' risk for performance bias. Another 30% of included studies was judged to be at 'unclear' risk for this domain since authors did not describe blinding methods. In the remaining forty-four studies (24%), no effort was made to blind participants and personnel to the allocated uterotonics, and these studies were assessed as 'high' risk for performance bias.

Detection bias:

In almost half of the included studies (46%), outcome assessors were adequately blinded to the randomised interventions; we judged these studies as 'low' risk for detection bias. In seventy-six studies (42%), the risk for this domain was found to be 'unclear' since no relevant information was provided in the study report, or the available information was vague. Twelve per cent of the contributing studies were assessed as 'high' risk for detection bias given that outcome assessors were not masked to the randomised interventions.

Objective assessment of blood loss:

About half of the included studies (54%) reported adequate methods of blood loss assessment (e.g., calibrated drapes and bedpans) and were assessed as 'low' risk of bias fir this domain. Thirty-five studies (19%) did not report methods of measuring blood loss, or the objectivity of the applied methods was questioned during the risk of bias assessment, and thus these studies were found to be at 'unclear' risk. The remaining forty-eight studies (27%) were judged to be at 'high' risk for blood loss measurements, since reported results relied on visual estimations of the attending personnel.

Attrition bias:

Most studies (74%) reported <10% lost to follow-up cases and attrition was balanced across arms; these studies were assessed as 'low' risk of bias for this domain. In thirty-one studies (17%), it was not specified whether there were any lost to follow-up randomised participants, and thus these cases were found to be at 'unclear' risk for incomplete outcome. In 9% of included studies, lost to follow-up cases were >10%, or attrition was not balanced across study arms; the final assessment for these sixteen studies was 'high' risk for attrition bias.

Reporting bias:

In 16% of included studies, a prospectively registered protocol was available and matching the study report; these studies were found to be at 'low' risk for reporting bias. For most contributing studies (76%) no protocol was available, or it was registered after the enrolment of the first case, and thus these studies were judged as 'unclear' risk for this domain. The remaining fourteen studies (8%) were assessed as 'high' risk for reporting bias either because the published protocol was not matching the study report or because there was obvious selection in the reporting of results (e.g., reported methods of blood loss measurement or algorithm for additional uterotonic administration without reporting of the respective results).

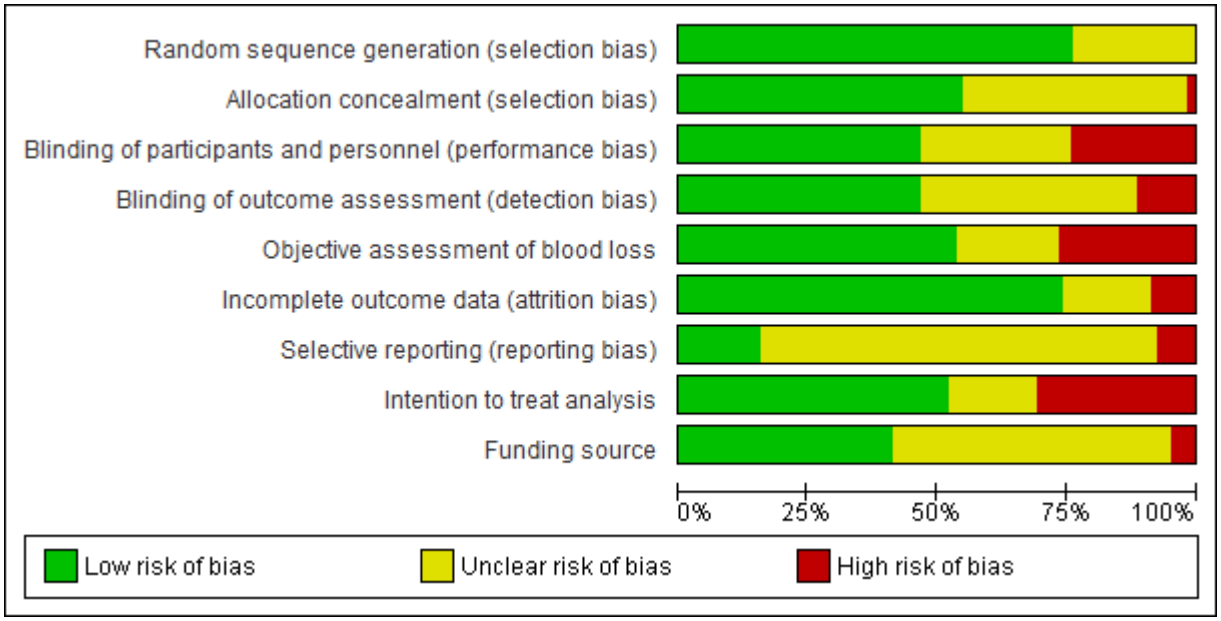
Intention to treat analysis:

Half of the included studies (52%) reported analysis of results on an intention-to-treat basis and were judged to be at 'low' risk for this domain. In thirty-one studies (17%), it was not clear whether all randomised participants were analysed in the groups in which they were initially randomised. Therefore, these studies were assessed as 'unclear' risk for this domain. In fifty-six studies (31%), post-randomisation exclusions were noted and the overall risk for this bias domain was found to be 'high'.

Funding source:

Seventy-four studies (41%) received university or institutional funds or were supported by non-governmental organizations; these studies were judged to be at 'low' risk for this domain. However, in most cases (54%), funding sources were not reported, and thus these studies were assessed as 'unclear' risk. The remaining nine studies (5%) were found to be at 'high' risk of bias since financial support was provided by pharmaceutical companies.

Figure 8: Risk of bias summary for the Routes-NMA



Summary of Findings Tables

Table 4: PPH ≥500 mL-Summary of Findings Table-Routes-NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: PPH ≥500 mL

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	0.78 0.62-0.97 HIGH	0.78 0.59-1.04 LOW[1]	0.75 0.59-0.97 HIGH	115 per 1000	86 per 1000	29 fewer per 1000 (from 4 to 47 fewer)
Oxytocin IV(I)	0.77 0.60-0.99 HIGH	0.95 0.70-1.30 LOW[1]	0.87 0.67-1.11 MODERATE[1]	115 per 1000	100 per 1000	15 fewer per 1000 (from 38 fewer to 13 more)
Oxytocin IV(B+I)	Not estimable	Not estimable	0.71 0.41-1.25 MODERATE[2]	115 per 1000	82 per 1000	33 fewer per 1000 (from 68 fewer to 29 more)
Carbetocin IM	0.99 0.92-1.06 HIGH	0.56 0.32-1.00 LOW[1]	0.73 0.48-1.12 MODERATE[3]	115 per 1000	84 per 1000	31 fewer per 1000 (from 60 fewer to 14 more)
Carbetocin IV(B)	Not estimable	Not estimable	0.58 0.40-0.84 MODERATE[2]	115 per 1000	67 per 1000	48 fewer per 1000 (from 18 to 69 fewer)
Carbetocin IV(I)	Not estimable	Not estimable	0.96 0.47-1.94 MODERATE[2]	115 per 1000	110 per 1000	5 fewer per 1000 (from 61 fewer to 108 more)
Carboprost IM	1.86 0.07-51.05 VERY LOW[1]	1.15 0.68-1.96 LOW[1]	1.16 0.71-1.88 LOW[4]	115 per 1000	133 per 1000	18 more per 1000 (from 33 fewer to 101 more)
Ergometrine IM	0.25 0.07-0.88 MODERATE[2]	1.61 1.04-2.51 LOW[2]	1.35 0.88-2.07 LOW[5]	115 per 1000	155 per 1000	40 more per 1000 (from 14 fewer to 123 more)
Ergometrine IV(B)	1.39 0.70-2.74 LOW[3]	0.65 0.42-1.02 LOW[1]	0.76 0.51-1.13 VERY LOW[6]	115 per 1000	87 per 1000	28 fewer per 1000 (from 56 fewer to 14 more)
Misoprostol PO	1.14 0.77-1.69 MODERATE[4]	0.78 0.59-1.05 MODERATE[3]	0.91 0.72-1.14 LOW[7]	115 per 1000	105 per 1000	10 fewer per 1000 (from 32 fewer to 16 more)
Misoprostol	0.67	1.00	0.87	115 per	100 per	15 fewer per

PR	0.39-1.13 VERY LOW[5]	0.65-1.55 VERY LOW[4]	0.61-1.24 VERY LOW[8]	1000	1.000	1000 (from 45 fewer to 28 more)
Misoprostol SL	0.86 0.42-1.79 MODERATE[4]	1.06 0.77-1.47 MODERATE[3]	1.02 0.78-1.32 MODERATE[9]	115 per 1000	117 per 1.000	2 more per 1000 (from 25 fewer to 37 more)
Syntometrine and Syntometrine-like IM	0.78 0.53-1.15 LOW[3]	0.70 0.50-0.97 MODERATE[2]	0.71 0.56-0.91 MODERATE[10]	115 per 1000	82 per 1.000	33 fewer per 1000 (from 10 to 51 fewer)
Sulprostone IM	0.91 0.33-2.48 VERY LOW[1]	0.75 0.12-4.56 VERY LOW[5]	0.86 0.31-2.39 VERY LOW[8]	115 per 1000	99 per 1.000	16 fewer per 1000 (from 79 fewer to 160 more)
Placebo or control	1.59 1.27-1.99 MODERATE[6]	1.41 1.03-1.93 MODERATE[2]	1.52 1.22-1.90 MODERATE[11]	115 per 1000	175 per 1.000	60 more per 1000 (from 25 to 104 more)

Direct evidence:
1. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
2. Downgraded -1 due to serious imprecision (small number of events).
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.
4. Downgraded -1 due to serious imprecision (wide CIs).
5. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
6. Downgraded -1 due to crucial limitations in study design.

Indirect evidence:
1. Downgraded -2 due to crucial limitations in study design and serious imprecision.
2. Downgraded -1 due to crucial limitations in study design.
3. Downgraded -1 due to serious imprecision.
4. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
5. Downgraded -3 due to crucial limitations in study design and very serious imprecision.

Network evidence:
1. Downgraded -1 due to high certainty direct evidence and imprecision of the network estimate (no intransitivity, no incoherence).
2. Downgraded -1 due to moderate certainty indirect loop evidence.
3. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
4. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
5. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
6. Downgraded -3 due to low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
7. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
8. Downgraded -3 due to very low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
9. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
10. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, no imprecision).
11. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence, no imprecision).

Table 5: PPH ≥1000 mL-Summary of Findings Table-Routes NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: PPH ≥1000 mL

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	0.56 0.35-0.89 HIGH	1.03 0.75-1.42 MODERATE[1]	0.86 0.64-1.15 MODERATE[1]	26 per 1000	22 per 1000	4 fewer per 1000 (from 9 fewer to 4 more)
Oxytocin IV(I)	0.81 0.31-2.12 MODERATE[1]	1.32 0.84-2.07 VERY LOW[2]	1.09 0.75-1.57 LOW[2]	26 per 1000	28 per 1000	2 more per 1000 (from 7 fewer to 15 more)
Oxytocin IV(B+I)	Not estimable	Not estimable	0.70 0.47-1.05 MODERATE[3]	26 per 1000	18 per 1000	8 fewer per 1000 (from 14 fewer to 1 more)
Carbetocin IM	1.05 0.87-1.26 HIGH	0.54 0.08-3.53 VERY LOW[2]	1.02 0.70-1.48 MODERATE[1]	26 per 1000	27 per 1000	1 more per 1000 (from 8 fewer to 13 more)
Carbetocin IV(B)	Not estimable	Not estimable	0.76 0.50-1.14 MODERATE[3]	26 per 1000	20 per 1000	6 fewer per 1000 (from 13 fewer to 4 more)
Carbetocin IV(I)	Not estimable	Not estimable	1.07 0.44-2.59 MODERATE[3]	26 per 1000	28 per 1000	2 more per 1000 (from 15 fewer to 41 more)
Carboprost IM	5.00 0.25- 99.16 VERY LOW[2]	1.48 0.42-5.18 VERY LOW[3]	1.97 0.66-5.87 VERY LOW[4]	26 per 1000	51 per 1000	25 more per 1000 (from 9 fewer to 127 more)
Ergometrine IM	Not estimable	Not estimable	1.01 0.35-2.87 MODERATE[3]	26 per 1000	26 per 1000	No difference per 1000 (from 17 fewer to 49 more)
Ergometrine IV(B)	1.33 0.40-4.41 LOW[3]	0.59 0.19-1.82 LOW[4]	0.88 0.38-2.01 LOW[5]	26 per 1000	23 per 1000	3 fewer per 1000 (from 16 fewer to 26 more)
Misoprostol PO	1.04 0.62-1.74 MODERATE[1]	1.13 0.78-1.62 MODERATE[1]	1.11 0.83-1.49 MODERATE[6]	26 per 1000	29 per 1000	3 more per 1000 (from 4 fewer to 13 more)
Misoprostol PR	0.32 0.06-1.63	0.99 0.56-1.73	0.88 0.51-1.50	26 per 1000	23 per 1000	3 fewer per 1000 (from

	VERY LOW[4]	VERY LOW[2]	VERY LOW[7]			13 fewer to 13 more)
Misoprostol SL	1.45 0.80-2.62 MODERATE[1]	0.86 0.56-1.32 MODERATE[1]	1.00 0.70-1.42 LOW[8]	26 per 1000	26 per 1000	No difference per 1000 (from 8 fewer to 11 more)
Syntometrine and Syntometrine-like IM	0.82 0.62-1.08 VERY LOW[4]	0.77 0.47-1.27 VERY LOW[2]	0.79 0.59-1.06 VERY LOW[9]	26 per 1000	21 per 1000	5 fewer per 1000 (from 11 fewer to 2 more)
Sulprostone IM	0.64 0.06-6.57 VERY LOW[2]	0.49 0.02-12.59 VERY LOW[3]	0.59 0.07-4.87 VERY LOW[9]	26 per 1000	15 per 1000	11 fewer per 1000 (from 24 fewer to 101 more)
Placebo or control	1.86 1.41-2.47 MODERATE[1]	1.31 0.95-1.81 MODERATE[1]	1.54 1.21-1.97 LOW[10]	26 per 1000	40 per 1000	14 more per 1000 (from 6 to 25 more)

Direct evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.
4. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
5. Downgraded -1 due to crucial limitations in study design.

Indirect evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
4. Downgraded -2 due to crucial limitations in study design and serious imprecision.

Network evidence:
1. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
2. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
3. Downgraded -1 due to moderate certainty indirect loop evidence.
4. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
5. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
6. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
7. Downgraded -3 due to very low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
8. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
9. Downgraded -3 due to very low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
10. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).

Table 6: Additional uterotonics-Summary of Findings Table-Routes NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: Additional uterotonics

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	0.92 0.75-1.12 HIGH	0.65 0.44-0.96 MODERATE[1]	0.69 0.49-0.97 MODERATE[1]	122 per 1000	84 per 1000	38 fewer per 1000 (from 4 to 62 fewer)
Oxytocin IV(I)	0.77 0.38-1.55 LOW[1]	0.98 0.66-1.45 LOW[2]	0.91 0.65-1.27 LOW[2]	122 per 1000	111 per 1000	11 fewer per 1000 (from 43 fewer to 33 more)
Oxytocin IV(B+I)	0.14 0.01-2.74 VERY LOW[2]	0.50 0.31-0.83 MODERATE[1]	0.49 0.30-0.80 LOW[3]	122 per 1000	60 per 1000	62 fewer per 1000 (from 24 to 85 fewer)
Carbetocin IM	1.00 0.94-1.06 HIGH	0.52 0.29-0.96 MODERATE[1]	0.69 0.43-1.09 MODERATE[4]	122 per 1000	84 per 1000	38 fewer per 1000 (from 70 fewer to 11 more)
Carbetocin IV(B)	Not estimable	Not estimable	0.31 0.20-0.48 MODERATE[5]	122 per 1000	38 per 1000	84 fewer per 1000 (from 63 to 98 fewer)
Carbetocin IV(I)	Not estimable	Not estimable	0.88 0.34-2.31 MODERATE[5]	122 per 1000	107 per 1000	15 fewer per 1000 (from 81 fewer to 160 more)
Carboprost IM	0.71 0.03-16.54 VERY LOW[2]	0.65 0.31-1.37 LOW[2]	0.57 0.30-1.08 LOW[2]	122 per 1000	70 per 1000	52 fewer per 1000 (from 85 fewer to 10 more)
Ergometrine IM	0.32 0.17-0.60 MODERATE[1]	1.32 0.69-2.51 LOW[2]	0.94 0.53-1.67 LOW[6]	122 per 1000	115 per 1000	7 fewer per 1000 (from 57 fewer to 82 more)
Ergometrine IV(B)	1.22 0.82-1.83 LOW[1]	0.69 0.39-1.23 LOW[2]	0.79 0.47-1.30 VERY LOW[7]	122 per 1000	96 per 1000	26 fewer per 1000 (from 65 fewer to 37 more)
Misoprostol PO	1.20 0.85-1.69 LOW[1]	0.84 0.56-1.25 LOW[2]	1.00 0.75-1.33 VERY LOW[7]	122 per 1000	122 per 1000	No difference per 1000 (from 31 fewer to 40 more)
Misoprostol PR	0.49 0.31-0.77 MODERATE[4]	1.07 0.66-1.75 LOW[2]	0.83 0.56-1.23 LOW[6]	122 per 1000	101 per 1000	21 fewer per 1000 (from 54 fewer to

						28 more)
Misoprostol SL	0.95 0.50-1.81 MODERATE[4]	0.68 0.44-1.05 VERY LOW[3]	0.75 0.52-1.07 MODERATE[8]	122 per 1000	92 per 1000	30 fewer per 1000 (from 59 fewer to 9 more)
Syntometrine and Syntometrine-like IM	0.81 0.69-0.96 MODERATE[4]	0.67 0.43-1.02 MODERATE[4]	0.73 0.52-1.02 LOW[6]	122 per 1000	89 per 1000	33 fewer per 1000 (from 59 fewer to 2 more)
Sulprostone IM	1.26 0.03-61.15 VERY LOW[2]	0.16 0.00-21.53 VERY LOW[5]	0.55 0.02-12.24 VERY LOW[9]	122 per 1000	67 per 1000	55 fewer per 1000 (from 120 fewer to 1000 more)
Placebo or control	2.16 1.44-3.22 LOW[5]	2.06 1.32-3.21 MODERATE[1]	2.09 1.47-2.96 MODERATE[10]	122 per 1000	255 per 1000	133 more per 1000 (from 57 to 239 more)

Direct evidence:
1. Downgraded -2 due to crucial limitations in study design and serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -1 due to serious imprecision.
4. Downgraded -1 due to crucial limitations in study design.
5. Downgraded -2 due to crucial limitations in study design.

Indirect evidence:
1. Downgraded -1 due to limitations in study design.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
4. Downgraded -1 due to serious imprecision.
5. Downgraded -3 due to crucial limitations in study design and very serious imprecision.

Network evidence:
1. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
2. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
3. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
4. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
5. Downgraded -1 due to moderate certainty indirect loop evidence.
6. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
7. Downgraded -3 due to low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
8. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence, imprecision present).
9. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
10. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence, no imprecision).

Table 7: Blood transfusion-Summary of Findings Table-Routes NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: Blood transfusion

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	0.34 0.16-0.72 HIGH	0.79 0.49-1.28 LOW[1]	0.61 0.40-0.93 MODERATE[1]	17 per 1000	10 per 1000	7 fewer per 1000 (from 1 to 10 fewer)
Oxytocin IV(I)	0.59 0.27-1.29 LOW[1]	0.87 0.45-1.67 LOW[1]	0.75 0.45-1.25 LOW[2]	17 per 1000	13 per 1000	4 fewer per 1000 (from 9 fewer to 4 more)
Oxytocin IV(B+I)	0.33 0.01-8.12 LOW[1]	0.49 0.23-1.04 LOW[1]	0.48 0.23-1.00 LOW[3]	17 per 1000	8 per 1000	9 fewer per 1000 (from no difference to 13 fewer)
Carbetocin IM	1.09 0.91-1.32 MODERATE[2]	1.04 0.39-2.83 MODERATE[2]	1.06 0.77-1.46 MODERATE[4]	17 per 1000	18 per 1000	1 more per 1000 (from 4 fewer to 8 more)
Carbetocin IV(B)	Not estimable	Not estimable	0.39 0.21-0.70 MODERATE[5]	17 per 1000	7 per 1000	10 fewer per 1000 (from 5 to 13 fewer)
Carbetocin IV(I)	Not estimable	Not estimable	0.37 0.04-3.07 MODERATE[5]	17 per 1000	6 per 1000	11 fewer per 1000 (from 16 fewer to 35 more)
Carboprost IM	1.01 0.04-23.65 VERY LOW[3]	0.25 0.03-2.09 VERY LOW[3]	0.66 0.17-2.62 VERY LOW[6]	17 per 1000	11 per 1000	6 fewer per 1000 (from 14 fewer to 28 more)
Ergometrine IM	0.11 0.01-0.88 HIGH	0.93 0.19-4.66 LOW[1]	0.42 0.12-1.52 LOW[7]	17 per 1000	7 per 1000	10 fewer per 1000 (from 15 fewer to 9 more)
Ergometrine IV(B)	1.30 0.26-6.56 LOW[1]	0.88 0.28-2.76 LOW[1]	1.01 0.40-2.57 LOW[3]	17 per 1000	17 per 1000	No difference per 1000 (from 10 fewer to 27 more)
Misoprostol PO	0.72 0.29-1.79 LOW[1]	0.79 0.4-1.32 VERY LOW[4]	0.78 0.50-1.22 VERY LOW[8]	17 per 1000	13 per 1.000	4 fewer per 1000 (from 9 fewer to 4 more)
Misoprostol PR	0.55 0.22-1.39 LOW[1]	0.59 0.26-1.33 LOW[1]	0.57 0.31-1.06 LOW[3]	17 per 1000	10 per 1.000	7 fewer per 1000 (from 12 fewer to 1 more)

Misoprostol SL	0.69 0.35-1.37 MODERATE[2]	0.43 0.19-0.96 LOW[5]	0.57 0.33-0.97 MODERATE[7]	17 per 1000	10 per 1000	7 fewer per 1000 (from 1 to 11 fewer)
Syntometrine and Syntometrine-like IM	0.98 0.73-1.31 MODERATE[2]	0.71 0.44-1.16 MODERATE[2]	0.88 0.65-1.19 LOW[10]	17 per 1000	15 per 1000	2 fewer per 1000 (from 6 fewer to 3 more)
Sulprostone IM	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	1.35 0.75-2.45 VERY LOW[4]	1.40 0.82-2.39 LOW[1]	1.38 0.92-2.08 LOW[3]	17 per 1000	24 per 1000	7 more per 1000 (from 1 fewer to 18 more)

Direct evidence:
1. Downgraded -2 due to crucial limitations in study design and serious imprecision.
2. Downgraded -1 due to serious imprecision.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
4. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.

Indirect evidence:
1. Downgraded -2 due to crucial limitations in study design and serious imprecision.
2. Downgraded -1 due to serious imprecision.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
4. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
5. Downgraded -2 due to multiple crucial limitations in study design.

Network evidence:
1. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
2. Downgraded -2 due to low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
3. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
4. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence, imprecision present).
5. Downgraded -1 due to moderate certainty indirect loop evidence.
6. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
7. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
8. Downgraded -3 due to low certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
9. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence). The network estimate is precise unlike the direct estimate since the dominant contributor is the indirect estimate. Therefore, the evidence was not further upgraded.
10. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).

Table 8: Fever-Summary of Findings Table-Routes NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: Fever

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	Not estimable	Not estimable	0.43 0.12-1.59 LOW[1]	23 per 1000	10 per 1000	13 fewer per 1000 (from 20 fewer to 14 more)
Oxytocin IV(I)	1.01 0.02-50.61 LOW[1]	1.04 0.44-2.48 MODERATE[1]	1.04 0.45-2.42 MODERATE[2]	23 per 1000	24 per 1000	1 more per 1000 (from 13 fewer to 34 more)
Oxytocin IV(B+I)	Not estimable	Not estimable	2.27 0.58-8.93 LOW[1]	23 per 1000	52 per 1000	29 more per 1000 (from 10 fewer to 182 more)
Carbetocin IM	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin IV(B)	Not estimable	Not estimable	2.01 0.61-6.69 LOW[1]	23 per 1000	46 per 1000	23 more per 1000 (from 9 fewer to 131 more)
Carbetocin IV(I)	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carboprost IM	2.00 0.18-21.71 VERY LOW[2]	0.82 0.19-3.61 LOW[2]	1.01 0.28-3.69 LOW[2]	23 per 1000	23 per 1000	No difference per 1000 (from 17 fewer to 62 more)
Ergometrine IM	Not estimable	Not estimable	1.12 0.49-2.55 MODERATE[4]	23 per 1000	26 per 1000	3 more per 1000 (from 12 fewer to 36 more)
Ergometrine IV(B)	2.97 0.97-9.05 VERY LOW[2]	0.38 0.12-1.18 MODERATE[1]	0.82 0.33-2.08 LOW[5]	23 per 1000	19 per 1000	4 fewer per 1000 (from 15 fewer to 455 more)
Misoprostol PO	4.06 2.09-7.87 HIGH	4.71 1.89-11.73 MODERATE[3]	4.14 2.44-7.01 HIGH	23 per 1000	95 per 1000	72 more per 1000 (from 33 to 138 more)
Misoprostol	1.90 0.95-3.83	1.76 0.68-4.59	1.84 1.01-3.37	23 per 1000	42 per 1000	19 more per 1000

PR	LOW[3]	MODERATE[1]	MODERATE[6]			(from no difference to 55 more)
Misoprostol SL	4.64 2.65-8.12 HIGH	7.05 3.24-15.34 MODERATE[3]	6.20 3.38-11.38 HIGH	23 per 1000	143 per 1000	120 more per 1000 (from 55 to 239 more)
Syntometrine and Syntometrine-like IM	Not estimable	Not estimable	0.47 0.15-1.48 MODERATE[4]	23 per 1000	11 per 1000	12 fewer per 1000 (from 20 fewer to 11 more)
Sulprostone IM	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	Not estimable	Not estimable	1.12 0.48-2.57 MODERATE[4]	23 per 1000	26 per 1000	3 more per 1000 (from 12 fewer to 36 more)

Direct evidence:
1. Downgraded -2 due to very serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.

Indirect evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -1 due to crucial limitations in study design.

Network evidence:
1. Downgraded -2 due to low certainty indirect loop evidence.
2. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
3. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
4. Downgraded -1 due to moderate certainty indirect loop evidence.
5. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
6. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, no imprecision).

Table 9: Hypertension-Summary of Findings Table-Routes-NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: Hypertension

Uterotonic Agent	Direct Evidence	Anticipated absolute effects for Direct estimate		
	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	Not estimable	Not estimable	Not estimable	Not estimable
Oxytocin IV(I)	1.34 0.81-2.20 MODERATE[1]	75 per 1000	101 per 1000	26 more per 1000 (from 14 fewer to 90 more)
Oxytocin IV(B+I)	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin IM	0.98 0.78-1.23 HIGH	75 per 1000	74 per 1000	1 fewer per 1000 (from 17 fewer to 17 more)
Carbetocin IV(B)	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin IV(I)	Not estimable	Not estimable	Not estimable	Not estimable
Carboprost IM	Not estimable	Not estimable	Not estimable	Not estimable
Ergometrine IM	15.20 0.88-263.78 LOW[2]	75 per 1000	1.000 per 1000*	From 9 fewer to 1000 more**
Ergometrine IV(B)	Not estimable	Not estimable	Not estimable	Not estimable
Misoprostol PO	3.10 0.13-75.68 LOW[2]	75 per 1000	233 per 1000	158 more per 1000 (from 65 fewer to 1000 more) **
Misoprostol PR	3.93 0.44-35.88 VERY LOW[3]	75 per 1000	295 per 1000	220 more per 1000 (from 42 fewer to 1000 more) **
Misoprostol SL	Not estimable	Not estimable	Not estimable	Not estimable
Syntometrine and Syntometrine-like IM	1.72 1.40-2.11 HIGH	75 per 1000	129 per 1000	54 more per 1000 (from 30 to 83 more)
Sulprostone IM	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	Not estimable	Not estimable	Not estimable	Not estimable

***Risk with intervention >1.000 and **Upper CI >1.000**
1. Downgraded -1 due to serious imprecision.
2. Downgraded -2 due to very serious imprecision.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.

Table 10: Vomiting-Summary of Findings Table-Routes NMA

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Misoprostol PO, Misoprostol PR, Misoprostol SL, Syntometrine® and Syntometrine®-like IM, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: Vomiting

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin IV(B)	1.00 0.02-50.40 LOW[1]	0.60 0.29-1.22 VERY LOW[1]	0.61 0.30-1.23 LOW[1]	24 per 1000	14 per 1000	10 fewer per 1000 (from 17 fewer to 5 more)
Oxytocin IV(I)	1.01 0.02-50.61 LOW[1]	2.29 1.22-4.29 LOW[2]	2.25 1.21-4.17 VERY LOW[2]	24 per 1000	55 per 1000	31 more per 1000 (from 5 to 79 more)
Oxytocin IV(B+I)	Not estimable	Not estimable	1.05 0.44-2.54 LOW[3]	24 per 1000	25 per 1000	1 more per 1000 (from 13 fewer to 37 more)
Carbetocin IM	1.03 0.81-1.32 MODERATE[2]	0.52 0.22-1.24 MODERATE[3]	0.84 0.50-1.40 LOW[4]	24 per 1000	20 per 1000	4 fewer per 1000 (from 12 fewer to 10 more)
Carbetocin IV(B)	Not estimable	Not estimable	1.11 0.53-2.32 LOW[3]	24 per 1000	27 per 1000	3 more per 1000 (from 11 fewer to 32 more)
Carbetocin IV(I)	Not estimable	Not estimable	1.70 0.31-9.51 VERY LOW[5]	24 per 1000	41 per 1000	17 more per 1000 (from 17 fewer to 204 more)
Carboprost IM	5.00 0.24-102.85 VERY LOW[3]	2.78 1.14-6.77 LOW[4]	2.90 1.24-6.83 LOW[6]	24 per 1000	70 per 1000	46 more per 1000 (from 6 to 140 more)
Ergometrine IM	4.05 0.46-35.85 LOW[1]	1.59 0.79-3.18 LOW[4]	1.72 0.89-3.33 VERY LOW[7]	24 per 1000	41 per 1000	17 more per 1000 (from 3 fewer to 56 more)
Ergometrine IV(B)	1.37 0.23-8.17 LOW[4]	2.96 1.47-5.96 LOW[2]	2.66 1.37-5.15 VERY LOW[2]	24 per 1000	64 per 1000	40 more per 1000 (from 9 to 100 more)
Misoprostol PO	1.21 0.69-2.12 MODERATE[2]	1.80 1.07-3.02 MODERATE[5]	1.55 1.02-2.37 HIGH[8]	24 per 1000	37 per 1000	13 more per 1000 (from 1 to 33 more)

Misoprostol PR	1.22 0.61-2.43 **VERY LOW**[5]	2.65 1.15-6.10 **MODERATE**[3]	1.71 0.94-3.10 **LOW**[9]	24 per 1000	41 per 1000	17 more per 1000 (from 1 fewer to 50 more)
Misoprostol SL	2.05 1.25-3.37 **HIGH**	2.15 1.10-4.22 **LOW**[2]	2.23 1.35-3.69 **HIGH**	24 per 1000	54 per 1000	30 more per 1000 (from 8 to 65 more)
Syntometrine and Syntometrine-like IM	3.91 2.45-6.26 **MODERATE**[6]	2.37 1.39-4.04 **HIGH**	3.10 2.12-4.53 **MODERATE**[10]	24 per 1000	74 per 1000	50 more per 1000 (from 27 to 85 more)
Sulprostone IM	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	0.68 0.19-2.41 **VERY LOW**[5]	1.18 0.63-2.22 **MODERATE**[3]	1.09 0.61-1.96 **MODERATE**[11]	24 per 1000	26 per 1000	2 more per 1000 (from 9 fewer to 23 more)

Direct evidence:
1. Downgraded -2 due to very serious imprecision.
2. Downgraded -1 due to serious imprecision.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
4. Downgraded -2 due to crucial limitations in study design and serious imprecision.
5. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
6. Downgraded -1 due to severe unexplained statistical heterogeneity.

Indirect evidence:
1. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
2. Downgraded -2 due to multiple crucial limitations in study design.
3. Downgraded -1 due to serious imprecision.
4. Downgraded -2 due to crucial limitations in study design and serious imprecision.
5. Downgraded -1 due to crucial limitations in study design.

Network evidence:
1. Downgraded -2 due to low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
2. Downgraded -3 due to low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
3. Downgraded -2 due to low certainty indirect loop evidence.
4. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
5. Downgraded -3 due to very low certainty indirect loop evidence.
6. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, no imprecision).
7. Downgraded -3 due to low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
8. Dominant direct evidence downgraded for imprecision. Network evidence upgraded +1 since network estimate is precise (no intransitivity, no incoherence).
9. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
10. Downgraded -1 due to high certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
11. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, imprecision present).

GRADE outcomes

PPH ≥500 mL

Relative and absolute effects: The network diagram and the forest plot for PPH ≥500 mL are presented in *Figure 9* and *Figure 10* respectively. Local and global inconsistency were generally low.

When compared with oxytocin IM, high certainty evidence suggests that oxytocin IV(B) (RR 0.75, 95% CI 0.59-0.97) reduces the risk for PPH ≥500 mL. In absolute terms, 115 per 1,000 women given oxytocin IM will experience blood loss of at least 500 mL, compared with 86 women given oxytocin IV(B) (see *Table 4: PPH ≥500 mL-Summary of Findings Table-Routes-NMA*).

Based on moderate certainty evidence, oxytocin IV(I) (RR 0.87, 95% CI 0.67-1.11), oxytocin IV(B+I) (RR 0.71, 95% CI 0.41-1.25), carbetocin IM (RR 0.73, 95% CI 0.48-1.12), carbetocin IV(I) (RR 0.96, 95% CI 0.47-1.94), and misoprostol SL (RR 1.02, 95% CI 0.78-1.32) probably make little or no difference to the risk for PPH ≥500 mL, when compared to oxytocin IM. Additional moderate certainty evidence indicates that, when compared with oxytocin IM, carbetocin IV(B) (RR 0.58, 95% CI 0.40-0.84) and ergometrine plus oxytocin combination IM (RR 0.71, 95% CI 0.56-0.91) probably reduce the risk for this outcome. In contrast, moderate certainty evidence also suggests that placebo (RR 1.52, 95% CI 1.22-1.90) probably increases the risk for PPH ≥500 mL, when compared with oxytocin IM. These results suggest that for every 1,000 women receiving oxytocin IM, 115 will experience PPH ≥500 mL, compared with 67 given carbetocin IV(B), 82 given ergometrine plus oxytocin combination IM, and 175 given placebo (see *Table 4: PPH ≥500 mL-Summary of Findings Table-Routes-NMA*).

According to low certainty evidence, carboprost IM (RR 1.16, 95% CI 0.71-1.88), ergometrine IM (RR 1.35, 95% CI 0.88-2.07), and misoprostol PO (RR 0.91, 95% CI 0.72-1.14) may make little or no difference to this outcome, compared with oxytocin IM.

The evidence for ergometrine IV(B) (RR 0.76, 95% CI 0.51-1.13), misoprostol PR (RR 0.87, 95% CI 0.61-1.24), and sulprostone IM (RR 0.86, 95% CI 0.31-2.39), compared with oxytocin IM, was of very low certainty.

Cumulative probabilities: Among the active agents, carbetocin IV(B) was ranked first with 91.9% probability of being the best uterotonic drug for preventing PPH ≥500 mL, oxytocin IM was ranked twelfth with probability 32.2%, and ergometrine IM was ranked last with probability 12% *(Figure 11).*

Figure 9: PPH ≥500 mL-Network diagram-Routes NMA

Network diagram for PPH ≥500 mL. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

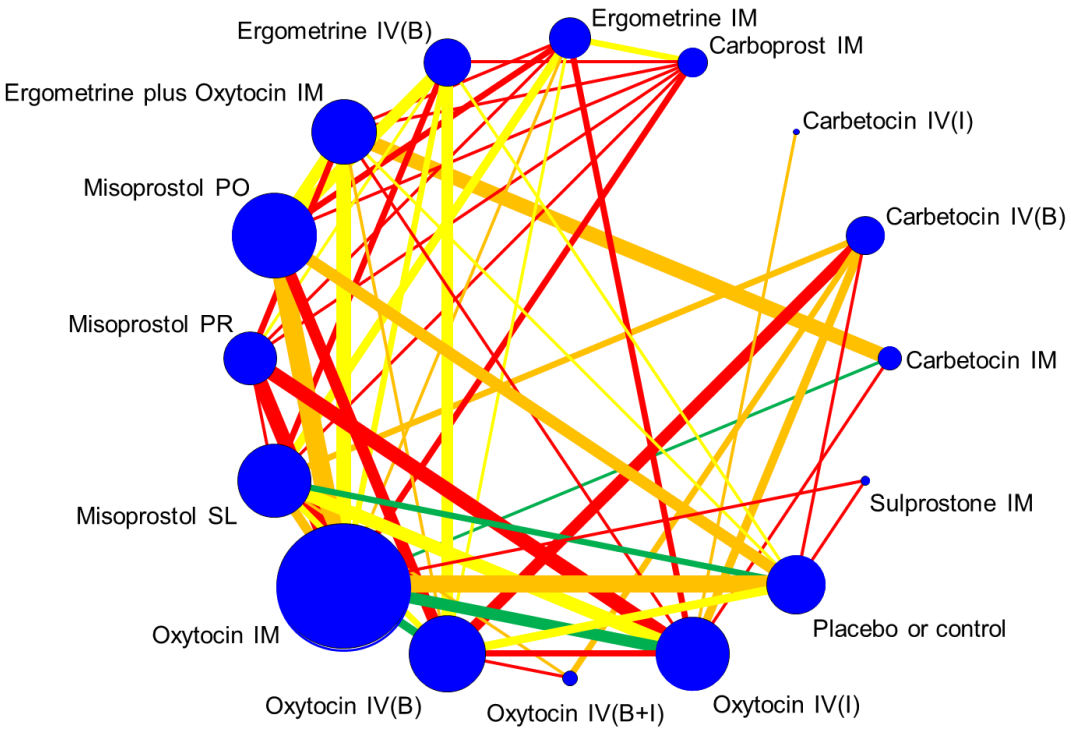


Figure 10: PPH ≥500 mL-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL

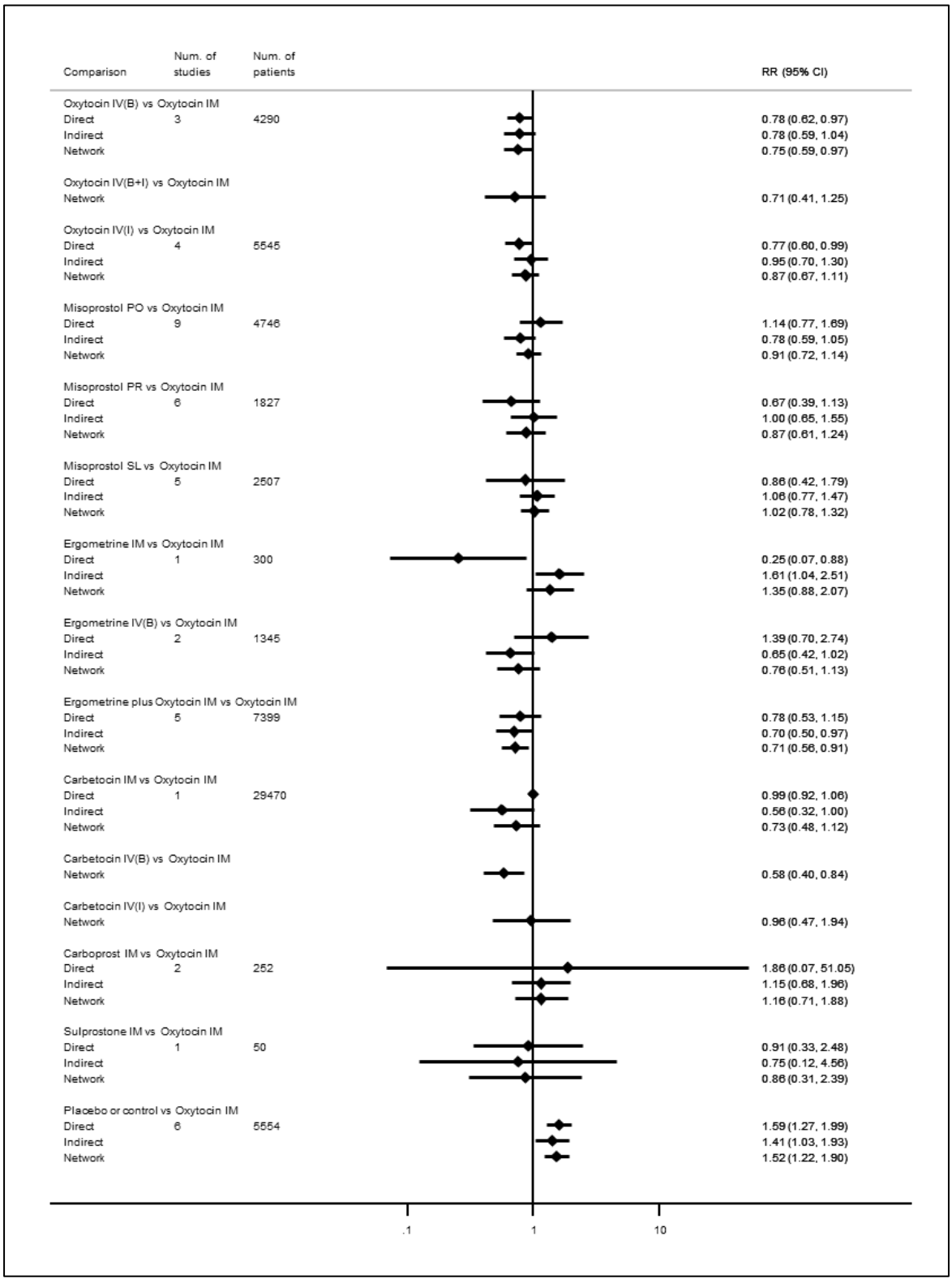
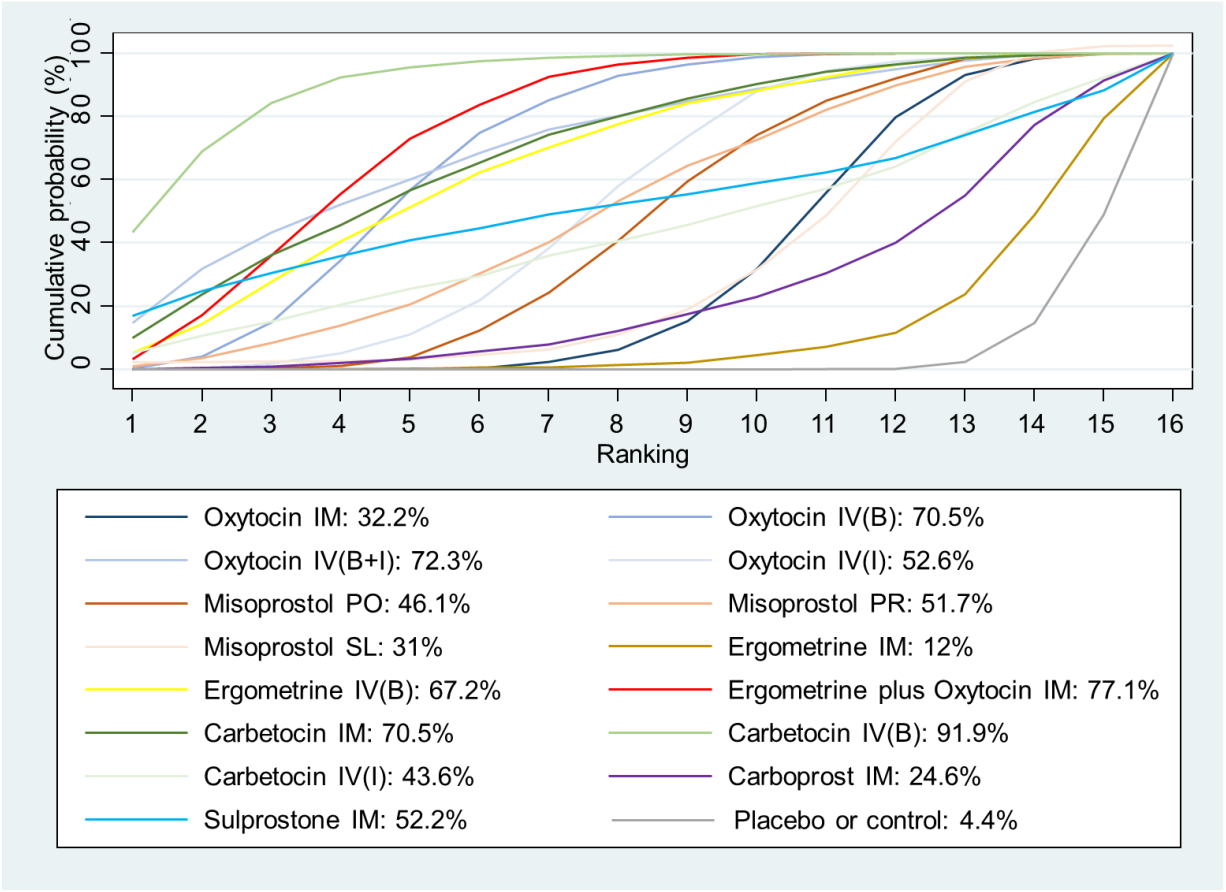


Figure 11: PPH ≥500 mL-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



PPH ≥1000 mL

Relative and absolute effects: The network diagram, the forest plot and the absolute effects for PPH ≥1000 mL are presented in *Figure 12, Figure 13, and Table 5: PPH ≥1000 mL-Summary of Findings Table-Routes NMA* respectively. Local and global inconsistency were generally low.

When compared with oxytocin IM, moderate certainty evidence suggests that oxytocin IV(B) (RR 0.86, 95% CI 0.64-1.15), oxytocin IV(B+I) (RR 0.70, 95% CI 0.47-1.05), carbetocin IM (RR 1.02, 95% CI 0.70-1.48), carbetocin IV(B) (RR 0.76, 95% CI 0.50-1.14), carbetocin IV(I) (RR 1.07, 95% CI 0.44-2.59), ergometrine IM (RR 1.01, 95% CI 0.35-2.87), and misoprostol PO (RR 1.11, 95% CI 0.83-1.49) probably make little or no difference to the risk for PPH ≥1000 mL.

Low certainty evidence suggests that, when compared with oxytocin IM, oxytocin IV(I) (RR 1.09, 95% CI 0.75-1.57), ergometrine IV(B) (RR 0.88, 95% CI 0.38-2.01), and misoprostol SL (RR 1.00, 95% CI 0.70-1.42) may make little or no difference to the risk for major PPH. Additional low certainty evidence suggests that placebo administration (RR 1.54, 95% CI 1.21-1.97) may increase the risk for PPH ≥1000 mL, compared with oxytocin IM.

The certainty of the generated network evidence was very low for carboprost IM (RR 1.97, 95% CI 0.66-5.87), misoprostol PR (RR 0.88, 95% CI 0.51-1.50), ergometrine plus oxytocin combination IM (RR 0.79, 95% CI 0.59-1.06), and sulprostone IM (RR 0.59, 95% CI 0.07-4.87), when compared with oxytocin IM.

Cumulative probabilities: Among the active agents, oxytocin IV(B+I) was ranked first with 83.7% probability of being the best uterotonic drug for preventing PPH ≥1000 mL, oxytocin IM was ranked tenth with probability 45.7%, and carboprost IM was ranked last with probability 12.5% *(Figure 14).*

Figure 12: PPH ≥1000 mL-Network diagram-Routes NMA

Network diagram for PPH ≥1000 mL. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

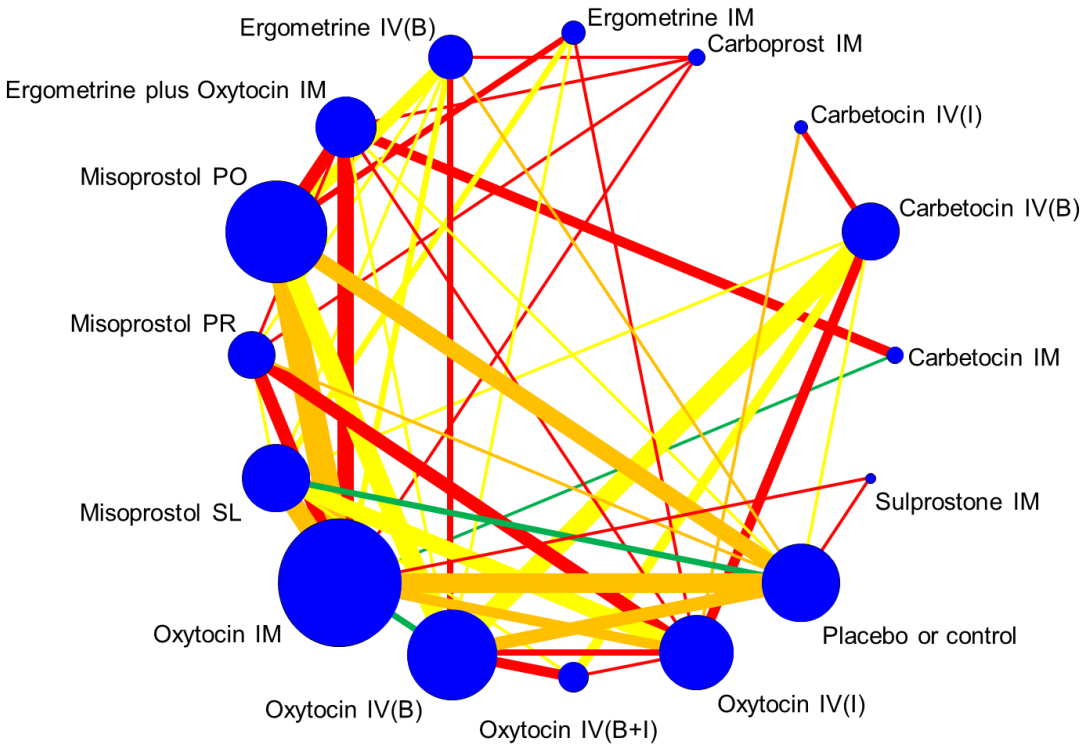


Figure 13: PPH ≥1000 mL-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL.

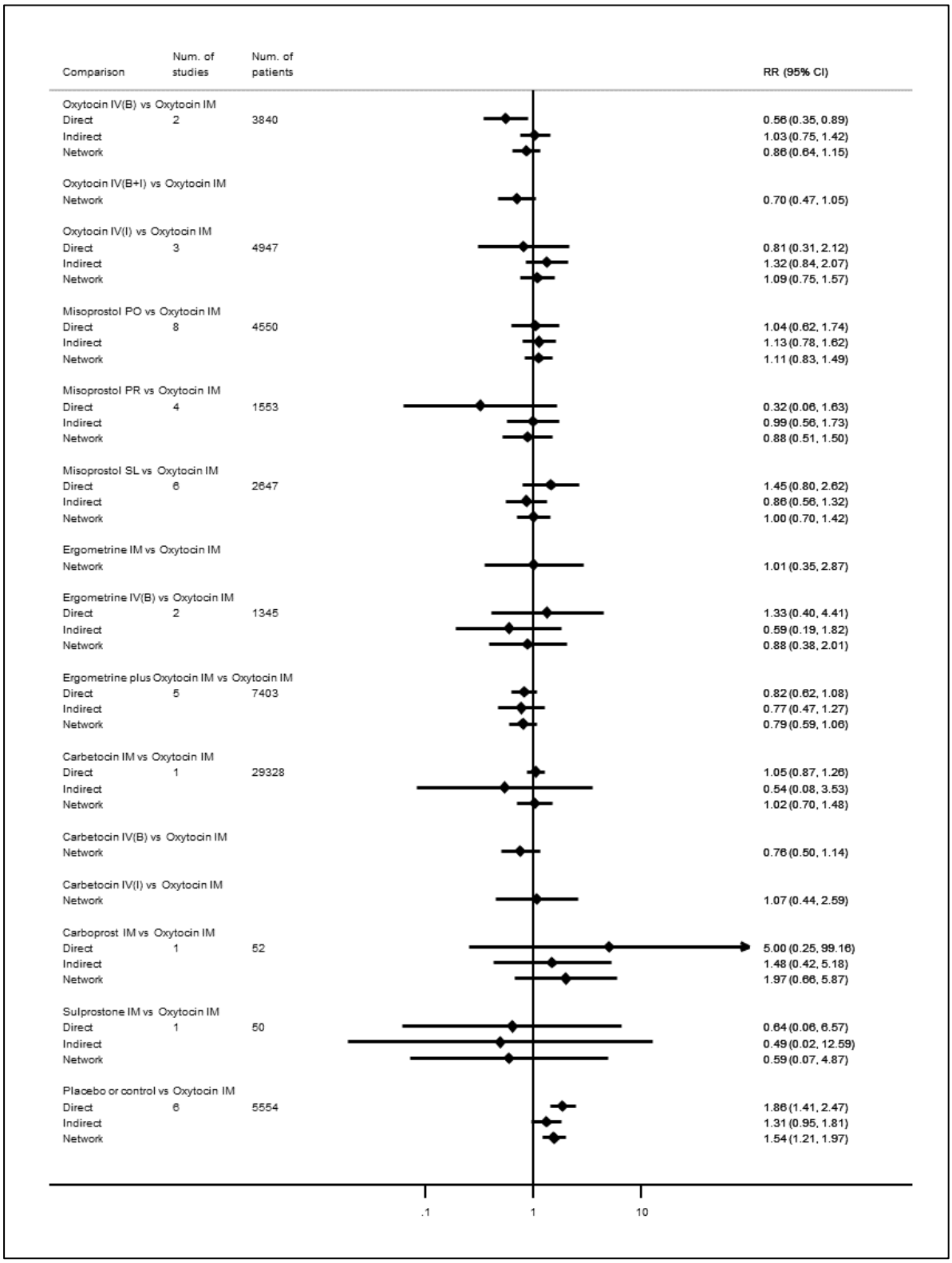
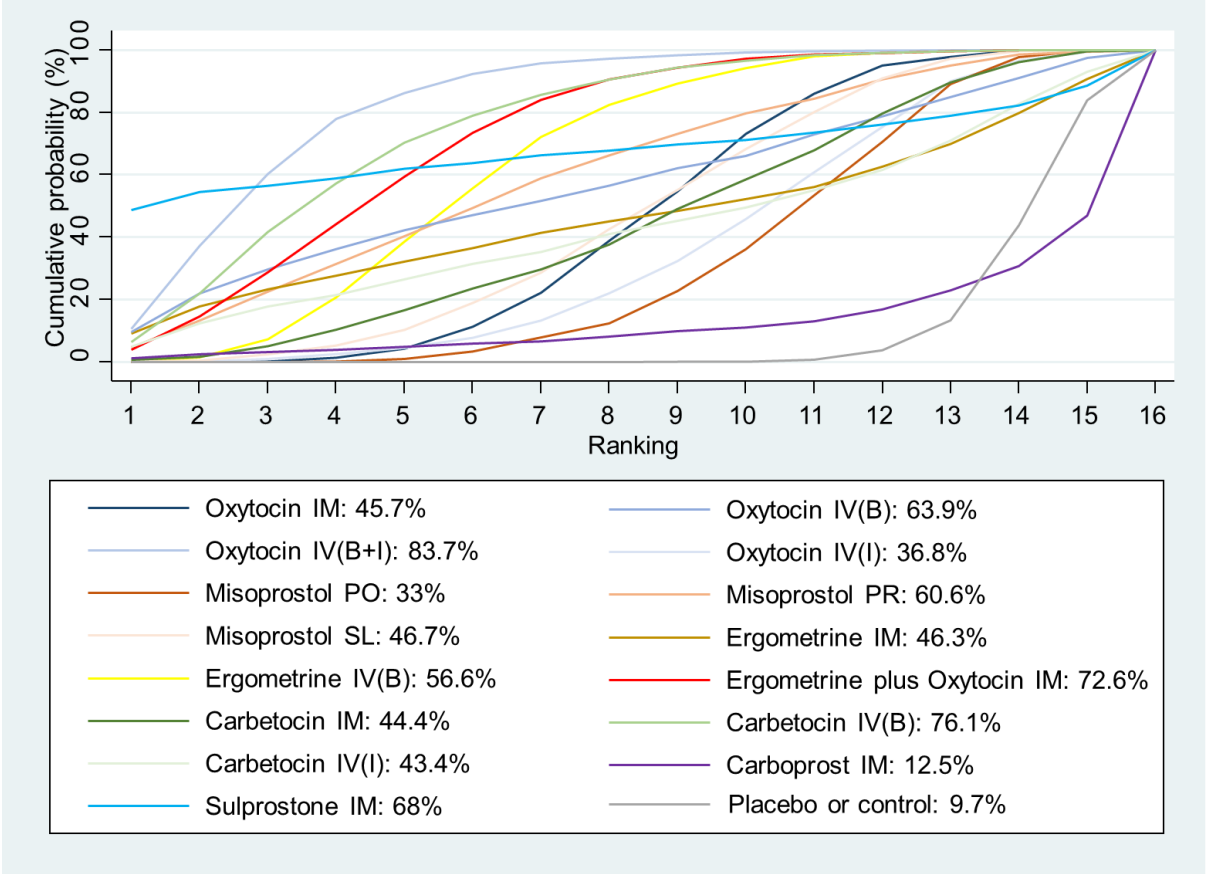


Figure 14: PPH ≥1000 mL-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Additional uterotonics

Relative and absolute effects: The network diagram and the forest plot for additional uterotonics are presented in *Figure 15* and *Figure 16* respectively. Local and global inconsistency were generally low.

Based on moderate certainty evidence, when compared with oxytocin IM, carbetocin IM (RR 0.69, 95% CI 0.43-1.09), carbetocin IV(I) (RR 0.88, 95% CI 0.34-2.31), and misoprostol SL (RR 0.75, 95% CI 0.52-1.07) probably make little or no difference to the use of additional uterotonics. Additional moderate certainty evidence suggests that oxytocin IV(B) (RR 0.69, 95% CI 0.49-0.97) and carbetocin IV(B) (RR 0.31, 95% CI 0.20-0.48) probably reduce the risk for additional uterotonic administration, when compared with oxytocin IM. In contrast, placebo (RR 2.09, 95% CI 1.47-2.96) probably increases the need for additional uterotonics compared with oxytocin IM. In absolute terms, 122 per 1,000 receiving oxytocin IM will require additional uterotonics, compared with 38 given carbetocin IV(B), 84 given oxytocin IV(B), and 255 given placebo (see *Table 6: Additional uterotonics-Summary of Findings Table-Routes NMA*).

Low certainty evidence suggests that, when compared with oxytocin IM, oxytocin IV(I) (RR 0.91, 95% CI 0.65-1.27), carboprost IM (RR 0.57, 95% CI 0.30-1.08), ergometrine IM (RR 0.94, 95% CI 0.53-1.67), misoprostol PR (RR 0.83, 95% CI 0.56-1.23), and ergometrine plus oxytocin combination IM (RR 0.73, 95% CI 0.52-1.02) may make little or no difference to the risk for additional uterotonics. Low certainty evidence also suggests that oxytocin IV(B+I) (RR 0.49, 95% CI 0.30-0.80) may decrease the use of additional uterotonics, when compared with oxytocin IM.

The certainty of the evidence was very low for the comparisons of ergometrine IV(B) (RR 0.79, 95% CI 0.47-1.30), misoprostol PO (RR 1.00, 95% CI 0.75-1.33), and sulprostone IM (RR 0.55, 95% CI 0.02-12.24) against oxytocin IM.

Cumulative probabilities: Among the active agents, carbetocin IV(B) was ranked first with 96.7% probability of being the best uterotonic drug for preventing additional uterotonic use, whereas oxytocin IM was ranked last with probability 23.1% *(Figure 17).*

Figure 15: Additional uterotonics-Network diagram-Routes NMA

Network diagram for additional uterotonics. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

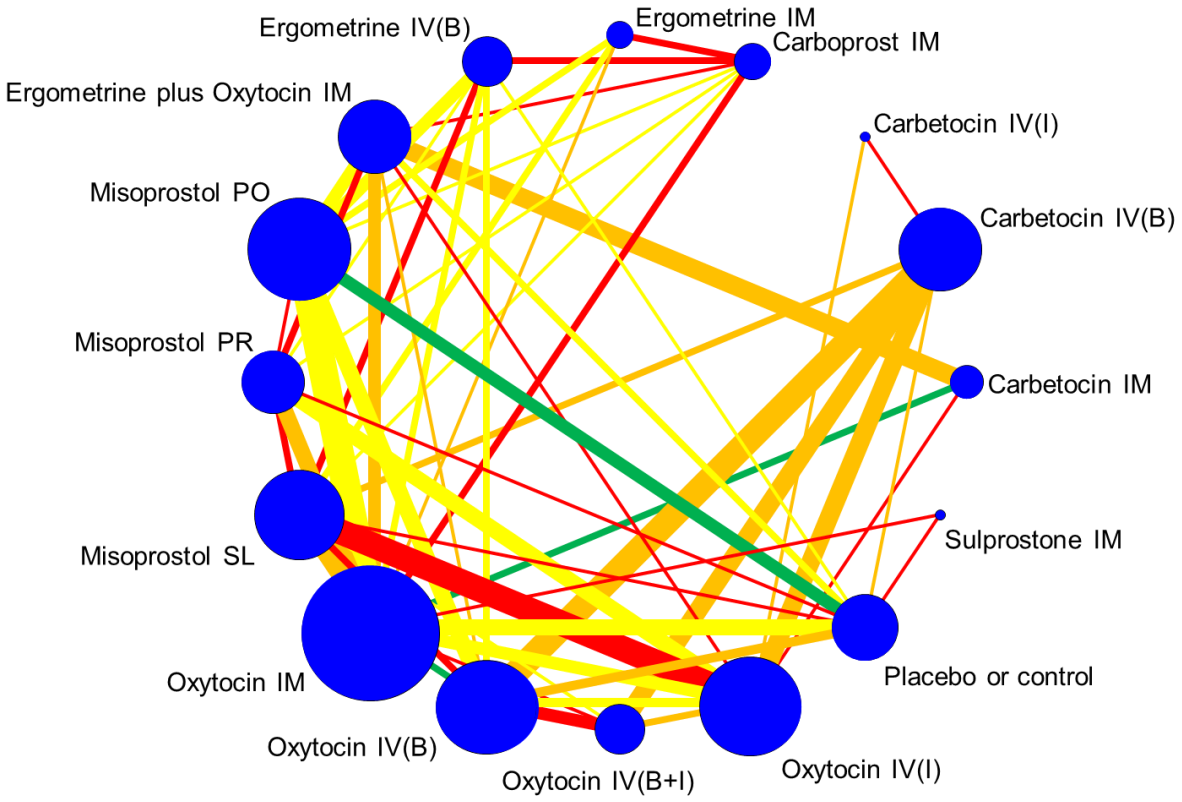


Figure 16: Additional uterotonics-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for additional uterotonics.

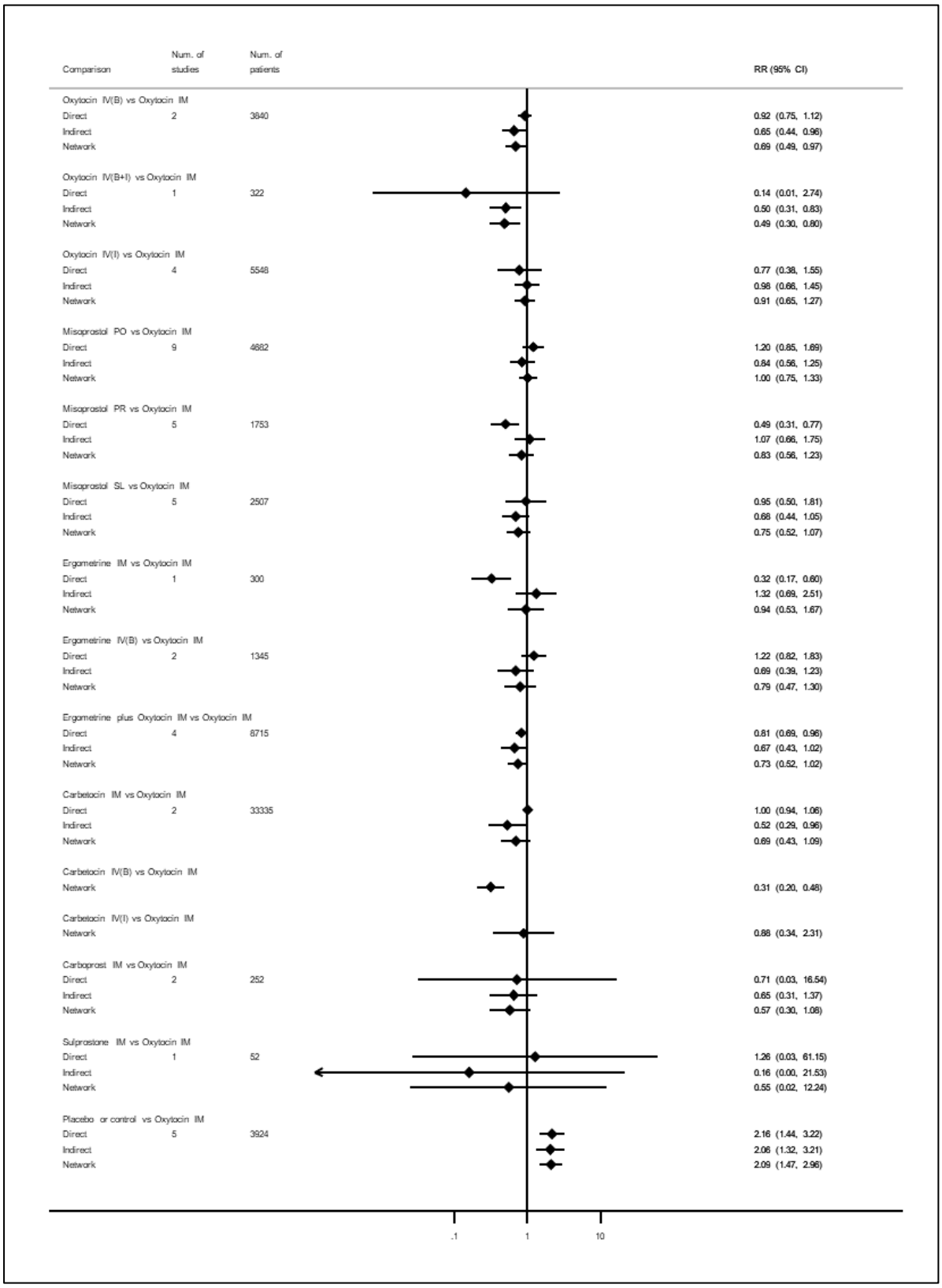
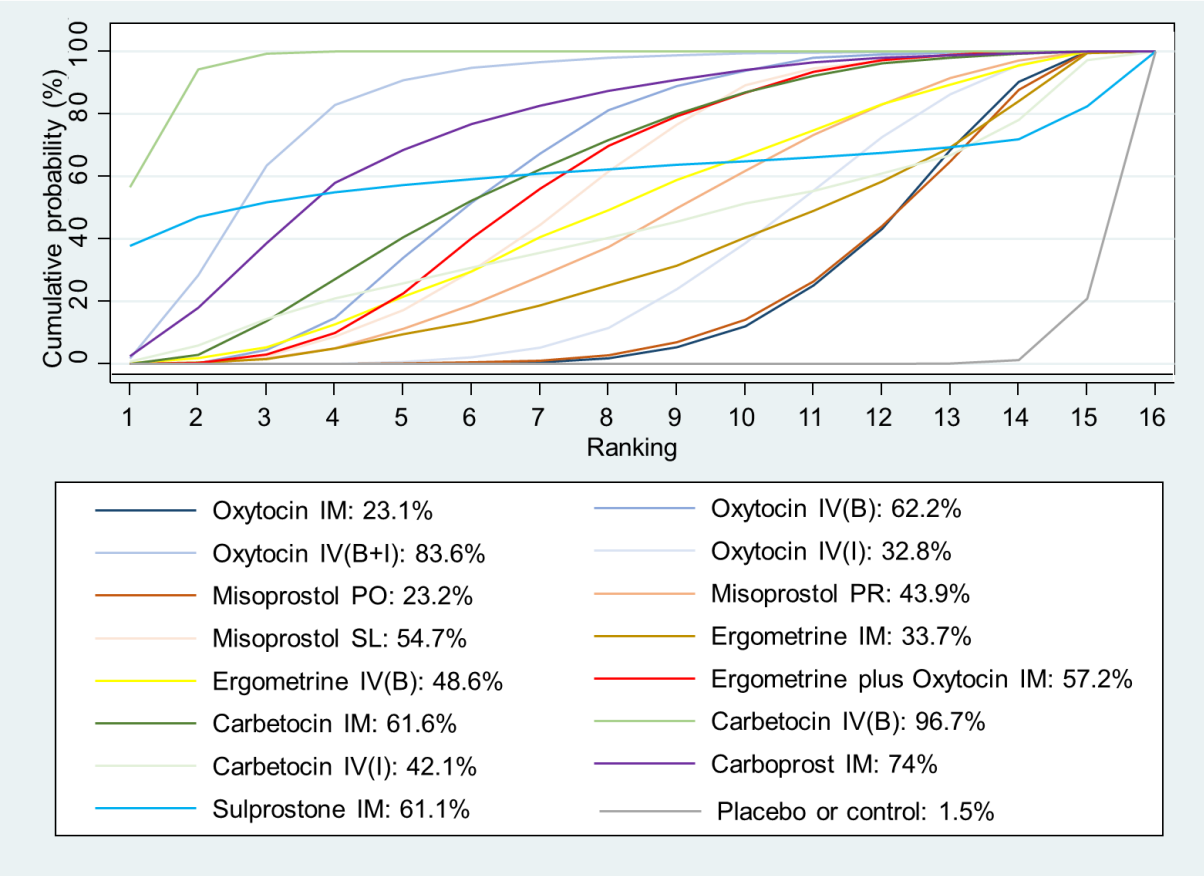


Figure 17: Additional uterotonics-Rankogram-Routes NMA

Cumulative rankogram for additional uterotonics. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Blood transfusion

Relative and absolute effects: The network diagram and the forest plot for blood transfusion are presented in *Figure 18* and *Figure 19* respectively. Local and global inconsistency were generally low.

Based on moderate certainty evidence, when compared with oxytocin IM, carbetocin IM (RR 1.06, 95% CI 0.77-1.46) and carbetocin IV(I) (RR 0.37, 95% CI 0.04-3.07) probably make little or no difference to the need for a blood transfusion. Additional moderate certainty evidence suggests that oxytocin IV(B) (RR 0.61, 95% CI 0.40-0.93), carbetocin IV(B) (RR 0.39, 95% CI 0.21-0.70), and misoprostol SL (RR 0.57, 95% CI 0.33-0.97), when compared with oxytocin IM, probably reduce the risk for a blood transfusion. For every 1,000 women receiving oxytocin IM, 17 will need a blood transfusion, compared with 10 receiving either oxytocin IV(B) or misoprostol SL and 7 given carbetocin IV(B) (see *Table 7: Blood transfusion-Summary of Findings Table-Routes NMA*).

According to low certainty evidence, oxytocin IV(I) (RR 0.75, 95% CI 0.45-1.25), oxytocin IV(B+I) (RR 0.48, 95% 0.23-1.00), ergometrine IM (RR 0.42, 95% CI 0.12-1.52), ergometrine IV(B) (RR 1.01, 95% CI 0.40-2.57), misoprostol PR (RR 0.57, 95% CI 0.31-1.06), ergometrine plus oxytocin combination IM (RR 0.88, 95% CI 0.65-1.19), and placebo (RR 1.38, 95% CI 0.92-2.08) may make little or no difference to the risk for a blood transfusion, when compared with oxytocin IM.

The certainty of the evidence was very low for the comparisons of carboprost IM (RR 0.66, 95% CI 0.17-2.62) and misoprostol PO (RR 0.78, 95% CI 0.50-1.22) against oxytocin IM.

No data were available for sulprostone IM compared with oxytocin IM.

Cumulative probabilities: Among the active agents, carbetocin IV(B) was ranked first with 86.4% probability of being the best uterotonic drug for preventing a blood transfusion, oxytocin IM was ranked thirteenth with probability 22.6%, and carbetocin IM was ranked last with probability 19.6% *(Figure 20).*

Figure 18: Blood transfusion-Network diagram-Routes NMA

Network diagram for blood transfusion. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

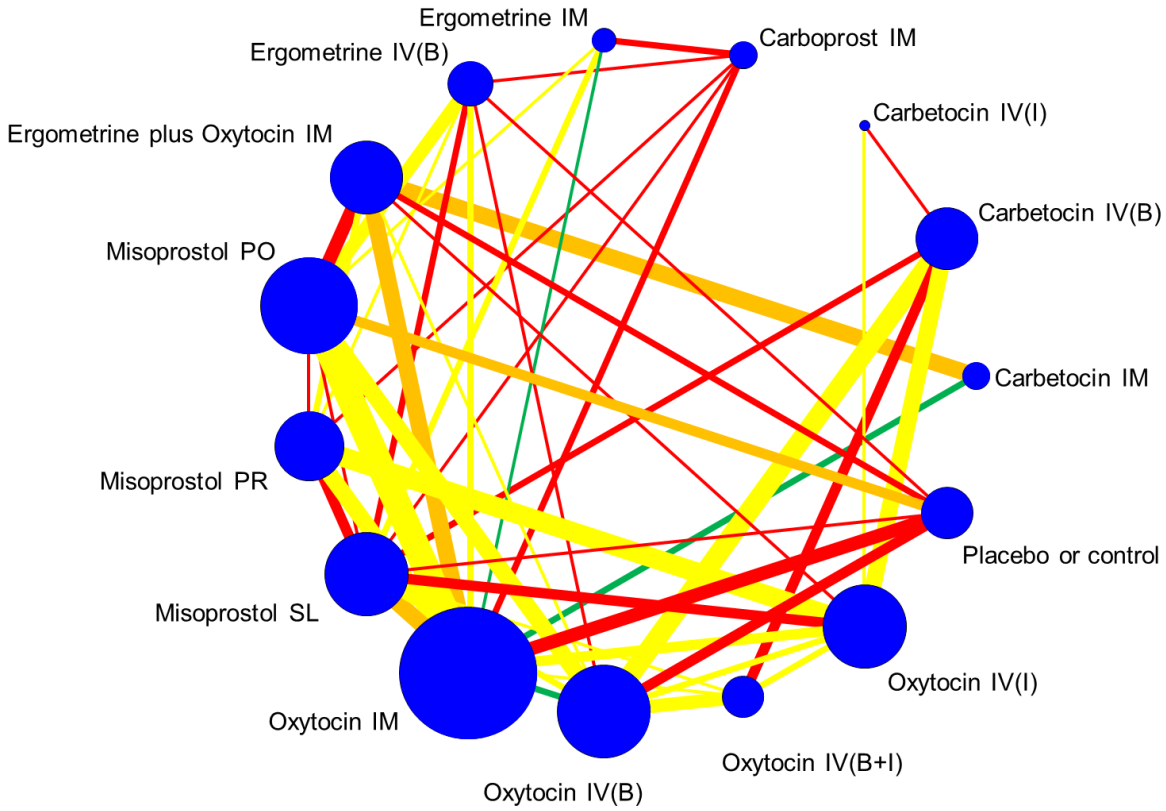


Figure 19: Blood transfusion-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for blood transfusion.

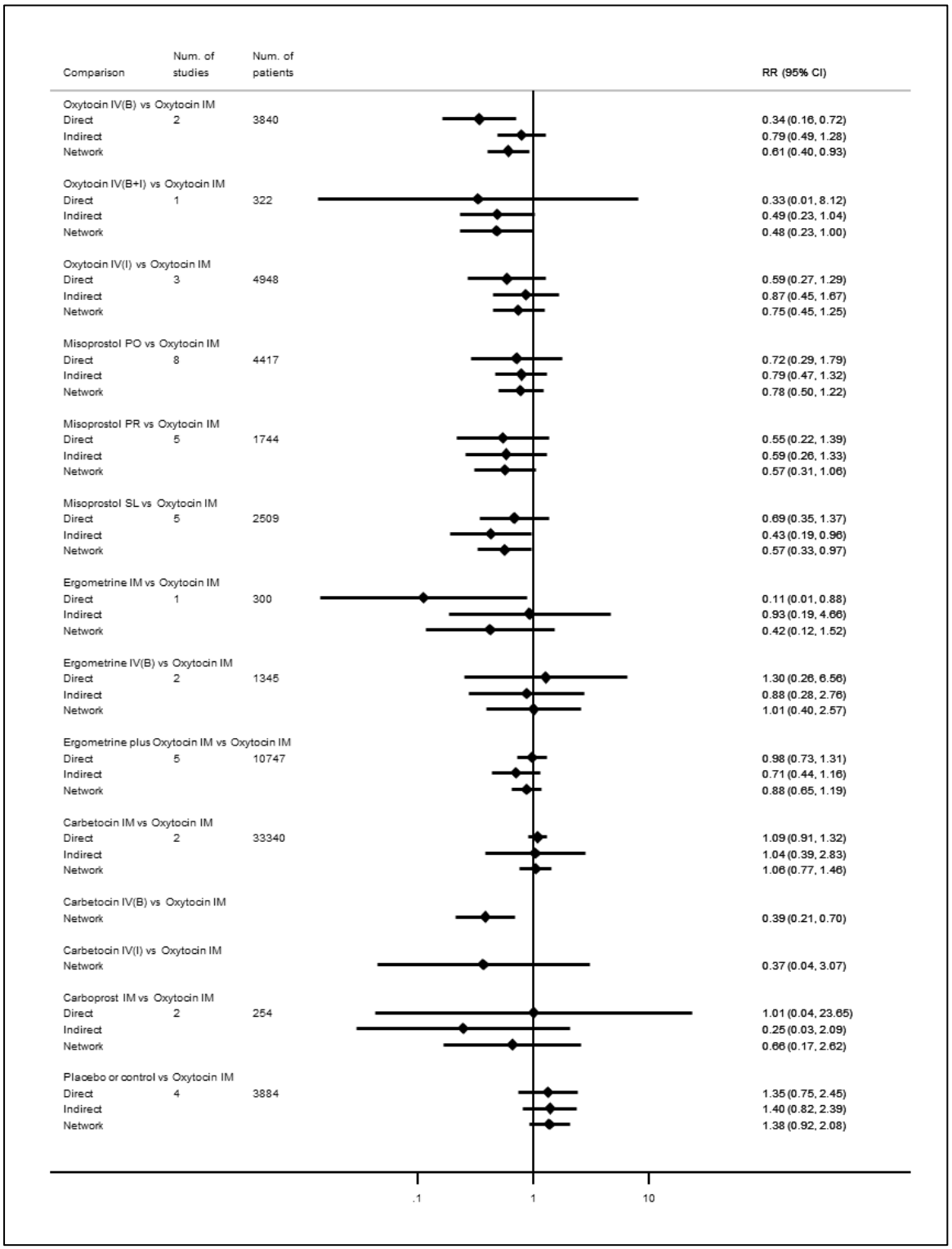
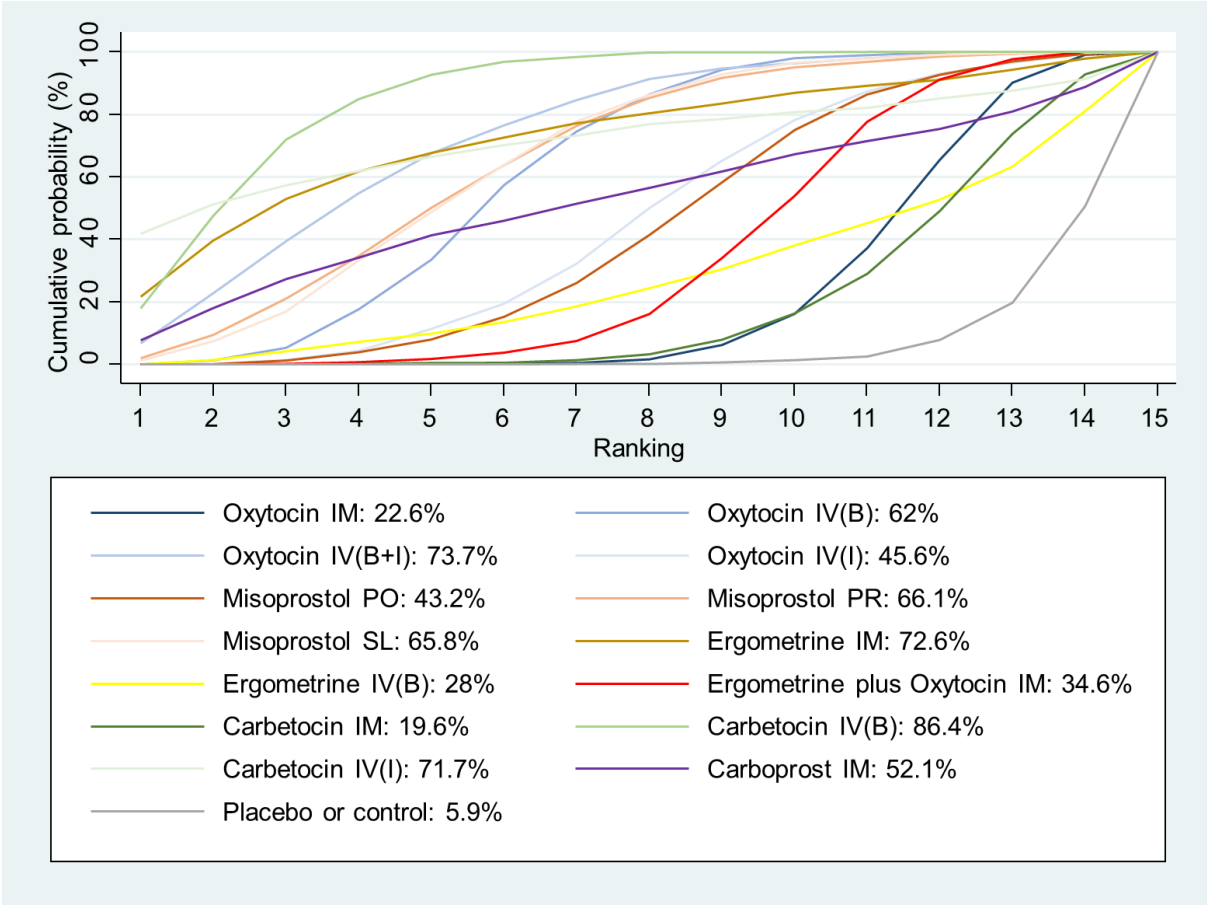


Figure 20: Blood transfusion-Rankogram-Routes NMA

Cumulative rankogram for blood transfusion. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Fever

Relative and absolute effects: The network diagram and the forest plot for fever are presented in *Figure 21* and *Figure 22* respectively. Local and global inconsistency were generally low.

When compared with oxytocin IM, high certainty evidence suggests that misoprostol PO (RR4.14, 95% CI 2.44-7.01) and misoprostol SL (RR 6.20, 95% CI 3.38-11.38) increase the risk for fever. In absolute terms, 23 per 1,000 receiving oxytocin IM will experience fever, compared with 95 receiving misoprostol PO and 143 given misoprostol SL (see *Table 8: Fever-Summary of Findings Table-Routes NMA*).

Based on moderate certainty evidence, oxytocin IV(I) (RR 1.04, 95% CI 0.45-2.42), ergometrine IM (RR 1.12, 95% CI 0.49-2.55), ergometrine plus oxytocin combination IM (RR 0.47, 95% CI 0.15-1.48) and placebo (RR 1.12, 95% CI 0.48-2.57) probably make little or no difference to the outcome of fever, when compared with oxytocin IM. Additional moderate certainty evidence indicates that, when compared with oxytocin IM, misoprostol PR (RR 1.84, 95% CI 1.01-3.37) probably increases the risk for fever. For every 1,000 women receiving oxytocin IM, 23 will experience fever, compared with 42 given misoprostol PR (see *Table 8: Fever-Summary of Findings Table-Routes NMA*).

Low certainty evidence suggests that, when compared with oxytocin IM, oxytocin IV(B) (RR 0.43, 95% CI 0.12-1.59), oxytocin IV(B+I) (RR 2.27, 95% CI 0.58-8.93), carbetocin IV(B) (RR 2.01, 95% CI 0.61-6.69), carboprost IM (RR 1.01, 95% CI 0.28-3.69), and ergometrine IV(B) (RR 0.82, 95% CI 0.33-2.08) may make little or no difference to the risk for fever.

No data were available for carbetocin IM, carbetocin IV(I), and sulprostone IM, compared with oxytocin IM.

Cumulative probabilities: Among the active agents, oxytocin IV(B) was ranked first with 88.6% probability of being the best uterotonic drug for not causing fever, oxytocin IM was ranked fourth with probability 62.6%, and misoprostol SL was ranked last with probability 1.2% *(Figure 23).*

Figure 21: Fever-Network diagram-Routes NMA

Network diagram for fever. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

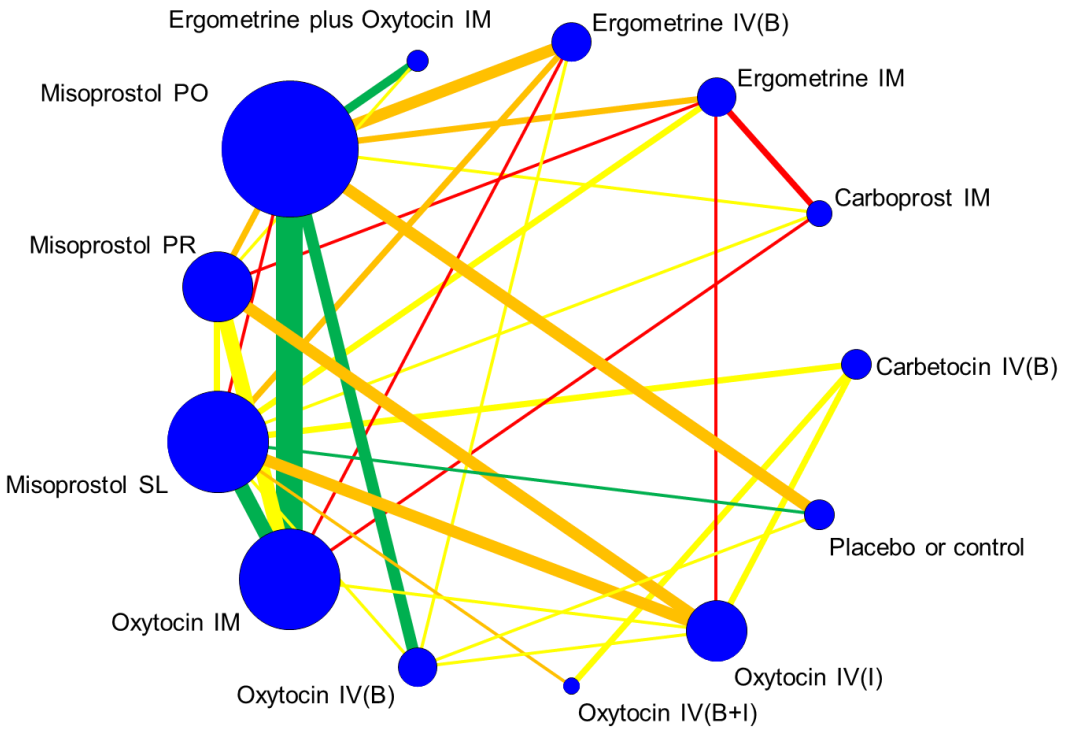


Figure 22: Fever-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for fever.

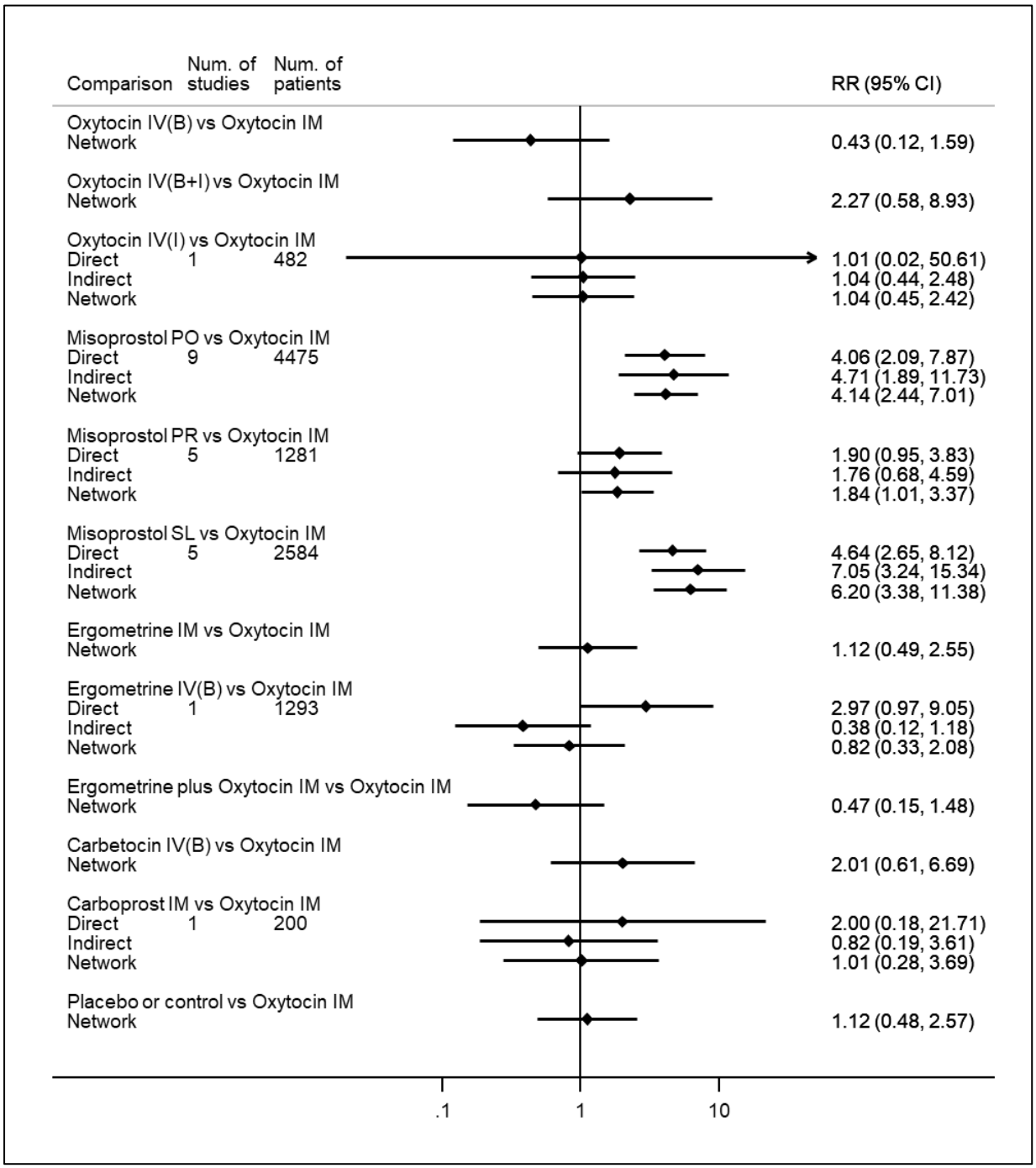
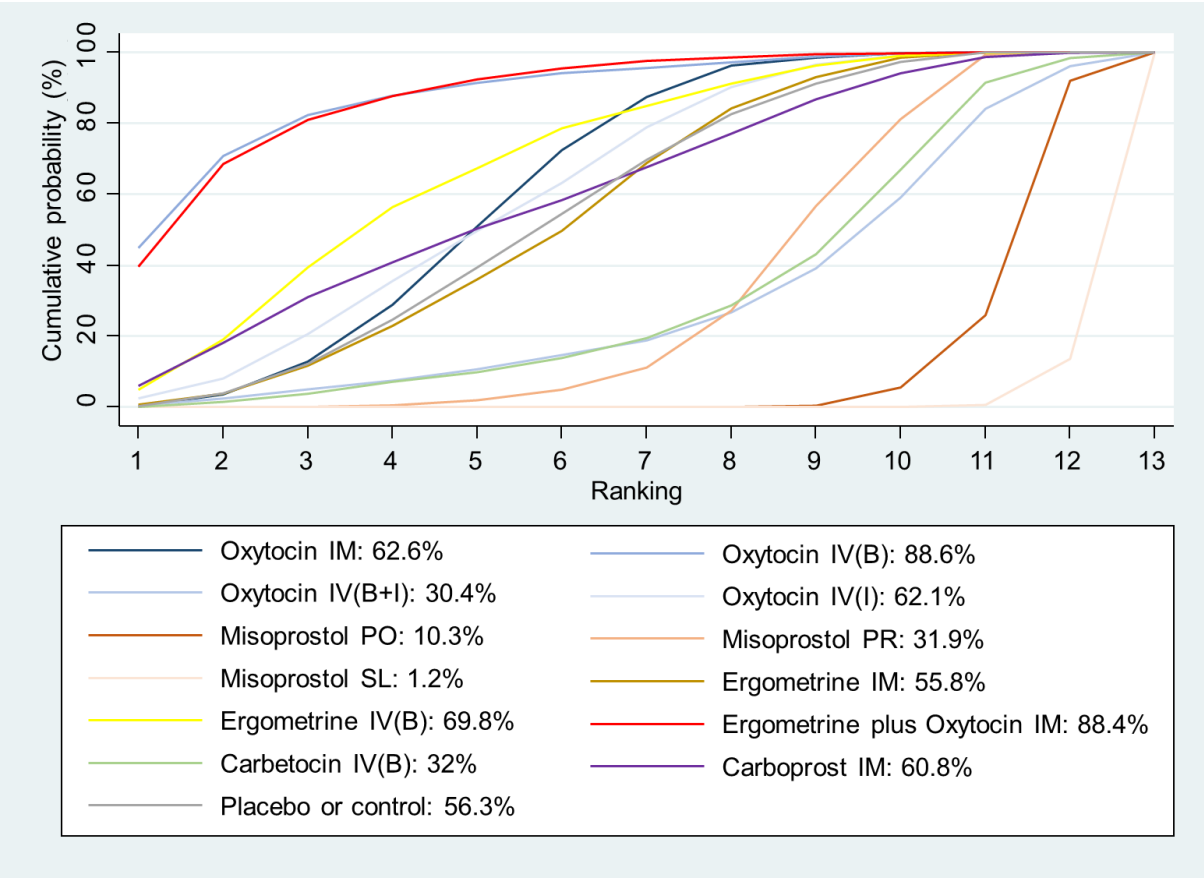


Figure 23: Fever-Rankogram-Routes NMA

Cumulative rankogram for fever. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Hypertension

Relative and absolute effects: A network meta-analysis was not possible due to the scarcity of data. The respective network diagram and forest plots showing the available direct comparisons are presented in *Figure 24* and *Figure 25.*

According to high certainty direct evidence, carbetocin IM (RR 0.98, 95% CI 0.78-1.23) makes little or no difference to the risk for hypertension, compared with oxytocin IM. Additional high certainty evidence indicates that ergometrine plus oxytocin combination IM (RR 1.72, 95% CI 1.40-2.11) increases the risk for this outcome, compared with oxytocin IM. In absolute terms 75 per 1,000 women receiving oxytocin IM will have high blood pressure, compared with 74 given carbetocin IM, and 129 given ergometrine plus oxytocin combination IM (see *Table 9: Hypertension-Summary of Findings Table-Routes-NMA*).

Moderate certainty evidence suggests that, when compared with oxytocin IM, oxytocin IV(I) (RR 1.34, 95% CI 0.81-2.20) probably makes little or no difference to the risk for this outcome. For every 1,000 women given oxytocin IM, 75 will experience hypertension, compared with 101 given oxytocin IV(I) (see *Table 9: Hypertension-Summary of Findings Table-Routes-NMA*).

Low certainty evidence is available for the comparisons of ergometrine IM (RR 15.20, 95% CI 0.88-263.78), and misoprostol PO (RR 3.10, 95% CI 0.13-75.68) against oxytocin IM. For the comparison of misoprostol PR versus oxytocin IM the generated direct evidence was of very low certainty (RR 3.93, 95% CI 0.44-35.88).

No data were available for oxytocin IV(B), oxytocin IV(B+I), carbetocin IV(B), carbetocin IV(I), carboprost IM, ergometrine IV(B), misoprostol SL, sulprostone IM, and placebo or control, compared with oxytocin IM.

Cumulative probabilities: It was not possible to generate a ranking of the available uterotonics drugs based on this outcome.

Figure 24: Hypertension-Network diagram-Routes NMA

Network diagram for hypertension. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

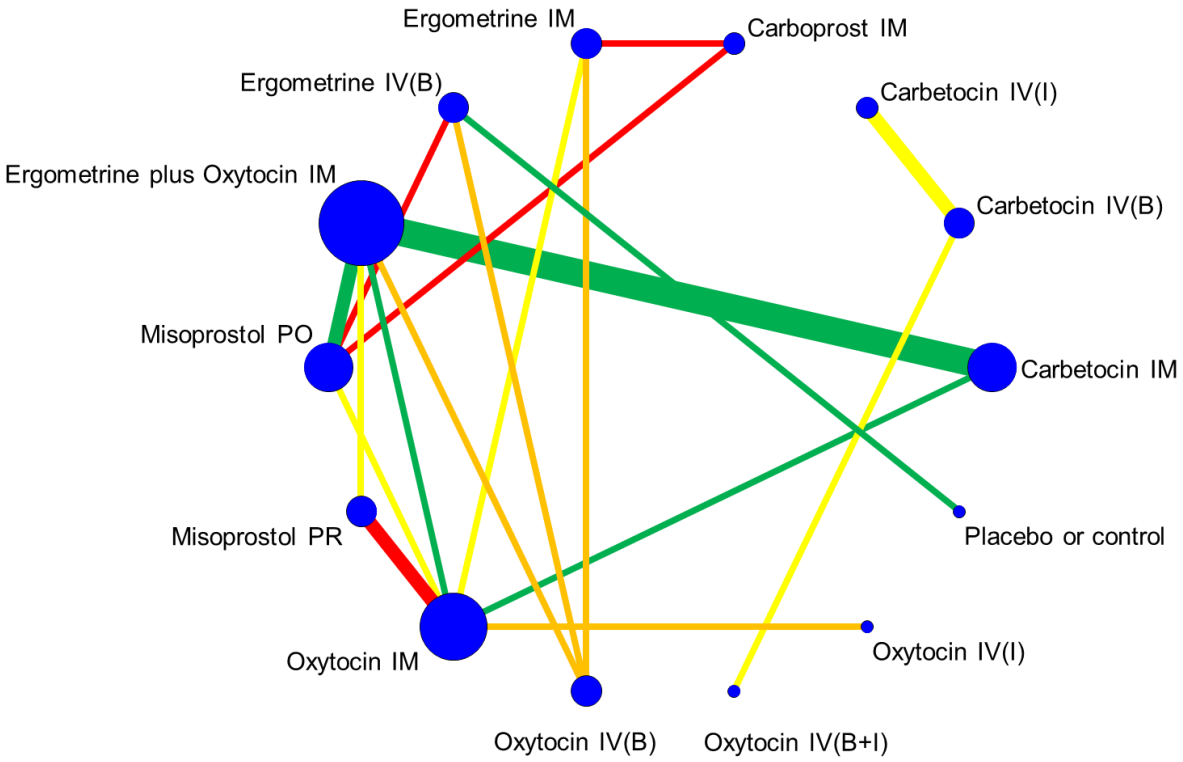
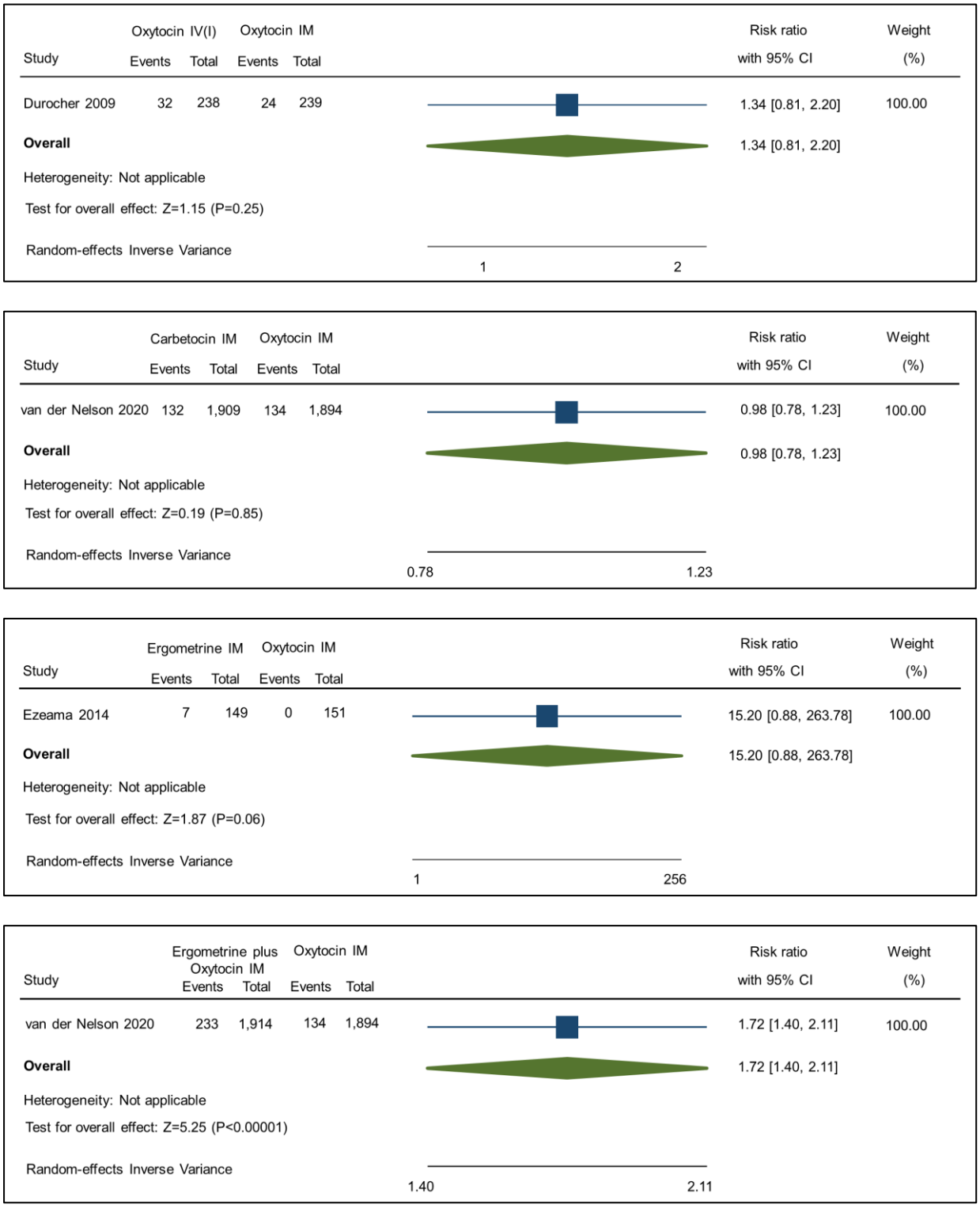
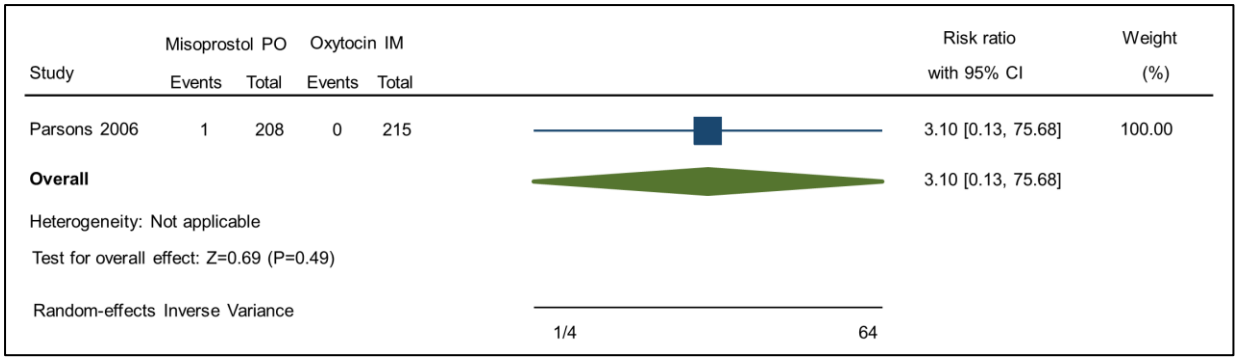
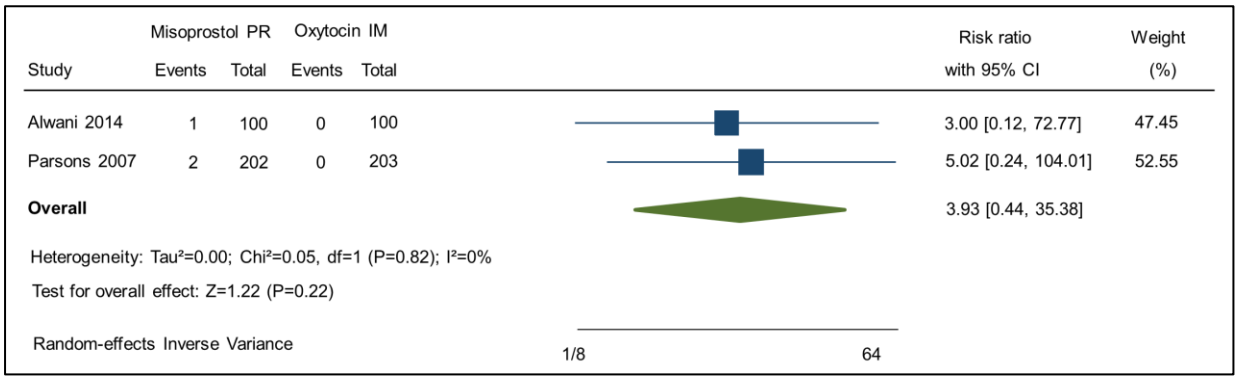


Figure 25: Hypertension-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise analyses for hypertension.




