

Meta-Analysis Without Missing the **Seeing the Forest for the Trees** Plot

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Plan for this session

1. Overview of different review types & their purposes
2. Systematic reviews: Key ingredients & best practices
3. Meta-analysis: The 2 reasons to meta-analyze (with examples)
4. Special topics in meta-analysis: Beyond the forest plot
 - Bayesian
 - Individual participant data
 - Network

Key tools & references

Cochrane Handbook: training.cochrane.org/handbook/current

Covidence: guides.library.ubc.ca/covidence

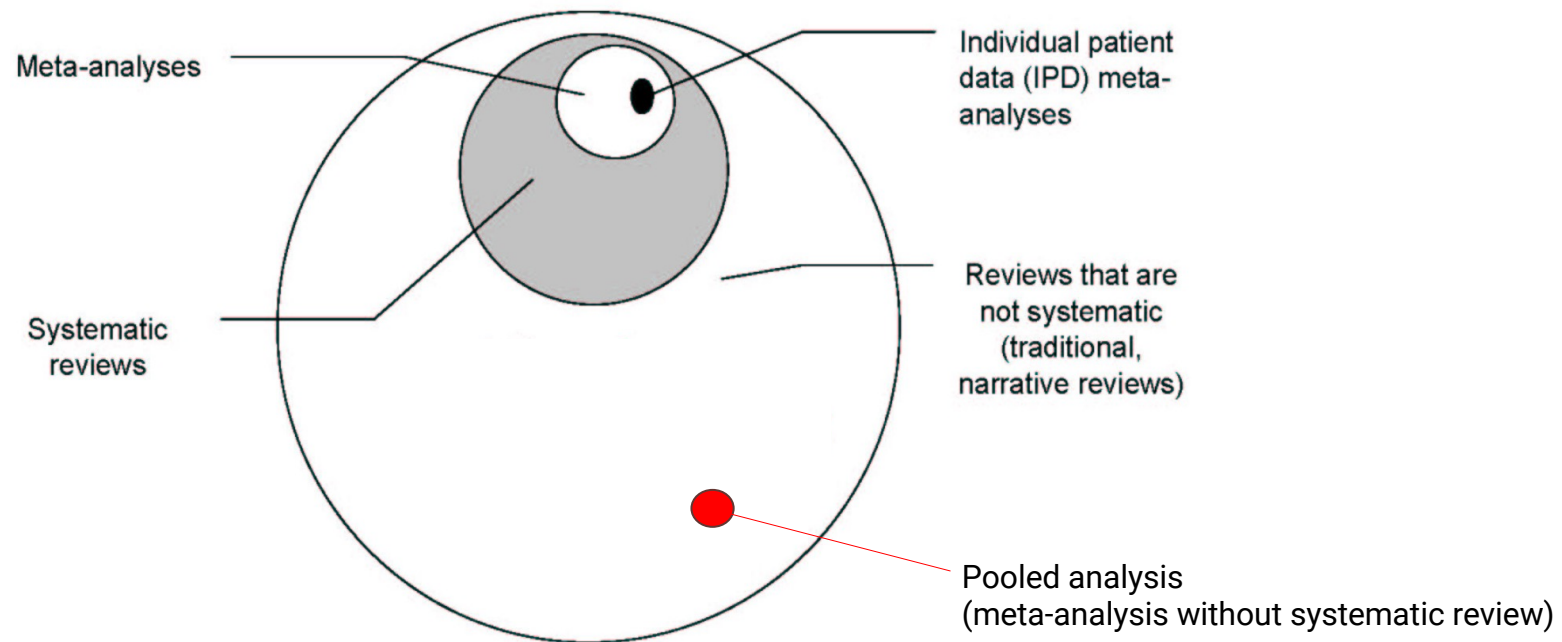
MiniMeta: minimeta.net/

PRISMA 2020 reporting checklist: prisma-statement.org/prisma-2020

ROBUST-RCT risk of bias tool: bmj.com/content/388/bmj-2024-081199

1: Overview of different review types & their purposes

Types of reviews



Comparison of major review types

	Narrative review	Systematic review	Scoping review
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Comparison of major review types

	Narrative review	Systematic review	Scoping review
Purpose	Usually broad questions	Specific, focused question ("PICO")	Map out a topic/concept, identify knowledge gaps

CLINICAL PRACTICE

Patrick G. O'Malley, M.D., M.P.H., Editor

Heart Failure with Preserved Ejection Fraction

Antonio Cannata, M.D., and Theresa A. McDonagh, M.D.



European Society of Cardiology
European Heart Journal (2025) 46, 2564–2575
<https://doi.org/10.1093/eurheartj/ehaf210>

FASTTRACK – CLINICAL RESEARCH
Ischaemic heart disease

Colchicine for secondary prevention of vascular events: a meta-analysis of trials

CJC Open 5 (2023) 136–147

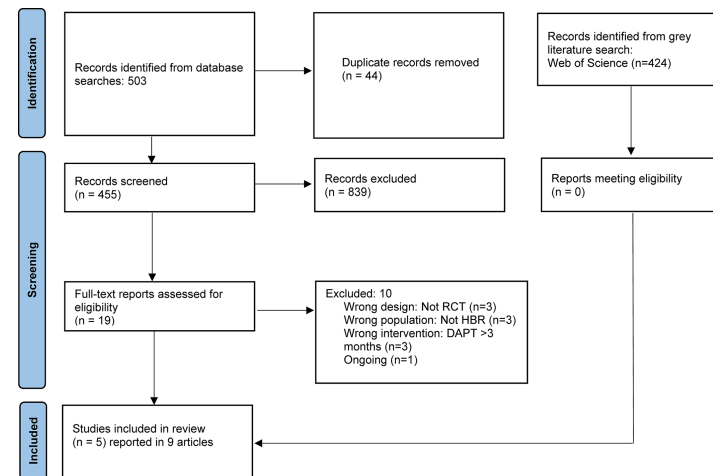
Systematic Review/Meta-analysis
Decisional Needs and Patient Treatment Preferences for Heart Failure Medications: A Scoping Review

Comparison of major review types

	Narrative review	Systematic review	Scoping review
Search strategy	Usually not described; often focused on published, high-impact articles	Exhaustive, transparent, reproducible; often includes unpublished articles	As with systematic reviews; sometimes broader/more iterative

