



Lecture 4

Basic parameters and analysis of star networks

Georgia Salanti

Statistical methods to fit NMA

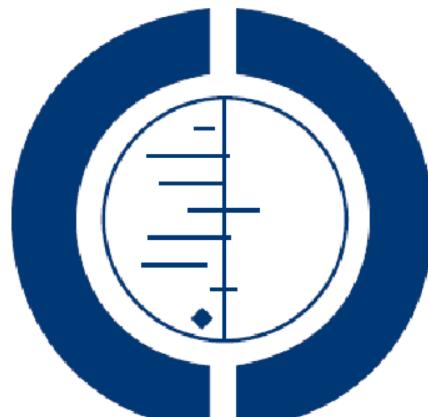
- You don't need to understand every single technical detail in order to fit NMA!
- But a certain degree of understanding is important
- NMA can be fitted as
 - a) meta-regression
 - b) multivariate meta-analysis
 - c) hierarchical model in a Bayesian setting
- Inconsistency can be evaluated in the full network

Steps to undertake in network meta-analysis

- Plot the network
- Select $T-1$ basic parameters (=comparisons) [*T the number of treatments*]
- Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons
- Employ the consistency equations to calculate all pairwise treatment effects

**Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus
(Review)**

Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM



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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library*
2009, Issue 3

<http://www.thecochranelibrary.com>

ABSTRACT

Background

It is unclear whether patients with type 2 diabetes who have poor glycaemic control despite maximal oral hypoglycaemic agents (OHAs) should be commenced on insulin as monotherapy, or insulin combined with oral hypoglycaemic agents (insulin-OHAs combination therapy).

Objectives

To assess the effects of insulin monotherapy versus insulin-OHA combinations therapy.

Search strategy

Eligible studies were identified by searching MEDLINE, EMBASE, and *The Cochrane Library*.

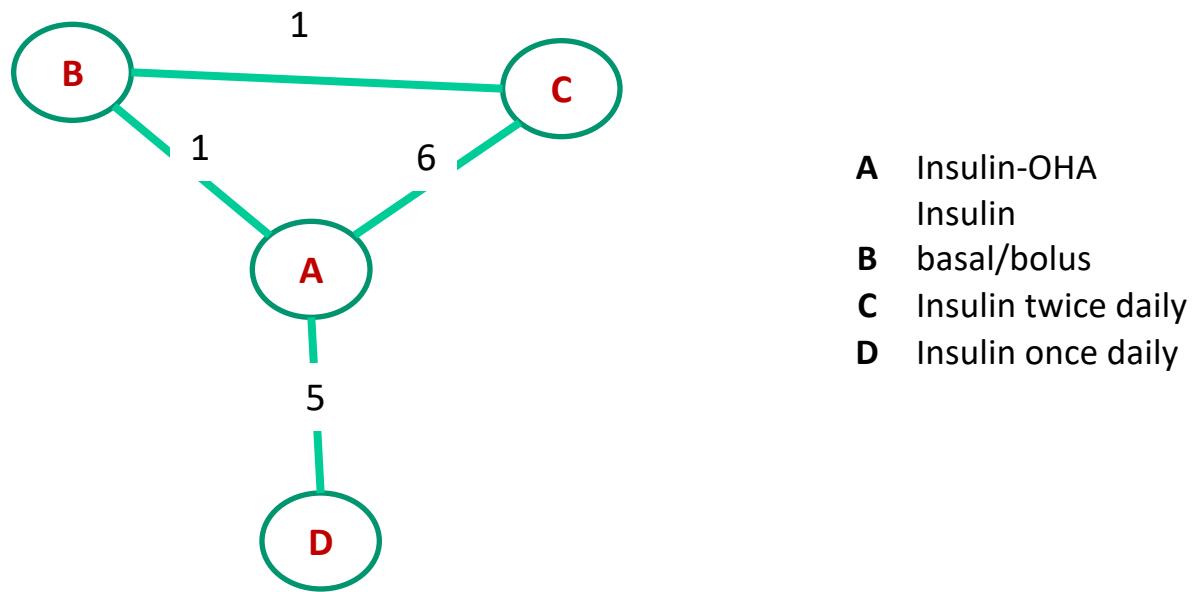
Selection criteria

Randomised controlled trials (RCTs) with 2 months minimum follow-up duration comparing insulin monotherapy (all schemes) with insulin-OHA combination therapy.

Data collection and analysis

Data extraction and assessment of study quality were undertaken by three reviewers in pairs.

Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus



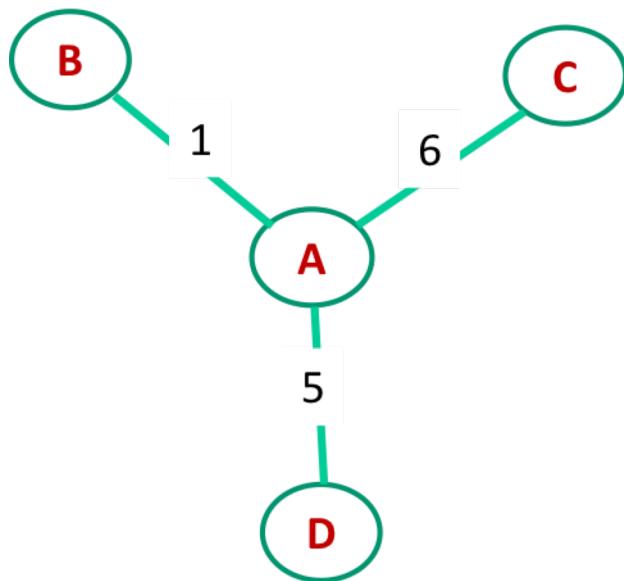
Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus

glycosylated haemoglobin

Study (name)	id	TREAT1	TREAT2	y1	sd1	n1	y2	sd2	n2	comp
Bastyr 1999	6	A	B	-1.21	1.21	135	-1.4	1.46	149	AB
Wolffenbuttel 1996	8	A	C	-2.52	1.17	33	-2.9	1.21	34	AC
Fvnyi 1997	9	A	C	-2.23	1.18	141	-1.4	1.11	145	AC
Yki-Jrvinen 1999	10	A	C	-2.1	1.4	23	-2	1.5	24	AC
Chow 1995	11	A	C	-1.4	1.22	27	-2.16	1.74	26	AC
Lotz 1988	12	A	C	-0.75	1.73	8	-1.72	1.6	8	AC
Wolffenbuttel 1991	13	A	C	-2.42	1.31	25	-3.1	1.26	22	AC
Sun 1995	1	A	D	-5.5	4.82	12	-3	3.53	11	AD
Riddle 1998	2	A	D	-2.2	1	72	-2.1	1	73	AD
Riddle 1992	3	A	D	-1.3	0.33	11	-0.8	0.63	10	AD
Shank 1995	4	A	D	-1.8	1.92	9	-0.7	1.74	9	AD
Du 2001	5	A	D	-1.7	1.57	45	-1.3	1.55	45	AD

Steps to undertake in network meta-analysis

Example



- *Plot the network*
- **Select T-1 basic parameters (=comparisons)**
- Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons
- Employ the consistency equations to calculate all pairwise treatment effects

Select basic parameters

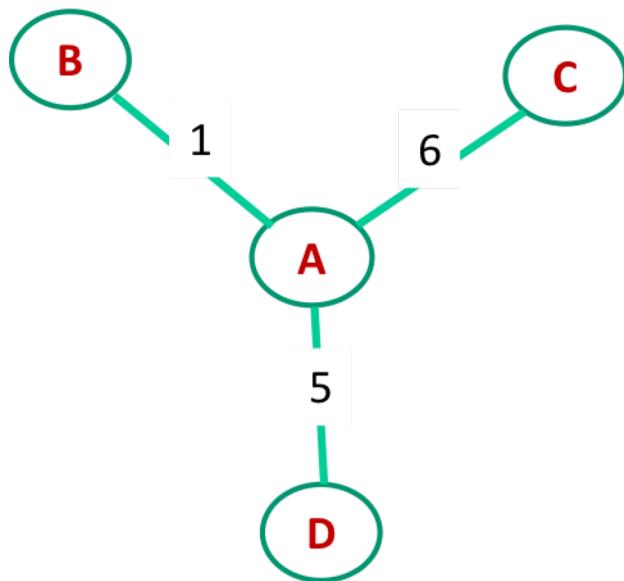
Select a number of comparisons equal with the number of treatments minus one that are independant and connected (see later)

For convenience: use all comparisons versus a common comparison

The results are insensitive to the choice of basic parameters

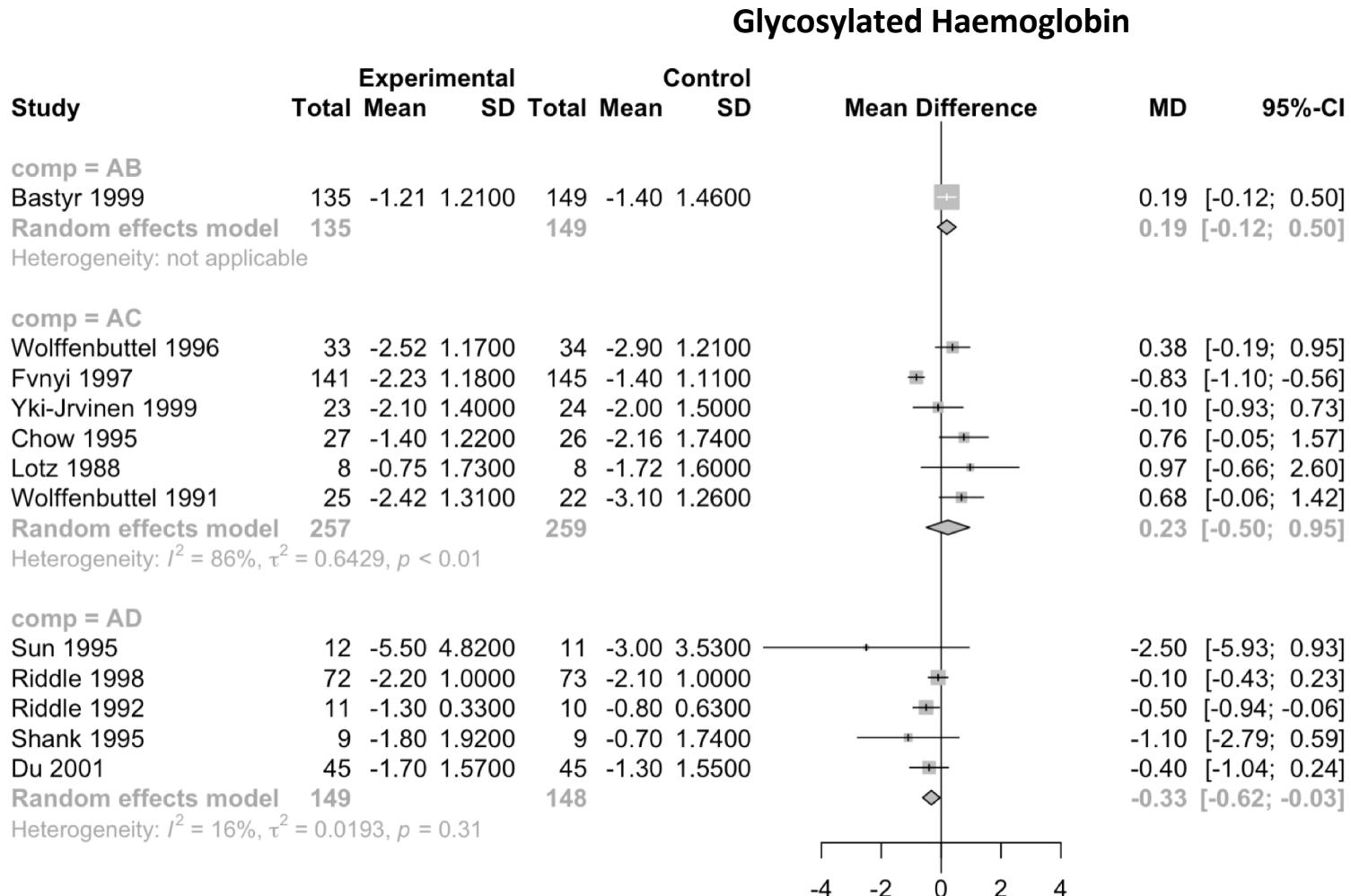
Steps to undertake in network meta-analysis