Misoprostol PO
Oxytocin IM
Study
Events
Total
Events
Total
Risk ratio with 95% CI
Weight (%)
Parsons 2006
1
208
0
215
3.10 [0.13, 75.68]
100.00
Overall
3.10 [0.13, 75.68]
Heterogeneity: Not applicable
Test for overall effect: Z=0.69 (P=0.49)
Random-effects Inverse Variance
1/4
64


Misoprostol PR
Oxytocin IM
Study
Events
Total
Events
Total
Risk ratio with 95% CI
Weight (%)
Alwani 2014
1
100
0
100
3.00 [0.12, 72.77]
47.45
Parsons 2007
2
202
0
203
5.02 [0.24, 104.01]
52.55
Overall
3.93 [0.44, 35.38]
Heterogeneity: Tau²=0.00; Chi²=0.05, df=1 (P=0.82); I²=0%
Test for overall effect: Z=1.22 (P=0.22)
Random-effects Inverse Variance
1/8
64

Vomiting

Relative and absolute effects: The network diagram and the forest plot for vomiting are presented in *Figure 26* and *Figure 27* respectively. Local and global inconsistency were generally low.

When compared with oxytocin IM, high certainty evidence suggests misoprostol PO (RR 1.55, 95% CI 1.02-2.37) and misoprostol SL (RR 2.23, 95% CI 1.35-3.69) increase the risk for vomiting. In absolute terms, 24 per 1,000 women receiving oxytocin IM will have vomiting, compared with 37 given misoprostol PO, and 54 given misoprostol SL (see *Table 10: Vomiting-Summary of Findings Table-Routes NMA*).

Moderate certainty evidence suggests that placebo (RR 1.09, 95% CI 0.61-1.96) probably makes little or no difference to the risk for vomiting, when compared with oxytocin IM. Additional moderate certainty evidence indicates that ergometrine plus oxytocin combination IM (RR 3.10, 95% CI 2.12-4.53) is probably associated with a higher risk for vomiting, compared with oxytocin IM. For every 1,000 women receiving oxytocin IM, 24 will experience vomiting, compared with 74 given ergometrine plus oxytocin combination IM (see *Table 10: Vomiting-Summary of Findings Table-Routes NMA*).

Low certainty evidence suggests that, when compared with oxytocin IM, oxytocin IV(B) (RR 0.61, 95% CI 0.30-1.23), oxytocin IV(B+I) (RR 1.05, 95% CI 0.44-2.54), carbetocin IM (RR 0.84, 95% CI 0.50-1.40), carbetocin IV(B) (RR 1.11, 95% CI 0.53-2.32), and misoprostol PR (RR 1.71, 95% CI 0.94-3.10) may make little or no difference to the risk for vomiting. In contrast, according to low certainty evidence, carboprost IM (RR 2.90, 95% CI 1.24-6.83) may be associated with more cases of vomiting, compared with oxytocin IM.

For the comparison of oxytocin IV(I) (RR 2.25, 95% CI 1.21-4.17), carbetocin IV(I) (RR 1.70, 95% CI 0.31-9.51), ergometrine IM (RR 1.72, 95% CI 0.89-3.33), and ergometrine IV (B) (RR 2.66, 95% CI 1.37-5.15), against oxytocin IM, the generated evidence was of very low certainty.

No data were available for sulprostone IM compared with oxytocin IM, and thus respective relative and absolute treatment effects remain unclear.

Cumulative probabilities: Among the active agents, oxytocin IV(B) was ranked first with 95% probability of being the best uterotonic drug for not increasing the risk for vomiting, oxytocin IM was ranked third with probability 76.2%, and ergometrine plus oxytocin combination IM was ranked last with probability 9.7% *(Figure 28).*

Figure 26: Vomiting-Network diagram-Routes NMA

Network diagram for vomiting. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

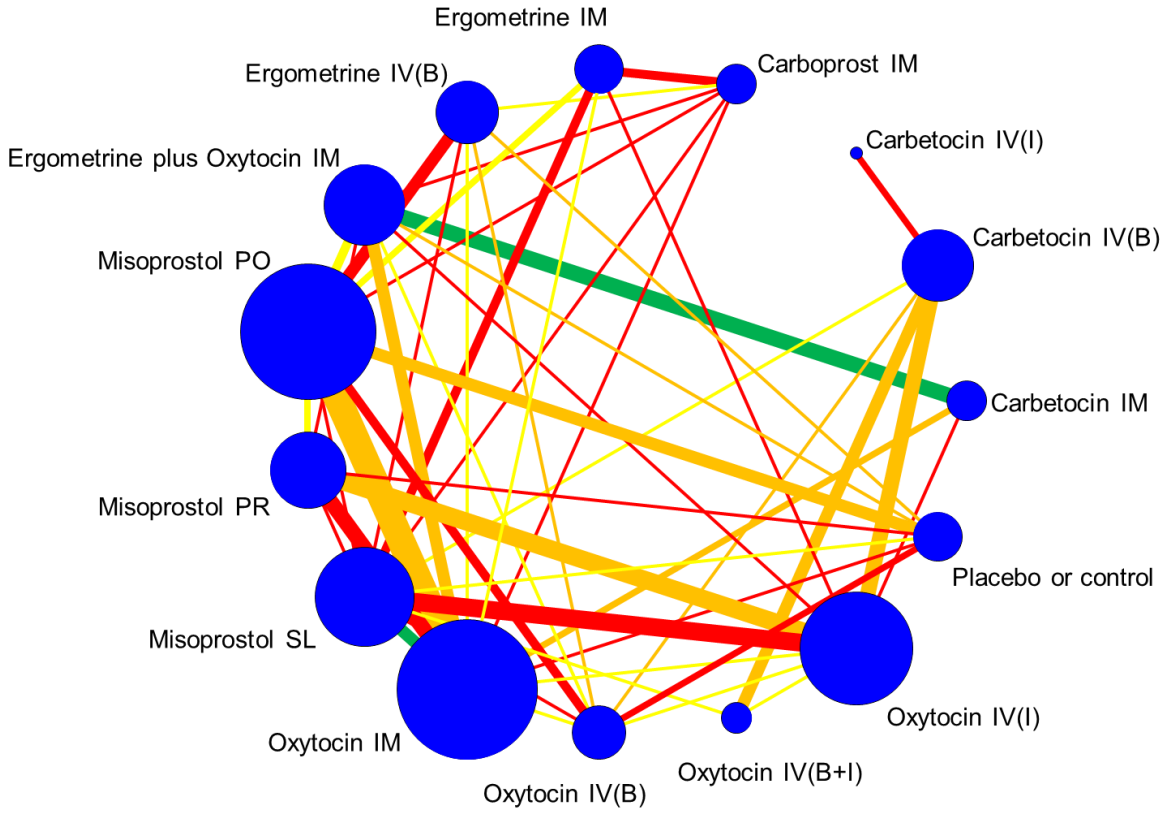


Figure 27: Vomiting-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for vomiting.

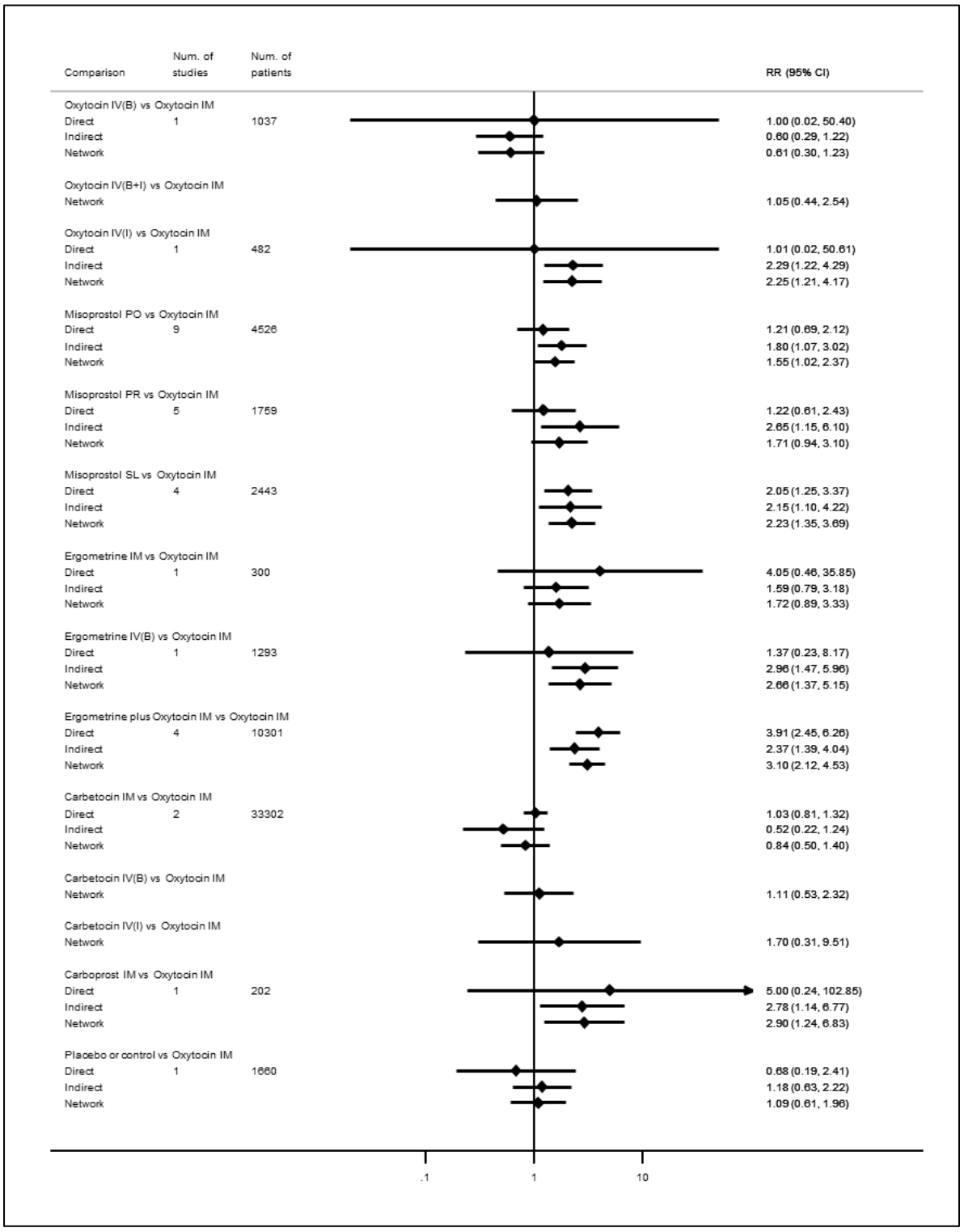
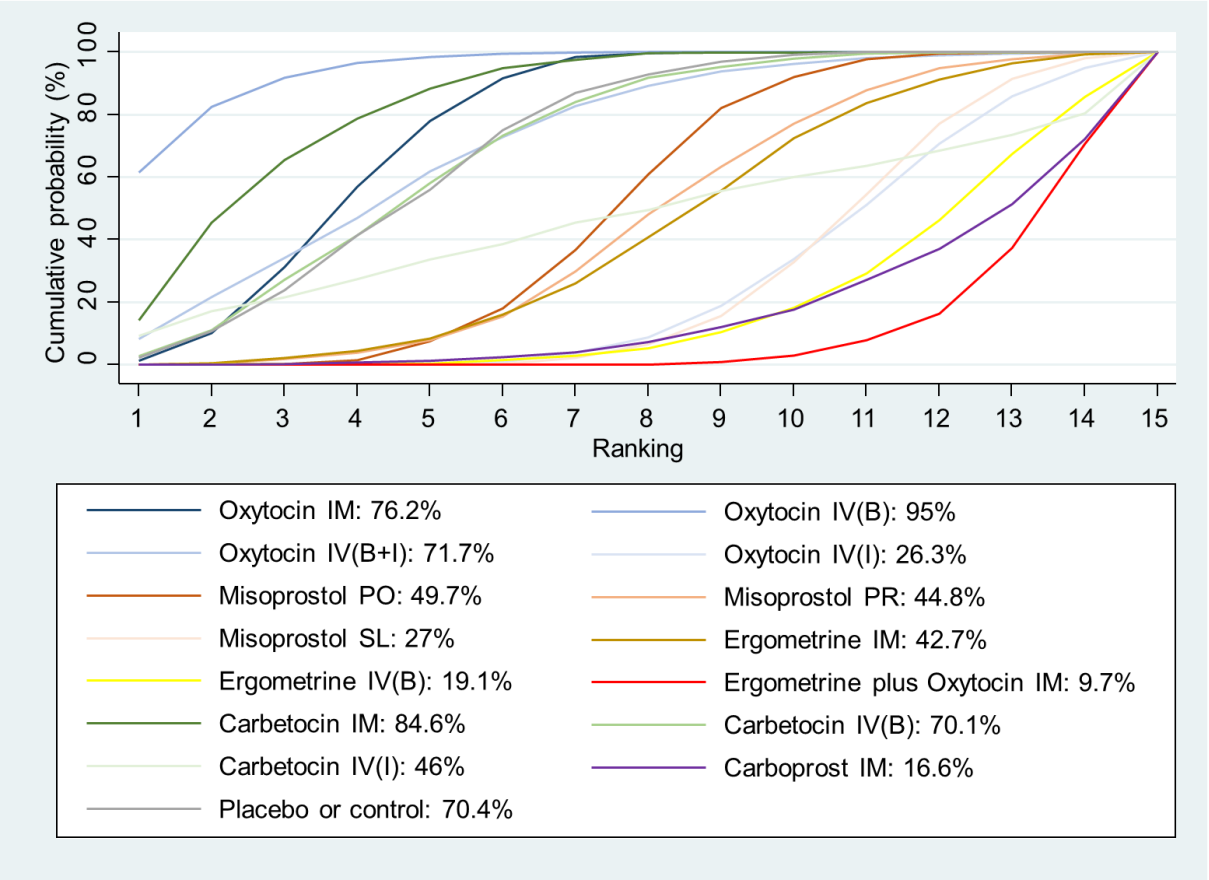


Figure 28: Vomiting-Rankogram-Routes NMA

Cumulative rankogram for vomiting. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Additional outcomes

All respective graphs (i.e., network diagrams, forest plots, and rankograms) can be found in *APPENDIX 2: Routes-NMA.*

It was not possible to perform a NMA in the following three cases:

1. **Maternal morbidity-shock:** This outcome was not reported by included studies.
2. **Breastfeeding at hospital discharge:** This outcome could not be used to provide a meaningful ranking of the available uterotonics, due to the scarcity of data.
3. **Maternal satisfaction and maternal sense of well-being:** Due to the endogenous heterogeneity of these outcomes no meta-analysis was performed.

The generated evidence for the secondary outcomes of this project was not assessed. The respective relative treatment effects can be found in the *APPENDIX 2: Routes-NMA*. The ranking of all available uterotonics, based on their respective SUCRAs, for each secondary outcome is presented in *Table 11.* For effectiveness outcomes (i.e., maternal death, maternal morbidity-ICU admissions, blood loss, change in Hb) the best uterotonic is the one that is most likely to prevent an event. For side effects (i.e., abdominal pain, diarrhoea, headache, nausea, shivering) the best uterotonic is the one that is less likely to cause an event. Zero ranking corresponds to cases without data for a given uterotonic. For a better understanding, *Table 11* should be read together with the respective rankograms.

For the outcomes of **maternal death and maternal morbidity-ICU admissions**, data were provided by 50 and 20 studies, respectively. In most cases these data corresponded to zero events across all study arms. Given the great overlap of the available uterotonics, as shown

in the respective rankograms (*Figure 55* and *Figure 58*), no clear ranking can be produced based on these two outcomes.

The outcome of **blood loss** was a very well reported across 113 studies. As shown in *Table 11* oxytocin IV(B+I), carbetocin IV(B), and carbetocin IV(I) are ranked among the top three uterotonics for prevention of excessive bleeding.

Seventy studies provided data for another blood loss-related outcome, i.e., **change in Hb**. Available rankings in *Table 11* suggest that ergometrine plus oxytocin combination, carbetocin IM, and oxytocin IV(B+I) are the best available options for minimising the change in haemoglobin measurements before and after delivery.

For the outcomes of **abdominal pain, diarrhoea, headache, nausea and shivering,** as shown in *Table 11,* various routes of oxytocin, especially oxytocin given either IM or IV(I), and carbetocin IM are among the top uterotonic drugs with a favourable side-effect profile.

Table 11: Ranking of the available uterotonics based on secondary outcomes and according to their respective SUCRAs-Routes NMA.

Interventions & Outcomes	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Maternal death	**8**	12	2	7	13	9	6	4	11	4	10	3	1	5	0	2
Morbidity (ICU)	**6**	1	4	0	9	3	0	0	2	0	11	7	5	10	0	8
Blood loss	**11**	7	14	2	5	1	3	8	13	9	12	15	10	6	4	16
Hb change	**11**	4	13	3	1	5	0	6	12	9	2	7	8	10	0	14
Abdominal pain	**9**	8	5	3	4	7	15	6	1	14	13	12	11	2	0	10
Diarrhoea	**2**	5	3	0	0	0	0	11	7	9	4	8	6	10	0	1
Headache	**2**	9	14	6	3	8	7	13	15	10	11	5	12	4	0	1
Nausea	**5**	3	6	9	1	10	12	13	14	16	15	8	2	11	4	7
Shivering	**4**	7	2	13	1	10	6	3	12	5	8	14	11	15	0	9

Footnotes:
A: oxytocin IM, **B:** oxytocin IV(B), **C:** oxytocin IV(I), **D:** oxytocin IV (B+I), **E:** carbetocin IM, **F:** carbetocin IV(B), **G:** carbetocin IV(I), **H:** carboprost IM, **I:** ergometrine IM, **J:** ergometrine IV(B), **K:** ergometrine plus oxytocin IM, **L:** misoprostol PO, **M:** misoprostol PR, **N:** misoprostol SL, **O:** sulprostone IM, **P:** placebo or control

Subgroup and sensitivity analyses

Subgroup analyses

From the prespecified subgroups analyses (see *CHAPTER 2: METHODS*) none was possible. On one hand, no studies comparing oxytocin IM against any other eligible uterotonic were available for the subgroups of caesarean birth and high risk for PPH. On the other, only seven studies were conducted in a community setting, and thus the subgroup analysis by delivery setting was not possible.

Results for the subgroups of vaginal birth and low risk for PPH for the primary outcomes are summarised in *Table 12* and *Table 13* and reveal no substantial differences compared with the main analysis. In terms of ranking, based on SUCRAS that are available in *APPENDIX 2: Routes-NMA*, ergometrine plus oxytocin combination and carbetocin IV(B) are the top uterotonics for preventing PPH ≥500 mL. For the outcome of PPH ≥1000 mL, although no clear patterns were observed, ergometrine plus oxytocin combination seems to be among the best choices.

Table 12: Subgroup analysis for PPH ≥500 mL for the Routes-NMA.

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Ergometrine plus Oxytocin IM, Misoprostol PO, Misoprostol PR, Misoprostol SL, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: PPH ≥500 mL

Analysis restricted to	All studies	Vaginal births	Caesarean births	Low risk for PPH	High risk for PPH
Oxytocin IV(B)					
Direct estimate	**0.78 0.62-0.97**	**0.78 0.62-0.97**	Not estimable	0.45 0.16-1.29	Not estimable
Network estimate	0.75 0.59-0.97	0.77 0.58-1.03	Not estimable	0.58 0.27-1.24	Not estimable
Oxytocin IV(I)					
Direct estimate	**0.77 0.60-0.99**	**0.77 0.60-0.99**	Not estimable	Not estimable	Not estimable
Network estimate	0.87 0.67-1.11	0.78 0.57-1.06	Not estimable	0.61 0.14-2.68	Not estimable

Oxytocin IV(B+I)					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.71 0.41-1.25	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin IM					
Direct estimate	0.99 0.92-1.06	0.99 0.92-1.06	Not estimable	Not estimable	Not estimable
Network estimate	0.73 0.48-1.12	0.71 0.45-1.11	Not estimable	0.58 0.13-2.51	Not estimable
Carbetocin IV(B)					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	**0.58 0.40-0.84**	**0.13 0.03-0.65**	Not estimable	Not estimable	Not estimable
Carbetocin IV(I)					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.96 0.47-1.94	0.86 0.39-1.88	Not estimable	Not estimable	Not estimable
Carboprost IM					
Direct estimate	1.86 0.07-51.05	1.86 0.07-51.05	Not estimable	13.00 0.77-219.11	Not estimable
Network estimate	1.16 0.71-1.88	1.22 0.65-2.26	Not estimable	2.72 0.99-7.47	Not estimable
Ergometrine IM					
Direct estimate	**0.25 0.07-0.88**	**0.25 0.07-0.88**	Not estimable	Not estimable	Not estimable
Network estimate	1.35 0.88-2.07	1.32 0.84-2.08	Not estimable	2.65 1.11-6.33	Not estimable
Ergometrine IV(B)					
Direct estimate	1.39 0.70-2.74	1.39 0.70-2.74	Not estimable	1.00 0.02-48.52	Not estimable
Network estimate	0.76 0.51-1.13	0.78 0.51-1.18	Not estimable	0.46 0.20-1.09	Not estimable
Ergometrine plus Oxytocin IM					
Direct estimate	0.78 0.53-1.15	0.78 0.53-1.15	Not estimable	Not estimable	Not estimable
Network estimate	**0.71 0.56-0.91**	**0.71 0.55-0.93**	Not estimable	0.45 0.17-1.16	Not estimable
Misoprostol PO					
Direct estimate	1.14 0.77-1.69	1.14 0.77-1.69	Not estimable	1.12 0.79-1.60	Not estimable
Network estimate	0.91 0.72-1.14	0.93 0.73-1.19	Not estimable	0.78 0.47-1.30	Not estimable
Misoprostol PR					
Direct estimate	0.67 0.39-1.13	0.67 0.39-1.13	Not estimable	0.90 0.36-2.24	Not estimable
Network estimate	0.87 0.61-1.24	0.89 0.59-1.33	Not estimable	0.82 0.30-2.21	Not estimable

Misoprostol SL					
Direct estimate	0.86 0.42-1.79	0.86 0.42-1.79	Not estimable	0.61 0.20-1.84	Not estimable
Network estimate	1.02 0.78-1.32	0.97 0.70-1.34	Not estimable	1.04 0.53-2.04	Not estimable
Sulprostone IM					
Direct estimate	0.91 0.33-2.48	0.91 0.33-2.48	Not estimable	0.91 0.33-2.48	Not estimable
Network estimate	0.86 0.31-2.39	0.88 0.31-2.51	Not estimable	0.82 0.23-2.87	Not estimable
Placebo or control					
Direct estimate	**1.59** **1.27-1.99**	**1.59** **1.27-1.99**	Not estimable	**1.35** **1.20-1.52**	Not estimable
Network estimate	**1.52** **1.22-1.90**	**1.57** **1.23-2.00**	Not estimable	**1.39** **0.83-2.31**	Not estimable

Table 13: Subgroup analysis for PPH ≥1000 mL for the Routes-NMA.

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Ergometrine plus Oxytocin IM, Misoprostol PO, Misoprostol PR, Misoprostol SL, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: PPH ≥1000 mL

Analysis restricted to	**All studies**	**Vaginal births**	**Caesarean births**	**Low risk for PPH**	**High risk for PPH**
Oxytocin IV(B)					
Direct estimate	**0.56** **0.35-0.89**	**0.56** **0.35-0.89**	Not estimable	Not estimable	Not estimable
Network estimate	0.86 0.64-1.15	0.91 0.71-1.18	Not estimable	1.10 0.75-1.60	Not estimable
Oxytocin IV(I)					
Direct estimate	0.81 0.31-2.12	0.81 0.31-2.12	Not estimable	Not estimable	Not estimable
Network estimate	1.09 0.75-1.57	0.87 0.57-1.32	Not estimable	0.88 0.05-16.35	Not estimable
Oxytocin IV(B+I)					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.70 0.47-1.05	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin IM					
Direct estimate	1.05 0.87-1.26	1.05 0.87-1.26	Not estimable	Not estimable	Not estimable
Network estimate	1.02 0.70-1.48	1.04 0.86-1.26	Not estimable	0.38 0.04-3.49	Not estimable
Carbetocin IV(B)					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.76 0.50-1.14	0.89 0.06-14.15	Not estimable	Not estimable	Not estimable

Carbetocin IV(I)					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.07 0.44-2.59	0.78 0.30-2.00	Not estimable	Not estimable	Not estimable
Carboprost IM					
Direct estimate	5.00 0.25-99.16	5.00 0.25-99.16	Not estimable	5.00 0.25-99.16	Not estimable
Network estimate	1.97 0.66-5.87	4.79 0.65-35.44	Not estimable	4.23 0.55-32.69	Not estimable
Ergometrine IM					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.01 0.35-2.87	0.96 0.34-2.68	Not estimable	0.38 0.06-2.52	Not estimable
Ergometrine IV(B)					
Direct estimate	1.33 0.40-4.41	1.33 0.40-4.41	Not estimable	1.00 0.02-48.52	Not estimable
Network estimate	0.88 0.38-2.01	0.96 0.42-2.17	Not estimable	0.49 0.13-1.88	Not estimable
Ergometrine plus Oxytocin IM					
Direct estimate	0.82 0.62-1.08	0.82 0.62-1.08	Not estimable	Not estimable	Not estimable
Network estimate	0.79 0.59-1.06	0.79 0.62-1.01	Not estimable	0.55 0.16-1.89	Not estimable
Misoprostol PO					
Direct estimate	1.04 0.62-1.74	1.04 0.62-1.74	Not estimable	1.68 0.64-4.45	Not estimable
Network estimate	1.11 0.83-1.49	1.16 0.89-1.52	Not estimable	1.13 0.71-1.80	Not estimable
Misoprostol PR					
Direct estimate	0.32 0.06-1.63	0.32 0.06-1.63	Not estimable	1.00 0.02-48.52	Not estimable
Network estimate	0.88 0.51-1.50	0.92 0.55-1.52	Not estimable	1.23 0.60-2.53	Not estimable
Misoprostol SL					
Direct estimate	1.45 0.80-2.62	1.45 0.80-2.62	Not estimable	0.61 0.08-4.70	Not estimable
Network estimate	1.00 0.70-1.42	1.07 0.76-1.51	Not estimable	0.63 0.11-3.57	Not estimable
Sulprostone IM					
Direct estimate	0.64 0.06-6.57	0.64 0.06-6.57	Not estimable	0.64 0.06-6.57	Not estimable
Network estimate	0.59 0.07-4.87	0.60 0.07-4.86	Not estimable	0.66 0.08-5.33	Not estimable
Placebo or control					
Direct estimate	**1.86 1.41-2.47**	**1.86 1.41-2.47**	Not estimable	**1.78 1.33-2.38**	Not estimable
Network estimate	**1.54 1.21-1.97**	**1.59 1.30-1.96**	Not estimable	**1.84 1.39-2.44**	Not estimable

Sensitivity analyses

All prespecified sensitivity analyses were performed for the two primary outcomes: (a) analysis restricted to studies at low risk of bias, (b) restricted to studies at low risk for 'funding source', (c) restricted to studies at low risk for 'blood loss measurements', (d) restricted to studies with <10% attrition, and (e) restricted to studies with >400 participants.

Results are summarised in *Table 14* and *Table 15* and suggest no substantial differences from the main analysis. Based on cumulative probabilities and respective SUCRAS that can be found in *APPENDIX 2: Routes-NMA,* ergometrine plus oxytocin combination and carbetocin IV(B) are among the top three uterotonics for preventing PPH ≥500 mL. For the outcome of PPH ≥1000 mL, ergometrine plus oxytocin combination is consistently among the best three available options.

Table 14: Sensitivity analysis for PPH ≥500 mL for the Routes-NMA.

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Ergometrine plus Oxytocin IM, Misoprostol PO, Misoprostol PR, Misoprostol SL, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: PPH ≥500 mL

Analysis restricted to	All studies	Low risk of bias	Low risk for funding	Low risk for blood loss	Low risk for attrition	With >400 women
Oxytocin IV(B)						
Direct estimate	0.78 0.62-0.97	0.81 0.64-1.03	0.80 0.63-1.00	0.80 0.63-1.00	0.78 0.62-0.97	0.78 0.62-0.97
Network estimate	0.75 0.59-0.97	0.81 0.59-1.11	0.86 0.55-1.34	0.71 0.52-0.97	0.80 0.61-1.05	0.81 0.58-1.12
Oxytocin IV(I)						
Direct estimate	0.77 0.60-0.99	0.86 0.62-1.21	0.70 0.41-1.18	0.77 0.60-0.99	0.77 0.60-0.99	0.72 0.52-1.00
Network estimate	0.87 0.67-1.11	0.86 0.50-1.48	0.76 0.46-1.26	0.83 0.63-1.10	0.86 0.65-1.13	0.72 0.48-1.07
Oxytocin IV(B+I)						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.71 0.41-1.25	0.82 0.49-1.37	0.59 0.18-1.91	0.77 0.41-1.47	0.73 0.41-1.27	Not estimable

Carbetocin IM						
Direct estimate	0.99 0.92-1.06	0.99 0.92-1.06	0.99 0.92-1.06	0.99 0.92-1.06	0.99 0.92-1.06	0.99 0.92-1.06
Network estimate	0.73 0.48-1.12	0.99 0.66-1.47	0.88 0.42-1.88	0.75 0.46-1.22	0.85 0.54-1.33	0.99 0.49-1.98
Carbetocin IV(B)						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.58 0.40-0.84	0.68 0.44-1.06	0.70 0.28-1.73	0.52 0.31-0.87	0.63 0.43-0.93	0.62 0.33-1.17
Carbetocin IV(I)						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.96 0.47-1.94	0.95 0.46-1.99	0.84 0.31-2.25	0.92 0.47-1.79	0.95 0.47-1.93	0.79 0.34-1.83
Carboprost IM						
Direct estimate	1.86 0.07-51.05	Not estimable	13.00 0.77-219.11	1.86 0.07-51.05	Not estimable	Not estimable
Network estimate	1.16 0.71-1.88	Not estimable	1.58 0.45-5.53	1.34 0.67-2.69	1.17 0.57-2.40	0.98 0.41-2.32
Ergometrine IM						
Direct estimate	0.25 0.07-0.88	0.25 0.07-0.88	0.25 0.07-0.88	0.25 0.07-0.88	0.25 0.07-0.88	Not estimable
Network estimate	1.35 0.88-2.07	0.25 0.07-0.94	1.30 0.58-2.95	0.95 0.54-1.67	1.46 0.90-2.37	2.22 1.08-4.55
Ergometrine IV(B)						
Direct estimate	1.39 0.70-2.74	Not estimable	1.00 0.02-48.52	1.39 0.70-2.74	Not estimable	1.40 0.70-2.80
Network estimate	0.76 0.51-1.13	Not estimable	0.32 0.12-0.81	0.76 0.50-1.17	0.54 0.28-1.03	0.82 0.48-1.42
Ergometrine plus Oxytocin IM						
Direct estimate	0.78 0.53-1.15	0.81 0.58-1.14	0.36 0.14-0.89	0.87 0.56-1.36	0.78 0.53-1.15	0.78 0.53-1.15
Network estimate	0.71 0.56-0.91	0.75 0.55-1.02	0.52 0.27-1.00	0.95 0.62-1.45	0.68 0.53-0.87	0.67 0.50-0.90
Misoprostol PO						
Direct estimate	1.14 0.77-1.69	1.00 0.78-1.26	0.90 0.59-1.36	1.02 0.82-1.27	1.19 0.63-2.23	1.19 0.71-1.99
Network estimate	0.91 0.72-1.14	1.00 0.75-1.34	0.72 0.48-1.07	1.02 0.78-1.33	0.90 0.70-1.14	0.93 0.70-1.24
Misoprostol PR						
Direct estimate	0.67 0.39-1.13	Not estimable	0.75 0.41-1.37	0.70 0.39-1.23	0.73 0.42-1.26	0.57 0.30-1.09
Network estimate	0.87 0.61-1.24	0.76 0.37-1.54	0.87 0.49-1.54	0.82 0.56-1.21	0.87 0.59-1.30	0.77 0.45-1.32
Misoprostol SL						
Direct estimate	0.86 0.42-1.79	0.86 0.36-2.09	0.76 0.17-3.33	0.96 0.44-2.10	0.86 0.36-2.09	0.86 0.36-2.09
Network estimate	1.02 0.78-1.32	1.17 0.84-1.63	0.87 0.55-1.37	1.02 0.78-1.33	0.97 0.73-1.29	1.19 0.79-1.79

Sulprostone IM						
Direct estimate	0.91 0.33-2.48	0.91 0.33-2.48	Not estimable	0.91 0.33-2.48	0.91 0.33-2.48	Not estimable
Network estimate	0.86 0.31-2.39	0.84 0.32-2.17	Not estimable	0.87 0.32-2.35	0.84 0.31-2.33	Not estimable
Placebo or control						
Direct estimate	1.59 1.27-1.99	1.67 0.75-3.70	1.70 1.23-2.35	1.59 1.27-1.99	1.55 1.25-1.93	1.70 1.23-2.35
Network estimate	1.52 1.22-1.90	1.46 1.07-1.98	1.40 0.98-2.00	1.55 1.23-1.95	1.47 1.17-1.85	1.61 1.21-2.14

Table 15: Sensitivity analysis for PPH ≥1000 mL for the Routes-NMA.

Population: Women in the third stage of labour
Interventions: Oxytocin IV(B), Oxytocin IV(I), Oxytocin IV(B+I), Carbetocin IM, Carbetocin IV(B), Carbetocin IV(I), Carboprost IM, Ergometrine IM, Ergometrine IV(B), Ergometrine plus Oxytocin IM, Misoprostol PO, Misoprostol PR, Misoprostol SL, Sulprostone IM, Placebo or control
Comparison (reference): Oxytocin IM
Outcome: PPH ≥1000 mL

Analysis restricted to	All studies	Low risk of bias	Low risk for funding	Low risk for blood loss	Low risk for attrition	With >400 women
Oxytocin IV(B)						
Direct estimate	0.56 0.35-0.89	0.57 0.35-0.93	0.56 0.35-0.89	0.56 0.35-0.89	0.56 0.35-0.89	0.56 0.35-0.89
Network estimate	0.86 0.64-1.15	0.75 0.53-1.07	0.83 0.60-1.14	0.85 0.62-1.16	0.85 0.63-1.16	0.87 0.61-1.24
Oxytocin IV(I)						
Direct estimate	0.81 0.31-2.12	0.78 0.40-1.53	0.68 0.38-1.22	0.81 0.31-2.12	0.81 0.31-2.12	0.68 0.38-1.22
Network estimate	1.09 0.75-1.57	0.74 0.40-1.37	0.90 0.55-1.47	1.02 0.69-1.50	1.06 0.70-1.63	0.75 0.44-1.26
Oxytocin IV(B+I)						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.70 0.47-1.05	0.79 0.45-1.39	0.79 0.50-1.26	0.90 0.31-2.64	0.71 0.47-1.07	0.62 0.36-1.09
Carbetocin IM						
Direct estimate	1.05 0.87-1.26	1.05 0.87-1.26	1.05 0.87-1.26	1.05 0.87-1.26	1.05 0.87-1.26	1.05 0.87-1.26
Network estimate	1.02 0.70-1.48	1.04 0.87-1.26	1.05 0.78-1.42	1.04 0.77-1.40	1.02 0.69-1.50	1.05 0.65-1.70
Carbetocin IV(B)						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.76 0.50-1.14	0.75 0.46-1.24	0.86 0.50-1.48	0.81 0.45-1.47	0.80 0.52-1.23	1.28 0.48-3.36
Carbetocin IV(I)						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.07 0.44-2.59	0.66 0.23-1.88	0.93 0.37-2.36	0.91 0.35-2.38	1.08 0.43-2.73	0.67 0.23-1.99

Carboprost IM						
Direct estimate	5.00 0.25-99.16	Not estimable	5.00 0.25-99.16	5.00 0.25-99.16	Not estimable	Not estimable
Network estimate	1.97 0.66-5.87	Not estimable	2.40 0.29-20.07	4.81 0.64-36.07	Not estimable	1.31 0.34-4.99
Ergometrine IM						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.01 0.35-2.87	Not estimable	0.33 0.05-2.21	1.26 0.15-10.45	0.85 0.27-2.61	0.74 0.17-3.24
Ergometrine IV(B)						
Direct estimate	1.33 0.40-4.41	Not estimable	1.00 0.02-48.52	1.33 0.40-4.41	Not estimable	1.37 0.39-4.83
Network estimate	0.88 0.38-2.01	Not estimable	0.27 0.05-1.39	0.99 0.42-2.38	0.34 0.07-1.62	0.97 0.34-2.76
Ergometrine plus Oxytocin IM						
Direct estimate	0.82 0.62-1.08	0.82 0.61-1.10	0.34 0.01-8.21	0.81 0.34-1.96	0.82 0.62-1.08	0.82 0.62-1.08
Network estimate	0.79 0.59-1.06	0.80 0.60-1.06	0.42 0.19-0.96	0.78 0.42-1.44	0.78 0.58-1.05	0.74 0.53-1.04
Misoprostol PO						
Direct estimate	1.04 0.62-1.74	1.06 0.61-1.84	0.86 0.45-1.64	0.96 0.50-1.86	1.14 0.67-1.94	1.04 0.61-1.75
Network estimate	1.11 0.83-1.49	1.04 0.71-1.51	1.00 0.69-1.46	1.11 0.80-1.55	1.14 0.84-1.54	1.11 0.79-1.56
Misoprostol PR						
Direct estimate	0.32 0.06-1.63	Not estimable	0.45 0.06-3.20	0.31 0.05-2.08	0.35 0.04-3.32	0.25 0.04-1.51
Network estimate	0.88 0.51-1.50	0.18 0.03-1.27	0.40 0.10-1.67	0.90 0.52-1.53	0.77 0.39-1.52	0.84 0.45-1.56
Misoprostol SL						
Direct estimate	1.45 0.80-2.62	1.19 0.62-2.29	1.28 0.65-2.52	1.46 0.80-2.66	1.42 0.71-2.84	1.19 0.62-2.29
Network estimate	1.00 0.70-1.42	1.00 0.66-1.52	0.96 0.64-1.45	1.02 0.73-1.44	1.01 0.69-1.49	1.04 0.63-1.70
Sulprostone IM						
Direct estimate	0.64 0.06-6.57	0.64 0.06-6.57	Not estimable	0.64 0.06-6.57	0.64 0.06-6.57	Not estimable
Network estimate	0.59 0.07-4.87	0.55 0.07-4.47	Not estimable	0.59 0.07-4.82	0.58 0.07-4.82	Not estimable
Placebo or control						
Direct estimate	1.86 1.41-2.47	1.75 0.32-9.62	1.92 1.42-2.61	1.86 1.41-2.47	1.83 1.37-2.42	1.92 1.42-2.61
Network estimate	1.54 1.21-1.97	1.37 0.95-1.99	1.50 1.14-1.96	1.54 1.21-1.96	1.51 1.17-1.95	1.56 1.15-2.10

CHAPTER 4: RESULTS FOR THE DOSE NMA

Study characteristics

The study flow diagram is available in

Based on the above, larger scale randomised trials assessing different routes and doses of administration need to be conducted. Additionally, there is an urgent need for studies testing uterotonics that are not commonly used either because of licensing reasons, financial constraints, or theoretically expected side effects. In any case, future studies should focus not only on reporting blood loss related outcomes and side effects, but also on women's views and acceptability of the interventions.

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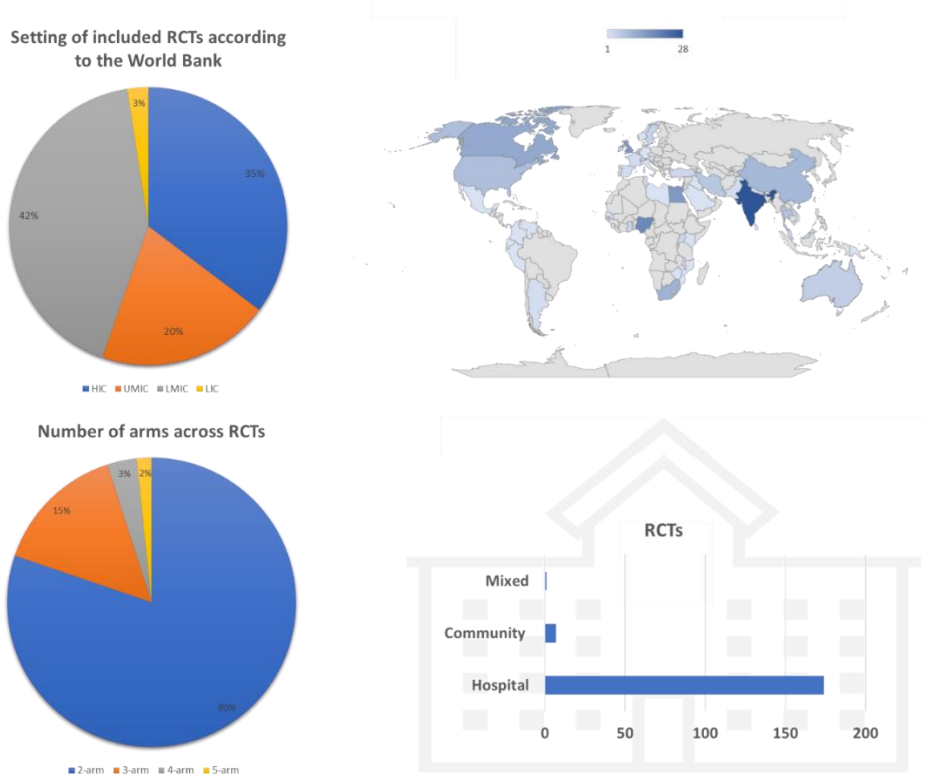
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APPENDIX 1: Additional information Routes-NMA & Doses-NMA. One hundred eighty-two studies, involving 132,593 randomised women, contributed data to the Doses-NMA. Most studies (80%) included two arms, twenty-seven (15%) had three arms, six (3%) had 4 arms, and three (2%) had 5 arms. Most studies (95%) were conducted in a hospital setting, seven (4%) were conducted in a community setting, and only one (1%) took place in a mixed setting. According to the World Bank classification, most studies (42%) were conducted in lower-middle income countries (LMIC), 35% was conducted in high-income countries (HIC), one fifth in upper-middle income countries (UMIC), and only 3% in low-income countries (LIC). India was the country where most studies were conducted. All information listed above is summarised in *Figure 29.*

Figure 29: Characteristics of studies included in the Doses-NMA



Participant characteristics across included studies

Participant characteristics are summarised in *Figure 30.* In most studies (64%) randomised participants delivered vaginally, in 35% of cases women gave birth by caesarean section, and in only 1% of included studies participants were eligible for randomisation irrespectively of the mode of birth. Among the sixty-four studies where women had a caesarean birth, 58% corresponded to elective caesarean sections (ELCS), 9% to emergency caesarean sections (EMCS), 28% to both ELCS and EMCS, whereas in the remaining 5% the type of caesarean section was not further specified. In one hundred twenty-five studies (69%) women had a singleton pregnancy, whereas in only two studies (1%) the gestation was multiple. In thirty-three studies (18%) both singleton and multiple gestations were included, while in the remaining twenty-two studies (12%) the type of gestation was not specified. In 44% of included studies participants were found to be at high risk for PPH, whereas in 26% of available studies the respective risk was judged to be low. In 29% of included studies the randomised population consisted of pregnant women both at high and low risk for PPH, while in 1% of cases the risk for excessive bleeding was neither reported nor possible to assess.

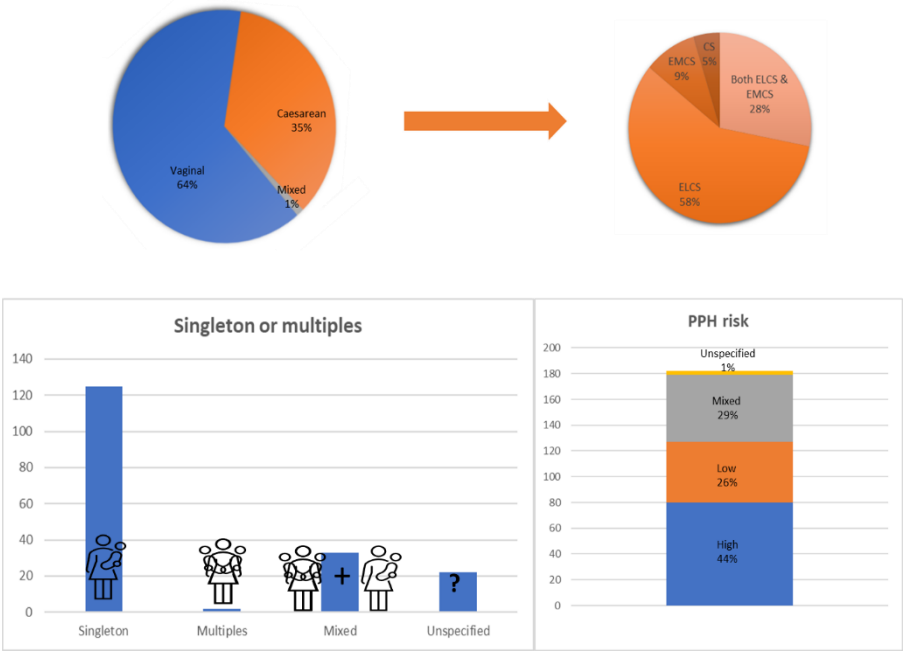


Figure 30: Participant characteristics for studies included in the Doses-NMA

Uterotonic interventions contributing to the analyses

One hundred eighty-two studies were available for the Doses-NMA and included four hundred twelve arms. From the total available arms 92% contributed data to the analyses as shown in *Table 16*. The remaining 8% of available arms were excluded for the following reasons: (a) the specific uterotonic intervention was excluded from the analysis (see *CHAPTER 2: METHODS*), (b) a non-uterotonic agent was tested, and (c) a non-pharmaceutical intervention was tested.

Table 16: Study arms for the Doses-NMA

Available studies included in total 412 arms				
Included		% of Included	Excluded	
Oxytocin 10 IU	63	16.6	**Uterotonic interventions**	
Oxytocin >10 IU	64	16.9	Oxytocin 10 IU (intraumbilically)	1
Oxytocin <10 IU	31	8.2	(Intramyometrial) Carboprost >125 mcg	1
Carbetocin 100 mcg	36	9.5	Carboprost plus Oxytocin 250 mcg plus 25 IU	1
Carbetocin >100 mcg	2	0.5	Ergometrine plus Oxytocin >200 mcg plus >10 IU	3
Carbetocin <100 mcg	8	2.1	Ergometrine plus Oxytocin 200 mcg plus 10 IU	2
Carboprost 125 mcg	7	1.8	Ergometrine plus Oxytocin 200 mcg plus >10 IU	2
Carboprost >125 mcg	4	1.1	Ergometrine plus Oxytocin 200 mcg plus <10 IU	2
Ergometrine 200 mcg	19	5.0	Misoprostol plus Oxytocin >400 mcg plus 10 IU	3
Ergometrine >200 mcg	11	2.9	Misoprostol plus Oxytocin >400 mcg plus >10 IU	1
Misoprostol 400 mcg	40	10.6	Misoprostol plus Oxytocin >400 mcg plus <10 IU	2
Misoprostol >400 mcg	42	11.1	Misoprostol plus Oxytocin 400 mcg plus 10 IU	4
Misoprostol <400 mcg	4	1.1	Misoprostol plus Oxytocin 400 mcg plus >10 IU	4
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	24	6.3	Misoprostol plus Oxytocin <400 mcg plus 10 IU	1
Sulprostone 500 mcg	2	0.5	Misoprostol plus Oxytocin <400 mcg plus >10 IU	2
Placebo or control	22	5.8	Misoprostol plus Oxytocin <400 mcg plus <10 IU	2
Total	**379**	**100**	**Other interventions**	
			Acupuncture	1
			Tranexamic acid	1
			Total	**33**

Risk of Bias

Nine domains were assessed for risk of bias and the respective summary is presented in *Figure 31.* For most domains of assessment at least 50% of included studies were found to be at 'low' risk of bias. For the domains of 'selective reporting' and 'funding source' most studies were judged to be at 'unclear' risk.

Selection bias:

One hundred forty-one studies (78%) reported adequate methods of random sequence generation in sufficient detail, whereas the remaining forty-one (22%) did not provide this information and were found to be at unclear risk of bias for this domain. In terms of allocation concealment, most studies (60%) were judged to be at low risk of bias for this domain. In seventy-one studies (39%), authors did not provide sufficient information on the methods used to conceal the allocation, and these studies were assessed as 'unclear' risk for this domain. In only two studies (1%) investigators made no attempt to conceal the allocation of the randomised interventions, and thus these studies were judged to be at 'high' risk.

Performance bias:

Half of the included studies (50%) reported adequate blinding of the attending personnel and study participants. These studies were assessed as 'low' risk for performance bias. Fifty-two studies (29%) did not provide sufficient details and were found to be at 'unclear' risk of bias for this domain. In the remaining 38 studies (21%) there was lack of blinding either because there was no relevant effort or the methods used were ineffective, and thus these studies were assessed as 'high' risk for performance bias.

Detection bias:

Half of the included studies (51%) were found to be at low risk for detection bias since outcome assessors were blinded to treatment allocations. In seventy-one studies (39%), it was unclear whether outcome assessors were masked to allocations, and thus these studies were judged to be at 'unclear' risk for this domain. Nineteen studies (10%) were assessed as 'high' risk for detection bias since assessors were not blinded to the allocations.

Objective assessment of blood loss:

Half of the included studies (51%) reported objective methods of measuring blood loss such as the use of calibrated drapes and calibrated bedpans. Forty studies (23%) did not report methods of measuring blood loss, or the methods used were not described in sufficient detail. Therefore, these studies were judged as 'unclear' risk for this domain. In the remaining fifty studies (27%) assessment of blood loss was based on the visual estimation of the attending personnel. All these studies were found to be at 'high' risk for this specific domain.

Attrition bias:

In most studies (73%) there were no lost to follow up cases or noted attrition was <10% and balanced across arms. All these cases were found to be at 'low' risk for attrition bias. In thirty-two studies (18%) authors did not specify whether all those who were randomised and received study interventions contributed to the dataset. For such cases, the final assessment was 'unclear' risk for this domain. In the remaining eighteen studies (9%) lost to follow up cases were >10% of the randomised participants, and thus these studies were assessed as 'high' risk for incomplete outcome.

Reporting bias:

Only 14% of included studies were found to be at ‘low’ risk for reporting bias, since the study report was matching the protocol that was registered prospectively. In most cases (79%), the study protocol was not available for verification, or it was registered retrospectively, and thus these studies were found to be at ‘unclear’ risk for this domain. For the remaining 7%, the judgment was ‘high’ risk for reporting bias either because the registered protocol did not match the study report or there was obvious selection in the reporting of results, e.g., authors report methods of measuring blood loss but results for blood loss related outcomes are not presented.

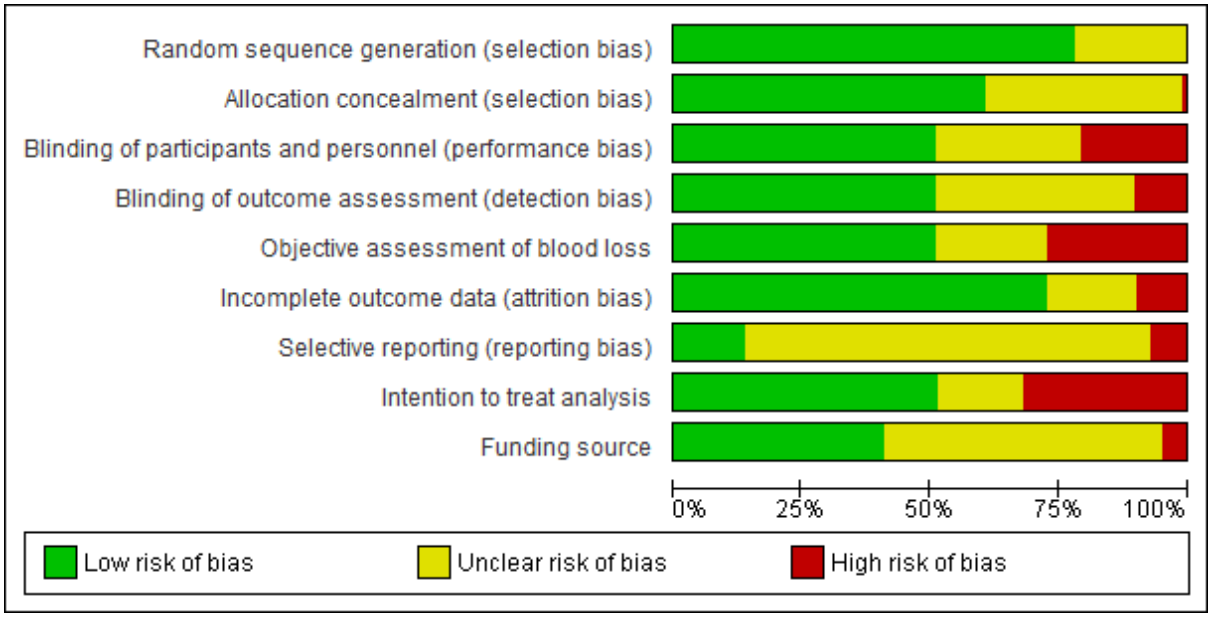
Intention to treat analysis:

In half of the included studies analysis was done on an intention-to-treat basis and thus these studies were assessed as ‘low’ risk for this domain. Nearly one fifth (17%) of included studies were found to be at ‘unclear’ risk since authors did not specify whether randomised participants were finally included in the analysis, in the groups to which they were initially randomised. The remaining fifty-eight studies (31%) were judged as ‘high’ risk of bias for this domain because of post-randomisation exclusions from the analysis.

Funding source:

Seventy-four of the included studies (41%) received university or institutional funds, or were supported by non-governmental organizations, and thus were judged to be at ‘low’ risk for this domain. Half of the included studies (54%) were found to be at ‘unclear’ risk for this domain since no details about funding sources were provided. Only nine studies (5%) were supported by pharmaceutical companies and were found to be at ‘high’ risk for this domain.

Figure 31: Risk of bias summary for the Doses-NMA



Summary of Findings Tables

Table 17: PPH ≥500 mL-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: PPH ≥500 mL

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	Not estimable	Not estimable	0.96 0.70 -1.32 MODERATE[1]	121 per 1000	116 per 1000	5 fewer per 1000 (from 36 fewer to 39 more)
Oxytocin <10 IU	Not estimable	Not estimable	1.12 0.83-1.51 MODERATE[1]	121 per 1000	136 per 1000	15 more per 1000 (from 21 fewer to 62 more)
Carbetocin 100 mcg	1.00 0.90-1.11 HIGH	0.61 0.41- 0.91 MODERATE[1]	0.78 0.60-1.02 MODERATE[2]	121 per 1000	94 per 1000	27 fewer per 1000 (from 48 fewer to 2 more)
Carbetocin >100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carboprost 125 mcg	1.86 0.07-51.05 VERY LOW[1]	1.37 0.62-2.99 VERY LOW[2]	1.34 0.69-2.58 VERY LOW[3]	121 per 1000	162 per 1000	41 more per 1000 (from 38 fewer to 191 more)
Carboprost >125 mcg	Not estimable	Not estimable	1.04 0.50-2.16 LOW[4]	121 per 1000	126 per 1000	5 more per 1000 (from 61 fewer to 140 more)
Ergometrine 200 mcg	1.39 0.70-2.74 LOW[2]	1.11 0.71-1.72 LOW[3]	1.15 0.77-1.71 LOW[5]	121 per 1000	139 per 1000	18 more per 1000 (from 29 fewer to 86 more)
Ergometrine >200 mcg	0.78 0.28-2.17 LOW[2]	1.38 0.77-2.50 VERY LOW[4]	1.15 0.73-1.82 LOW[6]	121 per 1000	139 per 1000	18 more per 1000 (from 33 fewer to 99 more)
Misoprostol 400 mcg	0.95 0.63-1.45	1.02 0.69-1.49	1.00 0.78-1.29	121 per 1000	121 per 1000	No difference

	LOW[2]	LOW[3]	LOW[5]			per 1000 (from 27 fewer to 35 more)
Misoprostol >400 mcg	1.09 0.74-1.60 LOW[2]	1.29 0.93-1.77 LOW[3]	1.17 0.94-1.46 LOW[5]	121 per 1000	142 per 1000	21 more per 1000 (from 7 fewer to 56 more)
Misoprostol <400 mcg	Not estimable	Not estimable	0.86 0.39-1.88 LOW[4]	121 per 1000	104 per 1000	17 fewer per 1000 (from 74 fewer to 107 more)
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	0.86 0.66-1.11 LOW[2]	0.75 0.53-1.08 MODERATE[5]	0.79 0.62-1.01 MODERATE[7]	121 per 1000	96 per 1000	25 fewer per 1000 (from 46 fewer to 1 more)
Sulprostone 500 mcg	Not estimable	Not estimable	1.01 0.35-2.93 LOW[4]	121 per 1000	122 per 1000	1 more per 1000 (from 79 fewer to 234 more)
Placebo or control	1.86 1.58-2.20 LOW[3]	1.79 1.30-2.45 MODERATE[1]	1.83 1.42-2.37 MODERATE[8]	121 per 1000	221 per 1000	100 more per 1000 (from 51 to 166 more)

Direct evidence:
1. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -2 due to multiple crucial limitations in study design.

Indirect evidence:
1. Downgraded -1 due to crucial limitations in study design.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.
4. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
5. Downgraded -1 due serious imprecision.

Network evidence:
1. Downgraded -1 due to moderate certainty indirect loop evidence.
2. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
3. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
4. Downgraded -2 due to low certainty indirect loop evidence.
5. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
6. Downgraded -2 due to low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
7. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
8. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, no imprecision).

Table 18: PPH ≥1000 mL-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: PPH ≥1000 mL

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	Not estimable	Not estimable	1.08 0.85-1.38 LOW[1]	30 per 1000	32 per 1000	2 more per 1000 (from 5 fewer to 11 more)
Oxytocin <10 IU	1.96 0.38-10.24 VERY LOW[1]	1.16 0.90-1.49 VERY LOW[1]	1.17 0.91-1.51 VERY LOW[2]	30 per 1000	35 per 1000	5 more per 1000 (from 3 fewer to 15 more)
Carbetocin 100 mcg	1.07 0.90-1.27 HIGH	0.89 0.59-1.37 LOW[2]	1.04 0.88-1.24 MODERATE[3]	30 per 1000	31 per 1000	1 more per 1000 (from 4 fewer to 7 more)
Carbetocin >100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg	Not estimable	Not estimable	0.95 0.61-1.47 VERY LOW[4]	30 per 1000	29 per 1000	1 fewer per 1000 (from 12 fewer to 14 more)
Carboprost 125 mcg	5.00 0.25-99.16 VERY LOW[1]	9.48 0.07-1354.9 VERY LOW[3]	6.17 0.84-45.30 VERY LOW[5]	30 per 1000	185 per 1000	155 more per 1000 (from 5 fewer to 1000 more)
Carboprost >125 mcg	Not estimable	Not estimable	1.45 0.42-5.02 VERY LOW[4]	30 per 1000	44 per 1000	14 more per 1000 (from 17 fewer to 121 more)
Ergometrine 200 mcg	1.33 0.40-4.41 LOW[2]	1.42 0.54-3.68 LOW[2]	1.41 0.67-2.97 LOW[6]	30 per 1000	42 per 1000	12 more per 1000 (from 10 fewer to 59 more)
Ergometrine >200 mcg	1.60 0.20-12.91 VERY LOW[1]	0.24 0.05-1.11 VERY LOW[3]	0.47 0.14-1.60 VERY LOW[2]	30 per 1000	14 per 1000	16 fewer per 1000 (from 26 fewer to 18 more)
Misoprostol	1.02	1.20	1.14	30 per	34 per	4 more per

400 mcg	0.62-1.69 LOW[2]	0.86-1.68 LOW[2]	0.87-1.49 LOW[6]	1000	1000	1000 (from 4 fewer to 15 more)
Misoprostol >400 mcg	1.38 1.18-1.60 HIGH	1.23 0.92-1.65 LOW[2]	1.33 1.11-1.60 HIGH	30 per 1000	40 per 1000	10 more per 1000 (from 3 to 18 more)
Misoprostol <400 mcg	7.00 0.88-55.37 VERY LOW[1]	0.76 0.24-2.42 VERY LOW[3]	1.29 0.47-3.54 VERY LOW[7]	30 per 1000	39 per 1000	9 more per 1000 (from 16 fewer to 76 more)
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	0.80 0.62-1.05 VERY LOW[3]	0.88 0.53-1.46 VERY LOW[1]	0.82 0.65-1.04 VERY LOW[5]	30 per 1000	25 per 1000	5 fewer per 1000 (from 11 fewer to 1 more)
Sulprostone 500 mcg	Not estimable	Not estimable	0.69 0.08-5.59 VERY LOW[4]	30 per 1000	21 per 1000	9 fewer per 1000 (from 28 fewer to 138 more)
Placebo or control	1.63 1.31-2.02 LOW[4]	2.01 1.60-2.51 LOW[4]	1.80 1.53-2.12 LOW[8]	30 per 1000	54 per 1000	24 more per 1000 (from 16 to 34 more)

Direct evidence:
1. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
4. Downgraded -2 due to multiple crucial limitations in study design.

Indirect evidence:
1. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
4. Downgraded -2 due to multiple crucial limitations in study design.

Network evidence:
1. Downgraded -1 due to low certainty indirect loop evidence.
2. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
3. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
4. Downgraded -3 due to very low certainty indirect loop evidence.
5. Downgraded -3 due to very low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
6. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
7. Downgraded -3 due to very low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
8. Downgraded -2 due to low certainty direct evidence (no intransitivity, no incoherence, no imprecision).

Table 19: Additional uterotonics-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: Additional uterotonics

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	0.52 0.01-24.65 VERY LOW[1]	1.25 0.86-1.80 LOW[1]	1.25 0.86-1.80 VERY LOW[1]	128 per 1000	160 per 1000	32 more per 1000 (from 18 fewer to 102 more)
Oxytocin <10 IU	7.49 1.27-44.22 MODERATE[2]	1.05 0.71-1.55 LOW[1]	1.14 0.78-1.67 LOW[2]	128 per 1000	146 per 1000	18 more per 1000 (from 28 fewer to 86 more)
Carbetocin 100 mcg	0.79 0.64-0.98 LOW[3]	0.52 0.34-0.80 LOW[2]	0.58 0.43-0.80 VERY LOW[3]	128 per 1000	74 per 1000	54 fewer per 1000 (from 26 to 73 fewer)
Carbetocin >100 mcg	Not estimable	Not estimable	0.91 0.17-4.91 LOW[4]	128 per 1000	117 per 1000	11 fewer per 1000 (from 106 fewer to 501 more)
Carbetocin <100 mcg	Not estimable	Not estimable	0.95 0.43-2.13 LOW[2]	128 per 1000	122 per 1000	6 fewer per 1000 (from 73 fewer to 145 more)
Carboprost 125 mcg	0.71 0.03-16.54 VERY LOW[1]	0.83 0.37-1.86 VERY LOW[3]	0.68 0.34-1.35 VERY LOW[5]	128 per 1000	87 per 1000	41 fewer per 1000 (from 85 fewer to 45 more)
Carboprost >125 mcg	Not estimable	Not estimable	0.36 0.03-4.61 VERY LOW[6]	128 per 1000	46 per 1000	82 fewer per 1000 (from 124 fewer to 462 more)
Ergometrine 200 mcg	1.22 0.82-1.83 LOW[4]	1.06 0.59-1.90 LOW[4]	1.09 0.65-1.82 LOW[7]	128 per 1000	140 per 1000	12 more per 1000 (from 45 fewer to 105 more)
Ergometrine >200 mcg	0.73 0.15-3.61	1.11 0.46-2.66	0.90 0.49-1.67	128 per 1000	115 per 1000	13 fewer per 1000

	LOW[4]	LOW[4]	LOW[8]			(from 65 fewer to 86 more)
Misoprostol 400 mcg	1.11 0.73-1.70 LOW[4]	1.09 0.73-1.63 LOW[4]	1.09 0.81-1.47 LOW[8]	128 per 1000	140 per 1000	12 more per 1000 (from 24 fewer to 60 more)
Misoprostol >400 mcg	1.05 0.63-1.75 LOW[4]	1.27 0.82-1.98 VERY LOW[5]	1.11 0.83-1.49 LOW[7]	128 per 1000	142 per 1000	14 more per 1000 (from 22 fewer to 63 more)
Misoprostol <400 mcg	Not estimable	Not estimable	1.46 0.34-6.19 VERY LOW[6]	128 per 1000	187 per 1000	59 more per 1000 (from 85 fewer to 664 more)
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	0.91 0.75-1.10 LOW[3]	0.61 0.39-0.94 LOW[2]	0.75 0.55-1.04 VERY LOW[1]	128 per 1000	96 per 1000	32 fewer per 1000 (from 58 fewer to 5 more)
Sulprostone 500 mcg	Not estimable	Not estimable	0.67 0.03-15.32 VERY LOW[6]	128 per 1000	86 per 1000	42 fewer per 1000 (from 124 fewer to 1000 more)
Placebo or control	2.15 1.45-3.18 HIGH	2.70 1.75-4.17 MODERATE[6]	2.57 1.76-3.76 HIGH	128 per 1000	329 per 1000	201 more per 1000 (from 97 to 353 more)

Direct evidence:
1. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
2. Downgraded -1 due to serious imprecision (small sample size).
3. Downgraded -2 due to crucial limitations in study design and severe unexplained statistical heterogeneity.
4. Downgraded -2 due to crucial limitations in study design and serious imprecision.

Indirect evidence:
1. Downgraded -2 due to crucial limitations in study design and serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and severe unexplained statistical heterogeneity.
3. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
4. Downgraded -2 due to crucial limitations in study design and serious imprecision.
5. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
6. Downgraded -1 due to crucial limitations in study design.

Network evidence:
1. Downgraded -3 due to low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
2. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
3. Downgraded -3 due to low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
4. Downgraded -2 due to low certainty indirect loop evidence.
5. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
6. Downgraded -3 due to very low certainty indirect loop evidence.
7. Downgraded -2 due to low certainty direct evidence (no intransitivity, no incoherence, imprecision present).
8. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).

Table 20: Blood transfusion-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: Blood transfusion

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	Not estimable	Not estimable	1.68 0.97-2.93 LOW[1]	17 per 1000	29 per 1000	12 more per 1000 (from 1 fewer to 33 more)
Oxytocin <10 IU	Not estimable	Not estimable	1.28 0.78-2.08 LOW[1]	17 per 1000	22 per 1000	5 more per 1000 (from 4 fewer to 18 more)
Carbetocin 100 mcg	1.05 0.90-1.24 HIGH	1.01 0.55-1.86 LOW[1]	0.98 0.74-1.30 MODERATE[2]	17 per 1000	17 per 1000	No difference per 1000 (from 4 fewer to 5 more)
Carbetocin >100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carboprost 125 mcg	1.01 0.04-23.65 VERY LOW[1]	0.68 0.09-5.37 VERY LOW[2]	1.04 0.27-4.07 VERY LOW[3]	17 per 1000	18 per 1000	1 more per 1000 (from 12 fewer to 52 more)
Carboprost >125 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Ergometrine 200 mcg	1.30 0.26-6.56 LOW[2]	1.42 0.53-3.83 LOW[1]	1.40 0.60-3.26 LOW[4]	17 per 1000	24 per 1000	7 more per 1000 (from 7 fewer to 38 more)
Ergometrine >200 mcg	0.11 0.01-0.88 HIGH	0.60 0.06-6.00 VERY LOW[3]	0.24 0.05-1.11 MODERATE[2]	17 per 1000	4 per 1000	13 fewer per 1000 (from 16 fewer to 2 more)
Misoprostol 400 mcg	1.09 0.52-2.25 MODERATE[3]	0.91 0.50-1.68 LOW[1]	0.99 0.63-1.56 MODERATE[5]	17 per 1000	17 per 1000	No difference per 1000 (from 6 fewer to 10

						more)
Misoprostol >400 mcg	0.71 0.54-0.93 **HIGH**	1.02 0.63-1.65 **LOW**[1]	0.79 0.60-1.05 **MODERATE**[6]	17 per 1000	13 per 1000	4 fewer per 1000 (from 7 fewer to 1 more)
Misoprostol <400 mcg	Not estimable	Not estimable	0.90 0.09-8.77 **VERY LOW**[7]	17 per 1000	15 per 1000	2 fewer per 1000 (from 16 fewer to 132 more)
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	1.10 0.81-1.48 **LOW**[2]	0.70 0.45-1.09 **MODERATE**[4]	0.94 0.74-1.21 **LOW**[8]	17 per 1000	16 per 1000	1 fewer per 1000 (from 4 fewer to 4 more)
Sulprostone 500 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	1.39 0.86-2.23 **VERY LOW**[4]	2.11 1.29-3.46 **MODERATE**[5]	1.71 1.19-2.45 **MODERATE**[9]	17 per 1000	29 per 1000	12 more per 1000 (from 3 to 25 more)

Direct evidence:

1. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -1 due to serious imprecision.
4. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.

Indirect evidence:

1. Downgraded -2 due to crucial limitations in study design and serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -3 due to multiple crucial limitations in study design and serious imprecision.
4. Downgraded -1 due to serious imprecision.
5. Downgraded -1 due to crucial limitations in study design.

Network evidence:

1. Downgraded -2 due to low certainty indirect loop evidence.
2. Downgraded -1 due to high certainty direct evidence and imprecision of the network estimate (no intransitivity, no incoherence).
3. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
4. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
5. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence, imprecision present).
6. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and the indirect estimate (no intransitivity, imprecision present).
7. Downgraded -3 due to very low certainty indirect loop evidence.
8. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and the indirect estimate (no intransitivity, imprecision present).
9. Downgraded -1 due to moderate certainty indirect evidence (no intransitivity, no incoherence, no imprecision).

Table 21: Fever-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: Fever

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	Not estimable	Not estimable	2.49 1.11-5.61 LOW[1]	12 per 1000	30 per 1000	18 more per 1000 (from 1 to 55 more)
Oxytocin <10 IU	Not estimable	Not estimable	0.65 0.26-1.60 MODERATE[2]	12 per 1000	8 per 1000	4 fewer per 1000 (from 9 fewer to 7 more)
Carbetocin 100 mcg	0.37 0.02-8.71 LOW[1]	2.15 0.67-6.87 MODERATE[1]	1.78 0.60-5.31 LOW[3]	12 per 1000	21 per 1000	9 more per 1000 (from 5 fewer to 52 more)
Carbetocin >100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carboprost 125 mcg	2.00 0.18-21.71 VERY LOW[2]	0.64 0.15-2.75 LOW[2]	0.83 0.23-2.99 LOW[4]	12 per 1000	10 per 1000	2 fewer per 1000 (from 9 fewer to 24 more)
Carboprost >125 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Ergometrine 200 mcg	2.97 0.97-9.05 LOW[3]	0.71 0.32-1.55 MODERATE[1]	0.92 0.46-1.85 LOW[3]	12 per 1000	11 per 1000	1 fewer per 1000 (from 7 fewer to 10 more)
Ergometrine >200 mcg	Not estimable	Not estimable	0.81 0.18-3.70 MODERATE[2]	12 per 1000	10 per 1000	2 fewer per 1000 (from 10 fewer to 32 more)
Misoprostol 400 mcg	4.20 1.59-11.07 HIGH	3.32 1.55-7.11 MODERATE[3]	3.57 2.10-6.09 HIGH	12 per 1000	43 per 1000	31 more per 1000 (from 13 to 61 more)
Misoprostol >400 mcg	4.13 2.79-6.12 HIGH	6.66 2.71-16.38 MODERATE[3]	4.50 2.92-6.94 MODERATE[5]	12 per 1000	54 per 1000	42 more per 1000 (from 23 to 71 more)
Misoprostol <400 mcg	3.00 0.32-28.13	3.53 1.11-11.27	3.43 1.21-9.73	12 per 1000	41 per 1000	29 more per 1000

	VERY LOW[2]	VERY LOW[4]	VERY LOW[6]			(from 3 to 105 more)
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	Not estimable	Not estimable	0.52 0.17-1.59 LOW[1]	12 per 1000	6 per 1000	6 fewer per 1000 (from 10 fewer to 7 more)
Sulprostone 500 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	Not estimable	Not estimable	1.10 0.49-2.46 MODERATE[2]	12 per 1000	13 per 1000	1 more per 1000 (from 6 fewer to 18 more)

Direct evidence:
1. Downgraded -2 due to very serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.

Indirect evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.
3. Downgraded -1 due to crucial limitations in study design.
4. Downgraded -3 due to crucial limitations in study design and very serious imprecision.

Network evidence:
1. Downgraded -2 due to low certainty indirect loop evidence.
2. Downgraded -1 due to moderate certainty indirect loop evidence.
3. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
4. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
5. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
6. Downgraded -3 due to very low certainty indirect evidence (no intransitivity, no incoherence, no imprecision).

Table 22: Hypertension-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: Hypertension

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	Not estimable	Not estimable	3.54 0.73-17.23 LOW[1]	72 per 1000	255 per 1000	183 more per 1000 (from 19 fewer to 1000 more)
Oxytocin <10 IU	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin 100 mcg	0.98 0.78-1.23 HIGH	1.69 0.56-5.12 MODERATE[1]	1.00 0.80-1.25 MODERATE[2]	72 per 1000	72 per 1000	No difference per 1000 (from 14 fewer to 18 more)
Carbetocin >100 mcg	Not estimable	Not estimable	3.20 0.56-18.38 LOW[1]	72 per 1000	230 per 1000	158 more per 1000 (from 32 fewer to 1.000 more)
Carbetocin <100 mcg	Not estimable	Not estimable	1.30 0.39-4.31 LOW[1]	72 per 1000	94 per 1000	22 more per 1000 (from 44 fewer to 238 more)
Carboprost 125 mcg	Not estimable	Not estimable	0.40 0.03-5.36 VERY LOW[3]	72 per 1000	29 per 1000	43 fewer per 1000 (from 70 fewer to 314 more)
Carboprost >125 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Ergometrine 200 mcg	Not estimable	Not estimable	4.88 0.39-60.65 VERY LOW[3]	72 per 1000	351 per 1000	279 more per 1000 (from 44 fewer to 1.000 more)
Ergometrine >200 mcg	13.39 2.01-89.44 LOW[1]	1.77 0.00-infinity VERY LOW[2]	4.99 3.50-7.13 VERY LOW[4]	72 per 1000	359 per 1000	287 more per 1000 (from 180 to 441

						more)
Misoprostol 400 mcg	Not estimable	Not estimable	1.06 0.34-3.30 LOW[1]	72 per 1000	76 per 1000	4 more per 1000 (from 48 fewer to 166 more)
Misoprostol >400 mcg	3.64 0.60-22.27 LOW[2]	0.97 0.56-1.67 MODERATE[1]	1.08 0.64-1.83 LOW[5]	72 per 1000	78 per 1000	6 more per 1000 (from 26 fewer to 60 more)
Misoprostol <400 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	1.75 1.44-2.13 HIGH	3.65 0.63-21.23 MODERATE[1]	1.77 1.46-2.16 MODERATE[2]	72 per 1000	127 per 1000	55 more per 1000 (from 33 to 84 more)
Sulprostone 500 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	Not estimable	Not estimable	0.69 0.26-1.88 LOW[1]	72 per 1000	50 per 1000	22 fewer per 1000 (from 53 fewer to 63 more)

Direct evidence:
1. Downgraded -2 due to crucial limitations in study design and severe unexplained statistical heterogeneity.
2. Downgraded -2 due to crucial limitations in study design and serious imprecision.

Indirect evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.

Network evidence:
1. Downgraded -2 due to low certainty indirect loop evidence.
2. Downgraded -1 due to high certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
3. Downgraded -3 due to very low certainty indirect loop evidence.
4. Downgraded -3 due to low certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
5. Downgraded -2 due to moderate certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).

Table 23: Vomiting-Summary of Findings Table-Doses NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Syntometrine® and Syntometrine®-like 500 mcg plus 5 IU, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: Vomiting

Uterotonic Agent	Direct Evidence	Indirect Evidence	Network Evidence	Anticipated absolute effects for NMA estimate		
	RR (95% CI) Certainty	RR (95% CI) Certainty	RR (95% CI) Certainty	Risk with Oxytocin IM	Risk with Intervention	Risk Difference
Oxytocin >10 IU	Not estimable	Not estimable	1.29 0.81-2.07 LOW[1]	26 per 1000	34 per 1000	8 more per 1000 (from 5 fewer to 28 more)
Oxytocin <10 IU	Not estimable	Not estimable	1.00 0.52-1.92 LOW[1]	26 per 1000	26 per 1000	No difference per 1000 (from 13 fewer to 24 more)
Carbetocin 100 mcg	0.70 0.36-1.37 MODERATE[1]	1.13 0.65-1.98 MODERATE[1]	0.92 0.63-1.33 MODERATE[2]	26 per 1000	24 per 1000	2 fewer per 1000 (from 10 fewer to 9 more)
Carbetocin >100 mcg	Not estimable	Not estimable	0.62 0.11-3.63 LOW[1]	26 per 1000	16 per 1000	10 fewer per 1000 (from 23 fewer to 68 more)
Carbetocin <100 mcg	Not estimable	Not estimable	0.49 0.14-1.75 LOW[1]	26 per 1000	13 per 1000	13 fewer per 1000 (from 22 fewer to 20 more)
Carboprost 125 mcg	5.00 0.24-102.85 VERY LOW[2]	0.46 0.10-2.15 VERY LOW[2]	0.74 0.19-2.92 VERY LOW[3]	26 per 1000	19 per 1000	7 fewer per 1000 (from 21 fewer to 50 more)
Carboprost >125 mcg	Not estimable	Not estimable	4.49 1.70-11.86 LOW[1]	26 per 1000	117 per 1000	91 more per 1000 (from 18 to 282 more)
Ergometrine 200 mcg	1.37 0.23-8.17 LOW[3]	1.35 0.78-2.31 LOW[3]	1.34 0.80-2.25 LOW[4]	26 per 1000	35 per 1000	9 more per 1000 (from 5 fewer to 33 more)
Ergometrine >200 mcg	10.13 5.84-17.57 MODERATE[4]	22.84 3.91-133.5 MODERATE[4]	11.12 5.24-23.59 LOW[5]	26 per 1000	289 per 1000	263 more per 1000 (from 110 to 587 more)

Misoprostol 400 mcg	1.46 0.82-2.58 MODERATE[1]	1.63 0.96-2.75 LOW[3]	1.56 1.05-2.32 MODERATE[2]	26 per 1000	41 per 1000	15 more per 1000 (from 1 to 34 more)
Misoprostol >400 mcg	1.88 1.41-2.51 HIGH	1.62 0.97-2.71 VERY LOW[2]	1.63 1.16-2.29 HIGH	26 per 1000	42 per 1000	16 more per 1000 (from 4 to 34 more)
Misoprostol <400 mcg	Not estimable	Not estimable	0.58 0.02-13.39 VERY LOW[6]	26 per 1000	15 per 1000	11 fewer per 1000 (from 26 fewer to 322 more)
Syntometrine and Syntometrine-like 500 mcg plus 5 IU	3.99 2.66-5.99 MODERATE[5]	2.60 1.63-4.15 HIGH	3.29 2.38-4.56 HIGH	26 per 1000	86 per 1000	60 more per 1000 (from 36 to 93 more)
Sulprostone 500 mcg	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Placebo or control	Not estimable	Not estimable	1.18 0.68-2.05 MODERATE[7]	26 per 1000	31 per 1000	5 more per 1000 (from 8 fewer to 27 more)

Direct evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.
4. Downgraded -1 due to crucial limitations in study design.
5. Downgraded -1 due severe unexplained statistical heterogeneity.

Indirect evidence:
1. Downgraded -1 due to serious imprecision.
2. Downgraded -3 due to crucial limitations in study design and very serious imprecision.
3. Downgraded -2 due to crucial limitations in study design and serious imprecision.
4. Downgraded -1 due to crucial limitations in study design.

Network evidence:
1. Downgraded -2 due to low certainty indirect loop evidence.
2. Downgraded -1 due to moderate certainty direct evidence (no intransitivity, no incoherence, imprecision present).
3. Downgraded -3 due to very low certainty indirect evidence and incoherence between the direct and indirect estimate (no intransitivity, imprecision present).
4. Downgraded -2 due to low certainty indirect evidence (no intransitivity, no incoherence, imprecision present).
5. Downgraded -2 due to moderate certainty direct evidence and incoherence between the direct and indirect estimate (no intransitivity, no imprecision).
6. Downgraded -3 due to very low certainty indirect loop evidence.
7. Downgraded -1 due to moderate certainty indirect loop evidence.

GRADE outcomes

PPH ≥500 mL

Relative and absolute effects: The network diagram and the forest plot for PPH ≥500 mL are presented in *Figure 32* and *Figure 33* respectively. Local and global inconsistency were generally low.

When compared with oxytocin 10 IU, moderate certainty evidence suggests that oxytocin >10 IU (RR 0.96, 95% CI 0.70 -1.32), oxytocin <10 IU (RR 1.12, 95% CI 0.83-1.51), carbetocin 100 mcg (RR 0.78, 95% CI 0.60-1.02), and ergometrine plus oxytocin combination (RR 0.79, 95% CI 0.62-1.01) probably make little or no difference to the risk for PPH ≥500 mL. Moderate certainty evidence also suggests that placebo administration probably increases the risk for this outcome (RR 1.83, 95% CI 1.42-2.37), compared with the administration of oxytocin 10 IU. In absolute terms, for every 1,000 women given oxytocin 10 IU for PPH prevention, 121 will experience PPH ≥500 mL, compared with 94 given carbetocin 100 mcg, 96 given ergometrine plus oxytocin combination, 116 given oxytocin >10 IU, 136 given oxytocin <10 IU, and 221 given placebo or no treatment (see *Table 17: PPH ≥500 mL-Summary of Findings Table-Doses NMA*).

Based on low certainty evidence carboprost >125 mcg (RR 1.04, 95% CI 0.50-2.16), ergometrine 200 mcg (RR 1.15, 95% CI 0.77-1.71), ergometrine >200 mcg (RR 1.15, 95% CI 0.73-1.82), misoprostol 400 mcg (RR 1.00, 95% CI 0.78-1.29), misoprostol >400 mcg (RR 1.17, 95% CI 0.94-1.46), misoprostol <400 mcg (0.86, 95% CI 0.39-1.88), and sulprostone 500 mcg (RR 1.01, 95% CI 0.35-2.93) may make little or no difference to the risk for PPH ≥500 mL, when compared with oxytocin 10 IU.

The evidence for carboprost 125 mcg (RR 1.34, 95% CI 0.69-2.58), compared with oxytocin 10 IU, was uncertain.

Compared with oxytocin 10 IU, no data were available for carbetocin >100 mcg and carbetocin <100 mcg, and thus their relative and absolute effects for this outcome were not estimable.

Cumulative probabilities: Among the active agents, carbetocin 100 mcg was ranked first with 85.9% probability of being the best uterotonic drug for preventing PPH ≥500 mL, oxytocin 10 IU was ranked fifth with probability 56.6%, and carboprost 125 mcg was ranked last with probability 28.7% *(Figure 34).*

Figure 32: PPH ≥500 mL-Network diagram-Doses NMA

Network diagram for PPH ≥500 mL. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

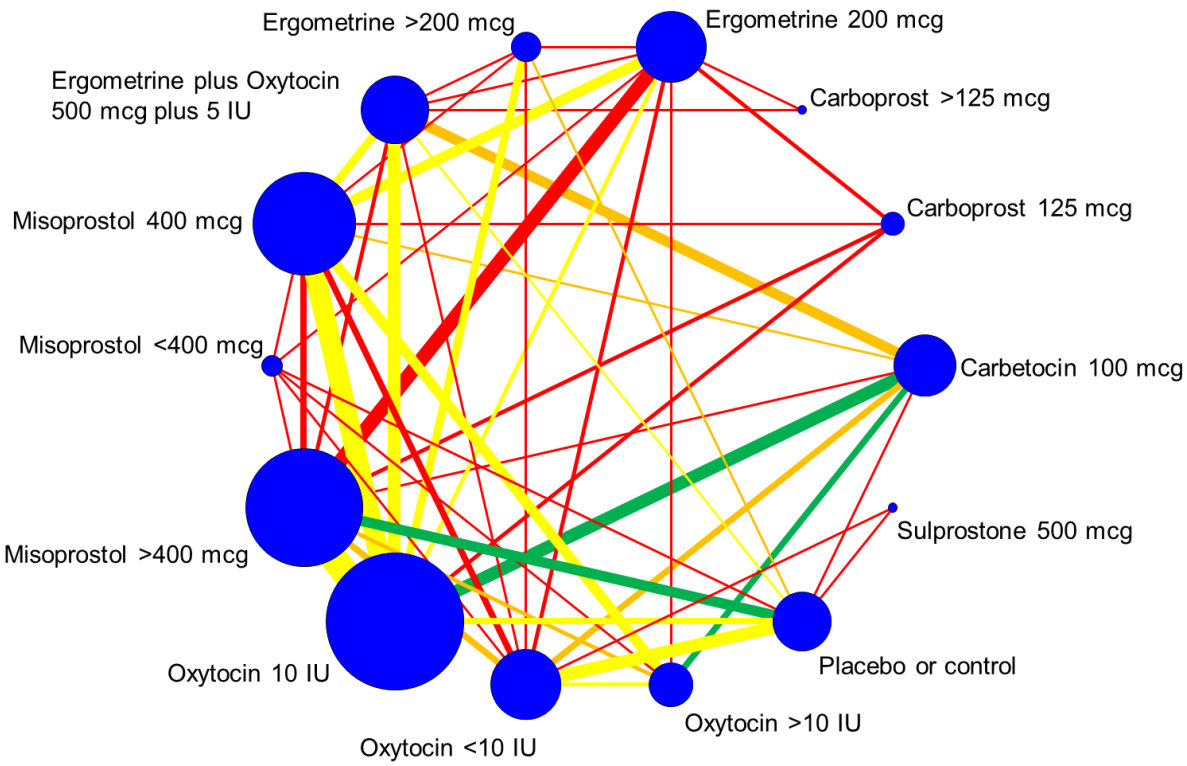


Figure 33: PPH ≥500 mL-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL.

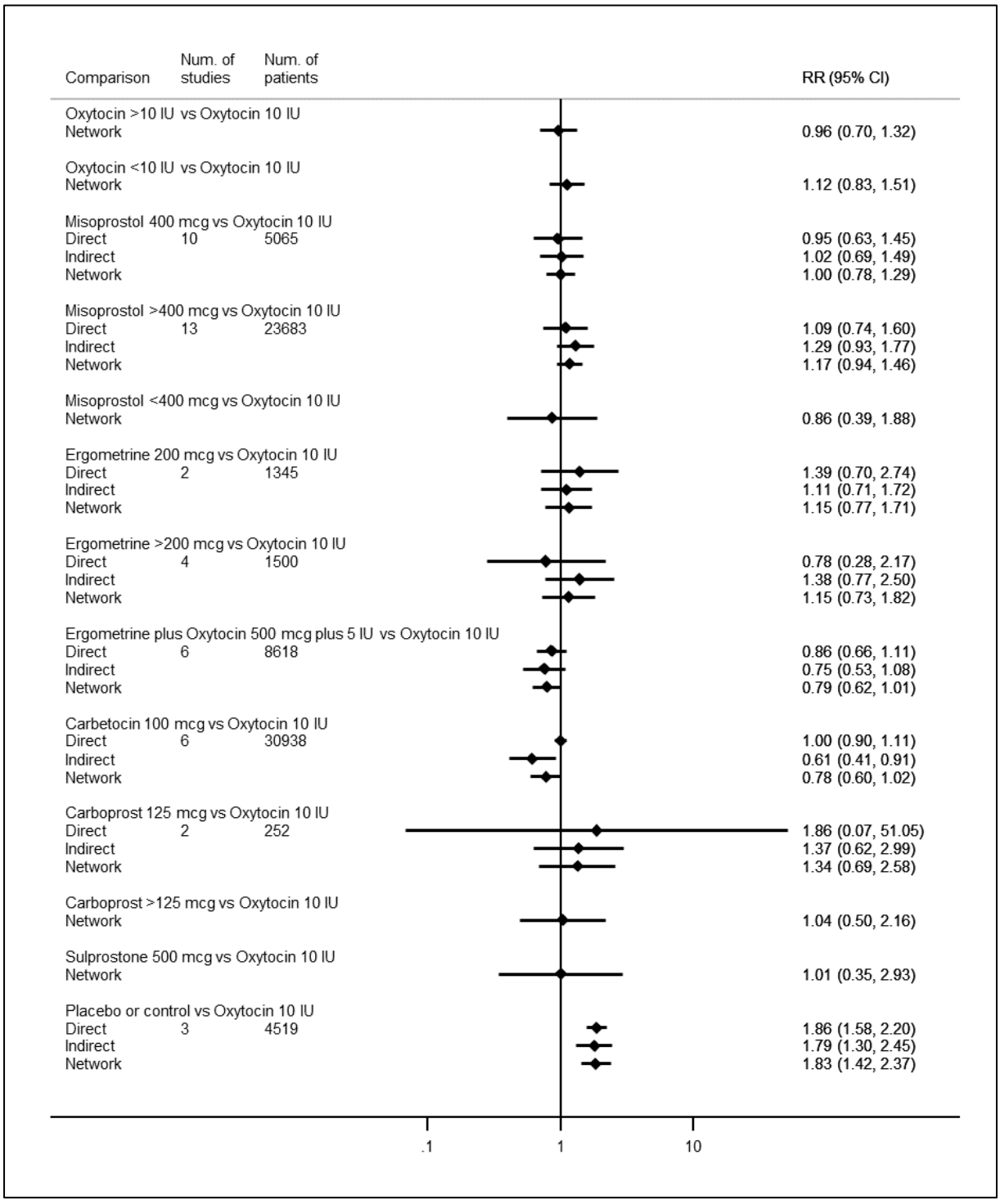
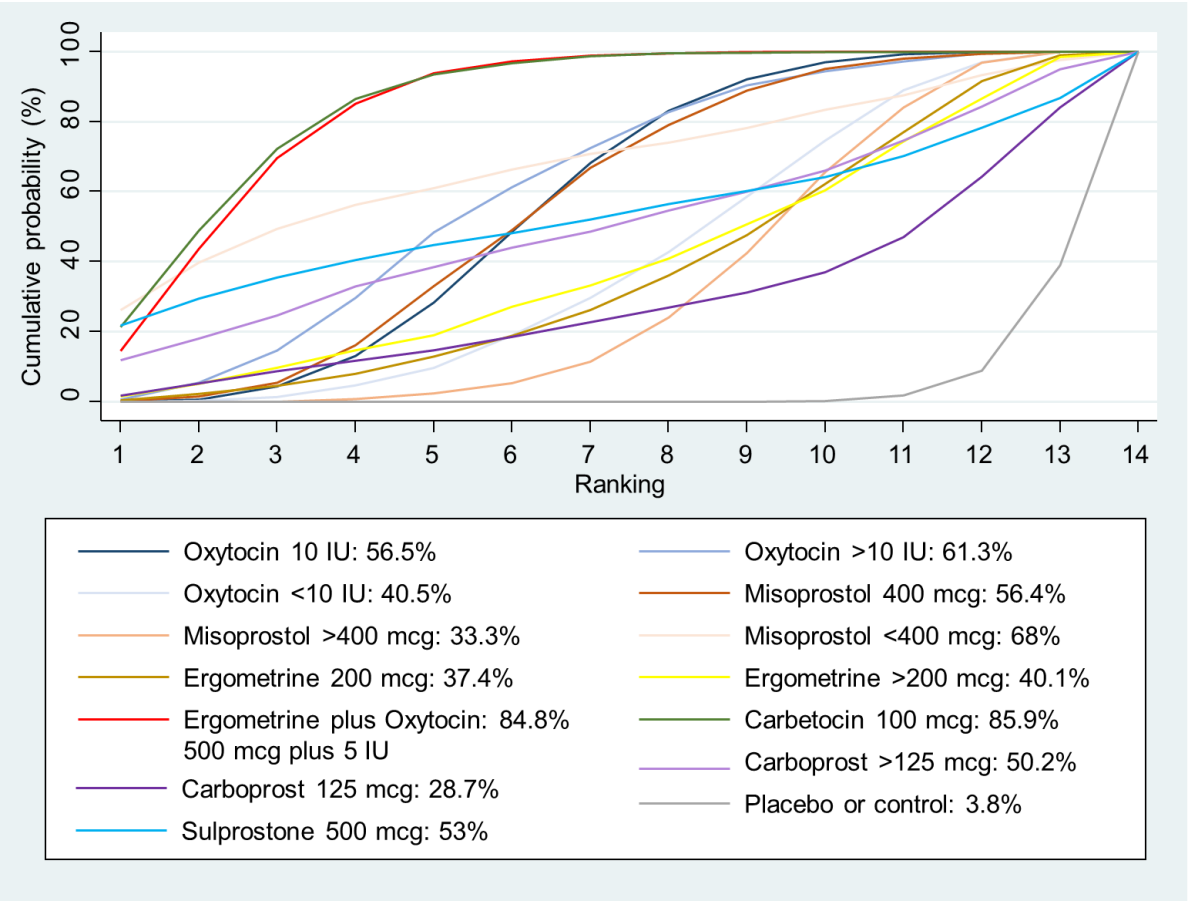


Figure 34: PPH ≥500 mL-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



PPH ≥1000 mL

Relative and absolute effects: The network diagram and the forest plot for PPH ≥1000 mL are presented in *Figure 35* and *Figure 36* respectively. Local and global inconsistency were generally low.

When compared with oxytocin 10 IU, high certainty evidence suggests that misoprostol >400 mcg increases the risk for PPH ≥1000 mL (RR 1.33, 95% CI 1.11-1.60). In absolute terms, for every 1,000 women given oxytocin 10 IU, 30 will experience major PPH, compared with 34 given misoprostol >400 mcg (see *Table 18: PPH ≥1000 mL-Summary of Findings Table-Doses NMA*Table 18: PPH ≥1000 mL-Summary of Findings Table).

According to moderate certainty evidence, when compared with oxytocin 10 IU, carbetocin 100 mcg probably makes little or no difference to this outcome (RR 1.04, 95% CI 0.88-1.24). These results suggest that about 30 per 1,000 women receiving oxytocin 10 IU will experience PPH ≥1000 mL, compared with 31 given carbetocin 100 mcg (see *Table 18: PPH ≥1000 mL-Summary of Findings Table-Doses NMA*Table 18: PPH ≥1000 mL-Summary of Findings Table).

Based on low certainty evidence, oxytocin >10 IU (RR 1.08, 95% CI 0.85-1.38), ergometrine 200 mcg (RR 1.41, 95% CI 0.67-2.97), and misoprostol 400 mcg (RR 1.14, 95% CI 0.87-1.49) may make little or no difference to the risk for PPH ≥1000 mL when compared with oxytocin 10 IU. Low certainty evidence also suggests that placebo may increase the risk for major PPH (RR 1.80, 95% CI 1.53-2.12), compared with oxytocin 10 IU.

For the same outcome, compared with oxytocin 10 IU, the evidence for oxytocin <10 IU (RR 1.17, 95% CI 0.91-1.51), carbetocin <100 mcg (RR 0.95, 95% CI 0.61-1.47), carboprost 125

mcg (RR 6.17, 95% CI 0.84-45.30), carboprost >125 mcg (1.45, 95% CI 0.42-5.02), ergometrine >200 mcg (RR 0.47, 95% CI 0.14-1.60), misoprostol <400 mcg (RR 1.29, 95% CI 0.47-3.54), ergometrine plus oxytocin combination (RR 0.82, 95% CI 0.65-1.04), and sulprostone 500 mcg (RR 0.69, 95% CI 0.08-5.59) was uncertain.

No data were available for the comparison of carbetocin >100 mcg against oxytocin 10 IU, and thus the respective relative and absolute effects remained unclear.

Cumulative probabilities: Among the active agents, ergometrine >200 mcg was ranked first with 88.8% probability of being the best uterotonic drug for preventing PPH ≥1000 mL, oxytocin 10 IU was ranked fifth with probability 66%, and carboprost 125 mcg was ranked last with probability 5% *(Figure 37).*

Figure 35: PPH ≥1000 mL-Network diagram-Doses NMA

Network diagram for PPH ≥1000 mL. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

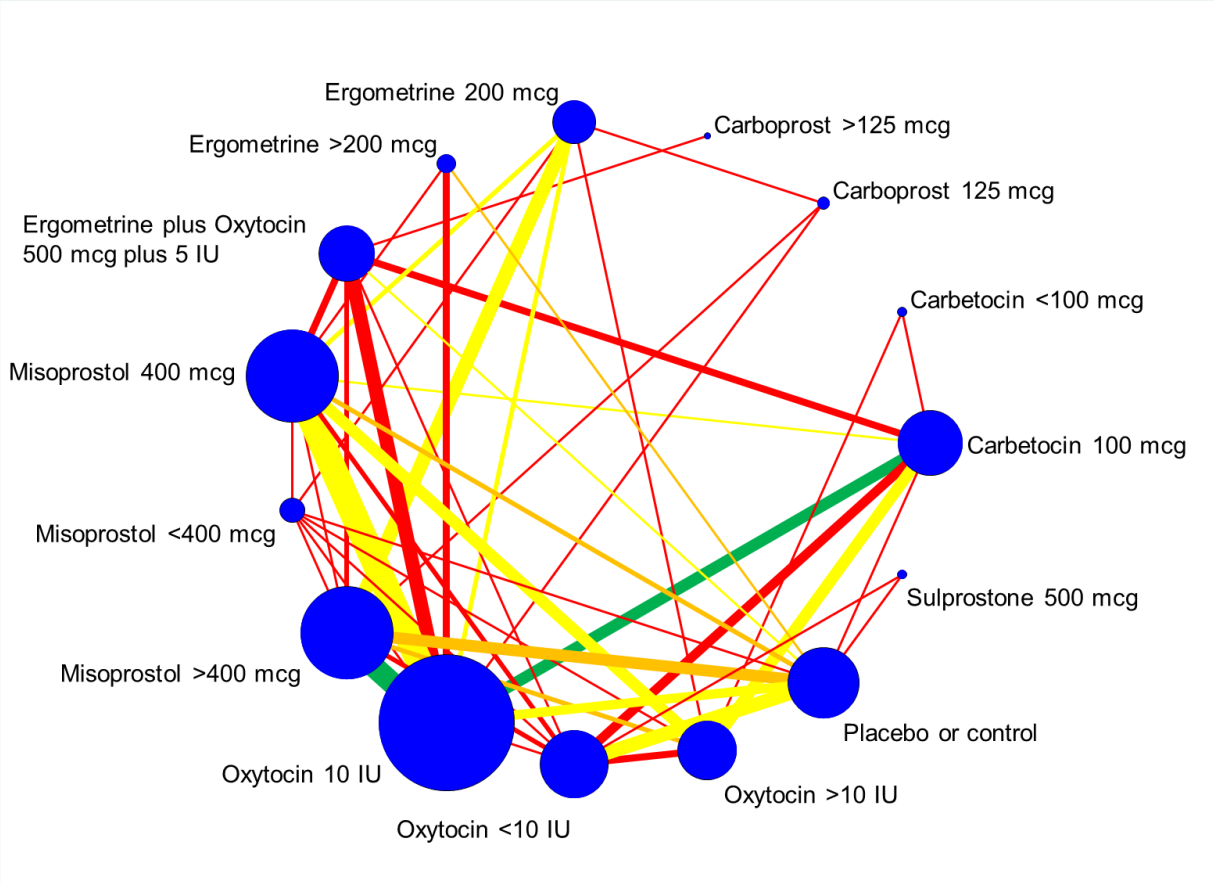


Figure 36: PPH ≥1000 mL-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL.

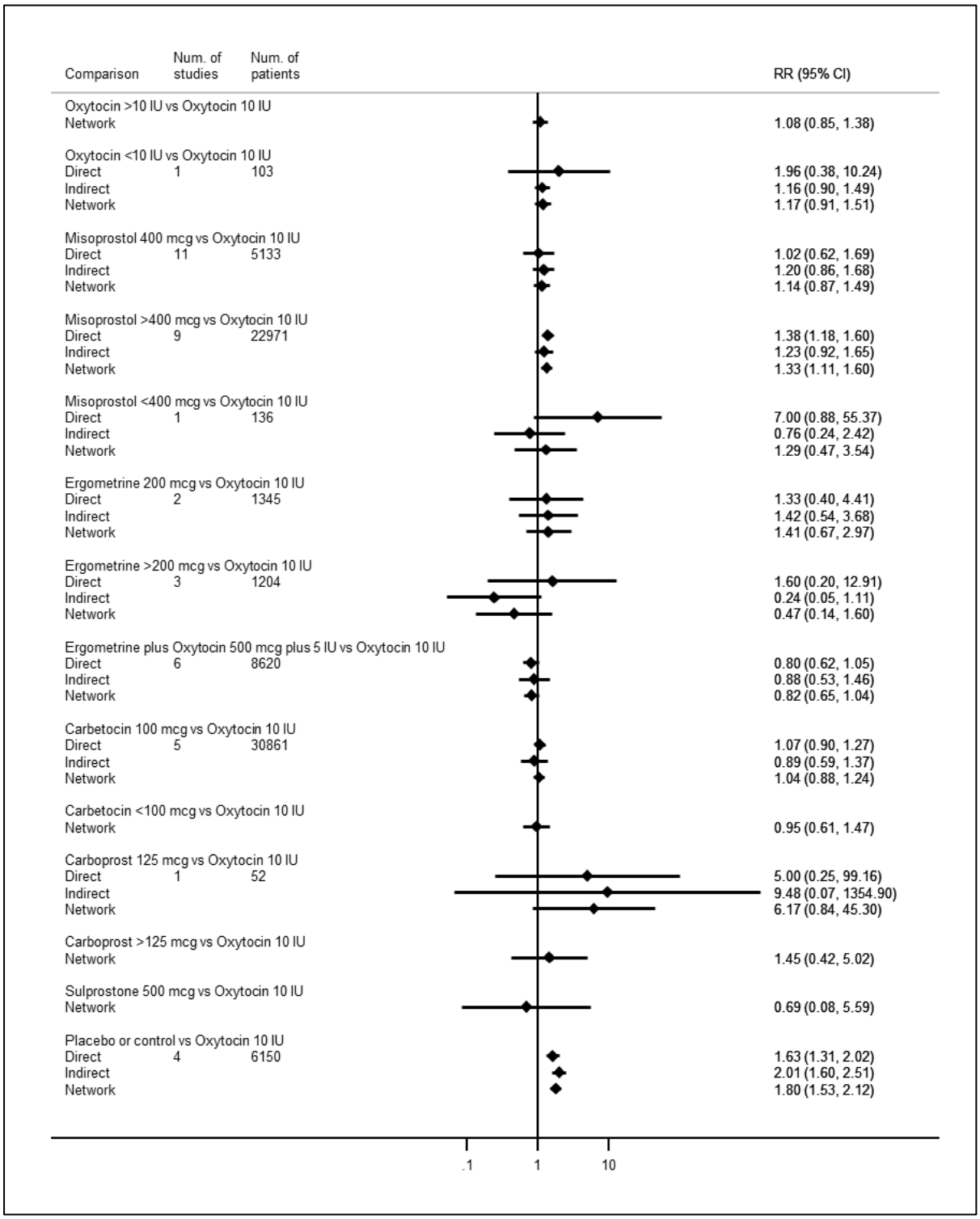
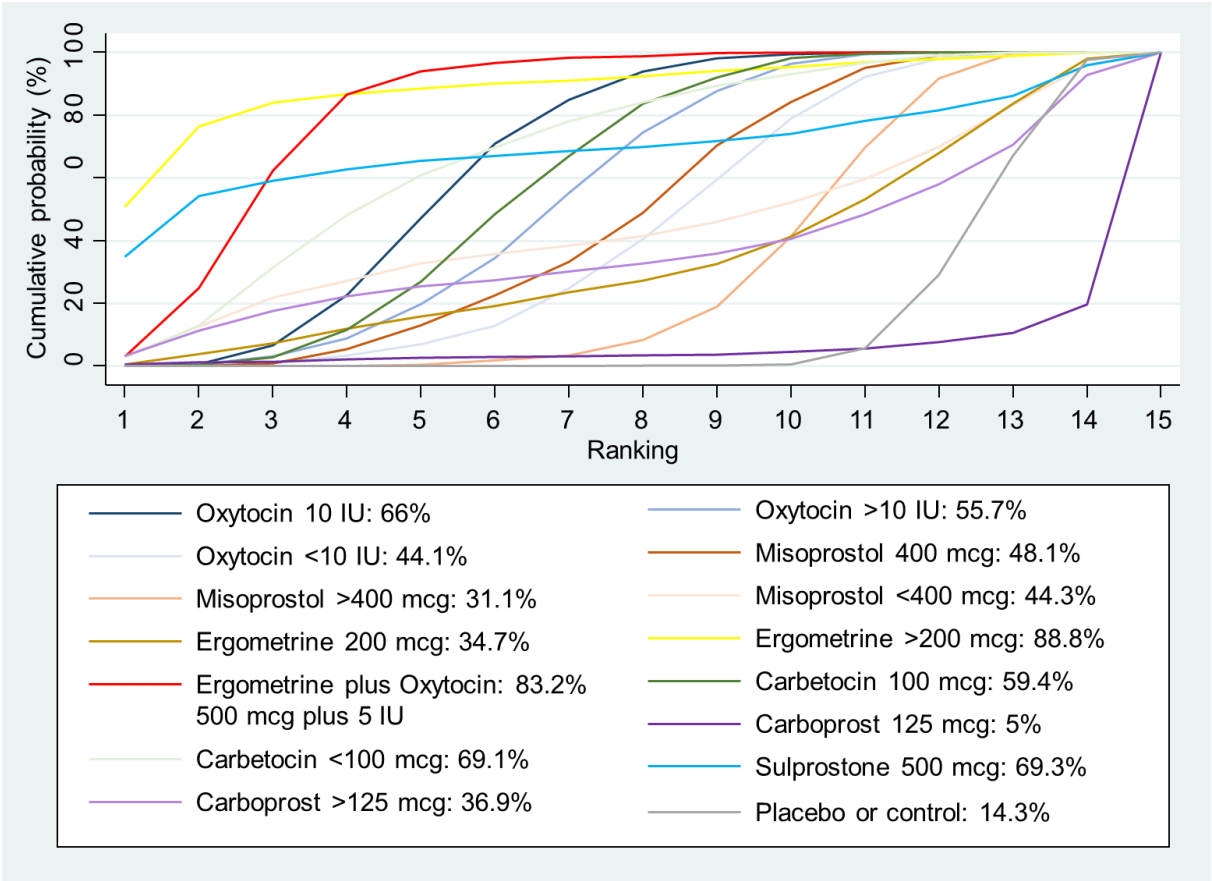


Figure 37: PPH ≥1000 mL-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Additional uterotonics

Relative and absolute effects: The network diagram and the forest plot for additional uterotonics are presented in *Figure 38* and *Figure 39* respectively. Local and global inconsistency were generally low.