S1 Appendix. Database search strategy

MEDLINE (inception to August 18, 2022)	Embase (2019 to August 18, 2022)	CENTRAL (2019 to August 18, 2022)
- percutaneous coronary intervention.mp. or Percutaneous Coronary Intervention/ - high bleed* risk.mp. - Platelet Aggregation Inhibitors/ or antiplatelet.mp. - Platelet Aggregation Inhibitors/ or p2y12.mp. - clopidogrel.mp. or Clopidogrel/ - prasugrel.mp. or Prasugrel Hydrochloride/ - ticagrelor.mp. or Ticagrelor/ 3 or 4 or 5 or 6 or 7 1 and 2 and 8 - limit 9 to "therapy (maximizes specificity)"	- percutaneous coronary intervention.mp. or percutaneous coronary intervention/ - high bleed* risk.mp. - dual antiplatelet therapy/ or antiplatelet.mp. - p2y12.mp. - acetylsalicylic acid plus clopidogrel/ or clopidogrel/ or clopidogrel.mp. - prasugrel.mp. or prasugrel/ - ticagrelor.mp. or ticagrelor/ 3 or 4 or 5 or 6 or 7 1 and 2 and 8 - limit 9 to "therapy (maximizes specificity)"	- percutaneous coronary intervention.mp. or Percutaneous Coronary Intervention/ - high bleed*.mp. - antiplatelet.mp. or Platelet Aggregation Inhibitors/ clopidogrel.mp. or Clopidogrel/ - prasugrel.mp. or Prasugrel Hydrochloride/ Ticagrelor/ 3 or 4 or 5 or 6 1 and 2 and 7 - limit 8 to medline records - limit 9 to embase records 11. 9 or 10 12. 8 not 11



Comparison of major review types

	Narrative review	Systematic review	Scoping review
Study eligibility criteria	Vague	Explicitly stated; Specific, narrow	Explicit stated; often broad/inclusive (especially of design)

Study selection and data extraction

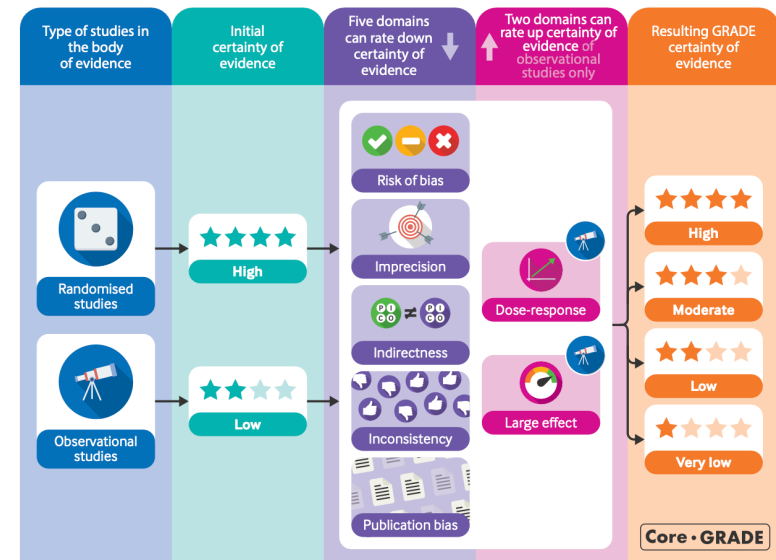
We included parallel randomized controlled trials (RCTs) that enrolled patients who underwent PCI for either ACS or non-ACS indications and had HBR, or reported on a subgroup of patients with HBR, and compared DAPT for 1–3 months followed by SAPT (“short DAPT”), to DAPT for 6–12 months (“standard DAPT”). We included RCTs if they defined HBR based on the ARC-HBR criteria or other explicitly defined criteria.

Comparison of major review types

	Narrative review	Systematic review	Scoping review
Quality/risk of bias assessment	Usually none	Core component; standardized	Not usually done, unless key gap to explore

Table 2 Risk of bias assessment[†]

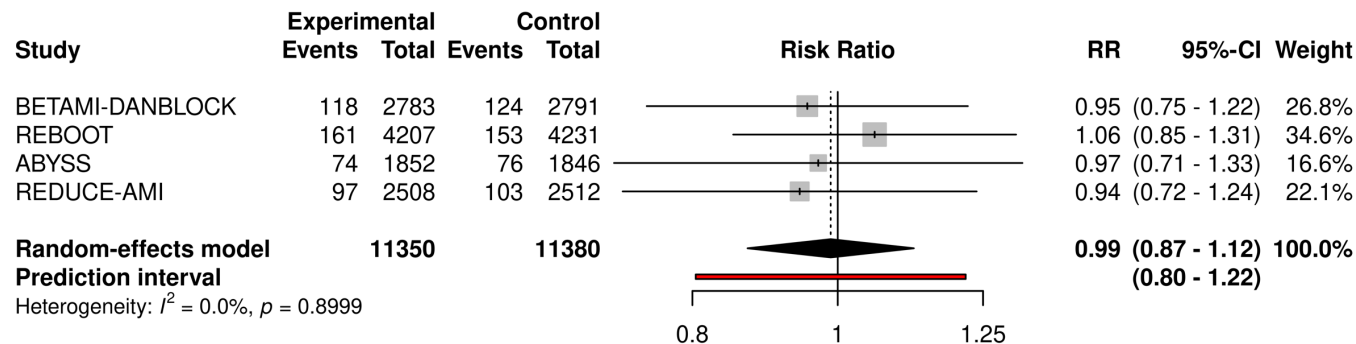
Trial	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Ussia ¹⁴	Some concerns	Some concerns	Low	Low	Low	Some concerns
SAT-TAVI ¹⁵	Some concerns	Low	Some concerns	Some concerns	Some concerns	Some concerns
ARTE ¹⁶	Low	Some concerns	Low	Some concerns	Low	Some concerns
GALILEO ¹⁷	Low	Some concerns	Low	Low	Low	Some concerns
POPular TAVI cohort B ¹⁸	Low	Low	Low	Low	Low	Low
POPular TAVI cohort A ¹⁹	Low	Low	Low	Low	Low	Low
LRT 2.0 ²⁰	Low	Some concerns	Low	Some concerns	Low	Some concerns
ENVISAGE-TAVI AF ²¹	Low	Low	Low	Low	Low	Low
ADAPT-TAVR ²²	Low	Some concerns	Low	Low	Low	Some concerns
ATLANTIS ²³	Low	Some concerns	Low	Low	Low	Some concerns



Turgeon, et al. EHJ – CVP 2024;10(5):454-64 <https://doi.org/10.1093/ehjcvp/pvad101>

Comparison of major review types

	Narrative review	Systematic review	Scoping review
Data synthesis	Narrative	Structured, quantitative ± meta-analysis	Typically descriptive, thematic, visual



2: Systematic reviews: Key ingredients & best practices

Key steps to conduct a systematic review

1. Establish a research team with appropriate areas of expertise
 2. Prepare the protocol
 - i. Define the research question(s) and scope of the review
 - ii. Design the search strategy
 - iii. Define inclusion and exclusion criteria
 - iv. Identify data to be collected from the included studies
 - v. Select tools and methods for assessing the risk of bias of included studies
 - vi. Determine the analytic plan
 3. Execute the search
 4. Screen citations for inclusion into the review
 5. Collect data from the included studies, including elements to describe the study-level PICO, risk of bias and for analytic purposes
 6. Evaluate the risk of bias of each included study, at the level of the outcome
 7. Synthesize evidence, either qualitatively or in combination with quantitative analytics (meta-analysis)
 8. Report the systematic review in accordance with established best practices
-