Example



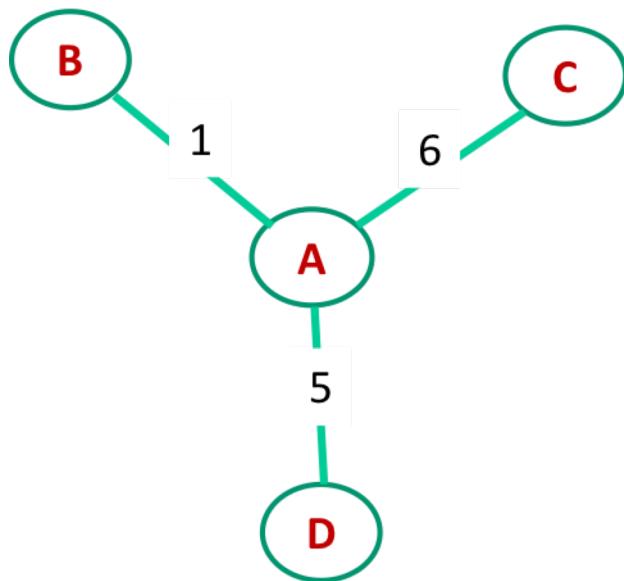
- *Plot the network*
- *Select $T-1$ basic parameters (=comparisons)*
- **Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons**
- Employ the consistency equations to calculate all pairwise treatment effects

Run subgroup analyses to estimate summary effects for each one of the B basic comparisons



Steps to undertake in network meta-analysis

Example



- *Plot the network*
- *Select $T-1$ basic parameters (=comparisons)*
- *Run subgroup analyses or meta-regressions to estimate summary effects for each one of the basic comparisons*
- **Employ the consistency equations to calculate all pairwise treatment effects**

Employ the consistency equations to calculate all pairwise treatment effects

Consistency equations: the equations that link all the comparisons!

With T treatments we have

- $T \times (T-1)/2$ possible treatment comparisons
- $T-1$ basic comparisons
- We need $T \times (T-1)/2 - (T-1)$ consistency equations

With 4 treatments A, B, C, D (as in the example) we have

- 6 possible treatment comparisons: AB, AC, AD, BC, BD, CD
- 3 basic comparisons: AB, AC, AD
- We need to write 3 consistency equations

Employ the consistency equations to calculate all pairwise treatment effects

- 6 possible treatment comparisons: AB, AC, AD, BC, BD, CD
- 3 basic comparisons: AB, AC, AD Estimated from the subgroup analysis

$$\mu_{AB}: 0.19 (-0.12, 0.50)$$

$$\mu_{AC}: 0.23 (-0.50, 0.95)$$

$$\mu_{AD}: -0.33 (-0.62, -0.03)$$

- We need to write 3 consistency equations

$$\mu_{BC} = \mu_{AC} - \mu_{AB} = 0.04$$

$$\mu_{BD} = \mu_{AD} - \mu_{AB} = -0.52$$

$$\mu_{CD} = \mu_{AD} - \mu_{AC} = -0.56$$

We cut some corners...