When compared with oxytocin 10 IU, high certainty evidence suggests that placebo increases the risk for additional uterotonic administration (RR 2.57, 95% CI 1.76-3.76). In absolute terms, these results suggest that for every 1,000 women receiving oxytocin 10 IU, 128 will require additional uterotonics, compared with 329 given placebo (see *Table 19: Additional uterotonics-Summary of Findings Table-Doses NMA*).

Based on low certainty evidence, oxytocin <10 IU (RR 1.14, 95% CI 0.78-1.67), carbetocin >100 mcg (RR 0.91, 95% CI 0.17-4.91), carbetocin <100 mcg (RR 0.95, 95% CI 0.43-2.13), ergometrine 200 mcg (RR 1.09, 95% CI 0.65-1.82), ergometrine >200 mcg (RR 0.90, 95% CI 0.49-1.67), misoprostol 400 mcg (RR 1.09, 95% CI 0.81-1.47), and misoprostol >400 mcg (RR 1.11, 95% CI 0.83-1.49) may make little or no difference to the outcome of additional uterotonic use, when compared with oxytocin 10 IU.

For the same outcome, compared with oxytocin 10 IU, the evidence for oxytocin >10 IU (RR 1.25, 95% CI 0.86-1.80), carbetocin 100 mcg (RR 0.58, 95% CI 0.43-0.80), carboprost 125 mcg (RR 0.68, 95% CI 0.34-1.35), carboprost > 125 mcg (RR 0.36, 95% CI 0.03-4.61), misoprostol <400 mcg (RR 1.46, 95% CI 0.34-6.19), ergometrine plus oxytocin combination (RR 0.75, 95% CI 0.55-1.04), and sulprostone 500 mcg (RR 0.67, 95% CI 0.03-15.32) was uncertain.

Cumulative probabilities: Among the active agents, carbetocin 100 mcg was ranked first with 85.6% probability of being the best uterotonic drug for preventing the use of additional uterotonics, oxytocin 10 IU was ranked ninth with probability 49.7%, and oxytocin >10 IU was ranked last with probability 27.7% *(Figure 40).*

Figure 38: Additional uterotonics-Network diagram-Doses NMA

Network diagram for additional uterotonics. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

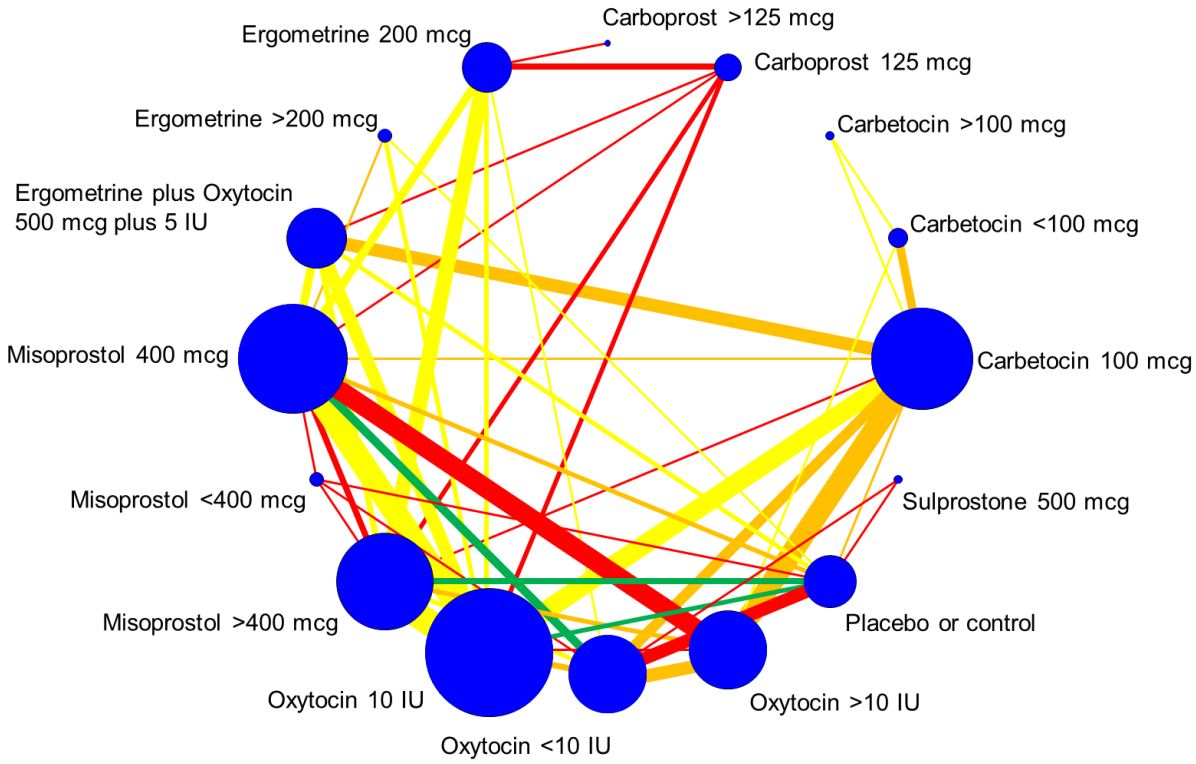


Figure 39: Additional uterotonics-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses additional uterotonics.

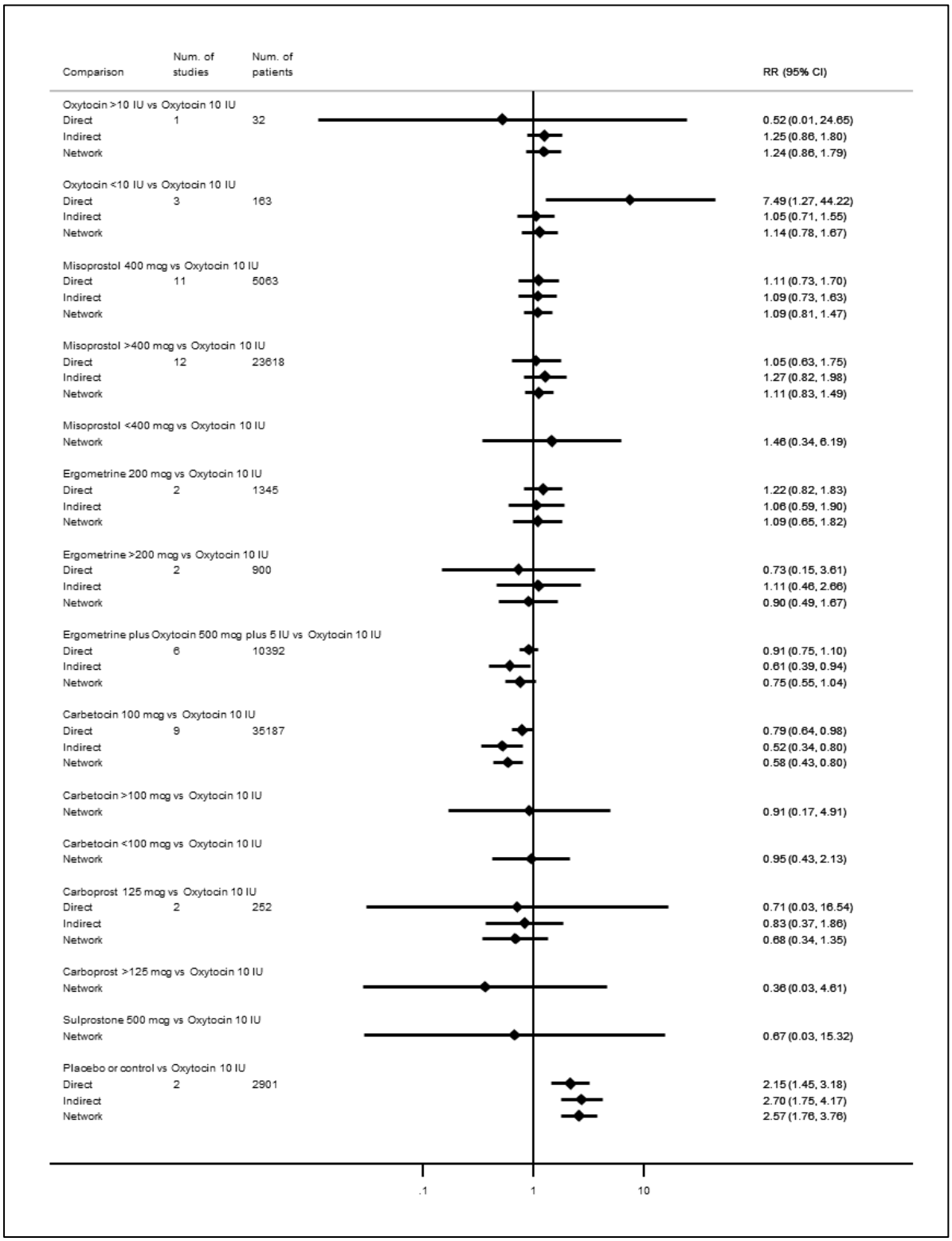
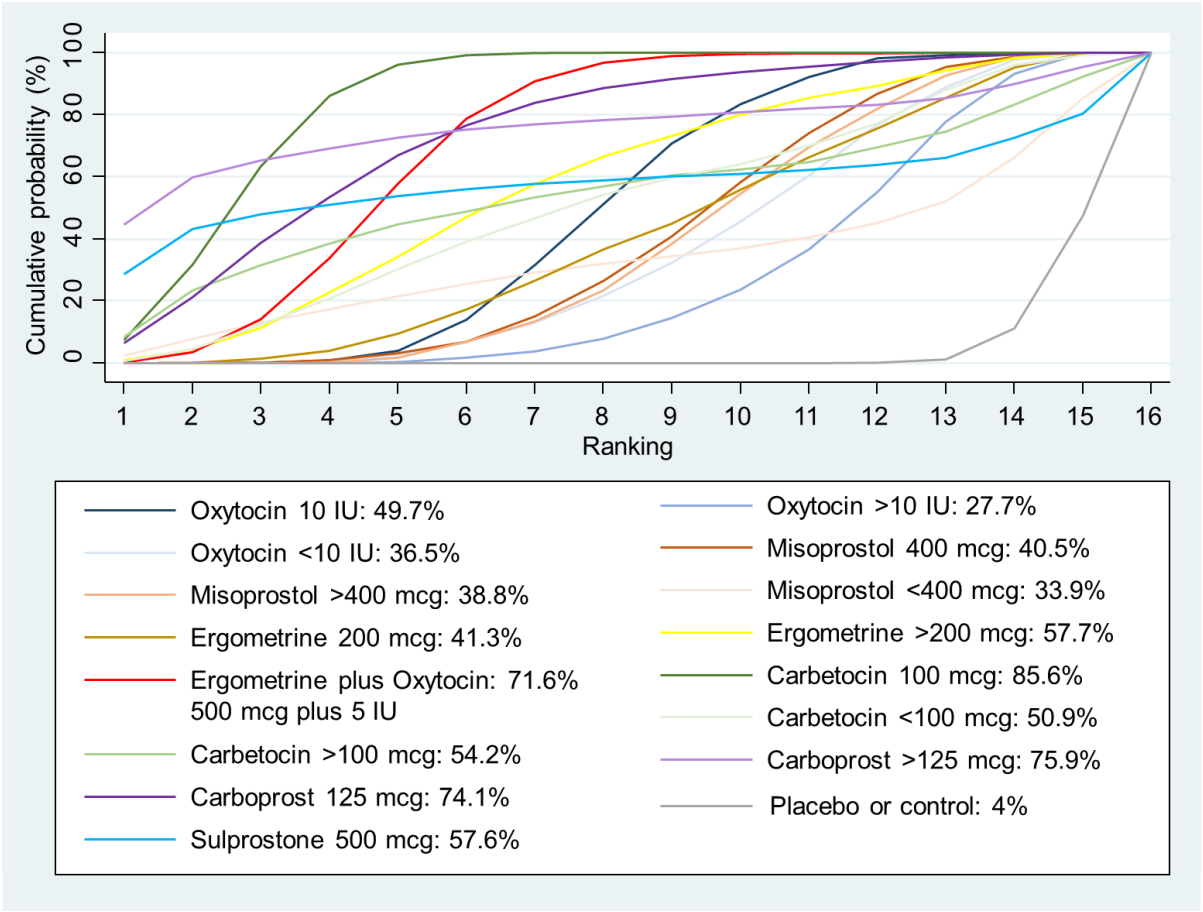


Figure 40: Additional uterotonics-Rankogram-Doses NMA

Cumulative rankogram for additional uterotonics. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Blood transfusion

Relative and absolute effects: The network diagram and the forest plot for blood transfusion are presented in *Figure 41* and *Figure 42* respectively. Local and global inconsistency were generally low.

When compared with oxytocin 10 IU, moderate certainty evidence suggests that carbetocin 100 mcg (RR 0.98, 95% CI 0.74-1.30), ergometrine >200 mcg (RR 0.24, 95% CI 0.05-1.11), misoprostol 400 mcg (RR 0.99, 95% CI 0.63-1.56), and misoprostol >400 mcg (RR 0.79, 95% CI 0.60-1.05) probably make little or no difference to the need for a blood transfusion. However, moderate certainty also suggests that placebo increases the risk for this outcome (RR 1.71, 95% CI 1.19-2.45), compared with oxytocin 10 IU. In absolute terms these results suggest that 17 per 1,000 women given oxytocin 10 IU will require a blood transfusion, compared with 4 given ergometrine >200 mcg, 13 given misoprostol >400 mcg, 17 given either carbetocin 100 mcg or misoprostol 400 mcg, and 29 given placebo (see *Table 20: Blood transfusion-Summary of Findings Table-Doses NMA*).

Based on low certainty evidence, oxytocin >10 IU (RR 1.71, 95% CI 1.19-2.45), oxytocin <10 IU (RR 1.28, 95% CI 0.78-2.08), ergometrine 200 mcg (RR 1.40, 95% CI 0.60-3.26), and ergometrine plus oxytocin combination (RR 0.94, 95% CI 0.74-1.21) may make little or no difference to the outcome of blood transfusion, when compared with oxytocin 10 IU.

For the same outcome, compared with oxytocin 10 IU, the evidence for carboprost 125 mcg (RR 1.04, 95% CI 0.27-4.07) and misoprostol >400 mcg (RR 0.90, 95% CI 0.09-8.77) was of very low certainty.

No data were available for carbetocin >100 mcg, carbetocin <100 mcg, carboprost >125 mcg, and sulprostone 500 mcg, and thus their relative and absolute effects, when compared with oxytocin 10 IU, remained unclear.

Cumulative probabilities: Among the active agents, ergometrine >200 mcg was ranked first with 95.4% probability of being the best uterotonic drug for preventing the use of additional uterotonics, oxytocin 10 IU was ranked seventh with probability 53.2%, and oxytocin >10 IU was ranked last with probability 16.2% *(Figure 43).*

Figure 41: Blood transfusion-Network diagram-Doses NMA

Network diagram for blood transfusion. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

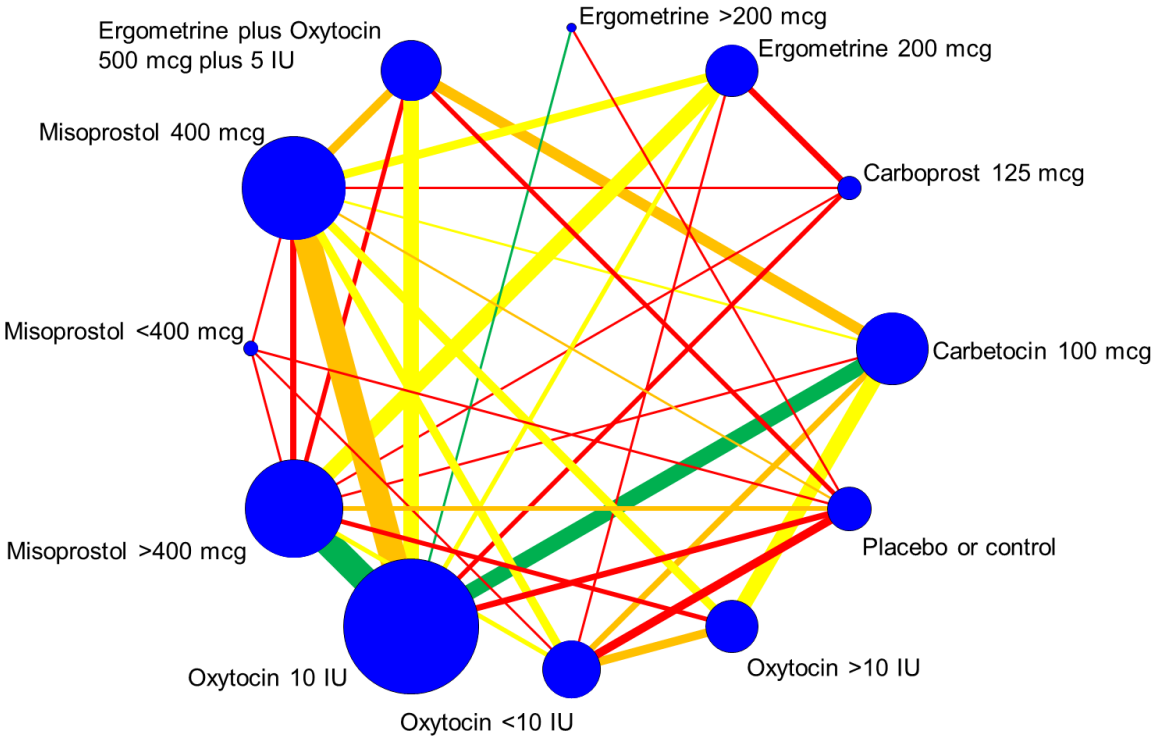


Figure 42: Blood transfusion-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses blood transfusion.

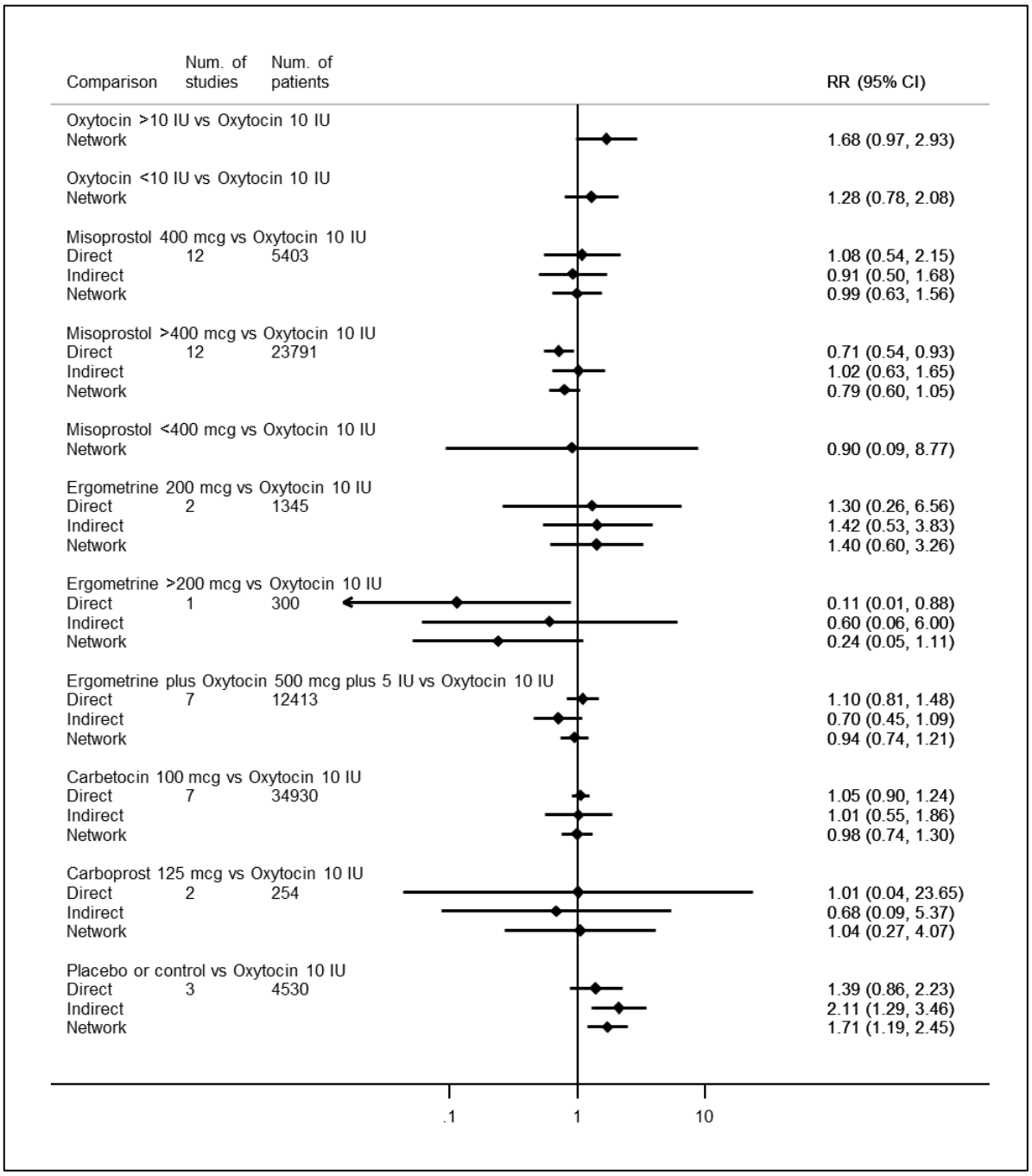
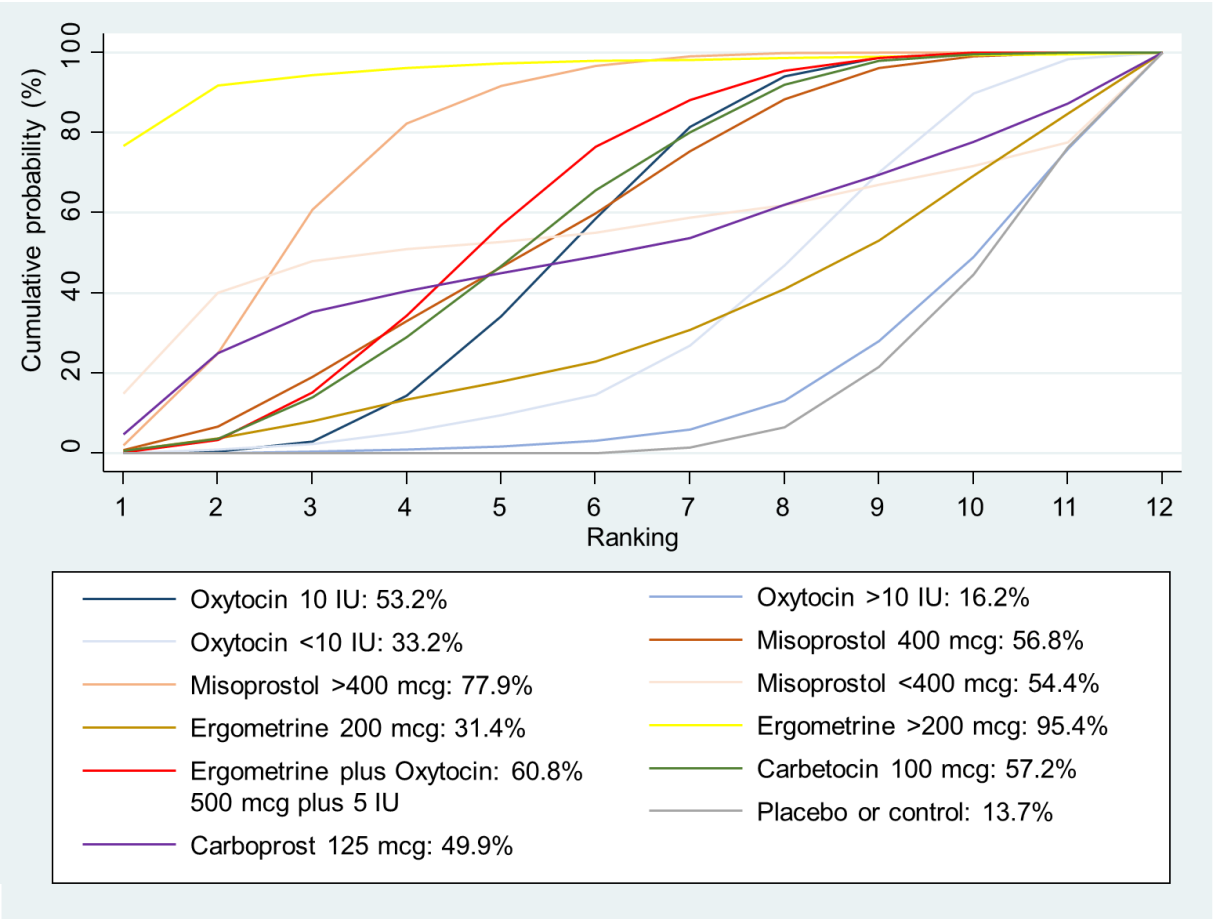


Figure 43: Blood transfusion-Rankogram-Doses NMA

Cumulative rankogram for blood transfusion. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Fever

Relative and absolute effects: The network diagram and the forest plot for fever are presented in *Figure 44* and *Figure 45* respectively. Local and global inconsistency were generally low.

High certainty evidence suggests that women receiving misoprostol 400 mcg are at higher risk for fever compared with women receiving oxytocin 10 IU (RR 3.57, 95% CI 2.10-6.09). In absolute terms, for every 1,000 receiving 10 IU of oxytocin, 12 will experience fever, compared with 43 receiving 400 mcg of misoprostol (see *Table 21: Fever-Summary of Findings Table-Doses NMA*).

According to moderate certainty evidence, when compared with oxytocin 10 IU, oxytocin <10 IU (RR 0.65, 95% CI 0.26-1.60), ergometrine >200 mcg (RR 0.81, 95% CI 0.18-3.70), and placebo (RR 1.10, 95% CI 0.49-2.46) probably make little or no difference to the risk for fever. Moderate certainty evidence also suggests that misoprostol >400 mcg carries a higher risk for fever compared with oxytocin 10 IU (RR 4.50, 95% CI 2.92-6.94). These results suggest that 12 per 1,000 women receiving oxytocin 10 IU will experience fever, compared with 8 given oxytocin <10 IU, 10 given ergometrine >200 mcg, 13 given placebo, and 54 given misoprostol >400 mcg (see *Table 21: Fever-Summary of Findings Table-Doses NMA*).

Based on low certainty evidence, oxytocin >10 IU may increase the risk for fever compared with oxytocin 10 IU (RR 2.49, 95% CI 1.11-5.61). Low certainty evidence also suggests that carbetocin 100 mcg (RR 1.78, 95% CI 0.60-5.31), carboprost 125 mcg (RR 0.83, 95% CI 0.23-2.99), ergometrine 200 mcg (RR 0.92, 95% CI 0.46-1.85), and ergometrine plus oxytocin combination (RR 0.52, 95% CI 0.17-1.59) may make little or no difference to this outcome.

The evidence for misoprostol <400 mcg (RR 3.43, 95% CI 1.21-9.73) compared with oxytocin 10 IU for the outcome of fever was of very low certainty.

No data were available for carbetocin >100 mcg, carbetocin <100 mcg, carboprost >125 mcg, and sulprostone 500 mcg, and thus their relative and absolute effects, when compared with oxytocin 10 IU, remained unclear.

Cumulative probabilities: Among the active agents, ergometrine plus oxytocin combination was ranked first with 86.4% probability of being the best uterotonic drug for not causing fever, oxytocin 10 IU was ranked sixth with probability 63.2%, and misoprostol >400 mcg was ranked last with probability 5% *(Figure 46).*

Figure 44: Fever-Network diagram-Doses NMA

Network diagram for fever. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

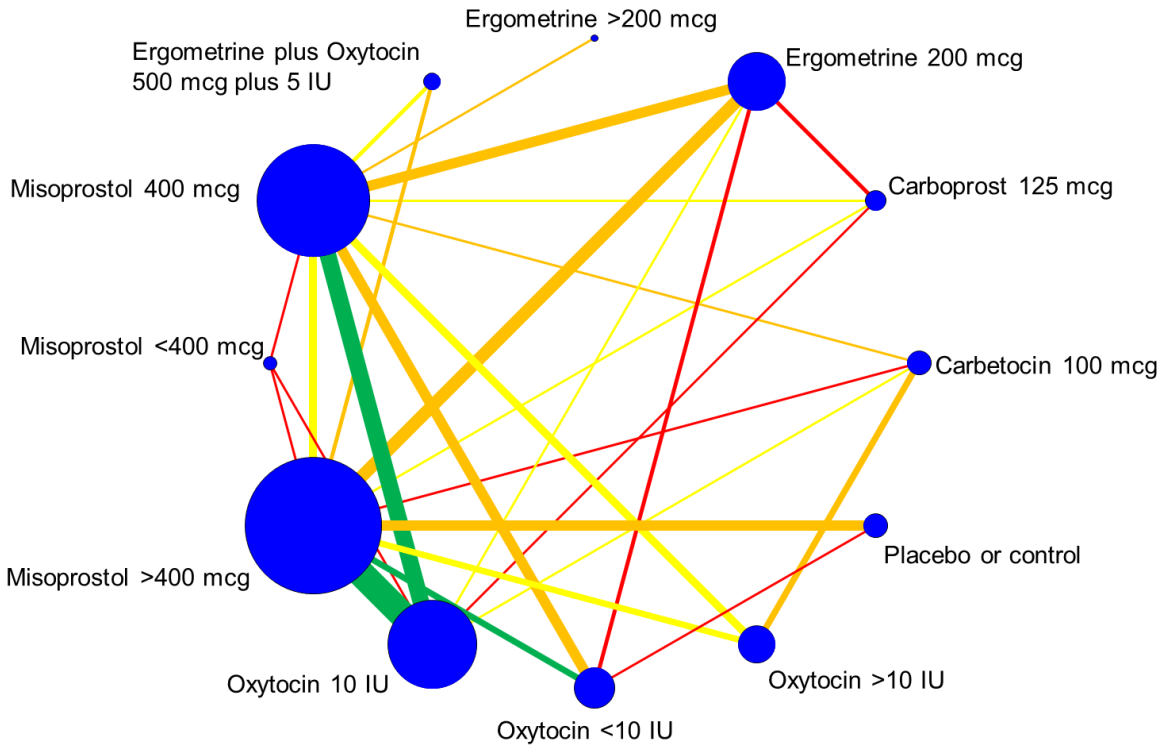


Figure 45: Fever-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network fever.

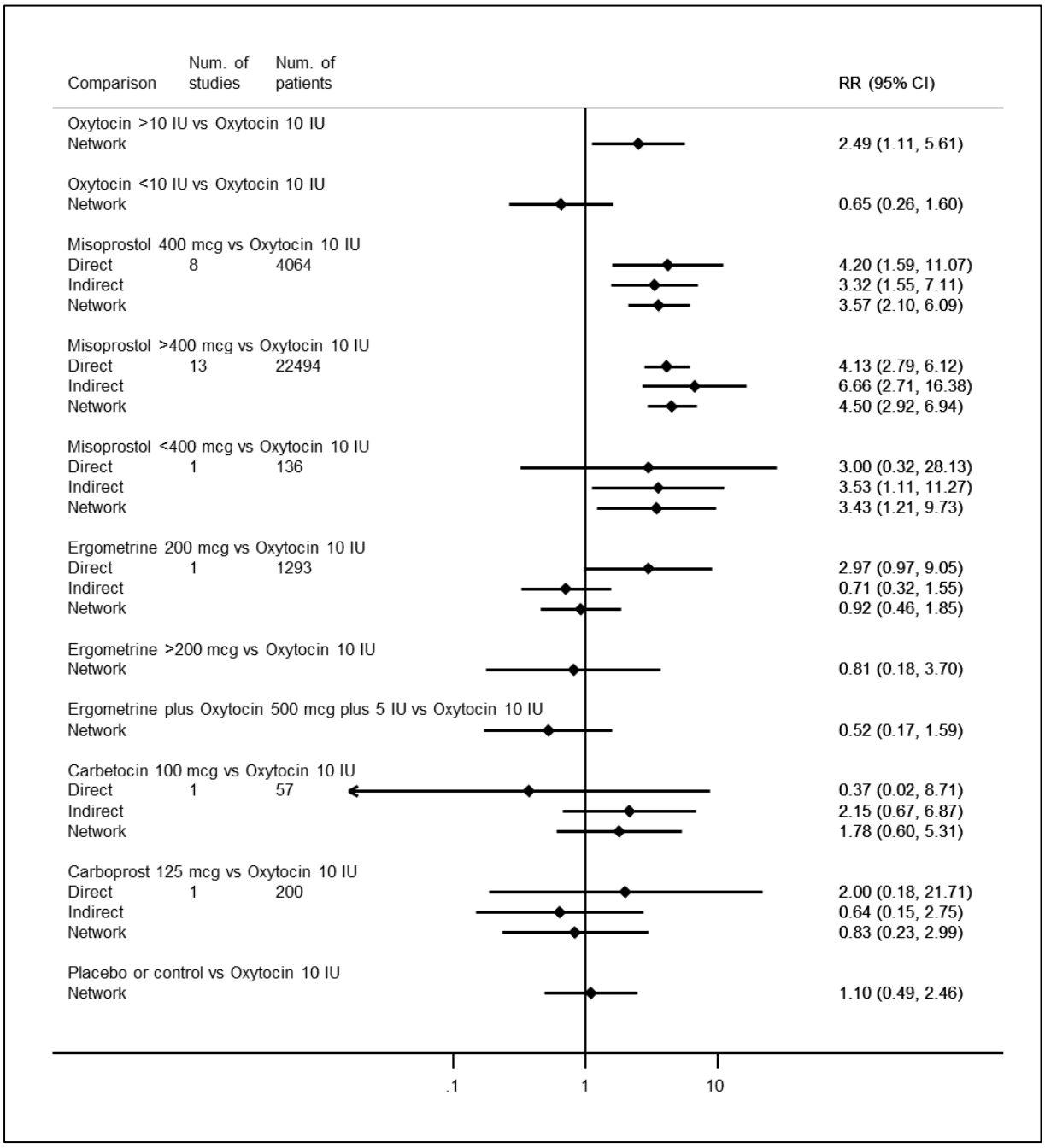
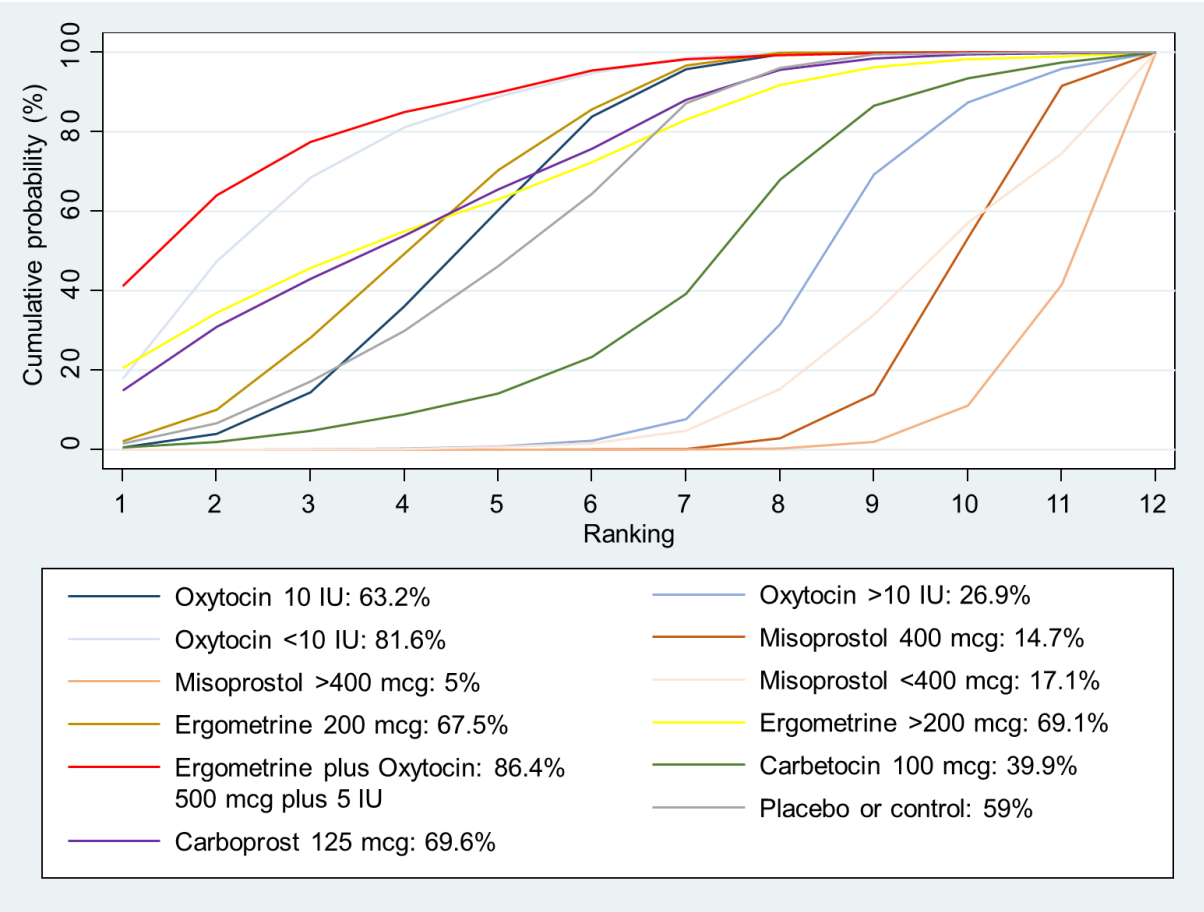


Figure 46: Fever-Rankogram-Doses NMA

Cumulative rankogram for fever. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Hypertension

Relative and absolute effects: The network diagram and the forest plot for hypertension are presented in *Figure 47* and *Figure 48* respectively. Local and global inconsistency were generally low.

According to moderate certainty evidence, when compared with oxytocin 10 IU, carbetocin 100 mcg (RR 1.00, 95% CI 0.80-1.25) probably makes little or no difference to the risk for hypertension, whereas ergometrine plus oxytocin combination (RR 1.77, 95% CI 1.46-2.16) probably increases this risk. These results suggest that 72 per 1,000 women receiving oxytocin 10 IU will have hypertension, compared with 72 given carbetocin 100 mcg and 127 given ergometrine plus oxytocin combination (see *Table 22: Hypertension-Summary of Findings Table-Doses NMA*).

Based on low certainty evidence, when compared with oxytocin 10 IU, oxytocin >10 IU (RR 3.54, 95% CI 0.73-17.23), carbetocin >100 mcg (RR 3.20, 95% CI 0.56-18.38), carbetocin <100 mcg (RR 1.30, 95% CI 0.39-4.31), misoprostol 400 mcg (RR 1.06, 95% CI 0.34-3.30), misoprostol >400 mcg (RR 1.08, 95% CI 0.64-1.83), and placebo (RR 0.69, 95% CI 0.26-1.88) may make little or no difference to the outcome of hypertension.

In the case of carboprost 125 mcg (RR 0.40, 95% CI 0.03-5.36), ergometrine 200 mcg (RR 4.88, 95% CI 0.39-60.65), and ergometrine >200 mcg (RR 4.99, 95% CI 3.50-7.13), compared with oxytocin 10 IU for the outcome of hypertension, the generated network evidence was of very low certainty.

No data were available for oxytocin <10 IU, carboprost >125 mcg, misoprostol <400 mcg, and sulprostone 500 mcg, and thus their relative and absolute effects, when compared with oxytocin 10 IU, remained unclear.

Cumulative probabilities: Among the active agents, carboprost 125 mcg was ranked first with 84% probability of being the best uterotonic drug for not causing hypertension, oxytocin 10 IU was ranked third with probability 67.9%, and ergometrine >200 mcg was ranked last with probability 10.8% *(Figure 49).*

Figure 47: Hypertension-Network diagram-Doses NMA

Network diagram for hypertension. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

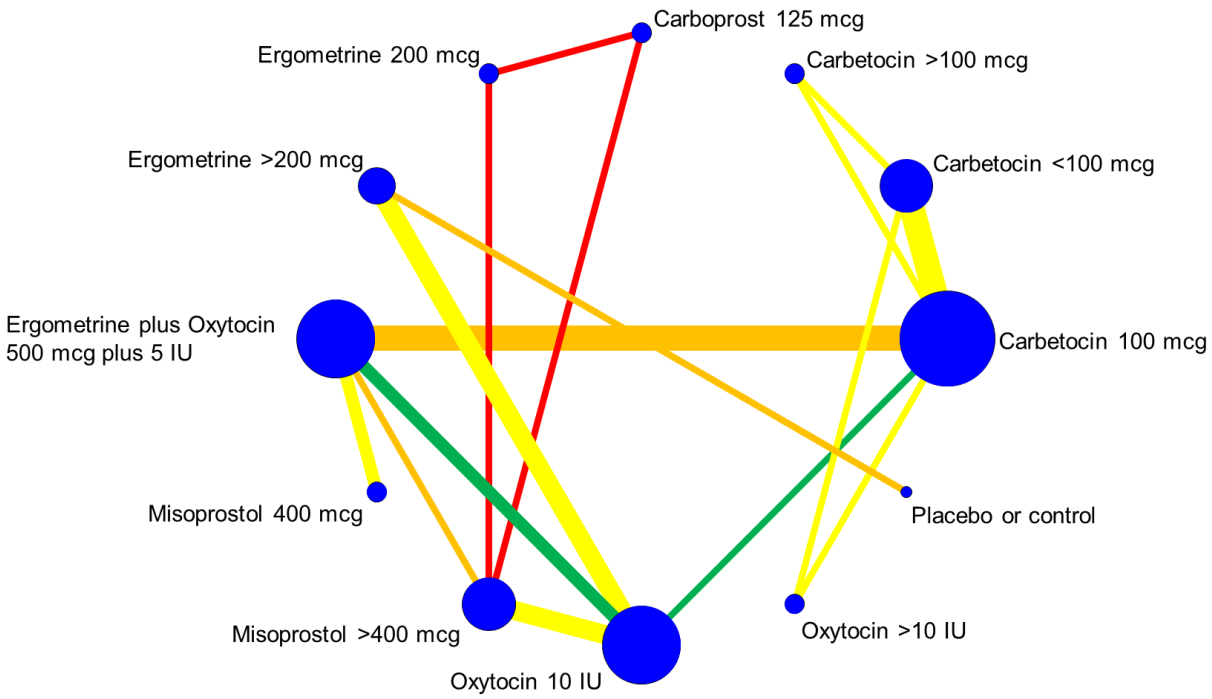


Figure 48: Hypertension-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network hypertension.

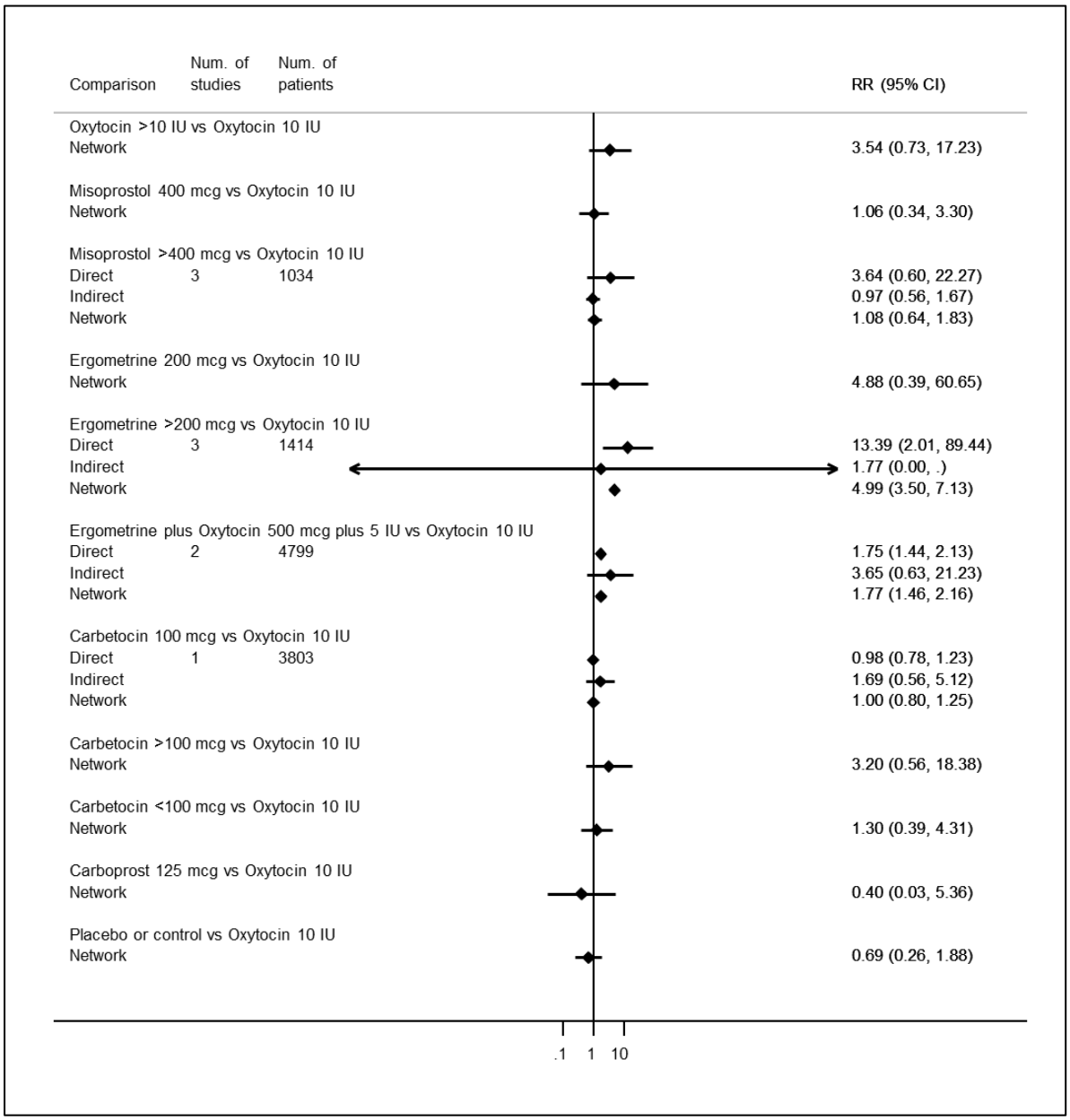
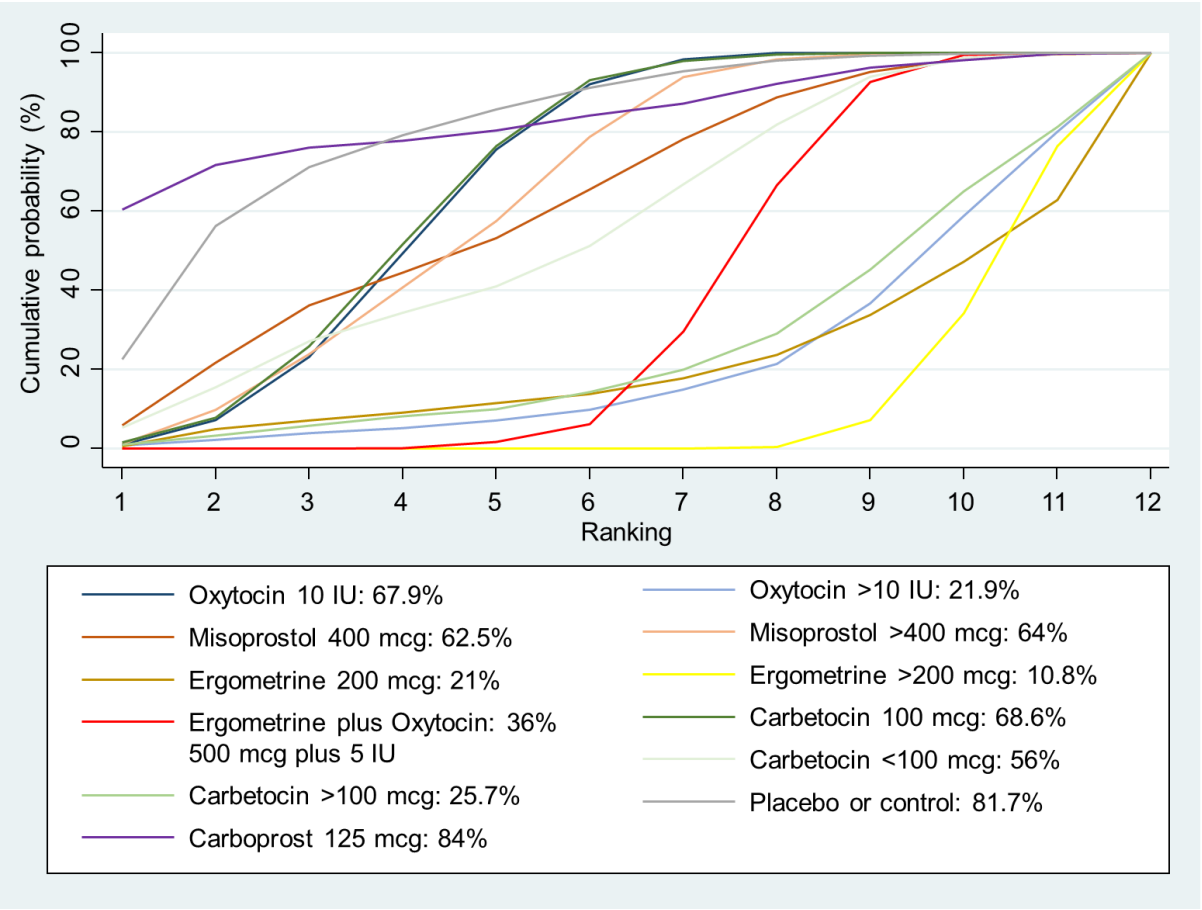


Figure 49: Hypertension-Rankogram-Doses NMA

Cumulative rankogram for hypertension. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Vomiting

Relative and absolute effects: The network diagram and the forest plot for hypertension are presented in *Figure 50* and *Figure 51* respectively. Local and global inconsistency were generally low.

According to high certainty evidence, when compared with oxytocin 10 IU, misoprostol >400 mcg (RR 1.63, 95% CI 1.16-2.29) and ergometrine plus oxytocin combination (RR 3.29, 95% CI 2.38-4.56) increase the risk for vomiting. These results suggests that 26 per 1,000 receiving oxytocin 10 IU will experience vomiting, compared with 42 and 86 given misoprostol >400 mcg and ergometrine plus oxytocin combination respectively (see *Table 23: Vomiting-Summary of Findings Table-Doses NMA*).

Moderate certainty evidence suggests that, when compared with oxytocin 10 IU, misoprostol 400 mcg probably increases the risk for vomiting (RR 1.56, 95% CI 1.05-2.32). Additional moderate certainty evidence suggests that carbetocin 100 mcg (RR 0.92, 95% CI 0.63-1.33) and placebo (RR 1.18, 95% CI 0.68-2.05) probably make little or no difference to the outcome of vomiting, when compared with oxytocin 10 IU. In absolute terms, for every 1,000 women receiving oxytocin 10 IU, 26 will experience vomiting, compared with 24 given carbetocin, 31 given placebo, and 41 given misoprostol 400 mcg (see *Table 23: Vomiting-Summary of Findings Table-Doses NMA*).

Based on low certainty evidence, when compared with oxytocin 10 IU, carboprost >125 mcg (RR 4.49, 95% CI 1.70-11.86) and ergometrine >200 mcg (RR 11.12, 95% CI 5.24-23.59) may be associated with a higher risk for vomiting. Low certainty evidence also suggests that oxytocin >10 IU (RR 1.29, 95% CI 0.81-2.07), oxytocin <10 IU (RR 1.00, 95% CI 0.52-1.92), carbetocin >100 mcg (RR 0.62, 95% CI 0.11-3.63), carbetocin <100 mcg (RR 0.49, 95% CI

0.14-1.75), and ergometrine 200 mcg (RR 1.34, 95% CI 0.80-2.25) may make little or no difference to this outcome, when compared with oxytocin 10 IU.

For the outcome of vomiting, the generated network evidence was of very low certainty for carboprost 125 mcg (RR 0.74, 95% CI 0.19-2.92) and misoprostol <400 mcg (RR 0.58, 95% CI 0.02-13.39) compared with oxytocin 10 IU.

No data were available for the comparison of sulprostone 500 mcg against oxytocin 10 IU, and thus the relative and absolute effects remained unclear.

Cumulative probabilities: Among the active agents, carbetocin <100 mcg was ranked first with 86% probability of being the best uterotonic drug for not causing vomiting, oxytocin 10 IU was ranked sixth with probability 67.3%, and ergometrine >200 mcg was ranked last with probability 0.8% *(Figure 52*Figure 52*).*

Figure 50: Vomiting-Network diagram-Doses NMA

Network diagram for vomiting. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison. The colour of the lines reflects the certainty of the direct evidence: green for high certainty evidence, orange for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

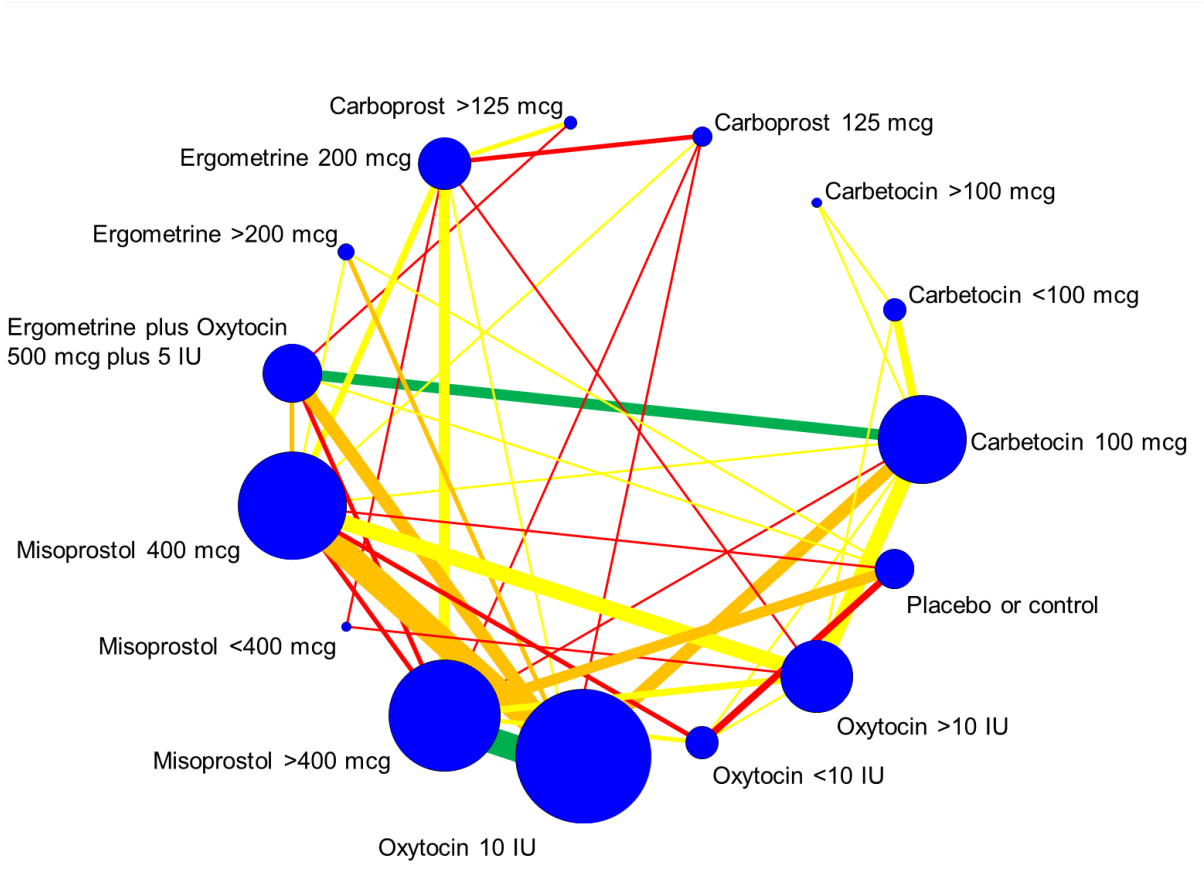


Figure 51: Vomiting-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network vomiting.

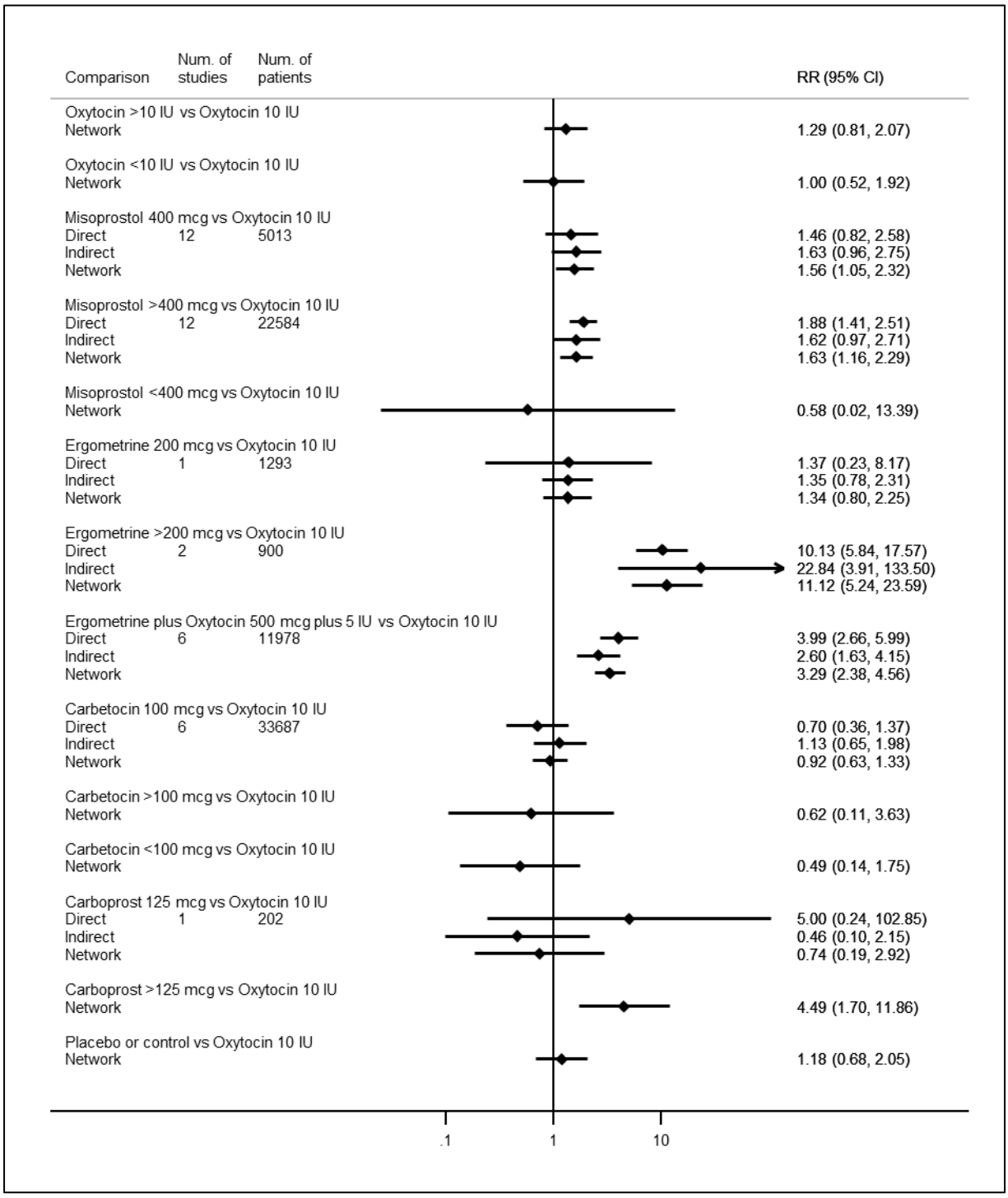
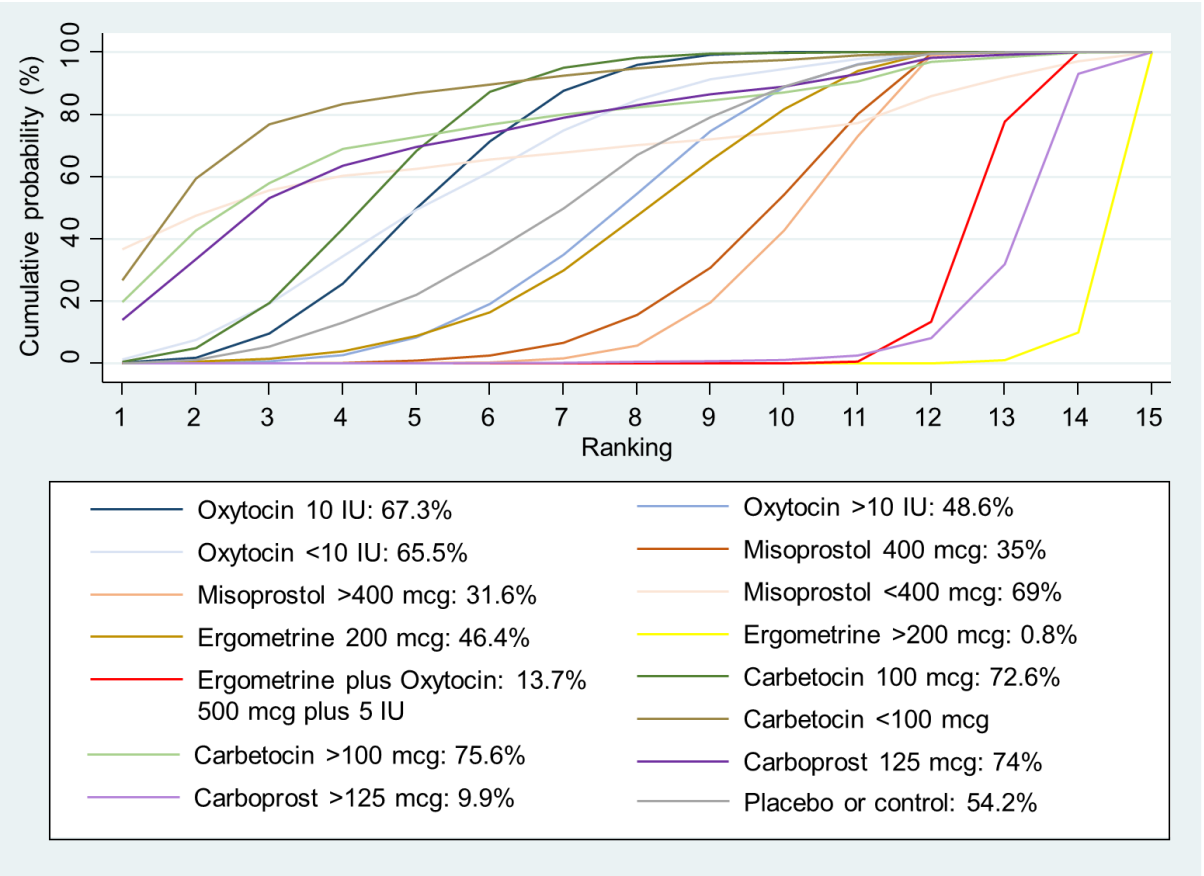


Figure 52: Vomiting-Rankogram-Doses NMA

Cumulative rankogram for vomiting. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Additional outcomes

All respective graphs (i.e., network diagrams, forest plots, and rankograms) can be found in *APPENDIX 3: Doses-NMA.*

It was not possible to perform a NMA in the following cases:

4. **Maternal morbidity-shock:** Included studies did not report this outcome.
5. **Breastfeeding at hospital discharge:** Due to the scarcity of data only few pairwise comparisons are available. Therefore, this outcome could not be used to provide a meaningful ranking of the available agents.
6. **Maternal satisfaction and maternal sense of well-being:** Due to the endogenous heterogeneity of these outcomes no meta-analysis was performed.

The certainty of the generated evidence for the secondary outcomes of this project was not assessed. Therefore, it would be meaningless to report the respective relative treatment effects that can be found in *APPENDIX 3: Doses-NMA*. However, *Table 24* presents the ranking of the available agents based on their respective SUCRAs for a given secondary outcome. For effectiveness outcomes (i.e., maternal death, maternal morbidity-ICU admissions, blood loss, change in Hb) the best agent is the one that is most likely to prevent an event. For side effects (i.e., abdominal pain, diarrhoea, headache, nausea, shivering) the best agent is the one that is less likely to cause an event. Zero ranking represents cases of no available data for a given agent. For a better understanding, *Table 24* should be read together with the respective rankograms.

For the outcomes of **maternal death and maternal morbidity-ICU admissions,** 45 and 17 studies provided data respectively, with most of them reporting zero events across arms. As

shown in the respective rankograms (*Figure 130* and *Figure 133*) there is a great overlap between the available uterotonic drugs, and thus a clear ranking cannot be produced.

In contrast, **blood loss** was a very well reported outcome across 109 studies. As shown in *Table 24,* injectable prostaglandins, namely carboprost >125 mcg and sulprostone 500 mcg, and carbetocin 100 mcg are ranked among the top three agents for prevention of excessive bleeding.

Another blood loss-related outcome, i.e., **change in Hb**, was reported across 65 studies. Available rankings in *Table 24* suggest that ergometrine plus oxytocin combination, carbetocin 100 mcg, and misoprostol 400 mcg are the top three uterotonics for minimising the change in haemoglobin measurements before and after delivery.

Table 24: Ranking of the available uterotonics based on secondary outcomes and according to their respective SUCRAs-Doses NMA.

Interventions & Outcomes	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**
Maternal death	**3**	7	10	11	0	0	6	8	9	3	5	4	1	0	0	2
Morbidity (ICU)	**3**	6	2	5	0	0	0	0	0	1	9	4	7	0	0	8
Blood loss	**4**	15	12	2	14	11	13	1	8	7	6	5	9	10	3	16
Hb change	**9**	5	7	2	0	0	4	0	6	11	1	3	8	10	0	12
Interventions & Outcomes	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**
Abdominal pain	**11**	5	4	8	0	0	3	9	1	12	13	6	10	2	0	7
Diarrhoea	**1**	3	7	0	0	0	10	11	8	5	6	4	9	0	0	2
Headache	**10**	6	9	3	9	7	1	12	8	13	11	5	4	0	0	2
Nausea	**9**	8	1	5	2	3	7	14	12	15	13	11	10	0	4	6
Shivering	**4**	6	3	1	0	0	2	0	5	10	8	11	12	9	0	7

Footnotes:
A: oxytocin 10 IU, **B:** oxytocin >10 IU, **C:** oxytocin <10 IU, **D:** carbetocin 100 mcg, **E:** carbetocin >100 mcg, **F:** carbetocin <100 mcg, **G:** carboprost 125 mcg, **H:** carboprost >125 mcg, **I:** ergometrine 200 mcg, **J:** ergometrine >200 mcg, **K:** ergometrine plus oxytocin 500 mcg plus 5 IU, **L:** misoprostol 400 mcg, **M:** misoprostol >400 mcg, **N:** misoprostol <400 mcg, **O:** sulprostone 500 mcg, **P:** placebo or control

For the outcomes of **abdominal pain, diarrhoea, headache, nausea and shivering,** as shown in *Table 24,* various doses of oxytocin (oxytocin 10 IU, >10 IU or <10 IU), carbetocin (100 mcg, >100 mcg, <100 mcg), and carboprost 125 mcg are among the top three agents with a favourable side-effect profile.

Subgroup and sensitivity analyses

Subgroup analyses

From the prespecified subgroup analyses (see *CHAPTER 2: METHODS*), two were performed for the primary outcomes (PPH ≥500 mL, PPH ≥1000 mL): (a) according to the mode of birth (i.e., vaginal births, caesarean births), and (b) according to the prior risk of PPH (i.e., women at high risk, women at low risk). It was not possible to perform a subgroup analysis according to delivery settings (i.e., hospital or community) given that only seven of the available studies (4%) were conducted in a community setting.

Results from the main and the available subgroup analyses are presented in *Table 25* and *Table 26.* These results suggest that there are no substantial differences in terms of statistically significant findings. The respective rankograms are available in *APPENDIX 3: Doses-NMA.* Cumulative probabilities and respective SUCRAs suggest that for the outcome of PPH ≥500 mL, carbetocin 100 mcg, ergometrine plus oxytocin combination, and various doses of misoprostol are among the top three uterotonics drugs for PPH prevention. For the outcome of PPH ≥1000 mL, high doses of ergometrine and misoprostol (>200 mcg and >400 mcg, respectively), and ergometrine plus oxytocin combination perform better than other available uterotonic drugs.

Table 25: Subgroup analysis for PPH ≥500 mL for the Doses-NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Ergometrine plus Oxytocin 500 mcg plus 5 IU, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: PPH ≥500 mL

Analysis restricted to	All studies	Vaginal Births	Caesarean births	Low risk for PPH	High risk for PPH
Oxytocin >10 IU					
Direct estimate	Not estimable	Not Estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.96 0.70 -1.32	0.85 0.47-1.54	1.11 0.70-1.76	Not estimable	1.20 0.80-1.80
Oxytocin <10 IU					
Direct estimate	Not estimable	Not Estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.12 0.83-1.51	1.14 0.79-1.66	1.19 0.67-2.10	1.39 0.51-3.81	1.33 0.82-2.18
Carbetocin 100 mcg					
Direct estimate	1.00 0.90-1.11	1.00 0.93-1.07	0.79 0.39-1.58	Not estimable	0.98 0.79-1.23
Network estimate	0.78 0.60-1.02	0.77 0.52-1.14	0.84 0.55-1.28	0.73 0.15-3.44	0.90 0.65-1.23
Carbetocin >100 mcg					
Direct estimate	Not estimable	Not Estimable	Not estimable	Not estimable	Not estimable
Network estimate	Not estimable	Not Estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg					
Direct estimate	Not estimable	Not Estimable	Not estimable	Not estimable	Not estimable
Network estimate	Not estimable	Not Estimable	Not estimable	Not estimable	Not estimable
Carboprost 125 mcg					
Direct estimate	1.86 0.07-51.05	1.86 0.07-51.05	Not estimable	13.00 0.77-219.11	Not estimable
Network estimate	1.34 0.69-2.58	1.29 0.65-2.53	Not estimable	2.58 0.74-8.96	Not estimable
Carboprost >125 mcg					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.04 0.50-2.16	0.73 0.16-3.23	Not estimable	0.83 0.11-6.10	Not estimable

Ergometrine 200 mcg					
Direct estimate	1.39 0.70-2.74	1.39 0.70-2.74	Not estimable	1.00 0.02-48.52	Not estimable
Network estimate	1.15 0.77-1.71	1.09 0.71-1.67	Not estimable	1.24 0.48-3.20	0.50 0.04-5.96
Ergometrine >200 mcg					
Direct estimate	0.78 0.28-2.17	0.78 0.28-.217	Not estimable	1.00 0.15-6.79	Not estimable
Network estimate	1.15 0.73-1.82	1.14 0.70-1.83	Not estimable	1.44 0.50-4.17	1.87 0.69-5.07
Ergometrine plus Oxytocin 500 mcg plus 5 IU					
Direct estimate	0.86 0.66-1.11	0.86 0.66-1.11	Not estimable	0.87 0.50-1.50	Not estimable
Network estimate	0.79 0.62-1.01	0.79 0.61-1.03	Not estimable	0.56 0.21-1.52	1.96 0.82-4.69
Misoprostol 400 mcg					
Direct estimate	0.95 0.63-1.45	0.90 0.53-1.52	1.27 0.91-1.77	0.74 0.39-1.40	1.27 0.91-1.77
Network estimate	1.00 0.78-1.29	0.87 0.64-1.18	1.37 0.86-2.17	0.76 0.41-1.41	1.45 0.96-2.18
Misoprostol >400 mcg					
Direct estimate	1.09 0.74-1.60	1.11 0.70-1.77	1.00 0.77-1.30	1.23 0.58-2.60	1.00 0.77-1.30
Network estimate	1.17 0.94-1.46	1.23 0.96-1.58	0.90 0.54-1.52	1.29 0.71-2.35	1.01 0.63-1.60
Misoprostol <400 mcg					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.86 0.39-1.88	0.83 0.36-1.87	Not estimable	0.95 0.03-32.49	Not estimable
Sulprostone 500 mcg					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.01 0.35-2.93	1.04 0.35-3.13	Not estimable	1.27 0.25-6.56	Not estimable
Placebo or control					
Direct estimate	1.86 1.58-2.20	1.86 1.58-2.20	Not estimable	Not estimable	Not estimable
Network estimate	1.83 1.42-2.37	1.90 1.43-2.53	1.54 0.54-4.36	2.33 0.96-5.68	1.67 0.63-4.45

Table 26: Subgroup analysis for PPH ≥1000 mL for the Doses-NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Ergometrine plus Oxytocin 500 mcg plus 5 IU, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: PPH ≥1000 mL

Analysis restricted to	All studies	Vaginal births	Caesarean births	Low risk for PPH	High risk for PPH
Oxytocin >10 IU					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.08 0.85-1.38	1.33 0.68-2.61	1.45 0.79-2.65	0.96 0.66-1.41	1.35 0.77-2.35
Oxytocin <10 IU					
Direct estimate	1.96 0.38-10.24	Not estimable	1.96 0.38-10.24	Not estimable	1.96 0.38-10.24
Network estimate	1.17 0.91-1.51	1.00 0.75-1.34	1.91 0.99-3.68	Not estimable	1.77 0.96-3.25
Carbetocin 100 mcg					
Direct estimate	1.07 0.90-1.27	1.04 0.87-1.25	Not estimable	Not estimable	1.20 0.78-1.83
Network estimate	1.04 0.88-1.24	1.04 0.86-1.24	Not estimable	0.36 0.04-3.21	1.18 0.75-1.88
Carbetocin >100 mcg					
Direct estimate	Not estimable	Not estimable	1.33 0.81-2.19	Not estimable	Not estimable
Network estimate	Not estimable	Not estimable	1.28 0.75-2.19	Not estimable	Not estimable
Carbetocin <100 mcg					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.95 0.61-1.47	Not estimable	1.21 0.53-2.77	Not estimable	1.13 0.52-2.43
Carboprost 125 mcg					
Direct estimate	5.00 0.25-99.16	5.00 0.25-99.16	Not estimable	5.00 0.25-99.16	Not estimable
Network estimate	6.17 0.84-45.30	6.30 0.86-46.19	Not estimable	3.77 0.47-30.43	Not estimable
Carboprost >125 mcg					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.45 0.42-5.02	Not estimable	Not estimable	Not estimable	Not estimable

Ergometrine 200 mcg					
Direct estimate	1.33 0.40-4.41	1.33 0.40-4.41	Not estimable	1.00 0.02-48.52	Not estimable
Network estimate	1.41 0.67-2.97	1.49 0.70-3.18	Not estimable	0.50 0.09-2.91	0.59 0.01-37.33
Ergometrine >200 mcg					
Direct estimate	1.60 0.20-12.91	1.60 0.20-12.91	Not estimable	3.00 0.13-71.70	Not estimable
Network estimate	0.47 0.14-1.60	0.47 0.14-1.62	Not estimable	0.38 0.10-1.53	Not estimable
Ergometrine plus Oxytocin 500 mcg plus 5 IU					
Direct estimate	0.80 0.62-1.05	0.80 0.62-1.05	Not estimable	0.49 0.12-1.95	Not estimable
Network estimate	0.82 0.65-1.04	0.82 0.65-1.04	Not estimable	0.51 0.15-1.71	Not estimable
Misoprostol 400 mcg					
Direct estimate	1.02 0.62-1.69	1.17 0.55-2.50	0.93 0.48-1.79	1.42 0.58-3.49	0.93 0.48-1.79
Network estimate	1.14 0.87-1.49	1.23 0.88-1.73	1.16 0.61-2.20	1.18 0.76-1.83	1.11 0.60-2.05
Misoprostol >400 mcg					
Direct estimate	1.38 1.18-1.60	1.38 1.19-1.61	1.00 0.23-4.37	1.00 0.14-7.06	1.00 0.23-4.37
Network estimate	1.33 1.11-1.60	1.34 1.17-1.54	0.61 0.17-2.22	0.85 0.44-1.64	0.59 0.16-2.15
Misoprostol <400 mcg					
Direct estimate	7.00 0.88-55.37	7.00 0.88-55.37	Not estimable	Not estimable	Not estimable
Network estimate	1.29 0.47-3.54	1.31 0.48-3.61	Not estimable	0.96 0.03-27.54	Not estimable
Sulprostone 500 mcg					
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.69 0.08-5.59	0.64 0.08-5.18	Not estimable	0.62 0.08-5.08	Not estimable
Placebo or control					
Direct estimate	1.63 1.31-2.02	1.63 1.31-2.02	Not estimable	1.66 1.29-2.14	Not estimable
Network estimate	1.80 1.53-2.12	1.75 1.49-2.07	1.59 0.05-49.73	1.71 1.34-2.19	1.47 0.05-45.43

Sensitivity analyses

For the two primary outcomes (PPH ≥500 mL, PPH ≥1000 mL) the following sensitivity analyses were performed: (a) analysis restricted to studies at low risk of bias, (b) restricted to studies at low risk for 'funding source', (c) restricted to studies at low risk for 'blood loss measurements', (d) restricted to studies with <10% attrition, and (e) restricted to studies with >400 participants.

Results are summarised in ***Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε.*** and

Table 28 and suggest no substantial differences. However, once the analysis is restricted to low risk of bias studies, there is a change in the direction and magnitude of effects for the comparison of ergometrine 200 mcg versus oxytocin 10 IU, favouring ergometrine 200 mcg for the outcome of PPH ≥500 mL. It should be noted that this change is not reflected on the respective cumulative probabilities and SCUCRAs, which can be found in *APPENDIX 3: Doses-NMA.* Overall, for the outcome of PPH ≥500 mL, carbetocin 100 mcg and ergometrine plus oxytocin combination are among the top three uterotonics drugs for PPH prevention. For the outcome of PPH ≥1000 mL, high doses of ergometrine and ergometrine plus oxytocin combination perform better than other available uterotonic drugs.

Table 27 Sensitivity analysis for PPH ≥500 mL for the Doses-NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Ergometrine plus Oxytocin 500 mcg plus 5 IU, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: PPH ≥500 mL

Analysis restricted to	All studies	Low risk of bias	Low risk for funding	Low risk for blood loss	Low risk for attrition	With >400 women
Oxytocin >10 IU						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.96 0.70 -1.32	1.11 0.73-1.70	0.45 0.25-0.82	1.11 0.80-1.55	0.86 0.60-1.25	0.95 0.41-2.18
Oxytocin <10 IU						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.12 0.83-1.51	1.33 0.89-1.99	0.93 0.59-1.48	0.98 0.71-1.35	1.12 0.80-1.56	1.10 0.66-1.84
Carbetocin 100 mcg						
Direct estimate	1.00 0.90-1.11	1.00 0.93-1.07	1.00 0.93-1.07	0.95 0.75-1.20	1.00 0.88-1.13	1.00 0.94-1.07
Network estimate	0.78 0.60-1.02	0.99 0.72-1.35	0.95 0.63-1.43	0.79 0.59-1.04	0.81 0.61-1.08	1.05 0.67-1.65
Carbetocin >100 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carboprost 125 mcg						
Direct estimate	1.86 0.07-51.05	Not estimable	13.00 0.77- 219.11	1.86 0.07-51.05	Not estimable	Not estimable
Network estimate	1.34 0.69-2.58	Not estimable	2.30 0.69-7.70	1.60 0.82-3.14	1.17 0.51-2.68	Not estimable
Carboprost >125 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.04 0.50-2.16	Not estimable	Not estimable	Not estimable	0.83 0.18-3.83	1.08 0.43-2.73
Ergometrine 200 mcg						
Direct estimate	1.39 0.70-2.74	**0.25 0.07-0.88**	1.00 0.02-48.52	1.39 0.70-2.74	Not estimable	1.40 0.70-2.80
Network estimate	1.15 0.77-1.71	**0.25 0.06-0.99**	0.79 0.27-2.33	1.27 0.83-1.96	1.24 0.70-2.21	1.20 0.63-2.30
Ergometrine >200 mcg						
Direct estimate	0.78 0.28-2.17	Not estimable	**0.25 0.07-0.88**	0.41 0.11-1.49	0.41 0.15-1.11	1.45 0.72-2.93

Network estimate	1.15 0.73-1.82	Not estimable	0.70 0.36-1.35	0.62 0.36-1.08	0.94 0.51-1.73	1.36 0.74-2.53
Ergometrine plus Oxytocin 500 mcg plus 5 IU						
Direct estimate	0.86 0.66-1.11	0.91 0.80-1.04	Not estimable	0.88 0.63-1.21	0.86 0.66-1.11	0.86 0.66-1.11
Network estimate	0.79 0.62-1.01	0.79 0.56-1.10	**0.49** **0.28-0.89**	1.00 0.68-1.47	**0.76** **0.58-0.99**	0.75 0.55-1.01
Misoprostol 400 mcg						
Direct estimate	0.95 0.63-1.45	0.72 0.36-1.45	**0.46** **0.27-0.78**	0.94 0.66-1.33	0.93 0.48-1.81	0.96 0.54-1.71
Network estimate	1.00 0.78-1.29	1.15 0.80-1.66	**0.41** **0.26-0.67**	1.12 0.86-1.45	0.91 0.67-1.24	0.88 0.61-1.28
Misoprostol >400 mcg						
Direct estimate	1.09 0.74-1.60	**1.44** **1.35-1.54**	0.96 0.64-1.45	**1.46** **1.16-1.84**	0.96 0.63-1.45	0.93 0.51-1.70
Network estimate	1.17 0.94-1.46	1.33 0.97-1.81	1.10 0.84-1.43	**1.31** **1.03-1.67**	1.12 0.88-1.42	1.16 0.86-1.56
Misoprostol <400 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.86 0.39-1.88	Not estimable	0.65 0.02-19.17	1.07 0.31-3.67	0.75 0.28-2.01	Not estimable
Sulprostone 500 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.01 0.35-2.93	1.09 0.39-3.07	Not estimable	0.92 0.33-2.51	0.98 0.33-2.92	Not estimable
Placebo or control						
Direct estimate	1.86 1.58-2.20	1.77 1.44-2.18	1.86 1.58-2.20	2.04 1.54-2.71	1.86 1.58-2.20	1.86 1.58-2.20
Network estimate	1.83 1.42-2.37	1.87 1.31-2.66	1.69 1.25-2.28	1.71 1.30-2.25	1.77 1.35-2.32	1.89 1.37-2.61

Table 28: Sensitivity analysis for PPH ≥1000 mL for the Doses-NMA

Population: Women in the third stage of labour
Interventions: Oxytocin >10 IU, Oxytocin <10 IU, Carbetocin 100 mcg, IM, Carbetocin >100 mcg, Carbetocin <100 mcg, Carboprost 125 mcg, Carboprost >125 mcg, Ergometrine 200 mcg, Ergometrine >200 mcg, Ergometrine plus Oxytocin 500 mcg plus 5 IU, Misoprostol 400 mcg, Misoprostol >400 mcg, Misoprostol <400 mcg, Sulprostone 500 mcg, Placebo or control
Comparison (reference): Oxytocin 10 IU
Outcome: PPH ≥1000 mL

Analysis restricted to	All studies	Low risk of bias	Low risk for funding	Low risk for blood loss	Low risk for attrition	With >400 women
Oxytocin >10 IU						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.08 0.85-1.38	1.08 0.74-1.57	0.99 0.70-1.40	1.43 0.84-2.41	1.04 0.80-1.34	0.84 0.55-1.30

Oxytocin <10 IU						
Direct estimate	1.96 0.38-10.24	Not estimable	1.96 0.38-10.24	Not estimable	Not estimable	Not estimable
Network estimate	1.17 0.91-1.51	1.08 0.66-1.79	1.00 0.74-1.34	1.07 0.80-1.44	1.14 0.87-1.49	1.01 0.70-1.45
Carbetocin 100 mcg						
Direct estimate	1.07 0.90-1.27	1.05 0.88-1.26	1.05 0.88-1.26	1.04 0.87-1.25	1.07 0.90-1.27	1.06 0.89-1.27
Network estimate	1.04 0.88-1.24	1.05 0.88-1.24	1.05 0.88-1.24	1.02 0.85-1.22	1.06 0.89-1.26	1.07 0.81-1.42
Carbetocin >100 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Carbetocin <100 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.95 0.61-1.47	0.95 0.59-1.53	Not estimable	Not estimable	0.93 0.59-1.44	Not estimable
Carboprost 125 mcg						
Direct estimate	5.00 0.25-99.16	Not estimable	5.00 0.25-99.16	5.00 0.25-99.16	Not estimable	Not estimable
Network estimate	6.17 0.84-45.30	Not estimable	5.18 0.64-41.69	6.41 0.87-47.28	Not estimable	Not estimable
Carboprost >125 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	1.45 0.42-5.02	Not estimable	Not estimable	Not estimable	Not estimable	1.41 0.39-5.02
Ergometrine 200 mcg						
Direct estimate	1.33 0.40-4.41	Not estimable	1.00 0.02-48.52	1.33 0.40-4.41	Not estimable	1.37 0.39-4.83
Network estimate	1.41 0.67-2.97	Not estimable	0.83 0.11-6.11	1.54 0.63-3.77	1.05 0.31-3.59	1.82 0.64-5.20
Ergometrine >200 mcg						
Direct estimate	1.60 0.20-12.91	Not estimable	Not estimable	3.00 0.13-71.70	1.95 0.17-22.92	0.99 0.06-15.85
Network estimate	0.47 0.14-1.60	Not estimable	0.23 0.05-1.05	0.39 0.07-2.19	0.44 0.12-1.61	0.33 0.09-1.29
Ergometrine plus Oxytocin 500 mcg plus 5 IU						
Direct estimate	0.80 0.62-1.05	0.81 0.61-1.08	Not estimable	0.72 0.40-1.32	0.80 0.62-1.05	0.80 0.62-1.05
Network estimate	0.82 0.65-1.04	0.82 0.62-1.08	0.51 0.23-1.10	0.80 0.45-1.44	0.82 0.65-1.04	0.80 0.60-1.05
Misoprostol 400 mcg						
Direct estimate	1.02 0.62-1.69	1.45 0.57-3.65	0.64 0.08-5.17	0.95 0.56-1.61	1.45 0.66-3.21	1.18 0.53-2.61
Network estimate	1.14 0.87-1.49	1.50 0.97-2.32	1.00 0.63-1.58	1.16 0.83-1.61	1.22 0.89-1.67	1.16 0.81-1.68

Misoprostol >400 mcg						
Direct estimate	1.38 1.18-1.60	1.39 1.19-1.62	1.38 1.18-1.60	1.39 1.19-1.61	1.38 1.18-1.60	1.38 1.19-1.61
Network estimate	1.33 1.11-1.60	1.35 1.17-1.56	1.34 1.17-1.54	1.37 1.19-1.57	1.33 1.11-1.60	1.28 1.02-1.61
Misoprostol <400 mcg						
Direct estimate	7.00 0.88-55.37	Not estimable	Not estimable	7.00 0.88-55.37	7.00 0.88-55.37	Not estimable
Network estimate	1.29 0.47-3.54	Not estimable	1.11 0.04-31.32	1.82 0.58-5.75	1.49 0.38-5.86	Not estimable
Sulprostone 500 mcg						
Direct estimate	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Network estimate	0.69 0.08-5.59	0.68 0.08-5.53	Not estimable	0.67 0.08-5.42	0.68 0.08-5.52	Not estimable
Placebo or control						
Direct estimate	1.63 1.31-2.02	1.42 0.91-2.20	1.63 1.31-2.02	1.70 1.33-2.18	1.63 1.31-2.02	1.63 1.31-2.02
Network estimate	1.80 1.53-2.12	1.83 1.44-2.34	1.76 1.48-2.09	1.80 1.50-2.15	1.79 1.51-2.11	1.73 1.40-2.14

CHAPTER 5: DISCUSSION

Agreement and disagreement with other systematic reviews and meta-analyses

Based on the two primary outcomes of this review, carbetocin IV(B), ergometrine plus oxytocin combination IM, and oxytocin IV(B+I) are the top three uterotonics in terms of effectiveness. Oxytocin IV(B) ranks among the top five uterotonics and is consistently better than oxytocin IM, whereas placebo always ranks last.

For PPH ≥500 mL, carbetocin IV(B) ranked first (SUCRA 91.9%), followed by ergometrine plus oxytocin combination IM (SUCRA 77%). According to moderate certainty evidence both uterotonics probably prevent more cases of PPH ≥500 mL, compared with oxytocin IM (SUCRA 32.2%). Oxytocin IV(B+I) ranked third (SUCRA 72.3%) and probably makes little or no difference to this outcome compared with oxytocin IM. Although oxytocin IV(B) ranked fifth (SUCRA 70.5%), high certainty evidence suggests that it decreases the risk for PPH compared with oxytocin IM.

Oxytocin IV(B+I) with SUCRA 83.7% and carbetocin IV(B) with SUCRA 76.1% probably make little or no difference to the risk for PPH ≥1000 mL, compared with oxytocin IM with SUCRA 45.7%. Ergometrine plus oxytocin combination IM ranked third with SUCRA 72.6%, but the generated network evidence was of very low certainty for its comparison against oxytocin IM.

For both additional uterotonic use and blood transfusion, carbetocin IV(B) and oxytocin IV(B+I) ranked best. Based on moderate certainty evidence, carbetocin IV(B) probably reduces the risk for both outcomes, when compared with oxytocin IM. Oxytocin IV(B+I) may

also decrease the risk for these outcomes, compared with oxytocin IM, although the available evidence is of low certainty. Even if oxytocin IV(B) was not among the top three uterotonics for both outcomes, it ranked better than oxytocin IM, and probably prevents more cases of additional uterotonic use or blood transfusion.

For blood loss, carbetocin IV(B) and oxytocin IV(B+I) ranked best, while for another blood loss related outcome, i.e., change in Hb, these uterotonics were among the top five available options.

In terms of side effects, oxytocin IM and carbetocin IM both had a more favourable side-effects profile compared with carbetocin IV(B), ergometrine plus oxytocin combination IM, oxytocin IV(B+I), and oxytocin IV(B).

Based on the two primary outcomes of this review, ergometrine plus oxytocin combination 500 mcg plus 5 IU is consistently among the top uterotonics in terms of effectiveness. In contrast, oxytocin 10 IU, which is the gold standard, is not listed among the top three uterotonics. All active uterotonic drugs, irrespectively of the administered dose, rank better than placebo.

For PPH ≥500 mL, carbetocin 100 mcg ranked first (SUCRA 85.9%), and ergometrine plus oxytocin combination 500 mcg plus 5 IU ranked second (SUCRA 84.8%), whereas oxytocin 10 IU ranked fifth (SUCRA 56.5%). Moderate certainty evidence suggests that the two highest ranked uterotonics probably make little or no difference to this outcome, when compared with oxytocin 10 IU.

For the outcome of major PPH, high doses of ergometrine, i.e., ergometrine >200 mcg, and ergometrine's combination with oxytocin are the best available options with SUCRA 88.8% and 83.2%, respectively. Oxytocin 10 IU ranked fifth with SUCRA 66%. However, the

generated evidence for the comparison of each of the two highest raked uterotonics against the gold standard is of very low certainty.

The certainty of the generated evidence is also very low for the comparisons of carbetocin 100 mcg and ergometrine plus oxytocin combination against oxytocin 10 IU for the outcome of additional uterotonic use. Carbetocin 100 mcg with SUCRA 85.6% and ergometrine plus oxytocin combination with SUCRA 71.6% ranked first and fourth respectively, whereas oxytocin 10 IU with SUCRA 49.7% ranked nineth for this outcome.

For the outcome of blood transfusion, ergometrine >200 mcg (SUCRA 95.4%), ergometrine plus oxytocin combination (SUCRA 60.8%), and carbetocin 100 mcg were among the top uterotonics, whereas oxytocin 10 IU ranked seventh (SUCRA 53.2%). When comparing the best options against oxytocin 10 IU, the generated evidence is either of low or moderate certainty without statistically significant results.

Carbetocin 100 mcg and ergometrine plus oxytocin combination were the two best uterotonics for the outcome of Hb change, and carbetocin 100 mcg also ranked among the top choices for the outcome of blood loss.

In terms of side effects, carbetocin 100 mcg was associated with a favourable profile in most cases.

No other NMA exploring different routes and doses of administration for all the available uterotonics exists.

In 2018, a Cochrane-registered NMA grouping all routes and doses of administration for each of the available uterotonics was updated. Although both carbetocin and combination

agents, i.e., ergometrine plus oxytocin and misoprostol plus oxytocin, performed better than oxytocin in terms of effectiveness, only carbetocin was associated with a more favourable side-effect profile.[5]

Another recently published NMA provided relative treatment effects and rankings of uterotonics given in women having a caesarean delivery. Authors chose as primary outcomes of their work 'blood loss' and 'additional uterotonics'.[39] Given that methods of blood loss measurement vary considerably across studies, their approach was susceptible to criticism.[40-42] But even the approach of Cochrane authors with dichotomisation of continuous outcomes, e.g., PPH ≥500 mL and PPH ≥ 1000 mL, is not universally accepted.[43,44] Irrespectively of which primary outcome has been evaluated, both NMAs agree that carbetocin performs best compared to other available options.

The work by Jaffer et al also suggests that oxytocin performs better when initiated as a bolus.[39] This finding is in accordance with the results from another Cochrane and a non-Cochrane review that were published in 2020, indicating than oxytocin given intravenously is better than oxytocin given intramuscularly.[45,46]

In terms of which dose is more effective for each of the available uterotonics, current evidence is inconclusive. More than a decade ago, WHO acknowledged the need to identify the optimal dose and performed a systematic review and meta-analysis exploring misoprostol doses. Authors concluded that although more research is required, high doses of misoprostol (i.e., >600 mcg) increase the risk for side effects without increasing the drugs' effectiveness.[47] This year, a research group from India performed a NMA exploring oxytocin's doses for prevention of PPH. Authors report that higher doses were associated with significant side effects, though evidence was scarce.[48] However, findings should be

interpreted with caution based on which oxytocin doses authors refer to as high. Interestingly, this NMA, also assessed the route of oxytocin administration and found that oxytocin bolus infusion followed by a continuous infusion was more effective, fact that correlates with research works already discussed.[39,45,46,48]

Strengths and limitations of this project

This is the first 'double' NMA assessing different routes and doses of the available uterotonics for preventing postpartum haemorrhage. For each of the outcomes of interest, relative treatment effect rankings for all available drugs have been created and the certainty of the generated evidence has been assessed using the GRADE approach. All results are reported according to the PRISMA NMA-checklist.[49]

All data extraction, RoB and trustworthiness assessment, statistical analyses, as well as the grade assessment of the generated evidence have been performed by the author of this Thesis. Ideally, at least two authors contribute to systematic reviews to eliminate errors in data extraction and subjective assessments.[6] The CINeMA approach is a relatively new method of grading the certainty of the generated network evidence, which can theoretically minimise the bias introduced by the assessor. However, as with the conventional grading approaches, CINeMA also lies on the initial RoB assessment, and thus has no extra benefit to offer to this project.[50]

Unfortunately, it was not possible to include in the analyses data for the misoprostol plus oxytocin combination. That is because of the high levels of inconsistency observed and the disrupted geometry of the network. In cases where WHO guidelines are unclear regarding the recommended dose, the cut off dose used for the analyses was based on an arbitrary decision (i.e., the lowest available dose).[3] Additionally, in the Doses-NMA no consistent patterns in terms of effectiveness and side effects were observed, and thus results remain inconclusive.

Implications for practice

Findings suggest that carbetocin IV(B), ergometrine plus oxytocin combination IM, oxytocin IV(B+I), and oxytocin IV(B) are probably more effective than oxytocin IM, in terms of reducing the risk for excessive bleeding, additional uterotonic use, and blood transfusion. However, intravenously administered uterotonics, as well as the combination of ergometrine plus oxytocin given intramuscularly, are associated with more side effects, compared to intramuscular oxytocin and carbetocin.

Findings indicate that ergometrine plus oxytocin combination 500 mcg plus 5 IU has high probability of being among the most effective uterotonics for preventing excessive bleeding, use of additional uterotonics, and administration of a blood transfusion. When compared with oxytocin 10 IU, the generated evidence was of very low to moderate certainty without statistically significant results. Additionally, for the same outcomes, carbetocin 100 mcg and ergometrine >200 mcg also ranked among the best available options, and when compared against oxytocin 10 IU, the respective generated evidence also varied from very low to moderate certainty with non-statistically significant estimates. Carbetocin 100 mcg was the uterotonic with a favourable side effects profile.

This research work shows that carbetocin IV(B), ergometrine plus oxytocin combination IM, and both oxytocin IV(B+I) and IV(B) are effective in preventing PPH and related morbidity outcomes. However, these agents are associated with a high risk for side effects. Additionally, although higher doses of a given agent are expected to be more effective and associated with more side effects, this pattern was not observed in the Doses-NMA, and thus no clear recommendations can be made.

Policy makers and stakeholders should take into consideration women's views and applicability of the evidence in given settings (e.g., intravenous access might not be available, appropriate transportation and storage of specific drugs might not be guaranteed) to produce context specific guidelines. Even if the generalisability of NMA findings is high (in cases of low indirectness, and low local and global inconsistency), there are always 'special' characteristics in given populations.

Implications for research

In most cases available studies compared one uterotonic against another active agent or placebo or no treatment. Only a few studies provided direct comparisons of different routes and/or doses of administration for a given uterotonic drug, and these studies were generally of small size. As a result, findings were not statistically significant, with low levels of certainty of the generated evidence, and no clear ranking of the available drugs, especially for the Doses-NMA.

Based on the above, larger scale randomised trials assessing different routes and doses of administration need to be conducted. Additionally, there is an urgent need for studies testing uterotonics that are not commonly used either because of licensing reasons, financial constraints, or theoretically expected side effects. In any case, future studies should focus not only on reporting blood loss related outcomes and side effects, but also on women's views and acceptability of the interventions.

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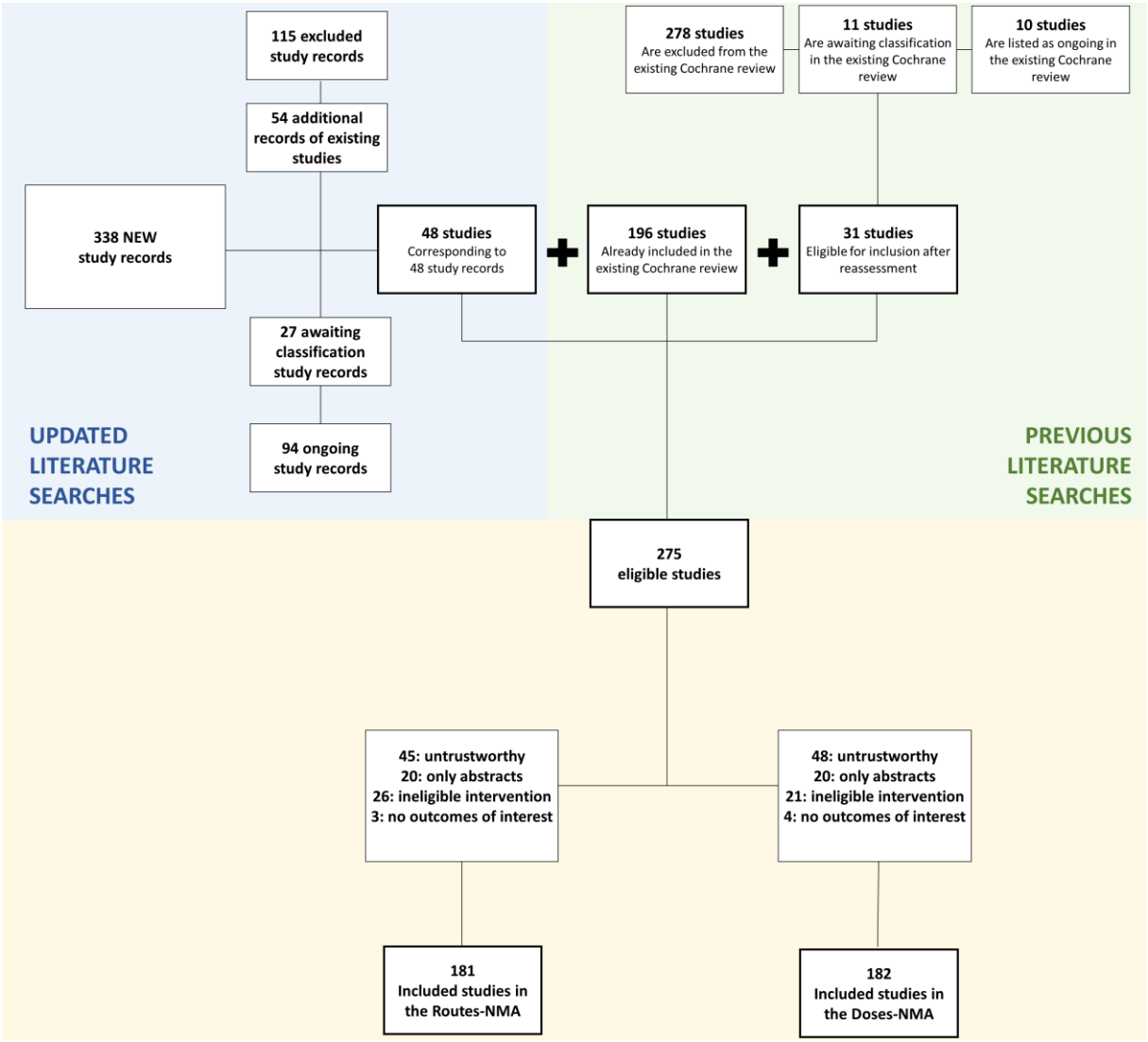
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APPENDIX 1: Additional information Routes-NMA & Doses-NMA

Search strategy

(carbetocin OR ergometrine OR ergonovine OR methylergonovine OR syntometrine OR misoprostol OR carboprost OR sulprostone OR prostaglandin OR oxytocin OR uterotonic) AND (PPH OR haemorrhage OR postpartum)

Study flow diagram



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APPENDIX 2: Routes-NMA

Additional outcomes

Figure 53: Maternal death-Network diagram-Routes NMA

Network diagram for maternal death. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

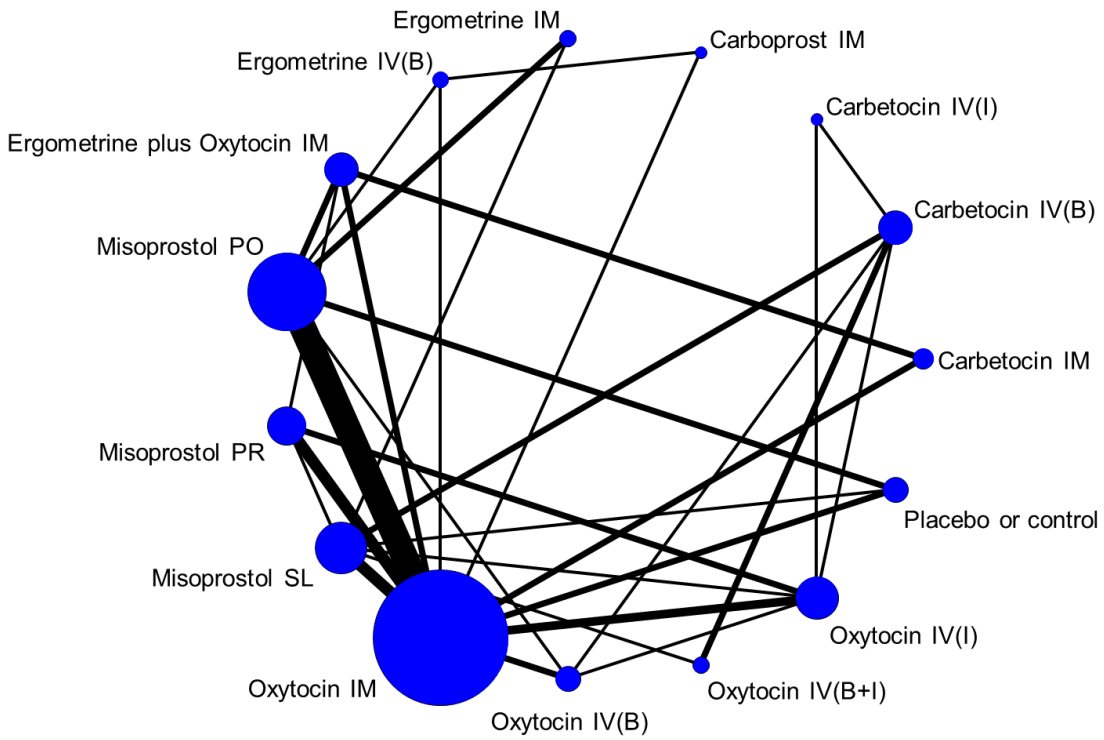


Figure 54: Maternal death-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for maternal death.