Key steps to conduct a systematic review: **Tools & tips**

1. Establish a research team with appropriate areas of expertise



Key team members:

- Librarian for the search
- Meta-analyst/statistician for the analysis

2. Prepare the protocol

- i. Define the research question(s) and scope of the review
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Covidence or Rayyan

5. Collect data from the included studies, including elements to describe the study-level PICO, risk of bias and for analytic purposes

6. Evaluate the risk of bias of each included study, at the level of the outcome



Risk of bias tools for RCTs:

- Cochrane RoB2
- ROBUST-RCT tool

7. Synthesize evidence, either qualitatively or in combination with quantitative analytics (meta-analysis)

8. Report the systematic review in accordance with established best practices

Key steps to conduct a systematic review **vs critical appraisal**

1. Establish a research team with appropriate areas of expertise
2. Prepare the protocol
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BOX 14-1

Users' Guides for Credibility of the Systematic Review Process

Did the review explicitly address a sensible clinical question?

Was the search for relevant studies exhaustive?

Was the risk of bias of the primary studies assessed?

Did the review address possible explanations of between-study differences in results?

Did the review present results that are ready for clinical application?

Were selection and assessments of studies reproducible?

Did the review address confidence in effect estimates?

*J Am Coll Clin Pharm 2021;4:849-54
Users' Guides to the Medical Literature 2015 (3rd ed)*

AI for evidence synthesis (in 2025)?

2025 systematic review (done by humans)

- 19 studies performing various SR tasks
 - 17 used ChatGPT (various models, including 4o)
 - Comparator: Human experts
 - Task success:
 - Searching: **Missed 68-96%** of relevant studies
 - Screening: **8-71% error rate** for titles/abstracts & 4-46% for full-text
 - Data extraction: **4-31% error rate**
 - Risk of bias assessment: **10-56% error rate**

AI for evidence synthesis (in 2025)?

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 - Data extraction: **4-31% error rate**
 - Risk of bias assessment: **10-56% error rate**
- **Authors' quote:** This suggests that we made a wise decision not to use GenAI to assist in conducting this review.

3: Meta-analysis: The 2 reasons to meta-analyze & examples

There are 2 reasons to meta-analyze:

#1. Increase power & precision

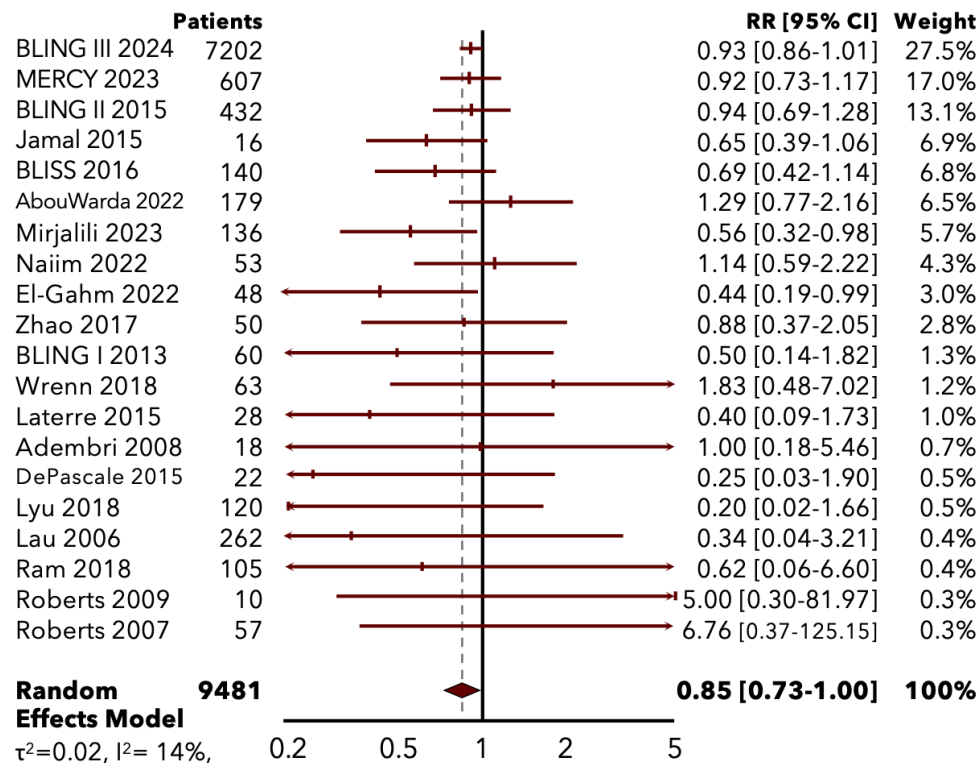
Combine data across studies that address a sufficiently similar PICO

Detect effects that may not be apparent in individual studies

- Death, when individual studies focused on broader composite endpoint
- Clinical endpoints, when individual studies focused on surrogates
- Safety, specific harms

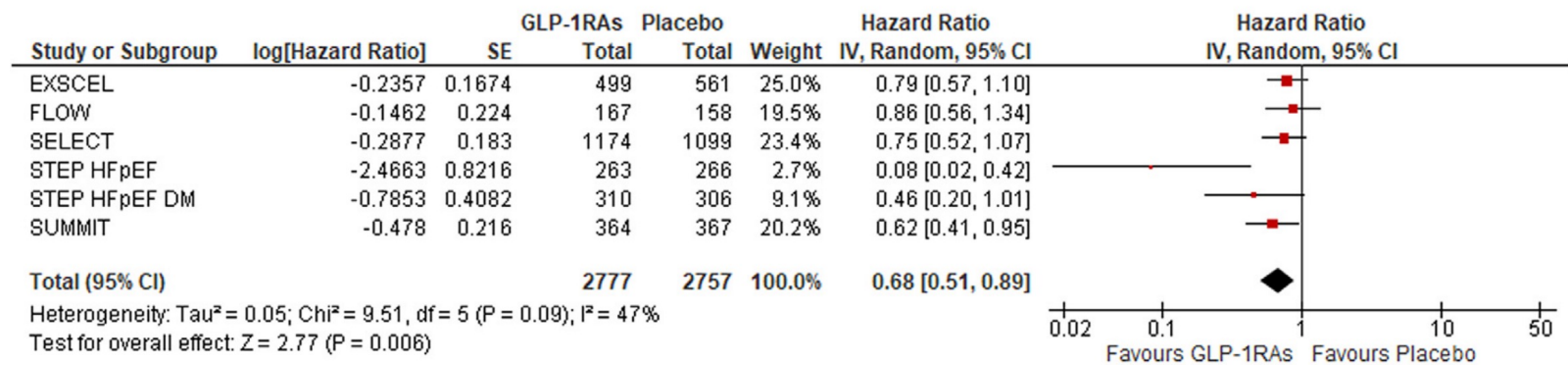
Result: Smaller p-values, narrower confidence intervals around effect size vs individual studies