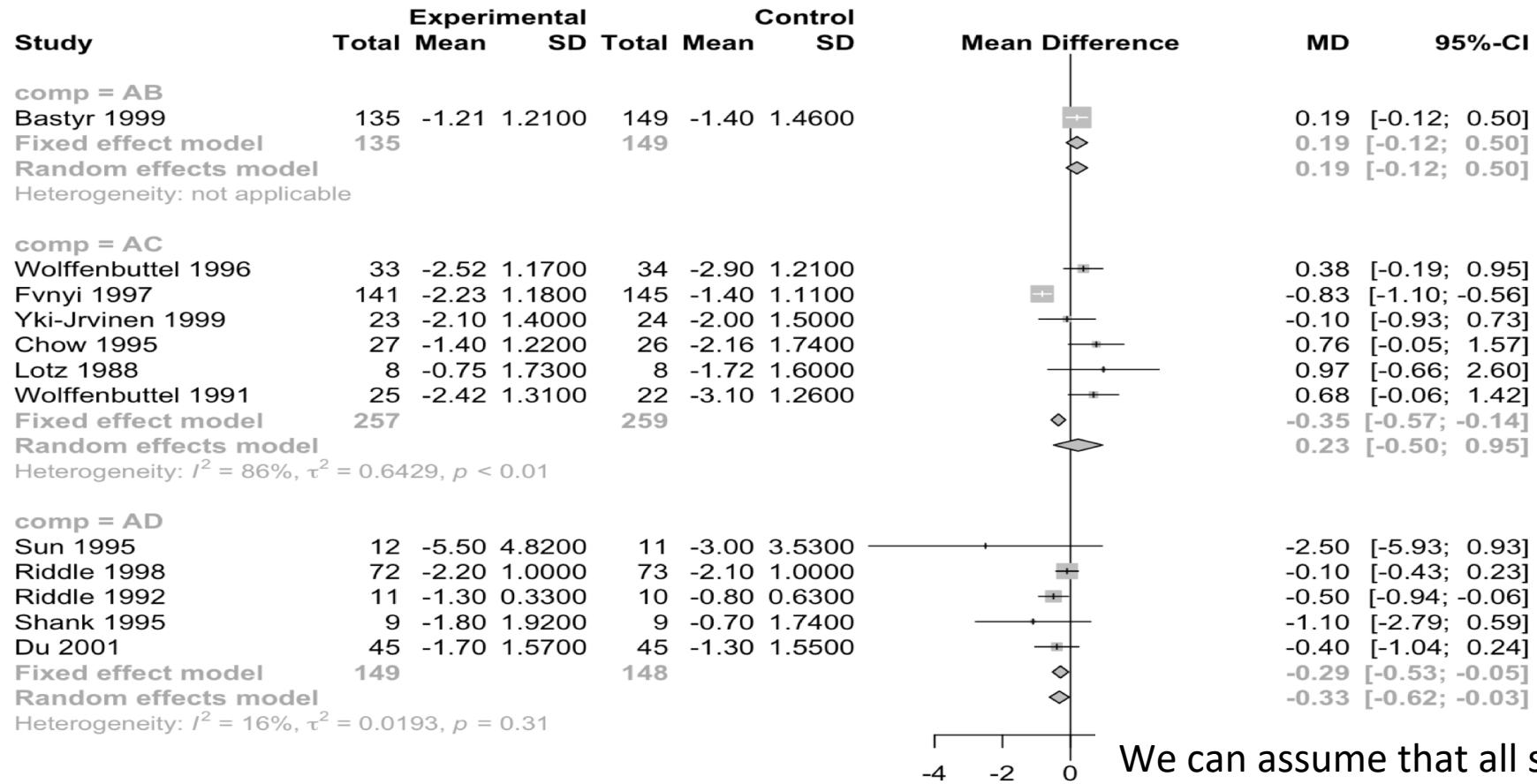
Random effects meta-analyses are more plausible in many clinical areas

(in the example we used fixed effects for simplicity)

Estimation of the heterogeneity parameter is an issue in random effects

- You need a few studies to estimate the heterogeneity variance properly...

Estimation of heterogeneity



Results for subgroups (random effects model):

	k	MD	95%-CI	Q	tau^2	I^2
comp = AB	1	0.1900	[-0.1208; 0.5008]	0.00	--	--
comp = AC	6	0.2273	[-0.4954; 0.9500]	36.42	0.6429	86.3%
comp = AD	5	-0.3260	[-0.6171; -0.0349]	4.78	0.0193	16.3%

We can assume that all studies have the same heterogeneity irrespectively of the comparison

Run subgroup analyses to estimate summary effects for each one of the B basic comparisons using the same heterogeneity

Results for subgroups (random effects model) equal heterogeneities

	k	MD	95%-CI	Q	tau^2	I^2
comp = AB	1	0.1900	[-1.0270; 1.4070]	0.00	--	--
comp = AC	6	0.1887	[-0.3876; 0.7651]	36.42	0.3604	86.3%
comp = AD	5	-0.4858	[-1.1642; 0.1927]	4.78	0.3604	16.3%

Results for subgroups (random effects model) different heterogeneities

	k	MD	95%-CI	Q	tau^2	I^2
comp = AB	1	0.1900	[-0.1208; 0.5008]	0.00	--	--
comp = AC	6	0.2273	[-0.4954; 0.9500]	36.42	0.6429	86.3%
comp = AD	5	-0.3260	[-0.6171; -0.0349]	4.78	0.0193	16.3%

Then the indirect treatment effects are:

$$\mu_{BC} = \mu_{AC} - \mu_{AB} = 0$$

$$\mu_{BD} = \mu_{AD} - \mu_{AB} = -0.68$$

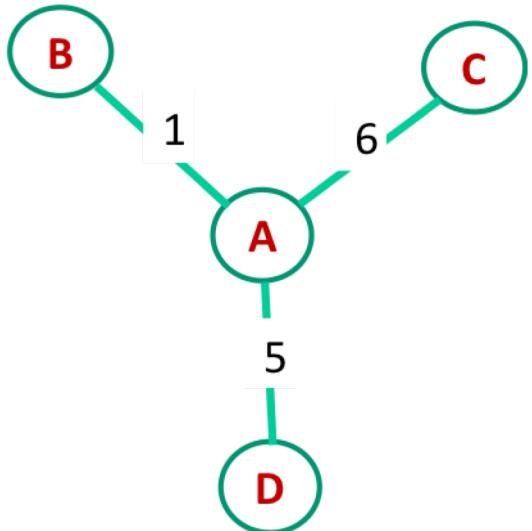
$$\mu_{CD} = \mu_{AD} - \mu_{AC} = -0.68$$