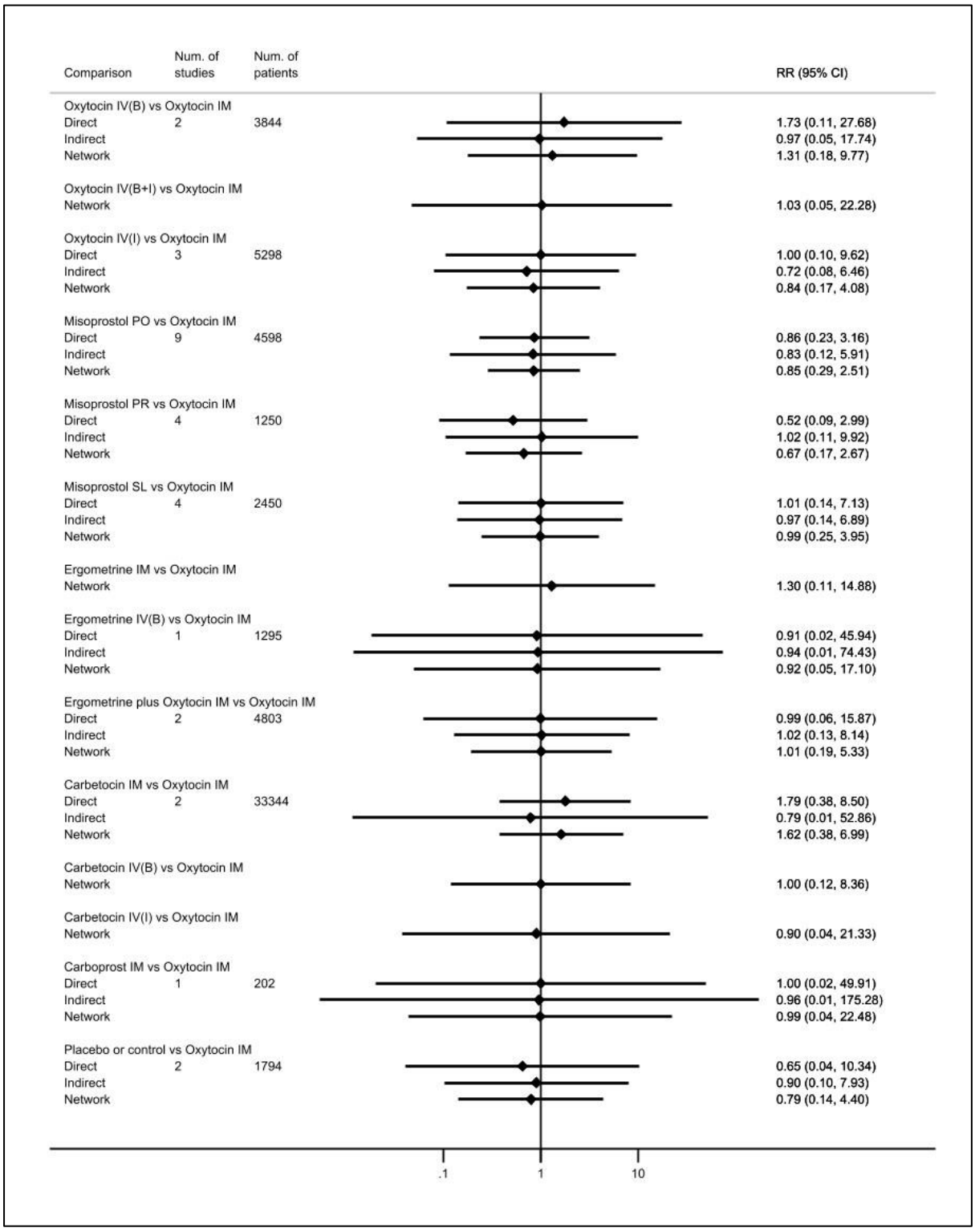


Figure 55: Maternal death-Rankogram-Routes NMA

Cumulative rankogram for maternal death. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

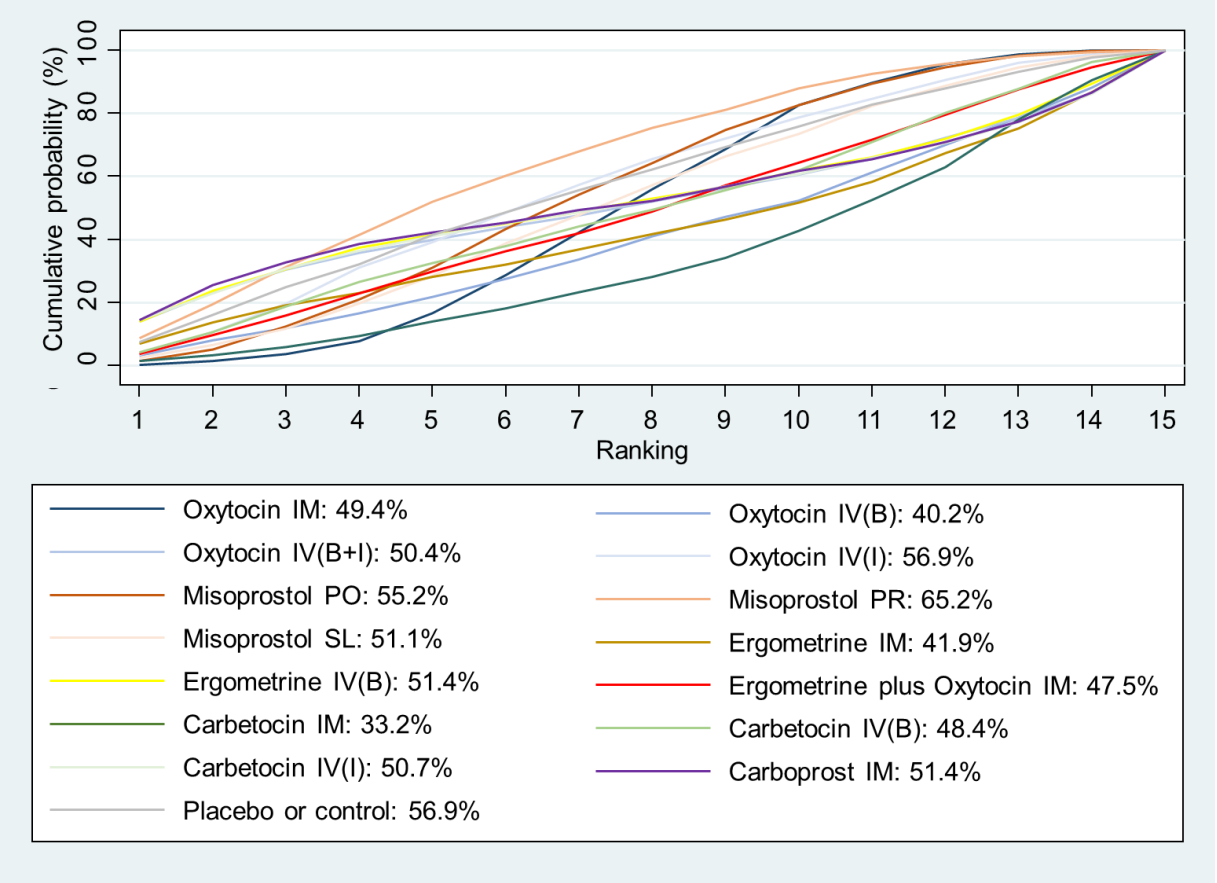


Figure 56: Maternal morbidity-Intensive Care Unit admissions-Network diagram-Routes NMA

Network diagram for maternal morbidity-ICU admissions. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

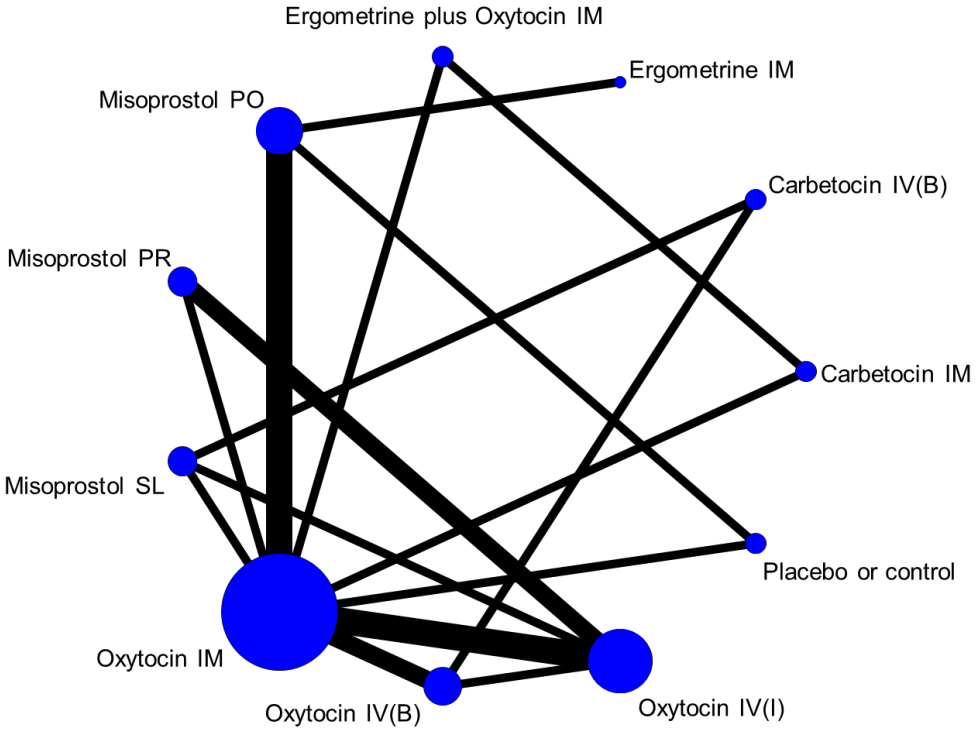


Figure 57: Maternal morbidity-Intensive Care Unit admissions-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for maternal morbidity-ICU admissions.

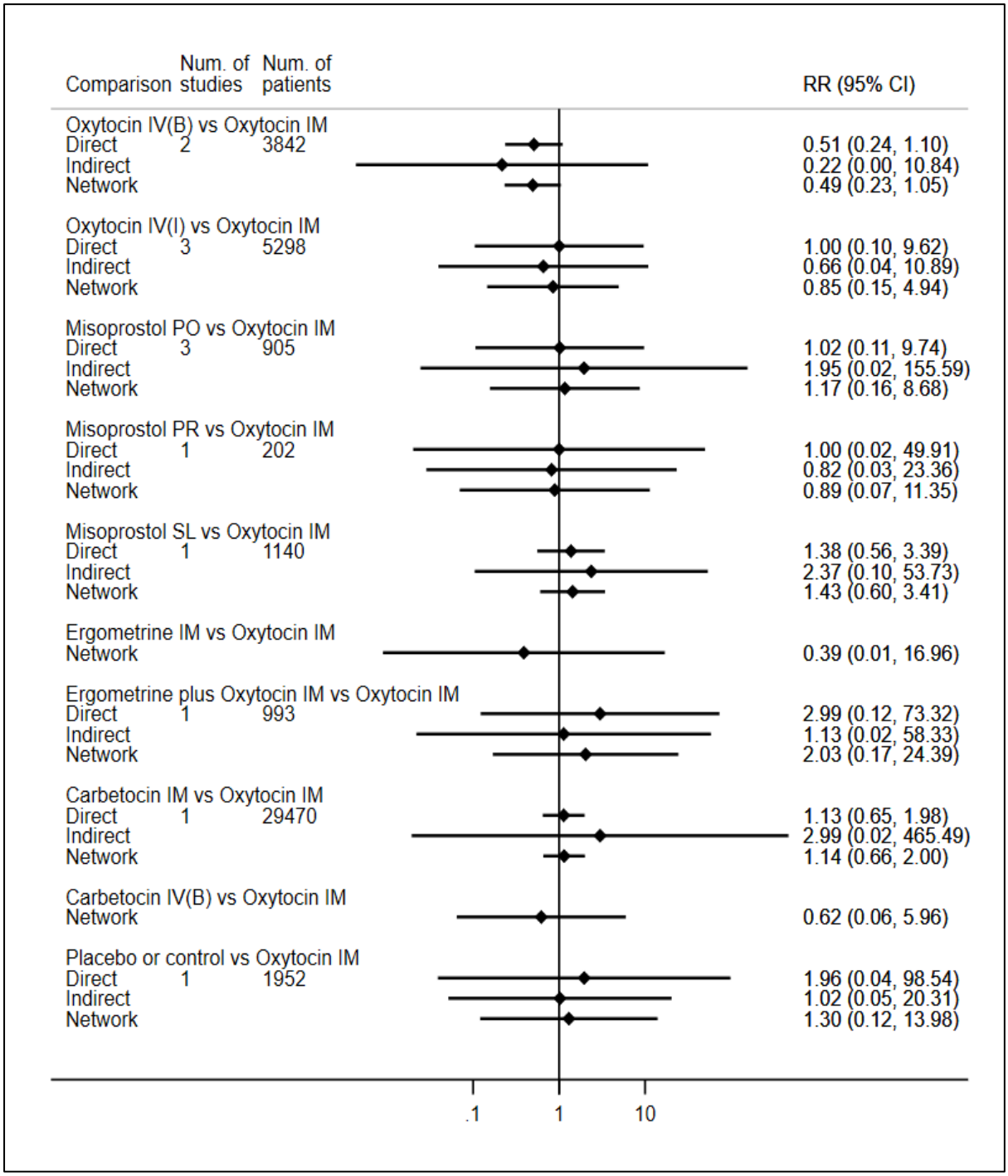


Figure 58: Maternal morbidity-Intensive Care Unit admissions-Rankogram-Routes NMA

Cumulative rankogram for for maternal morbidity-ICU admissions. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

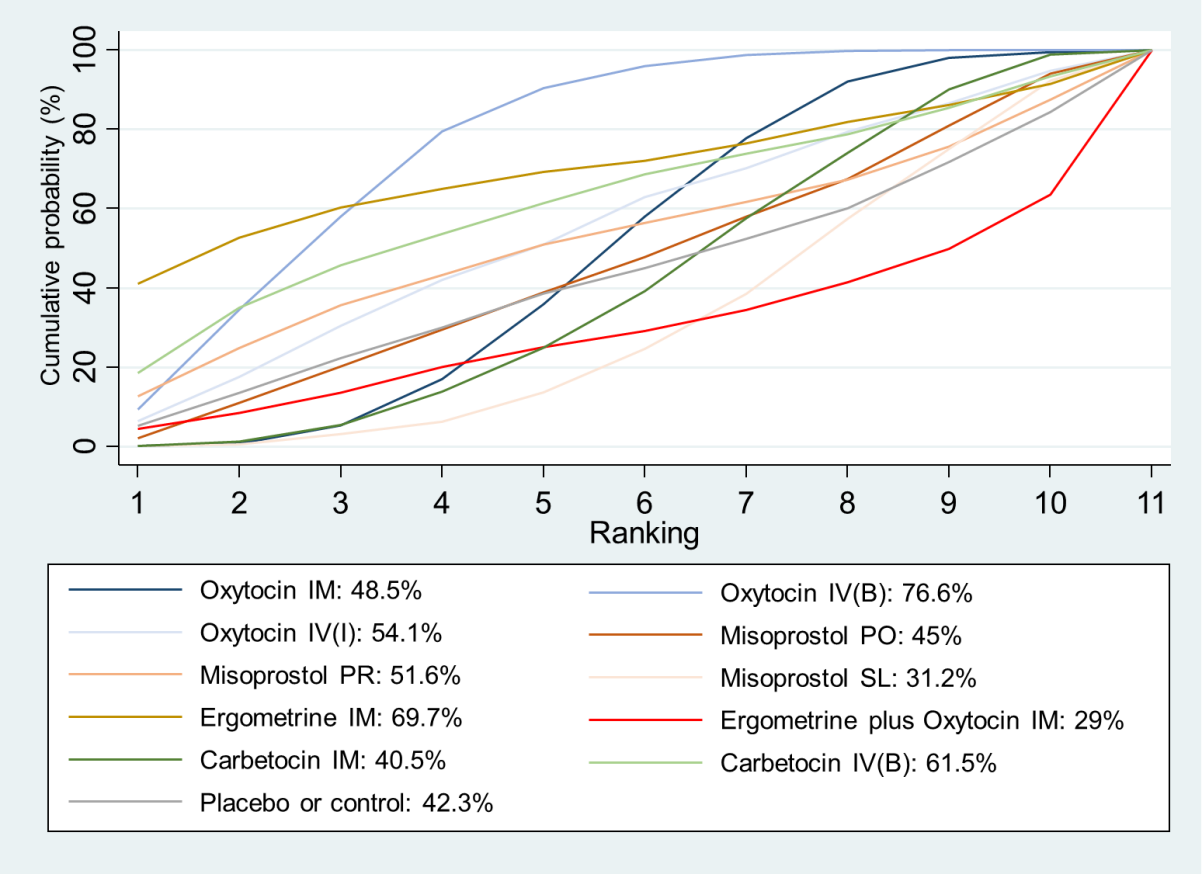


Figure 59: Blood loss-Network diagram-Routes NMA

Network diagram for blood loss. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

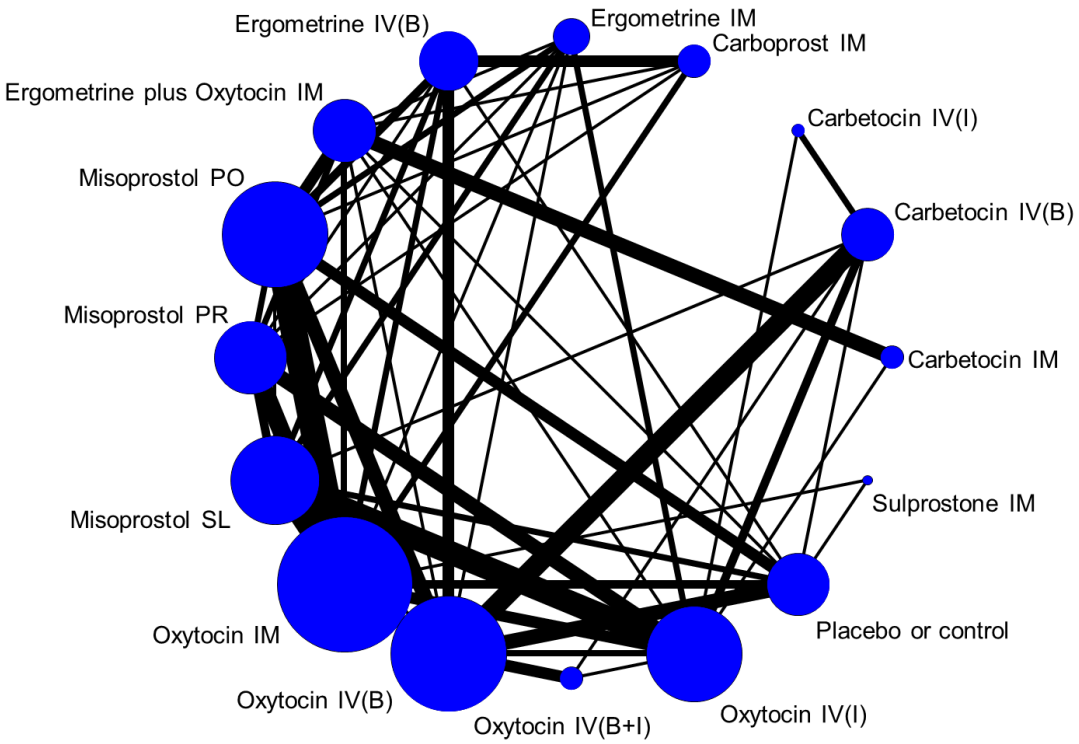


Figure 60: Blood loss-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for blood loss.

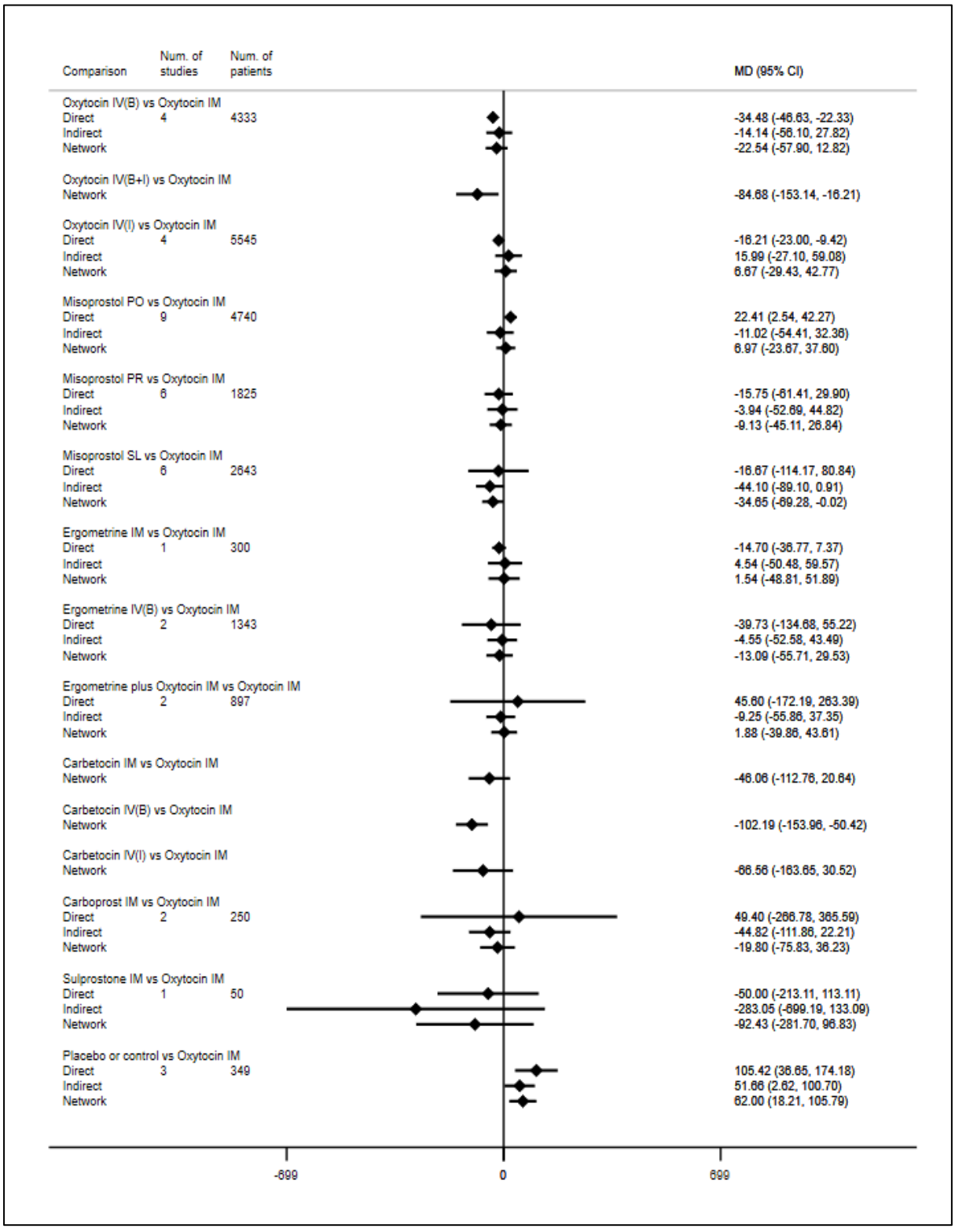


Figure 61: Blood loss-Rankogram-Routes NMA

Cumulative rankogram for blood loss. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

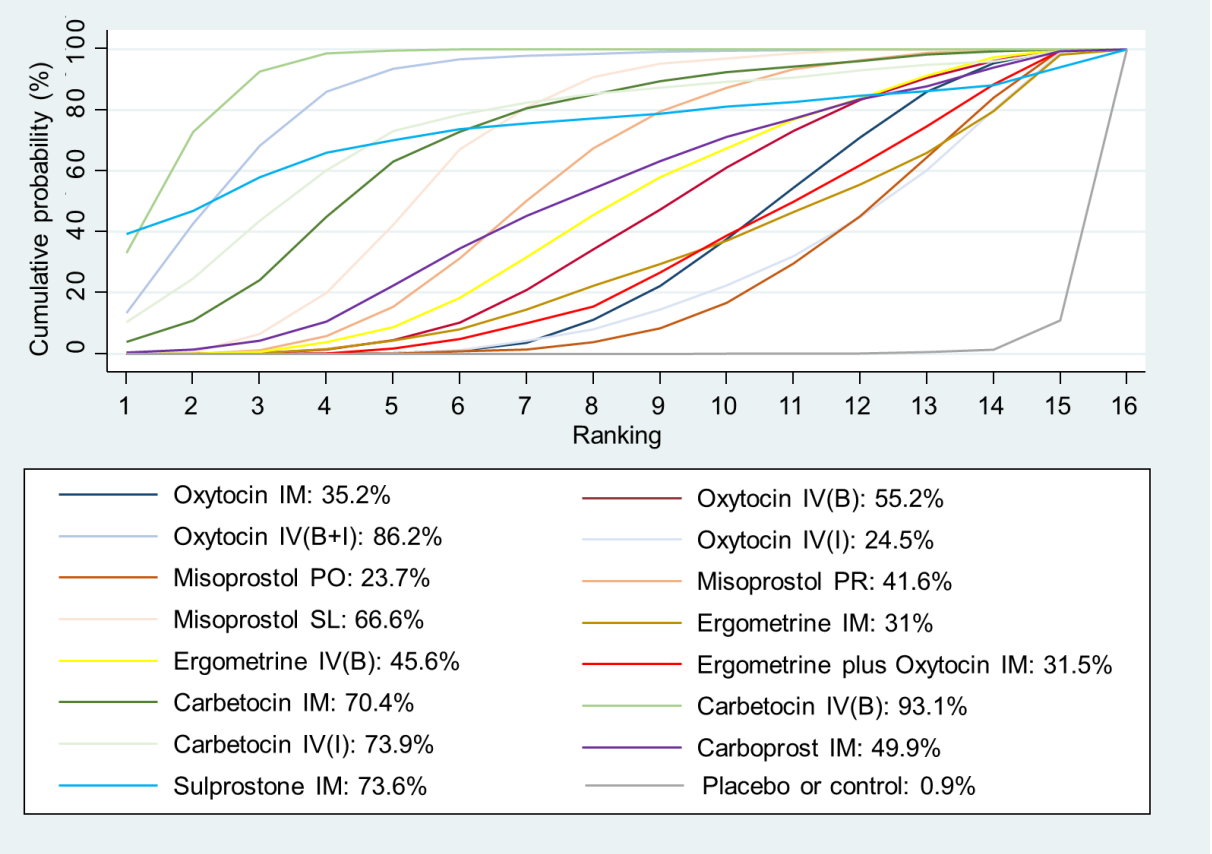


Figure 62: Hb change-Network diagram-Routes NMA

Network diagram for Hb change. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

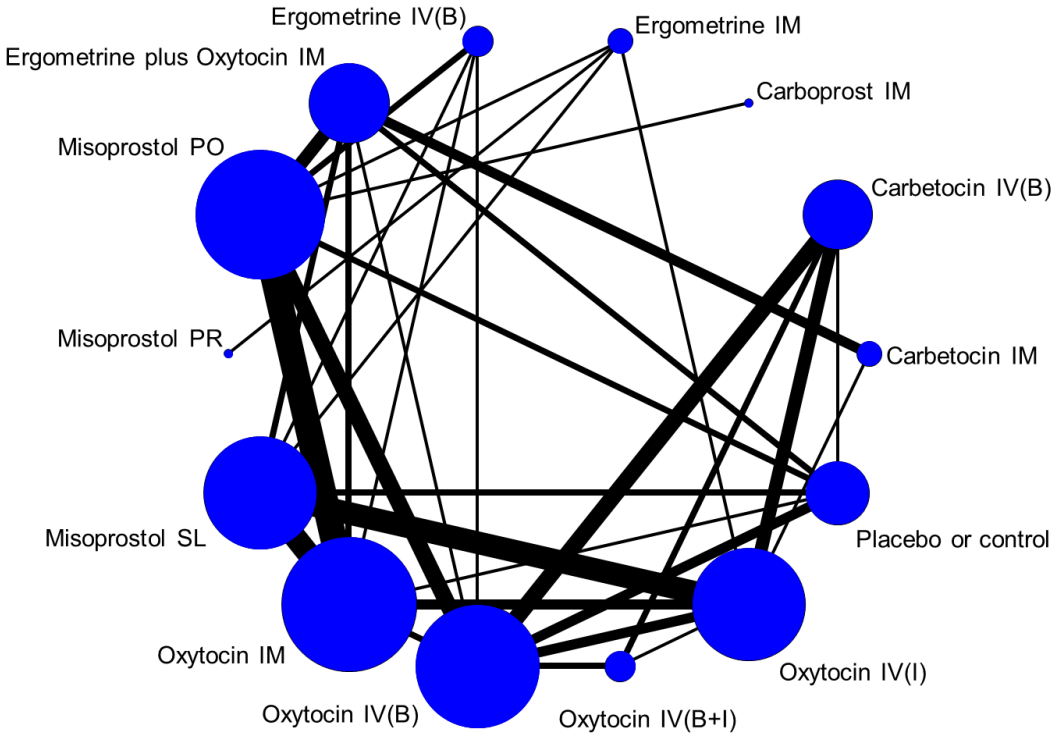


Figure 63: Hb change-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for Hb change.

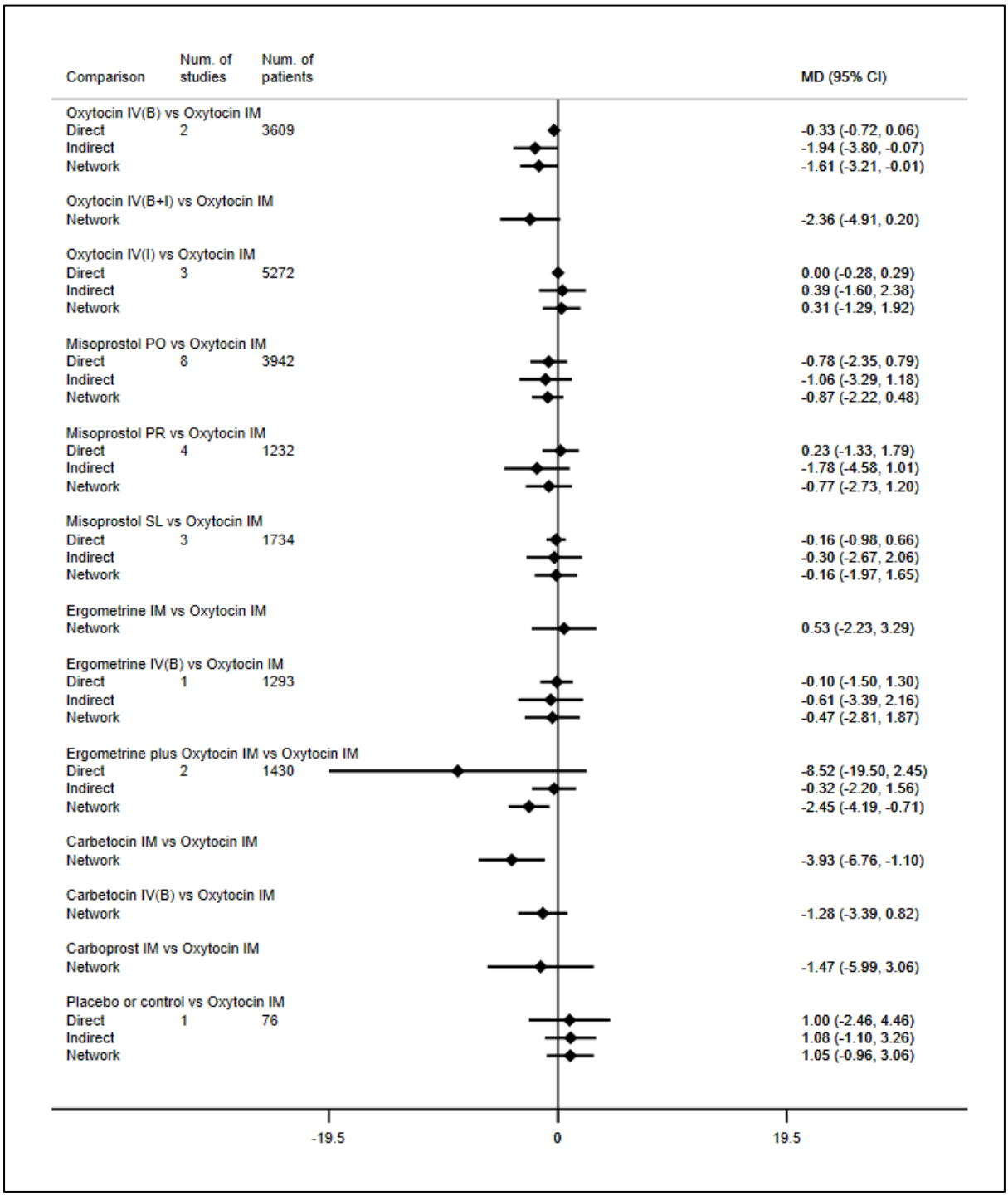


Figure 64: Hb change-Rankogram-Routes NMA

Cumulative rankogram for Hb change. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

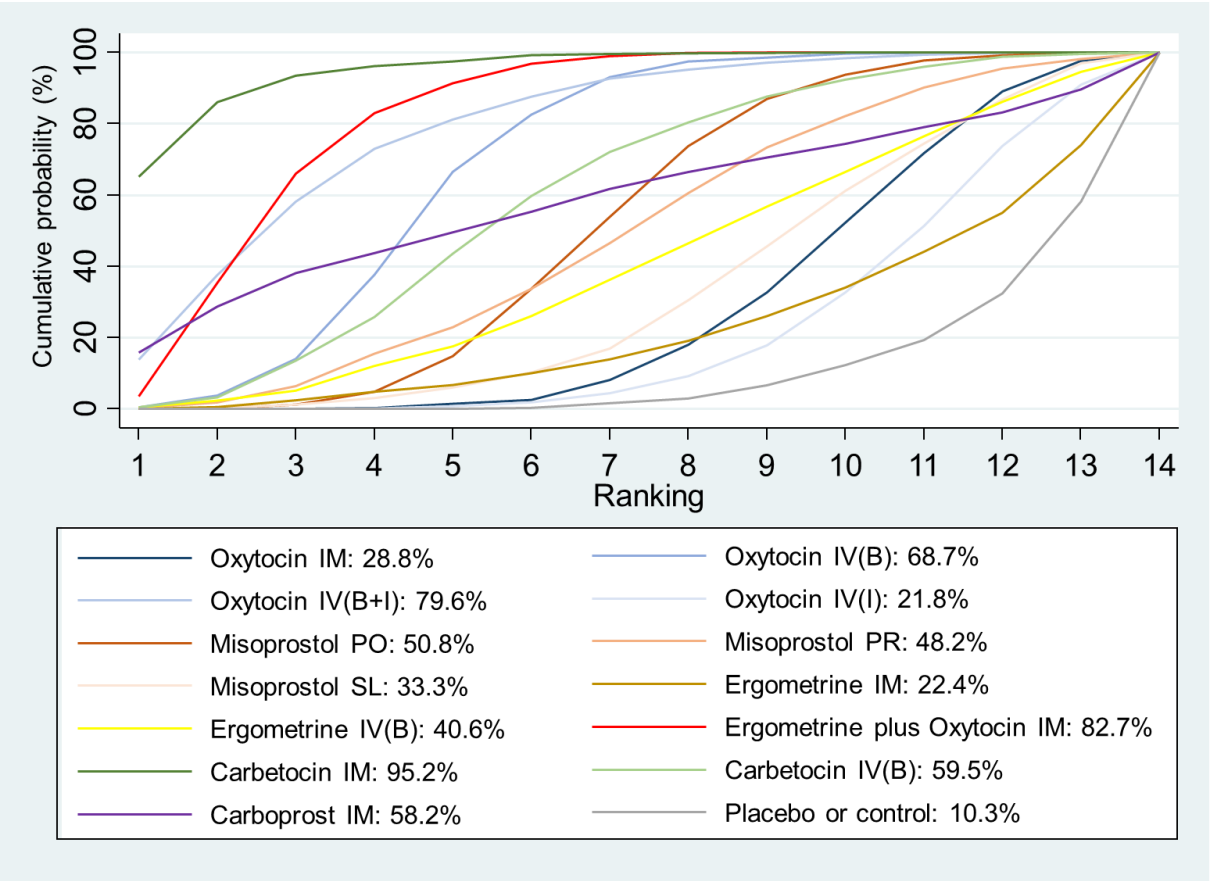


Figure 65: Breastfeeding-Network diagram-Routes NMA

Network diagram for breastfeeding. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

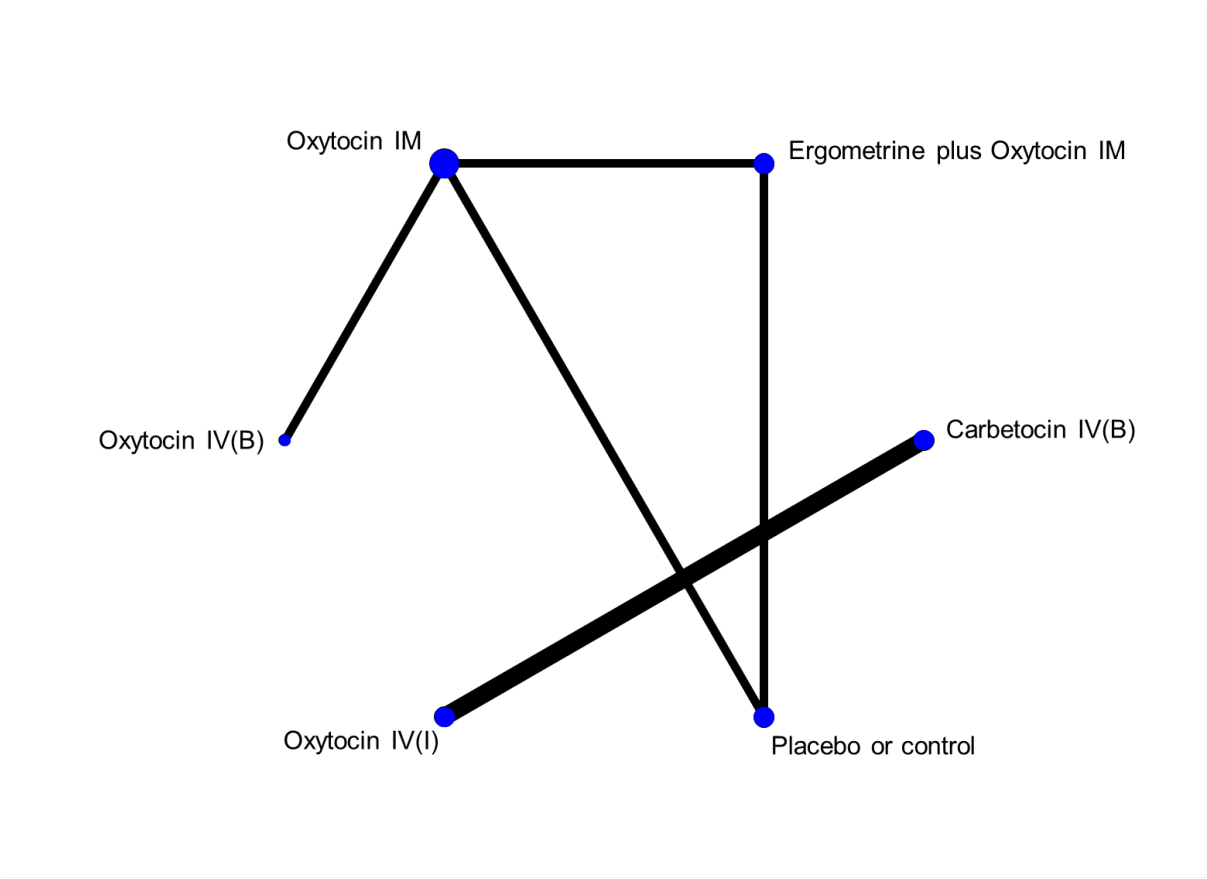


Figure 66: Breastfeeding-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise analyses for breastfeeding.

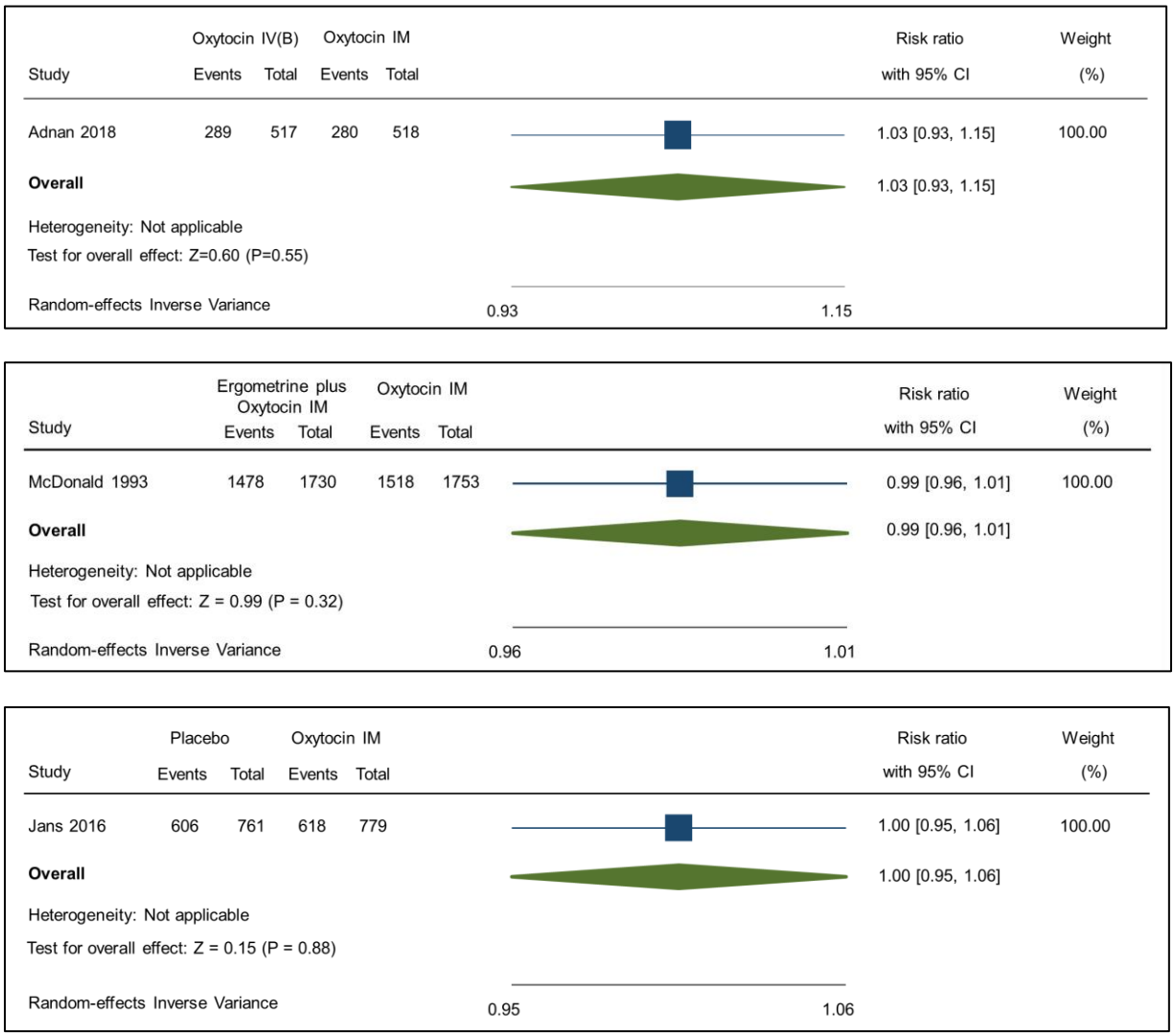


Figure 67: Abdominal pain-Network diagram-Routes NMA

Network diagram for abdominal pain. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

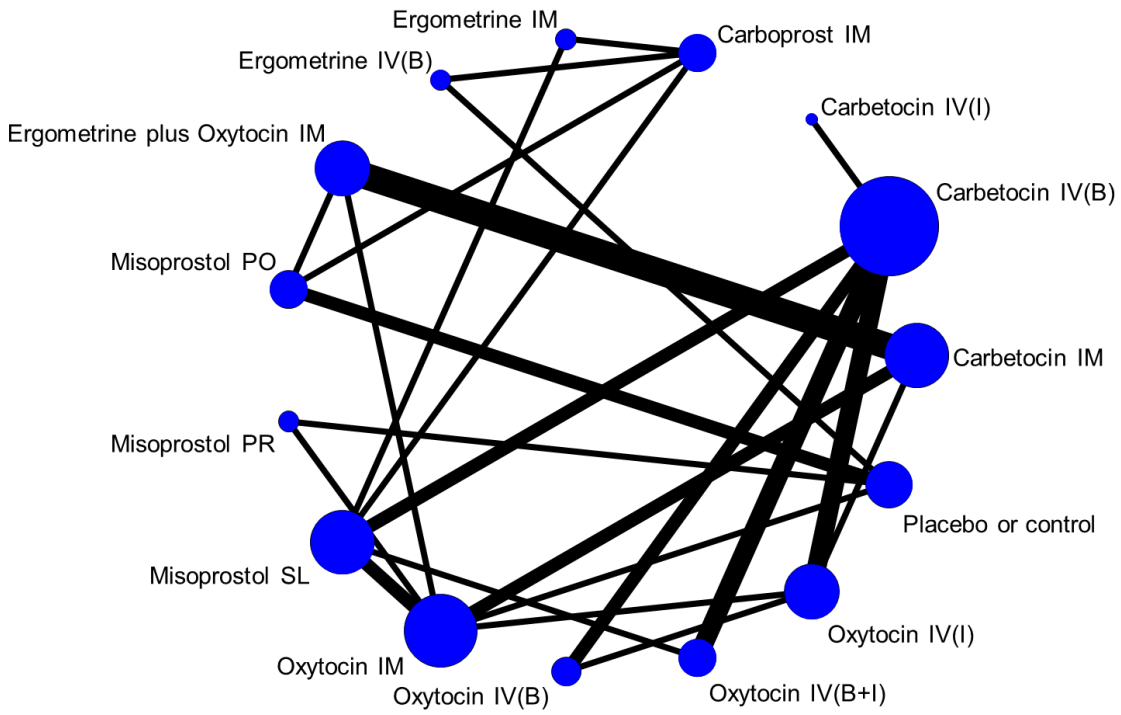


Figure 68: Abdominal pain-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for abdominal pain.

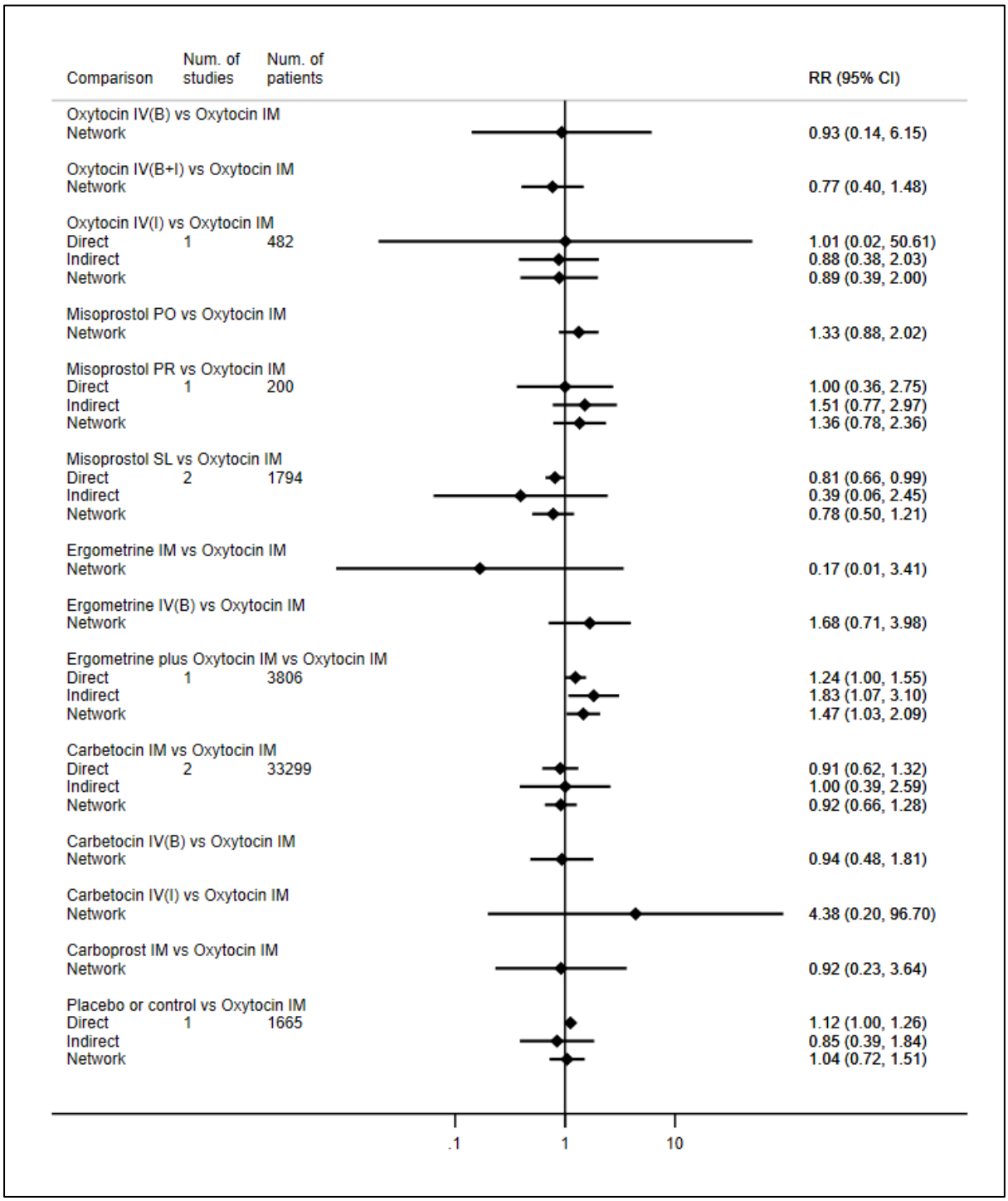


Figure 69: Abdominal pain-Rankogram-Routes NMA

Cumulative rankogram for abdominal pain. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

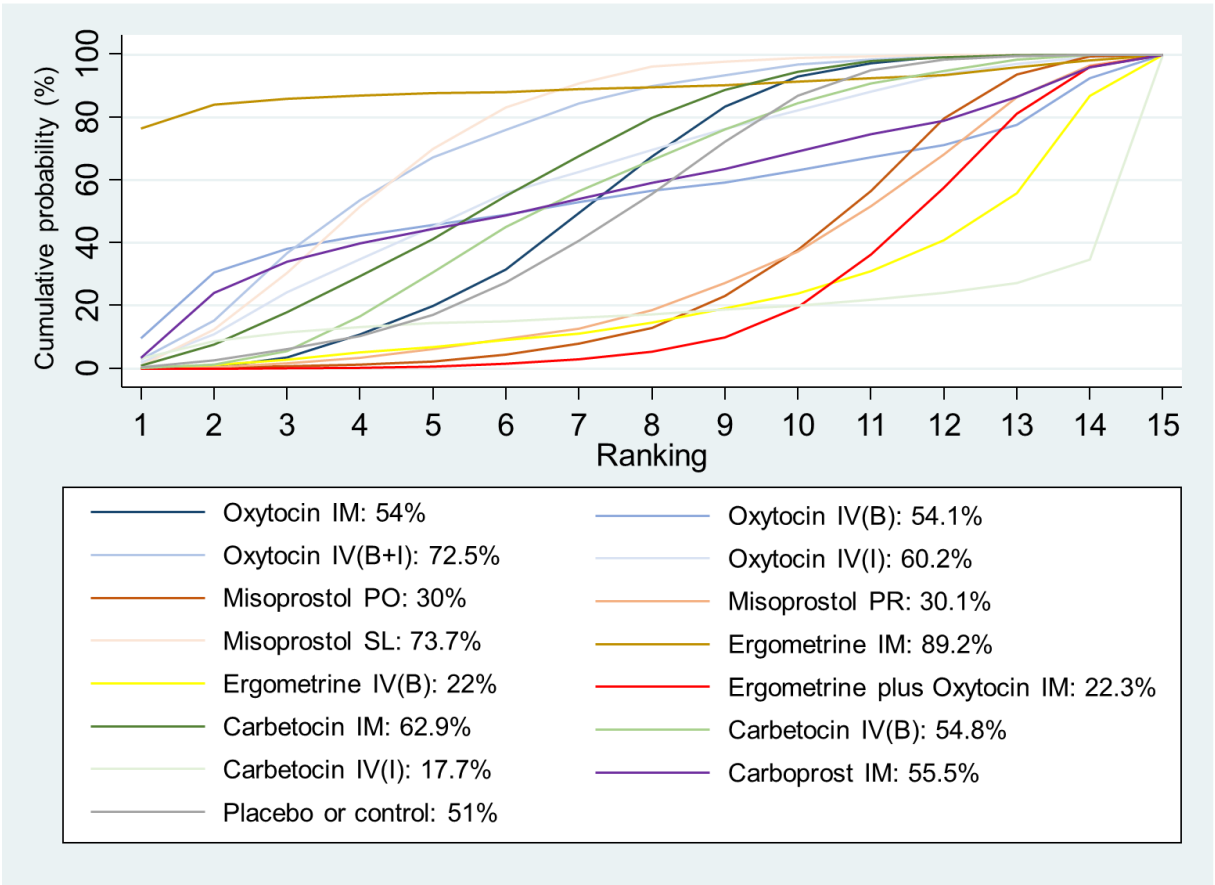


Figure 70: Diarrhoea-Network diagram-Routes NMA

Network diagram for diarrhoea. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

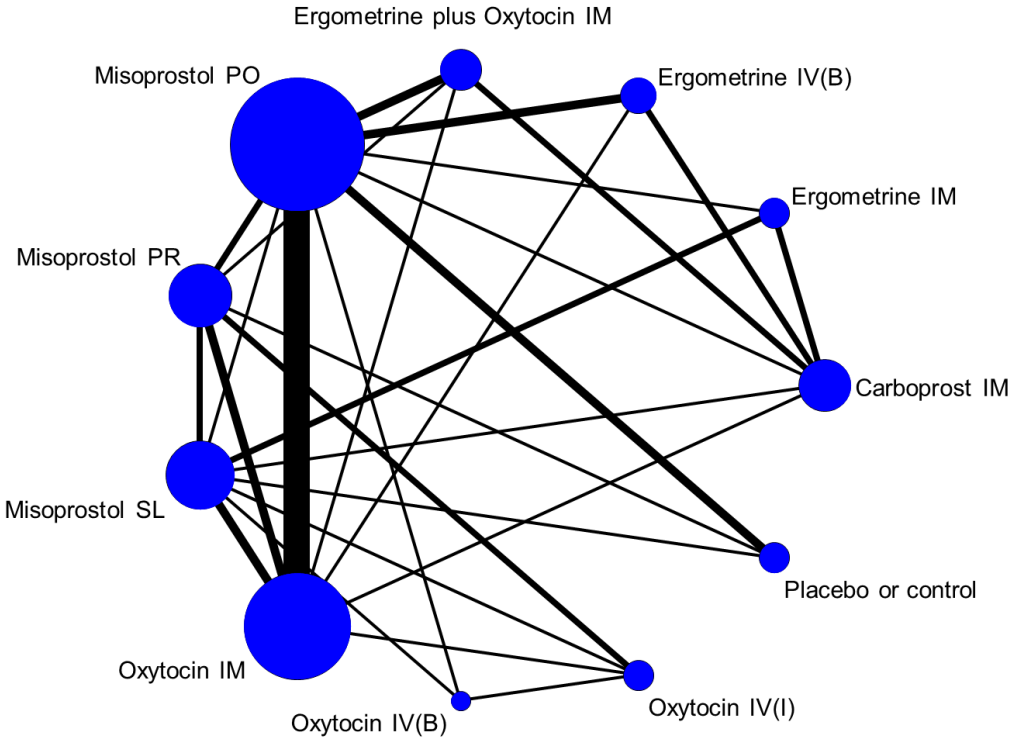


Figure 71: Diarrhoea-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for diarrhoea.

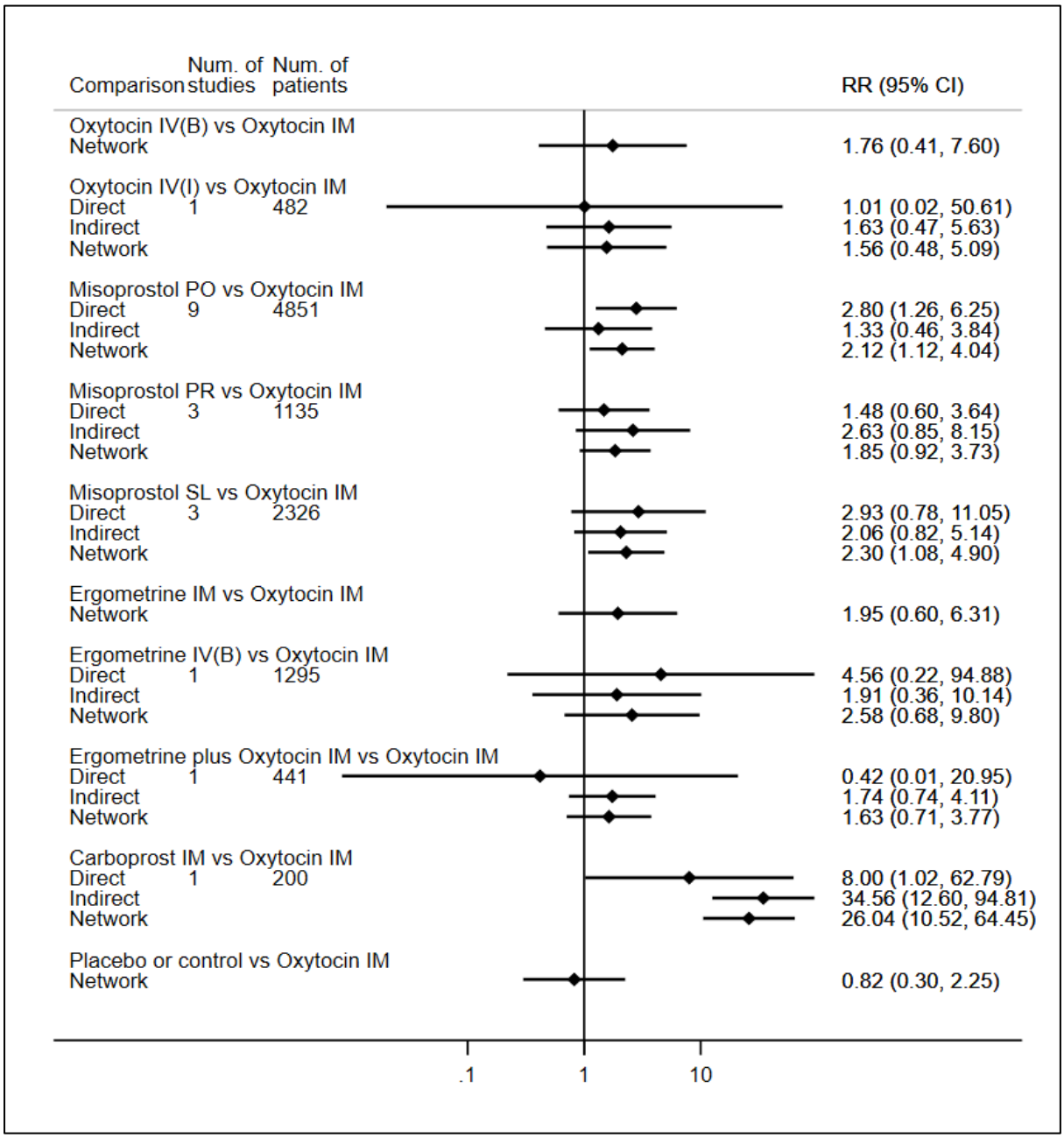


Figure 72: Diarrhoea-Rankogram-Routes NMA

Cumulative rankogram for diarrhoea. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

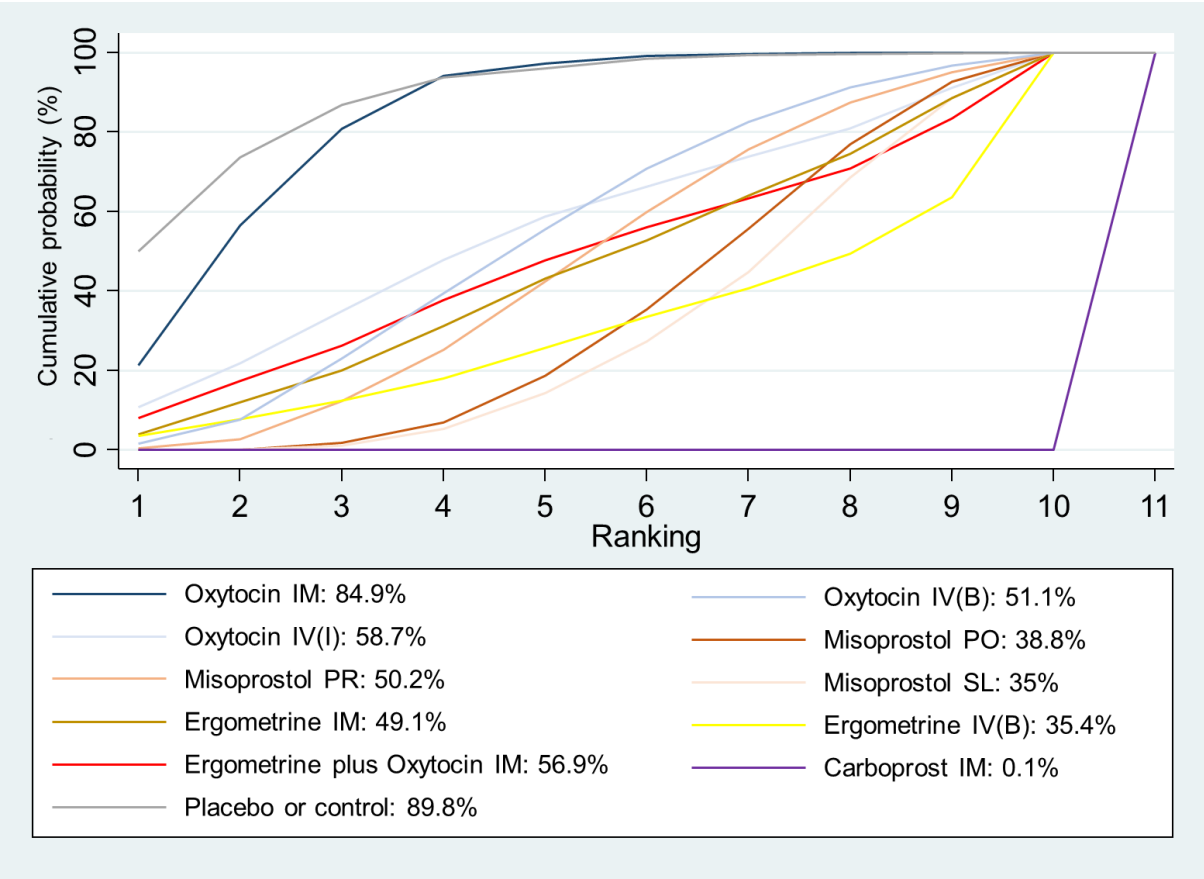


Figure 73: Headache-Network diagram-Routes NMA

Network diagram for headache. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

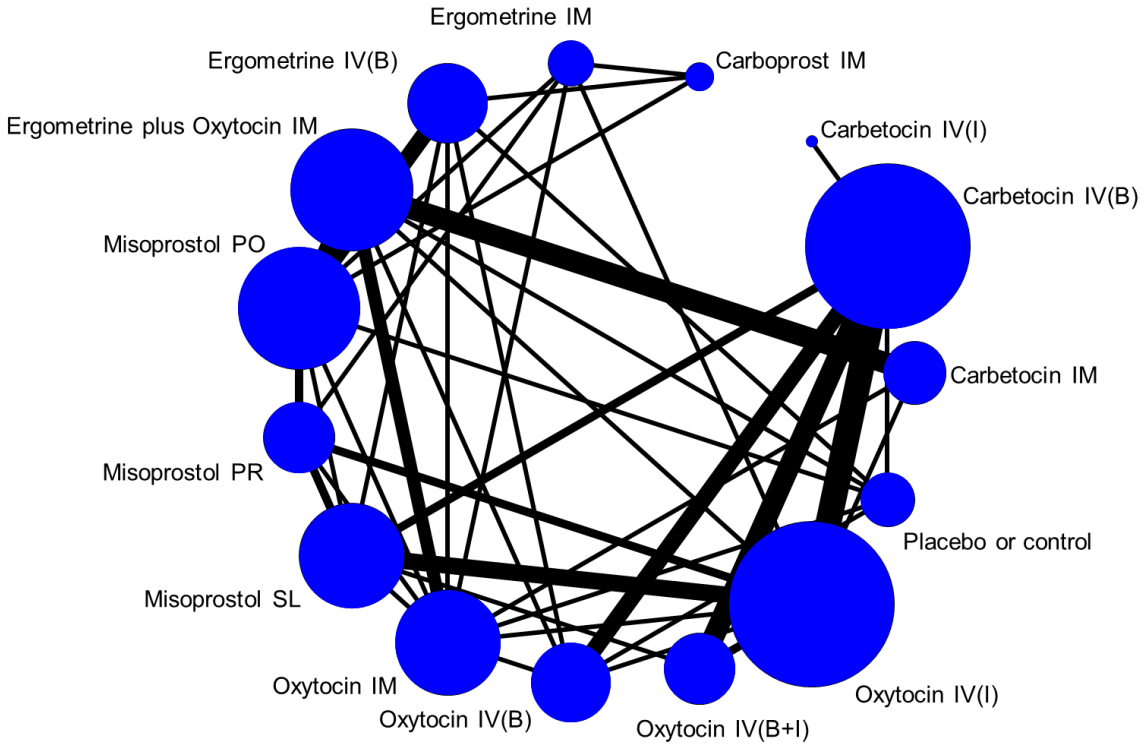


Figure 74: Headache-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for headache.

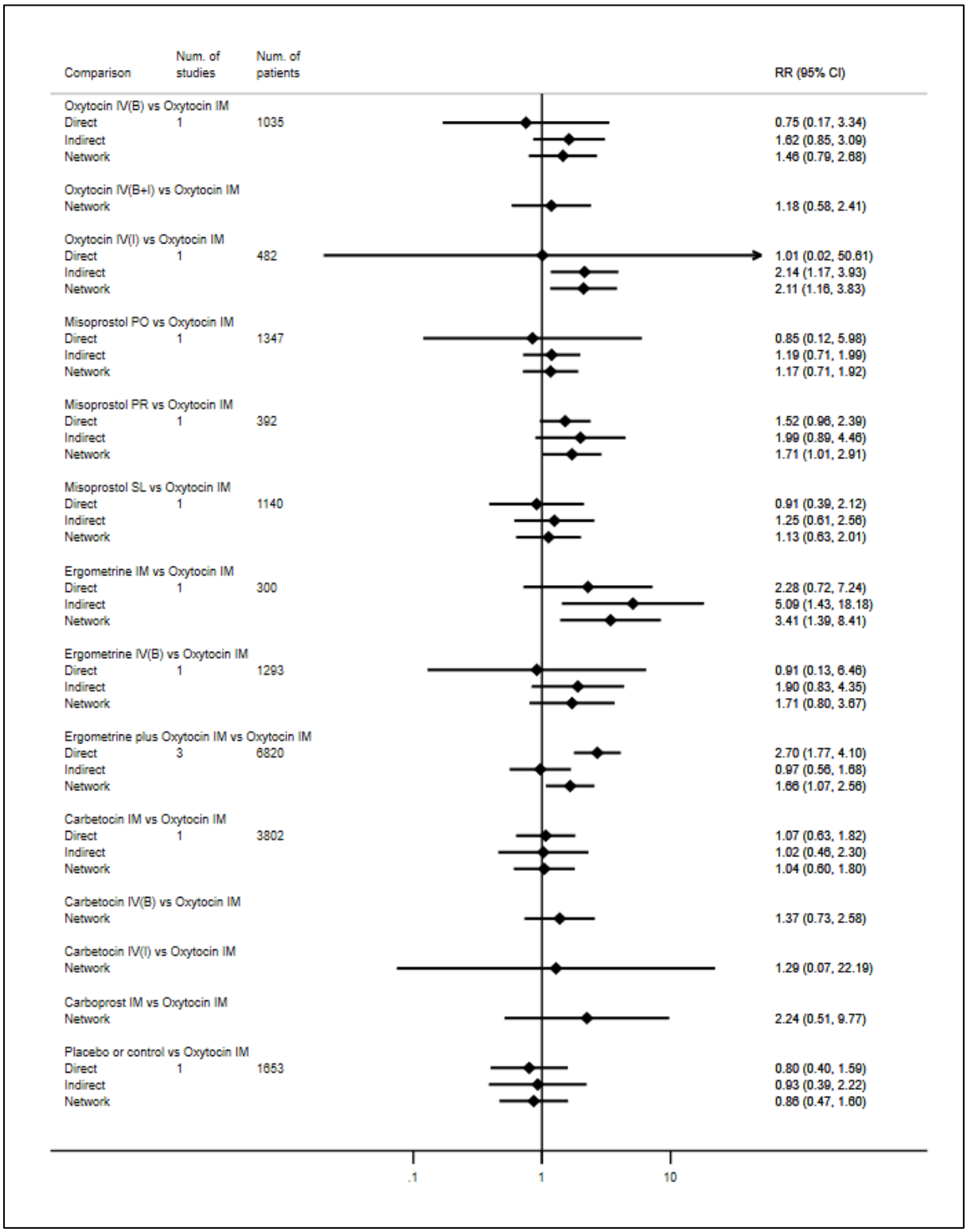


Figure 75: Headache-Rankogram-Routes NMA

Cumulative rankogram for headache. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

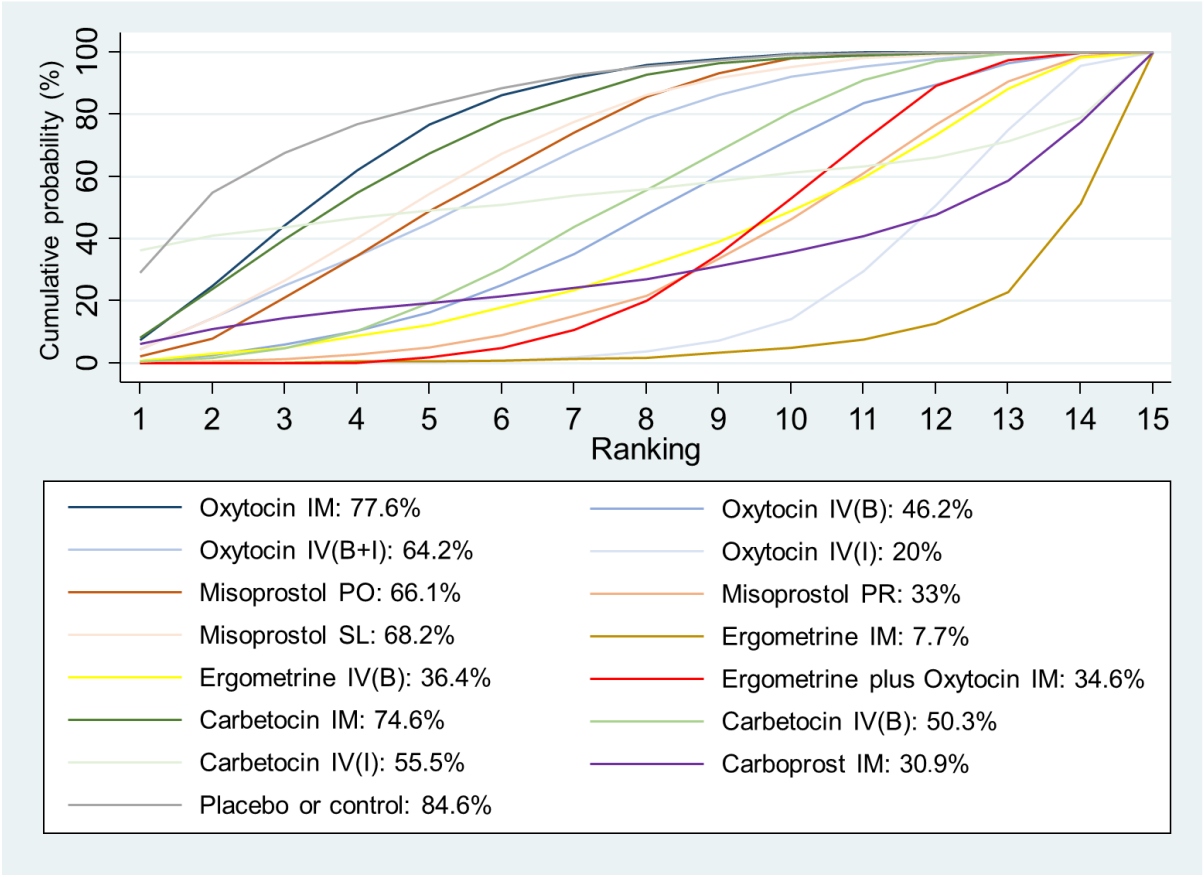


Figure 76: Nausea-Network diagram-Routes NMA

Network diagram for nausea. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

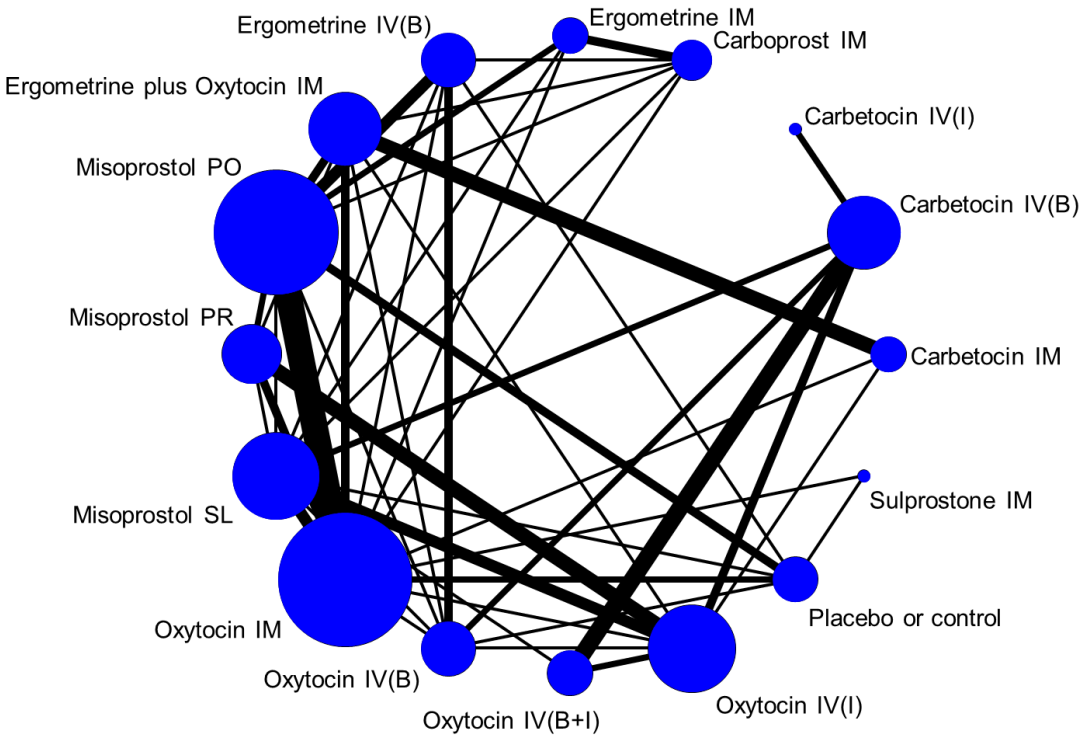


Figure 77: Nausea-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for nausea.

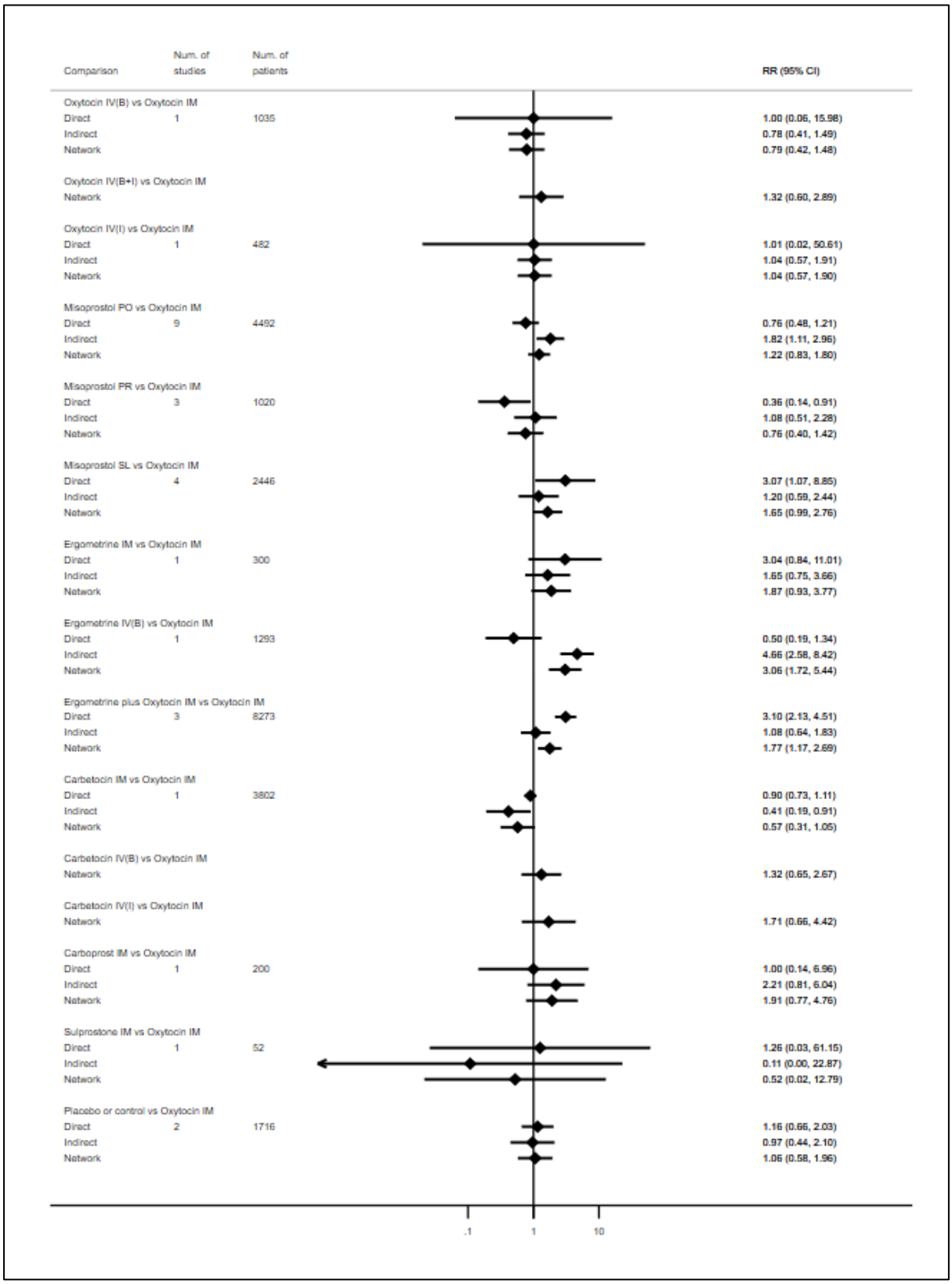


Figure 78: Nausea-Rankogram-Routes NMA

Cumulative rankogram for nausea. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

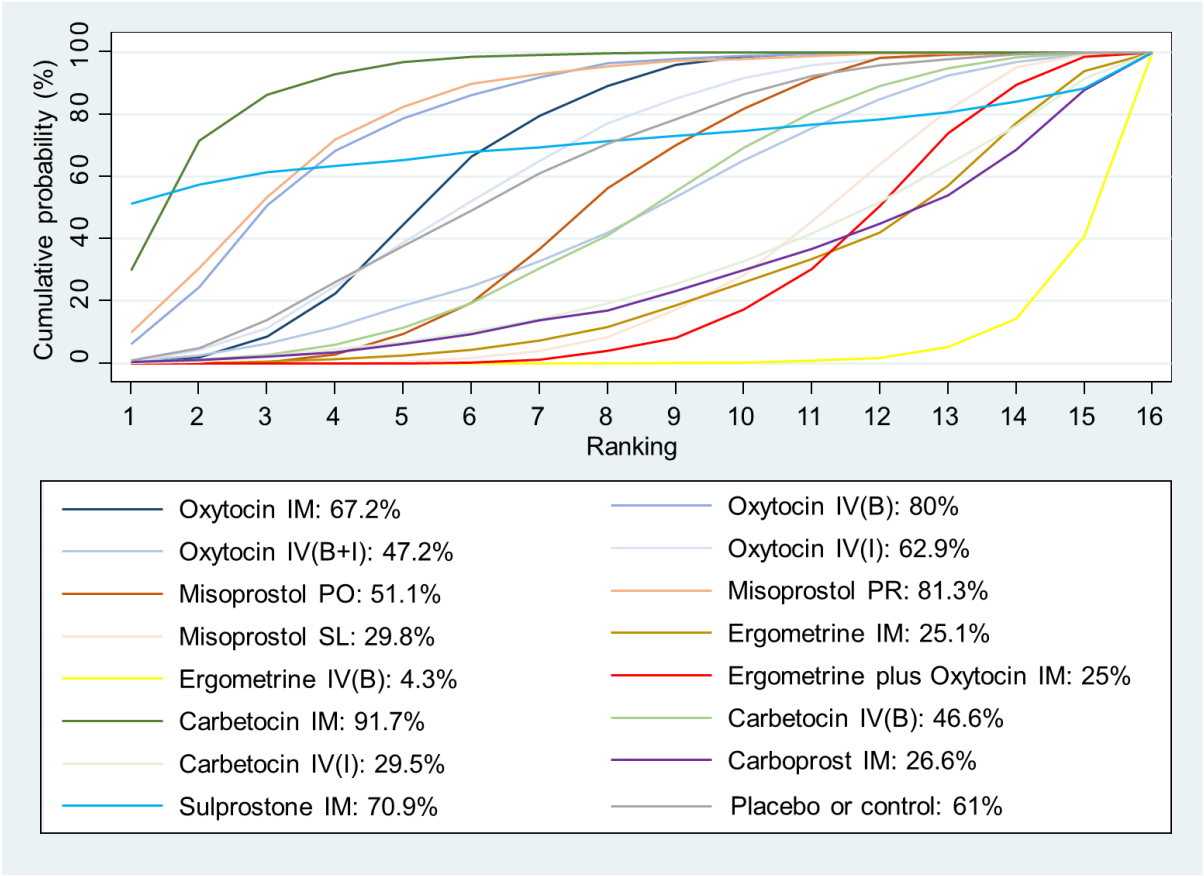


Figure 79: Shivering-Network diagram-Routes NMA

Network diagram for shivering. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

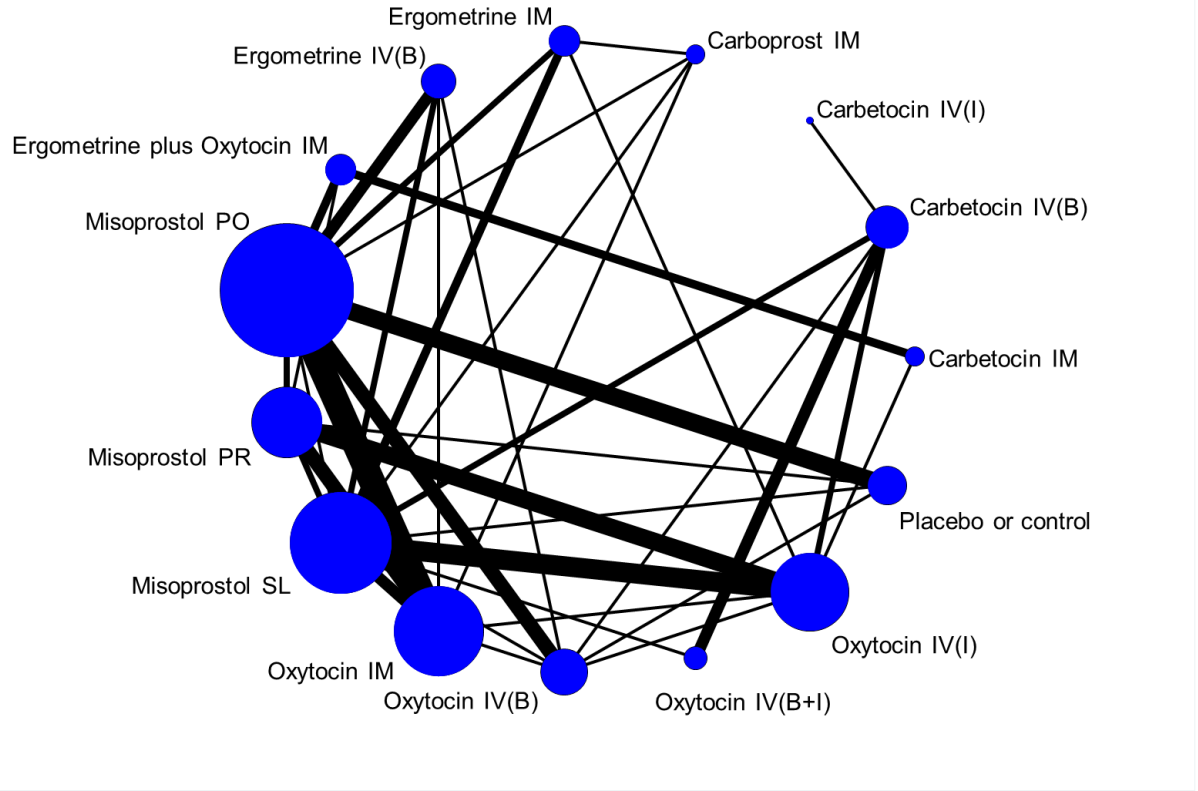


Figure 80: Shivering-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for shivering.

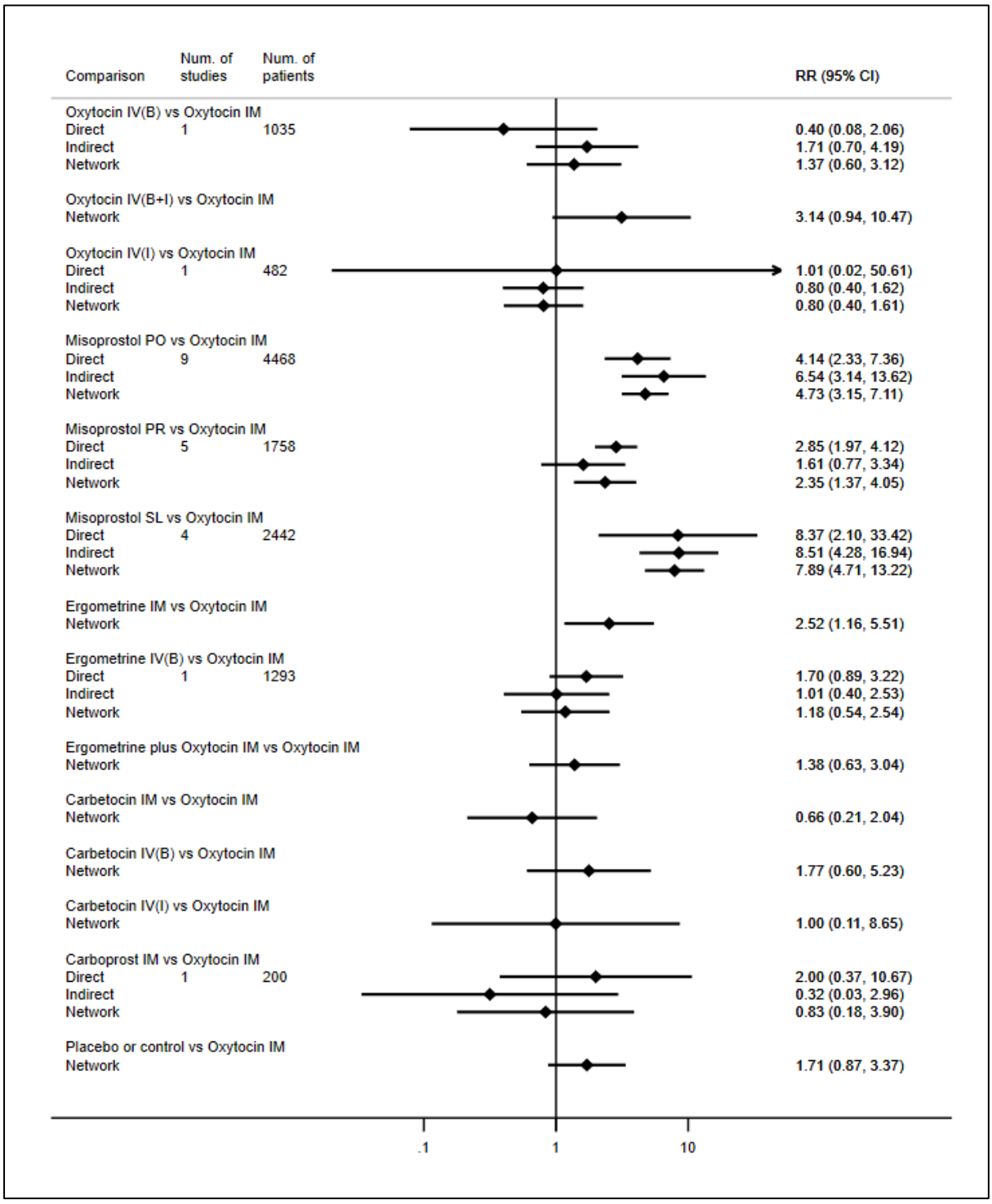
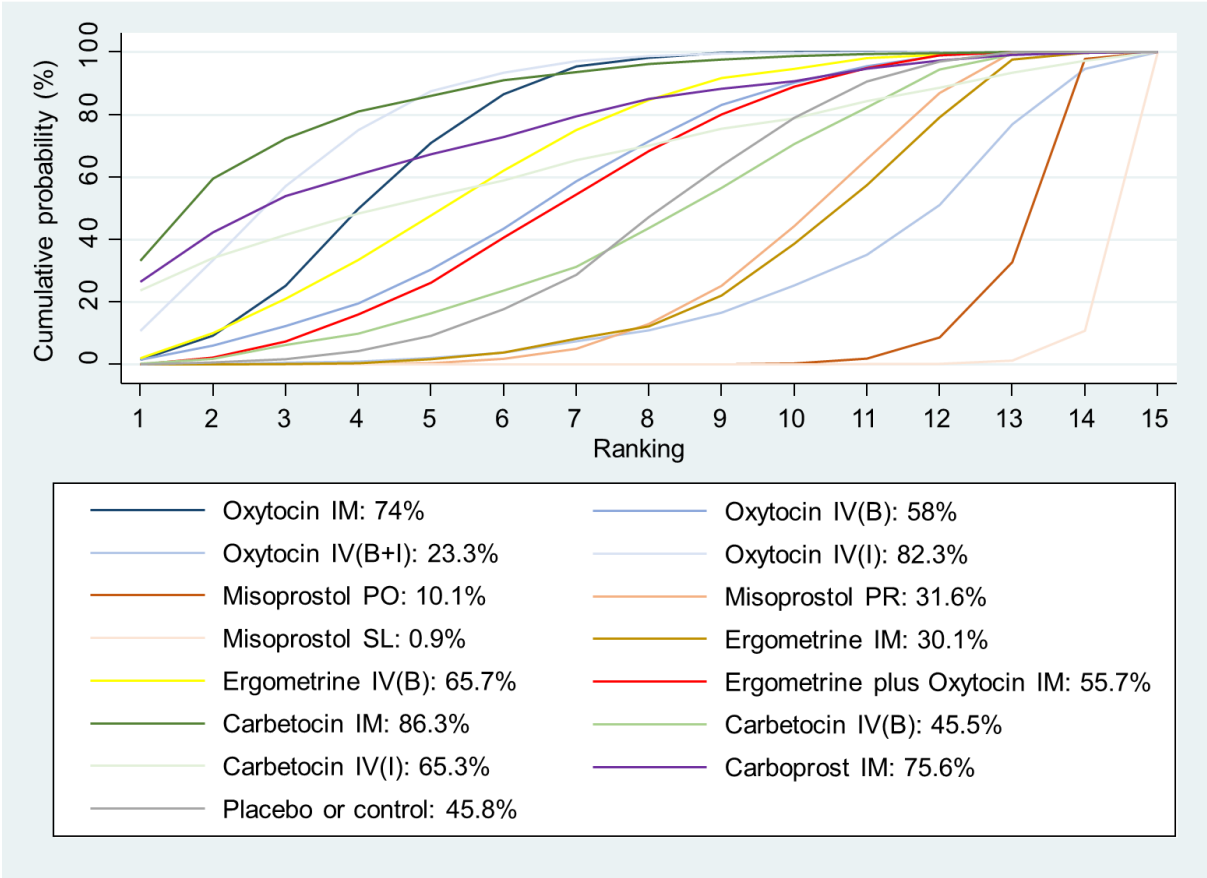


Figure 81: Shivering-Rankogram-Routes NMA

Cumulative rankogram for shivering. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Sensitivity analyses

Figure 82: PPH ≥500 mL restricted to studies at low Risk of Bias-Network diagram-Routes NMA

Network diagram for PPH ≥500 mL restricted to studies at low Risk of Bias. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

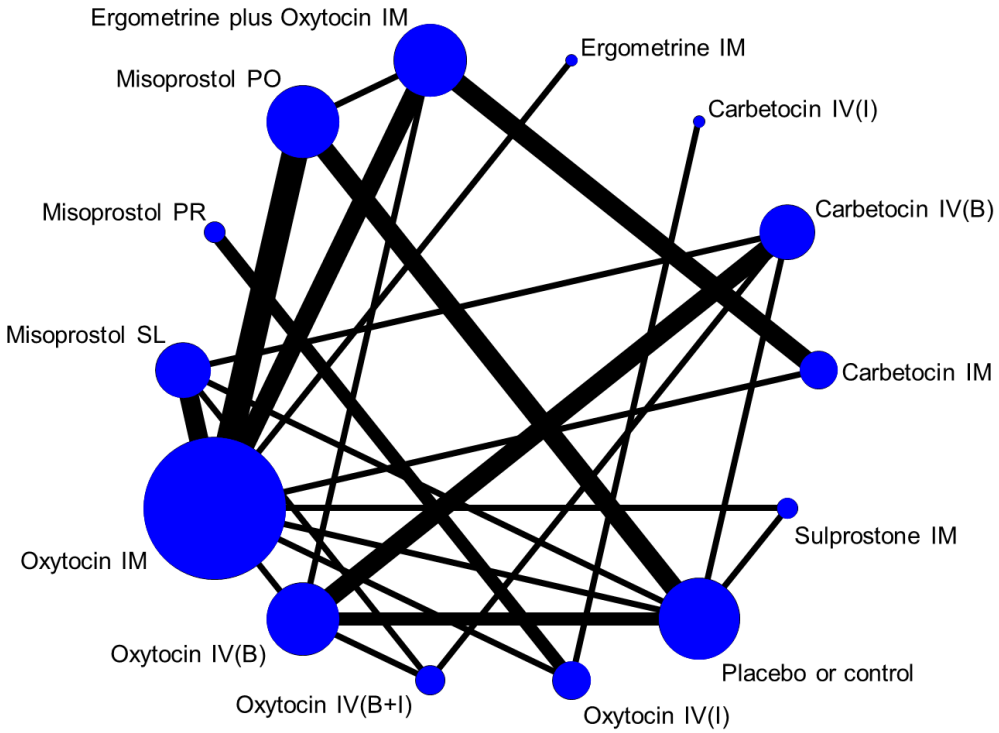


Figure 83: PPH ≥500 mL restricted to studies at low Risk of Bias-Forest plot-Routes NMA

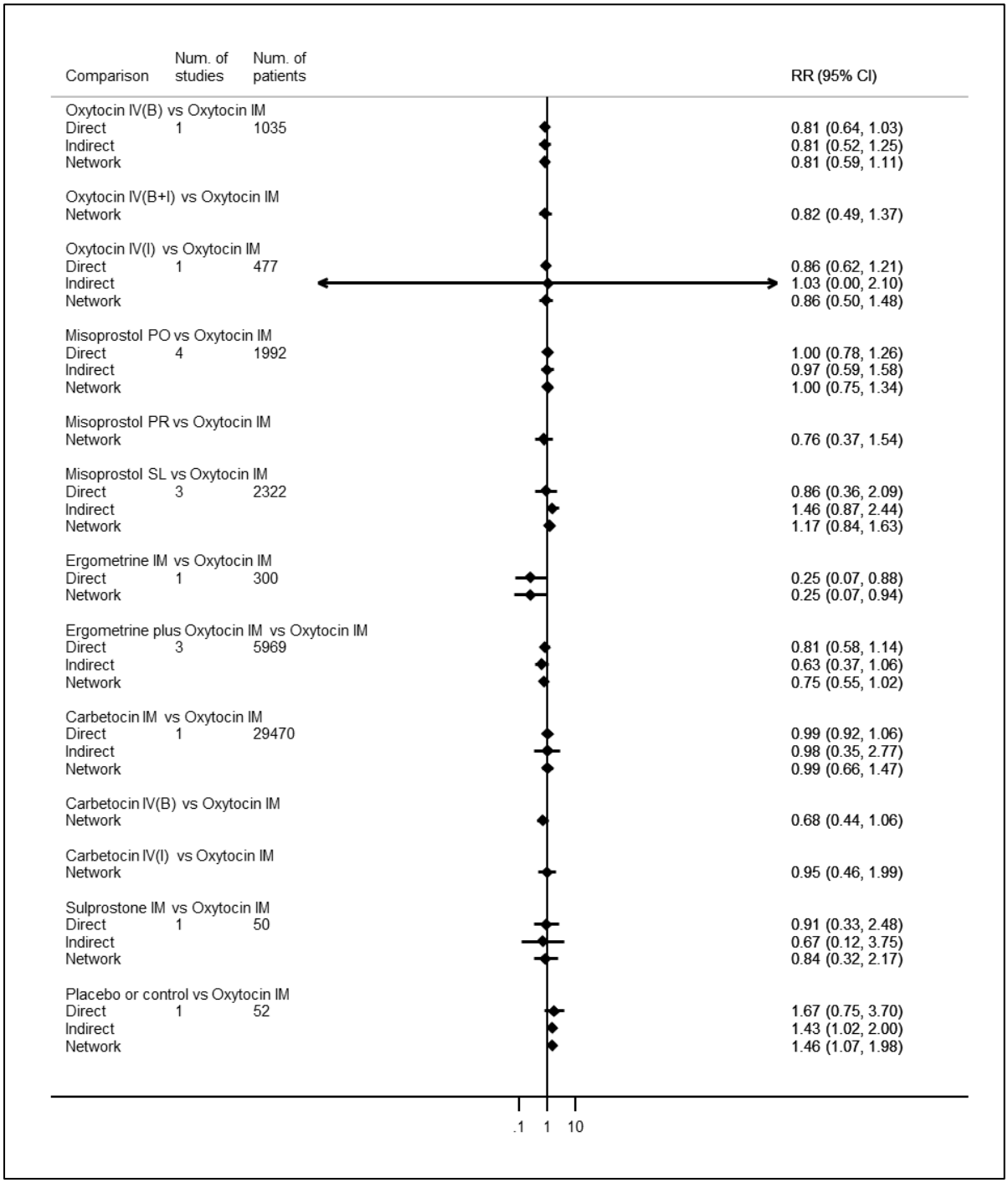


Figure 84: PPH ≥500 mL restricted to studies at low Risk of Bias-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies at low Risk of Bias. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

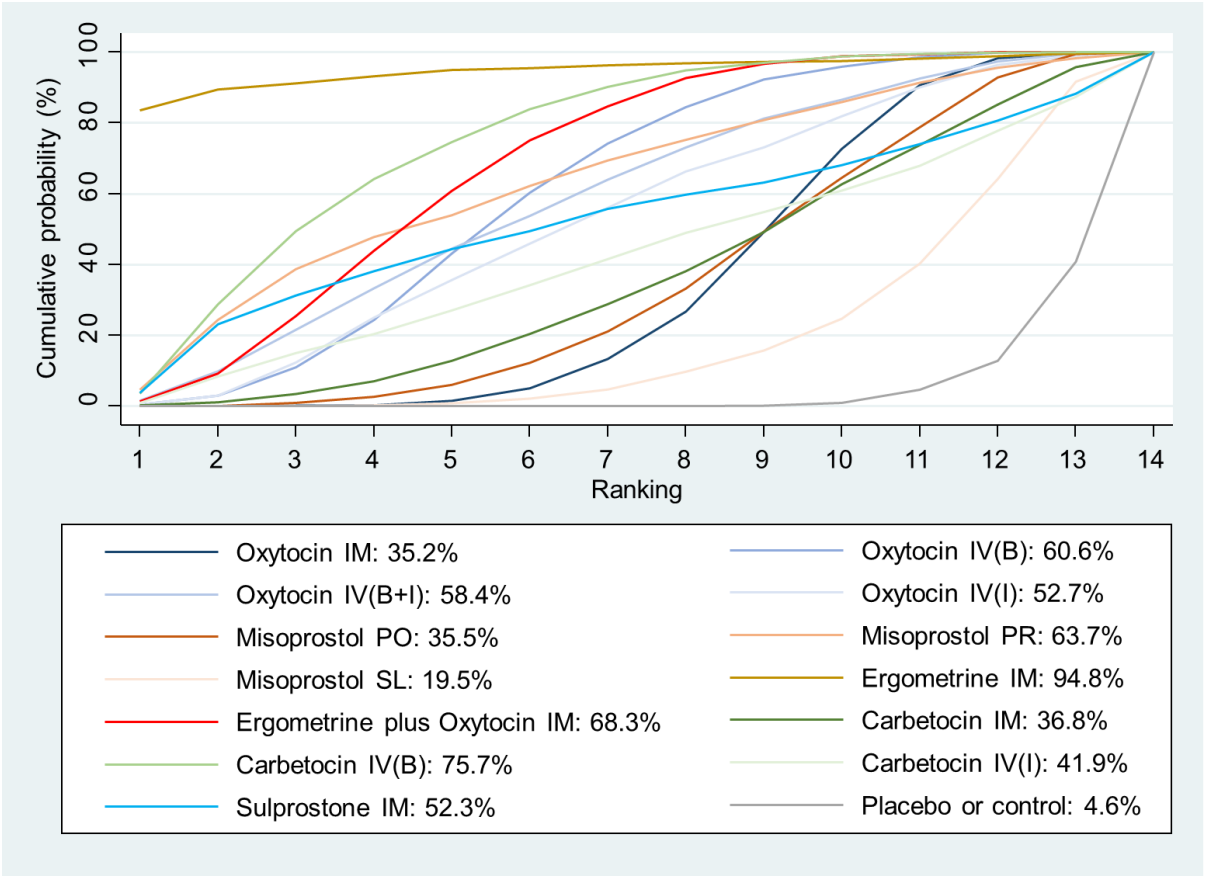


Figure 85: PPH ≥500 mL restricted to studies with public or no funding-Network diagram-Routes NMA

Network diagram for PPH ≥500 mL restricted to studies with public or no funding. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