E.g. 1, mortality: Prolonged vs intermittent infusions of IV antibiotics & mortality

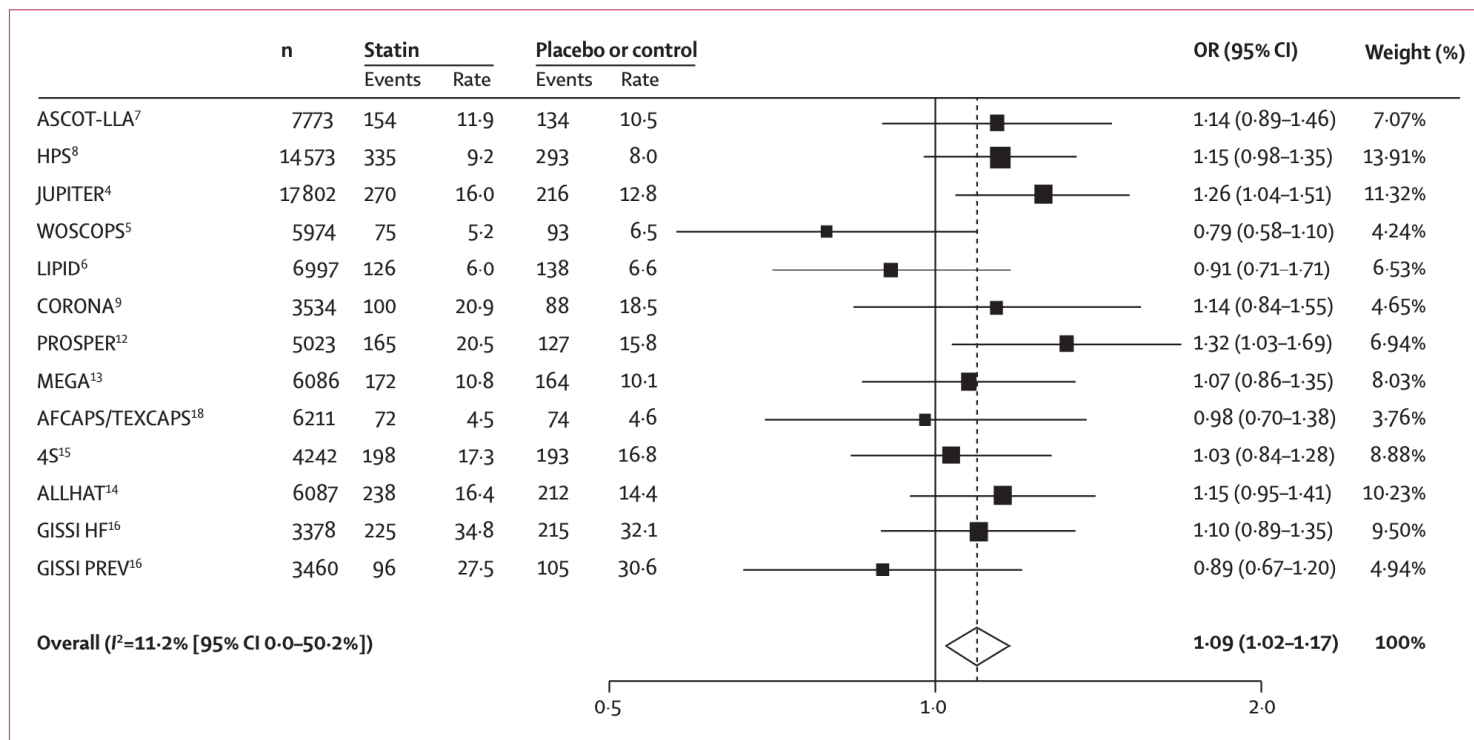


E.g. 2, underpowered secondary outcome: Incretin mimetics in HFmrEF/pEF & CV death/HFH

A) Composite of CV Death or Worsening HF event



E.g. 3, harms: Risk of incident diabetes with statin vs control in 13 RCTs



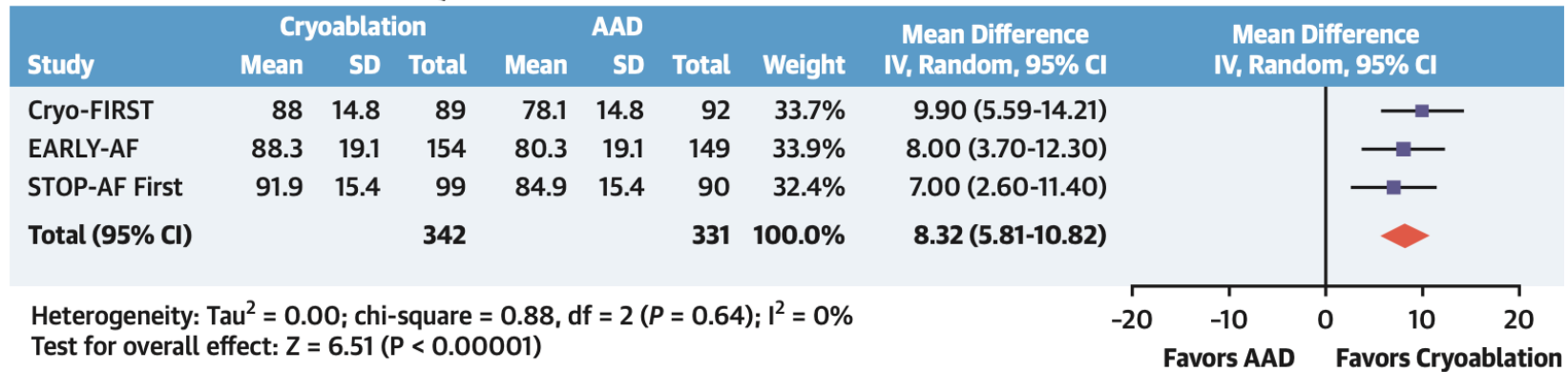
There are 2 reasons to meta-analyze:

#2. Identify & explain inconsistency

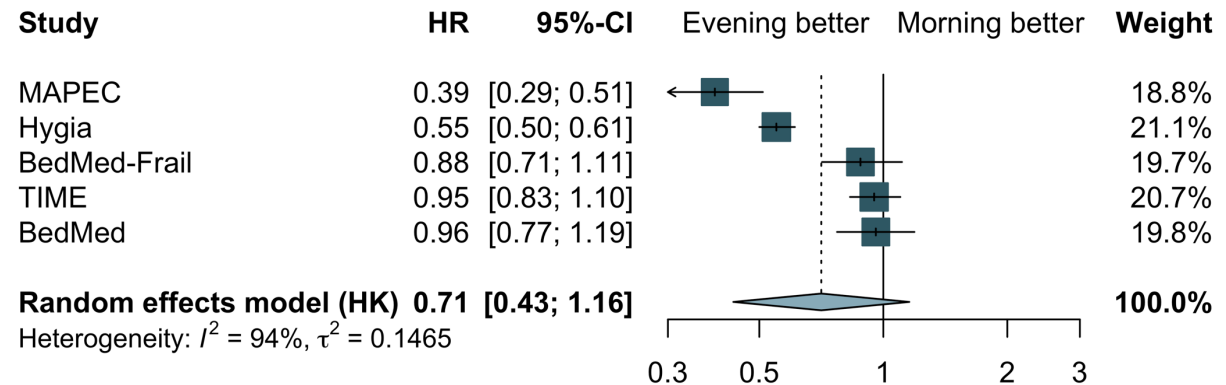
- **Detect differences in effect between studies (statistical heterogeneity)**
 - Visual differences apparent in the forest plot
 - Test for heterogeneity (e.g. I^2)
- **Explain heterogeneity**
 - Meta-regression
 - Sensitivity analyses (e.g. trial-level subgroup analysis, leave-one-out analysis)
- **Explore subgroup differences**, aka heterogeneity of treatment effect
 - Ideally within & between studies

E.g. 4, confirm consistency: Cryoablation vs antiarrhythmic drugs in early AF & quality of life

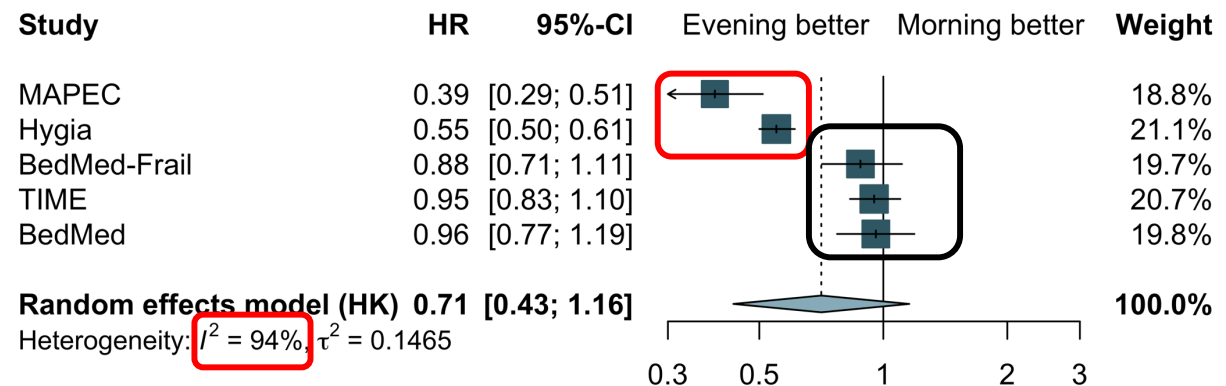
B Mean Difference in AFEQT Score



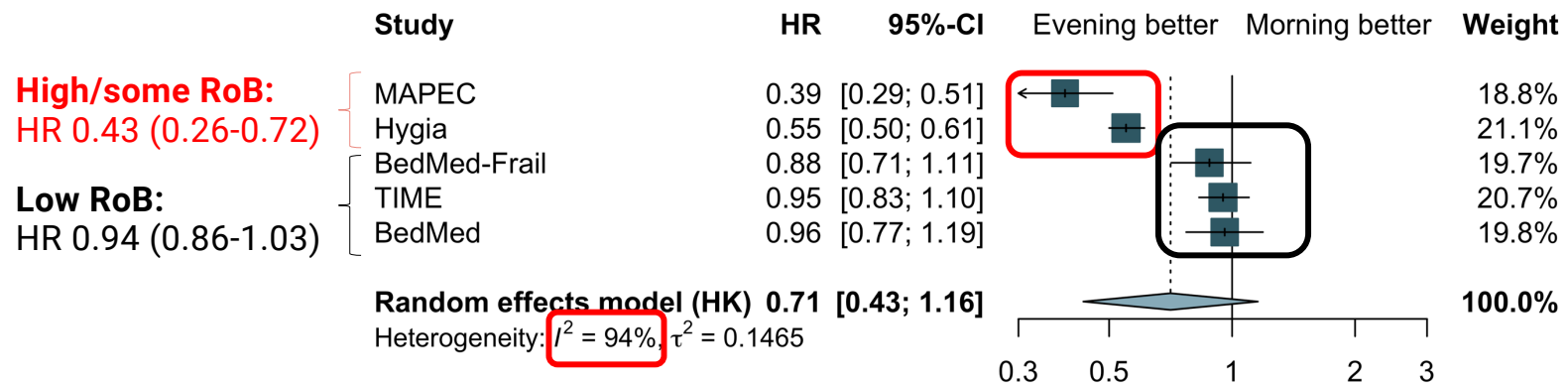
E.g. 5, heterogeneity: Timing of BP-lowering med administration & trial-level risk of bias



