Meta-Analysis to Meta-Cognition

Following the Bayesian Highway in Cardiology

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Overview

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- Why Bayesian thinking matters in modern evidence synthesis
- Revisiting meta-analysis through a Bayesian lens
- From Bayesian inference to *meta-cognition*
- Two current cardiovascular examples
  - Colchicine post-ACS
  - Early AVR in asymptomatic severe AS

What is Meta-Analysis** (MA)?

- Statistical method combines multiple studies to estimate a common effect, θ and between-study variation, τ
- Very common ($\approx$ 30,000 publications with MA in title so far in 2025)
- Common MA methods (frequentist) have limitations / assumptions
  - θ is a fixed (but unknown) constant and only the data are random
  - Thus 95% CI is a property of the data procedure, not of θ
  - IOW, if study repeatedmany times, 95% of intervals would cover θ
  - Ignores prior ancillary θ knowledge
  - Arbitrary decision thresholds ($p < 0.05$)
  - Can't make probability statements about θ or answer clinical questions like: "How likely is the effect big enough to matter in my setting?"

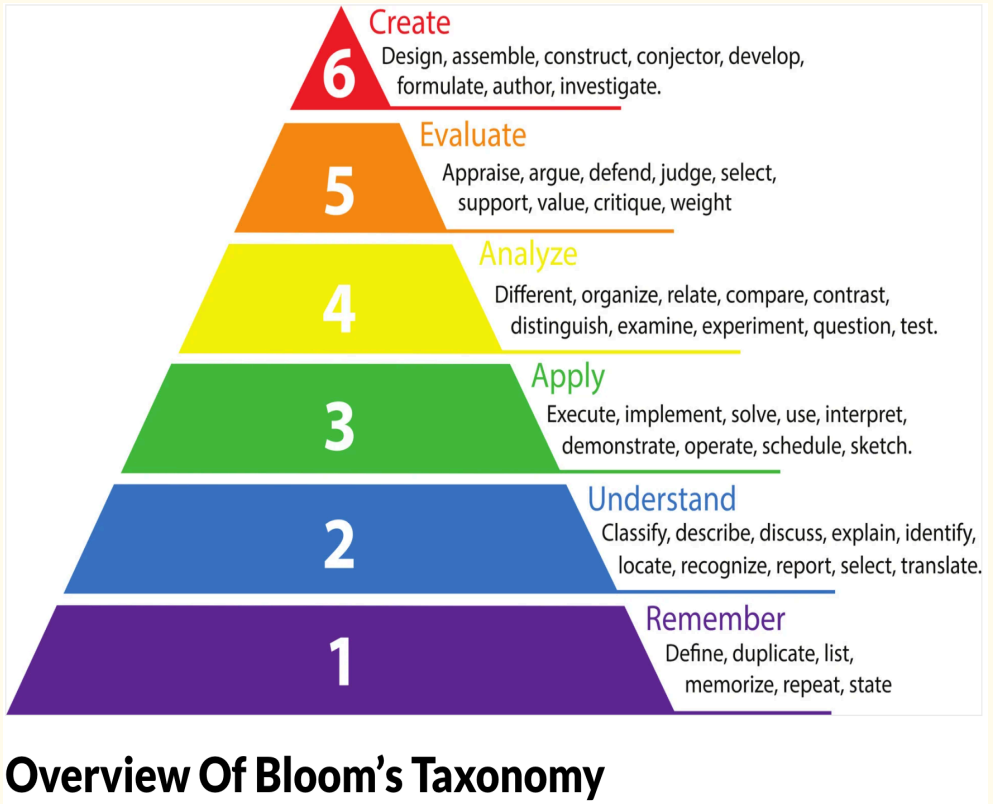
meta — prefix of Greek origin meaning "after, higher, beyond"

What is Meta-Cognition?

- Meta-cognition = thinking about thinking
- Traditional inference asks: “Is there an effect?”
- Meta-cognition extends with purposeful reflection and situational awareness:
  - “Is the effect large enough to matter?”
  - “What should I do given this evidence?”
- For example: RR = 0.82 with 95% CrI [0.66, 1.03], p = 0.11†
  - Recognize p > 0.05 doesn’t imply clinical irrelevance
  - Should you act, wait, or gather more evidence?
  - Probability benefit exceeds my clinically important difference (CID) threshold?