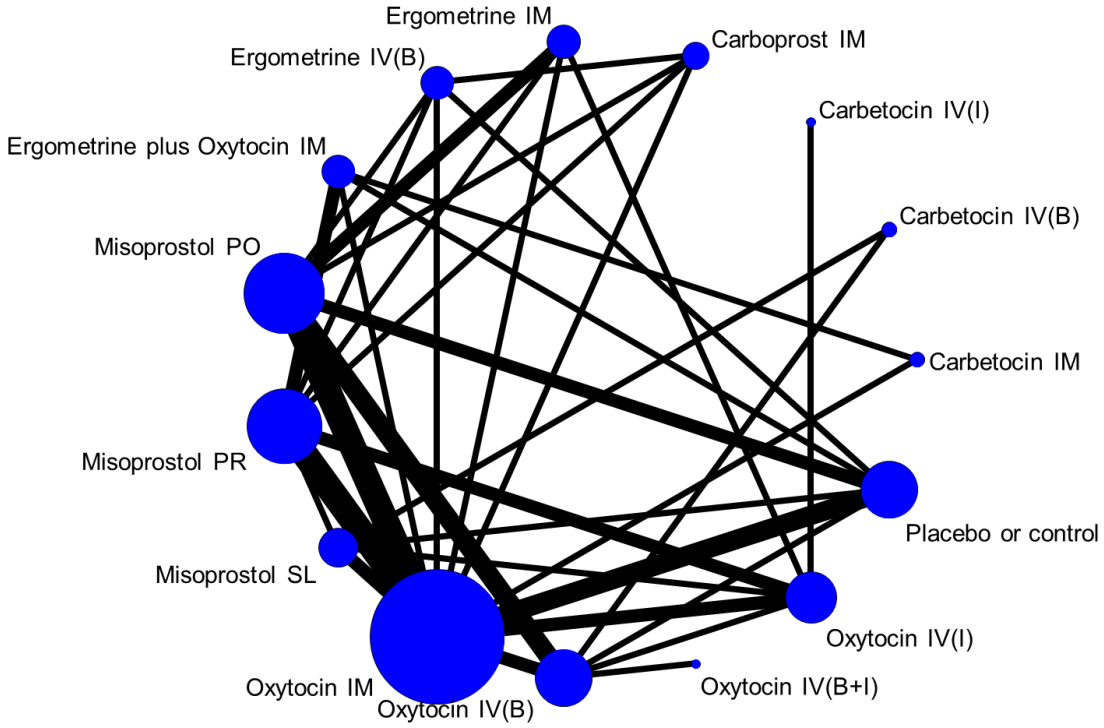


Figure 86: PPH ≥500 mL restricted to studies with public or no funding-Forest plot-Routes NMA

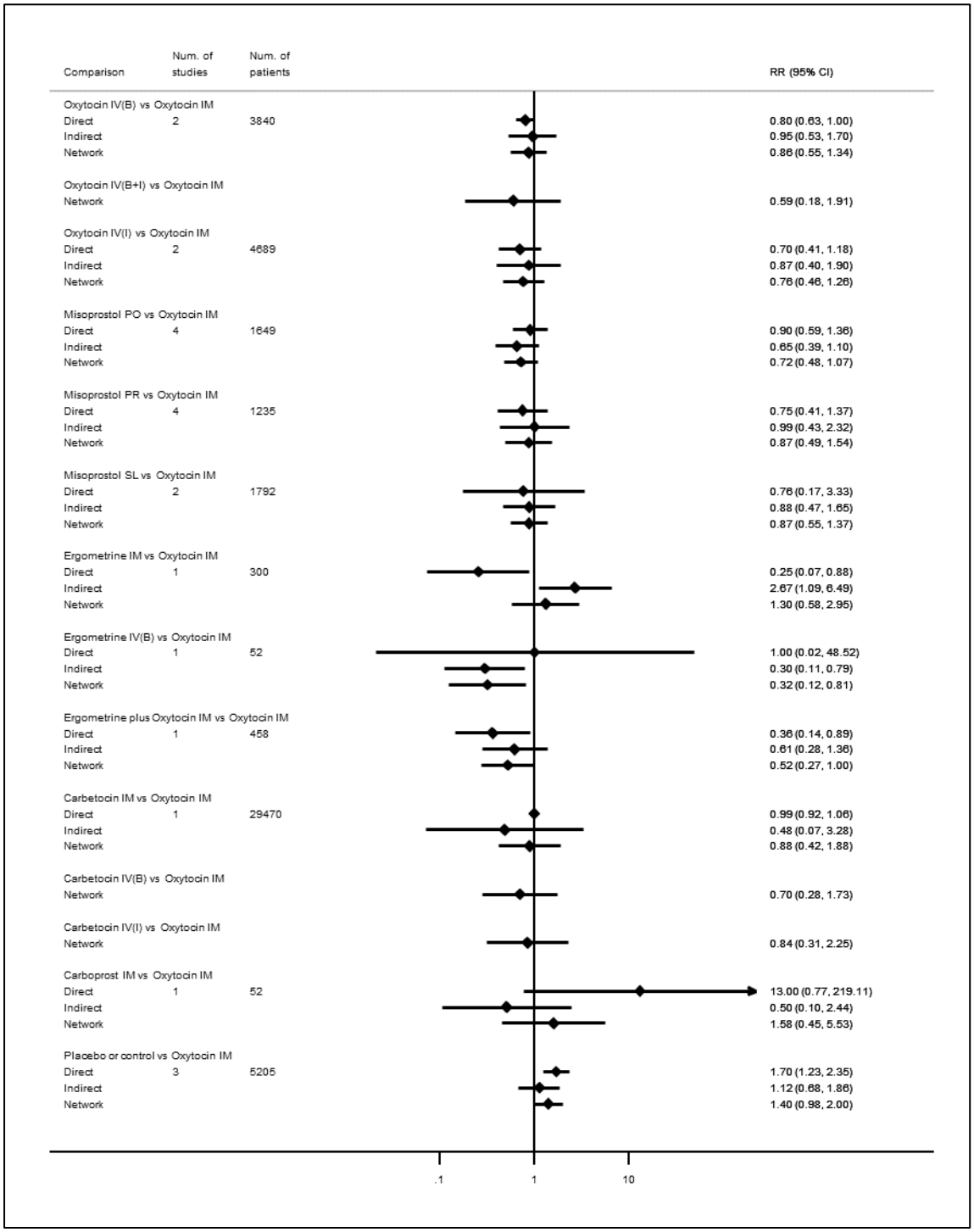


Figure 87: PPH ≥500 mL restricted to studies with public or no funding-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with public or no funding. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

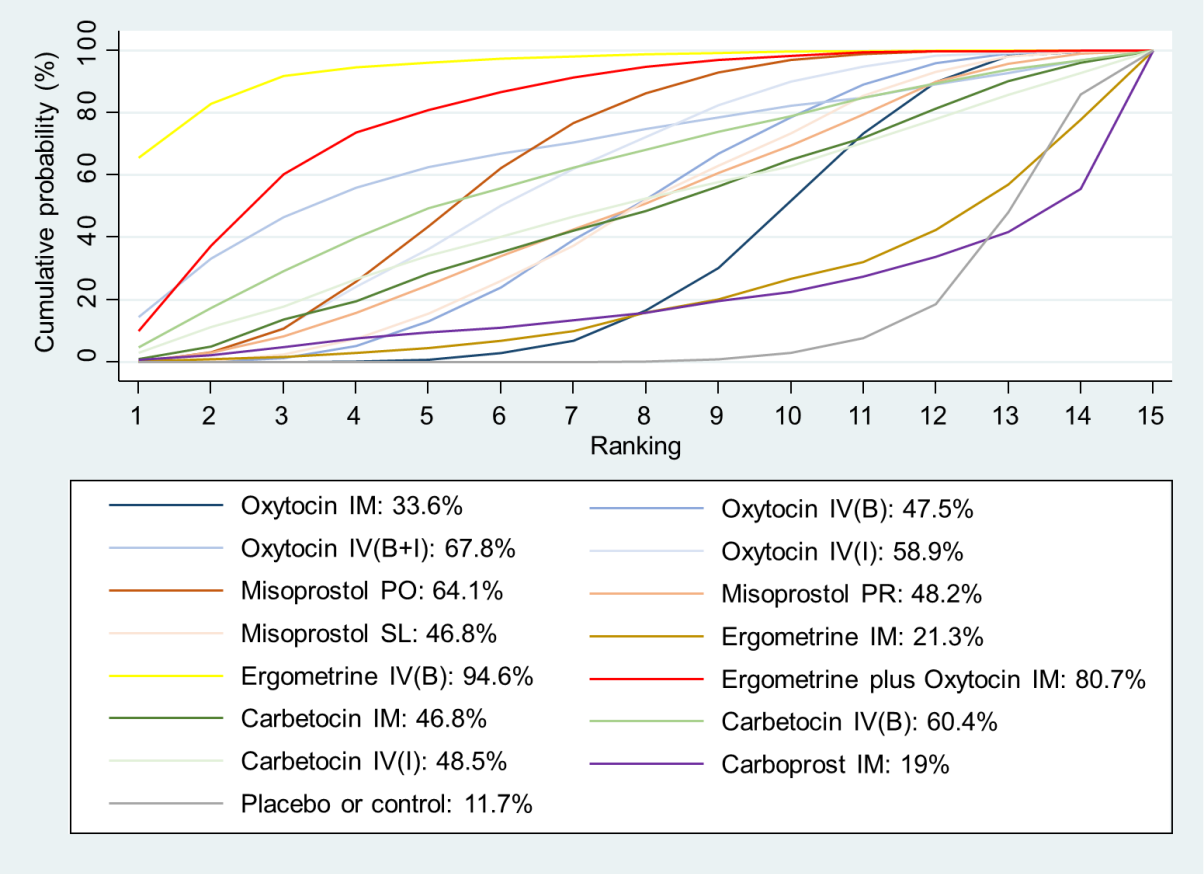


Figure 88: PPH ≥500 mL restricted to studies with objective methods of measuring blood loss-Network diagram-Routes NMA

Network diagram for PPH ≥500 mL restricted to studies with objective methods of measuring blood loss. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

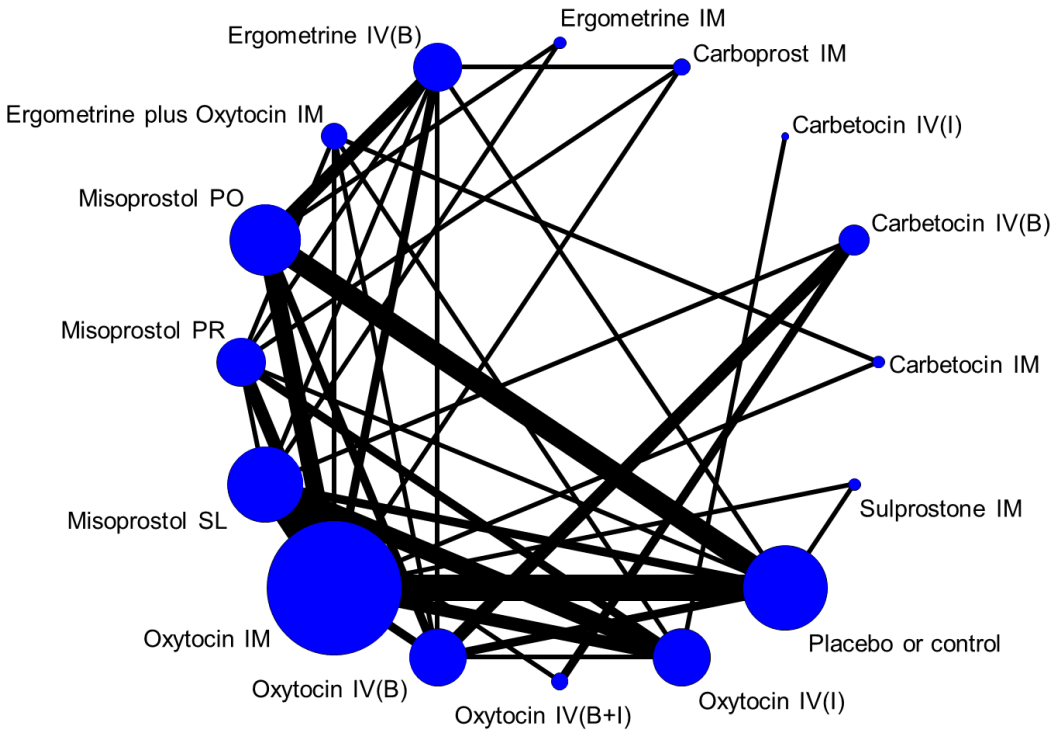


Figure 89: PPH ≥500 mL restricted to studies with objective methods of measuring blood loss-Forest plot-Routes NMA

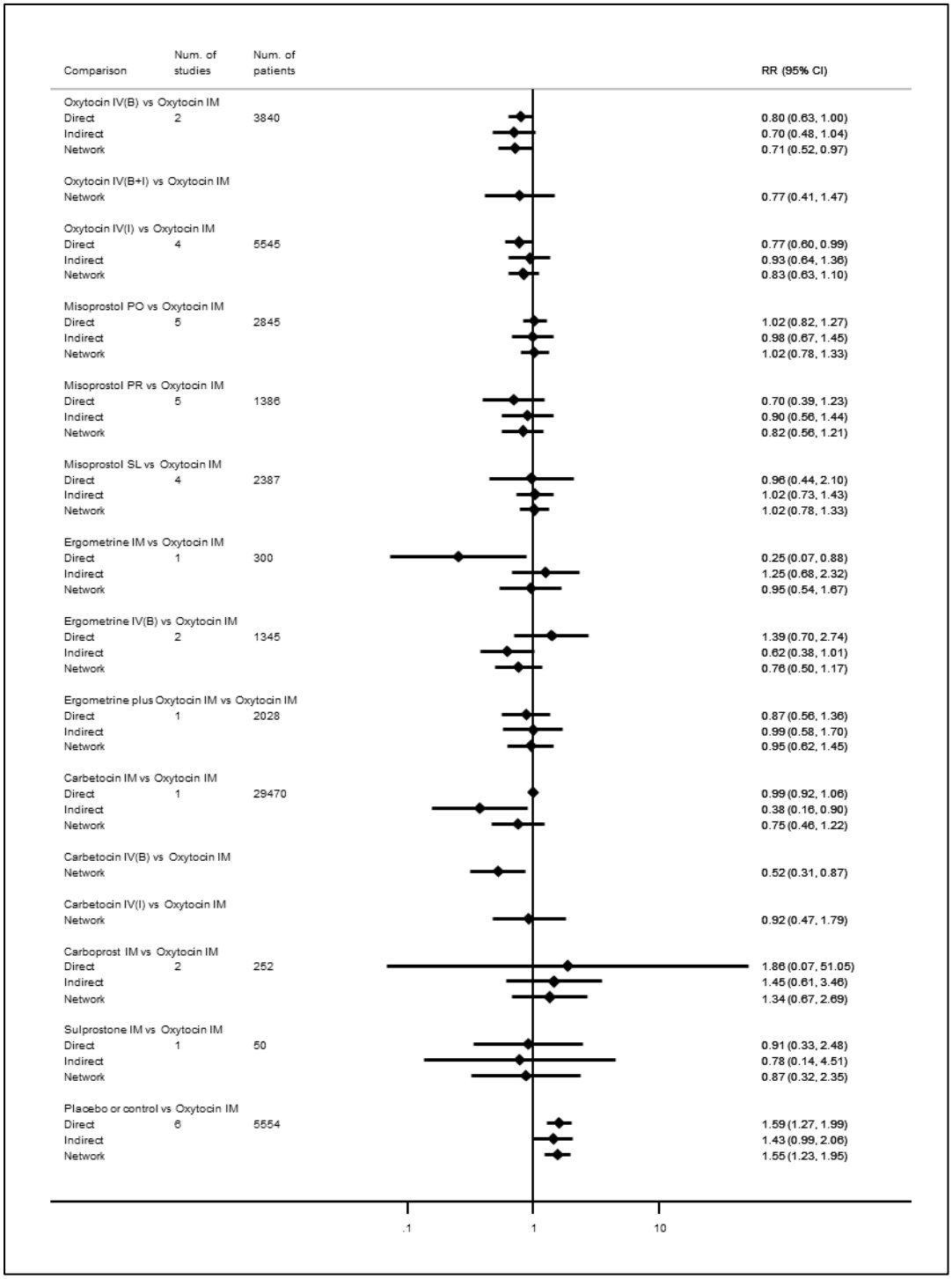


Figure 90: PPH ≥500 mL restricted to studies with objective methods of measuring blood loss-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with objective methods of measuring blood loss. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

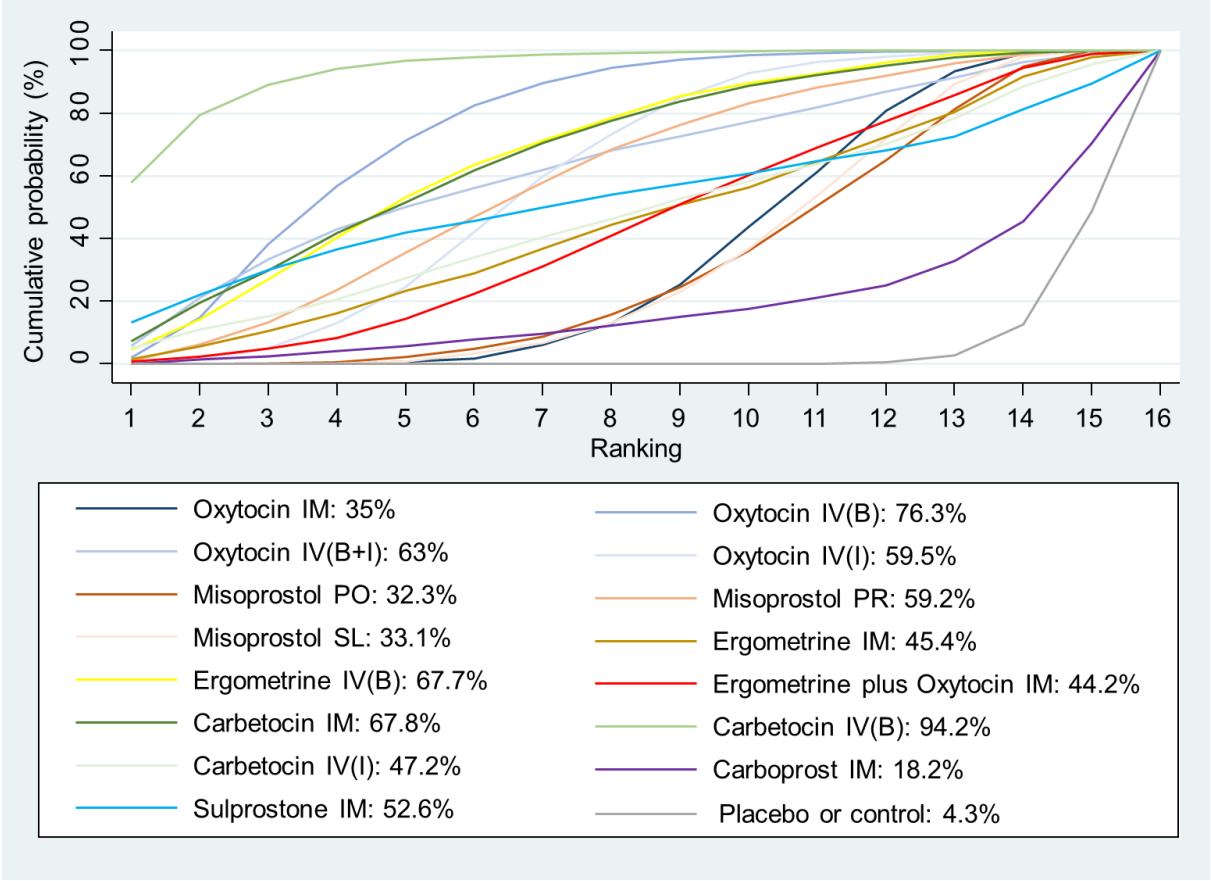


Figure 91: PPH ≥500 mL restricted to studies with <10% attrition-Network diagram-Routes NMA

Network diagram for PPH ≥500 mL restricted to studies with <10% attrition. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

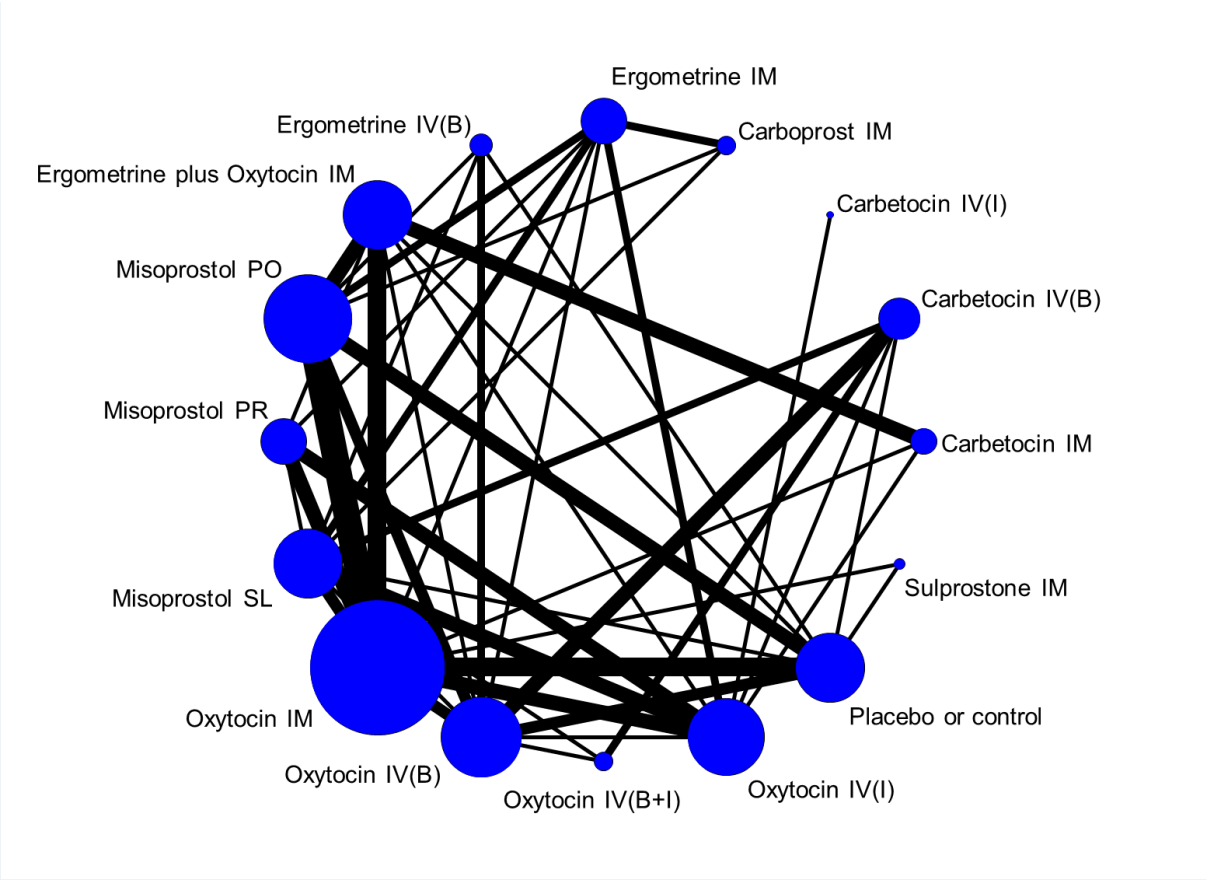


Figure 92: PPH ≥500 mL restricted to studies with <10% attrition-Forest plot-Routes NMA

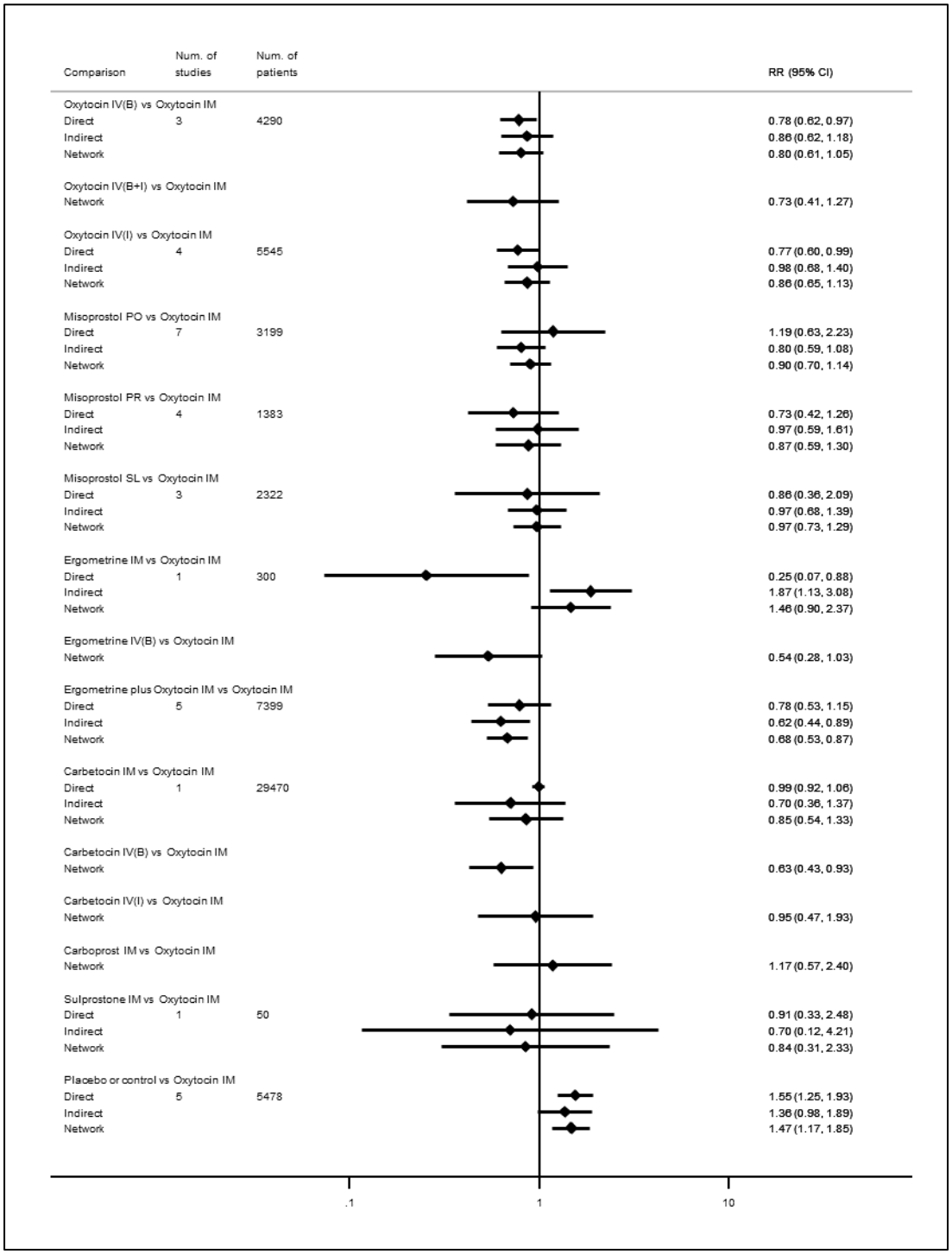


Figure 93: PPH ≥500 mL restricted to studies with <10% attrition-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with <10% attrition. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

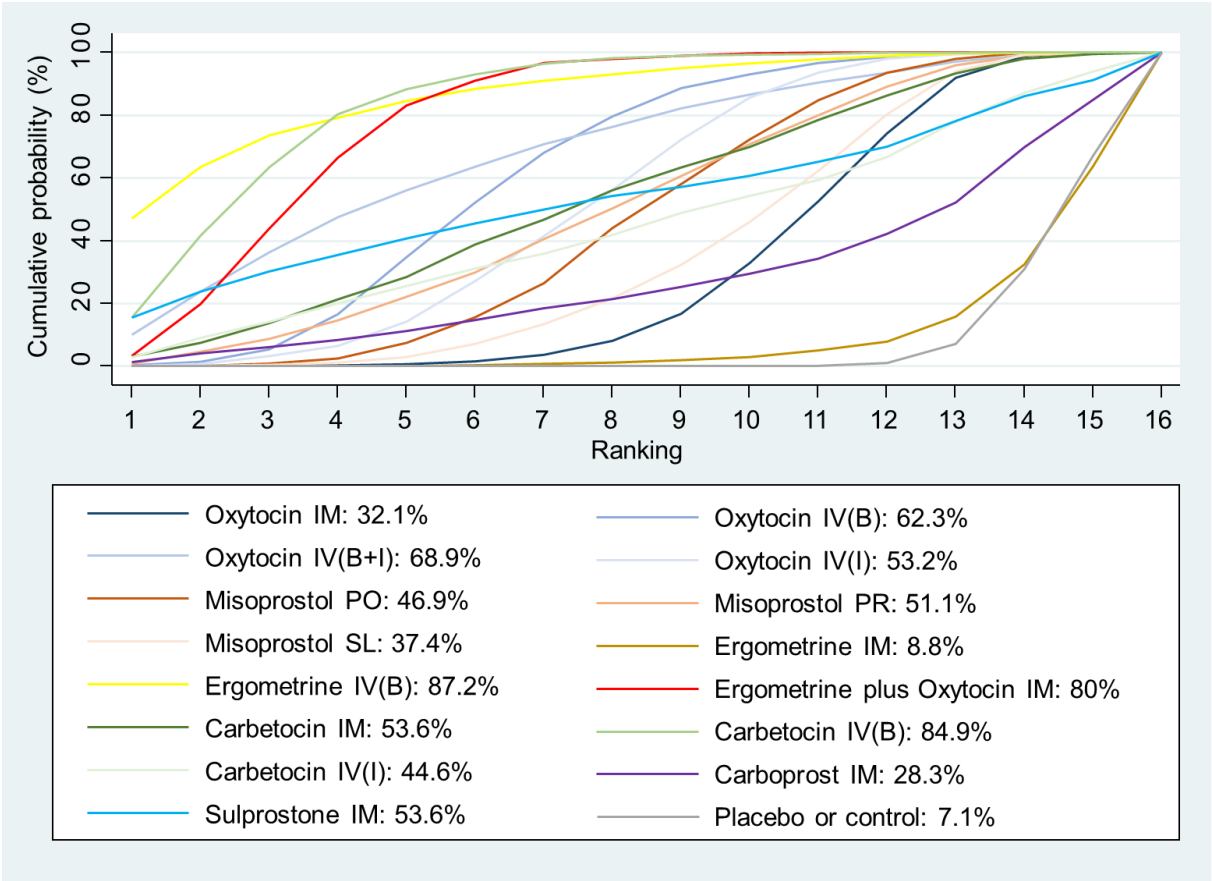


Figure 94: PPH ≥500 mL restricted to studies with at least 400 participants-Network diagram-Routes NMA

Network diagram for PPH ≥500 mL restricted to studies with at least 400 participants. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

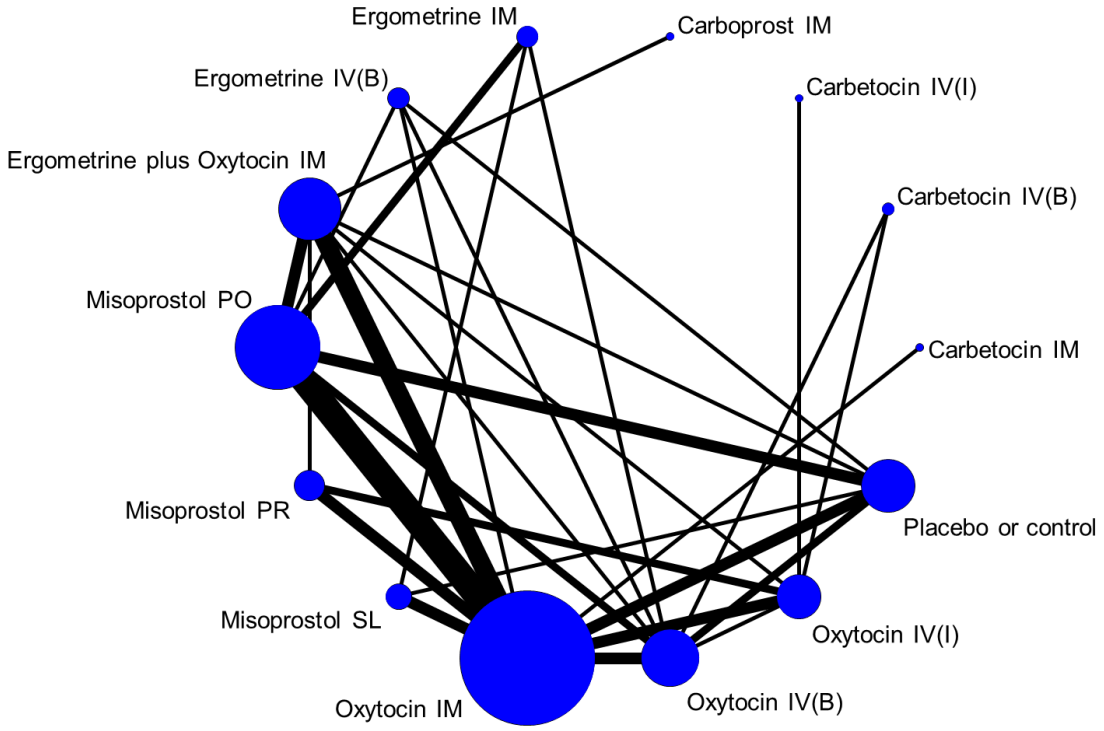


Figure 95: PPH ≥500 mL restricted to studies with at least 400 participants-Forest plot-Routes NMA

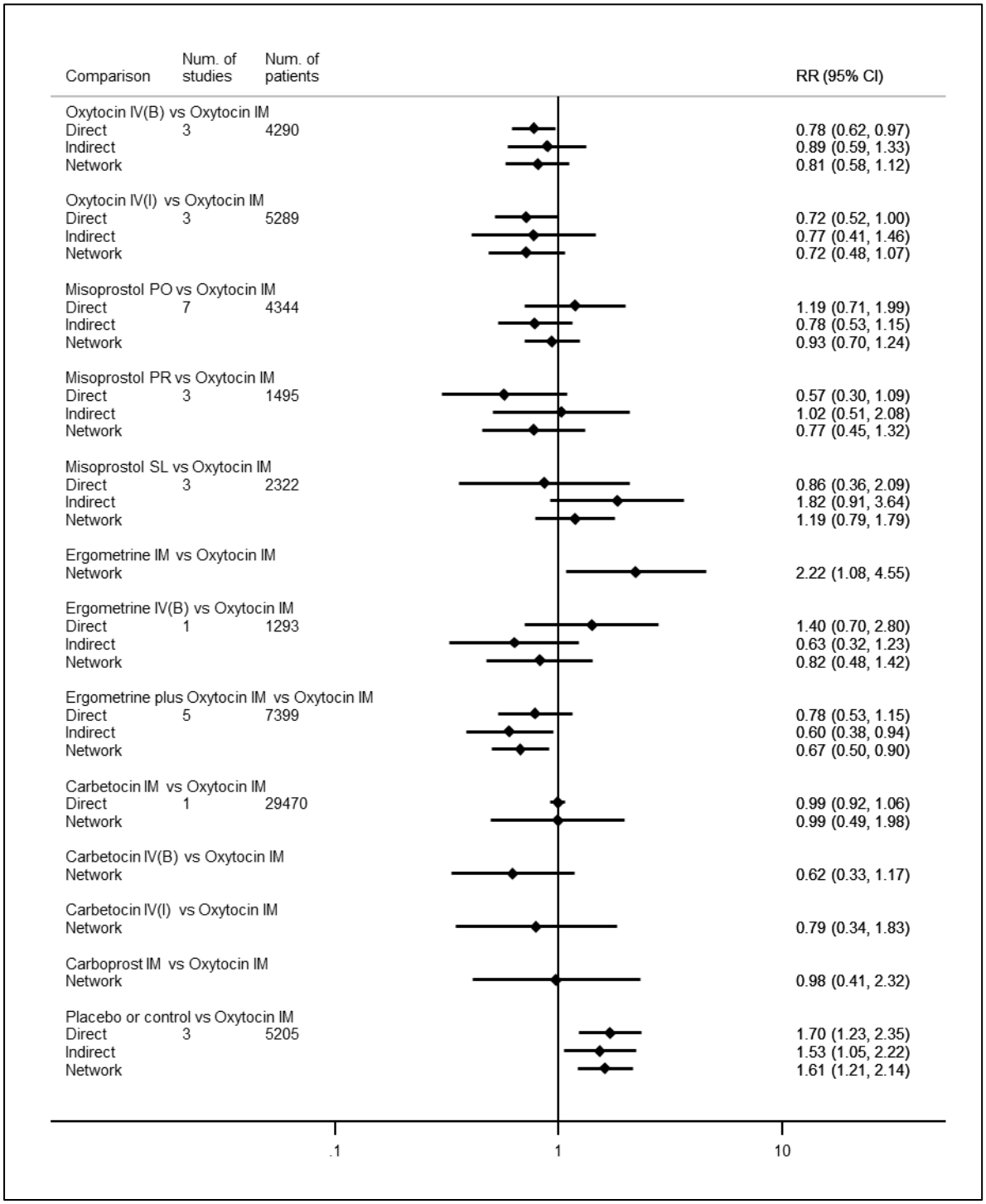


Figure 96: PPH ≥500 mL restricted to studies with at least 400 participants-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with at least 400 participants. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

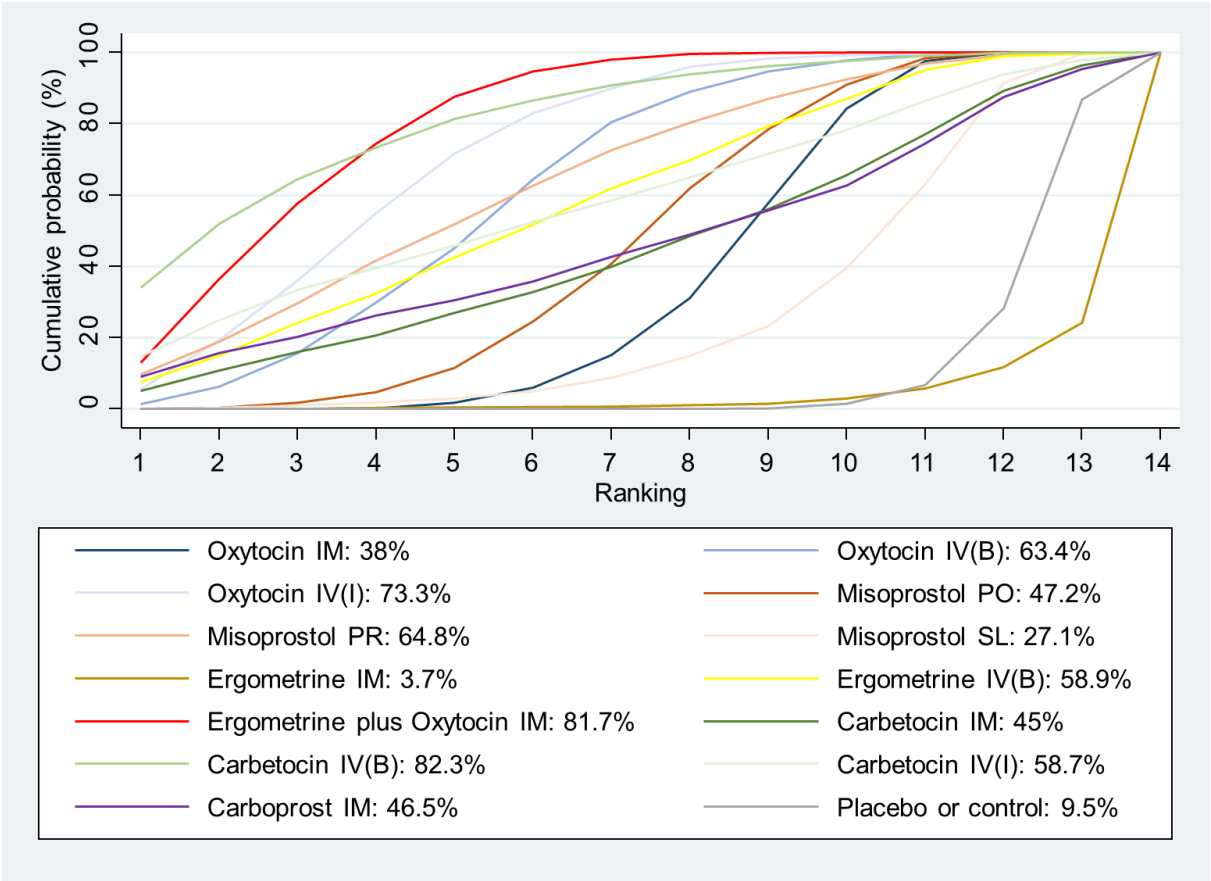


Figure 97: PPH ≥1000 mL restricted to studies at low Risk of Bias-Network diagram-Routes NMA

Network diagram for PPH ≥1000 mL restricted to studies at low Risk of Bias. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

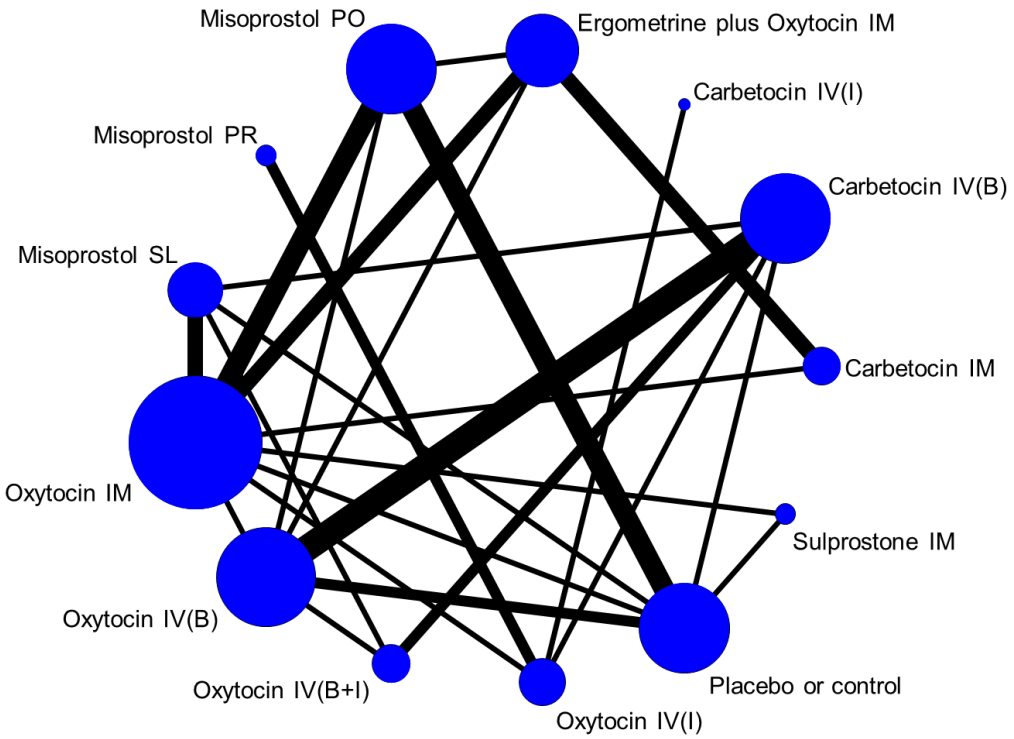


Figure 98: PPH ≥1000 mL restricted to studies at low Risk of Bias-Forest plot-Routes NMA

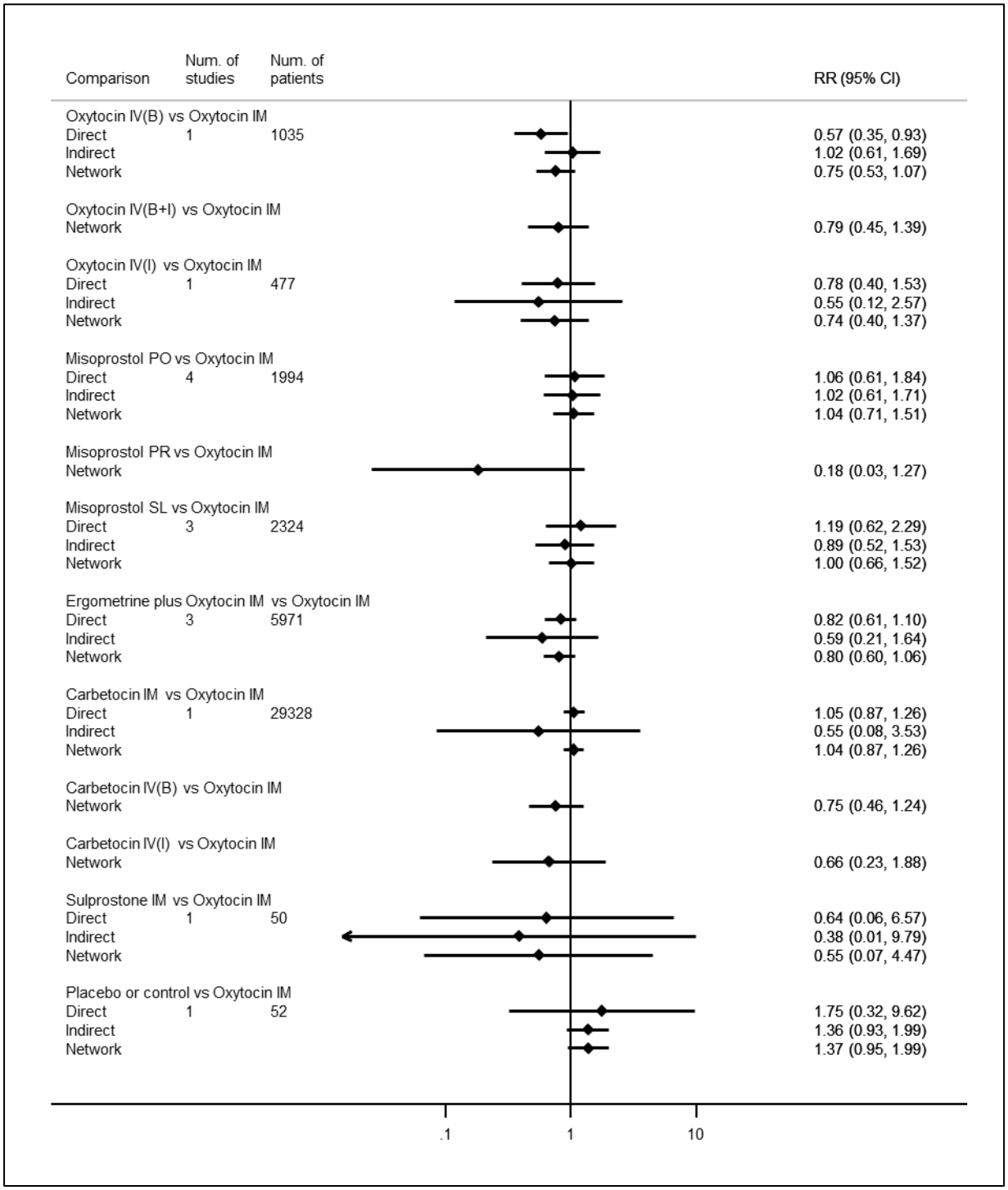


Figure 99: PPH ≥1000 mL restricted to studies at low Risk of Bias-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies at low Risk of Bias. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

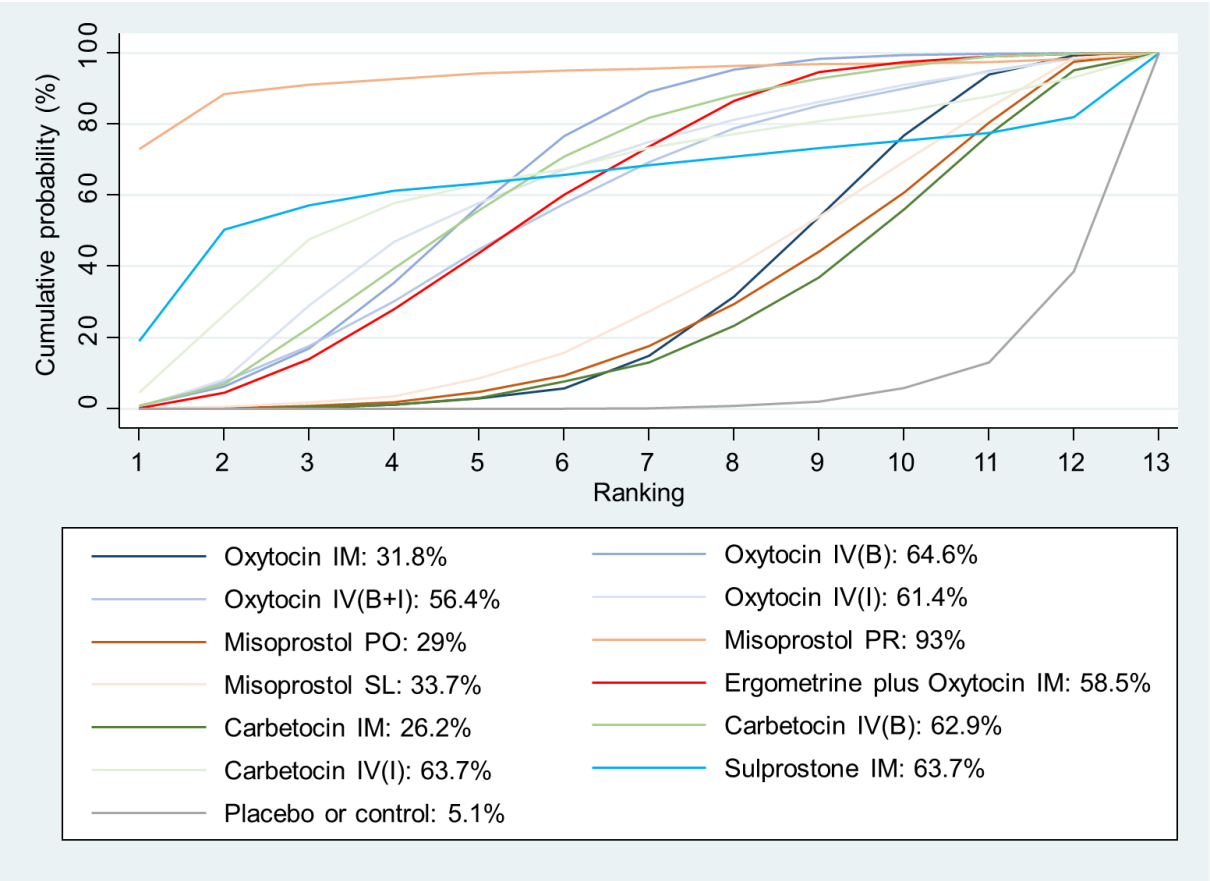


Figure 100: PPH ≥1000 mL restricted to studies with public or no funding-Network diagram-Routes NMA

Network diagram for PPH ≥1000 mL restricted to studies with public or no funding. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

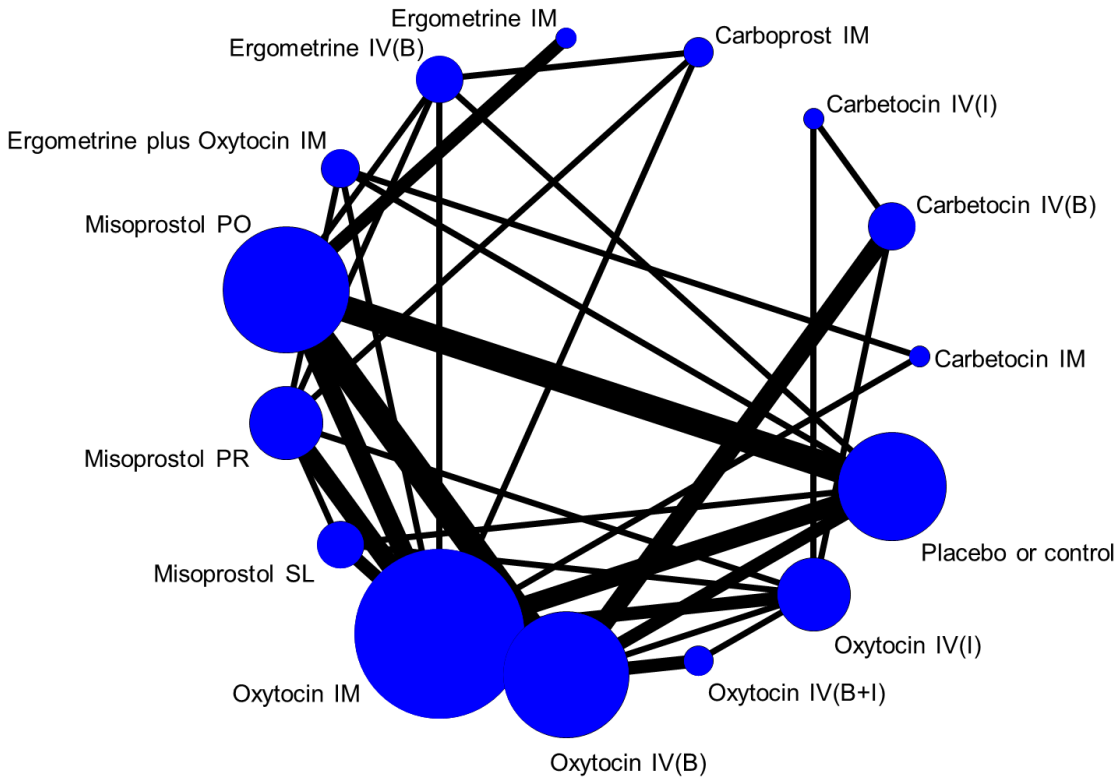


Figure 101: PPH ≥1000 mL restricted to studies with public or no funding-Forest plot-Routes NMA

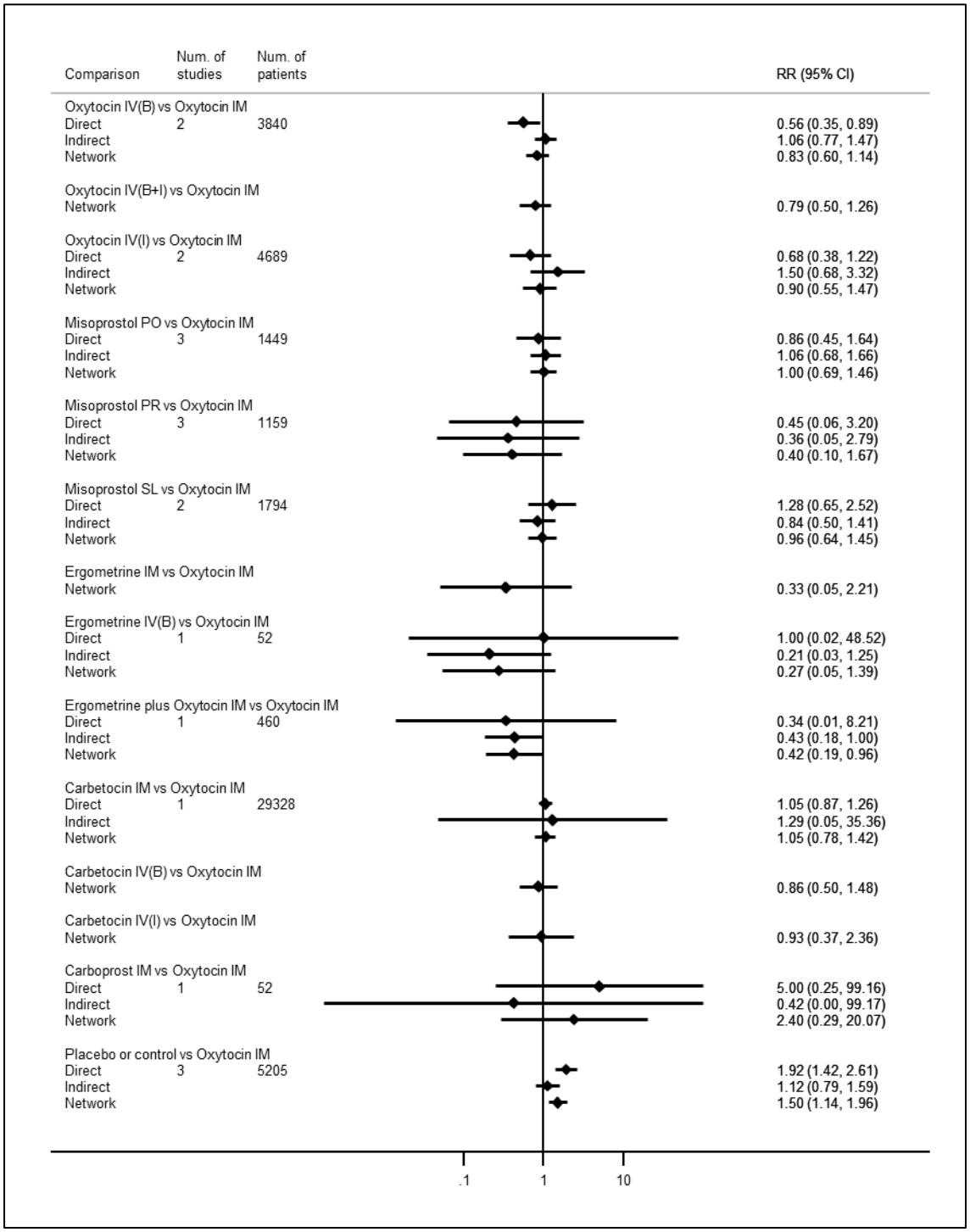


Figure 102: PPH ≥1000 mL restricted to studies with public or no funding-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with public or no funding. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

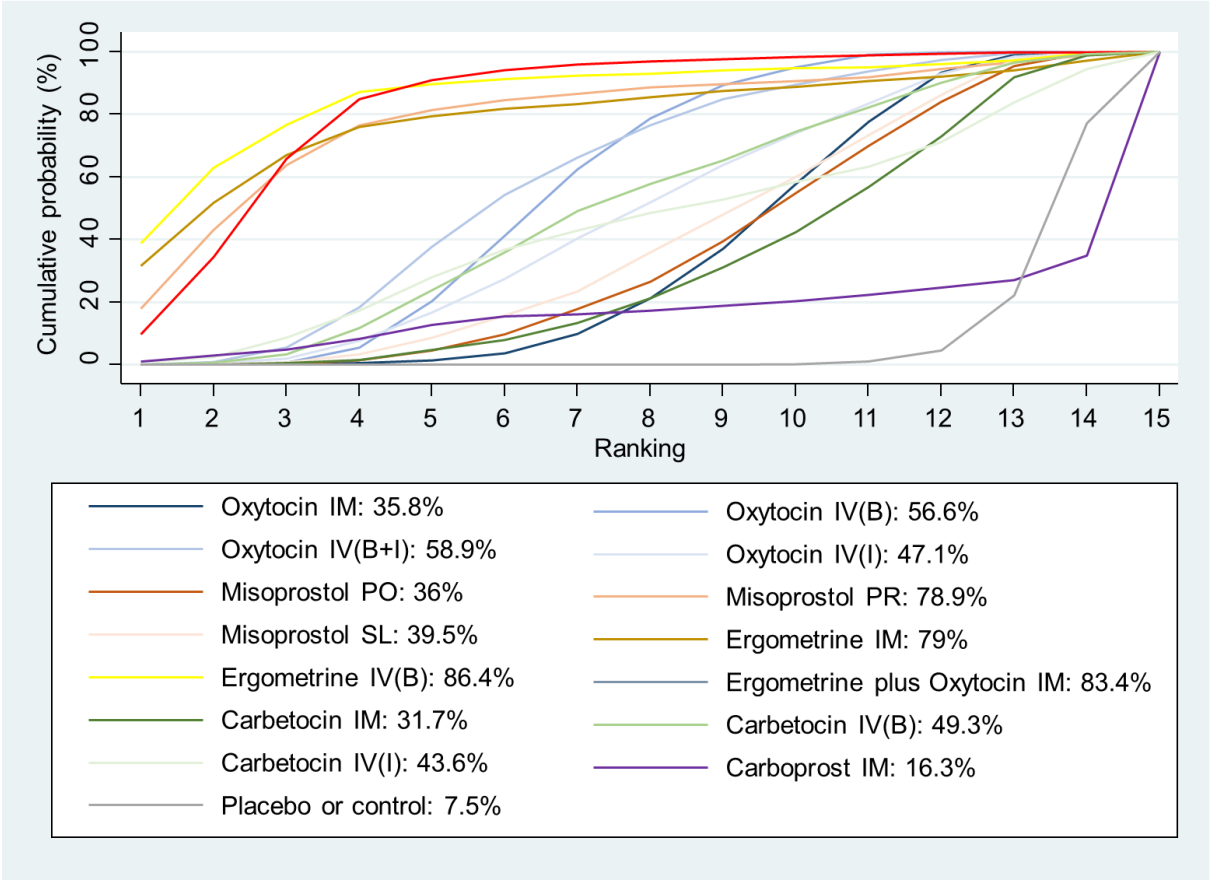


Figure 103: PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss-Network diagram-Routes NMA

Network diagram for PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

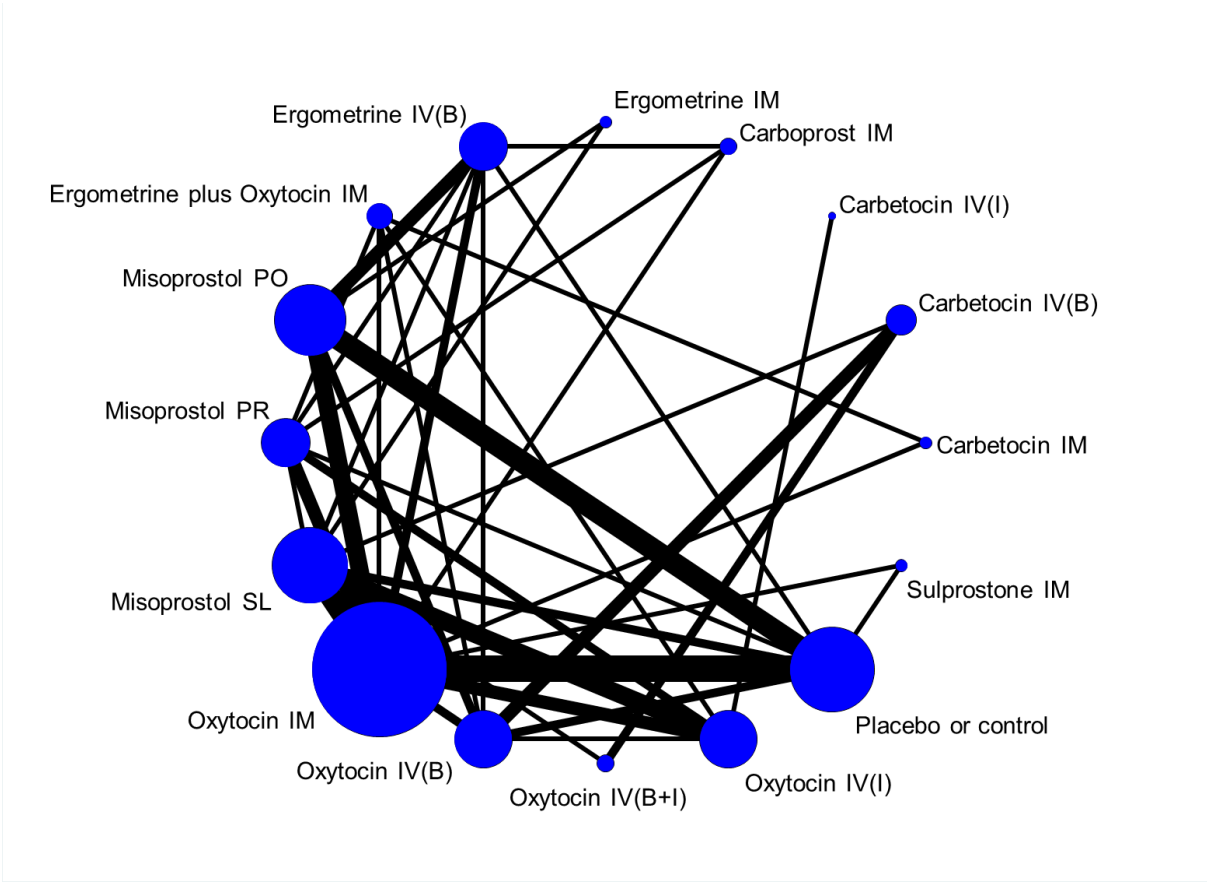


Figure 104: PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss-Forest plot-Routes NMA

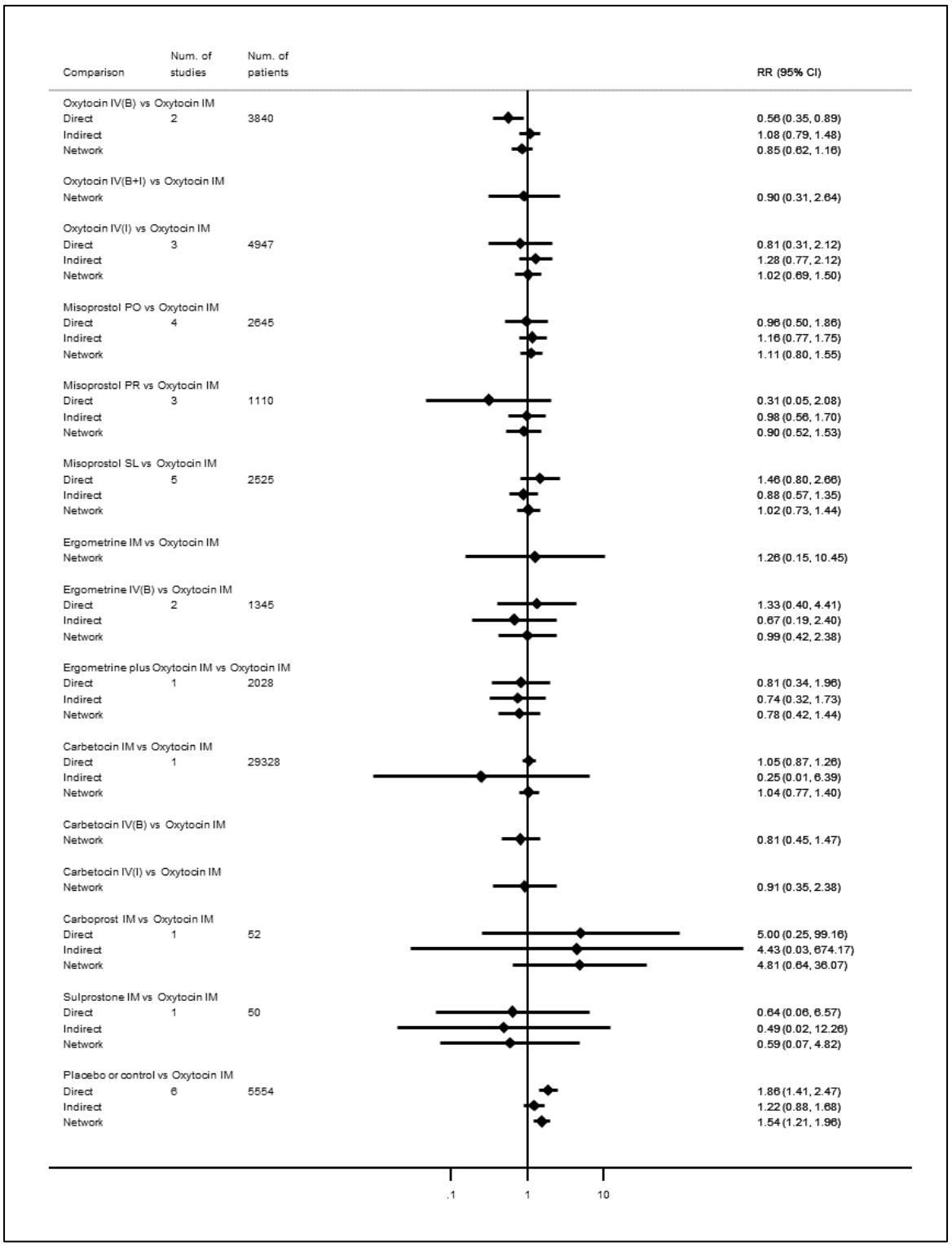


Figure 105: PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

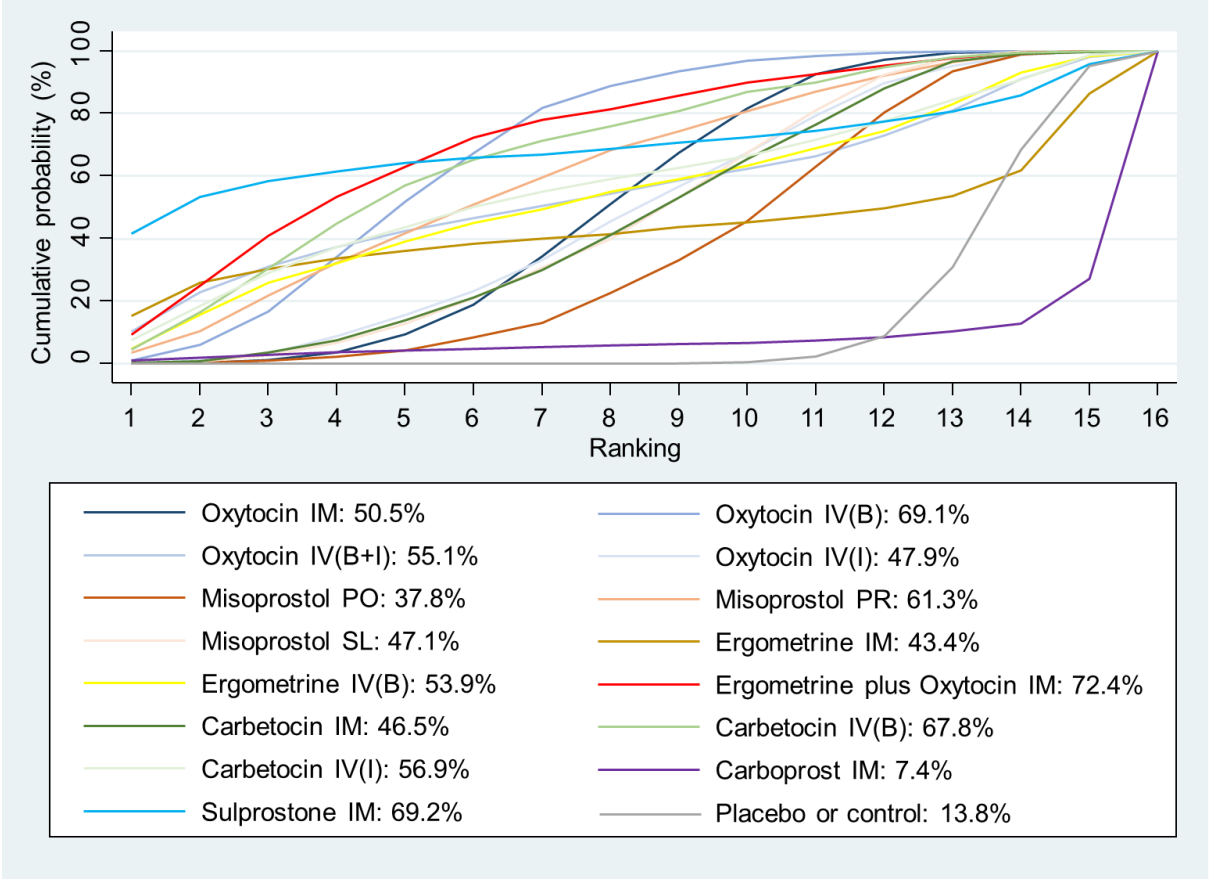


Figure 106: PPH ≥1000 mL restricted to studies with <10% attrition-Network diagram-Routes NMA

Network diagram for PPH ≥1000 mL restricted to studies with <10% attrition. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

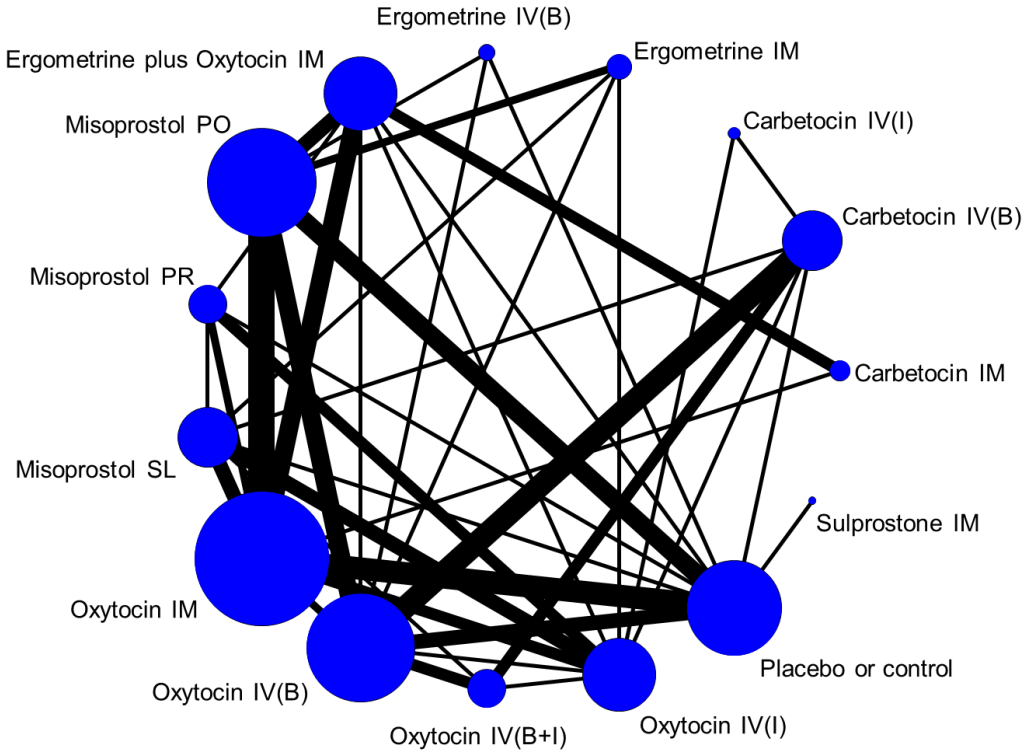


Figure 107: PPH ≥1000 mL restricted to studies with <10% attrition-Forest plot-Routes NMA

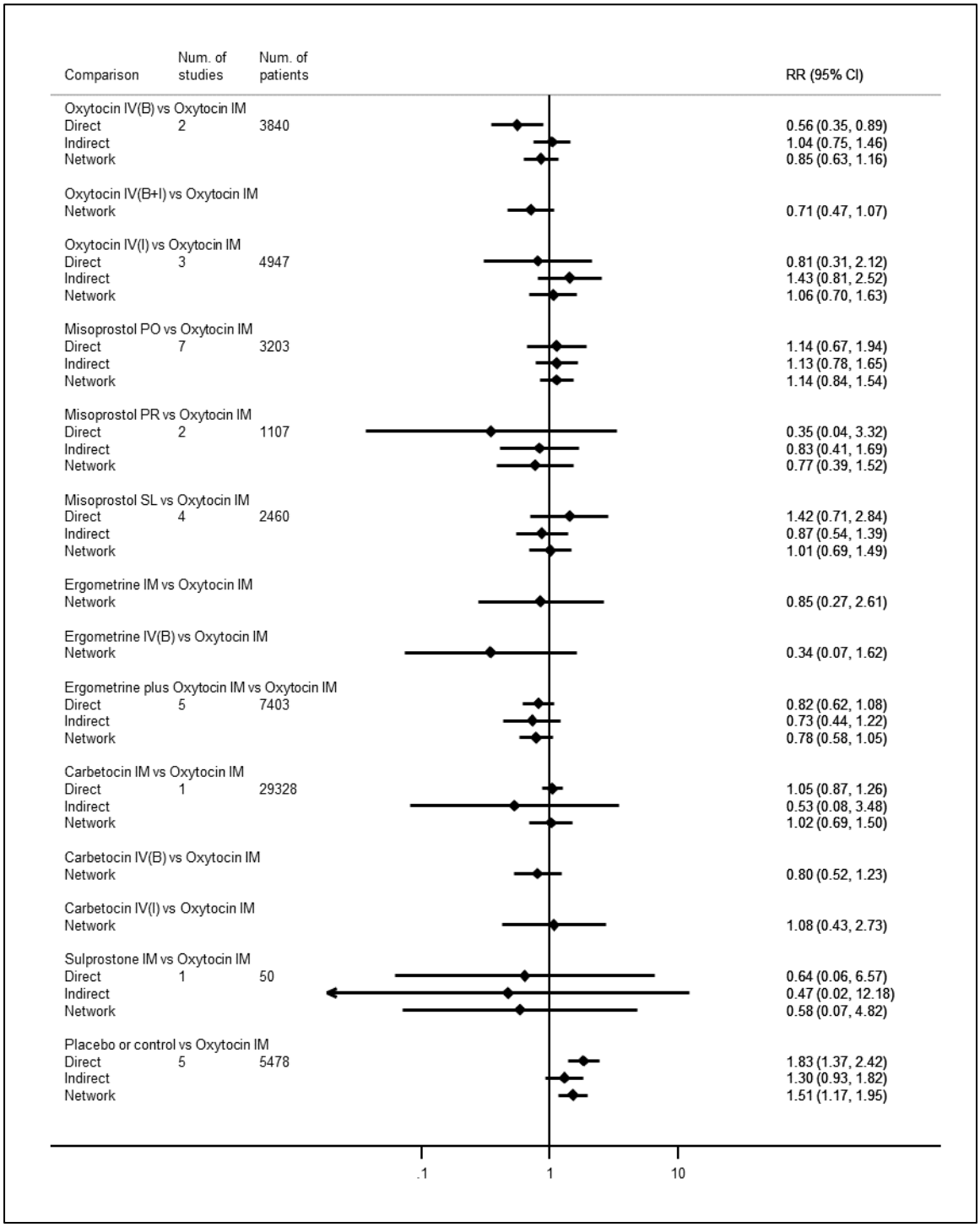


Figure 108: PPH ≥1000 mL restricted to studies with <10% attrition-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with <10% attrition. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

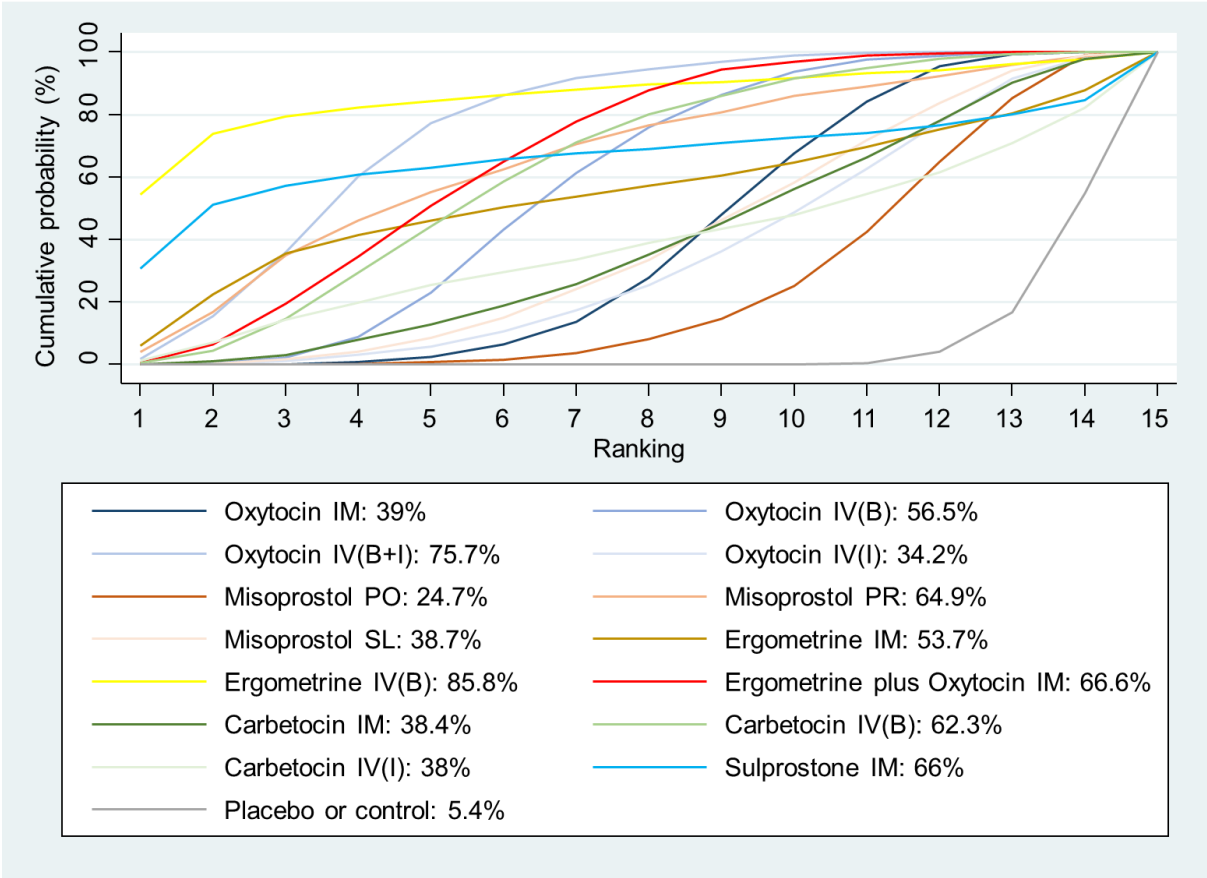


Figure 109: PPH ≥1000 mL restricted to studies with at least 400 participants-Network diagram-Routes NMA

Network diagram for PPH ≥1000 mL restricted to studies with at least 400 participants. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

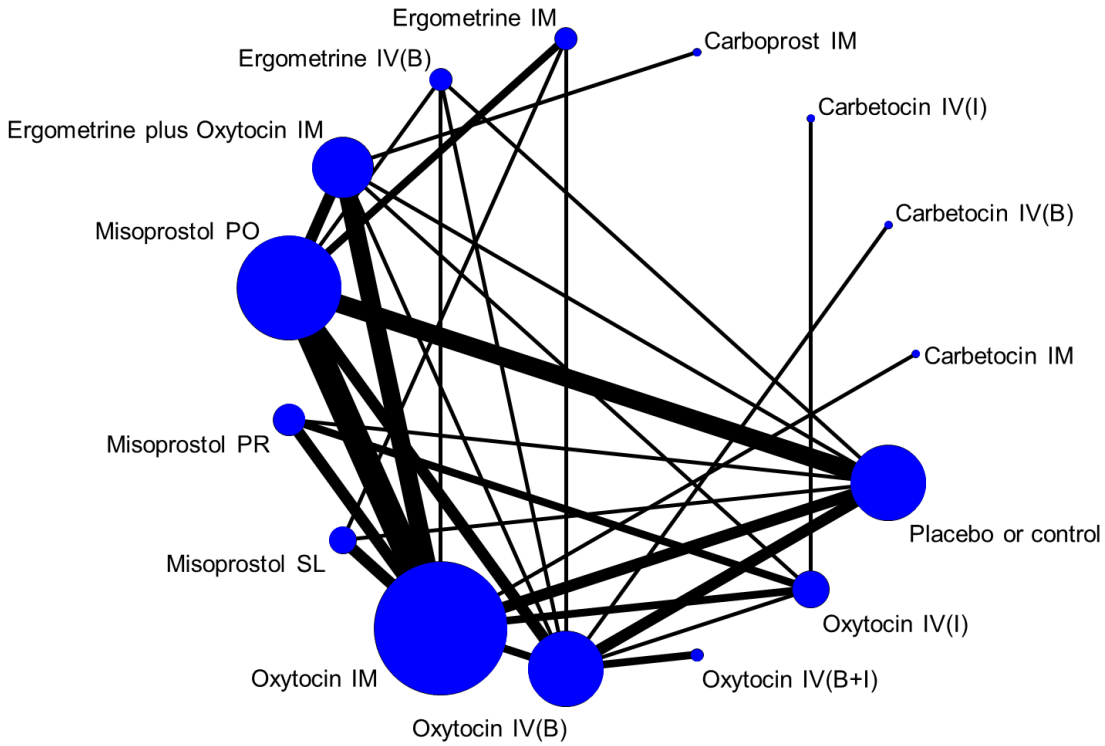


Figure 110: PPH ≥1000 mL restricted to studies with at least 400 participants-Forest plot-Routes NMA

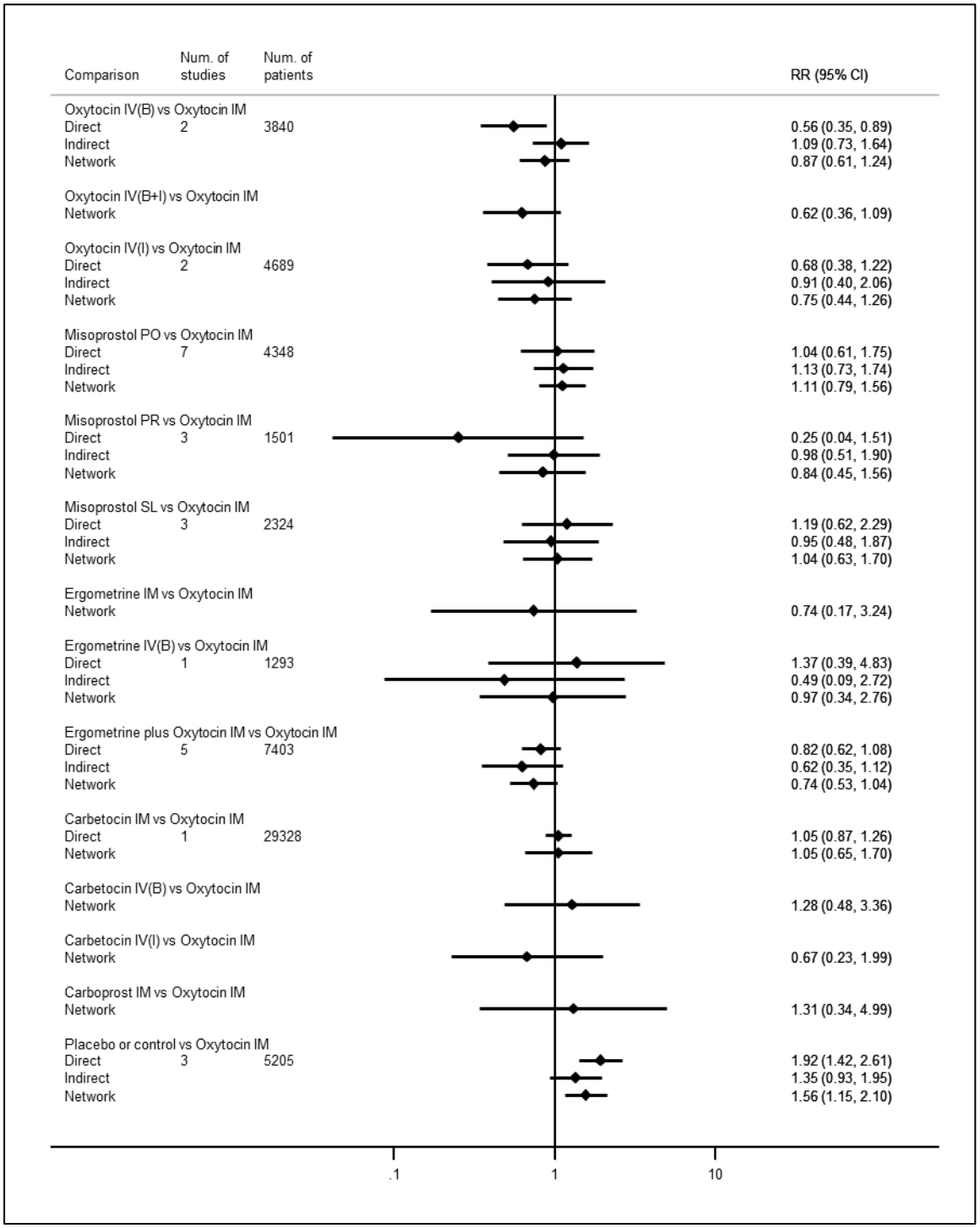
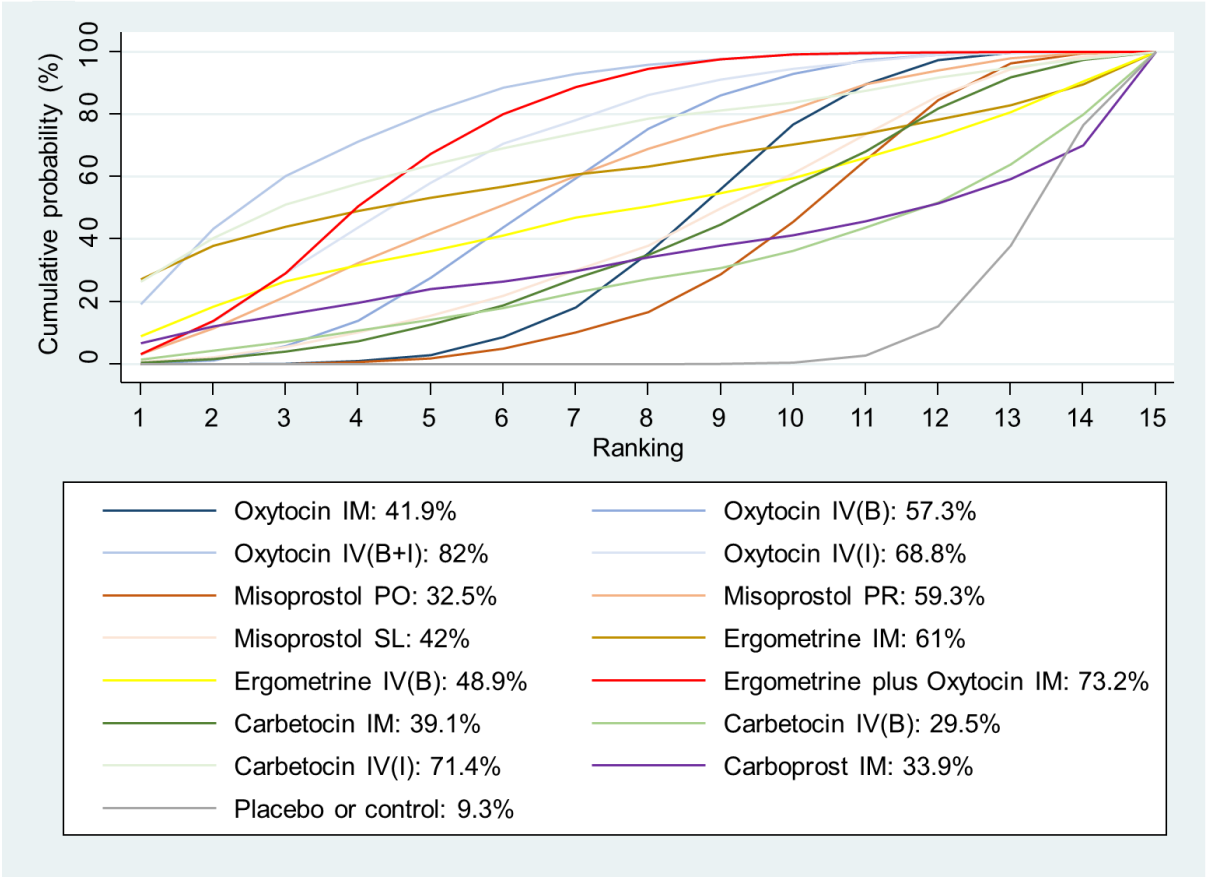


Figure 111: PPH ≥1000 mL restricted to studies with at least 400 participants-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with at least 400 participants. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Subgroup analyses

Figure 112: PPH ≥500 mL by mode of birth (vaginal birth)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥500 mL by mode of birth (vaginal birth). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

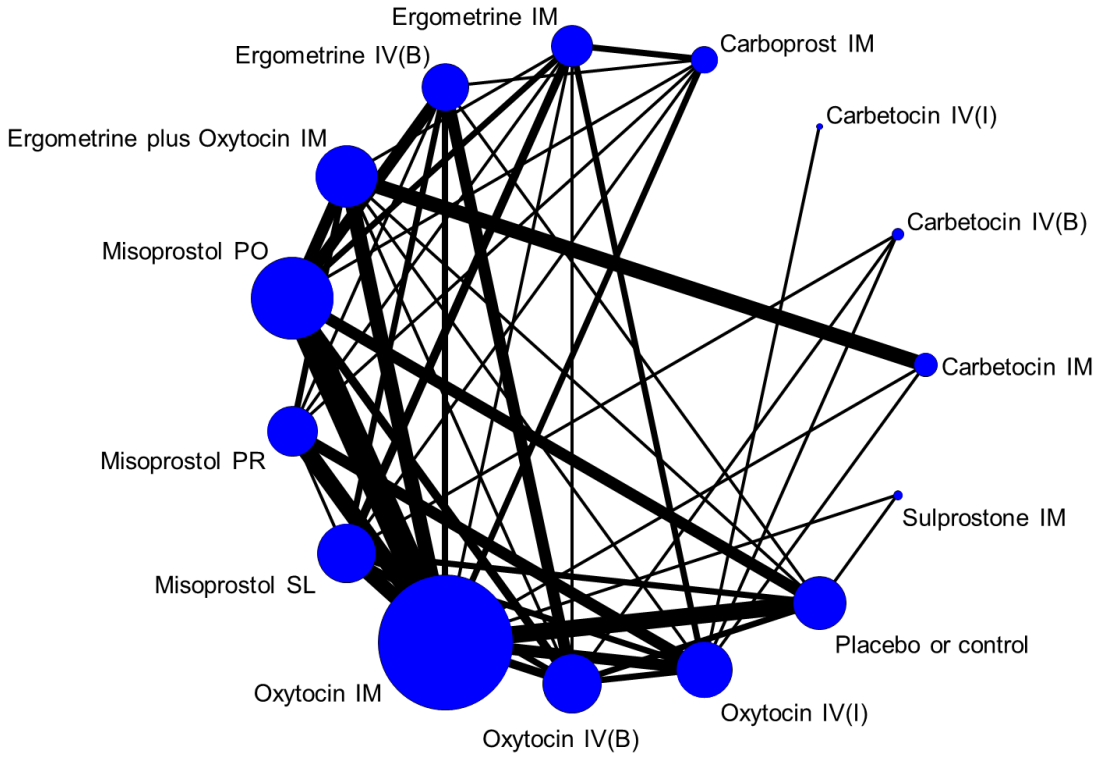


Figure 113: PPH ≥500 mL by mode of birth (vaginal birth)-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL by mode of birth (vaginal birth).

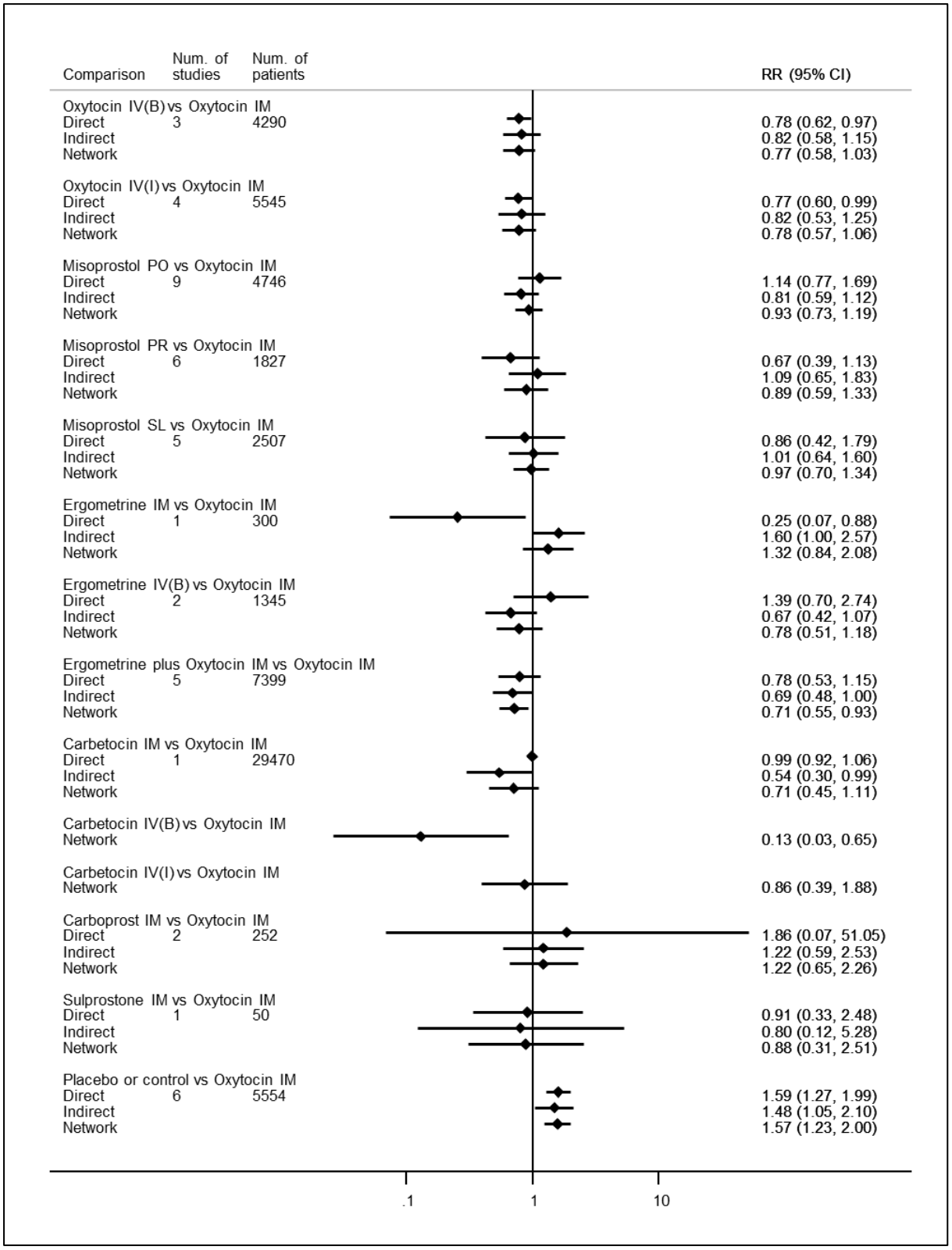


Figure 114: PPH ≥500 mL by mode of birth (vaginal birth)-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL by mode of birth (vaginal birth). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

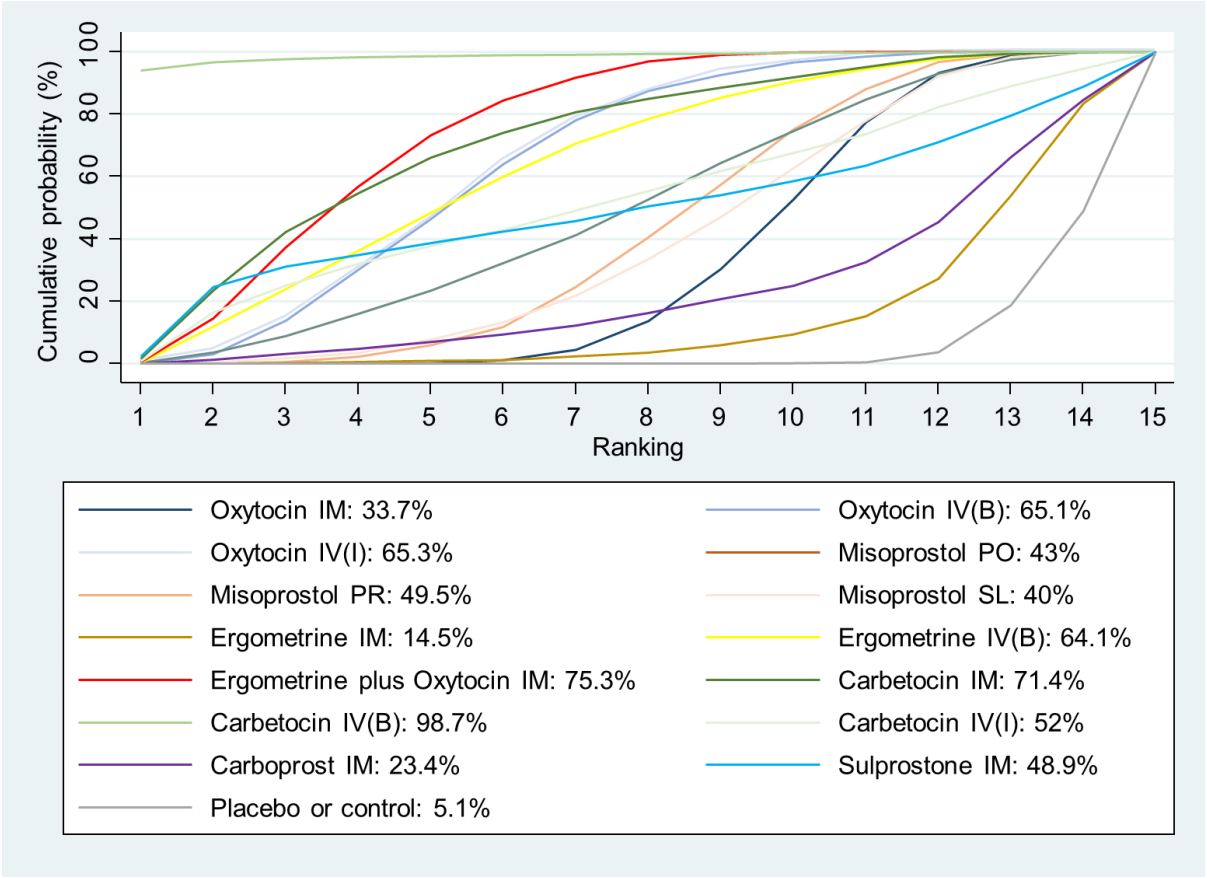


Figure 115: PPH ≥500 mL by mode of birth (caesarean section)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥500 mL by mode of birth (caesarean section). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

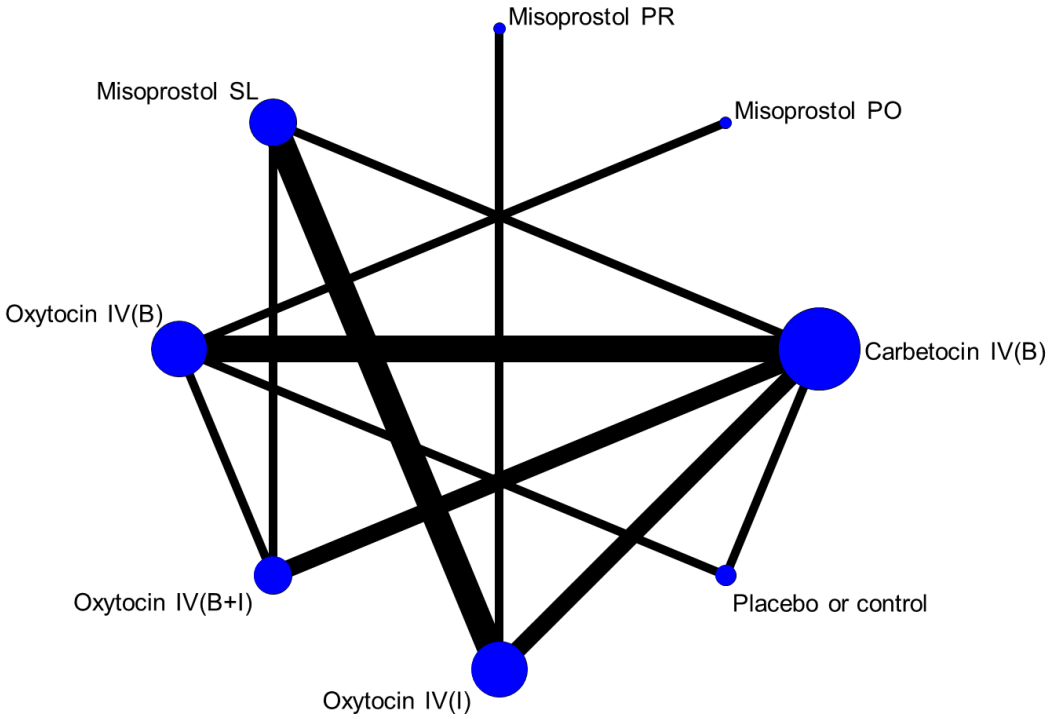


Figure 116: PPH ≥500 mL by prior risk for PPH (low risk)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥500 mL by prior risk for PPH (low risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

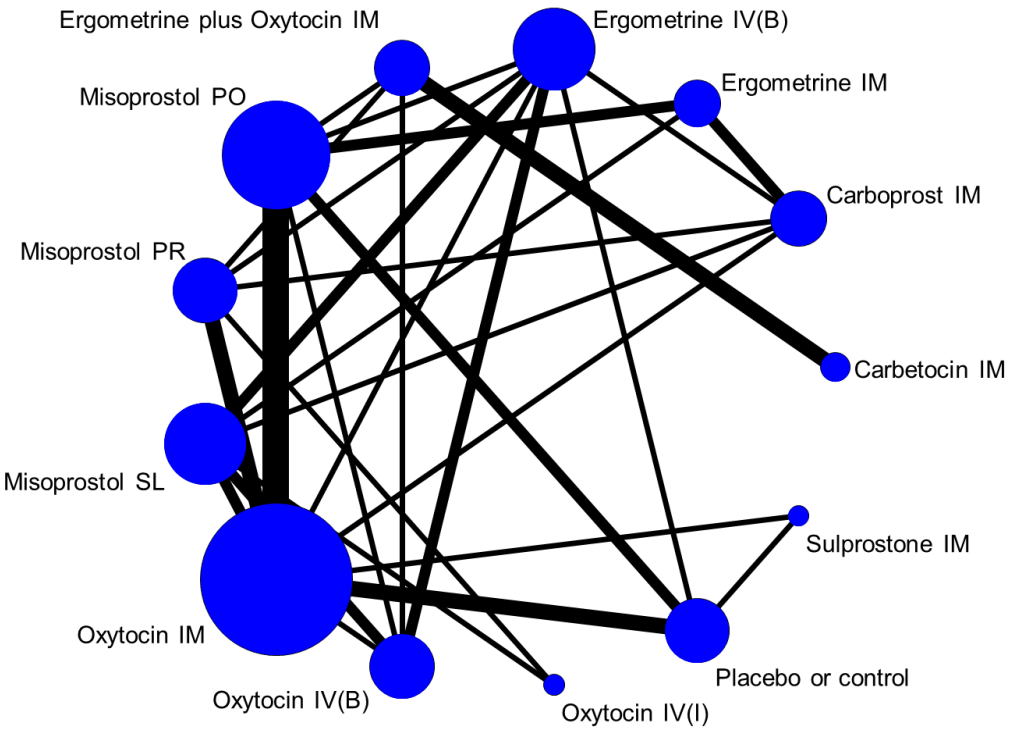


Figure 117: PPH ≥500 mL by prior risk for PPH (low risk)-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL by prior risk for PPH (low risk).