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \mu_{AD} \mathbf{AD} + \mu_{AB} \mathbf{AB} + \mu_{AC} \mathbf{AC}$$

μ_{AD} : the direct estimate AD
 μ_{AB} : the direct estimate AB
 μ_{AC} : the direct estimate AC

$\mu_{AB} - \mu_{AD}$: the indirect estimate DB
 $\mu_{AC} - \mu_{AD}$: the indirect estimate DC
 $\mu_{AC} - \mu_{AB}$: the indirect estimate BC



Author	comp	AB	AC	AD
Basty 1999	AB	1	0	0
Wolffenbuttel 1996	AC	0	1	0
Fvnyi 1997	AC	0	1	0
Yki-Jrvinen 1999	AC	0	1	0
Chow 1995	AC	0	1	0
Lotz 1988	AC	0	1	0
Wolffenbuttel 1991	AC	0	1	0
Sun 1995	AD	0	0	1
Riddle 1998	AD	0	0	1
Riddle 1992	AD	0	0	1
Shank 1995	AD	0	0	1
Du 2001	AD	0	0	1

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \alpha + \beta_1 AB + \beta_2 AC$$

α : the direct estimate AD μ_{AD}

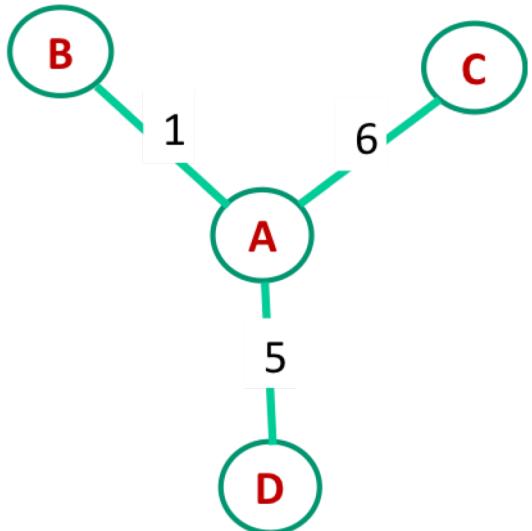
$\alpha + \beta_1$: the direct estimate AB μ_{AB}

$\alpha + \beta_2$: the direct estimate AC μ_{AC}

β_1 : the indirect estimate DB

β_2 : the indirect estimate DC

$\beta_2 - \beta_1$: the indirect estimate BC



Author	comp	AB	AC	AD
Bastyr 1999	AB	1	0	0
Wolffenbuttel 1996	AC	0	1	0
Fvnyi 1997	AC	0	1	0
Yki-Jrvinen 1999	AC	0	1	0
Chow 1995	AC	0	1	0
Lotz 1988	AC	0	1	0
Wolffenbuttel 1991	AC	0	1	0
Sun 1995	AD	0	0	1
Riddle 1998	AD	0	0	1
Riddle 1992	AD	0	0	1
Shank 1995	AD	0	0	1
Du 2001	AD	0	0	1

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$MD_i = \alpha + \beta_1 AB + \beta_2 AC$$

`metareg(HBStarmeta, ~AB+AC)` assumes equal heterogeneities

Model Results:

		estimate	se	zval	pval	ci.lb	ci.ub
Intrcpt	α	-0.4858	0.3461	-1.4033	0.1605	-1.1642	0.1927
AB	β_1	0.6758	0.7109	0.9506	0.3418	-0.7176	2.0691
AC	β_2	0.6745	0.4542	1.4850	0.1375	-0.2157	1.5647

Remember:

α : the direct estimate AD

β_1 : the indirect estimate DB

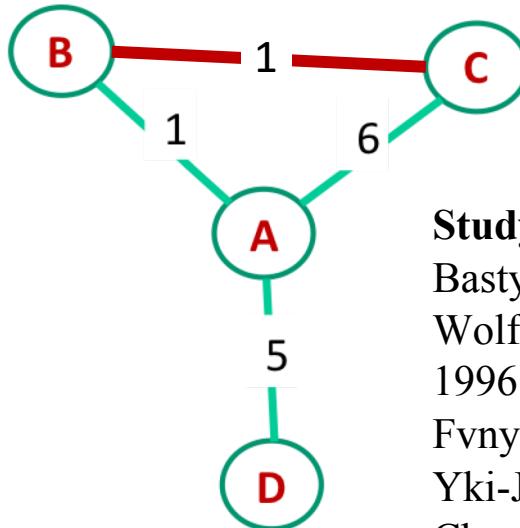
$\alpha + \beta_1$: the direct estimate AB