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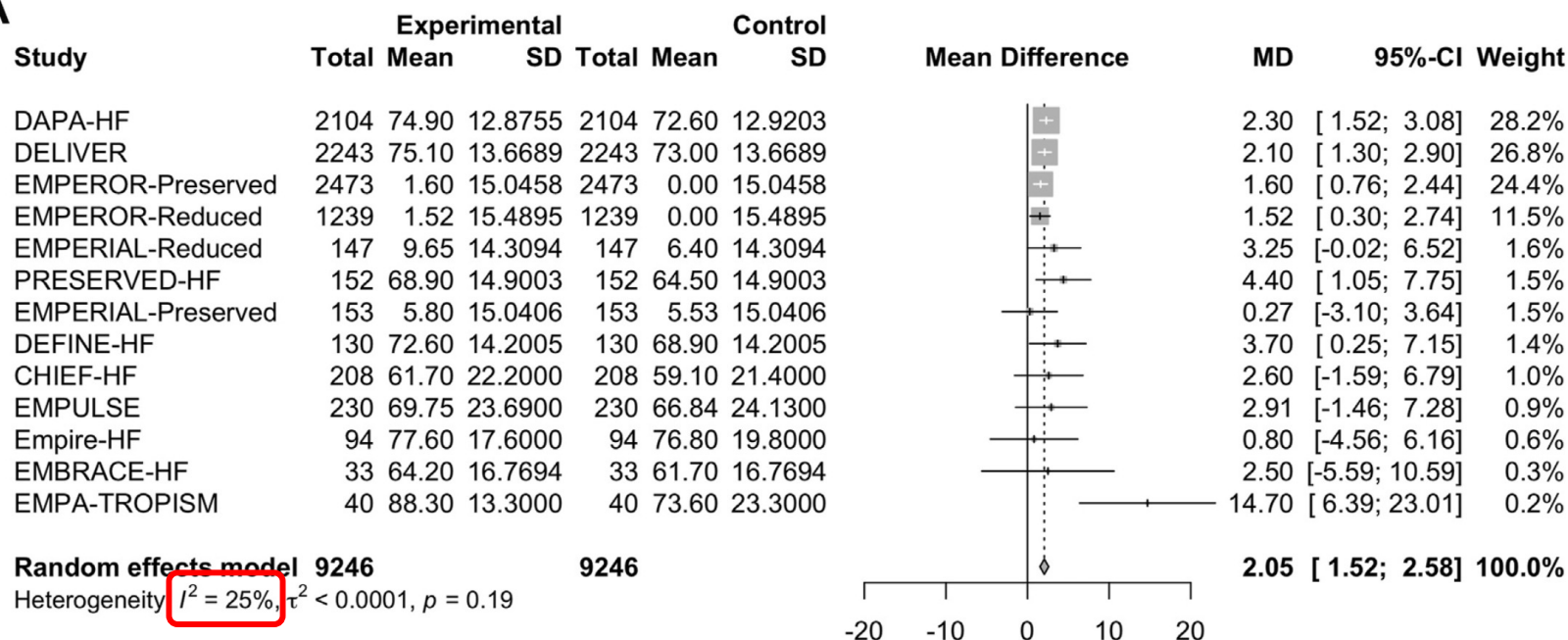


E.g. 5, heterogeneity: Timing of BP-lowering med administration & trial-level risk of bias



E.g. 6, identifying & explaining heterogeneity: SGLT2Is in HF & quality of life

A



E.g. 6, identifying & explaining heterogeneity: SGLT2Is in HF & quality of life

Table 3. Subgroup analyses

Outcome	KCCQ-OSS	
	MD (95% CI)	Number of studies (sample size, n)
Timepoint		$P = 0.04$
LVEF category, %		$P = 0.30$
≤ 40	2.15 (1.53–2.78)	5 (7428)
> 40	1.89 (1.33–2.45)	4 (10,042)
Mixed	3.96 (1.28–6.65)	4 (1022)
Agent		$P = 0.36$
Canagliflozin	2.60 (–1.59–6.79)	1 (416)
Dapagliflozin	2.30 (1.75–2.84)	4 (9258)
Empagliflozin	1.69 (1.05–2.34)	8 (8818)

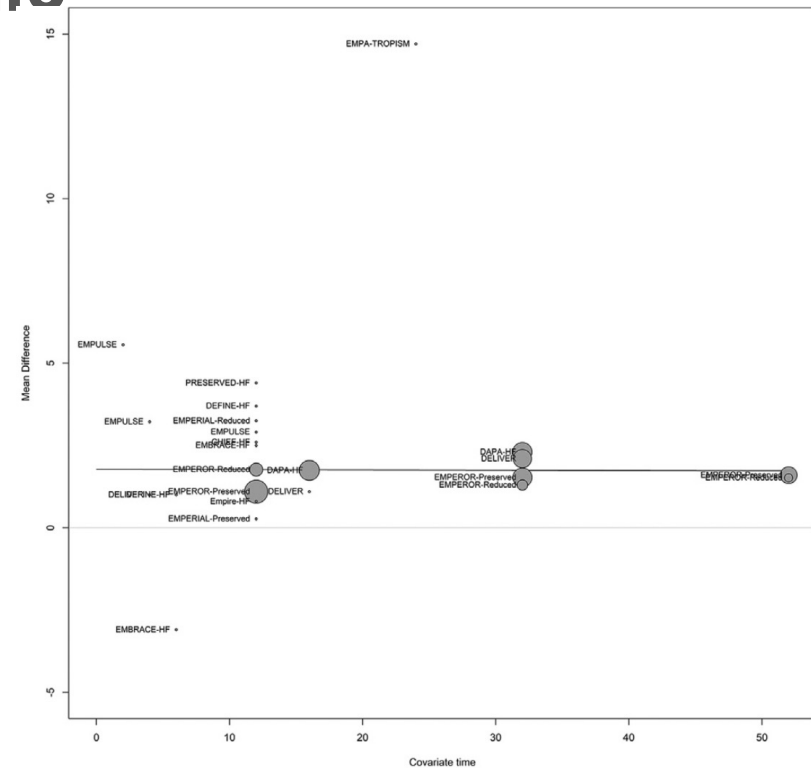
P values are for subgroup differences.

E.g. 6, identifying & explaining heterogeneity: SGLT2Is in HF & quality of life

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4: Special topics in meta-analysis: Beyond the forest plot

Bayesian meta-analysis

Advantages of Bayesian (vs frequentist) statistics:

- Incorporate prior information/evidence
 - More nuanced interpretations; less yo-yoing as evidence is produced
 - Tests robustness of evidence to “what ifs”, different beliefs
- Probabilistic interpretations
 - E.g. “99% probability of any benefit; 85% probability of a benefit > minimal important difference”
 - Can also quantify probability of null hypothesis (which cannot be done with traditional statistics)

Bayesian meta-analysis

Recommended reading

Canadian Journal of Cardiology 41 (2025) 30–44

Methods in Cardiovascular Research and Practice

Bayesian Analytical Methods in Cardiovascular Clinical Trials: Why, When, and How

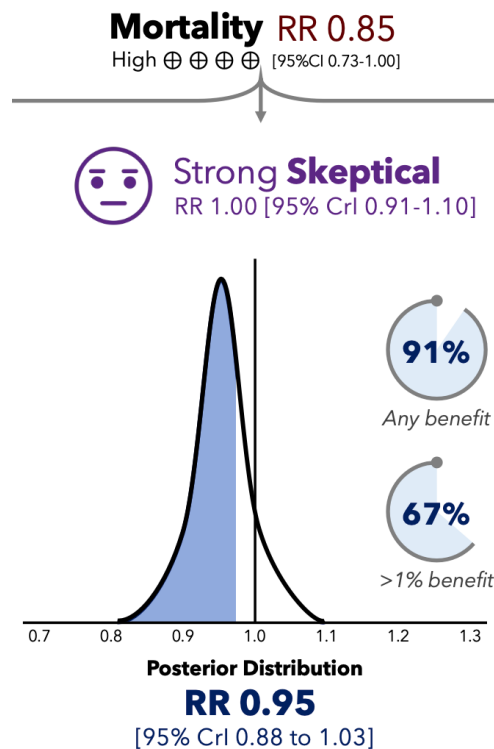
Samuel Heuts, MD, PhD,^{a,b} Michal J. Kawczynski, MD,^{a,b} Ahmed Sayed, MD,^c
Sarah M. Urbut, MD, PhD,^d Arthur M. Albuquerque, MD,^e John M. Mandrola, MD,^f
Sanjay Kaul, MD,^g Frank E. Harrell, Jr, PhD,^h Andrea Gabrio, PhD,^{i,j} and
James M. Brophy, MD, PhD^k