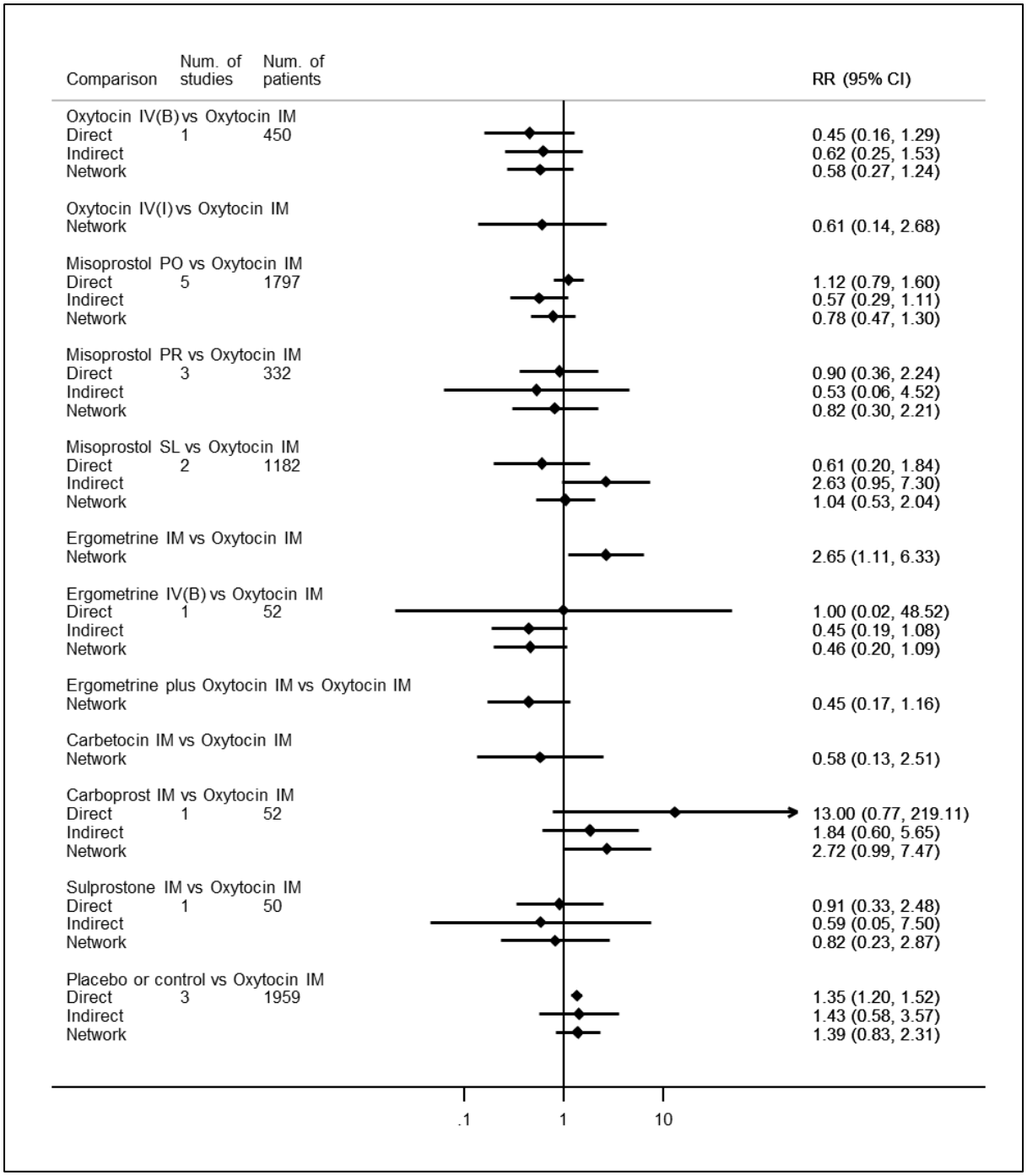


Figure 118: PPH ≥500 mL by prior risk for PPH (low risk)-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥500 mL by prior risk for PPH (low risk). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

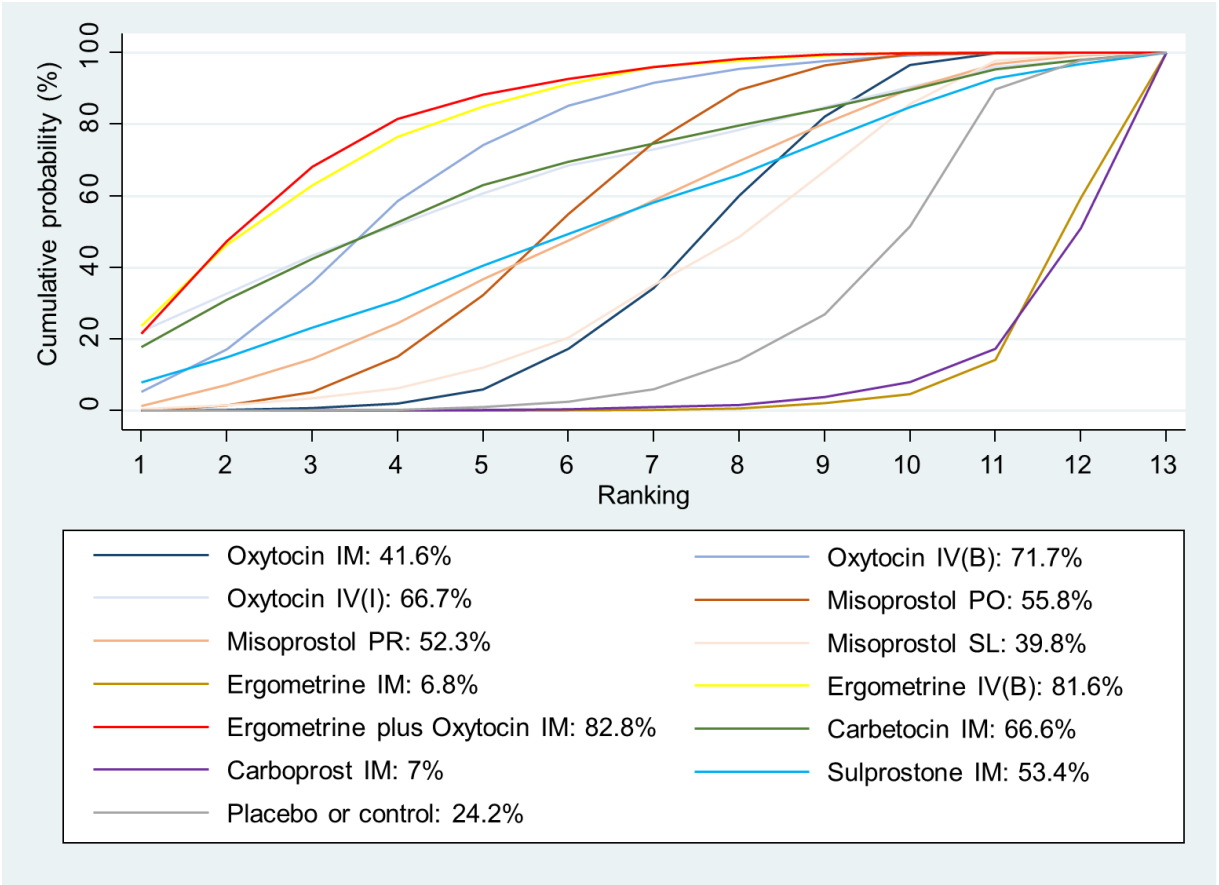


Figure 119: PPH ≥500 mL by prior risk for PPH (high risk)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥500 mL by prior risk for PPH (high risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

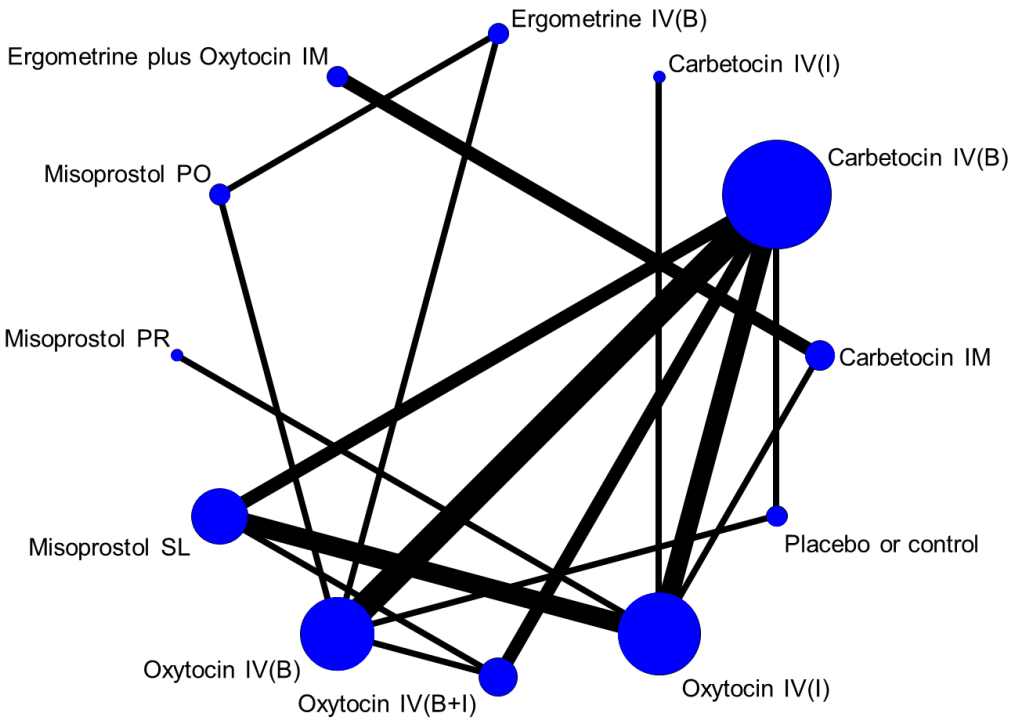


Figure 120: PPH ≥1000 mL by mode of birth (vaginal birth)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥1000 mL by mode of birth (vaginal birth). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

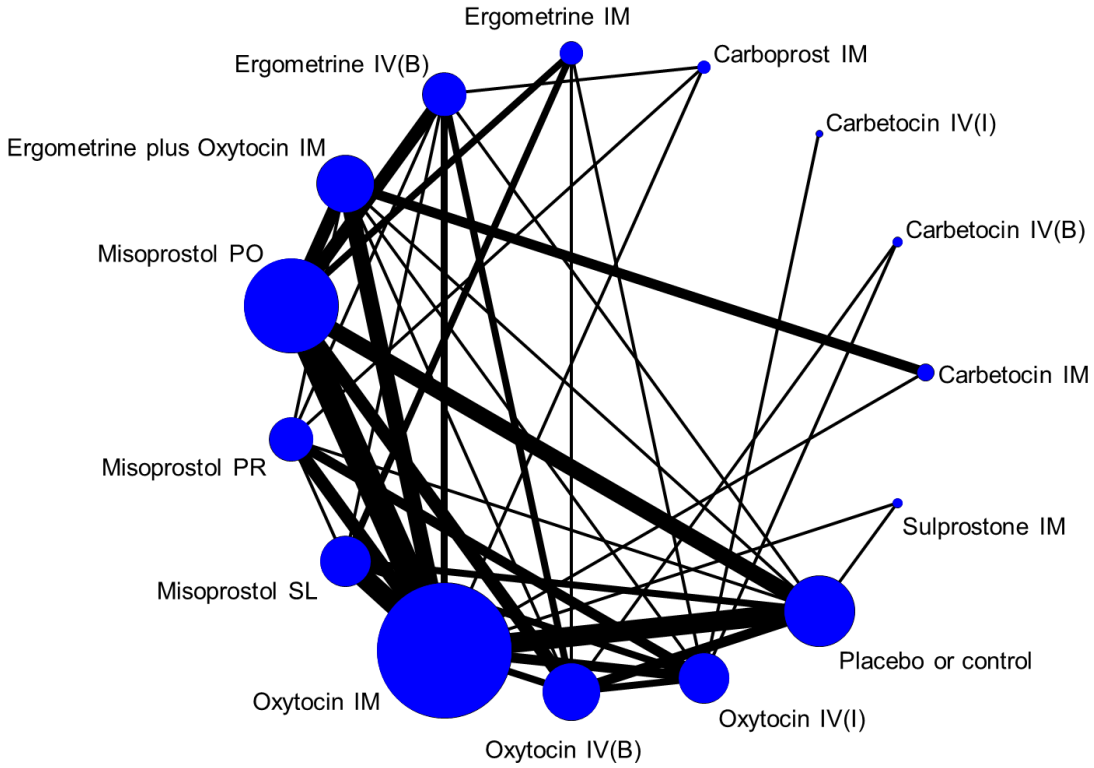


Figure 121: PPH ≥1000 mL by mode of birth (vaginal birth)-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL by mode of birth (vaginal birth).

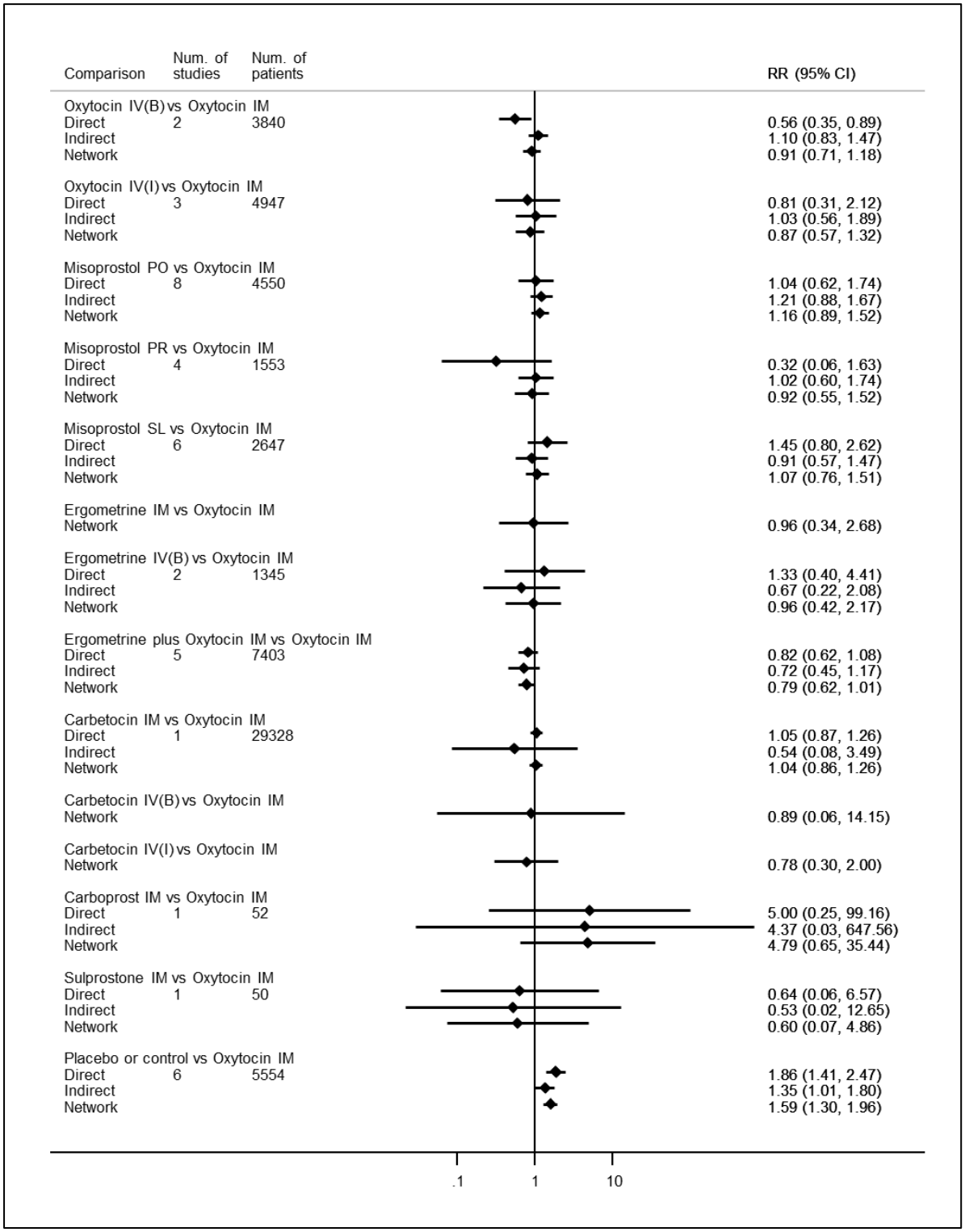


Figure 122: PPH ≥1000 mL by mode of birth (vaginal birth)-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL by mode of birth (vaginal birth). Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

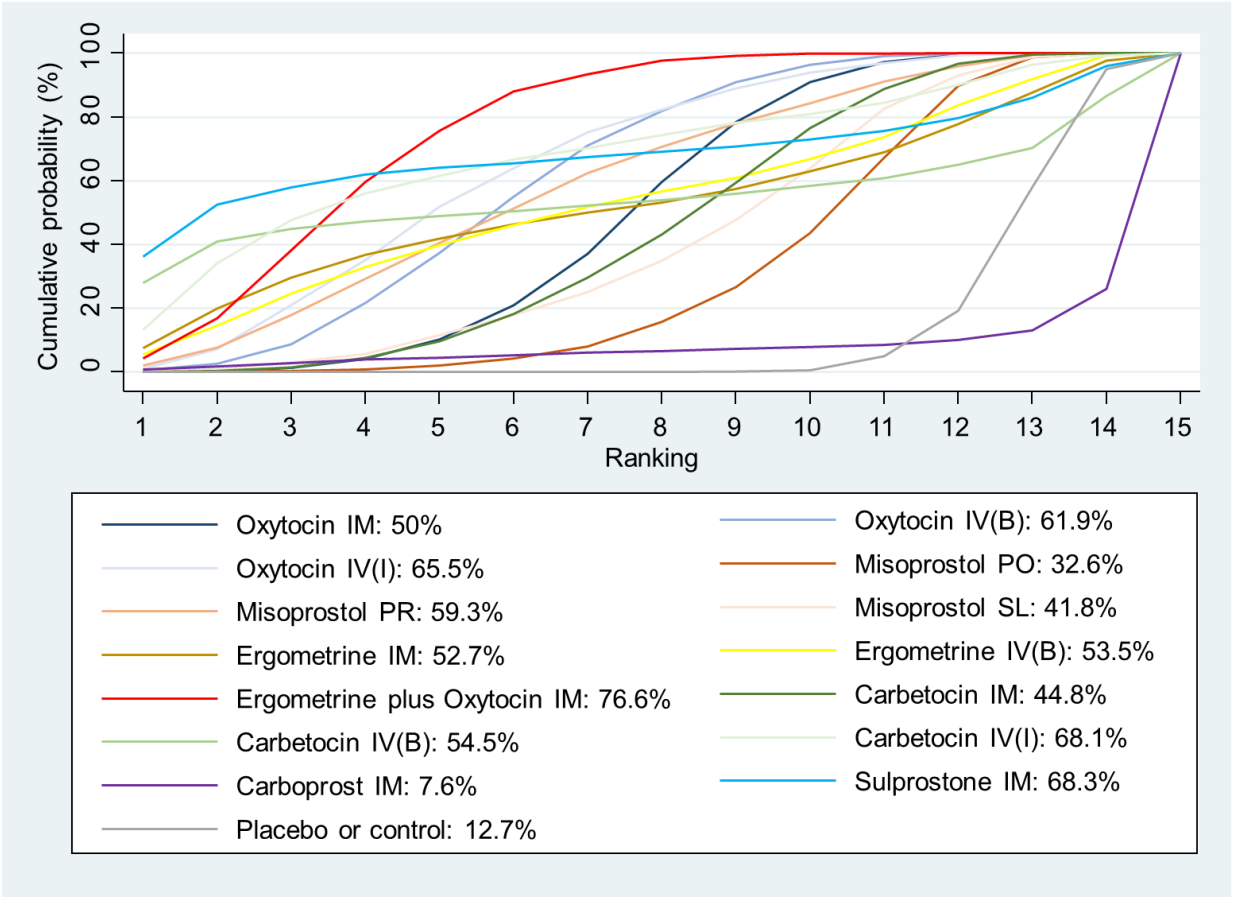


Figure 123: PPH ≥1000 mL by mode of birth (caesarean section)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥1000 mL by mode of birth (caesarean section). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

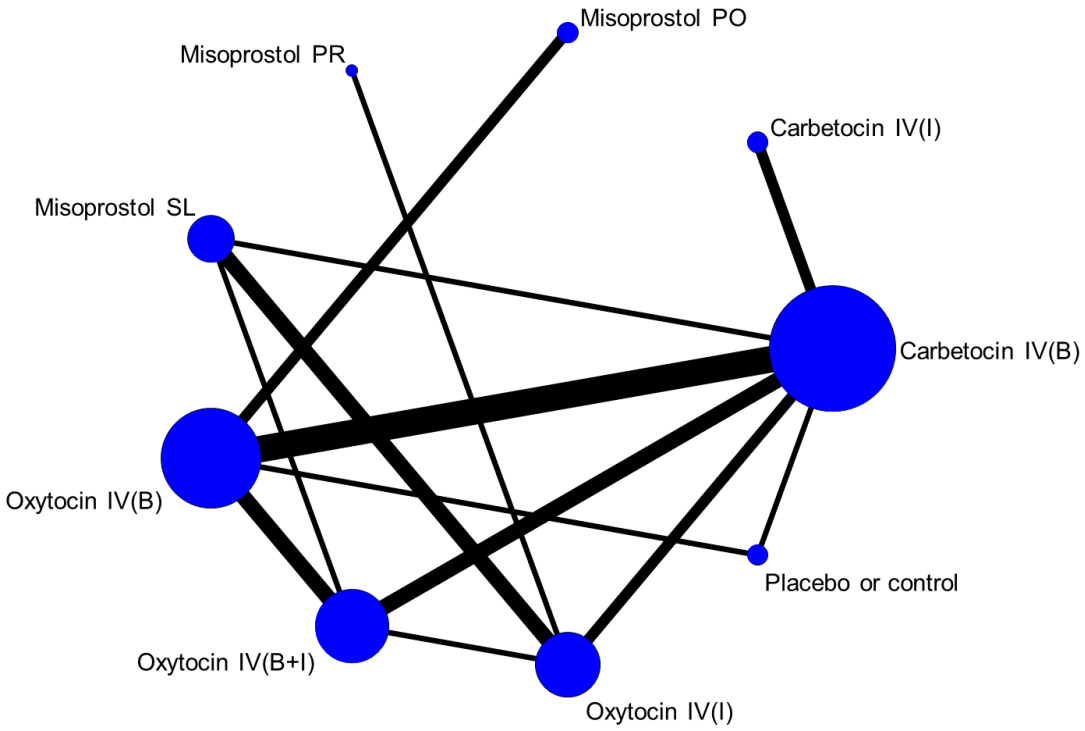


Figure 124: PPH ≥1000 mL by prior risk for PPH (low risk)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥1000 mL by prior risk for PPH (low risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

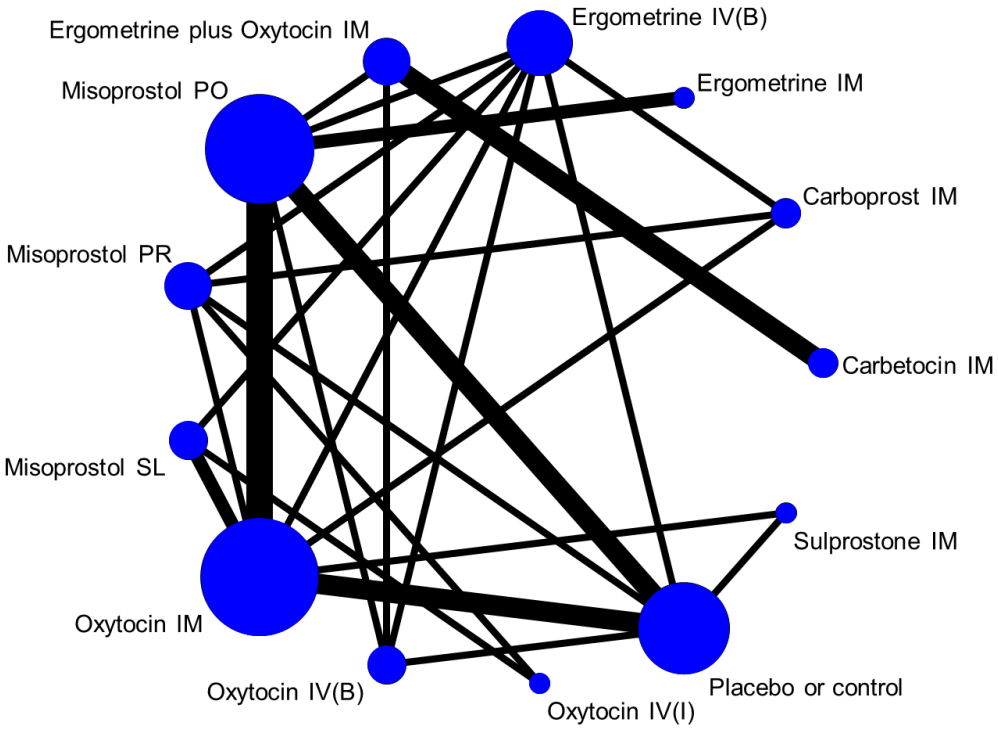


Figure 125: PPH ≥1000 mL by prior risk for PPH (low risk)-Forest plot-Routes NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL by prior risk for PPH (low risk).

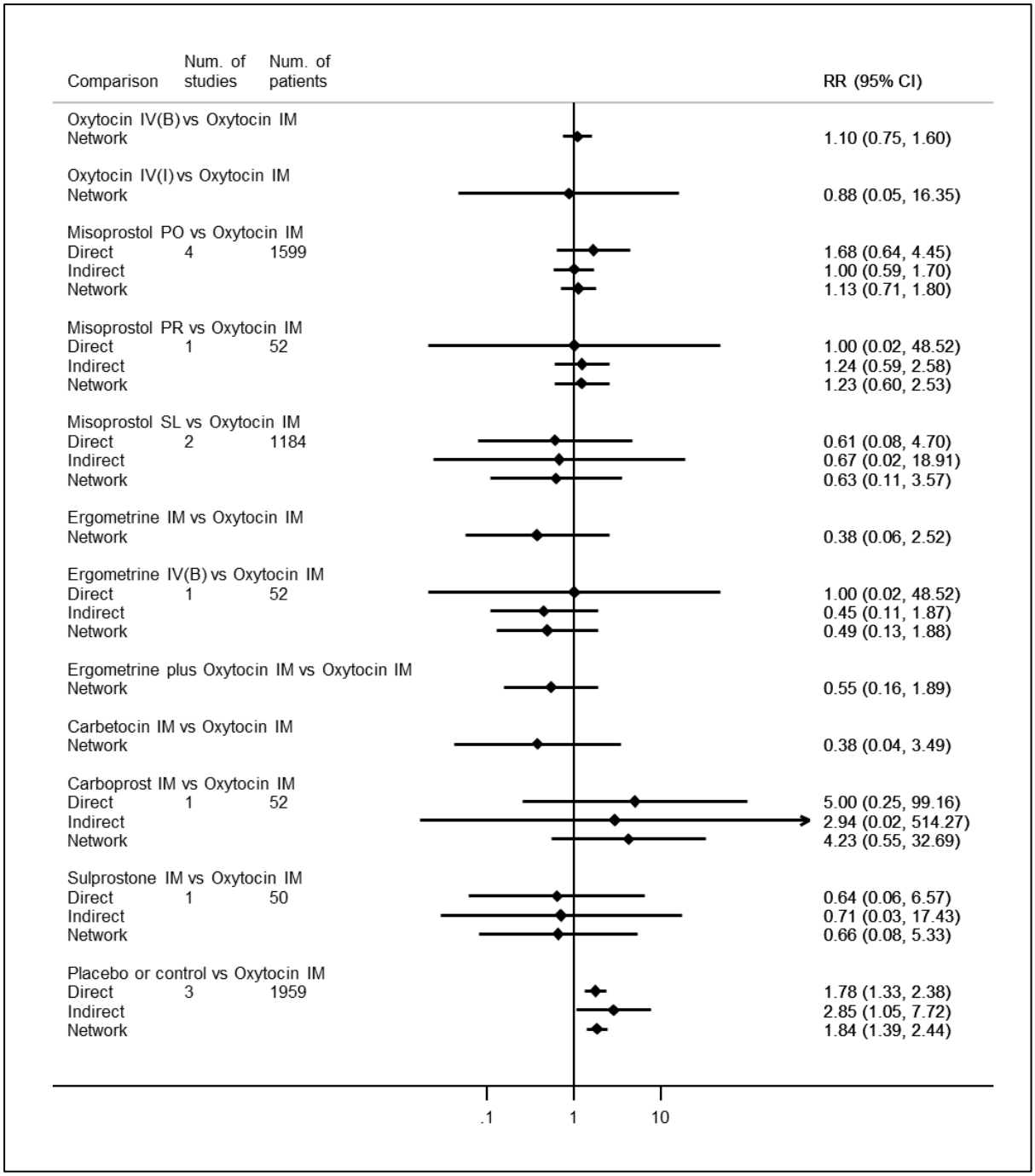


Figure 126: PPH ≥1000 mL by prior risk for PPH (low risk)-Rankogram-Routes NMA

Cumulative rankogram for PPH ≥1000 mL by prior risk for PPH (low risk). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

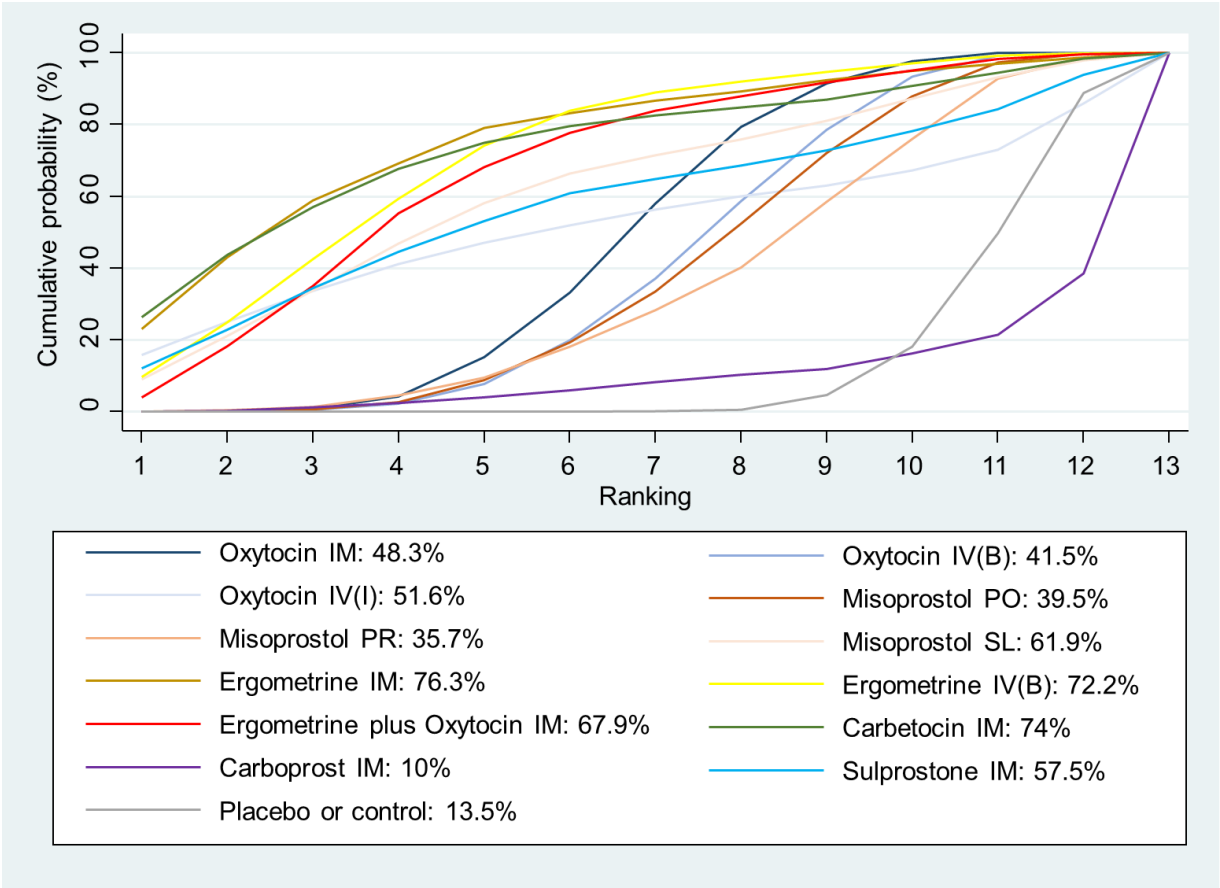
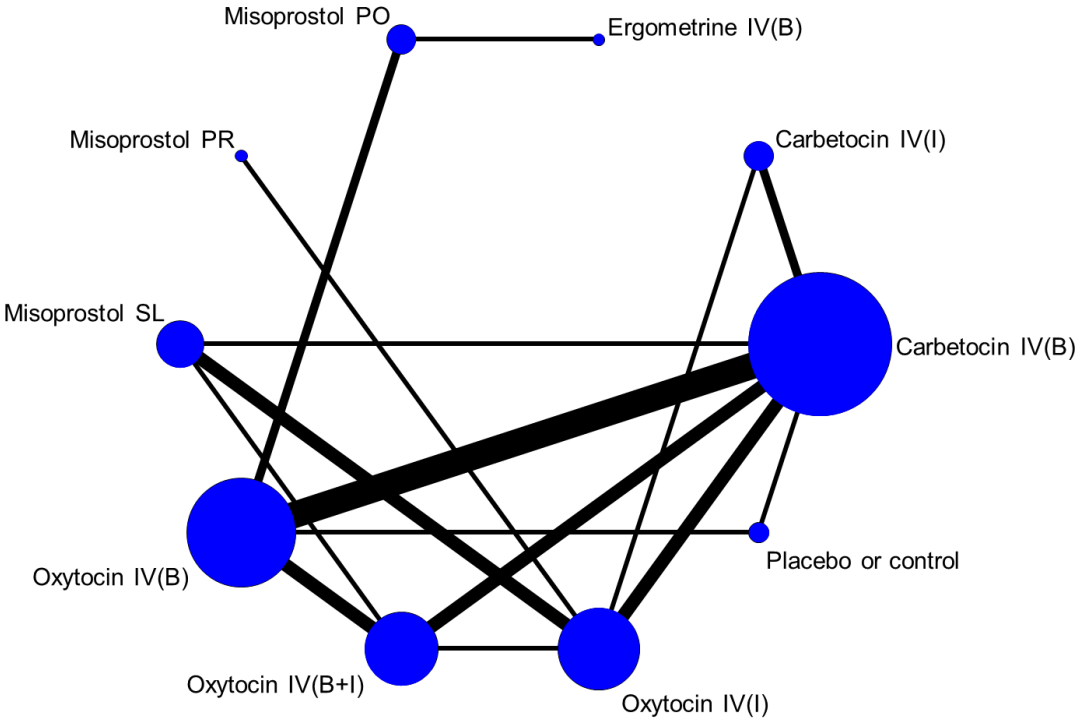


Figure 127: PPH ≥1000 mL by prior risk for PPH (high risk)-Network diagram-Routes NMA

Network diagram for prevention of PPH ≥1000 mL by prior risk for PPH (high risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.



APPENDIX 3: Doses-NMA

Additional outcomes

Figure 128: Maternal death-Network diagram-Doses NMA

Network diagram for maternal death. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

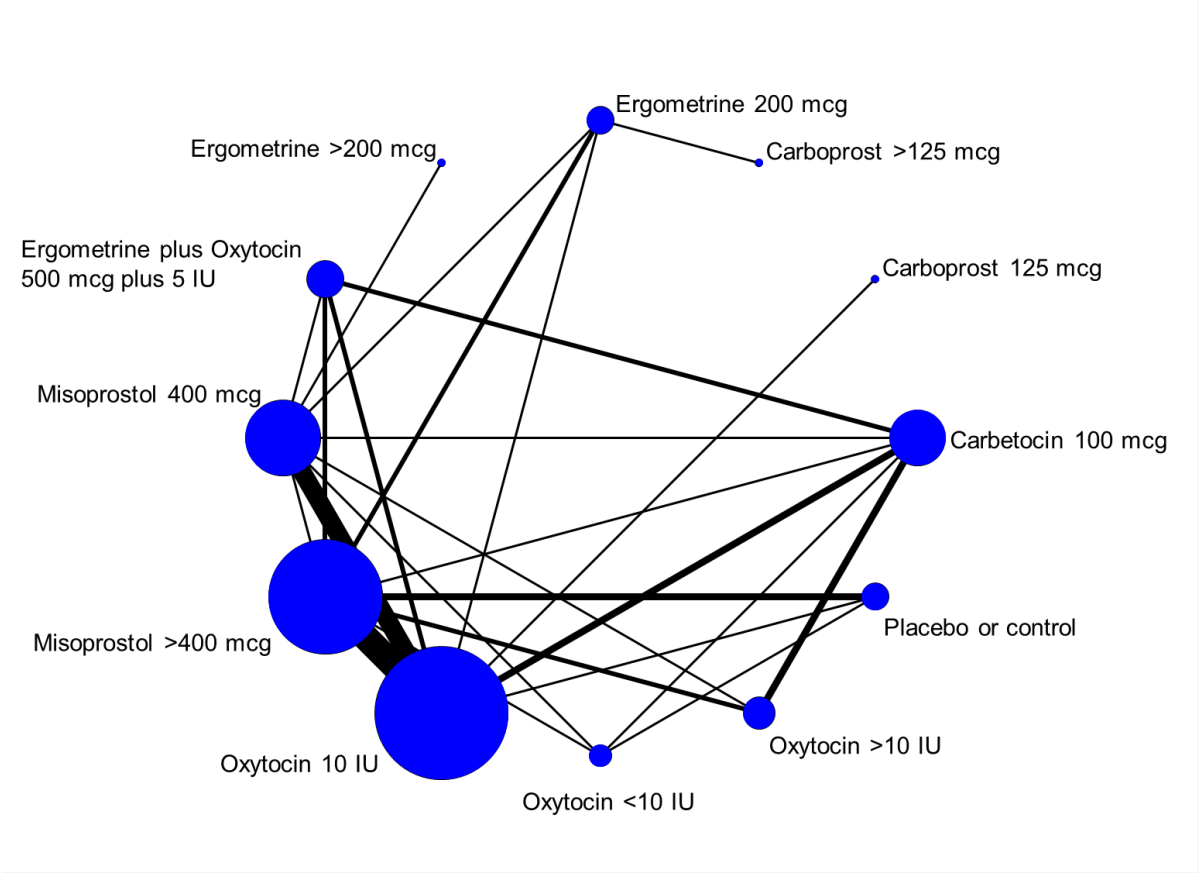


Figure 129: Maternal death-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for maternal death.

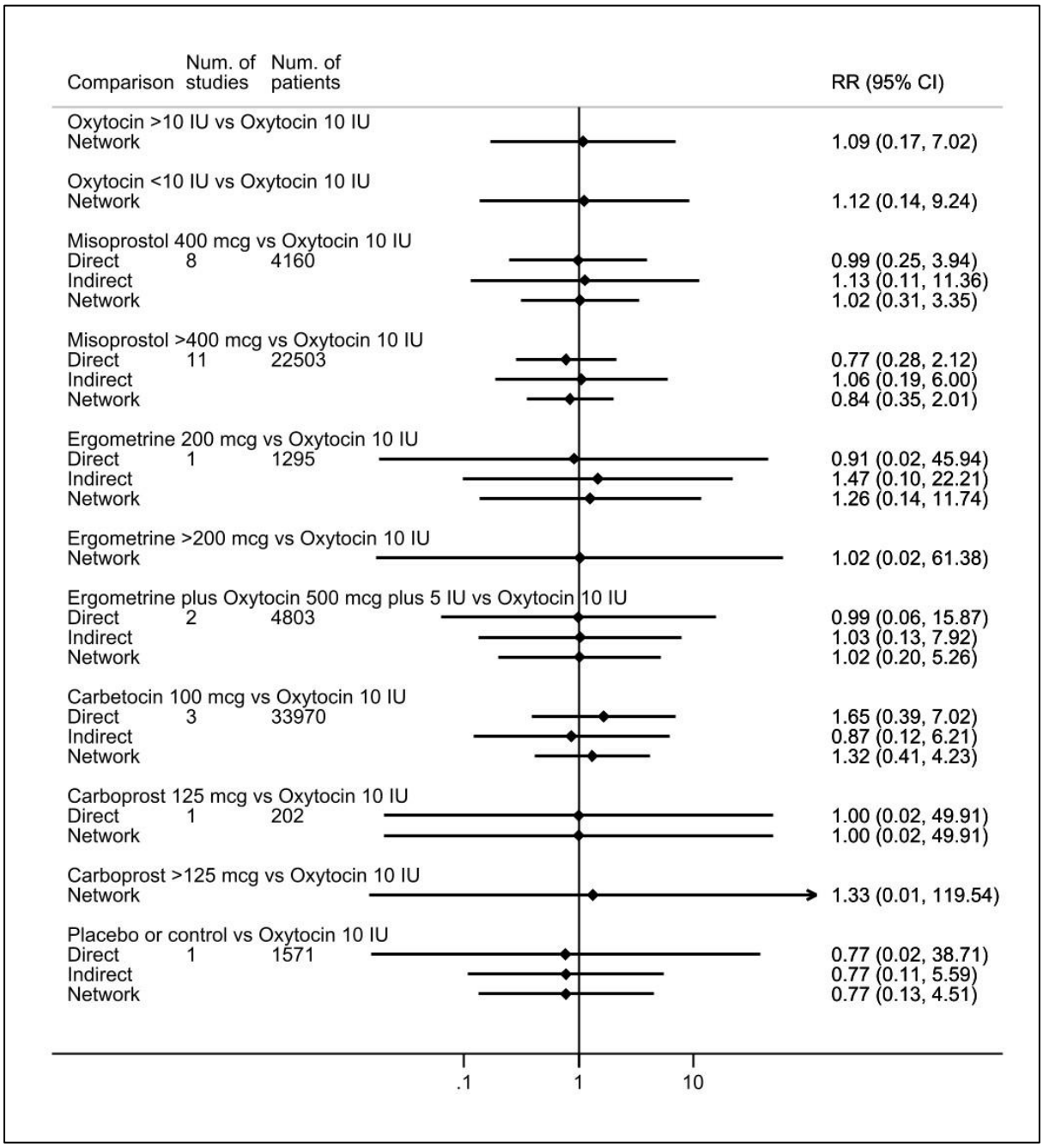


Figure 130: Maternal death-Rankogram-Doses NMA

Cumulative rankogram for maternal death. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

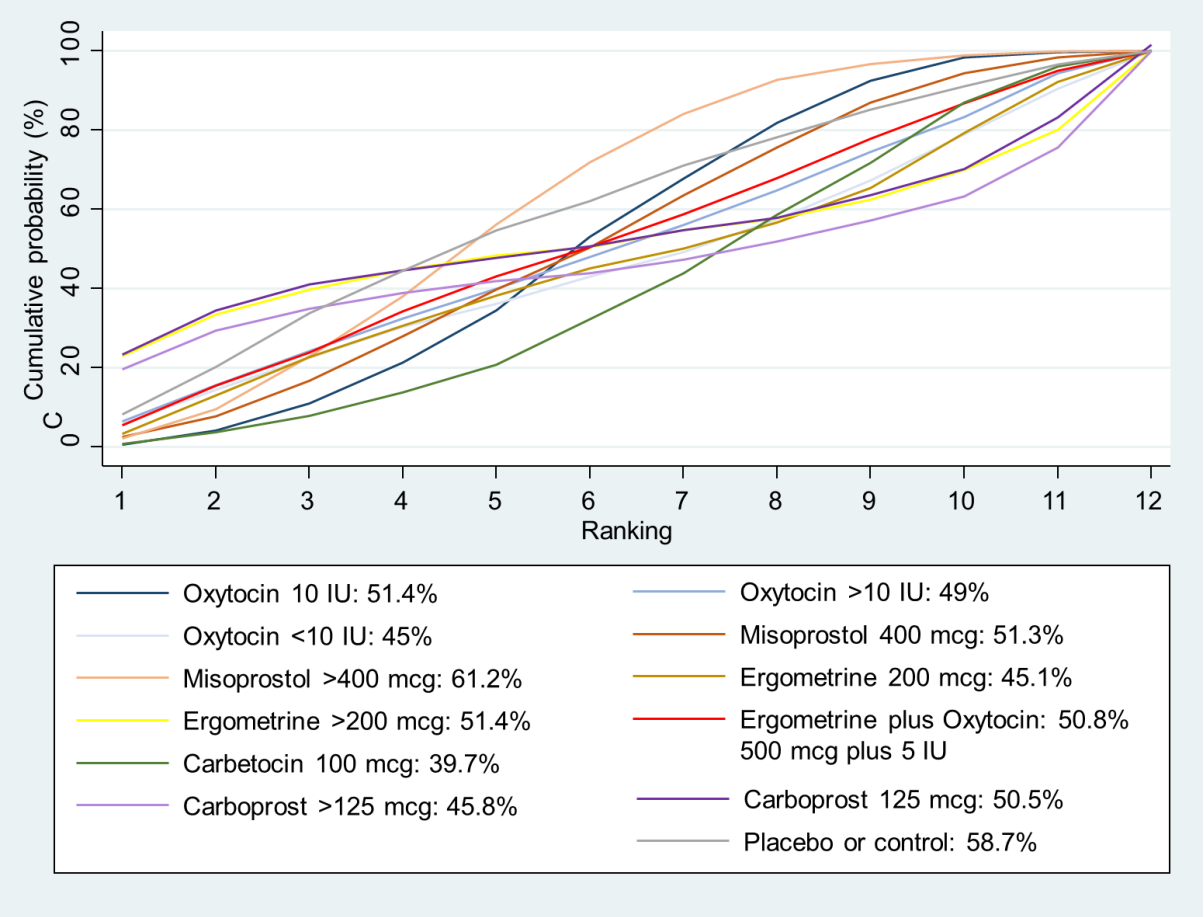


Figure 131: Maternal morbidity-Intensive Care Unit admissions-Network diagram-Doses NMA

Network diagram for maternal morbidity-ICU admissions. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

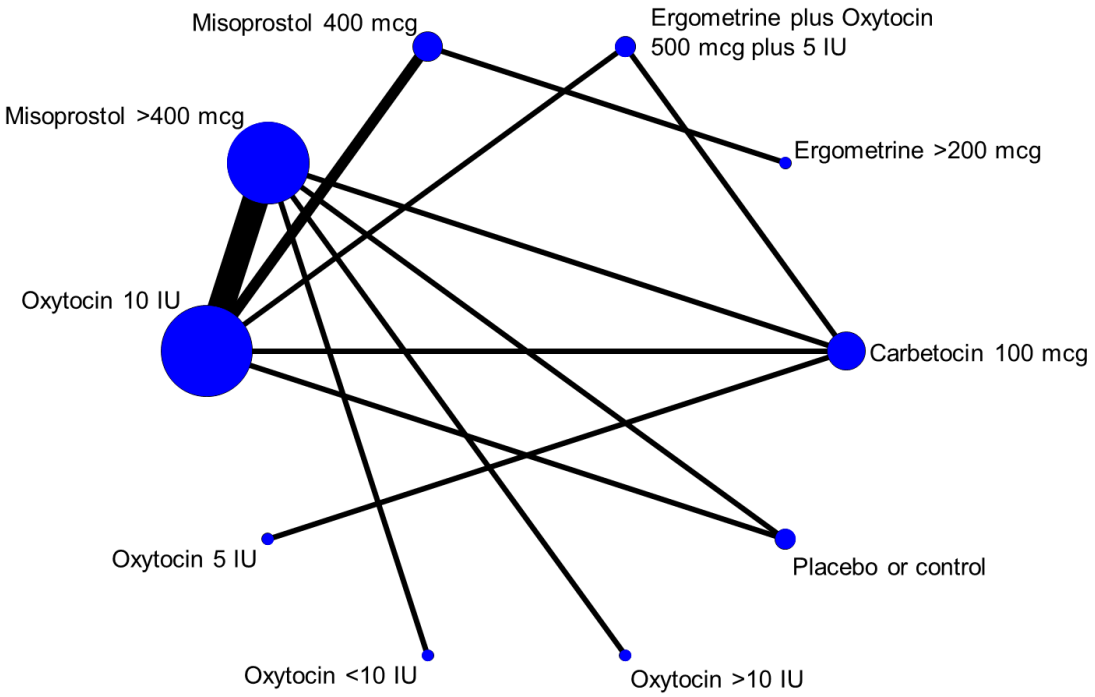


Figure 132: Maternal morbidity-Intensive Care Unit admissions-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for maternal morbidity-ICU admissions.

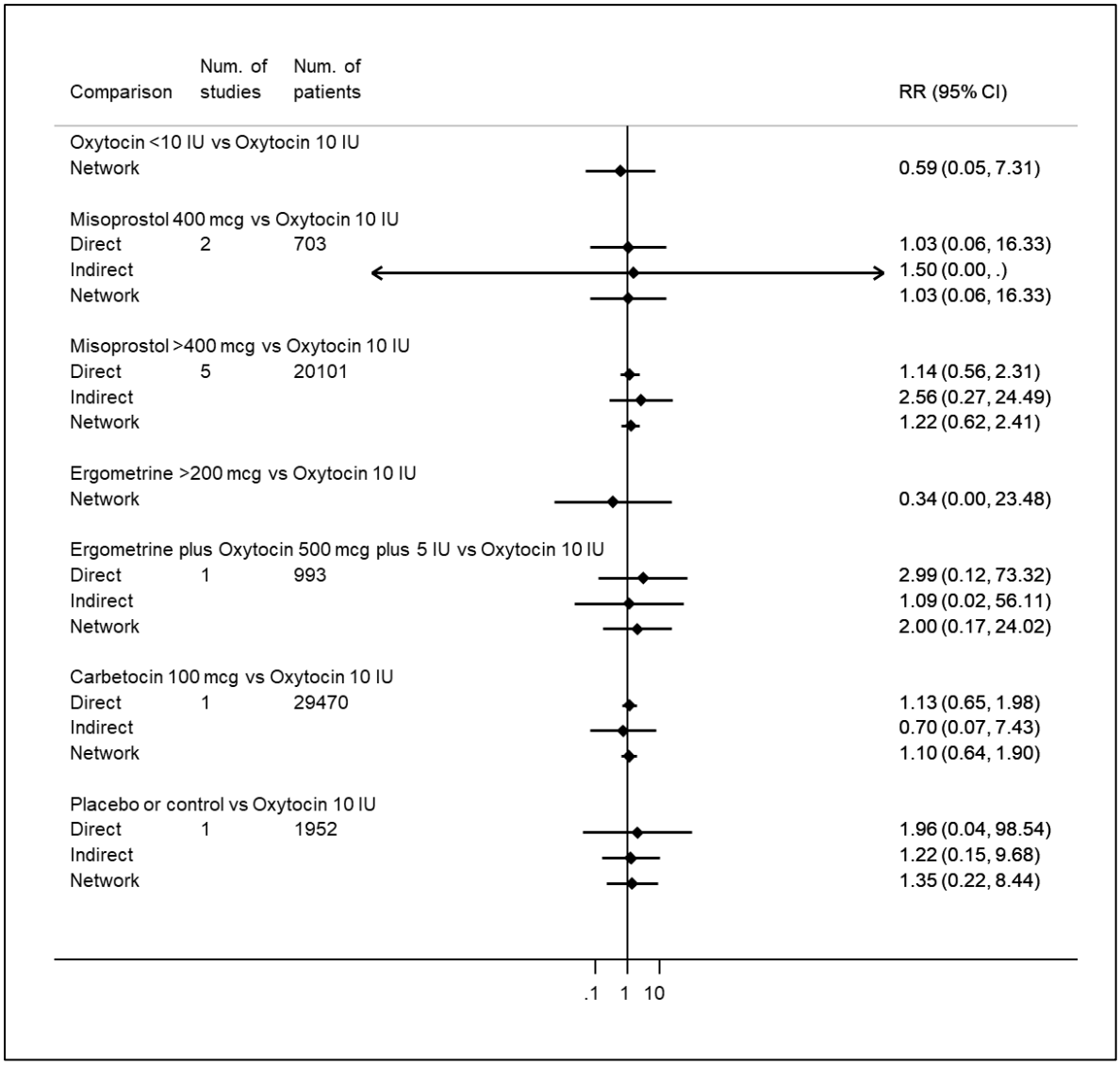


Figure 133: Maternal morbidity-Intensive Care Unit admissions-Rankogram-Doses NMA

Cumulative rankogram for maternal morbidity-ICU admissions. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

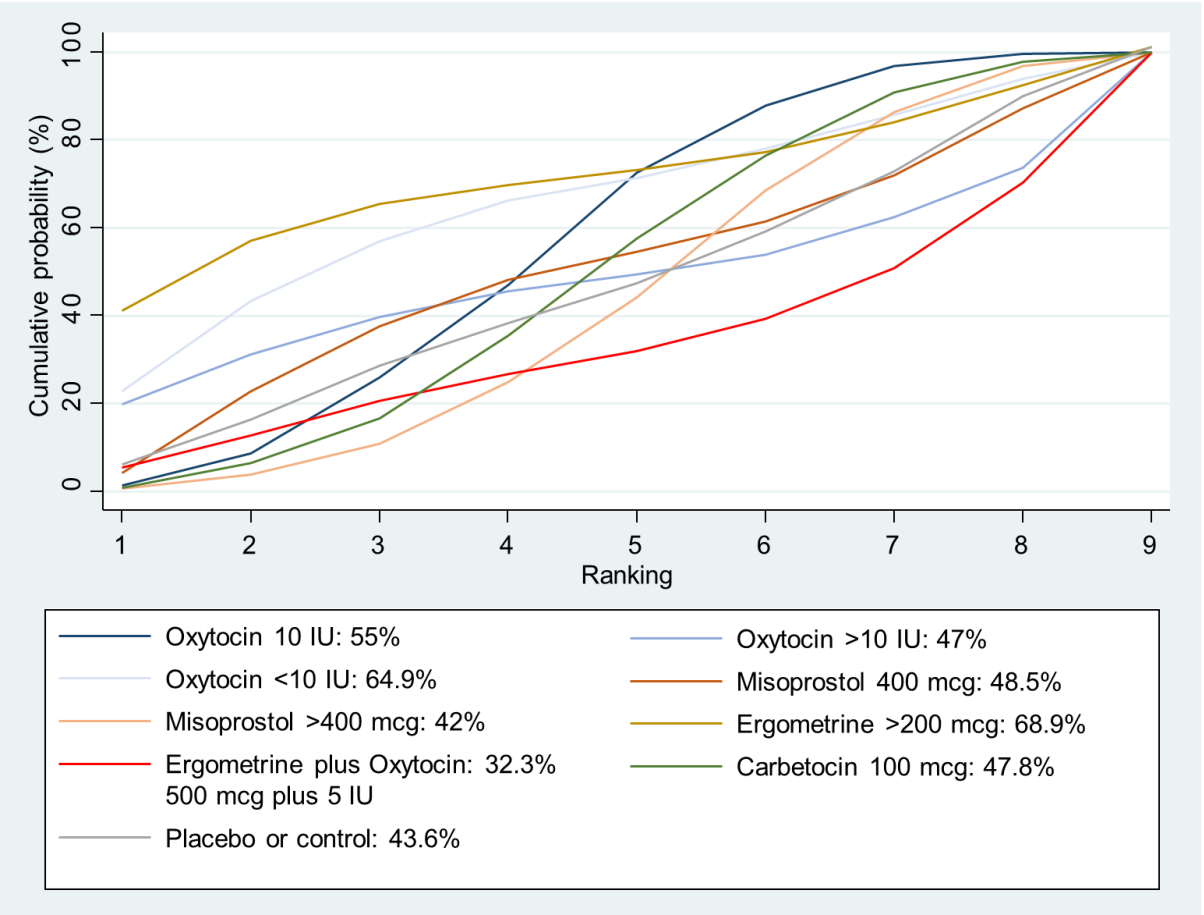


Figure 134: Blood loss-Network diagram-Doses NMA

Network diagram for blood loss. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

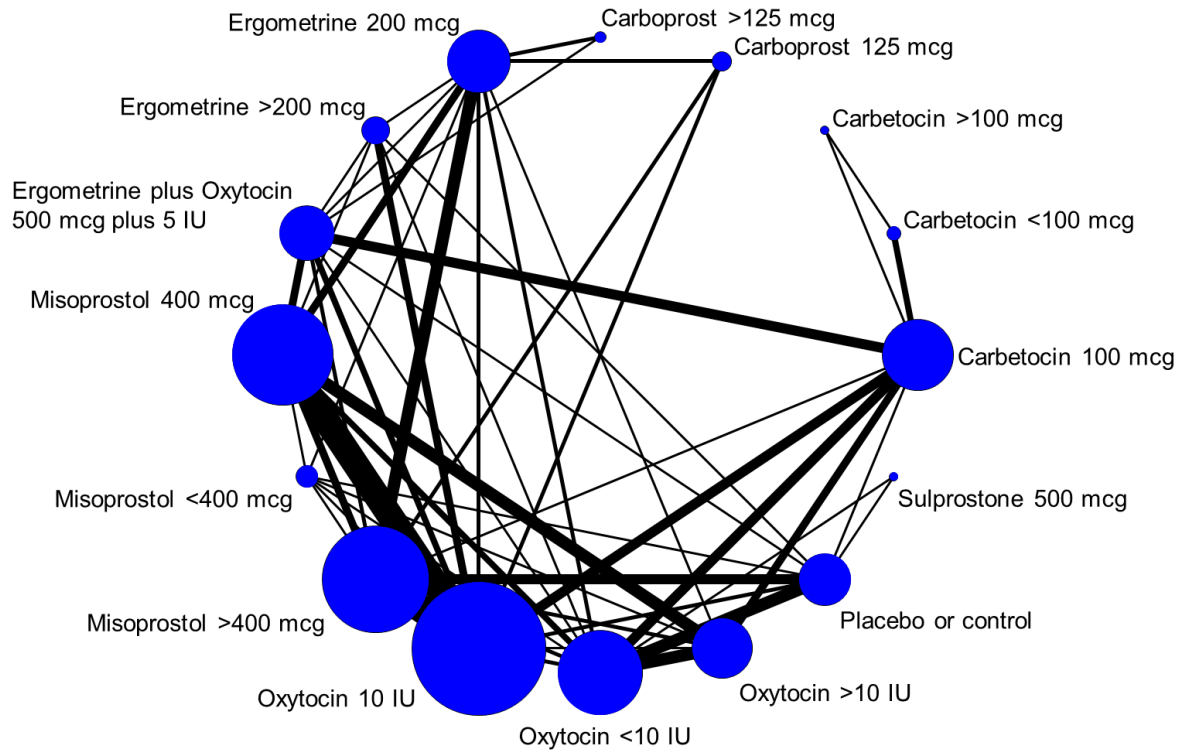


Figure 135: Blood loss-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for blood loss.

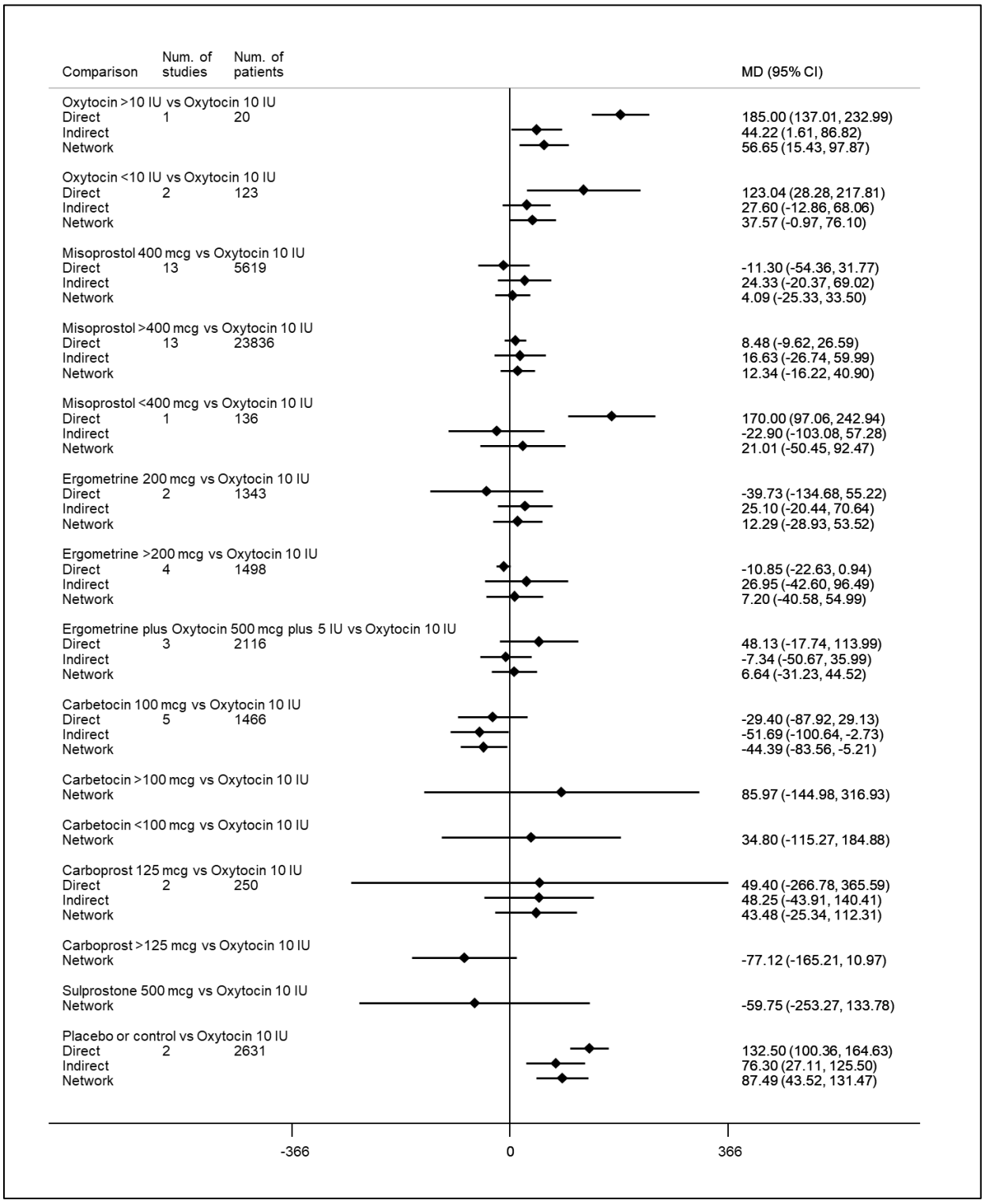


Figure 136: Blood loss-Rankogram-Doses NMA

Cumulative rankogram for blood loss. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

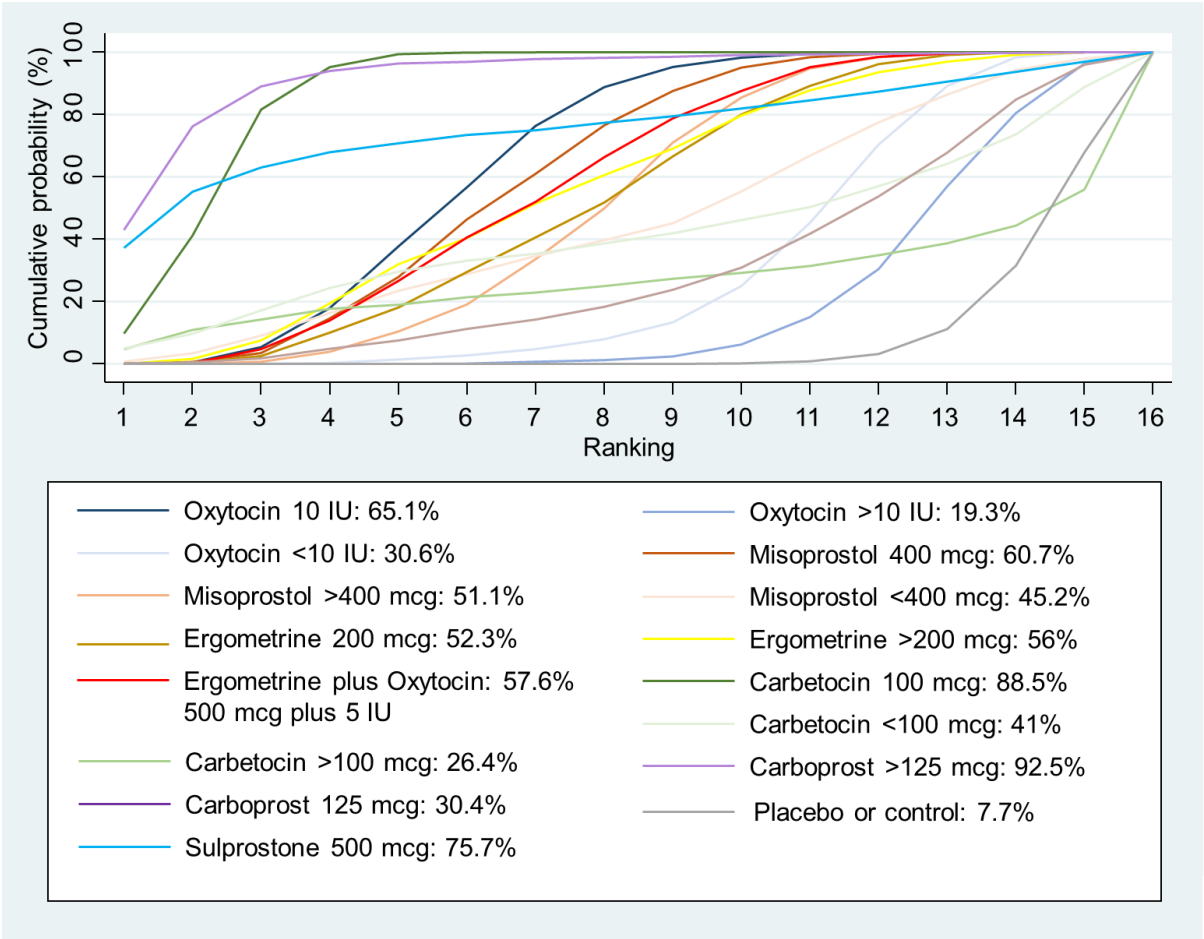


Figure 137: Hb change-Network diagram-Doses NMA

Network diagram for Hb change. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

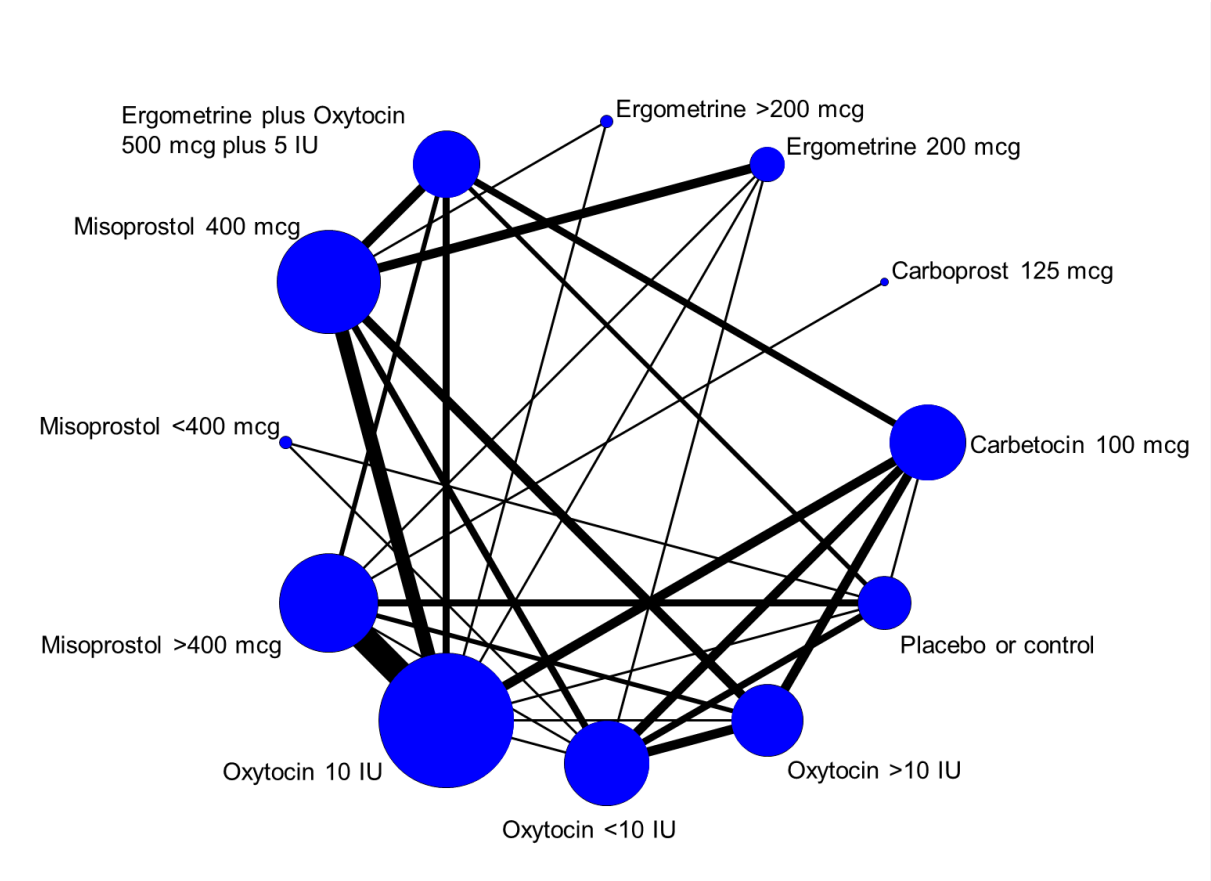


Figure 138: Hb change-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for Hb change.

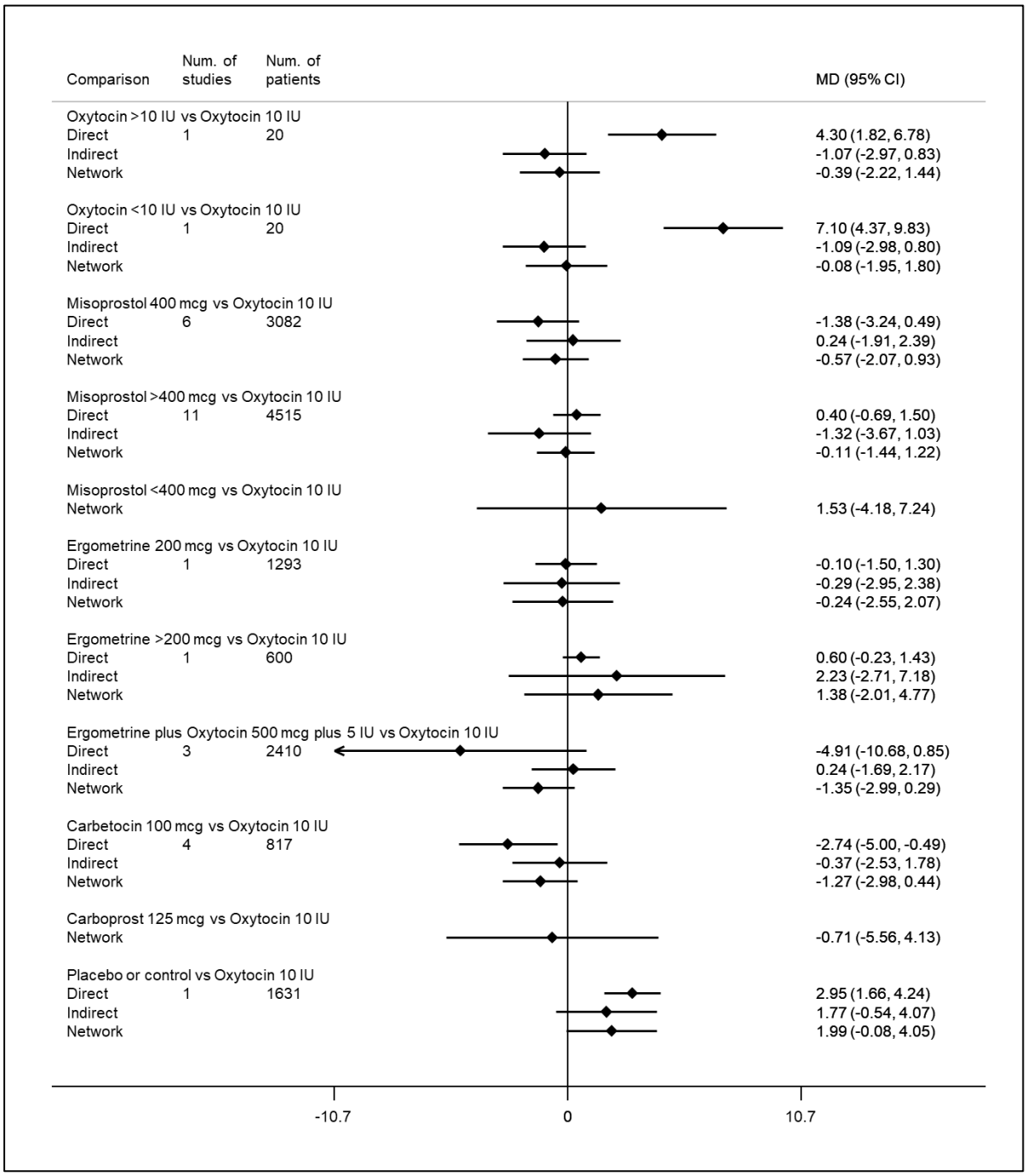


Figure 139: Hb change-Rankogram-Doses NMA

Cumulative rankogram for Hb change. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

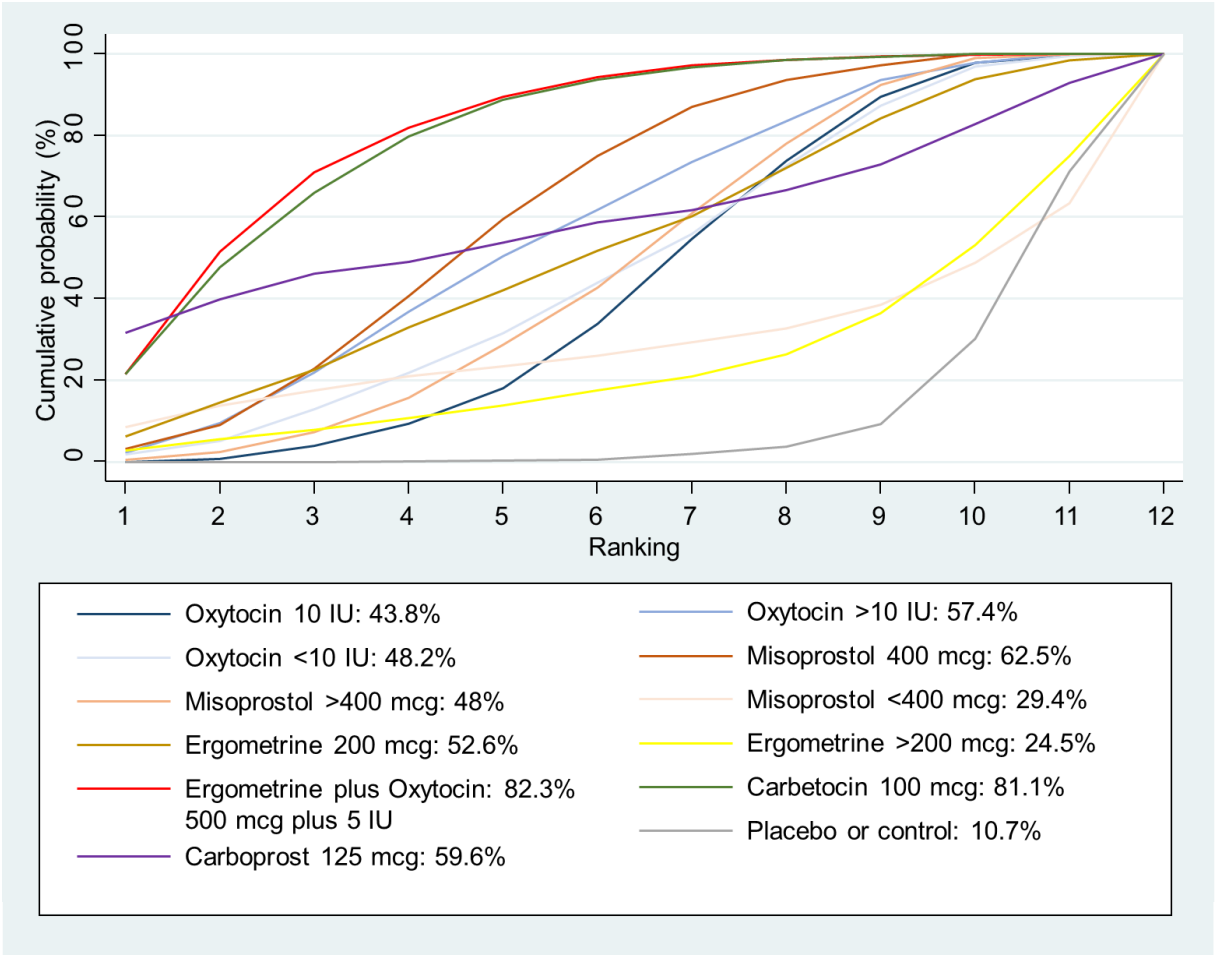


Figure 140: Breastfeeding-Network diagram-Doses NMA

Network diagram for breastfeeding. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

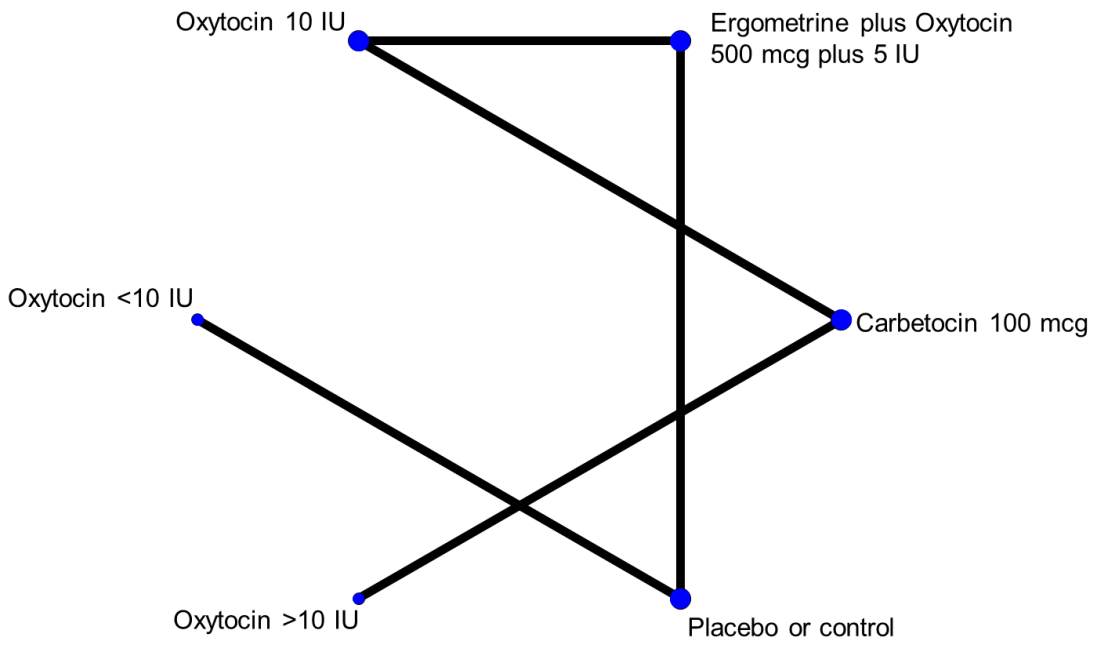
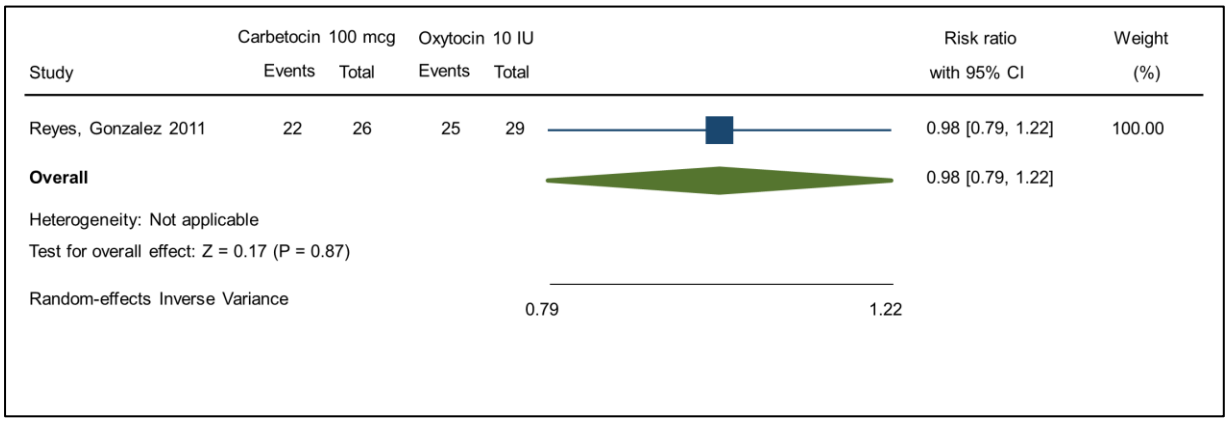


Figure 141: Breastfeeding-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise analyses for breastfeeding.



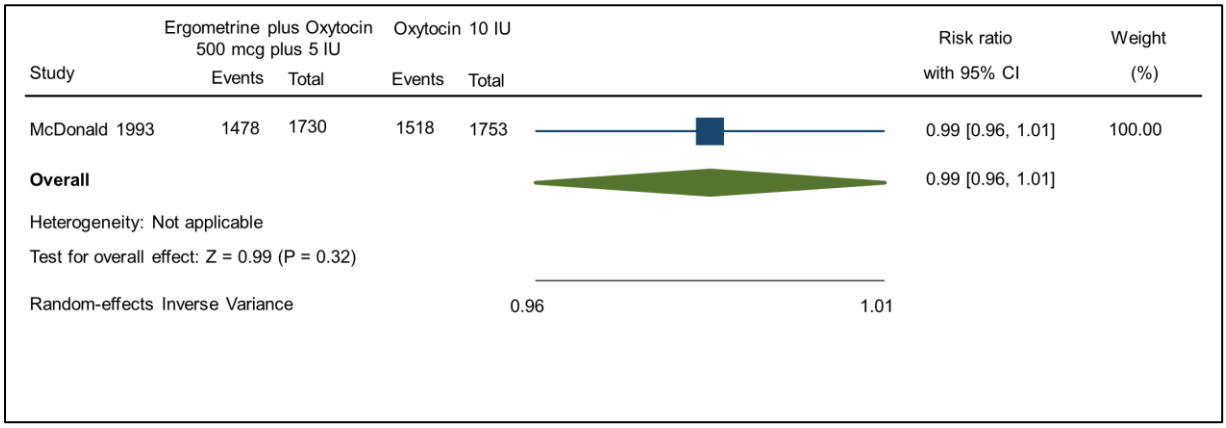


Figure 142: Abdominal pain-Network diagram-Doses NMA

Network diagram for abdominal pain. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

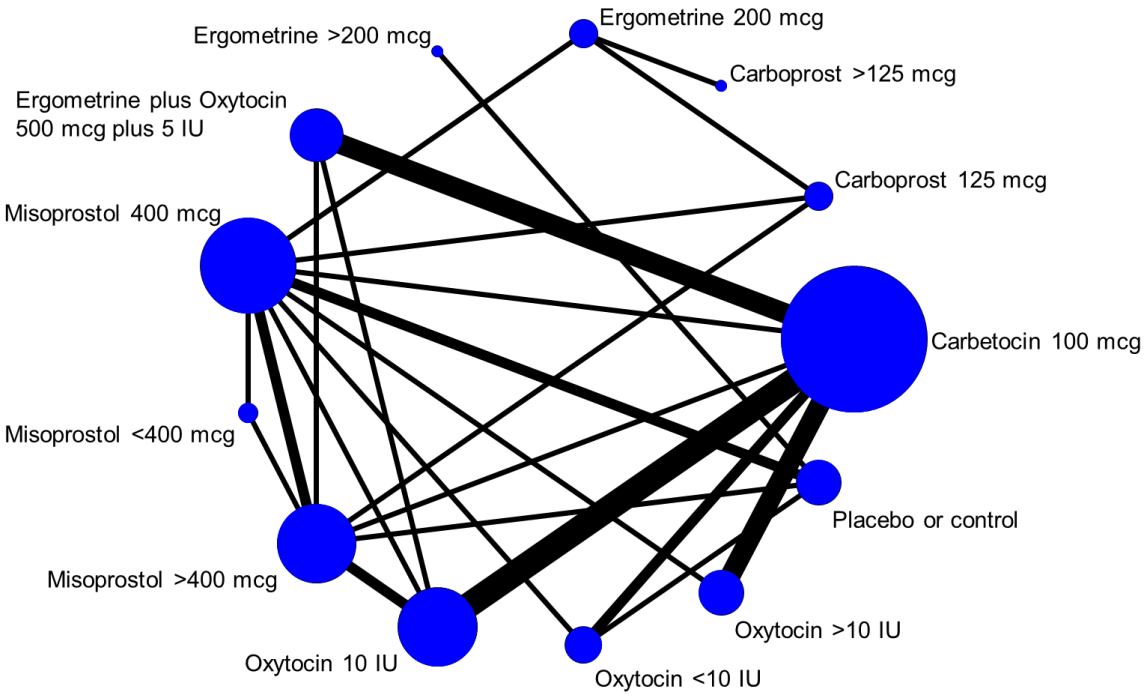


Figure 143: Abdominal pain-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for abdominal pain.

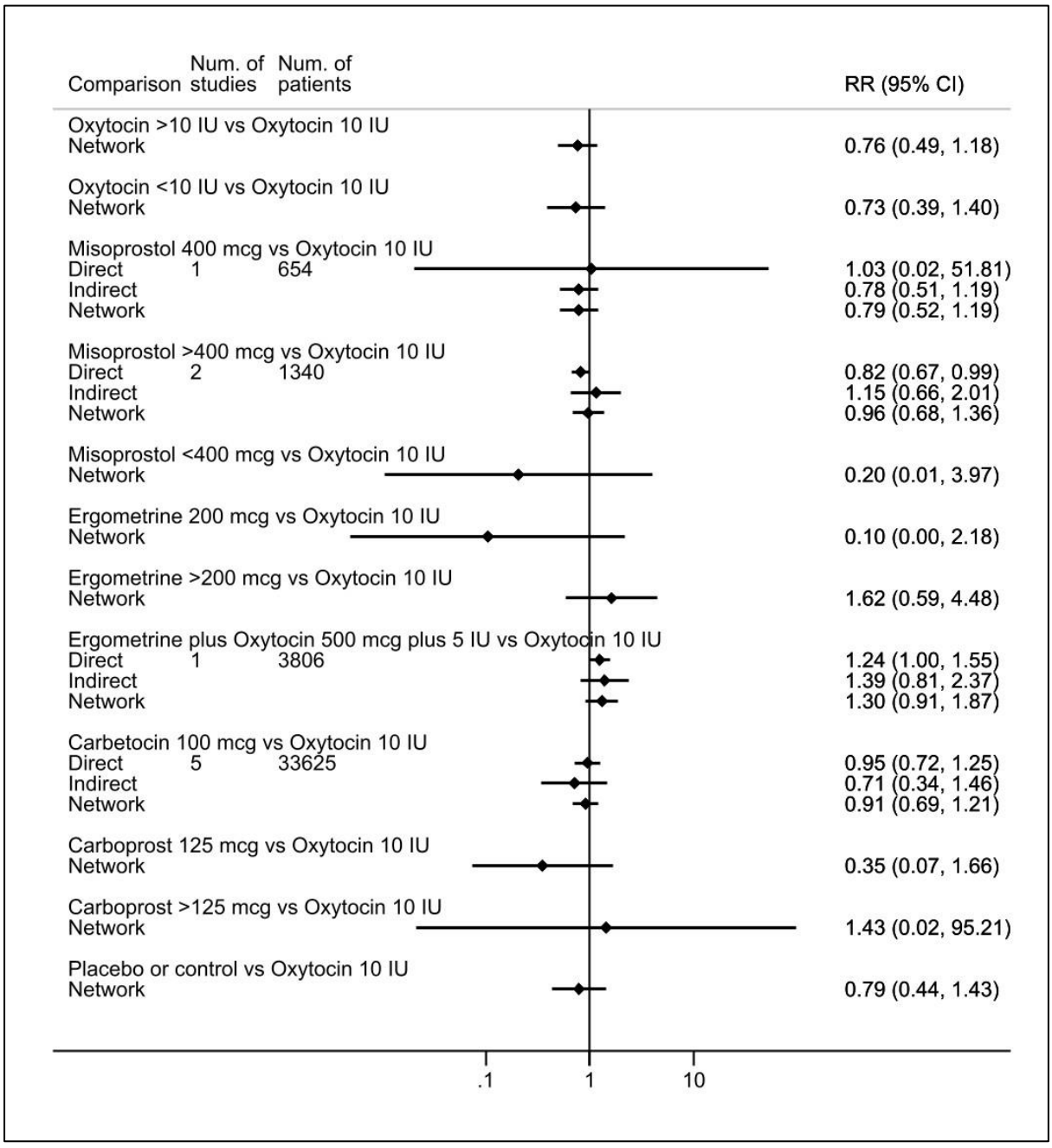


Figure 144: Abdominal pain-Rankogram-Doses NMA

Cumulative rankogram for abdominal pain. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

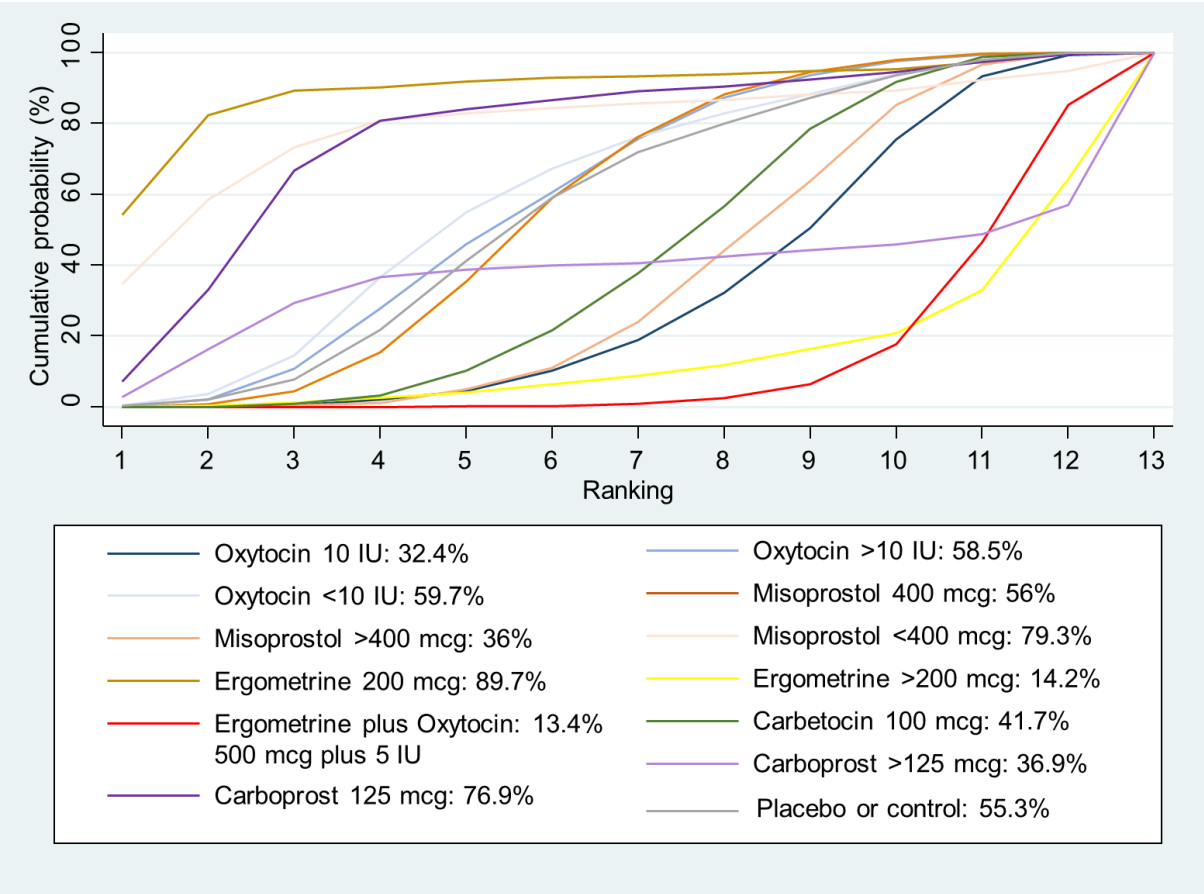


Figure 145: Diarrhoea-Network diagram-Doses NMA

Network diagram for diarrhoea. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

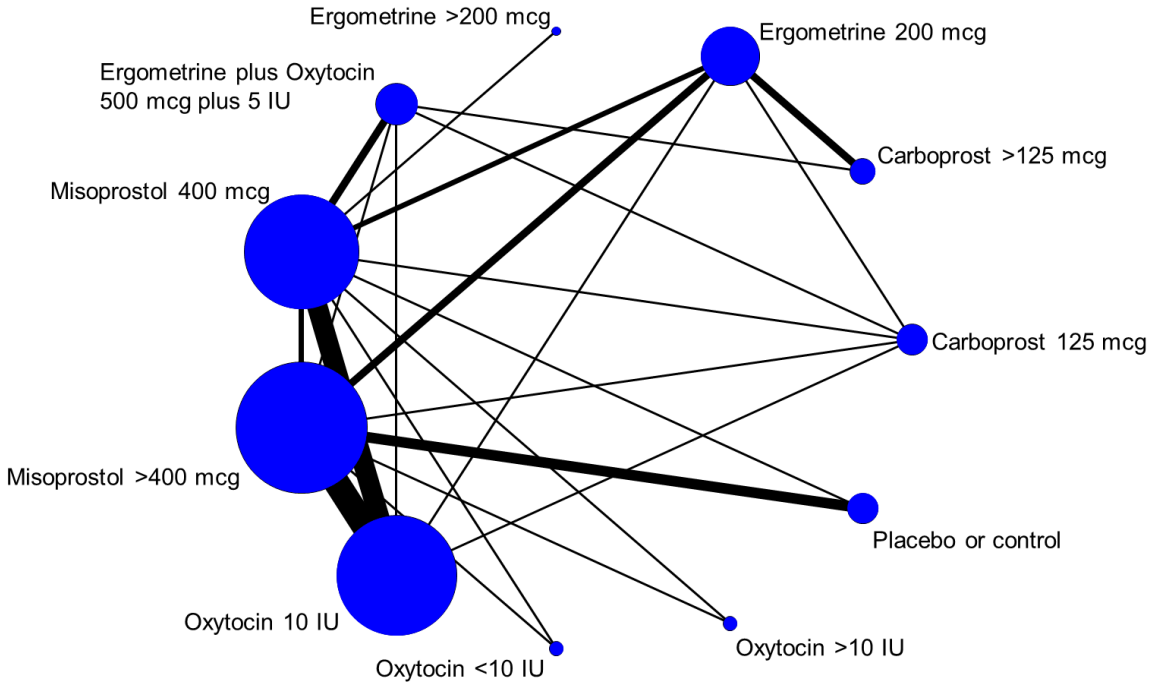


Figure 146: Diarrhoea-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for diarrhoea.

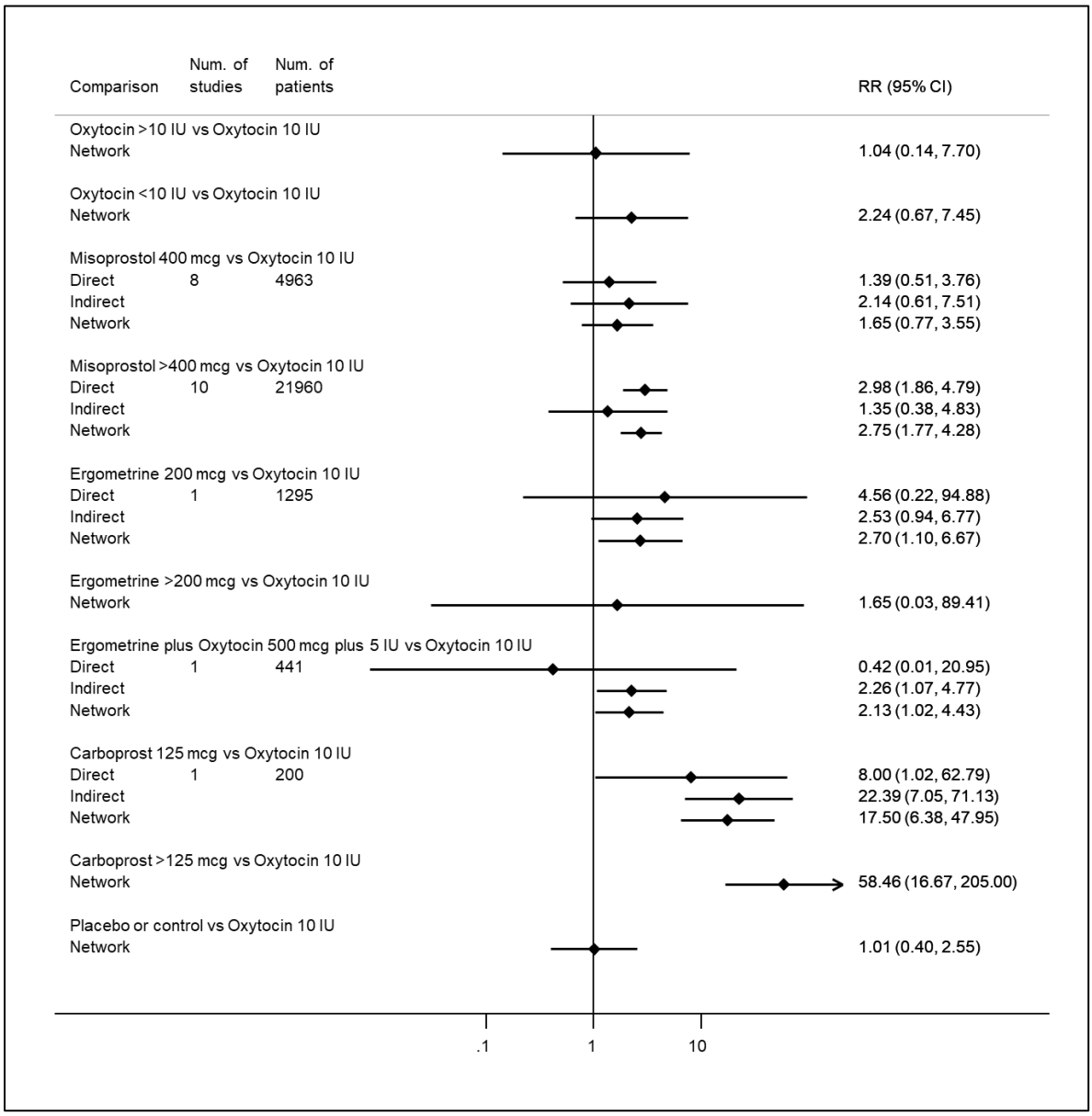


Figure 147: Diarrhoea-Rankogram-Doses NMA

Cumulative rankogram for diarrhoea. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

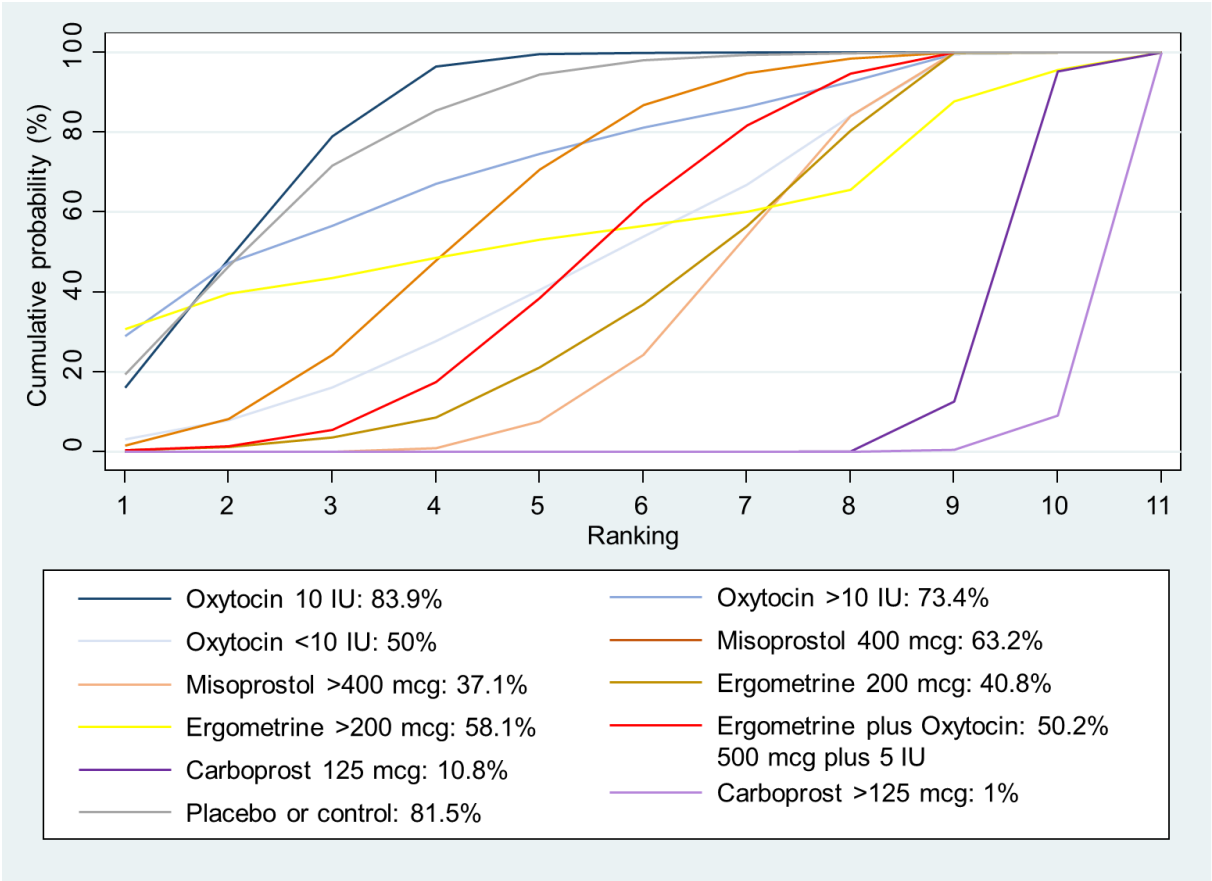


Figure 148: Headache-Network diagram-Doses NMA

Network diagram for headache. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

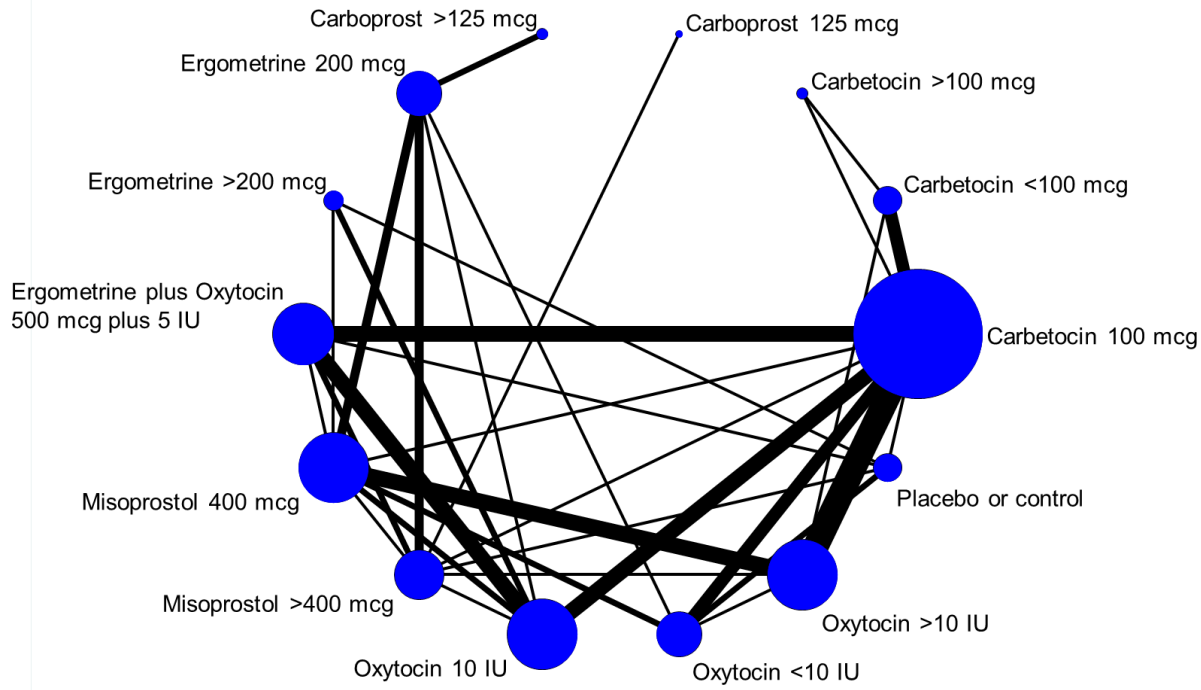


Figure 149: Headache-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for headache.