β_2 : the indirect estimate DC

$\alpha + \beta_2$: the direct estimate AC

$\beta_2 - \beta_1$: the indirect estimate BC

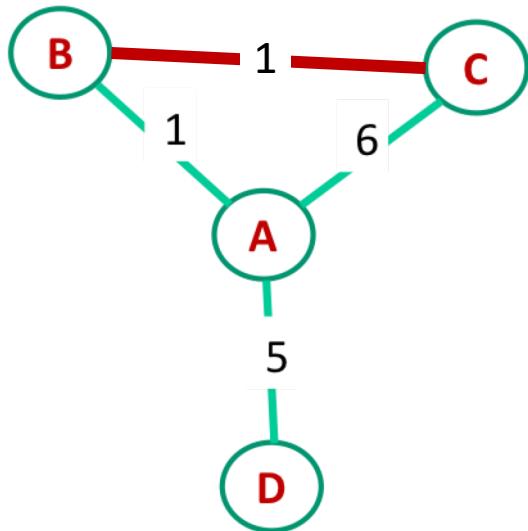
Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus



Study (name)	T1	T2	y1	sd1	n1	y2	sd2	n2 comp
Bastyr 1999	A	B	-1.21	1.21	135	-1.4	1.46	149 AB
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Yki-Jrvinen 1992	B	C	-1.6	1.6	30	-1.8	1.6	29 BC

What is difficult with it?

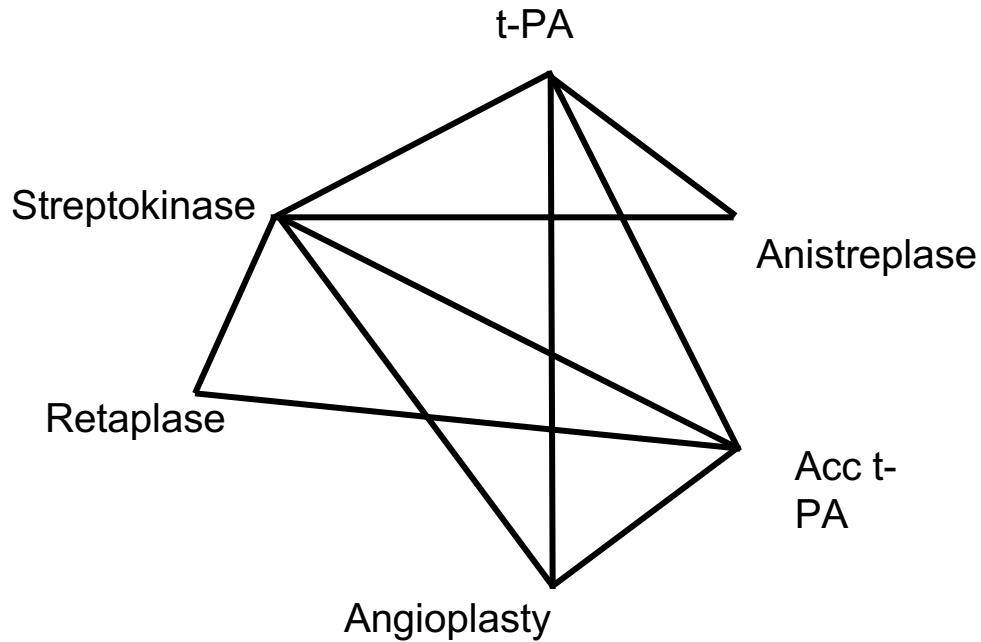
- The way that data informs you about the basic parameters
- The way the the consistency equations enter the model



That differentiates the 3 approaches meta-regression vs multivariate meta-analysis vs hierarchical Bayesian model

- Plot the network – **easy!**
- Select B basic parameters (=comparisons) – **relatively easy**
- Run subgroup analyses or **meta-regressions** to estimate summary effects for each one of the B basic comparisons
 - The way that data informs you about the basic parameters in the presence of a BC comparison (not basic parameter)
 - Multi-arm studies
- Employ the consistency equations to calculate all pairwise treatment effects – **easy although tedious process!**

Select basic parameters



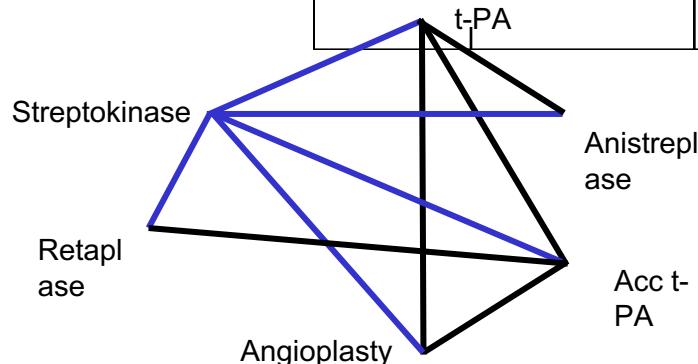
Treatments for MI and mortality Lumley Stat Med 2002

Run meta-regression to estimate summary effects for each one of the B basic comparisons

$$y_i = \mu_{tPA-S} tPA_i + \mu_{Anist-S} Anist_i + \mu_{AcctPA-S} AcctPA_i + \mu_{Ang-S} Ang_i + \mu_{Ret-S} Ret_i + \delta_i + e_i$$

Use as 'covariates'