Bayesian statistics for clinical research

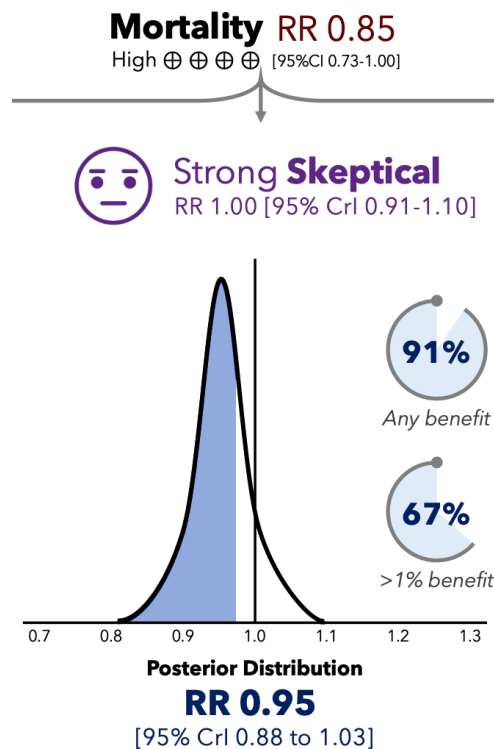
Ewan C Goligher, Anna Heath, Michael O Harhay

Lancet 2024; 404: 1067–76

E.g. 7, Bayesian MA: Prolonged antibiotic IV infusions & mortality



E.g. 7, Bayesian MA: Prolonged antibiotic IV infusions & mortality



		Any benefit	>1% benefit	>2% benefit
Optimistic	Weak	98 %	93 %	82 %
	Moderate	99 %	94 %	82 %
	Strong	100 %	97 %	85 %
Skeptical	Weak	98 %	92 %	80 %
	Moderate	97 %	89 %	74 %
	Strong	91 %	64 %	31 %
Pessimistic	Weak	97 %	90 %	76 %
	Moderate	94 %	82 %	63 %
	Strong	33 %	9 %	2 %

Individual participant data-level meta-analysis (IPDMA)

Key advantages of IPDMA (vs trial-level MA):

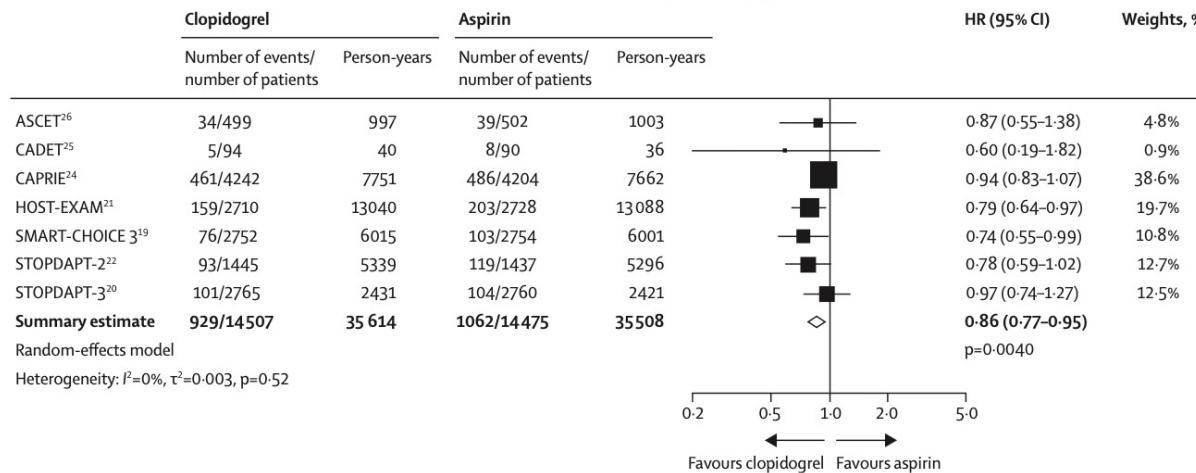
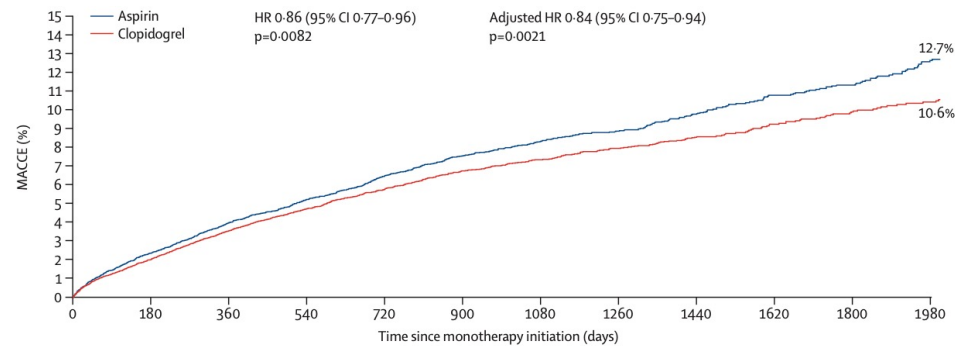
- Standardize across studies (inclusion/exclusion criteria, outcomes, follow-up duration, analysis, handling of missing data)
- Adjust for consistent set of prognostic factors
- More granular subgroup analyses

Challenges: Costly & time-consuming to obtain & analyze; requires advanced statistical expertise to fully leverage IPD with “1-stage” IPDMA

IPDfromKM: Software to reconstruct IPD for outcomes from published Kaplan-Meier

- Can be used to verify published analyses, but lack granularity for full IPDMA (events not tied to baseline characteristics/subgroups)

E.g. 8, IPDMA: Clopidogrel vs ASA in stable CAD/post-DAPT



Valgimigli M, et al. Lancet 2025

Network meta-analysis (NMA)

a.k.a. multiple treatment comparison MA

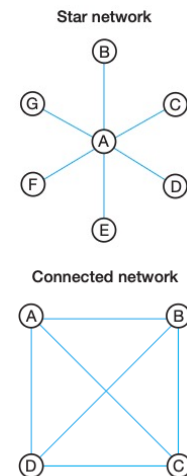
“Borrows” information from indirect evidence to:

- Allow indirect comparisons between 2 treatments (B-C) that have never been directly compared in an RCT, but have been compared to a common comparator (A-B; A-C)
- Increase precision of direct comparisons

Can be done using Bayesian (most common; reasonably easy to learn using R packages `gemtc`, `rjags`) or frequentist approach

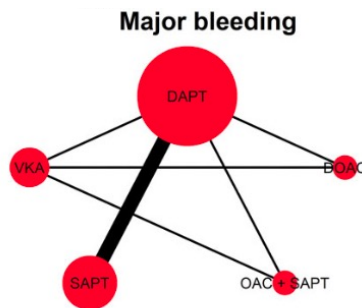
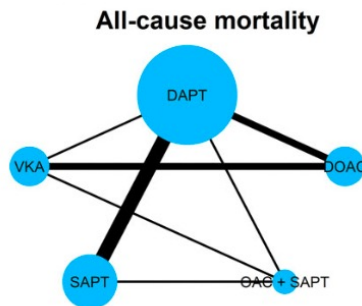
Relies on the **transitivity assumption** (*no important differences between trials, other than treatments being compared*)

- “Strong” assumption, requires a very well-defined PICO
- Assessed with statistical tests for coherence

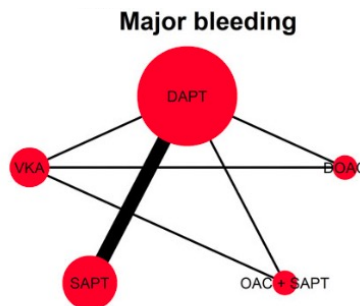
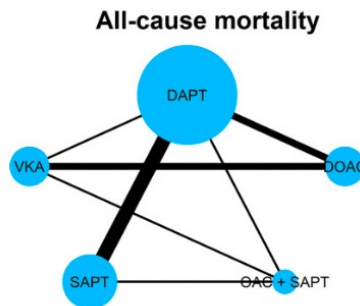


E.g. 9, NMA: Antithrombotic regimens post-TAVI

Network diagrams

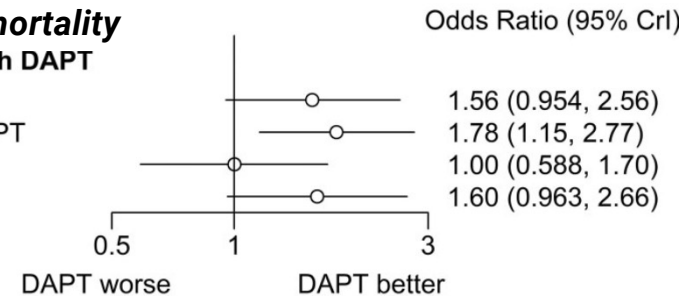


E.g. 9, NMA: Antithrombotic regimens post-TAVI



All-cause mortality Compared with DAPT

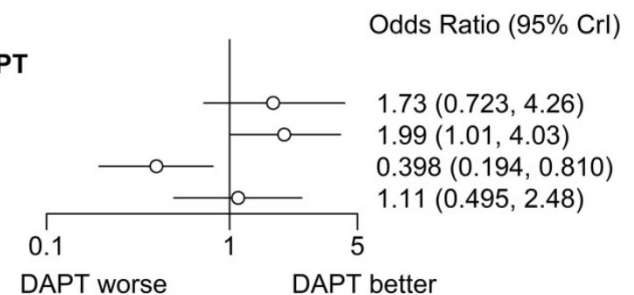
DOAC
OAC_plus_SAPT
SAPT
VKA



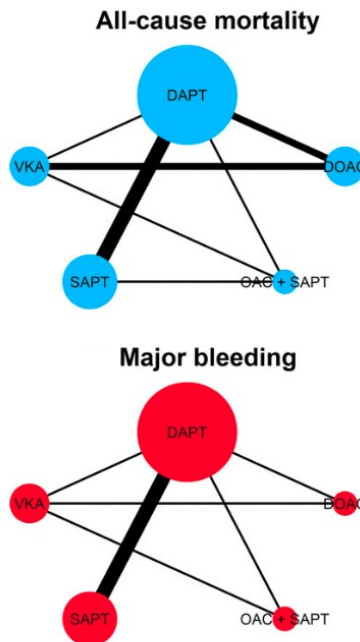
Major bleeding

Compared with DAPT

DOAC
OAC_plus_SAPT
SAPT
VKA



E.g. 9, NMA: Antithrombotic regimens post-TAVI

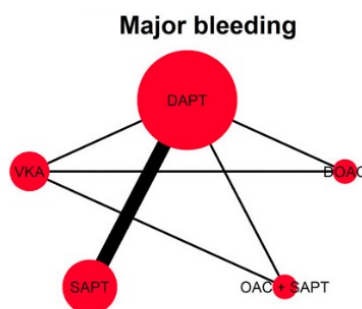
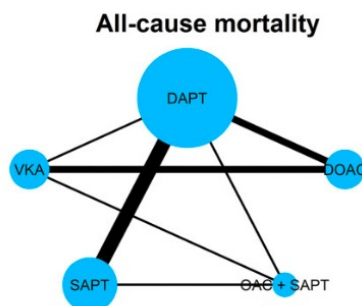


Network league table

Table 3 Pairwise comparisons for all-cause death (blue) vs. major bleeding (red)[†]

SAPT	0.40 (0.19–0.81)	0.23 (0.08–0.71)	0.36 (0.12–1.05)	0.20 (0.07–0.54)
1.00 (0.59–1.70)	DAPT	0.58 (0.23–1.38)	0.90 (0.40–2.02)	0.50 (0.25–0.99)
0.64 (0.31–1.32)	0.64 (0.39–1.05)	DOAC	1.55 (0.92–2.77)	0.87 (0.35–2.22)
0.62 (0.30–1.30)	0.62 (0.38–1.04)	0.97 (0.71–1.35)	VKA	0.56 (0.25–1.26)
0.56 (0.28–1.12)	0.56 (0.36–0.87)	0.87 (0.50–1.50)	0.90 (0.53–1.52)	OAC + SAPT

E.g. 9, NMA: Antithrombotic regimens post-TAVI



Network rankogram & SUCRA scores

Table 4 Rankings and surface under the cumulative ranking curve scores[†]

Outcome, rank (SUCRA)	SAPT	DAPT	DOAC	VKA	OAC + SAPT
All-cause death	2 (0.81)	2 (0.86)	4 (0.36)	4 (0.30)	5 (0.18)
Major bleeding	1 (0.99)	2 (0.62)	4 (0.19)	3 (0.58)	5 (0.12)

SUCRA (surface under the cumulative ranking curve) values can be interpreted as the probability of an intervention being among ranked best

(i.e. SUCRA=1 means 100% of comparators are worse than the selected intervention)

TURGEONLAB⁺

Thank you!

Questions?