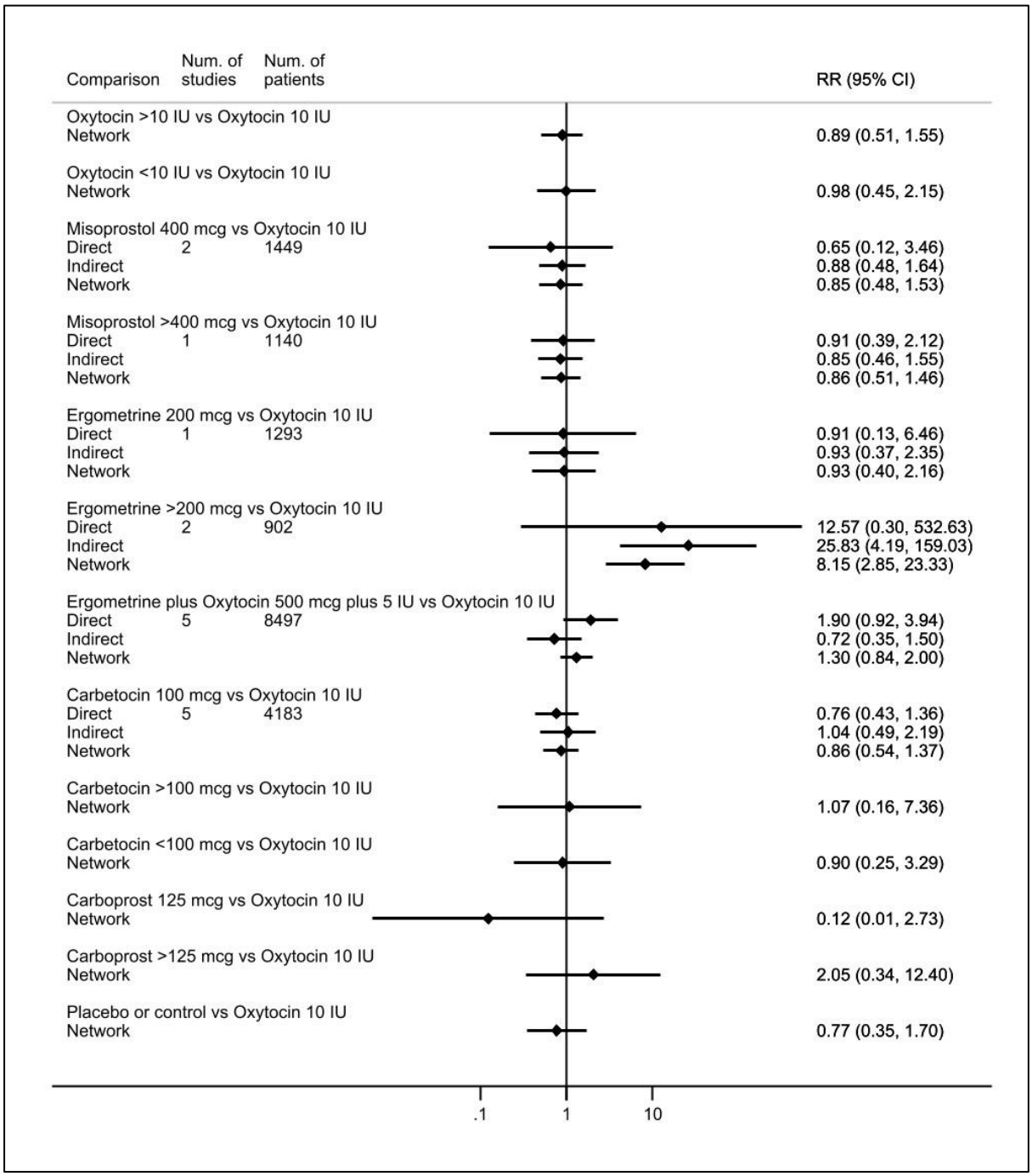


Figure 150: Headache-Rankogram-Doses NMA

Cumulative rankogram for headache. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

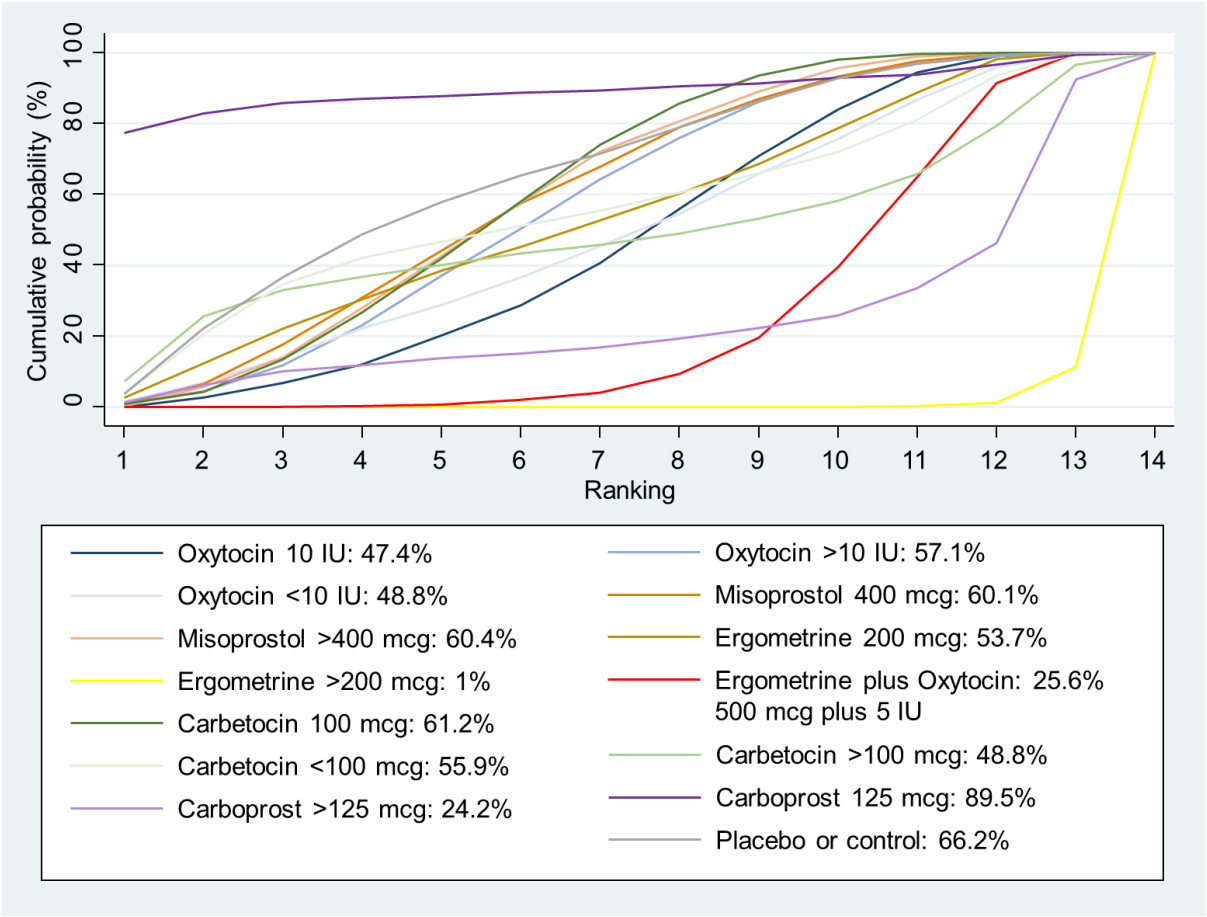


Figure 151: Nausea-Network diagram-Doses NMA

Network diagram for nausea. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

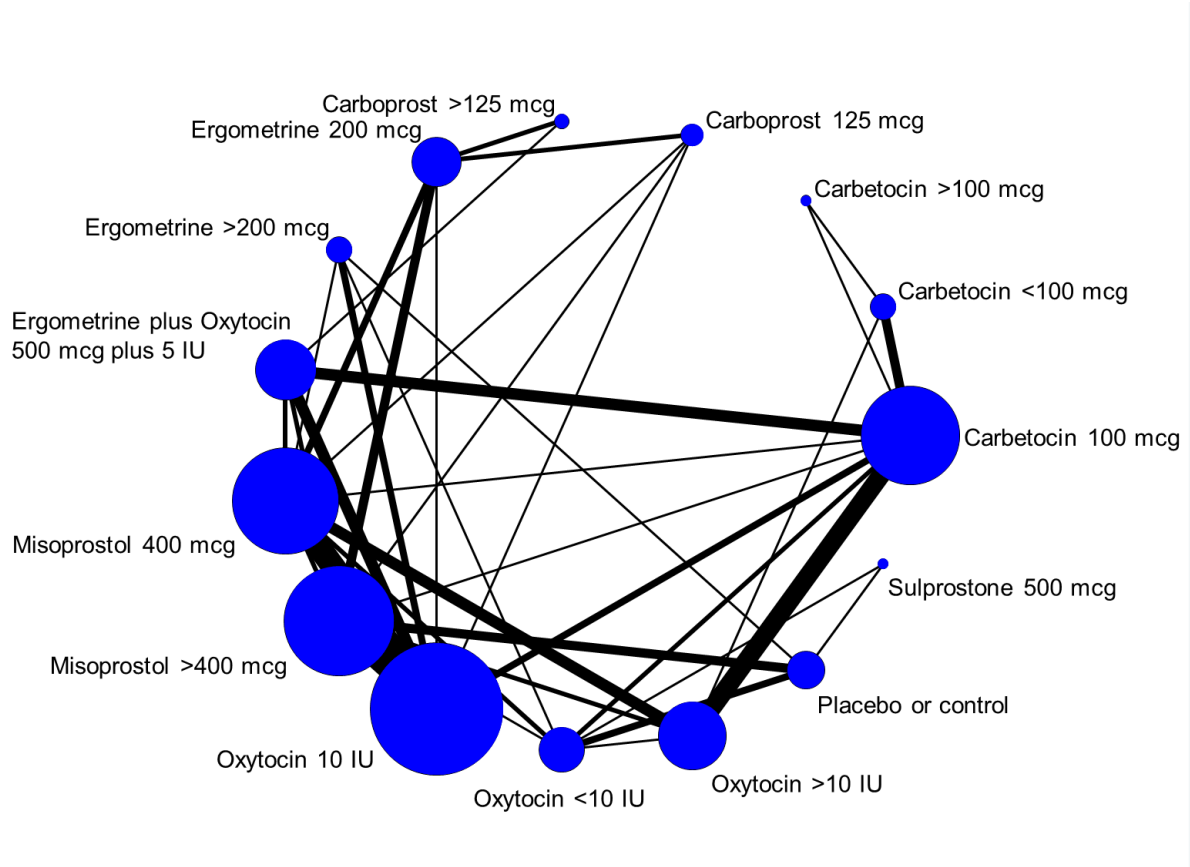


Figure 152: Nausea-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for nausea.

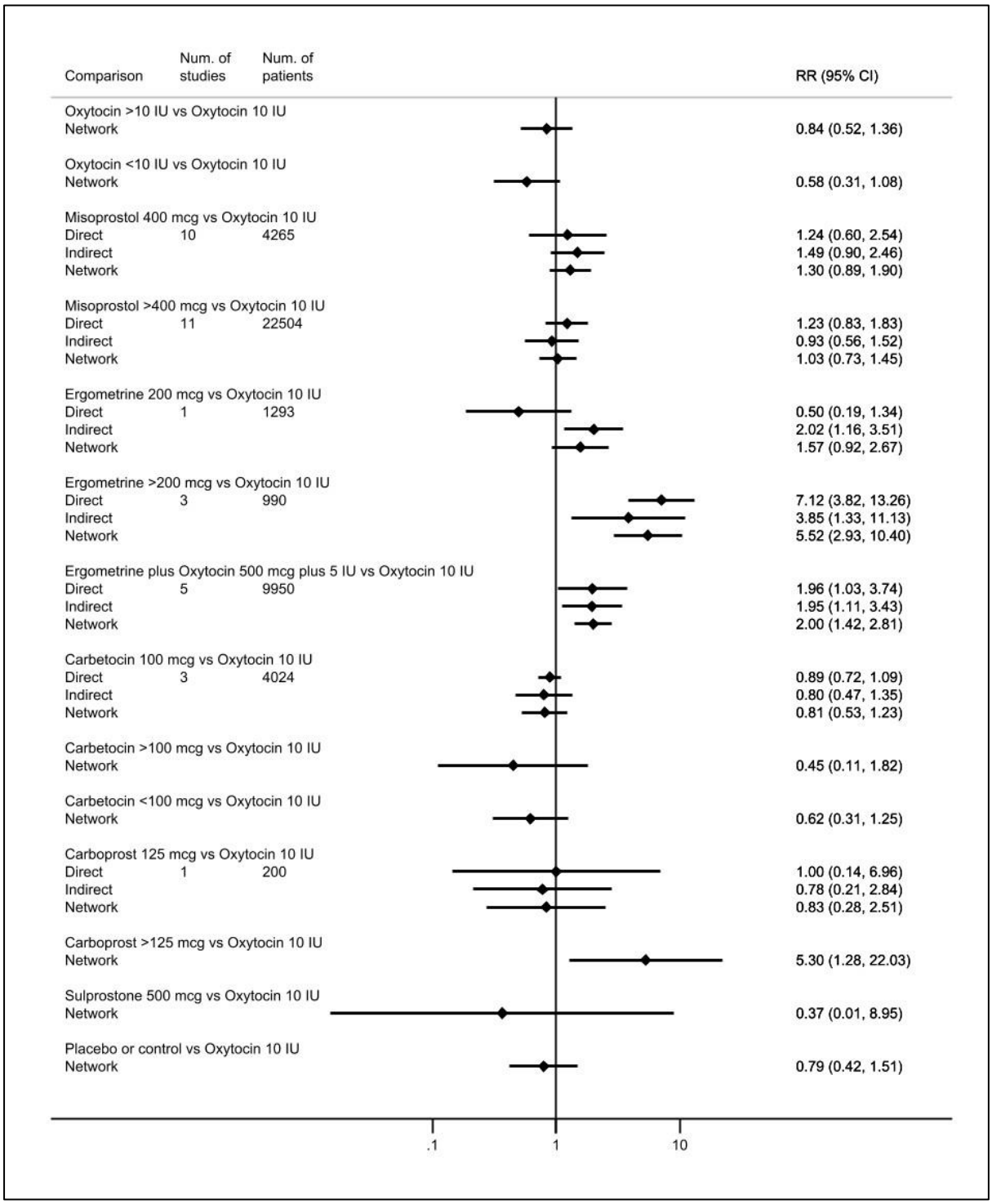


Figure 153: Nausea-Rankogram-Doses NMA

Cumulative rankogram for nausea. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

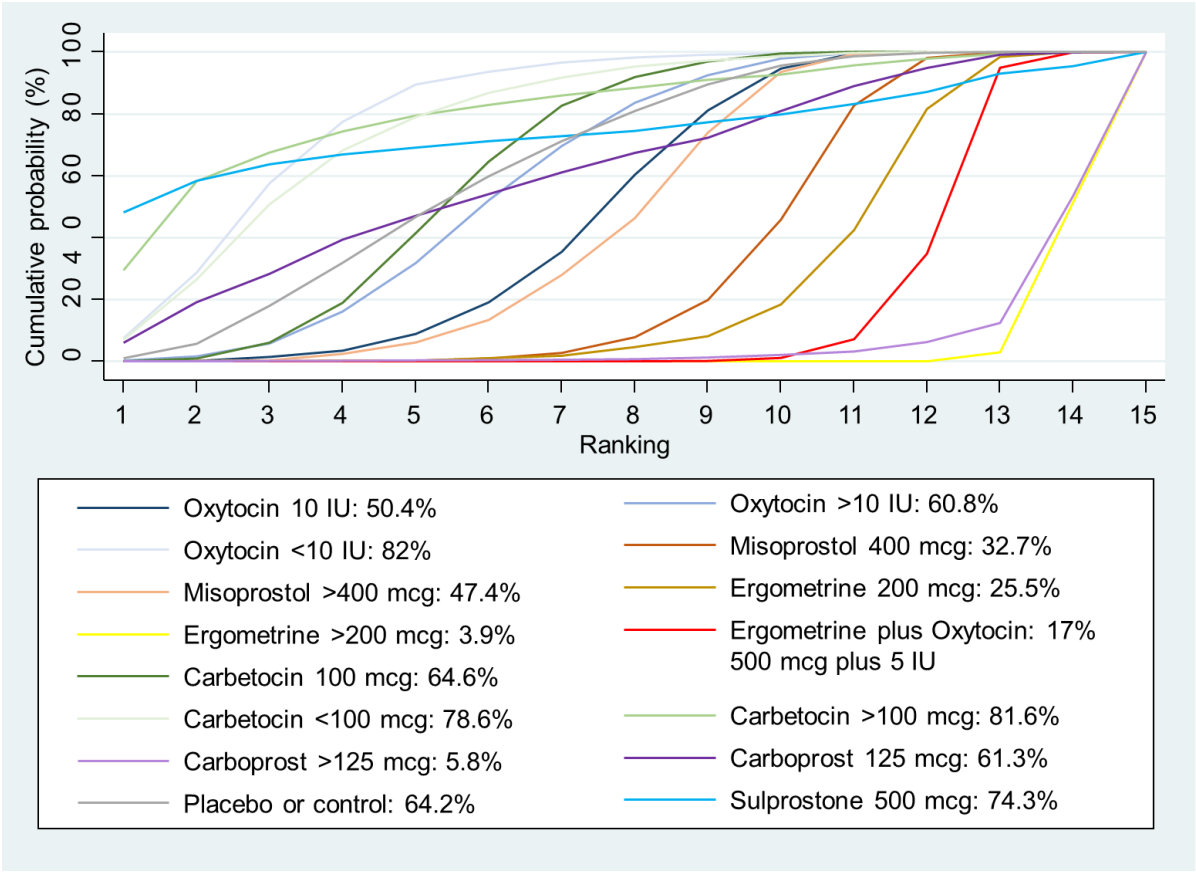


Figure 154: Shivering-Network diagram-Doses NMA

Network diagram for shivering. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

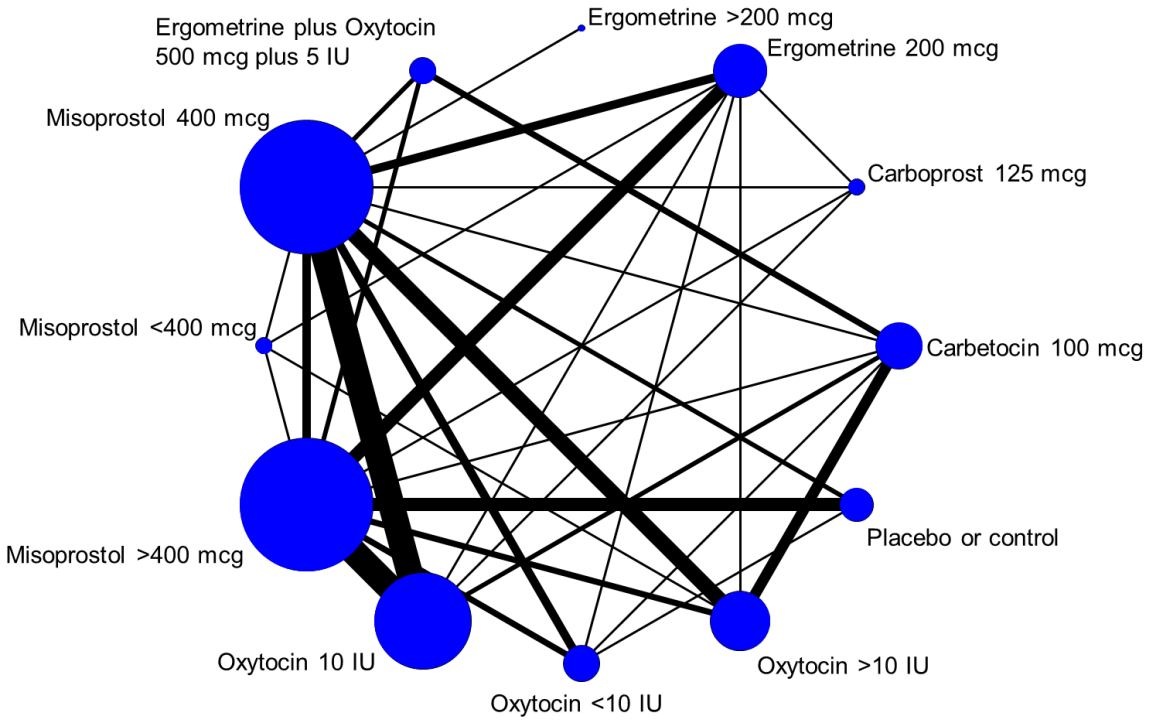


Figure 155: Shivering-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for shivering.

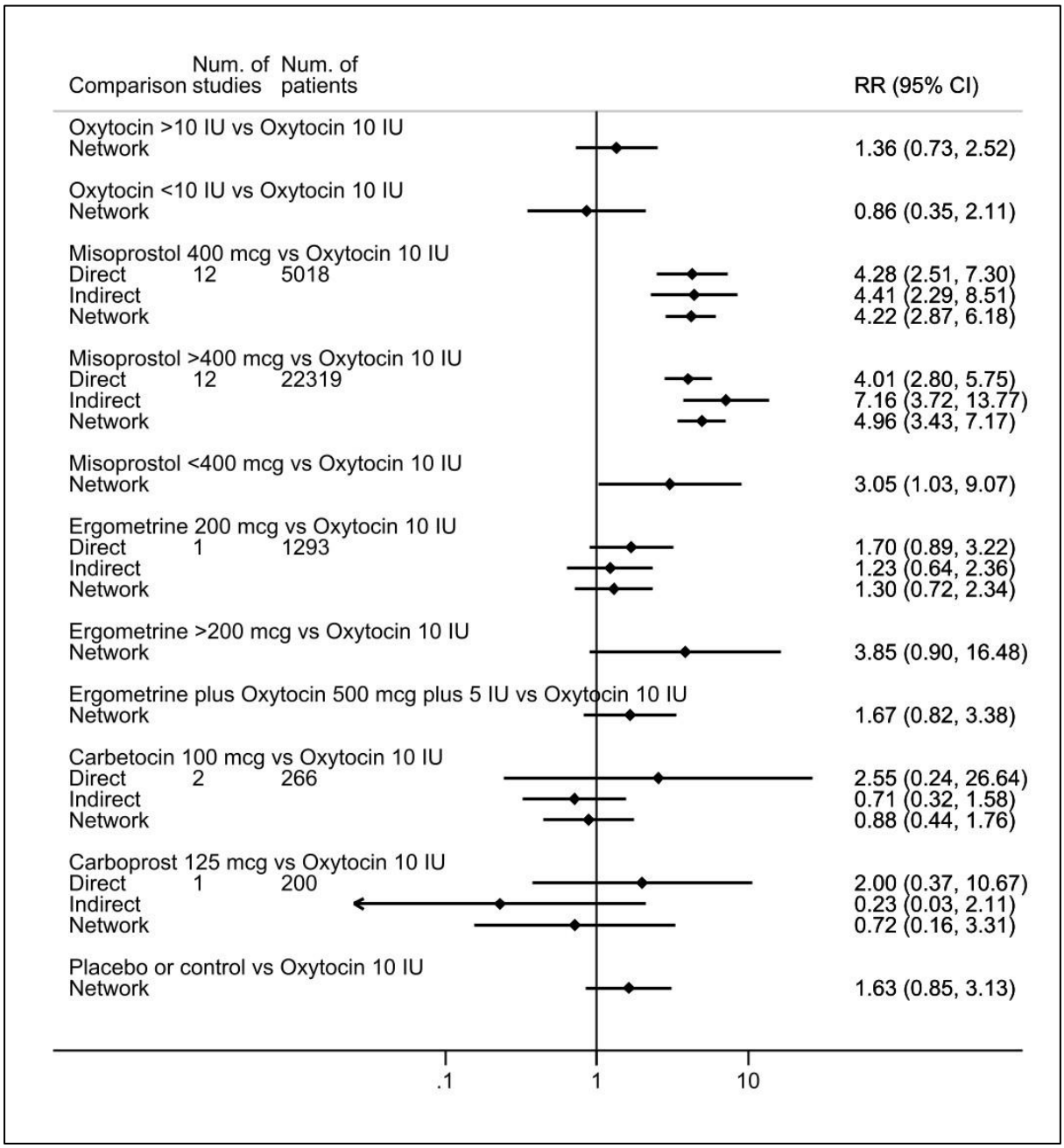
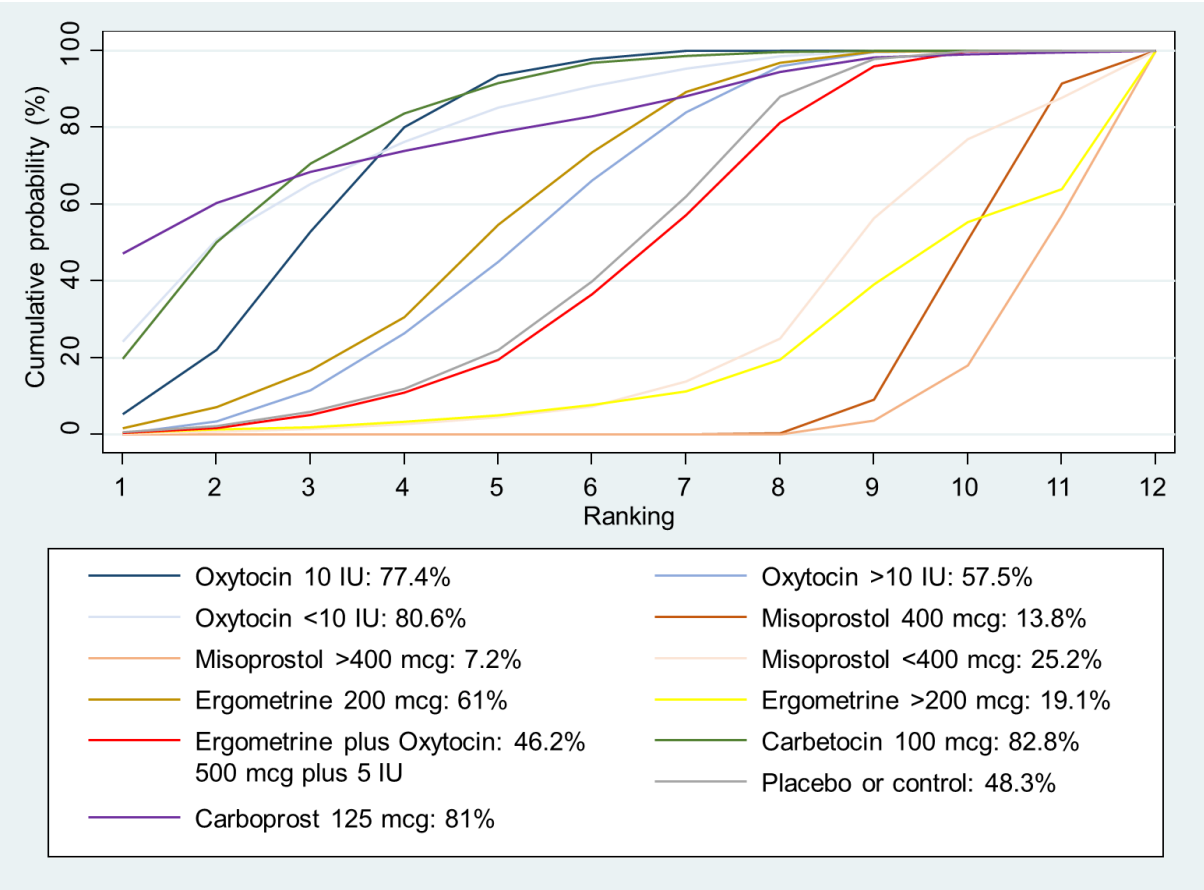


Figure 156: Shivering-Rankogram-Doses NMA

Cumulative rankogram for shivering. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Sensitivity analyses

Figure 157: PPH ≥500 mL restricted to studies at low Risk of Bias-Network diagram-Doses NMA

Network diagram for PPH ≥500 mL restricted to studies at low Risk of Bias. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

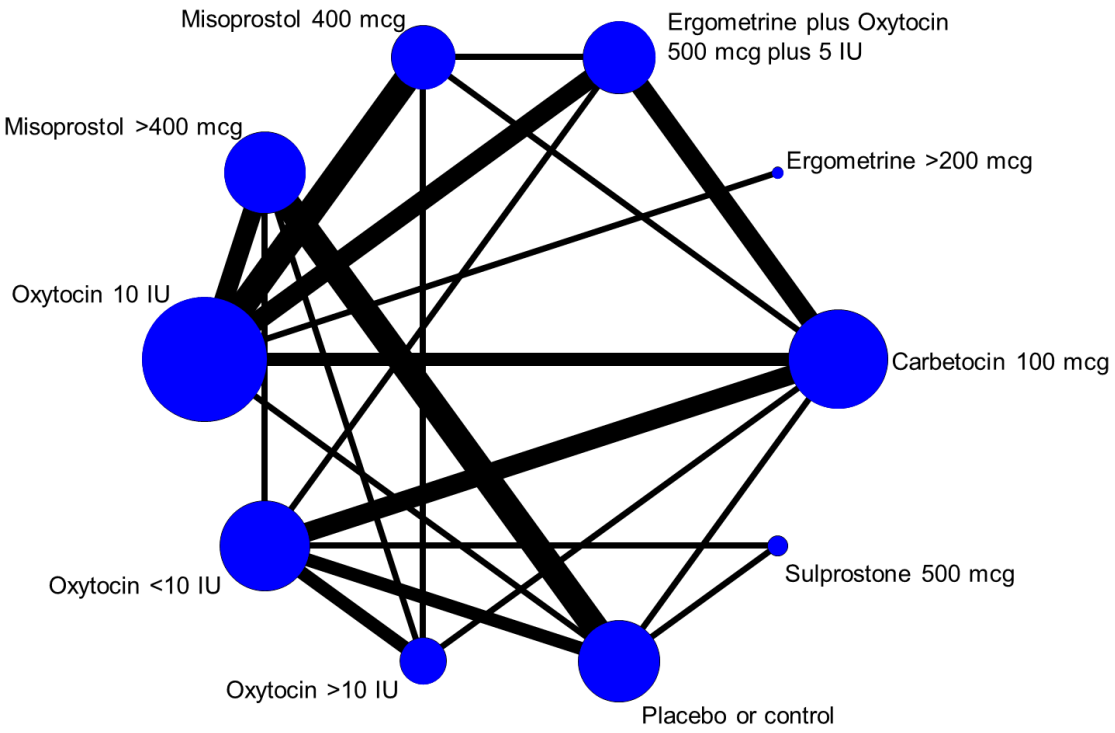


Figure 158: PPH ≥500 mL restricted to studies at low Risk of Bias-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

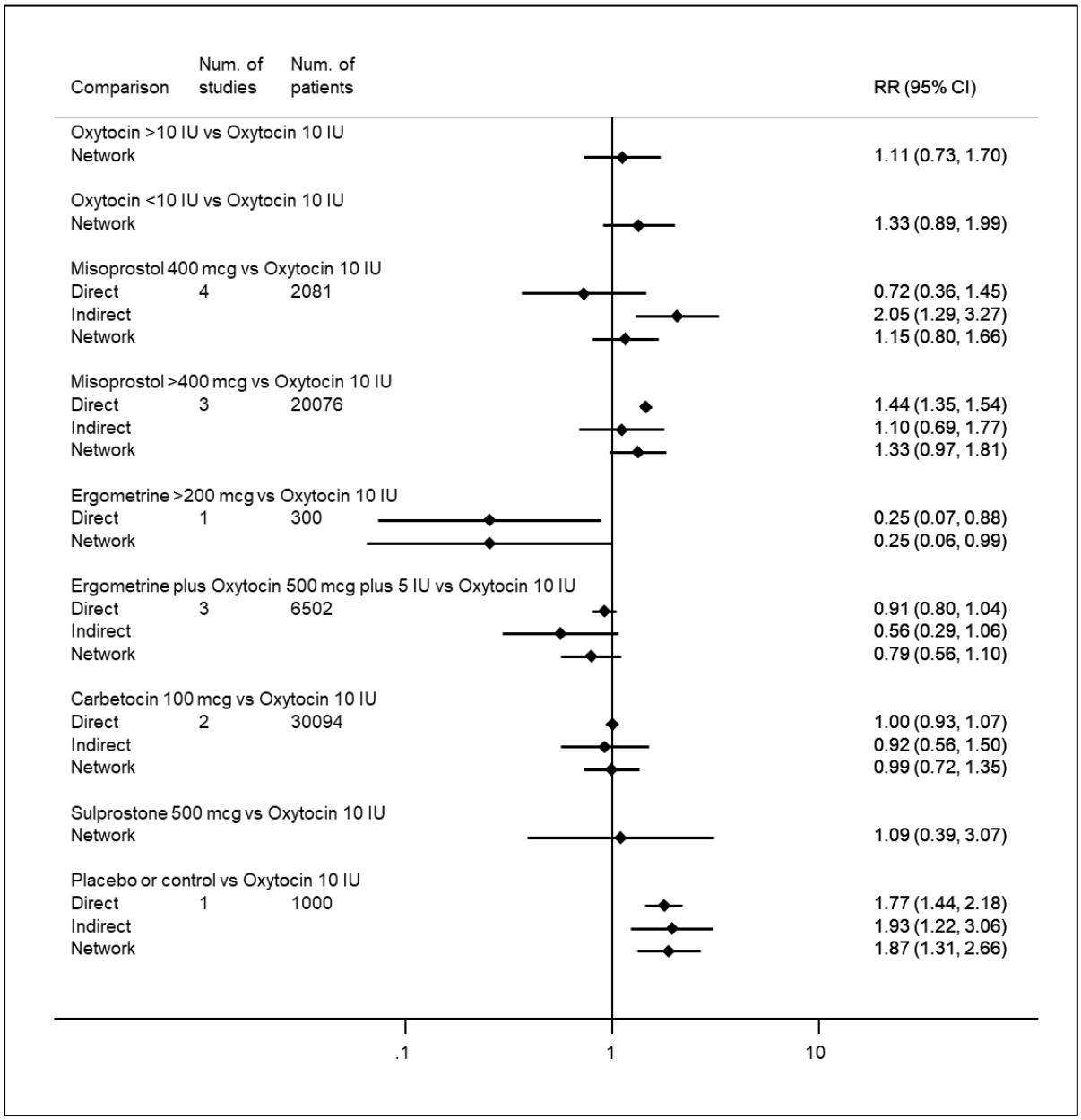


Figure 159: PPH ≥500 mL restricted to studies at low Risk of Bias-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies at low Risk of Bias. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

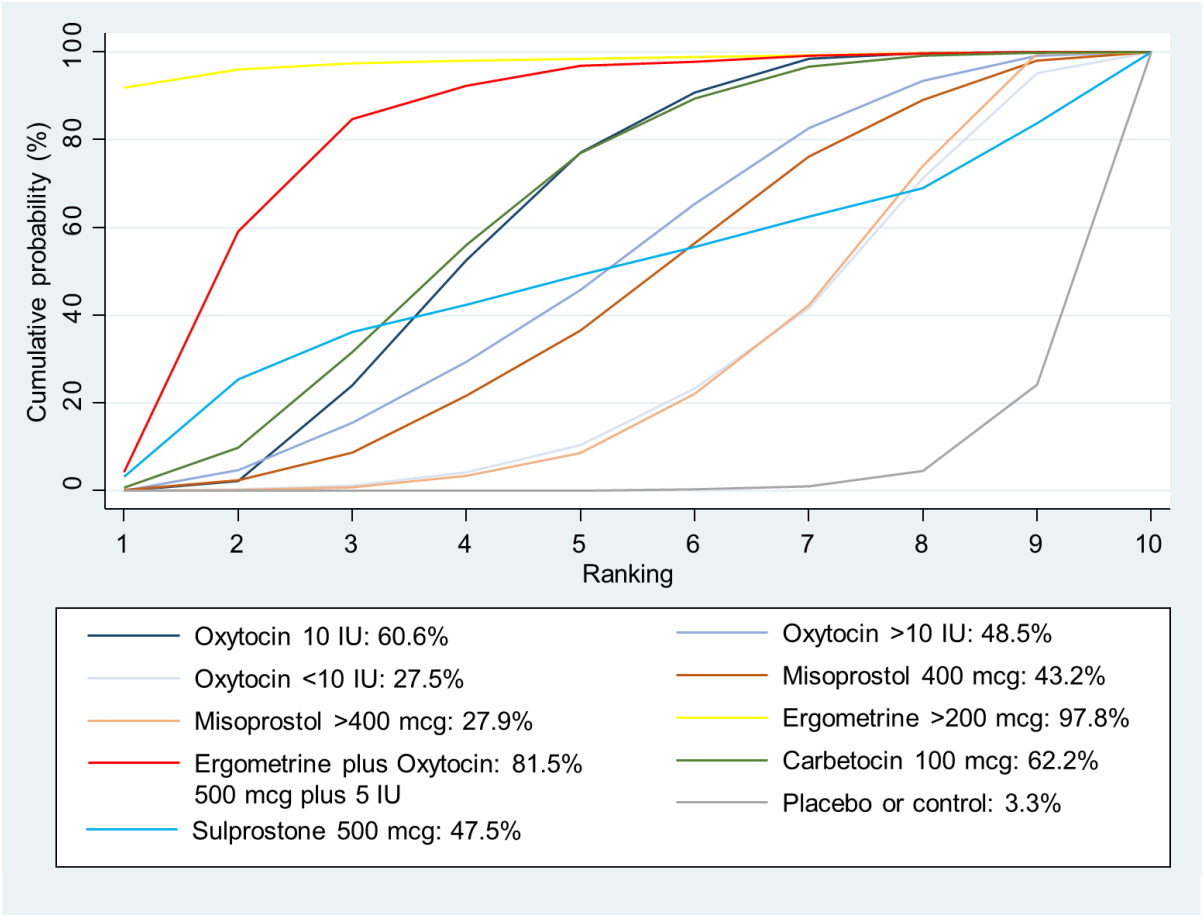


Figure 160: PPH ≥500 mL restricted to studies with public or no funding-Network diagram-Doses NMA

Network diagram for PPH ≥500 mL restricted to studies with public or no funding. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

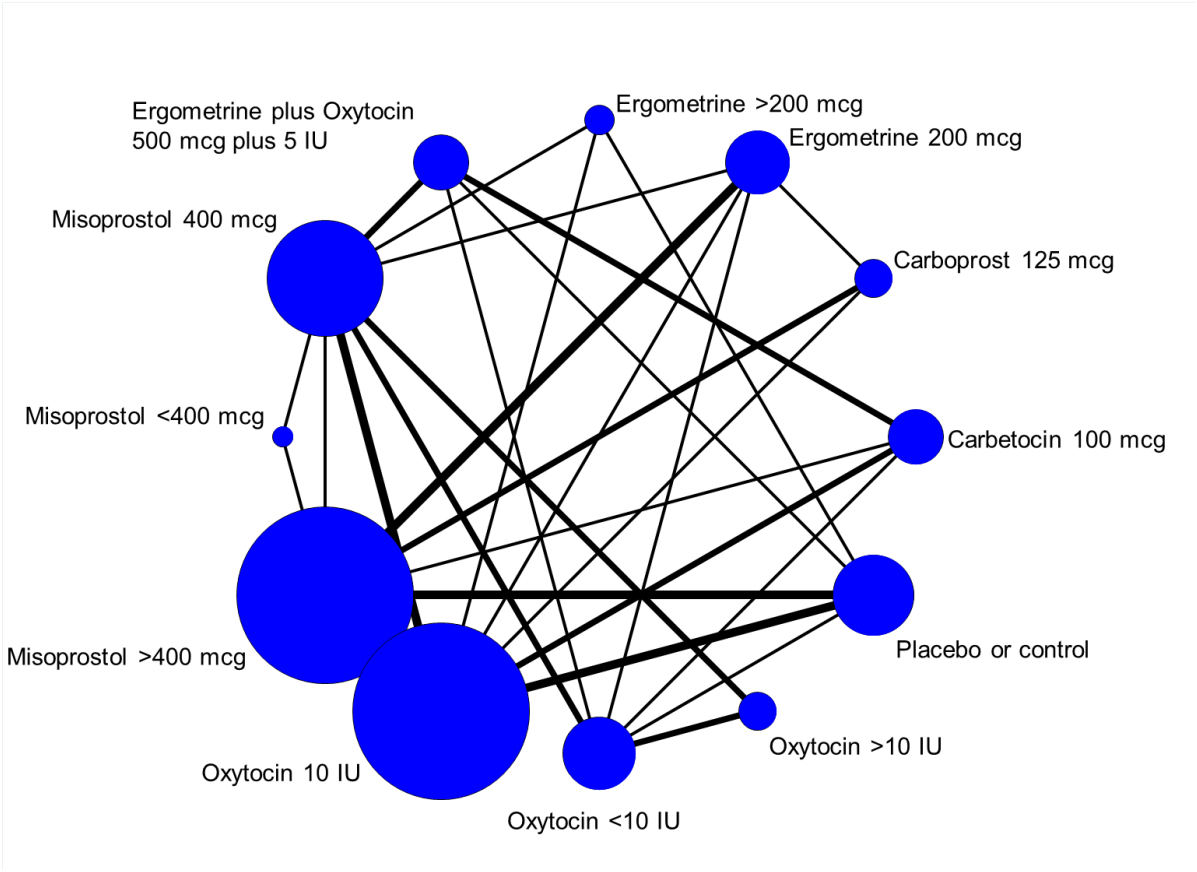


Figure 161: PPH ≥500 mL restricted to studies with public or no funding-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

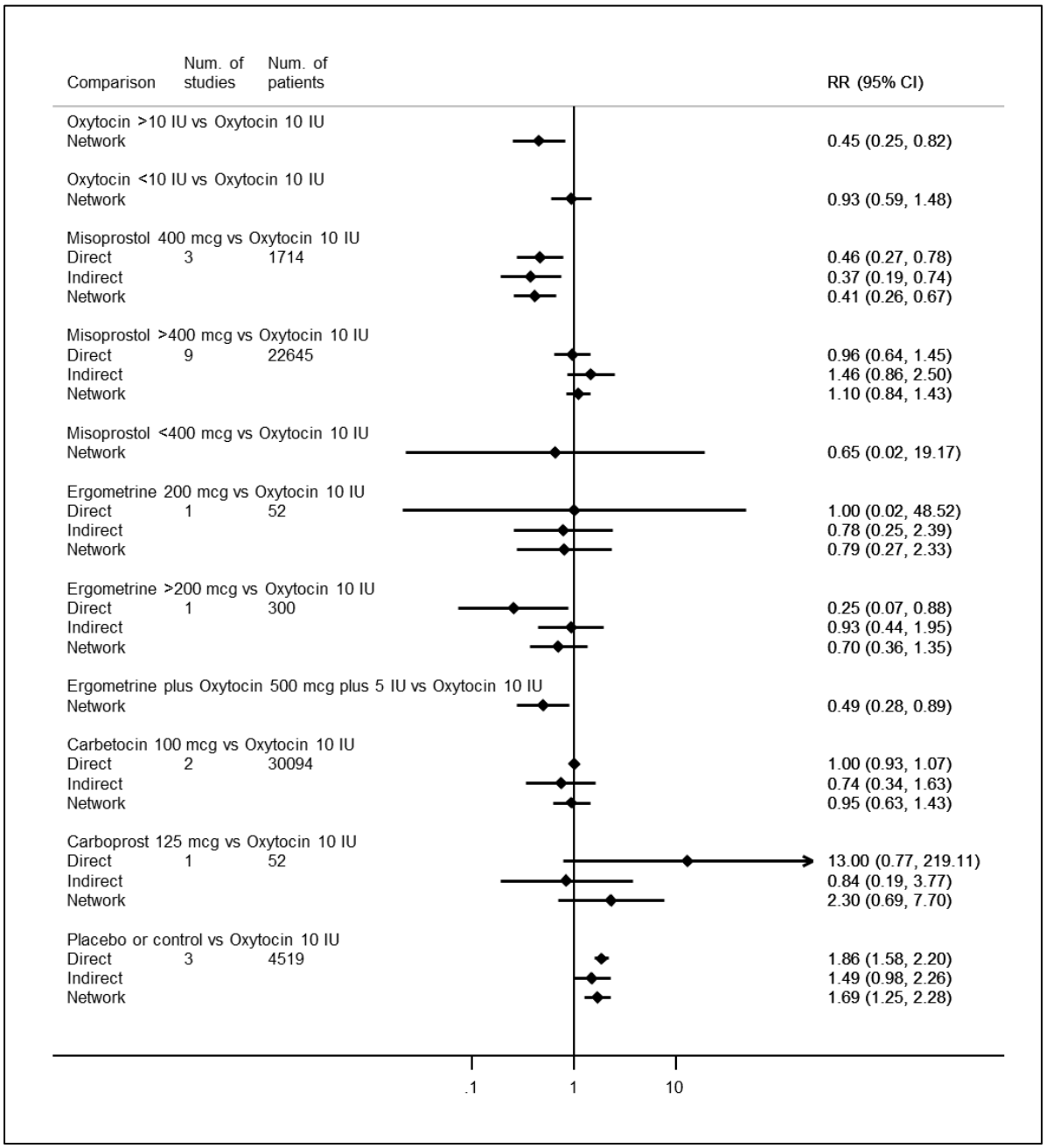


Figure 162: PPH ≥500 mL restricted to studies with public or no funding-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with public or no funding. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

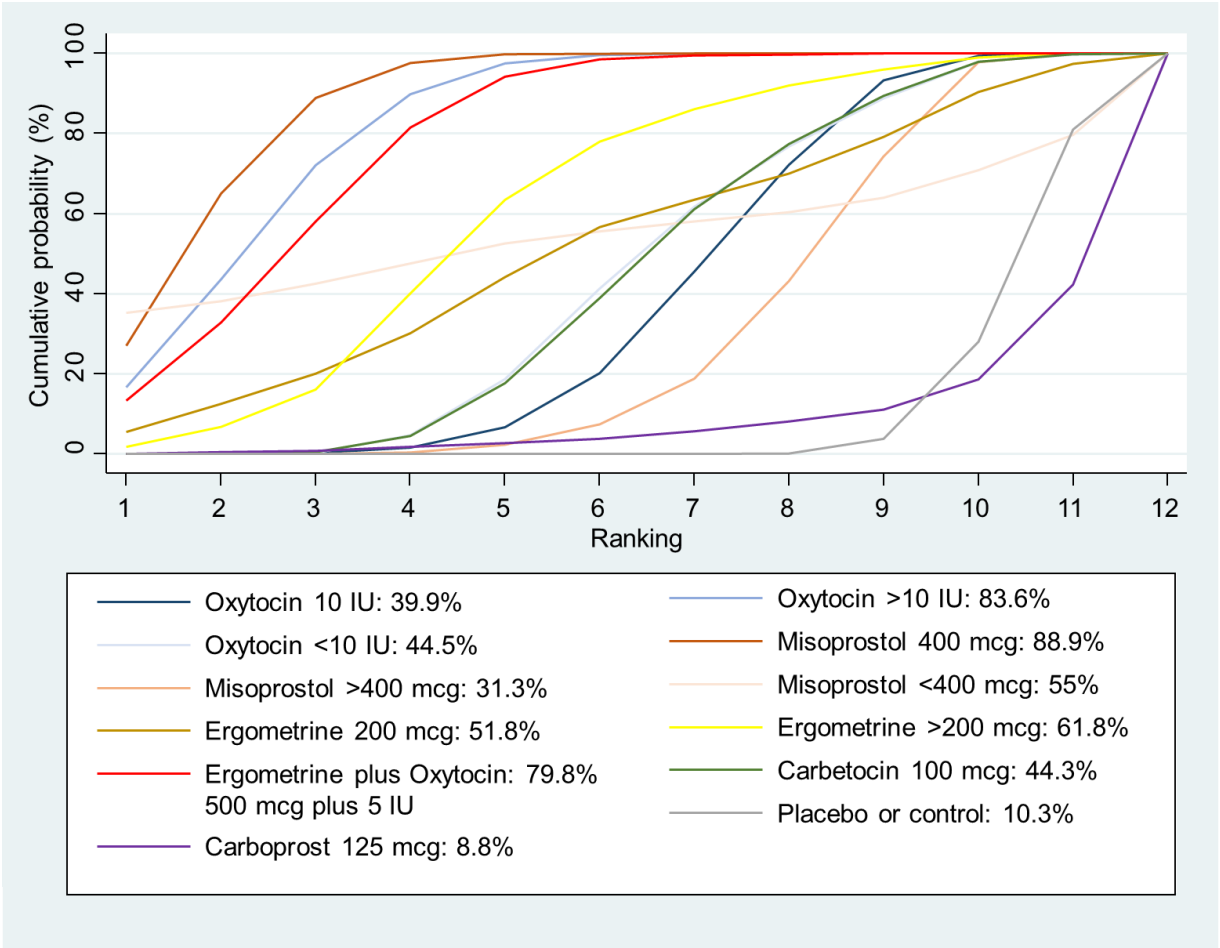


Figure 163: PPH ≥500 mL restricted to studies with objective methods of measuring blood loss-Network diagram-Doses NMA

Network diagram for PPH ≥500 mL restricted to studies with objective methods of measuring blood loss. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

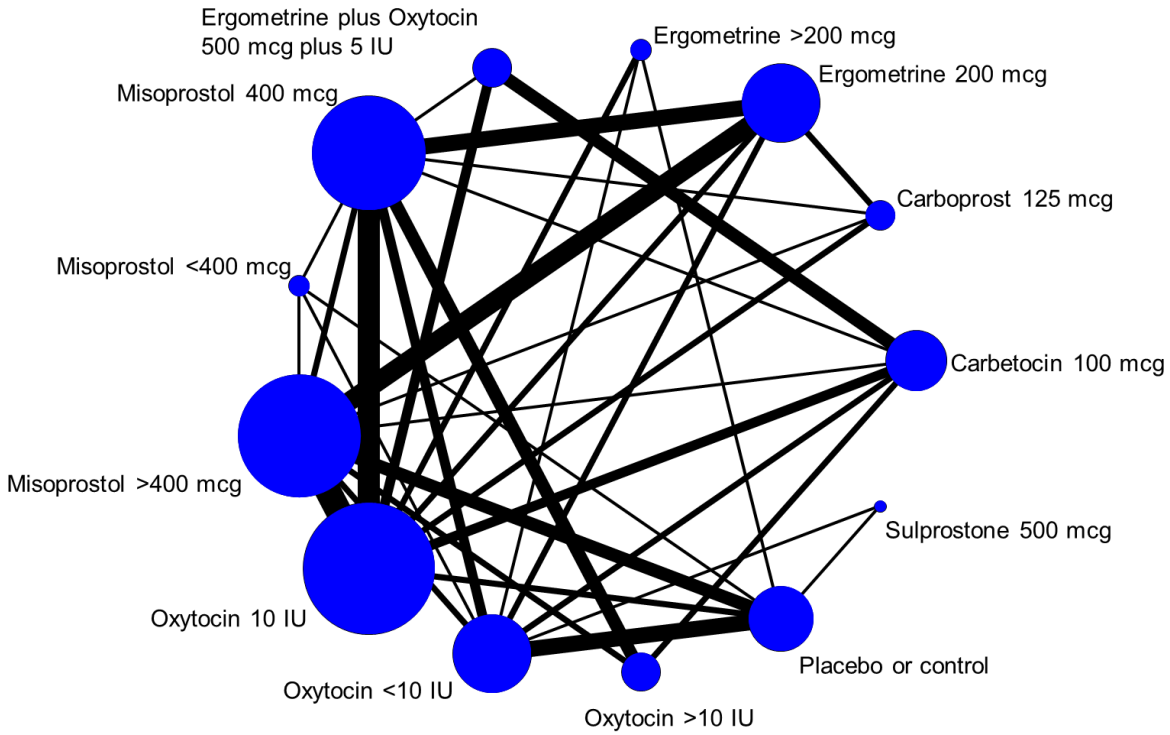


Figure 164: PPH ≥500 mL restricted to studies with objective methods of measuring blood loss-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

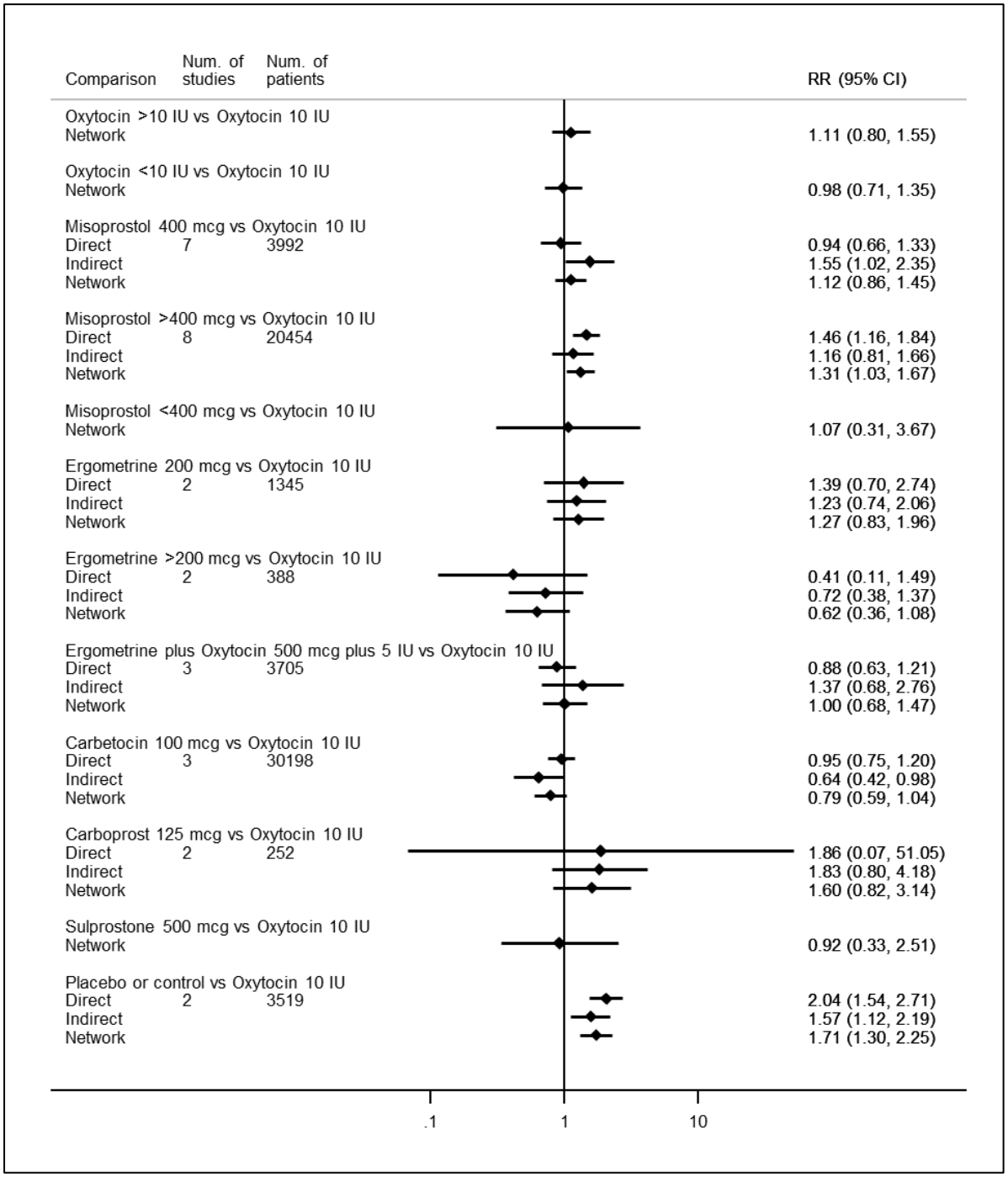


Figure 165: PPH ≥500 mL restricted to studies with objective methods of measuring blood loss-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with objective methods of measuring blood loss. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

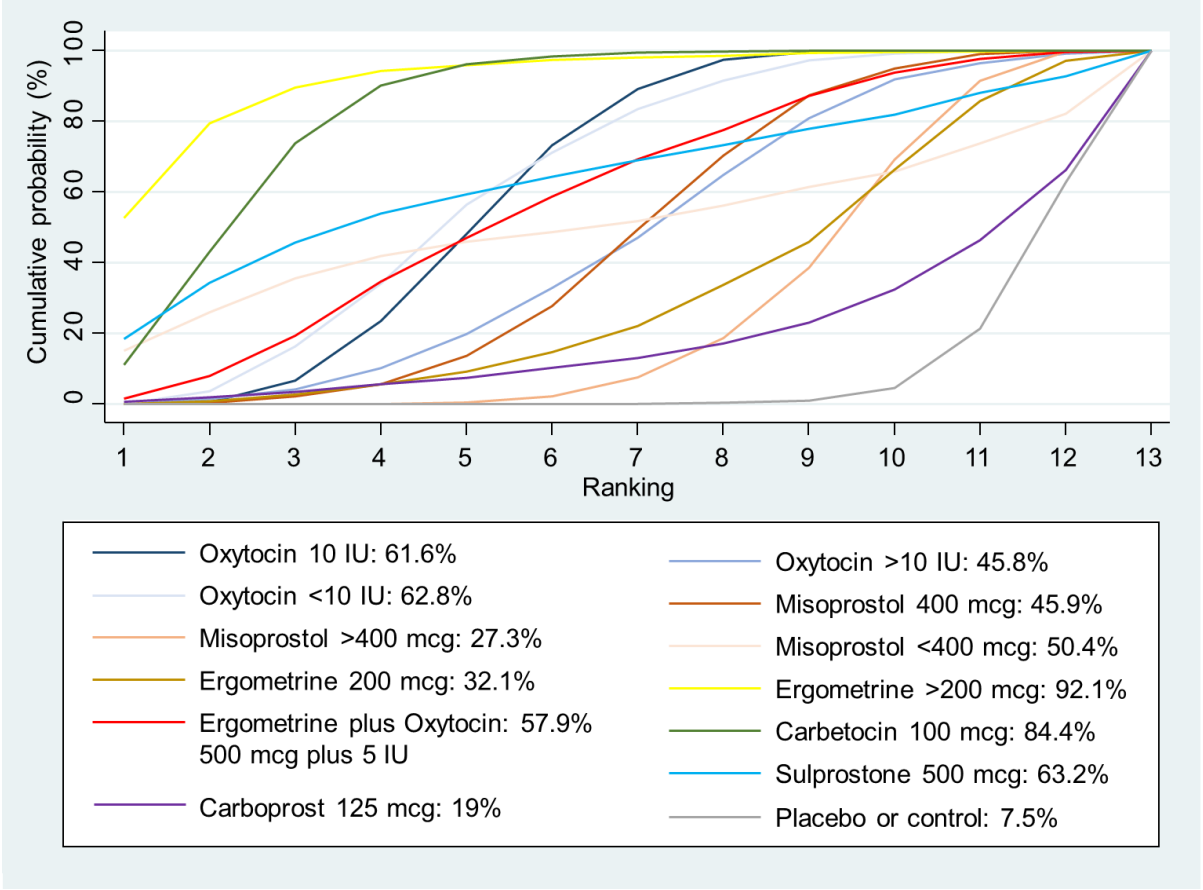


Figure 166: PPH ≥500 mL restricted to studies with <10% attrition-Network diagram-Doses NMA

Network diagram for PPH ≥500 mL restricted to studies with <10% attrition. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

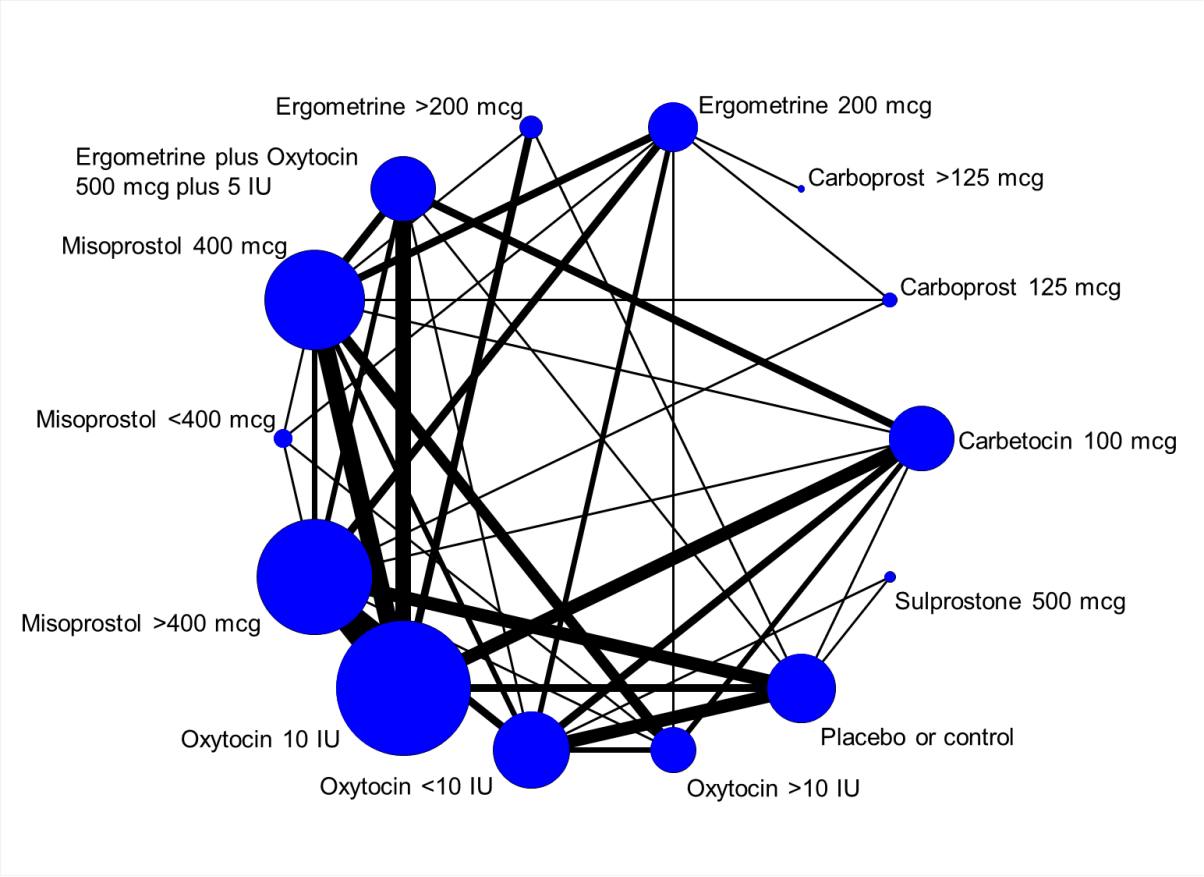


Figure 167: PPH ≥500 mL restricted to studies with <10% attrition-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

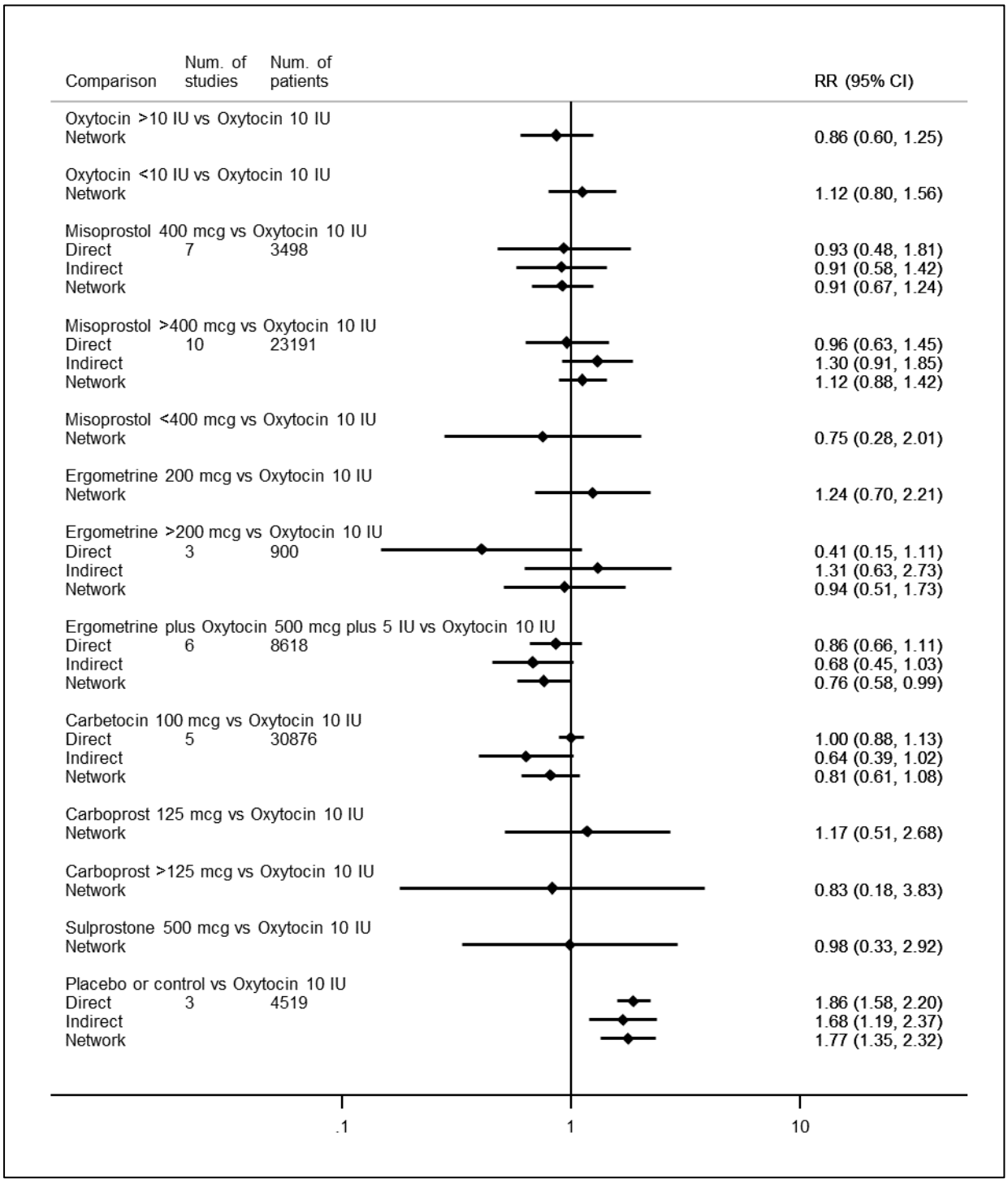


Figure 168: PPH ≥500 mL restricted to studies with <10% attrition-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with <10% attrition. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

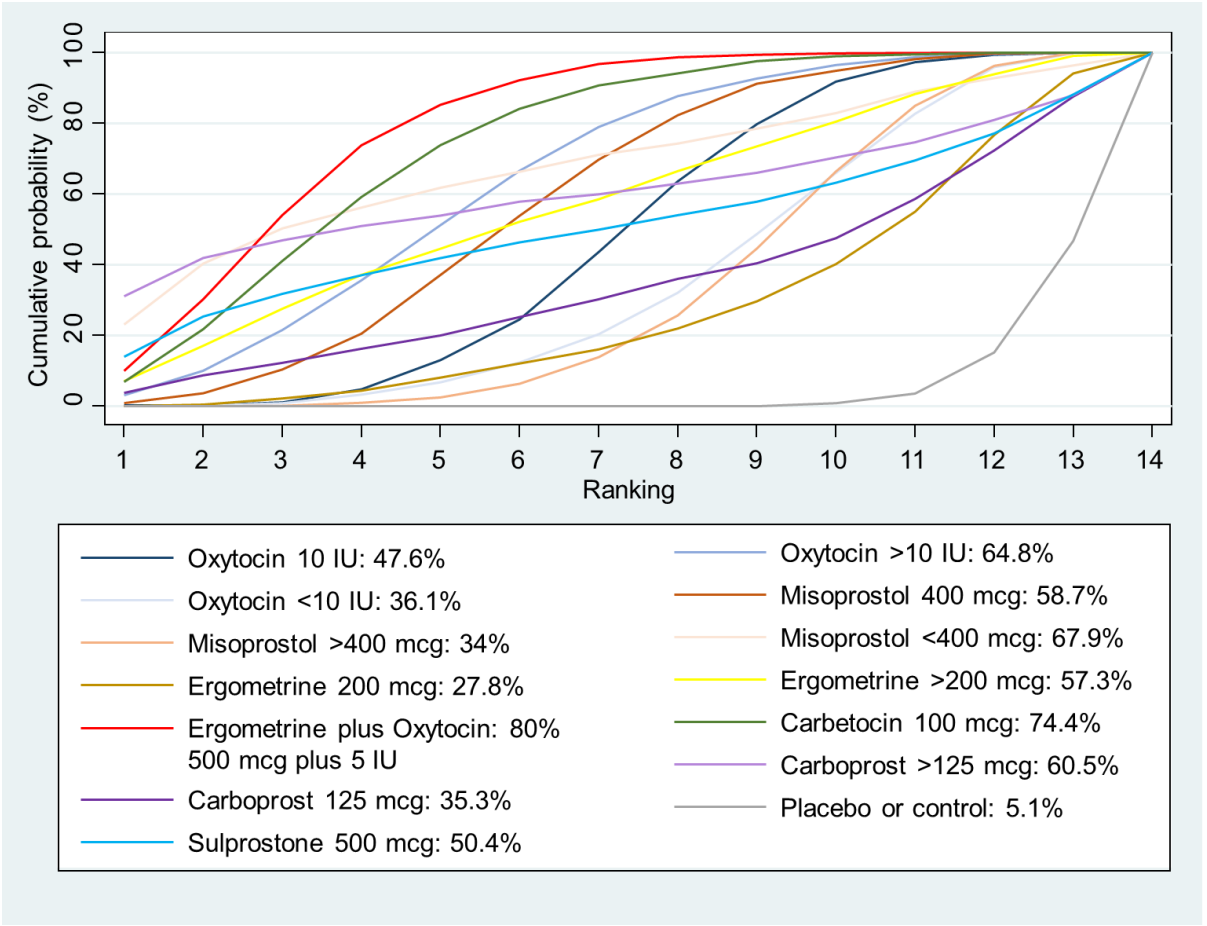


Figure 169: PPH ≥500 mL restricted to studies with at least 400 participants-Network diagram-Doses NMA

Network diagram for PPH ≥500 mL restricted to studies with at least 400 participants. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

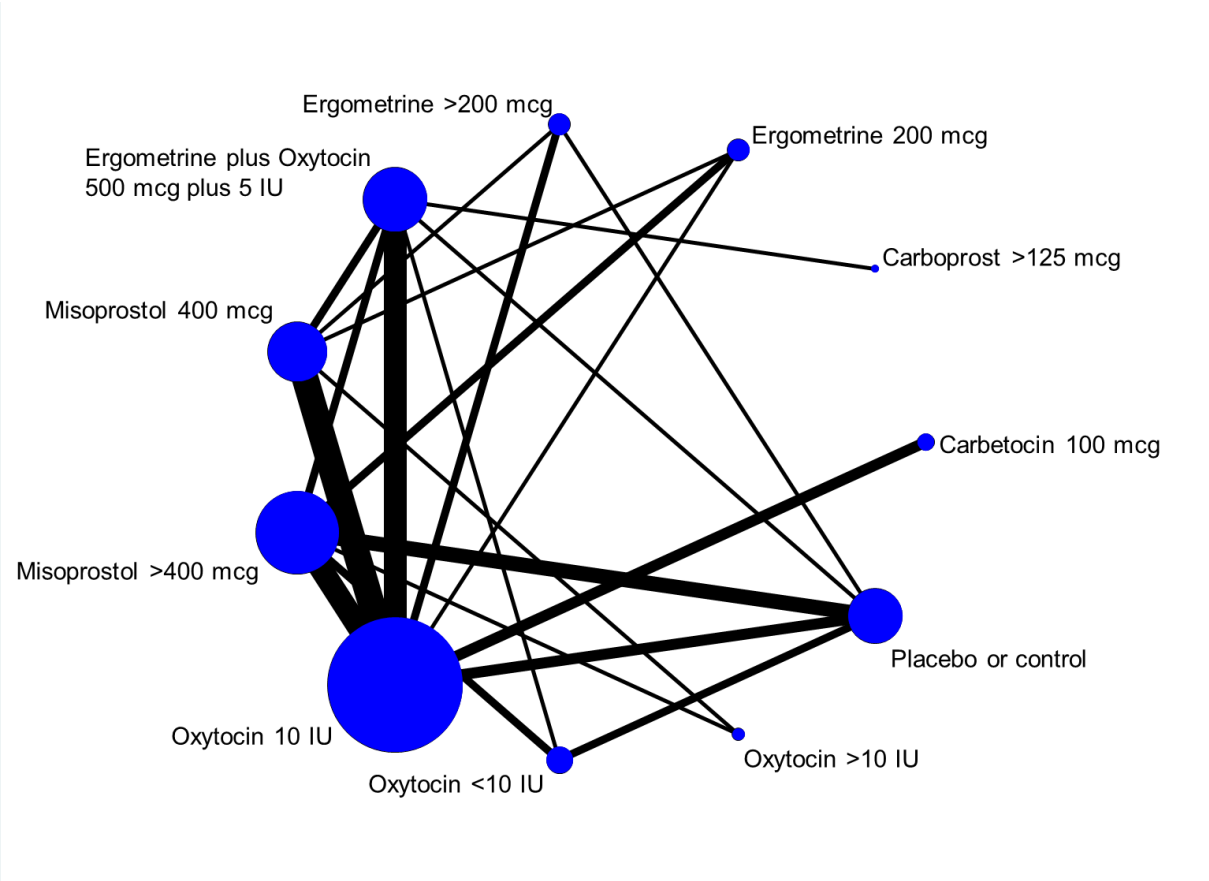


Figure 170: PPH ≥500 mL restricted to studies with at least 400 participants-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

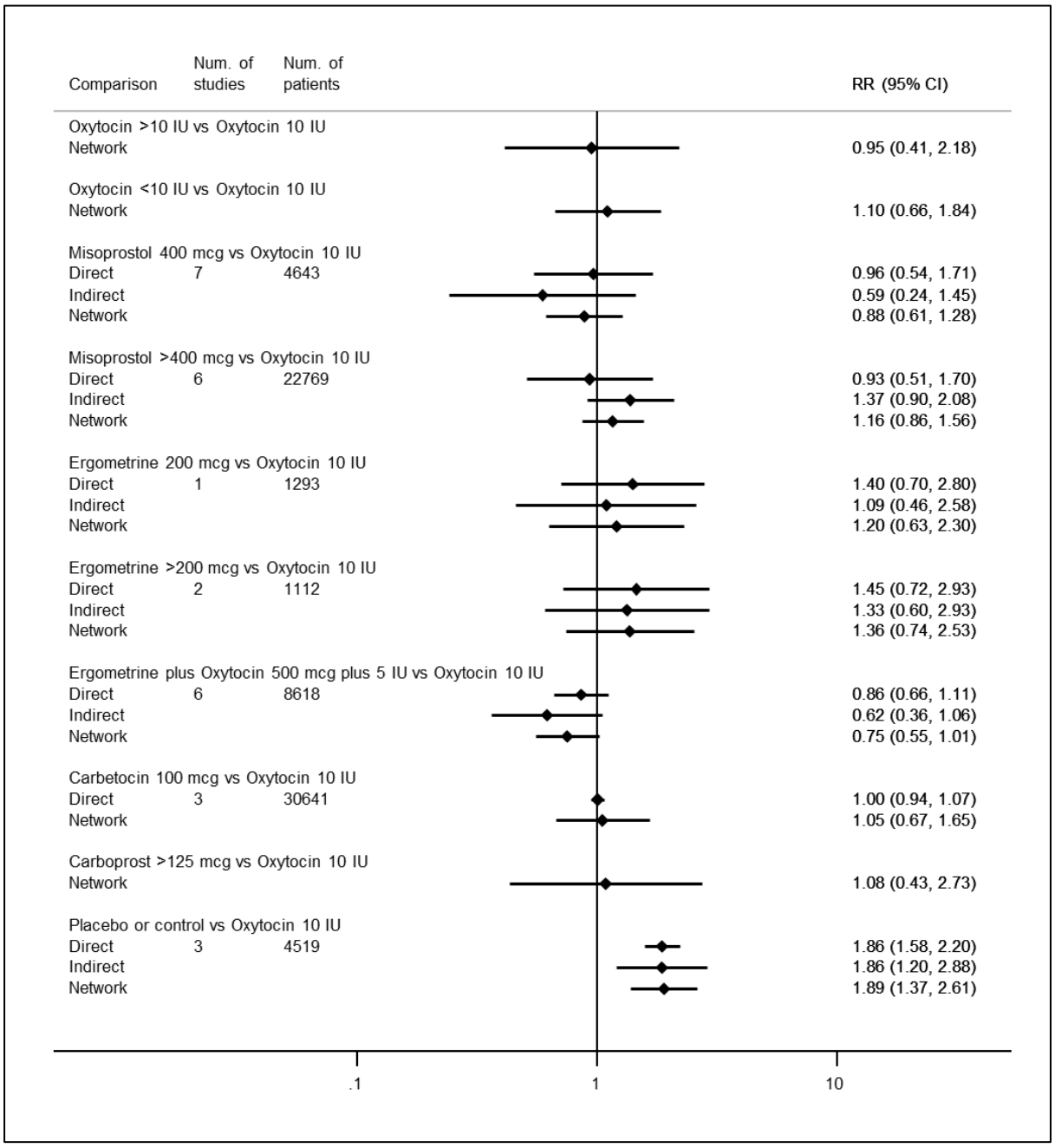


Figure 171: PPH ≥500 mL restricted to studies with at least 400 participants-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL restricted to studies with at least 400 participants. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

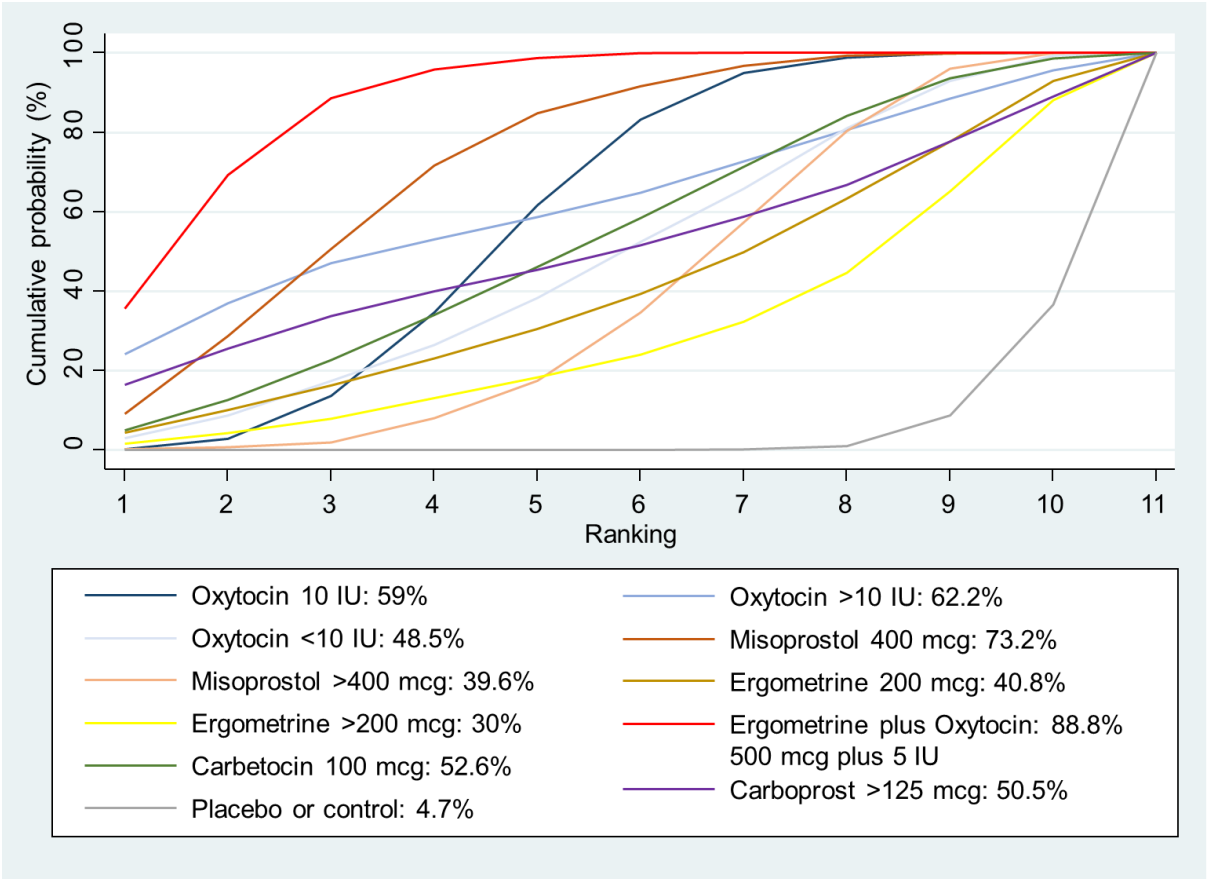


Figure 172: PPH ≥1000 mL restricted to studies at low Risk of Bias-Network diagram-Doses NMA

Network diagram for PPH ≥1000 mL restricted to studies at low Risk of Bias. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

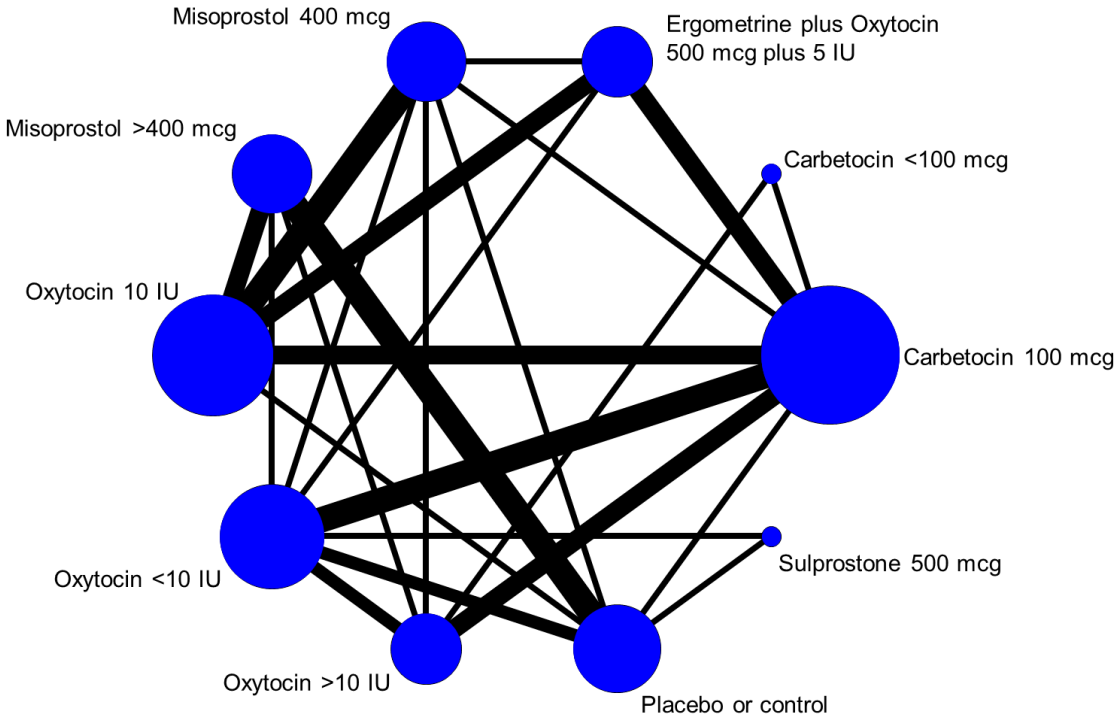


Figure 173: PPH ≥1000 mL restricted to studies at low Risk of Bias-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

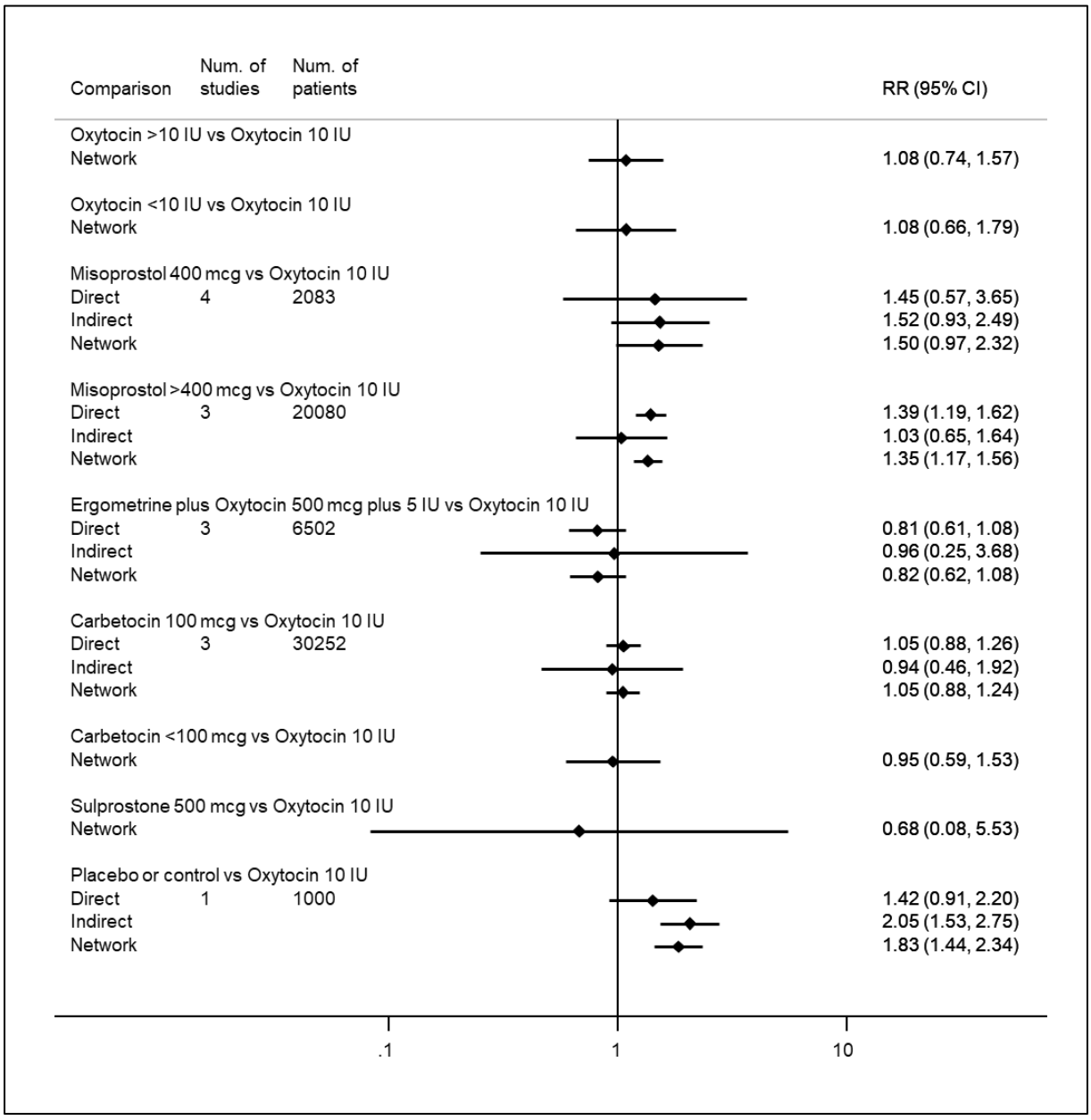


Figure 174: PPH ≥1000 mL restricted to studies at low Risk of Bias-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies at low Risk of Bias. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

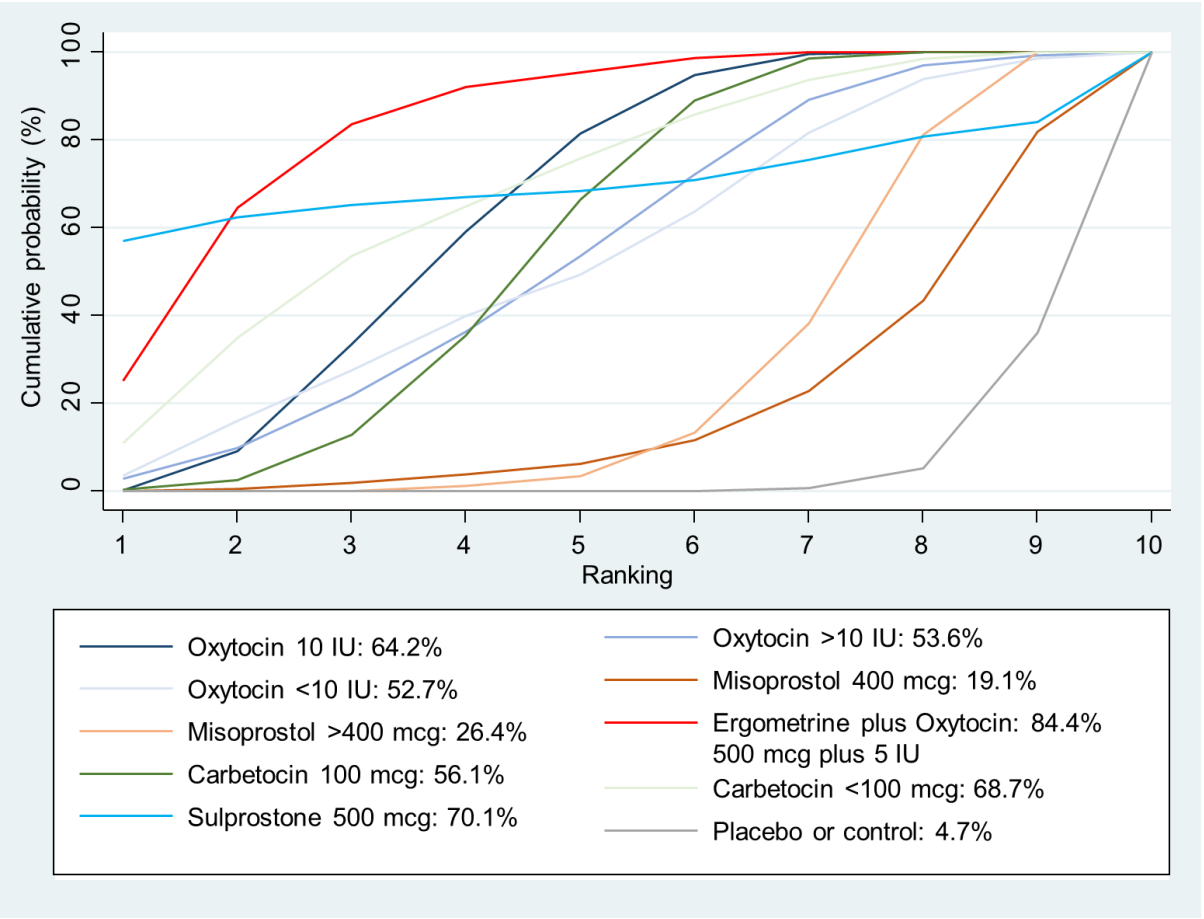


Figure 175: PPH ≥1000 mL restricted to studies with public or no funding-Network diagram-Doses NMA

Network diagram for PPH ≥1000 mL restricted to studies with public or no funding. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

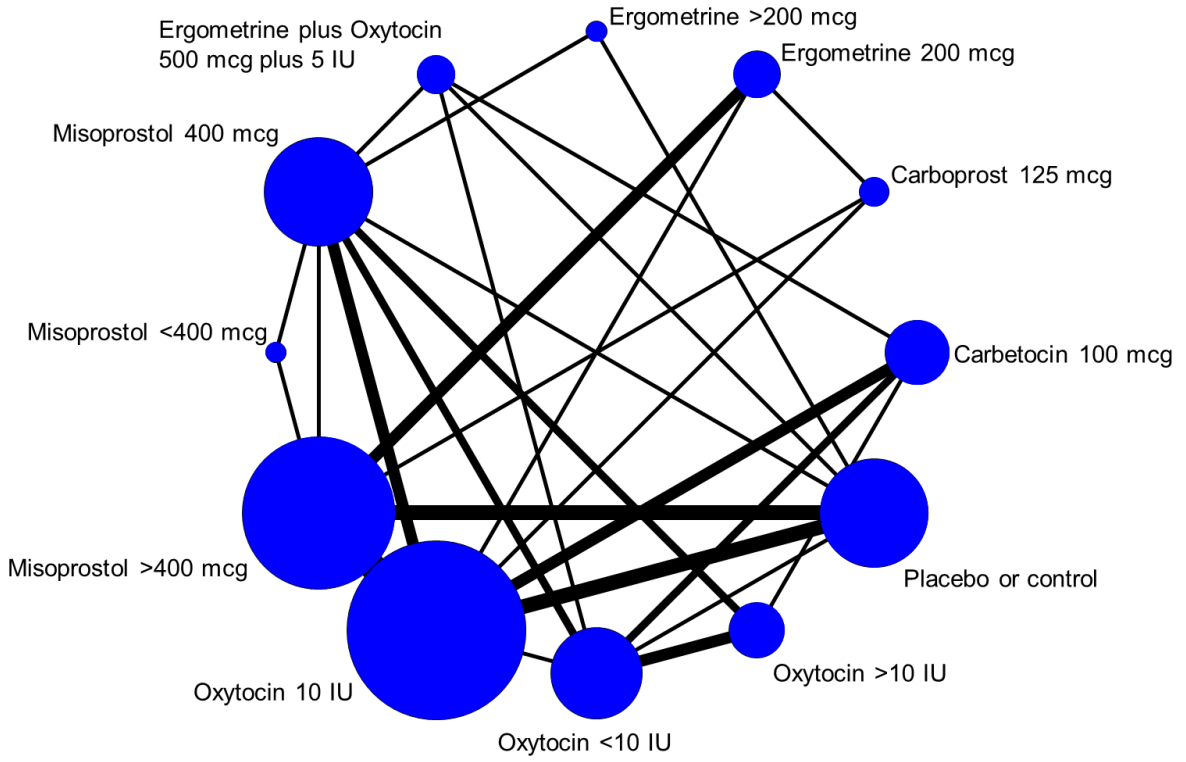


Figure 176: PPH ≥1000 mL restricted to studies with public or no funding-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

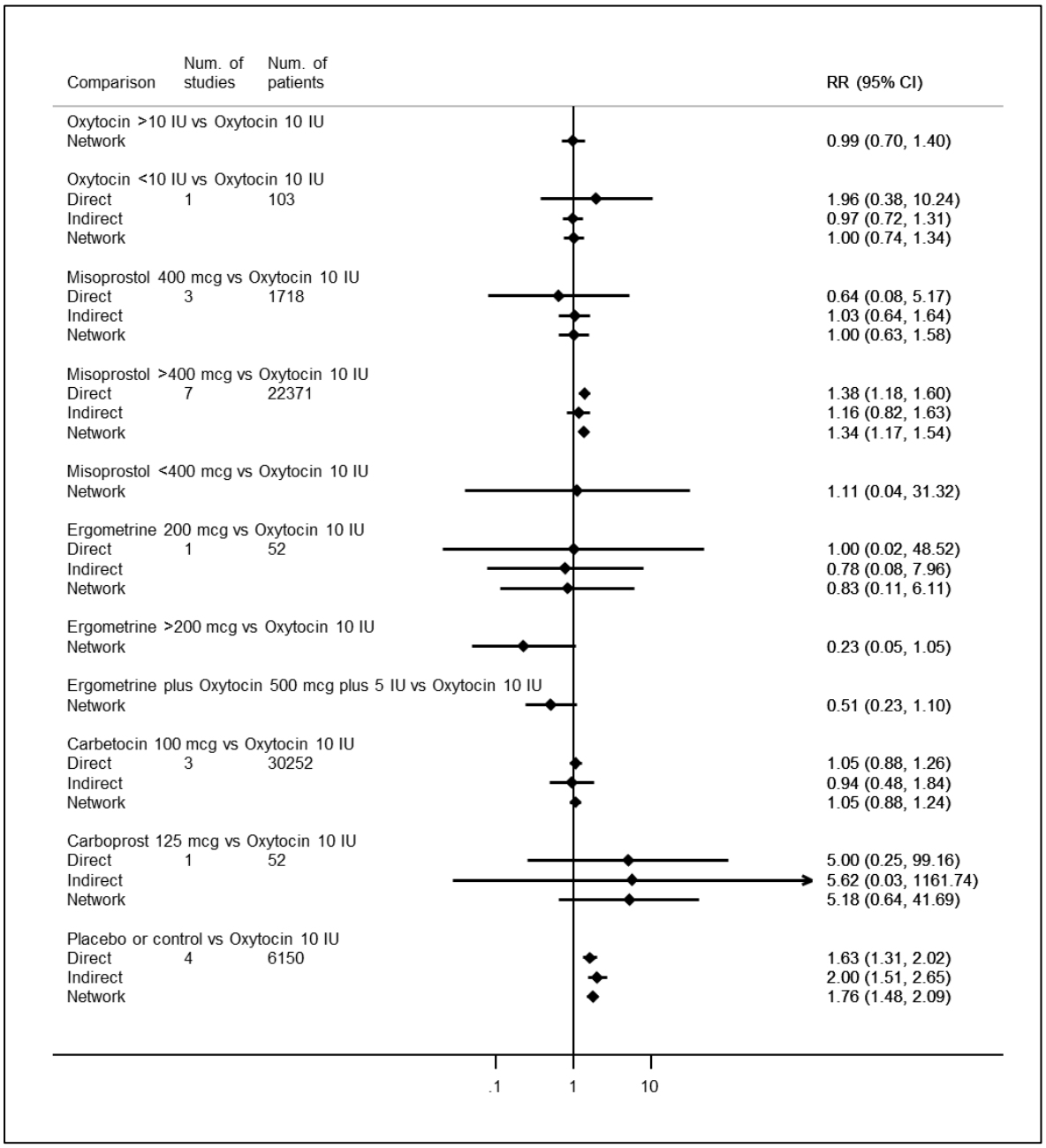


Figure 177: PPH ≥1000 mL restricted to studies with public or no funding-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with public or no funding. Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

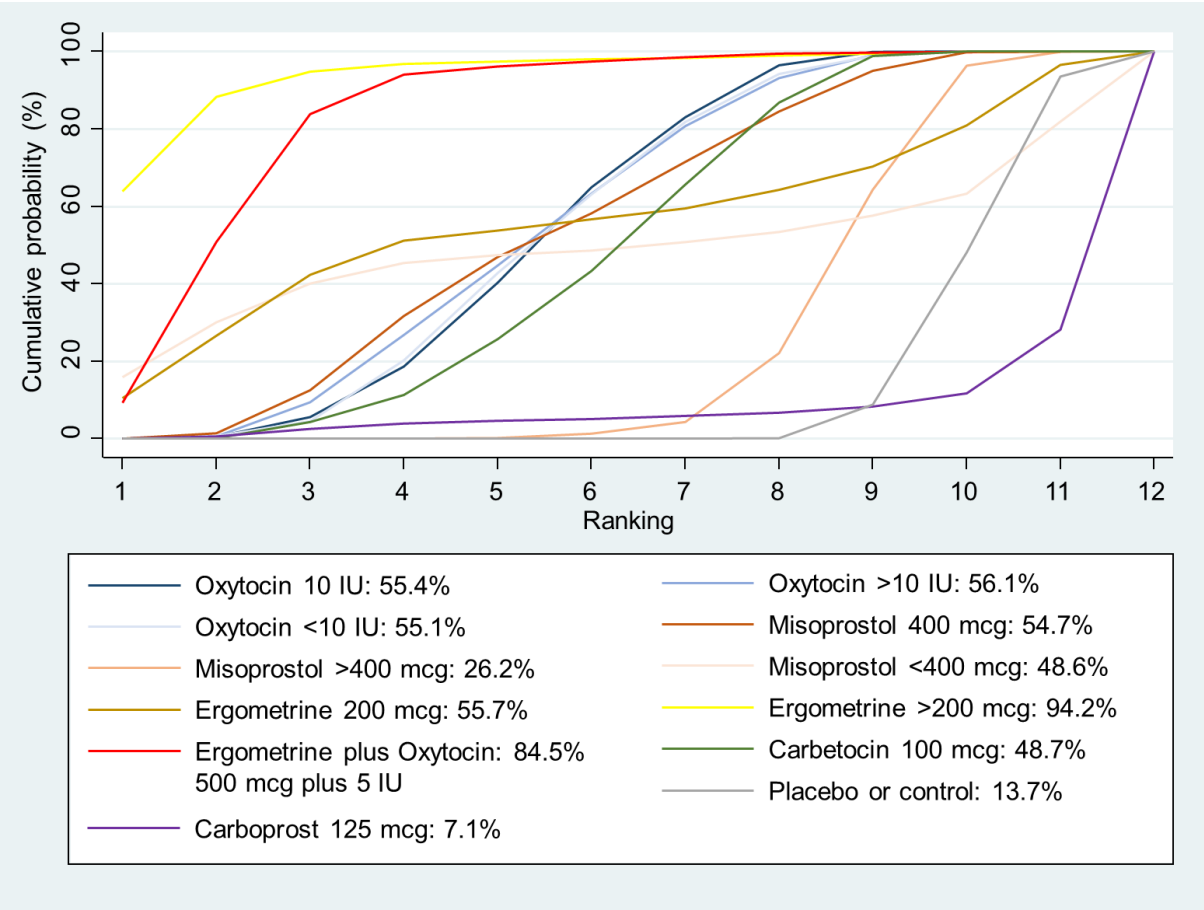


Figure 178: PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss-Network diagram-Doses NMA

Network diagram for PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

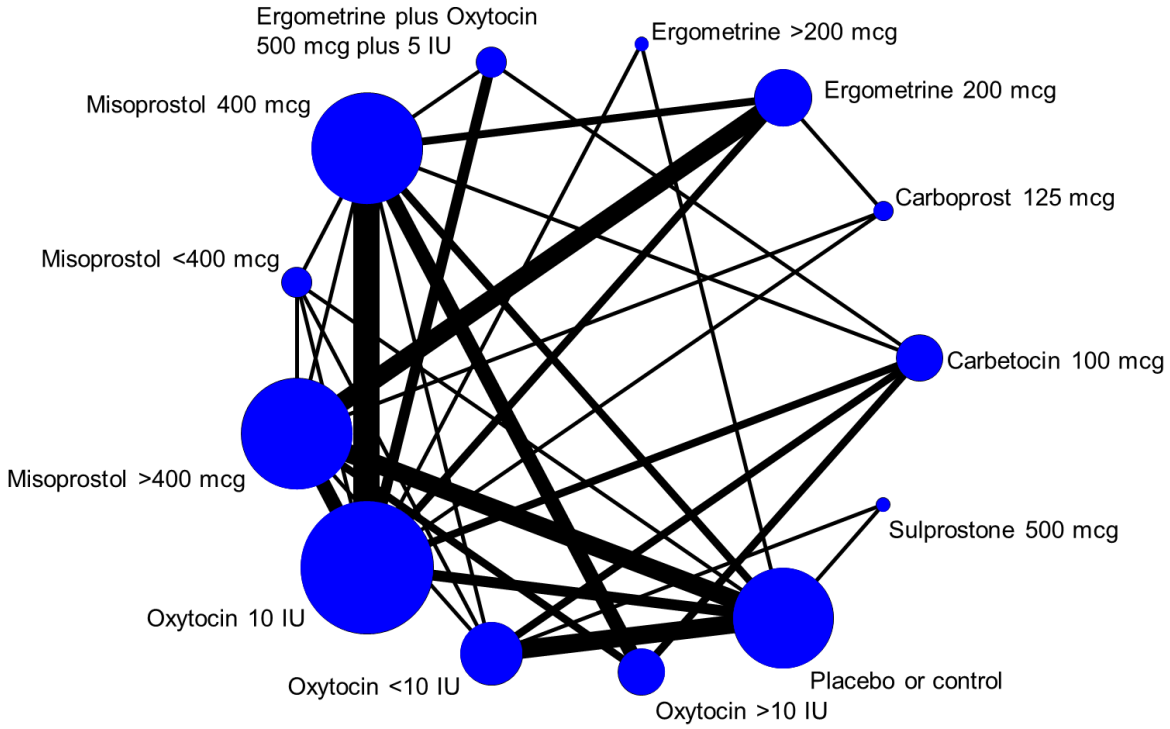


Figure 179: PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss- Forest plot- Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