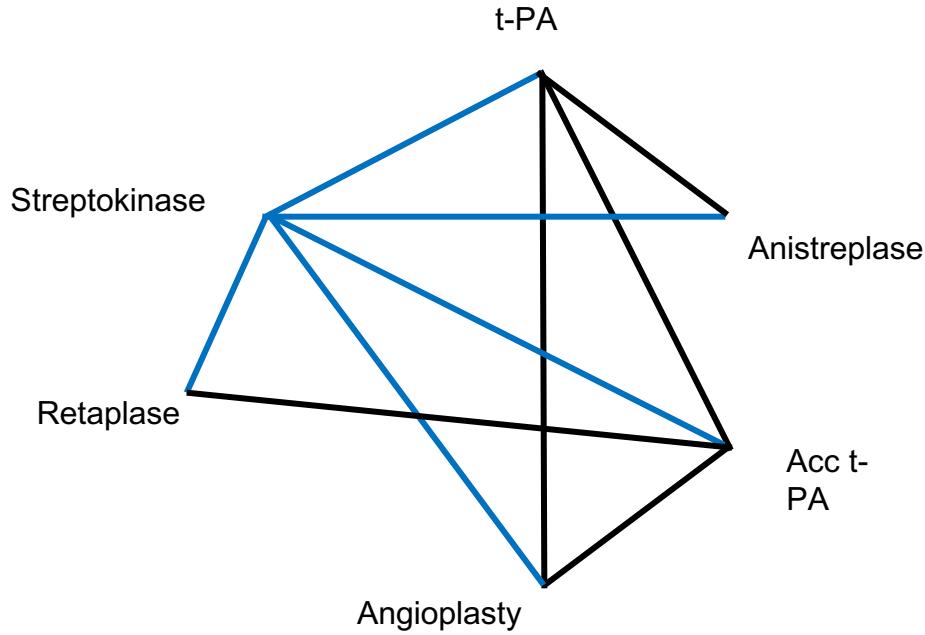
No. studies	Streptokinase	t-PA	Anistreplase	Acc t-PA	Angioplasty	Reteplase
3	Ref	1	0	0	0	0
1	Ref	0	1	0	0	0
1	Ref	0	0	1	0	0
3	Ref	0	0	0	1	0
1	Ref	0	0	0	0	1



We have ignored some studies

Employ the consistency equations to calculate all pairwise treatment effects

6 treatments, 15 possible comparisons, 5 basic comparisons, 10 consistency equations



10 consistency equations

$$\mu_{tPA \text{ vs } Anistr} = \mu_{Str \text{ vs } Anistr} - \mu_{Str \text{ vs } tPA}$$

$$\mu_{tPA \text{ vs } Reta} = \mu_{Str \text{ vs } Reta} - \mu_{Str \text{ vs } tPA}$$

.....

Design matrix

- The consistency equations are built into the design matrix
- This minimizes the number of parameters and allows us to gain precision

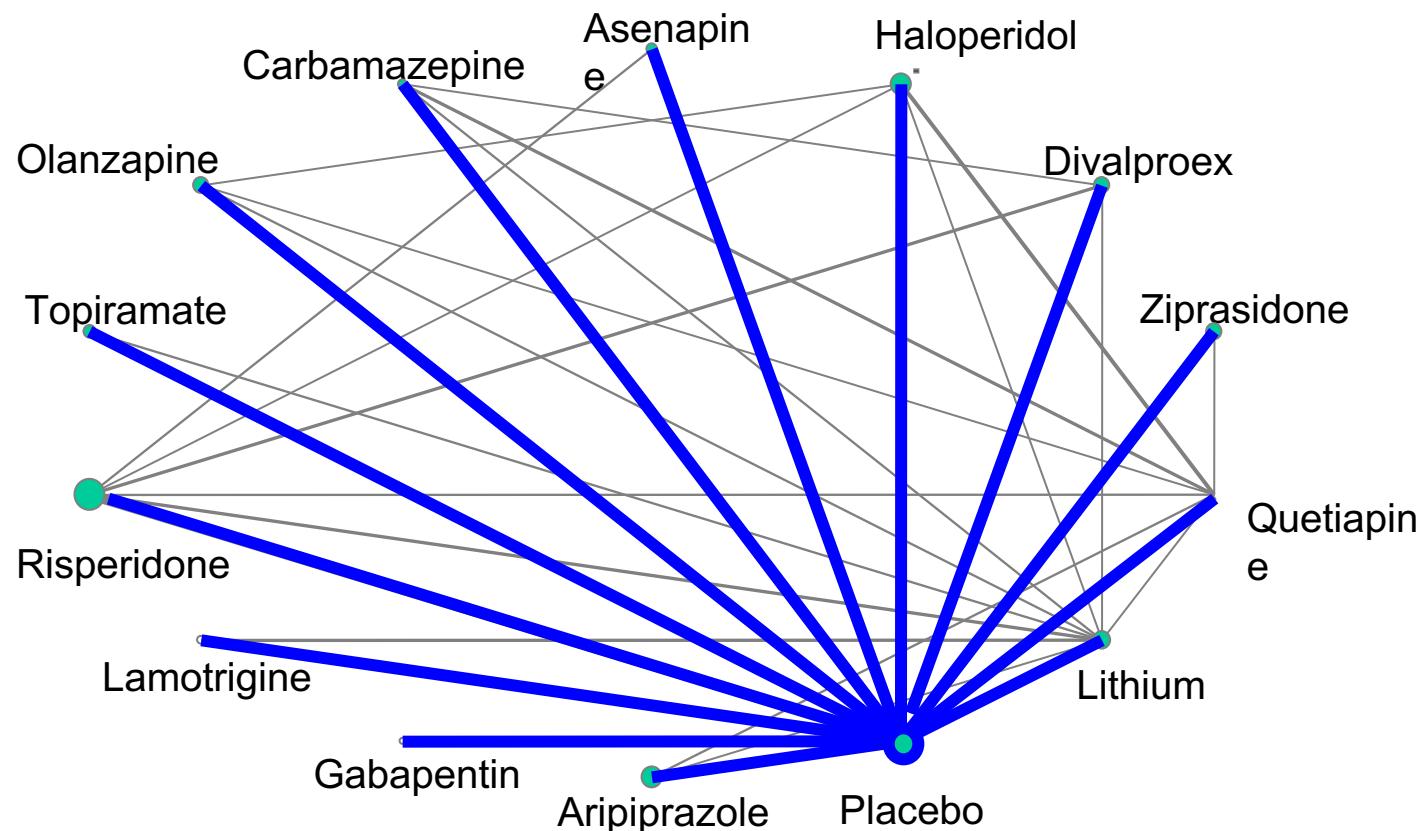
$$\boldsymbol{\mu} = \boldsymbol{\delta} + \mathbf{e}$$

$$\boldsymbol{\delta} \sim N(\mathbf{0}, \text{diag}\{\tau^2\})$$

$$\mathbf{e} \sim N(\mathbf{0}, \text{diag}\{\nu_i\})$$

$$X = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$
$$\boldsymbol{\mu} = \begin{pmatrix} \mu_{tPA-S} \\ \mu_{Anist-S} \\ \mu_{AcctPA-S} \\ \mu_{Ang-S} \\ \mu_{Ret-S} \end{pmatrix}$$

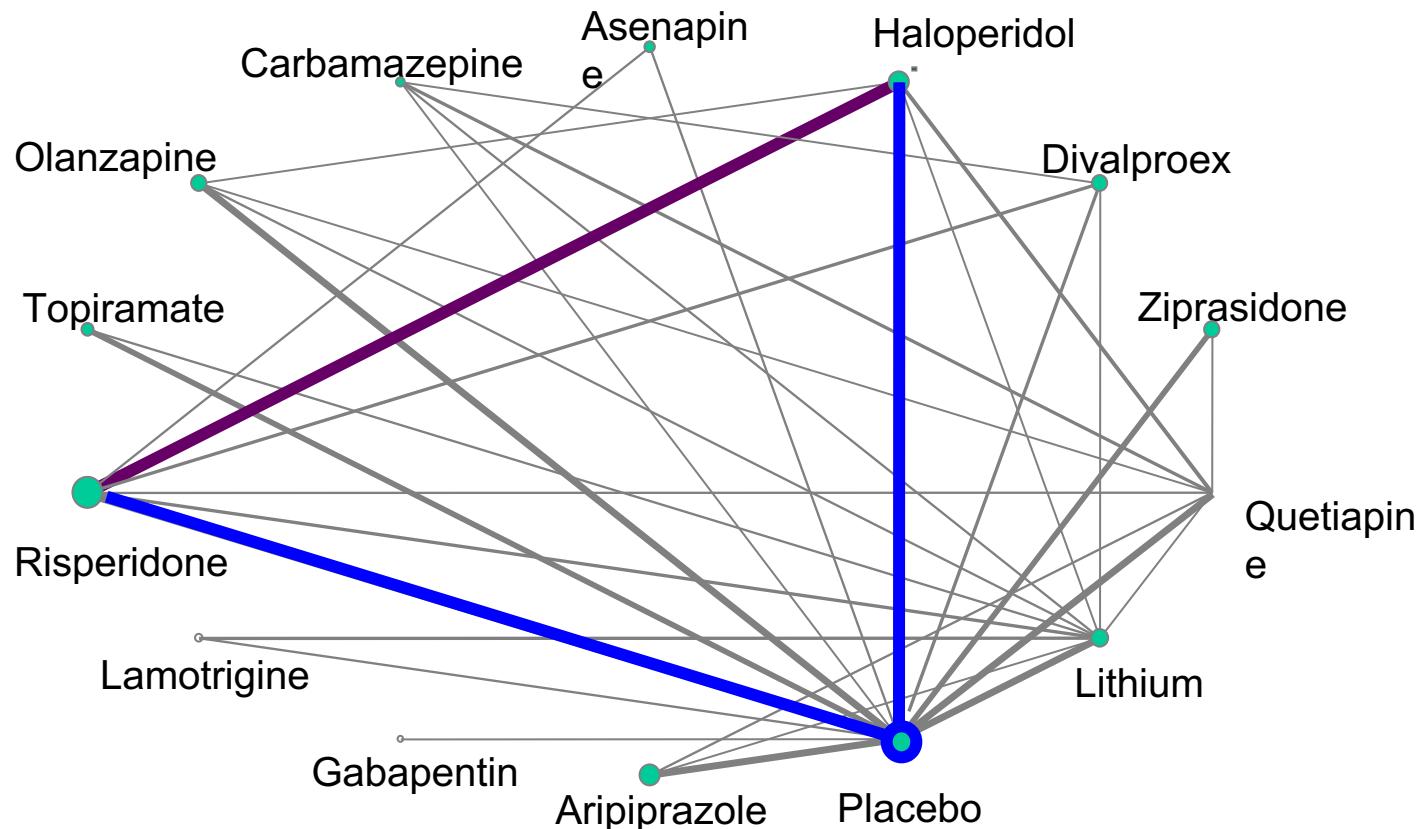
Select basic parameters (=comparisons)



Comparative efficacy and acceptability of antimanic drugs. Cipriani et al. **Lancet** 2011

Employ the consistency equations to calculate all pairwise treatment effects

15 treatments, 105 possible comparisons, 14 basic parameters, 91 consistency equations



Comparative efficacy and acceptability of antimanic drugs. Cipriani et al. **Lancet** 2011