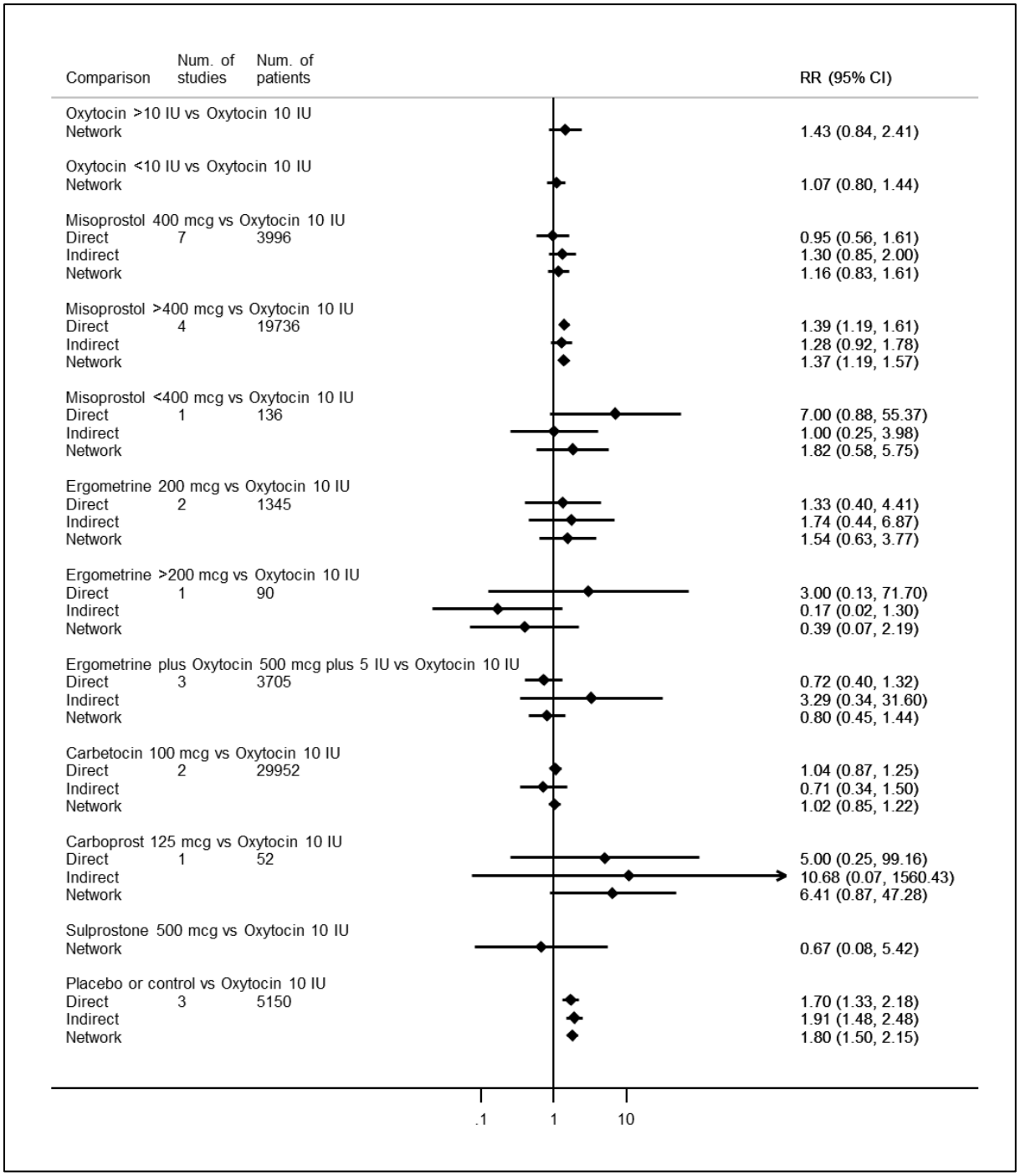


Figure 180: PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with objective methods of measuring blood loss. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

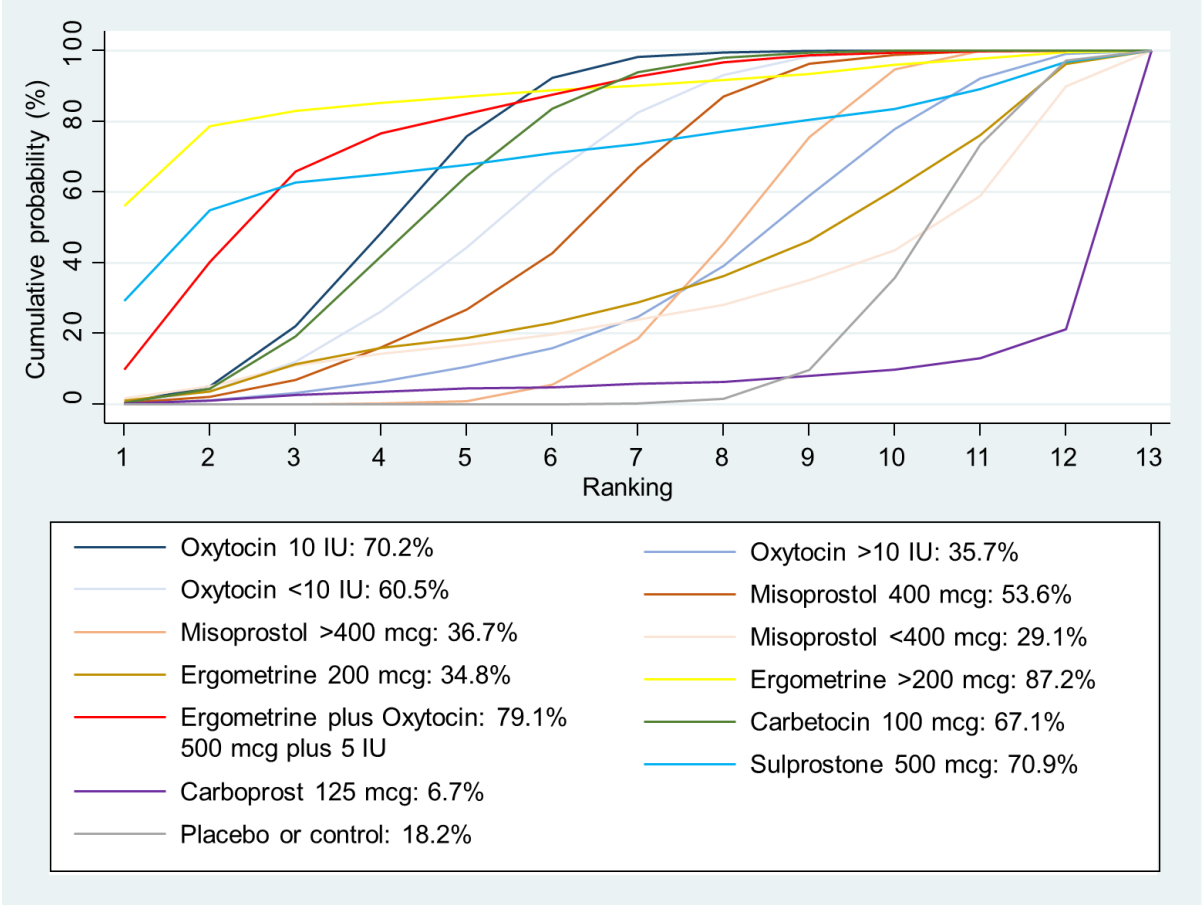


Figure 181: PPH ≥1000 mL restricted to studies with <10% attrition-Network diagram-Doses NMA

Network diagram for PPH ≥1000 mL restricted to studies with <10% attrition. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

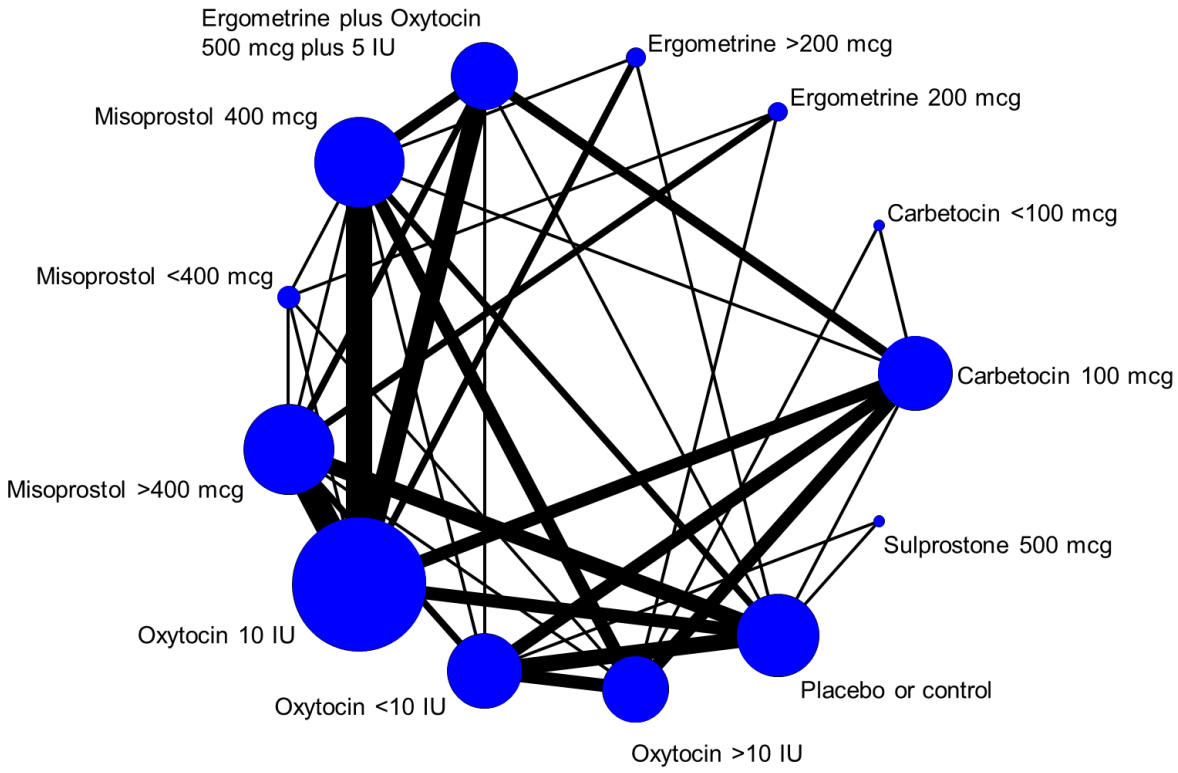


Figure 182: PPH ≥1000 mL restricted to studies with <10% attrition-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

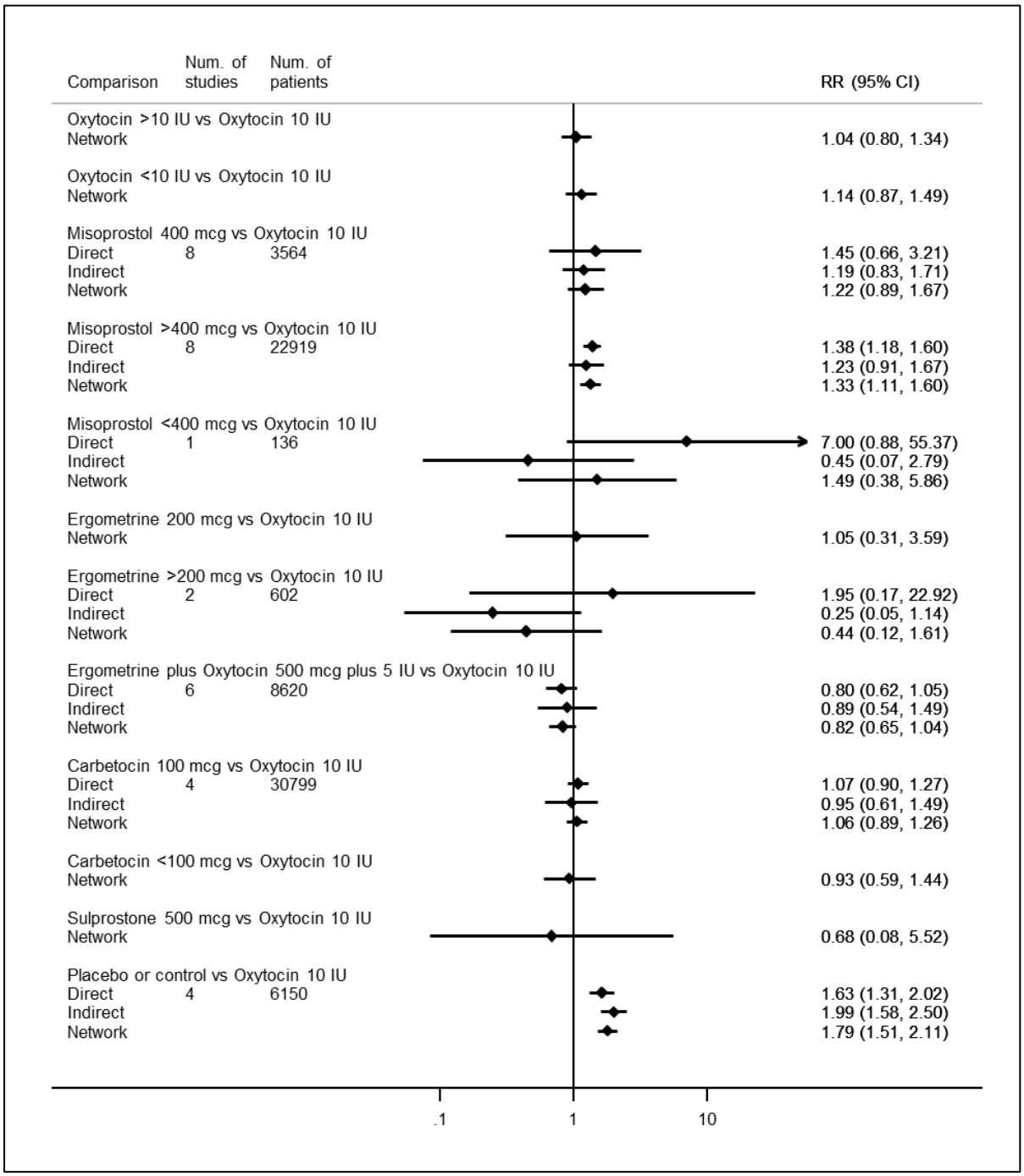


Figure 183: PPH ≥1000 mL restricted to studies with <10% attrition-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with <10% attrition. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

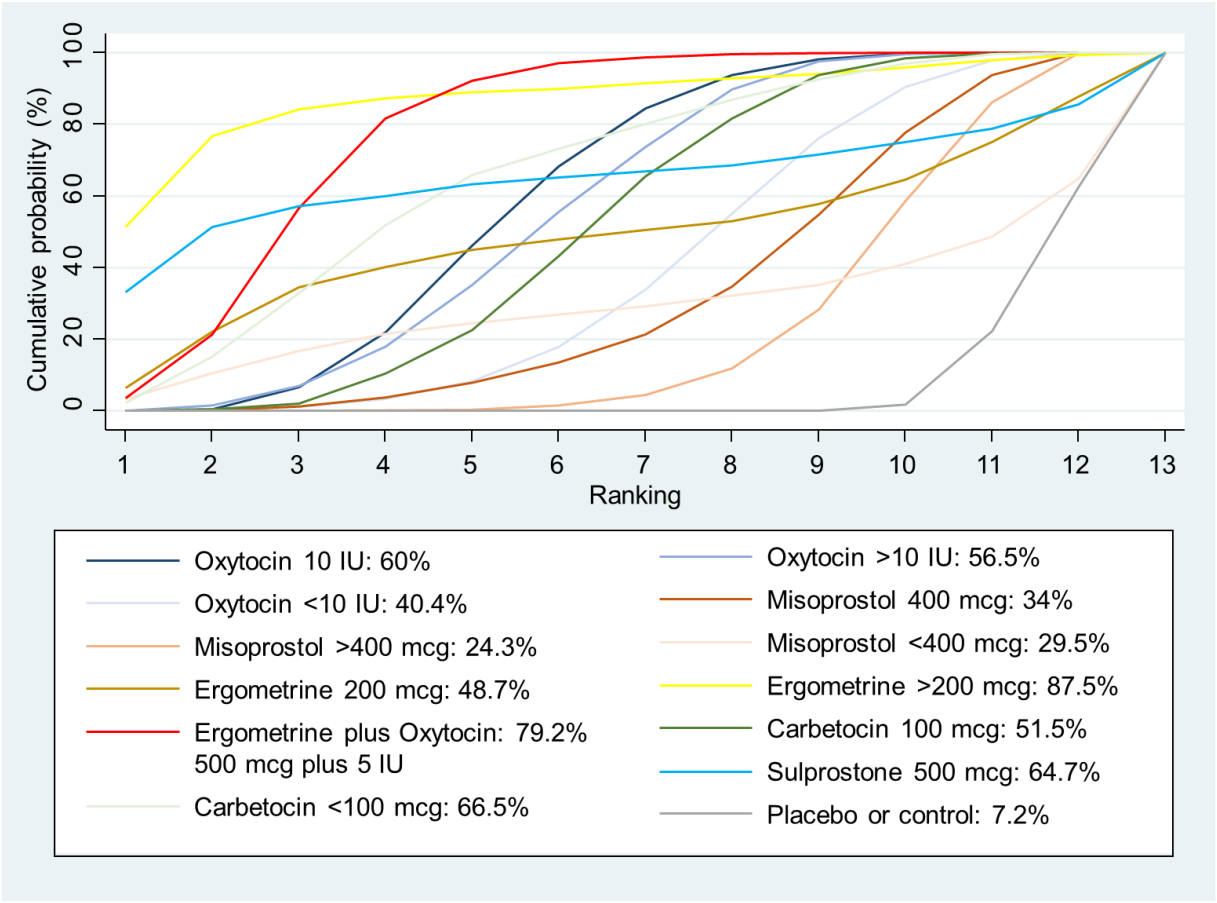


Figure 184: PPH ≥1000 mL restricted to studies with at least 400 participants-Network diagram-Doses NMA

Network diagram for PPH ≥1000 mL restricted to studies with at least 400 participants. The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

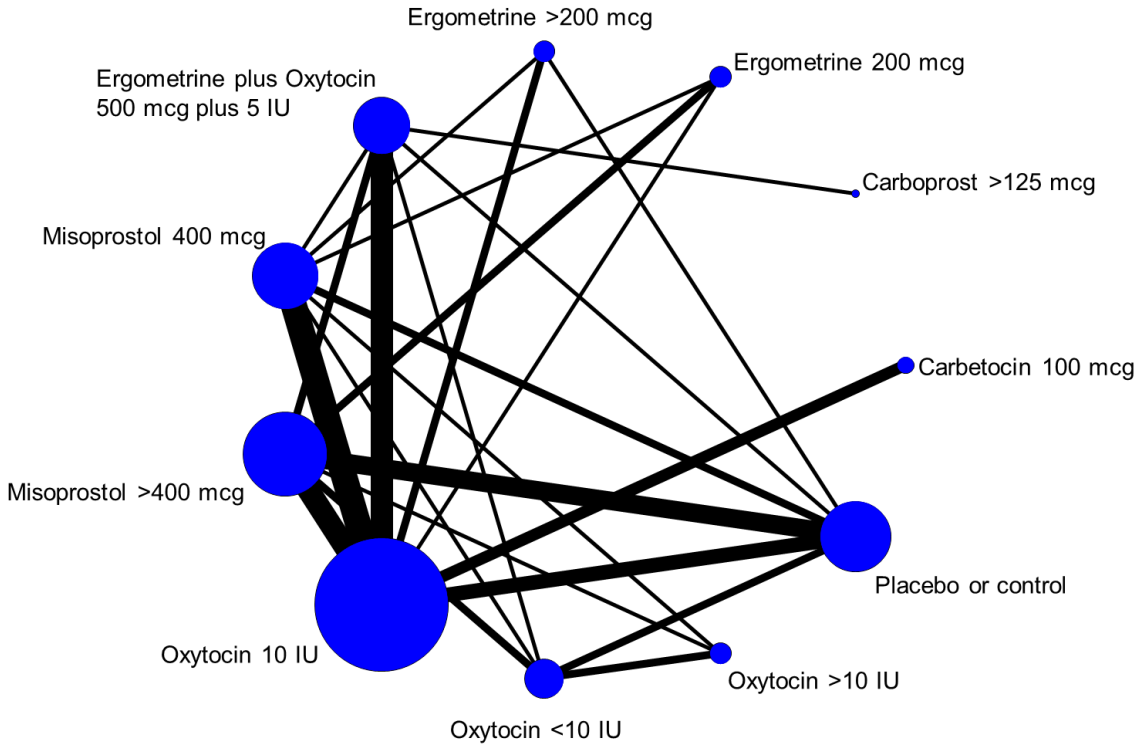


Figure 185: PPH ≥1000 mL restricted to studies with at least 400 participants-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses.

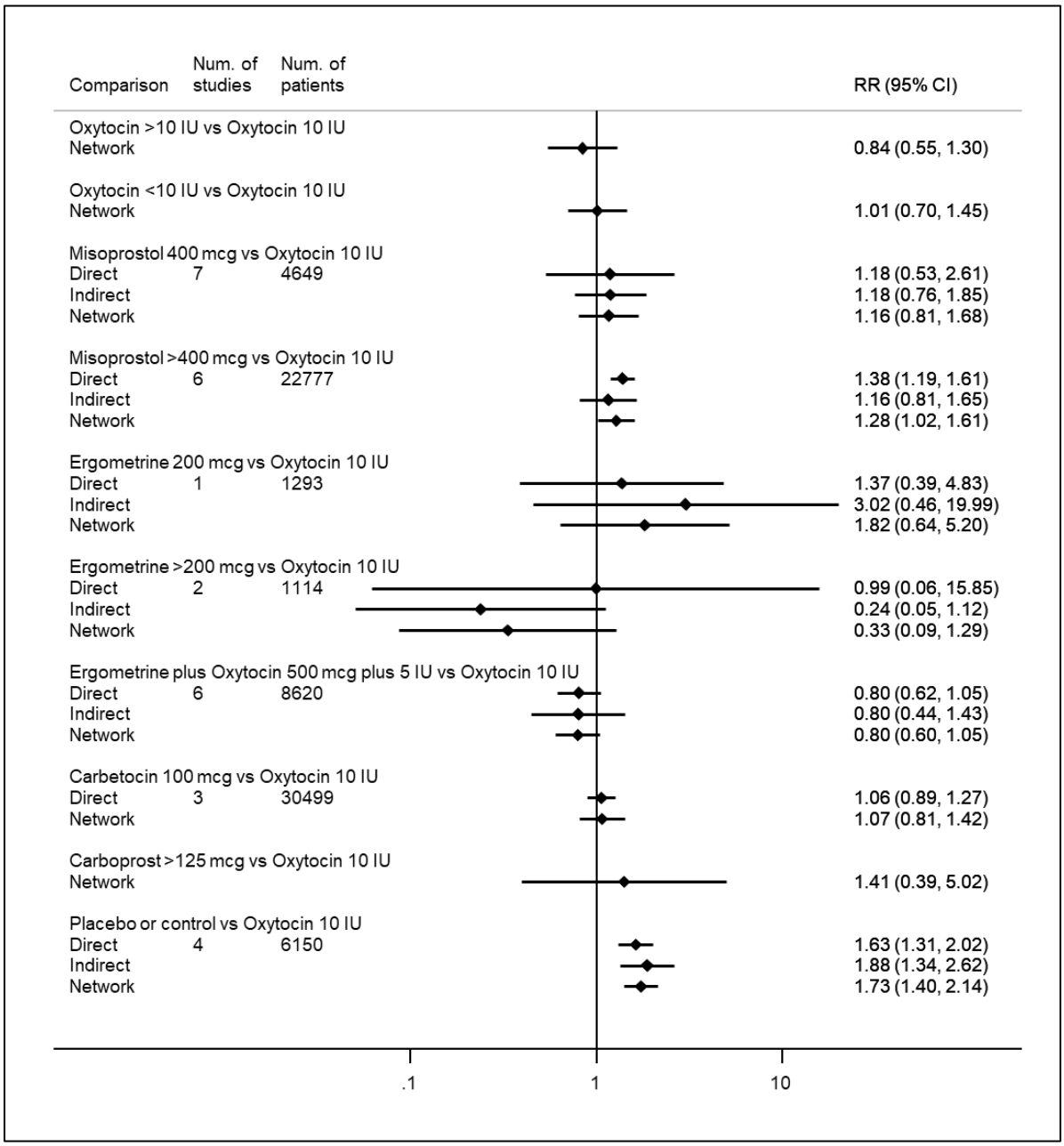
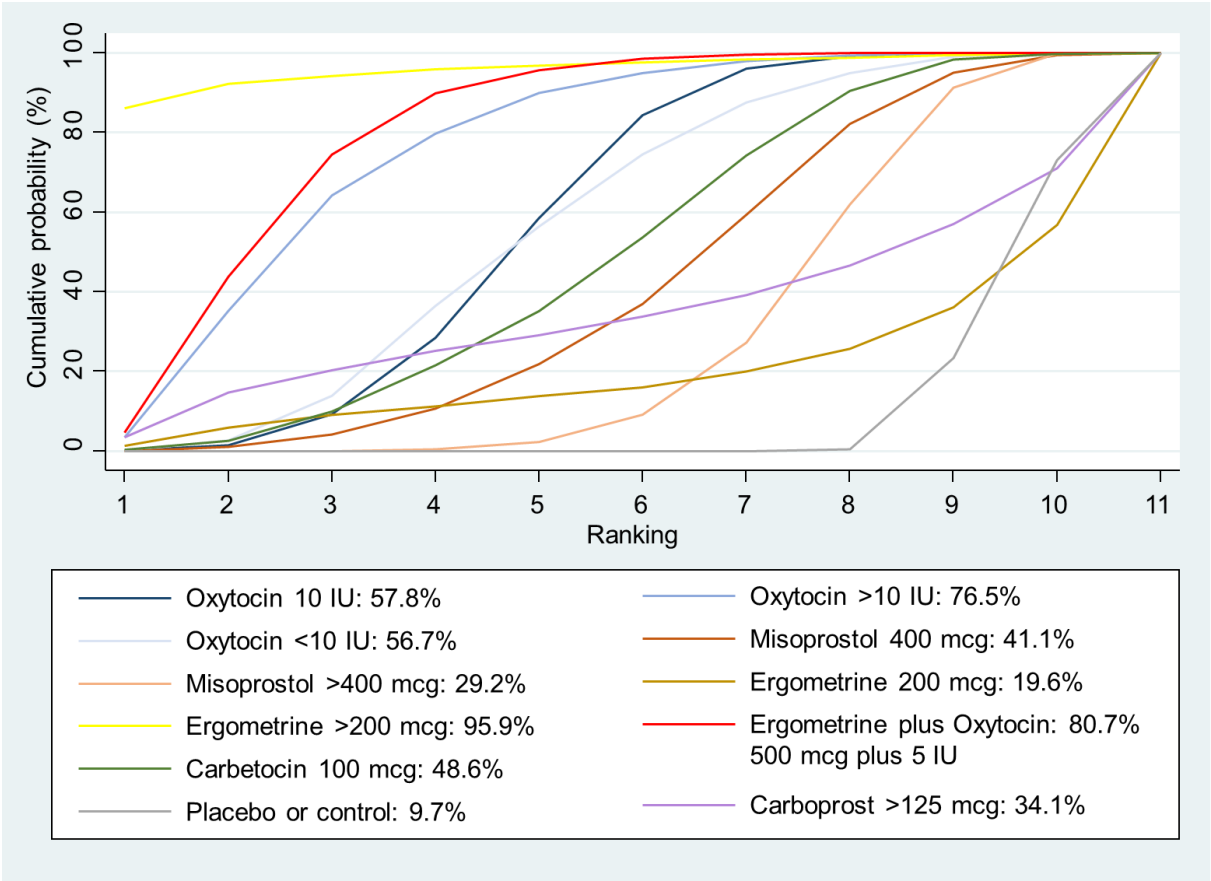


Figure 186: PPH ≥1000 mL restricted to studies with at least 400 participants-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL restricted to studies with at least 400 participants. Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.



Subgroup analyses

Figure 187: PPH ≥500 mL by mode of birth (vaginal birth)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥500 mL by mode of birth (vaginal birth). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

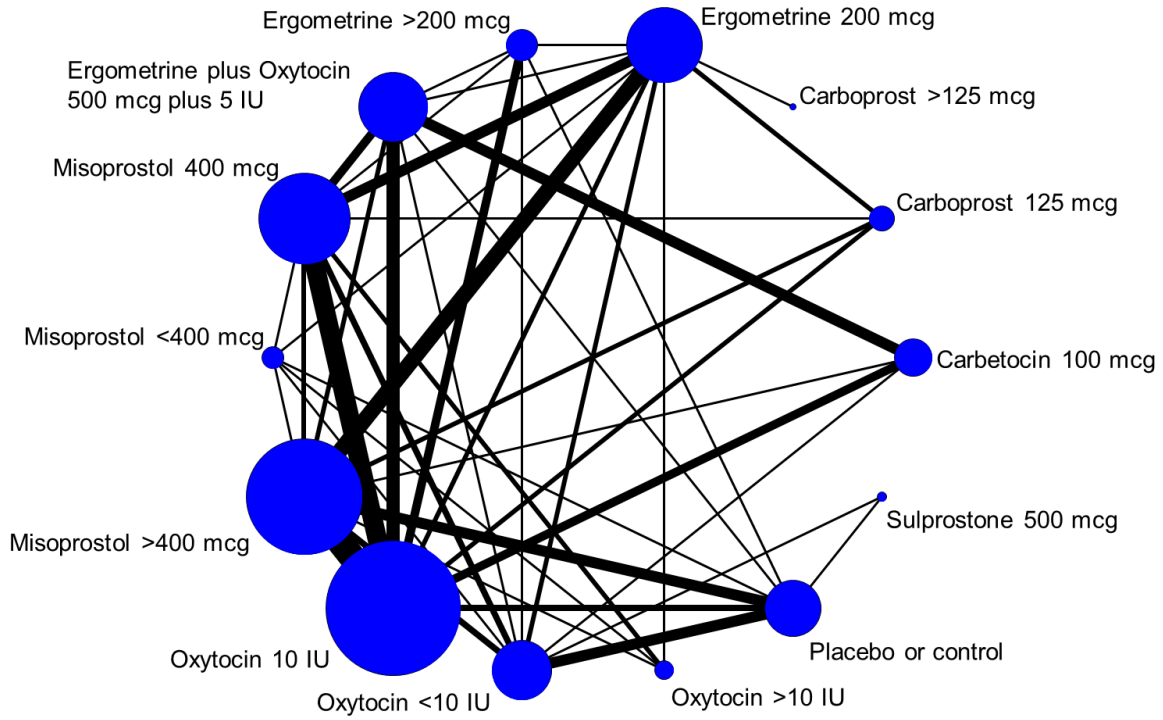


Figure 188: PPH ≥500 mL by mode of birth (vaginal birth)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL by mode of birth (vaginal birth).

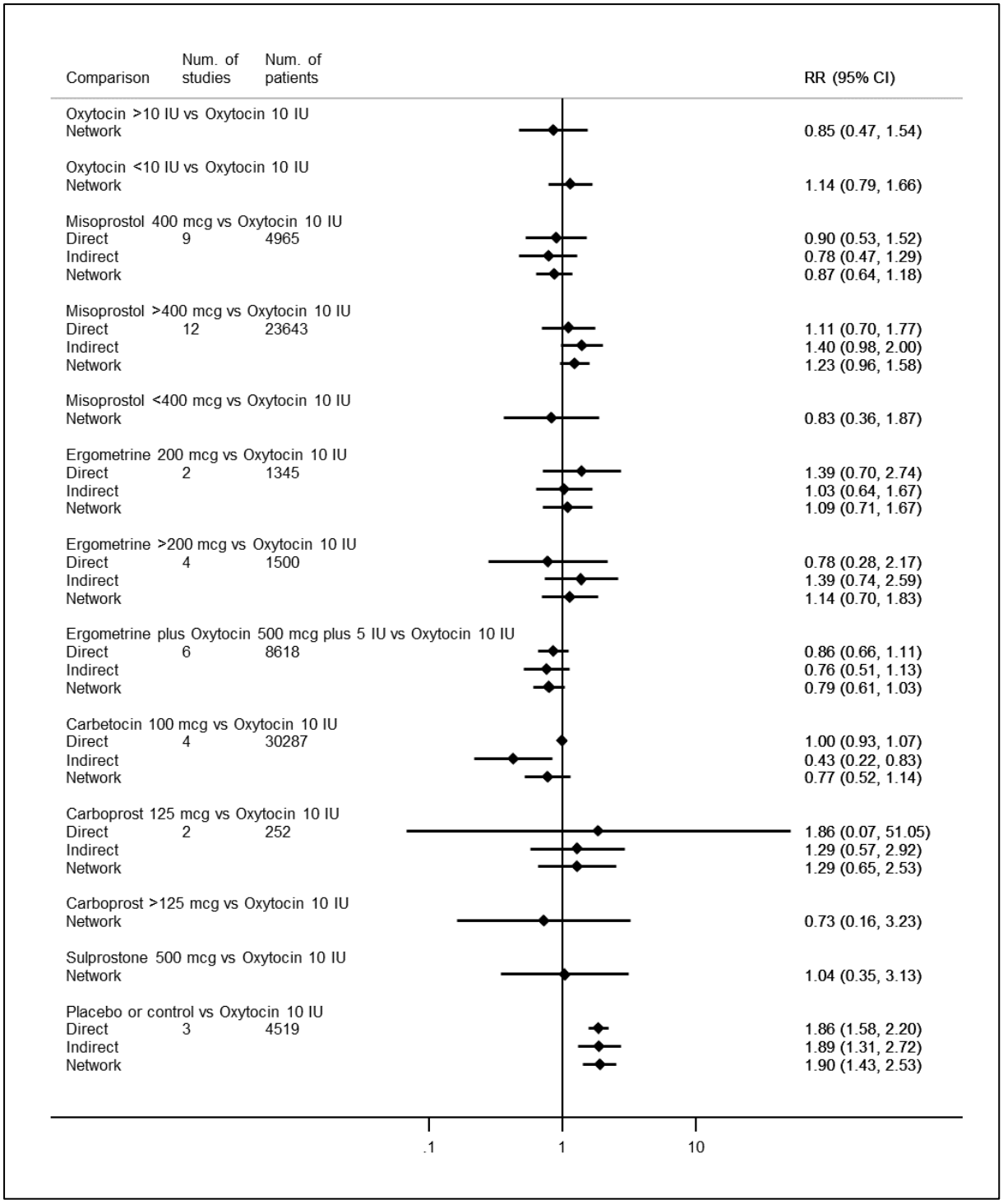


Figure 189: PPH ≥500 mL by mode of birth (vaginal birth)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL by mode of birth (vaginal birth). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

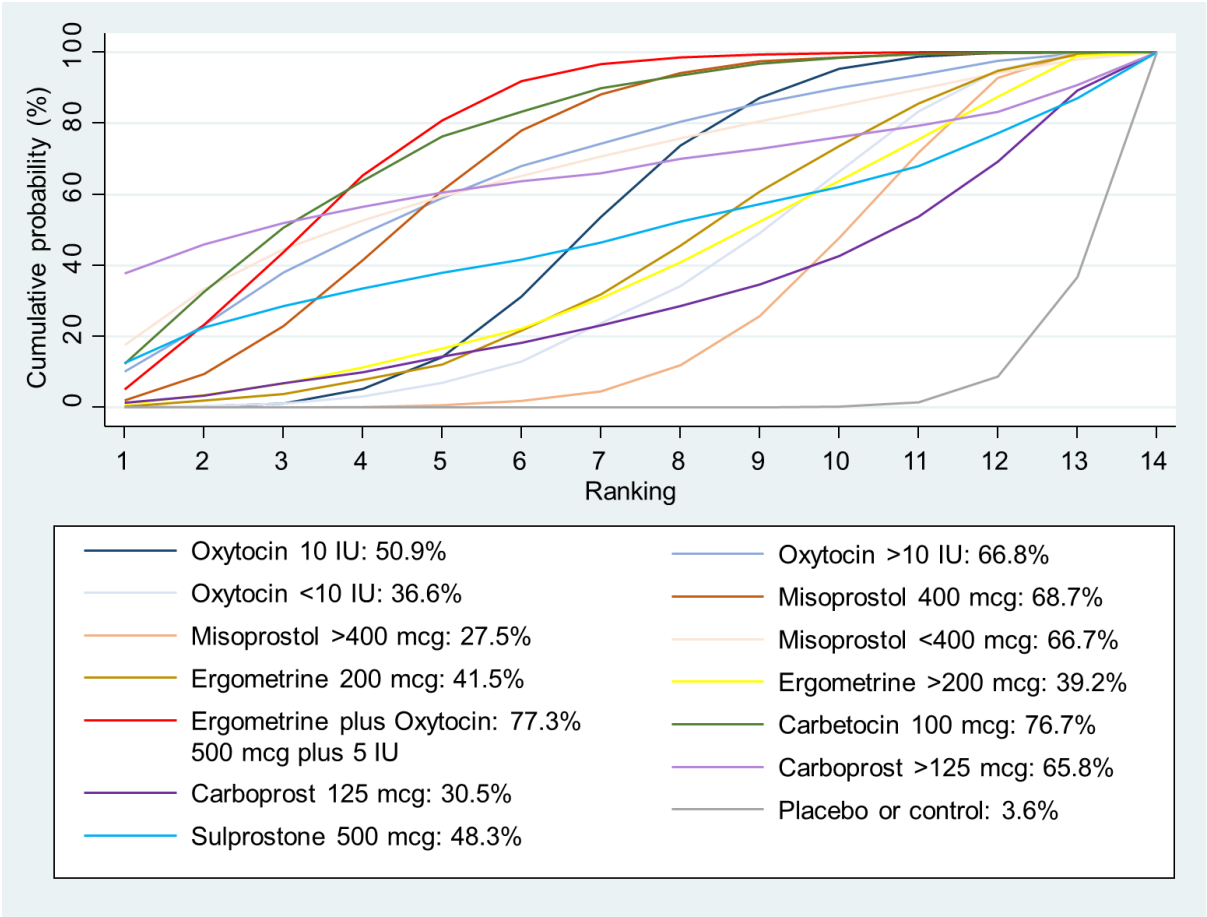


Figure 190: PPH ≥500 mL by mode of birth (caesarean section)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥500 mL by mode of birth (caesarean section). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

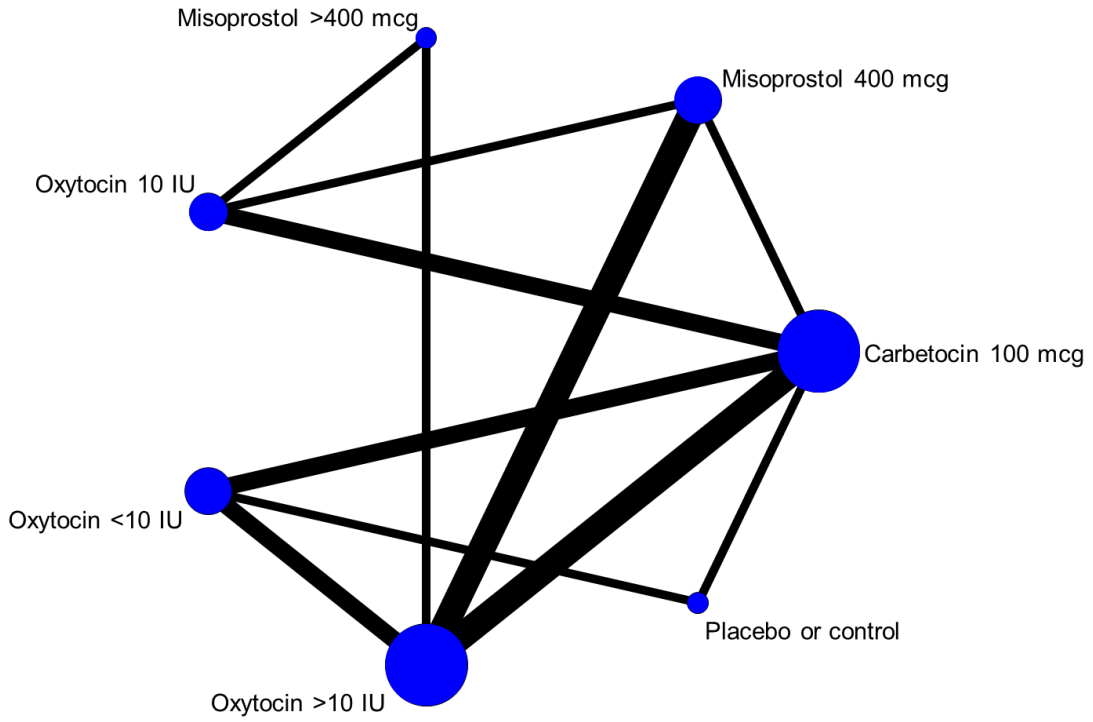


Figure 191: PPH ≥500 mL by mode of birth (caesarean section)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL by mode of birth (caesarean section).

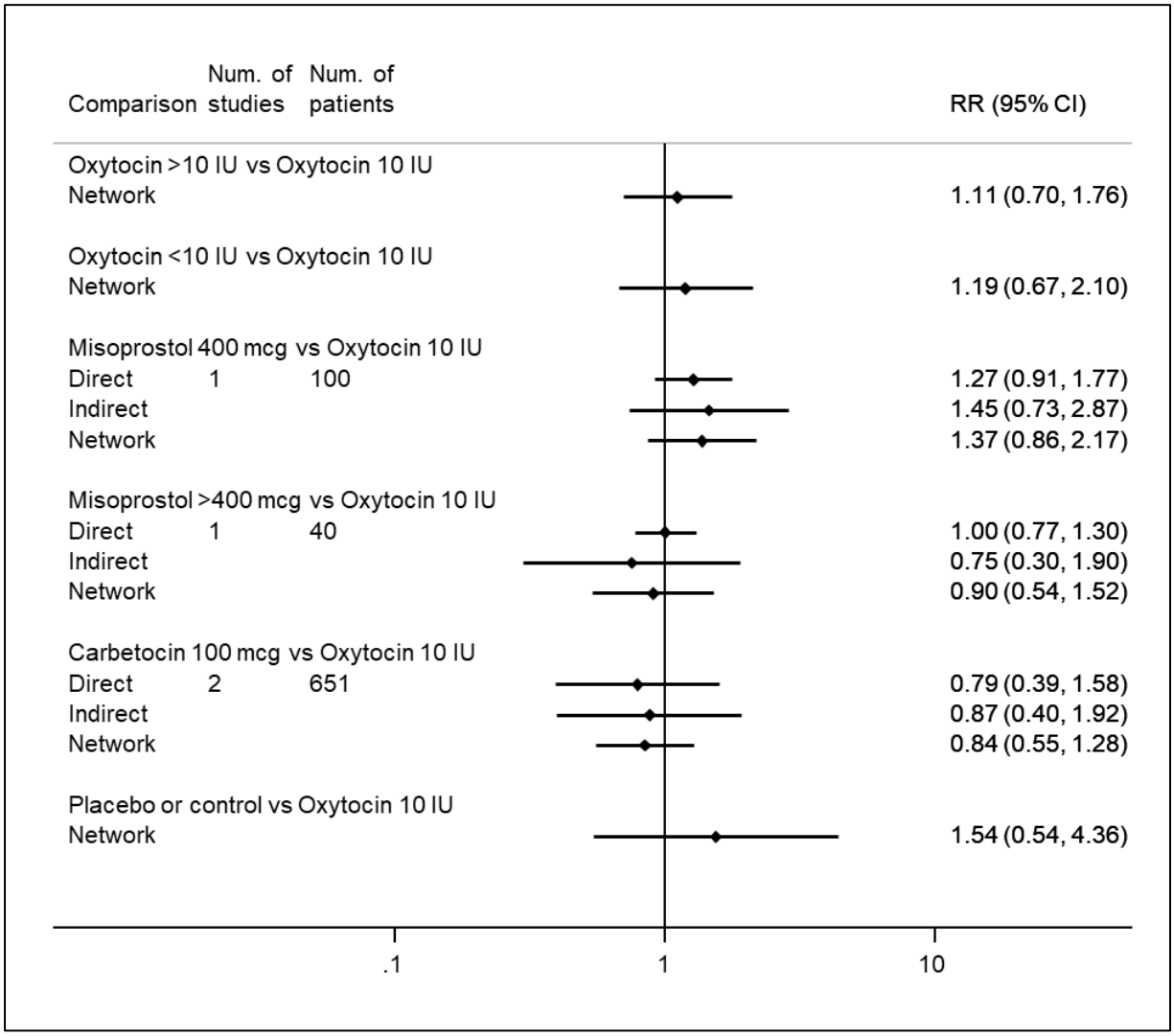


Figure 192: PPH ≥500 mL by mode of birth (caesarean section)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL by mode of birth (caesarean section). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

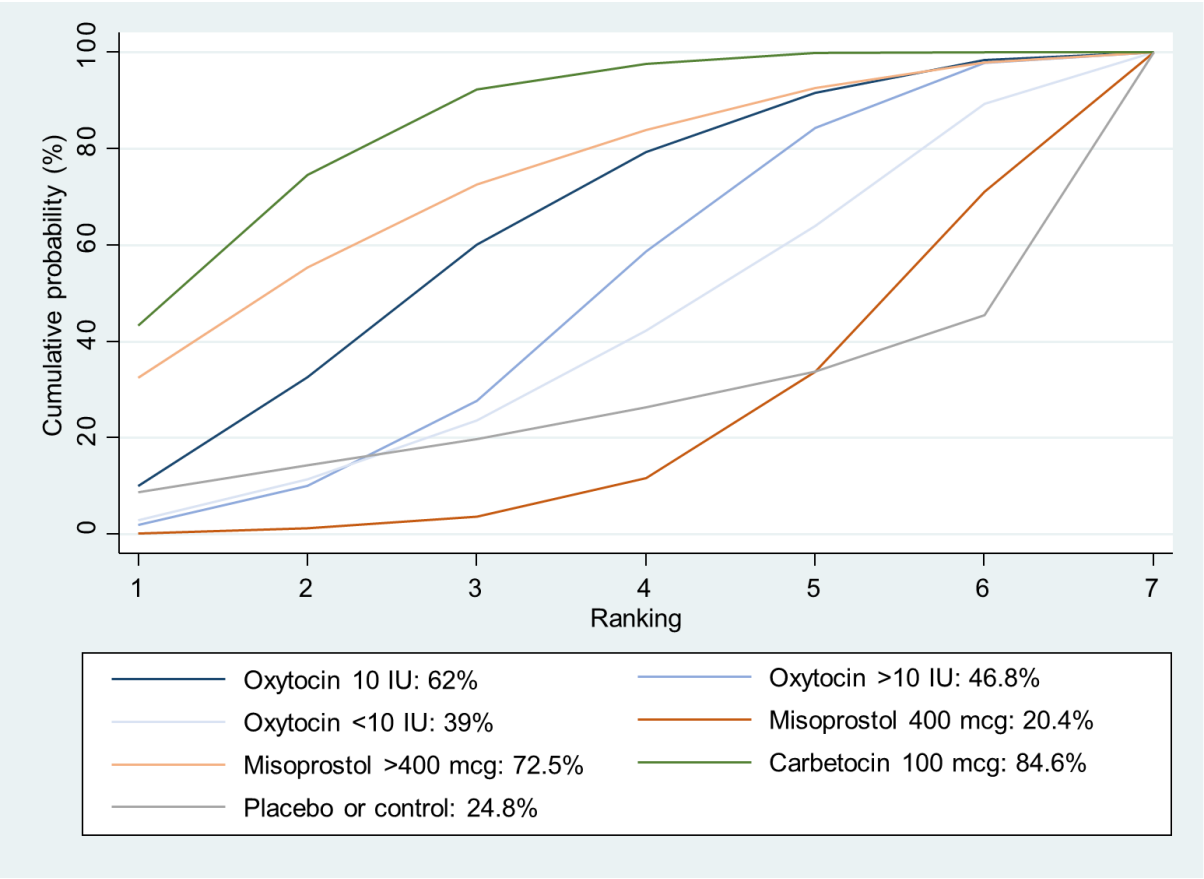


Figure 193: PPH ≥500 mL by prior risk for PPH (low risk)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥500 mL by prior risk for PPH (low risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

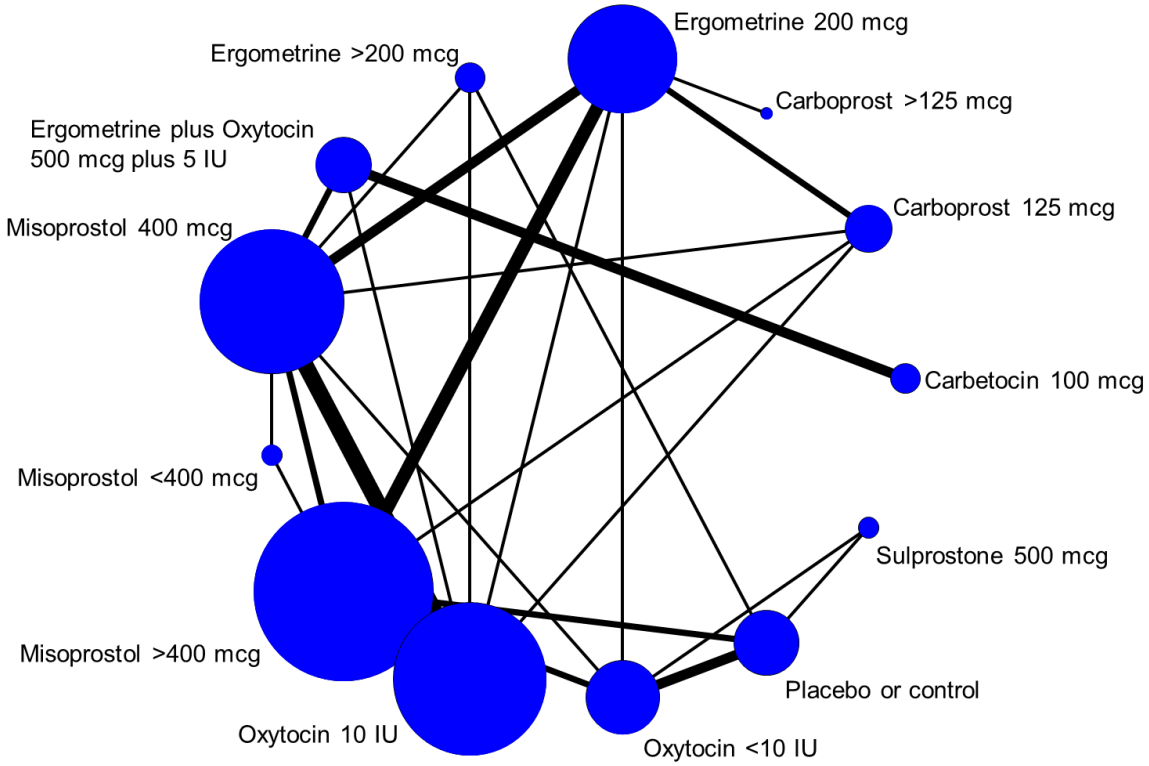


Figure 194: PPH ≥500 mL by prior risk for PPH (low risk)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL by prior risk for PPH (low risk).

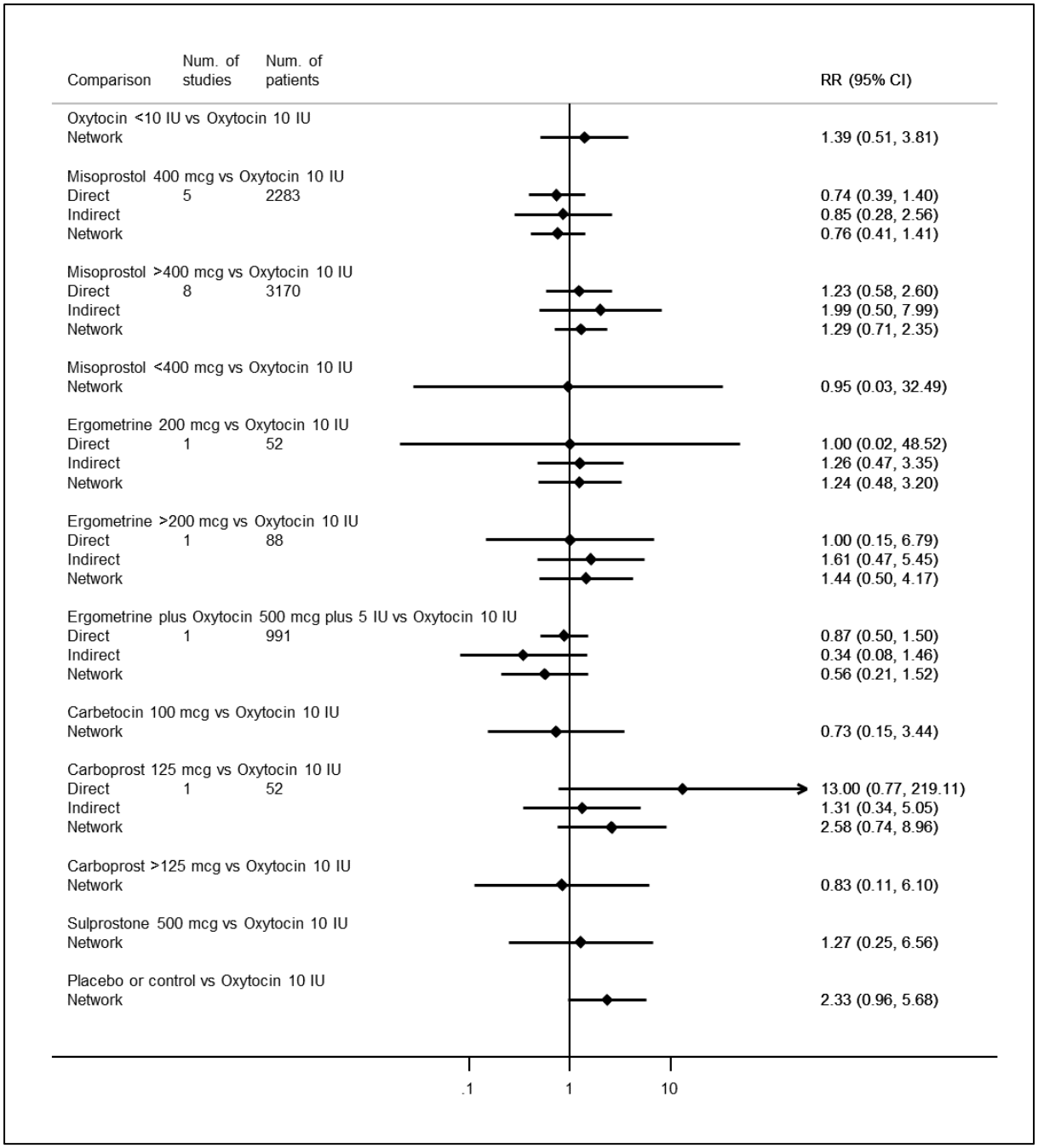


Figure 195: PPH ≥500 mL by prior risk for PPH (low risk)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL by prior risk for PPH (low risk). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

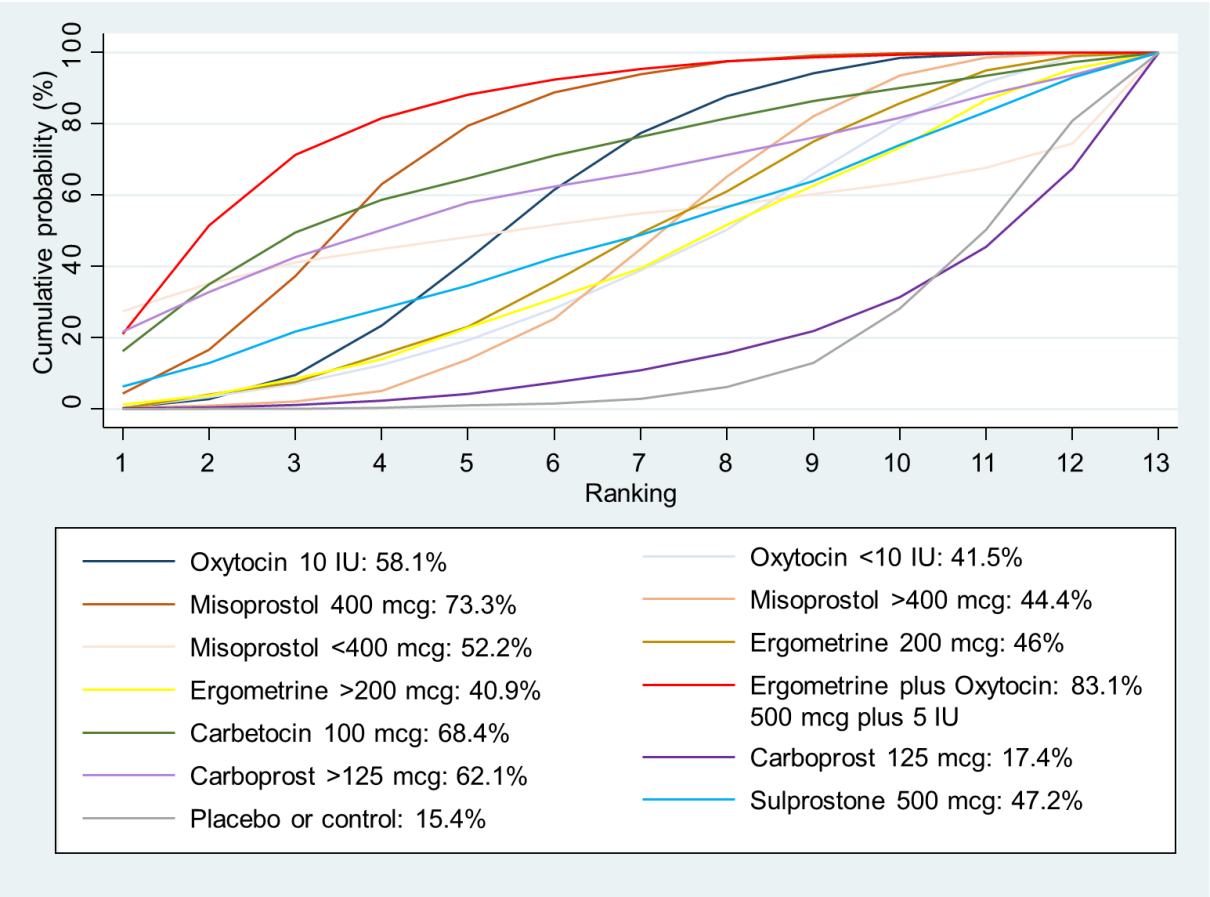


Figure 196: PPH ≥500 mL by prior risk for PPH (high risk)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥500 mL by prior risk for PPH (high risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

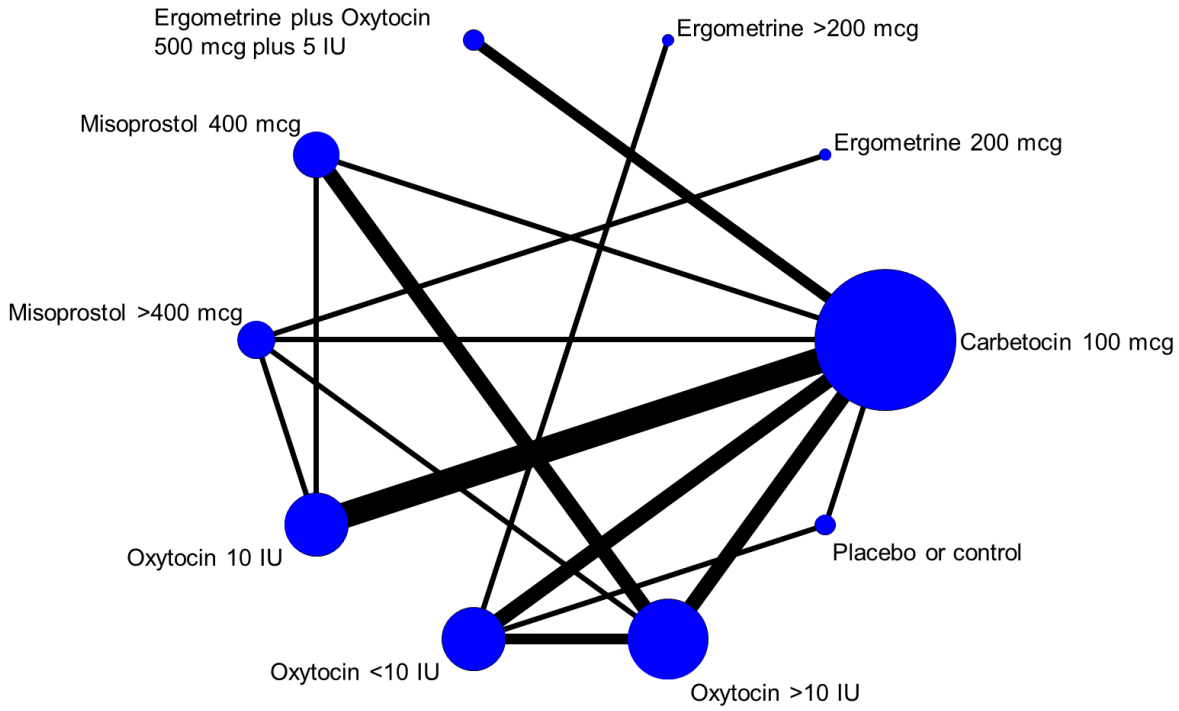


Figure 197: PPH ≥500 mL by prior risk for PPH (high risk)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥500 mL by prior risk for PPH (high risk).

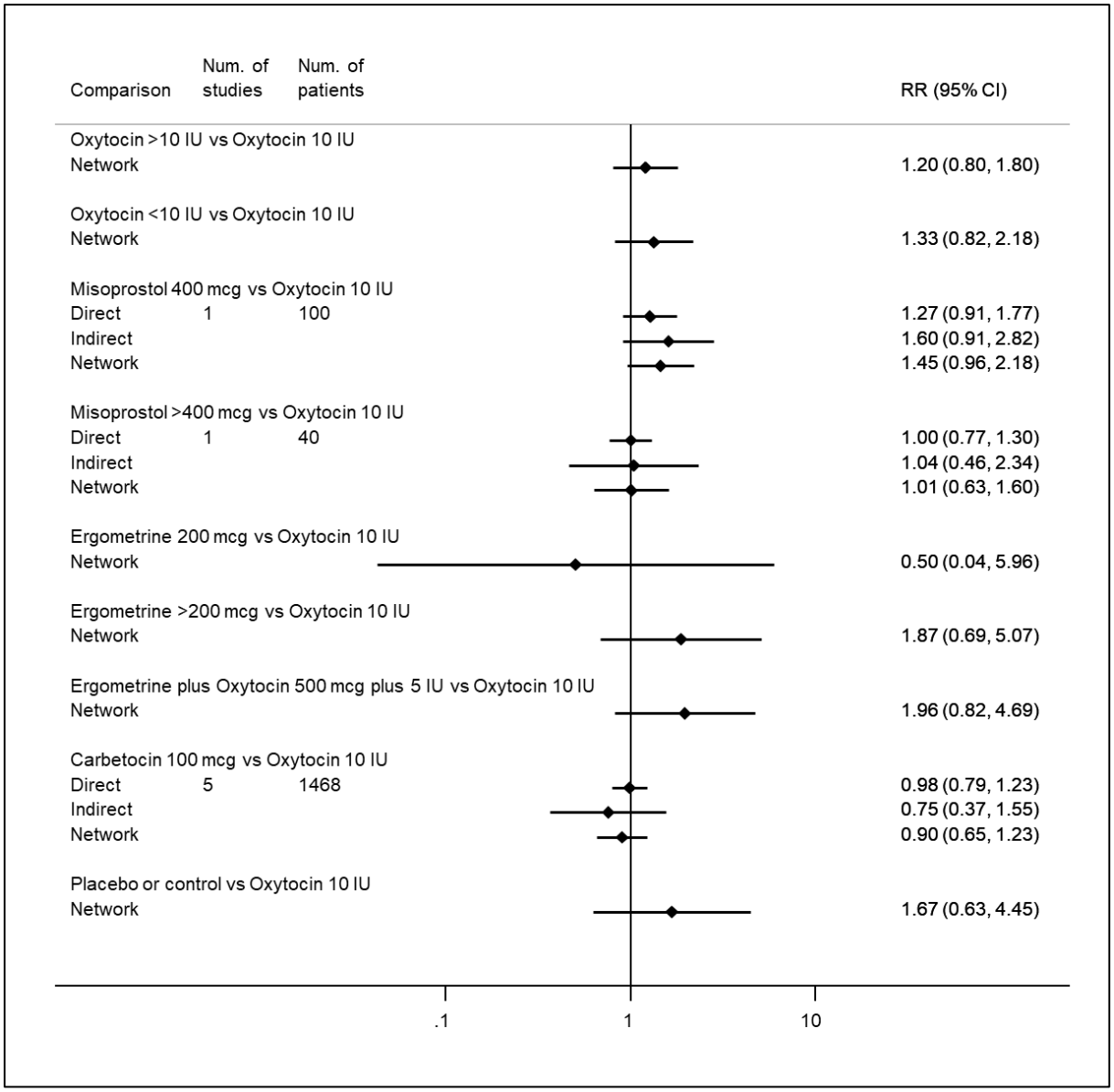


Figure 198: PPH ≥500 mL by prior risk for PPH (high risk)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥500 mL by prior risk for PPH (high risk). Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

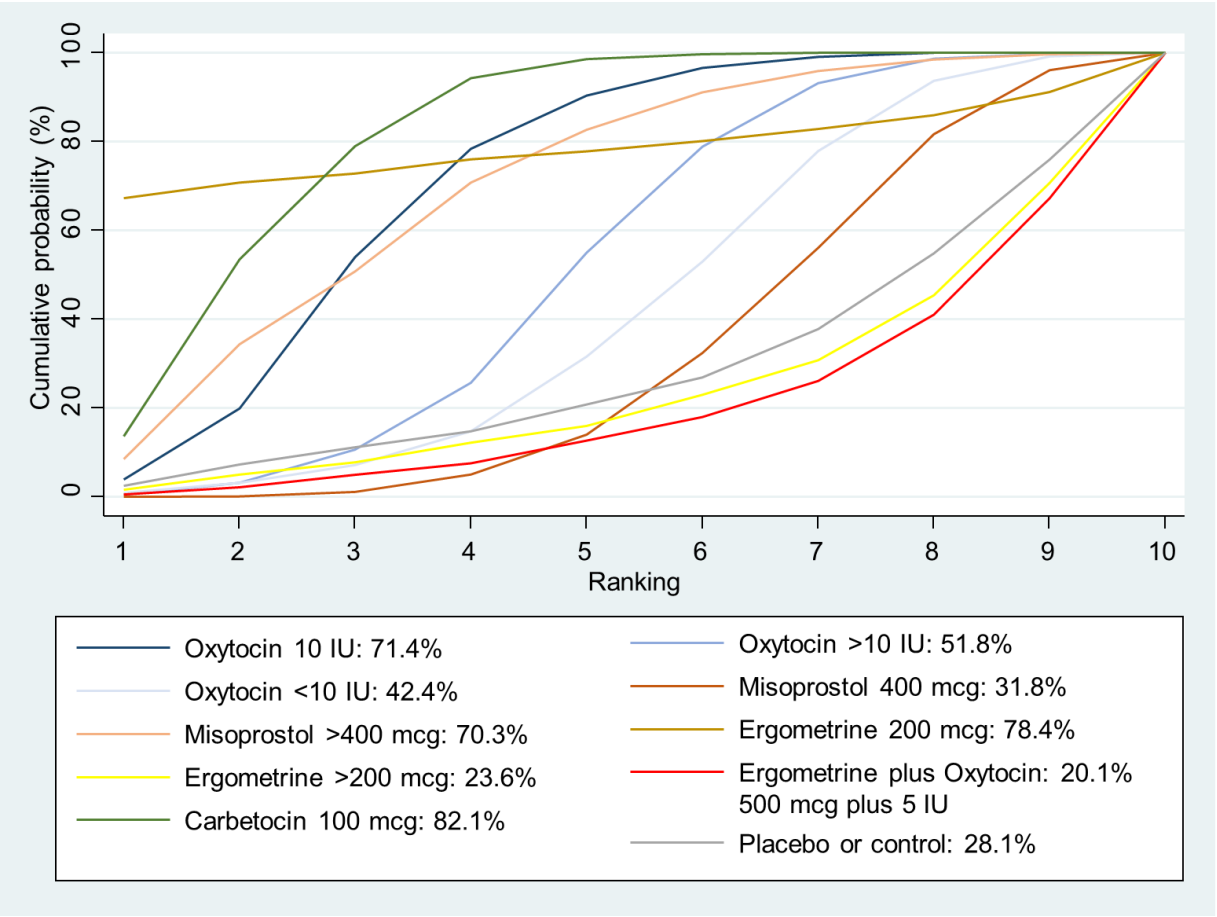


Figure 199: PPH ≥1000 mL by mode of birth (vaginal birth)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥1000 mL by mode of birth (vaginal birth). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

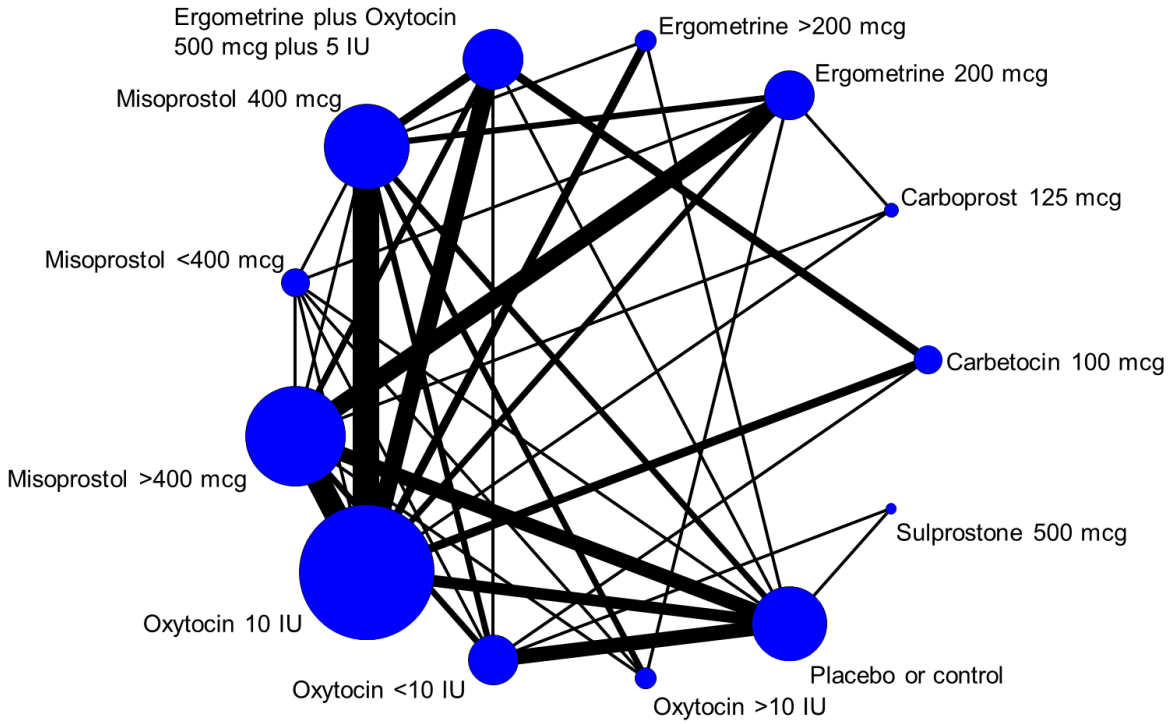


Figure 200: PPH ≥1000 mL by mode of birth (vaginal birth)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL by mode of birth (vaginal birth).

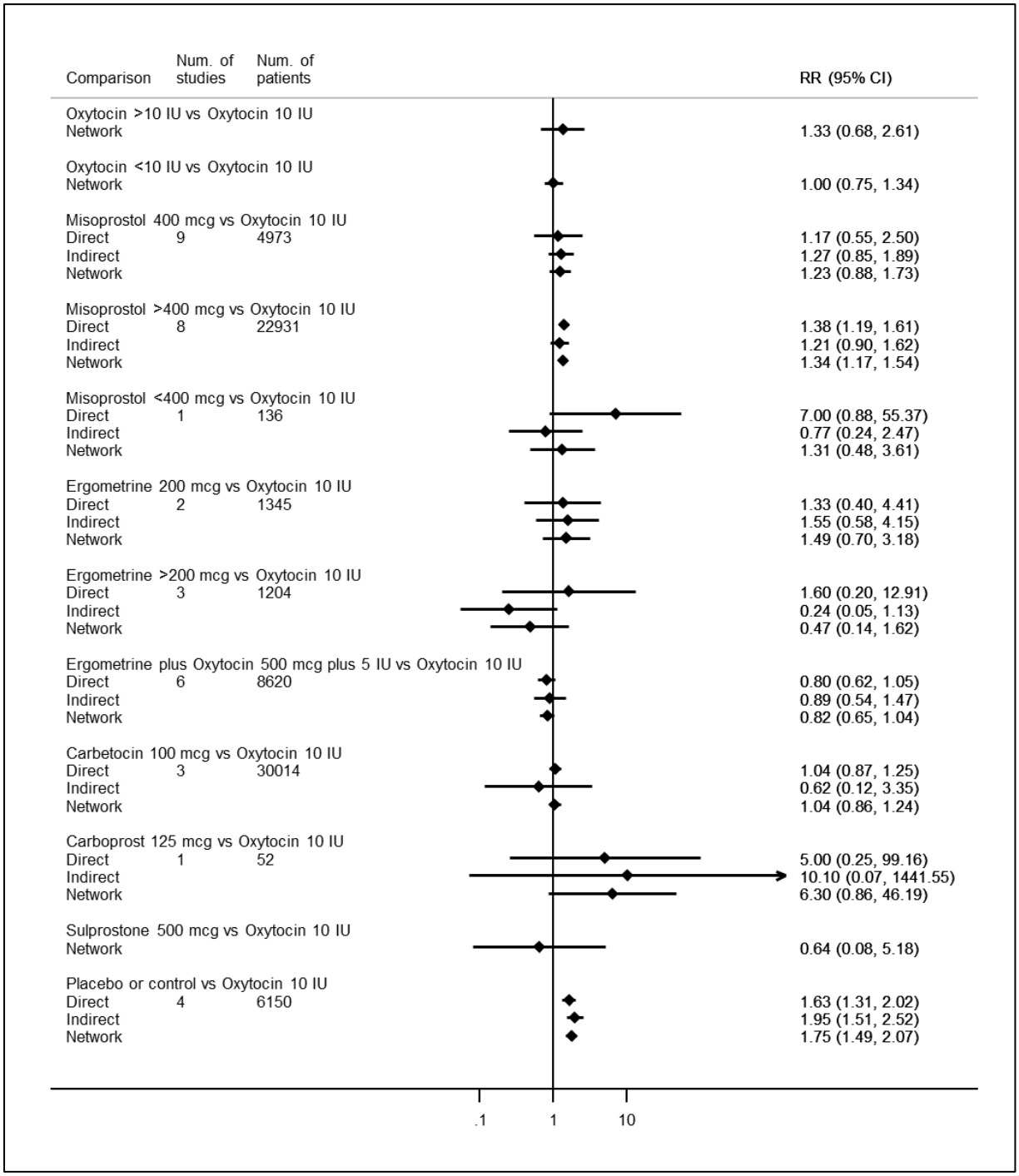


Figure 201: PPH ≥1000 mL by mode of birth (vaginal birth)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL by mode of birth (vaginal birth). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

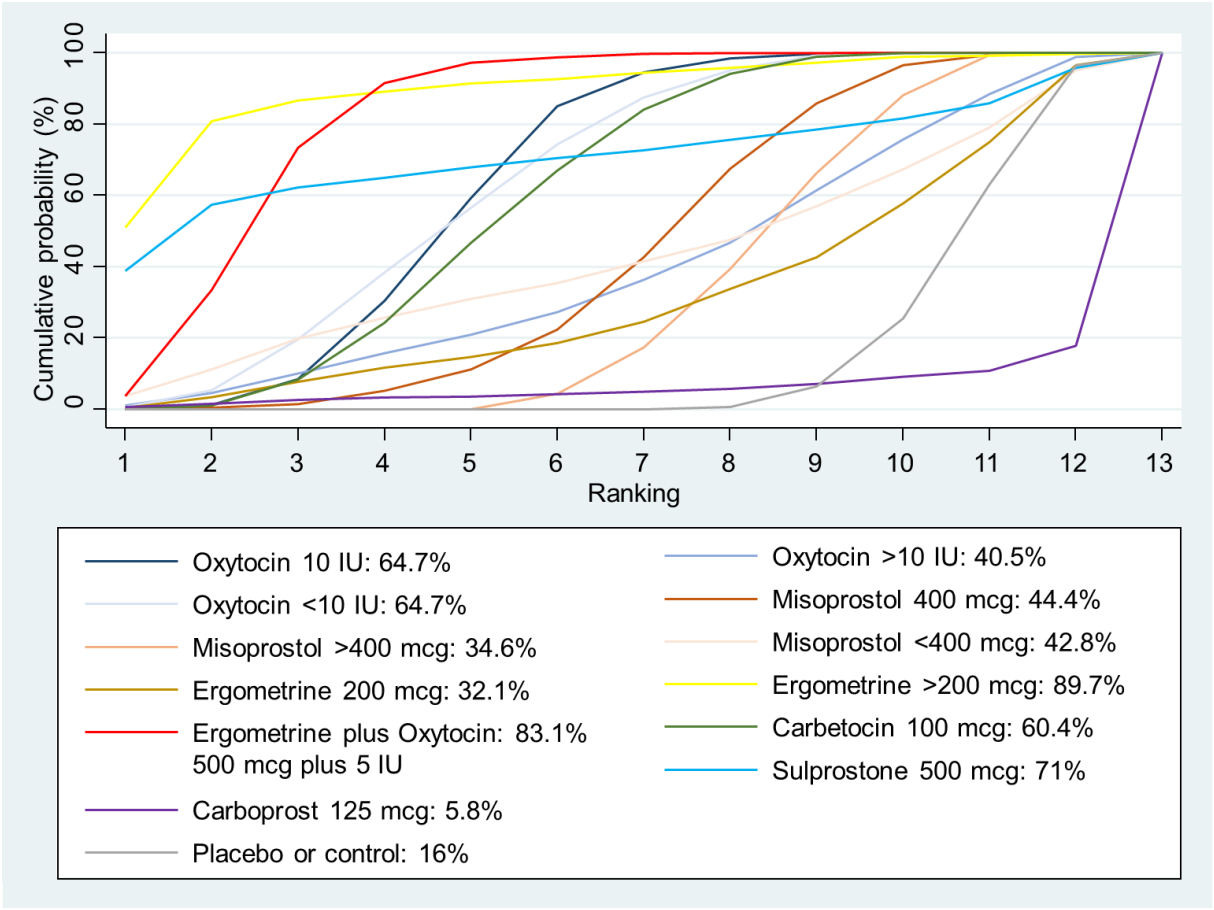


Figure 202: PPH ≥1000 mL by mode of birth (caesarean section)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥1000 mL by mode of birth (caesarean section). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

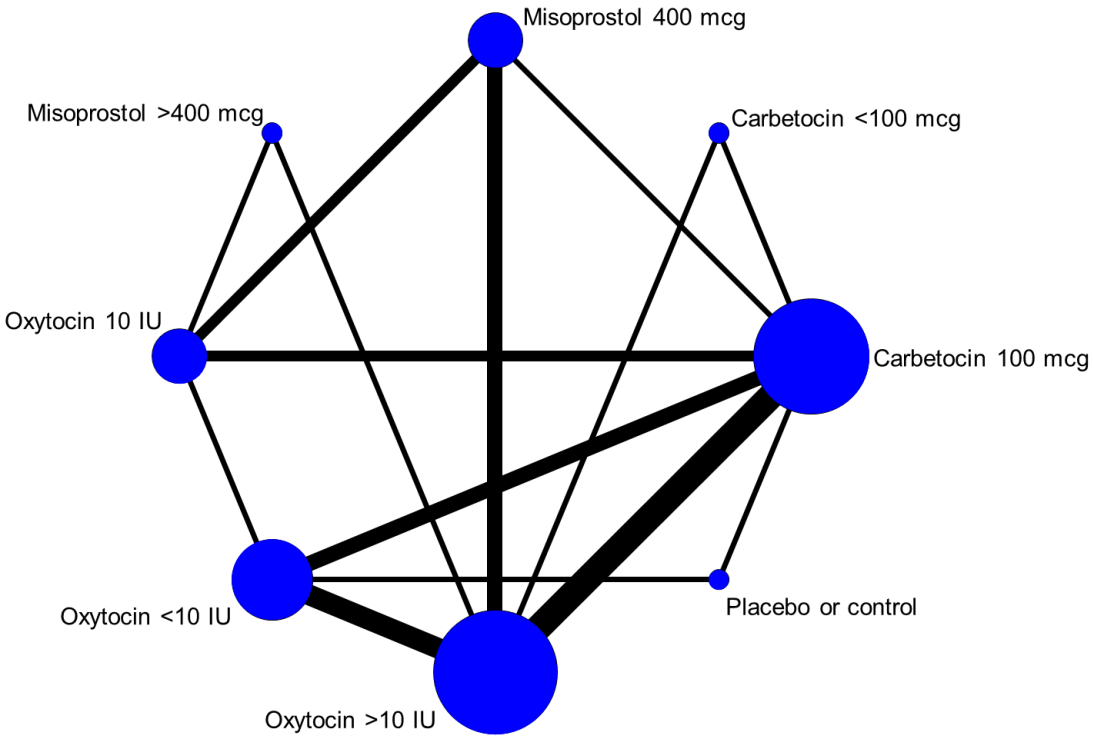


Figure 203: PPH ≥1000 mL by mode of birth (caesarean section)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL by mode of birth (caesarean section).

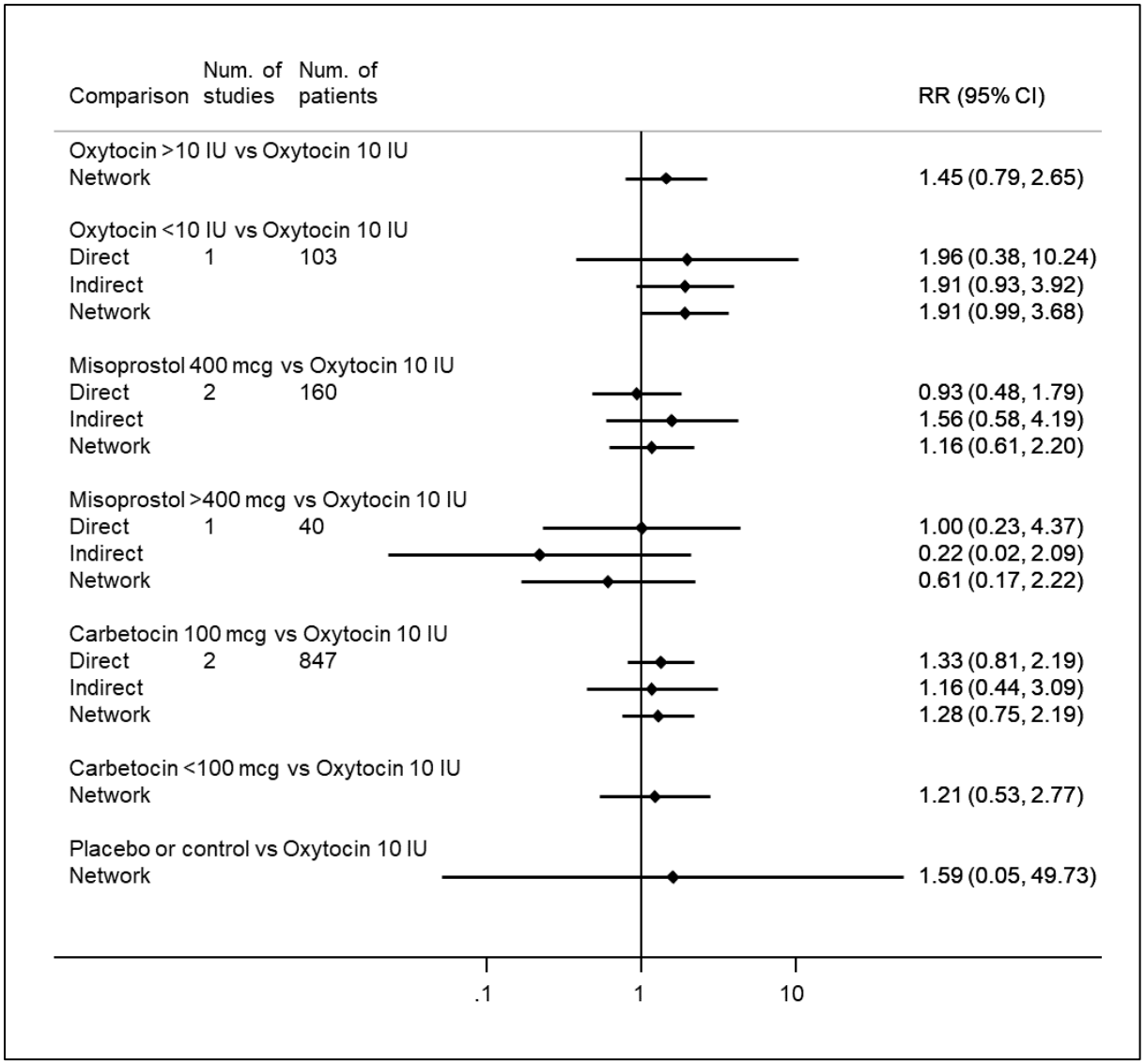


Figure 204: PPH ≥1000 mL by mode of birth (caesarean section)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL by mode of birth (caesarean section). Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

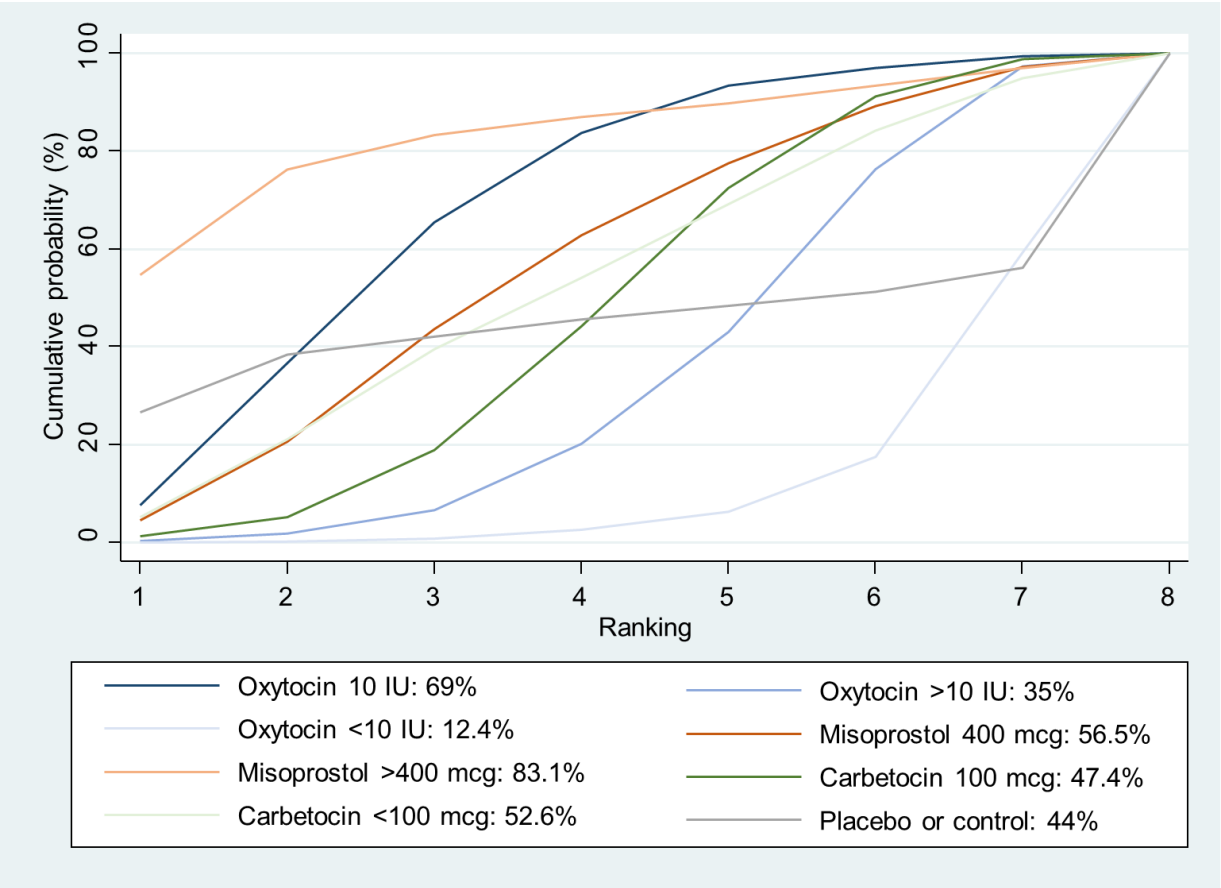


Figure 205: PPH ≥1000 mL by prior risk for PPH (low risk)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥1000 mL by prior risk for PPH (low risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

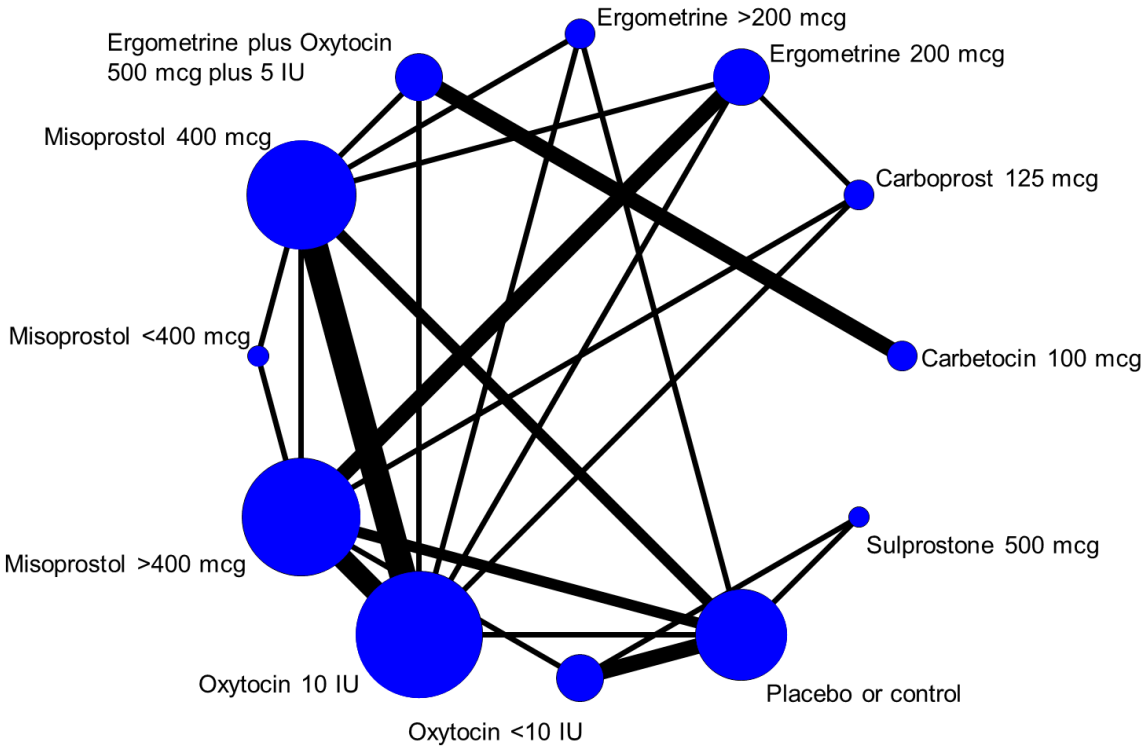


Figure 206: PPH ≥1000 mL by prior risk for PPH (low risk)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL by prior risk for PPH (low risk).

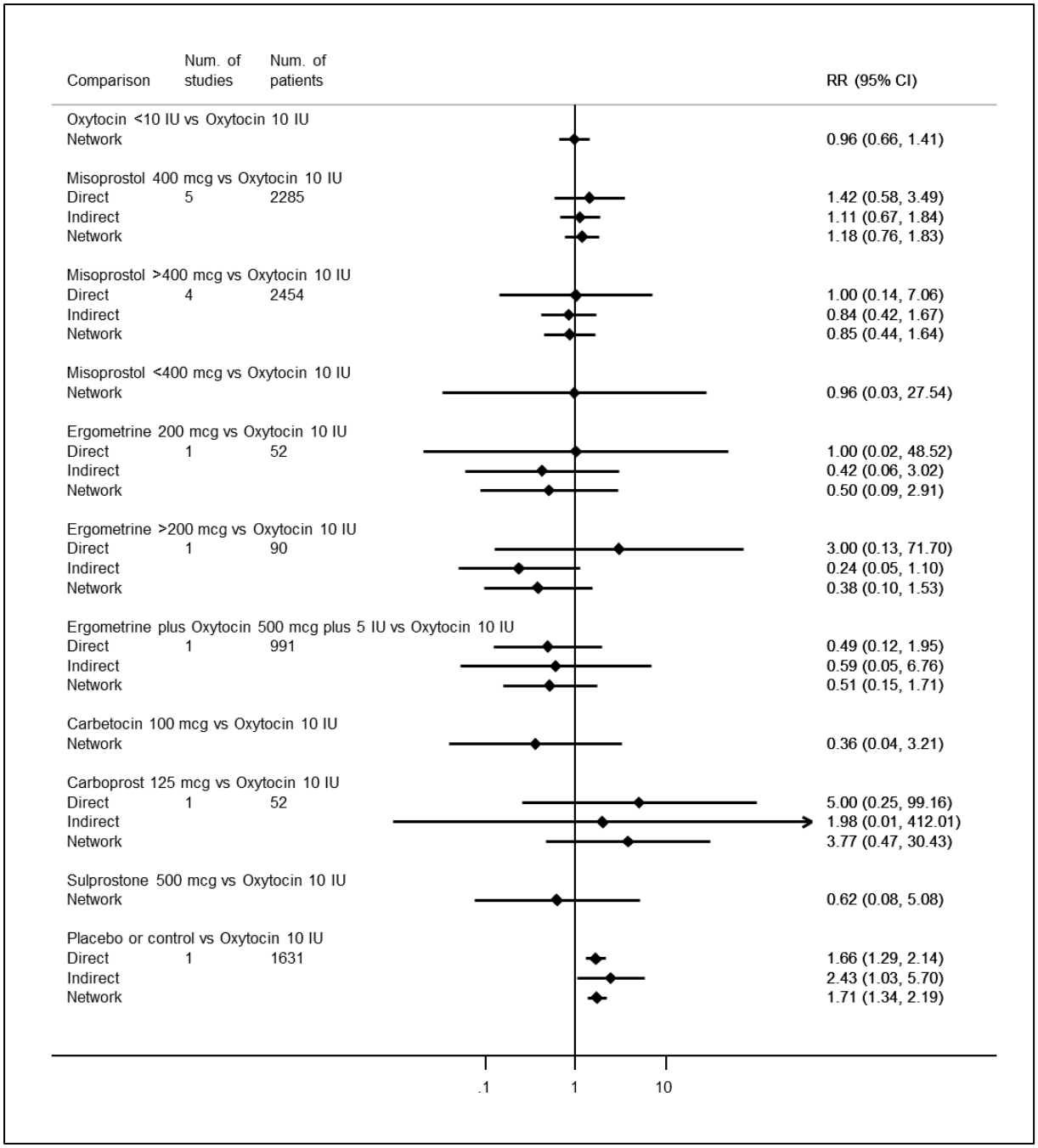


Figure 207: PPH ≥1000 mL by prior risk for PPH (low risk)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL by prior risk for PPH (low risk). Based on the estimated SURface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

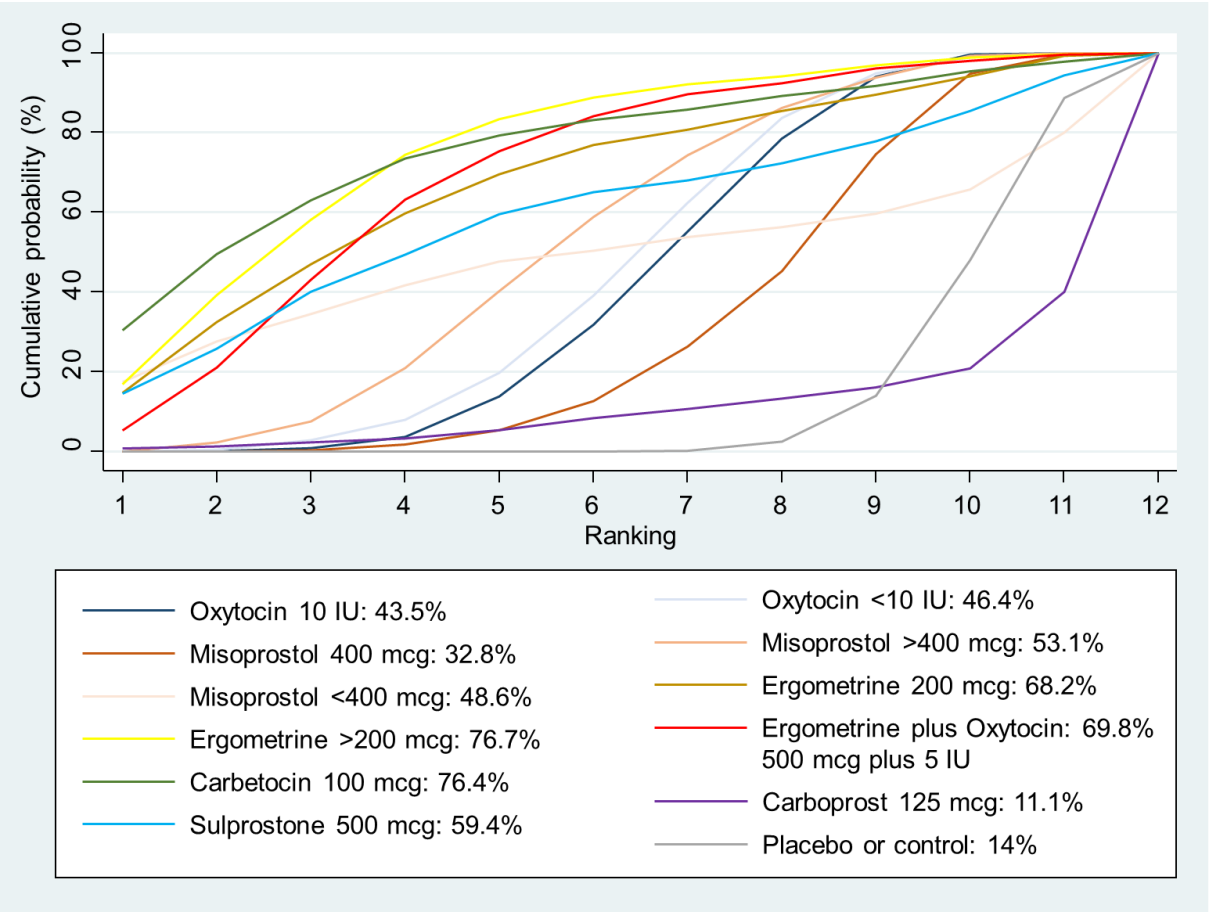


Figure 208: PPH ≥1000 mL by prior risk for PPH (high risk)-Network diagram-Doses NMA

Network diagram for prevention of PPH ≥1000 mL by prior risk for PPH (high risk). The nodes represent an intervention and their size is proportional to the number of studies comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of studies making each direct comparison.

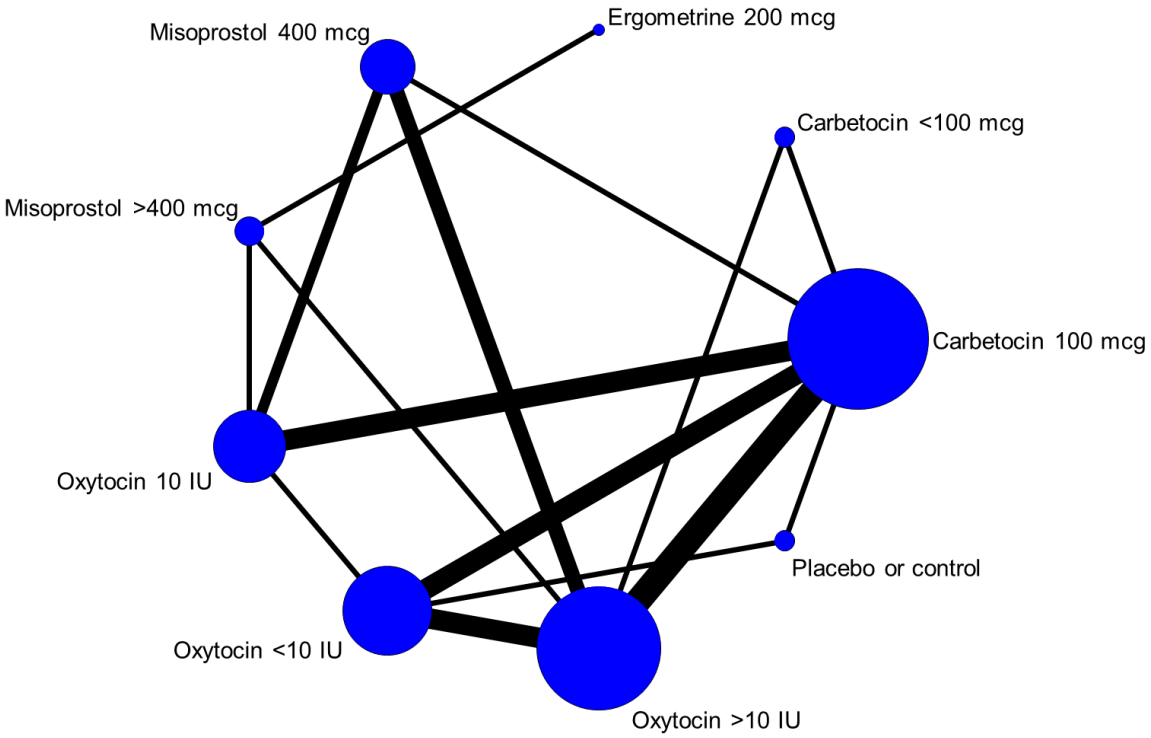


Figure 209: PPH ≥1000 mL by prior risk for PPH (high risk)-Forest plot-Doses NMA

Forest plot with risk ratios and 95% CIs from pairwise, indirect and network analyses for PPH ≥1000 mL by prior risk for PPH (high risk).

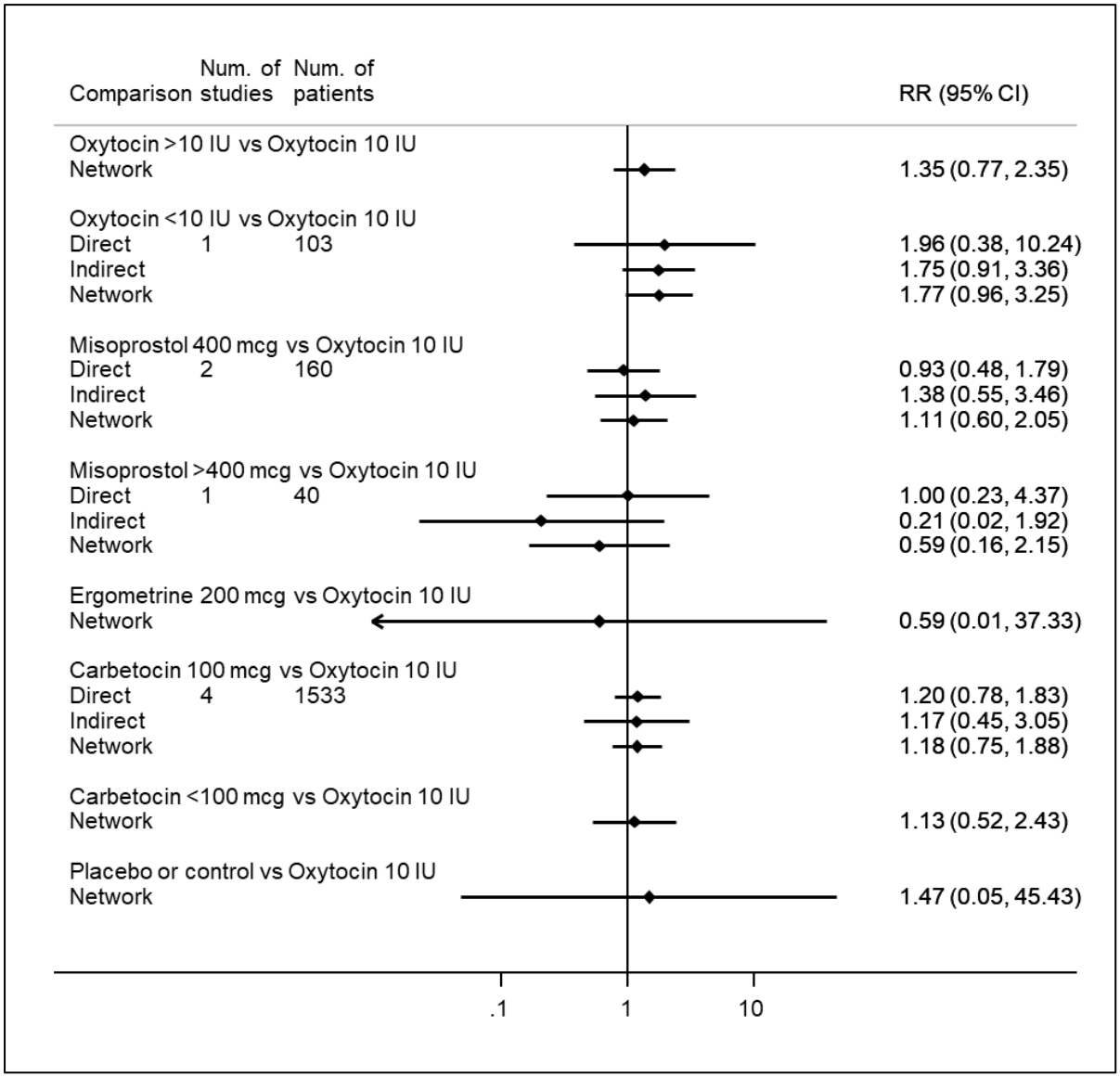


Figure 210: PPH ≥1000 mL by prior risk for PPH (high risk)-Rankogram-Doses NMA

Cumulative rankogram for PPH ≥1000 mL by prior risk for PPH (high risk). Based on the estimated SUrface underneath the Cumulative RAnking line (SUCRA), the ranking of the available agents indicates the cumulative probability of being the best agent, the second best, the third best, etc. The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking.