† POPular (AGE), *Lancet* 2020

Taxonomy of Learning



Overview Of Bloom's Taxonomy

- Meta-cognition - Reflects Bloom's top tiers: **Evaluate** and **Create**
- Evidence → Insight → Action
- Enables clinicians to:
  - Question assumptions
  - Integrate uncertainty
  - Move beyond binary decisions (significant vs not)
  - Tailor decisions (shared, informed) to context

Meta-Cognition and Bayesian Meta-Analysis

Meta-cognition: the **destination** — clinical wisdom beyond the numbers, deeper understanding, communication and wiser decisions

Bayesian meta-analysis: the **statistical engine** (the GPS) - **navigating uncertainty with purpose** - to get to our destination

Why Bayesian?

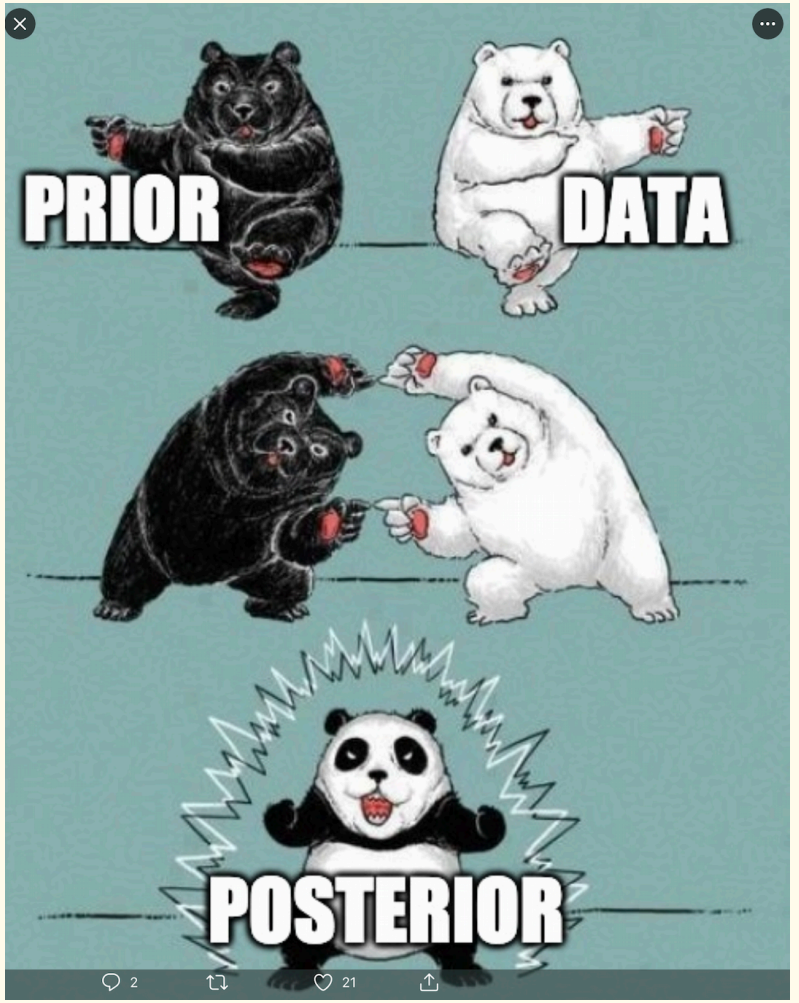
- Bayesian meta-analysis:
  - Combines data *and* prior information
  - Offers full probability distributions for effect sizes
  - Naturally accommodates uncertainty, decision-making, prediction

> "Bayesian inference - what you do when you believe you should condition on what you know." — Andrew Gelman

Bayesian Key Concept

$$\text{Posterior} \propto \text{Likelihood} \times \text{Prior}$$

- Prior: What you believe **before** the new evidence
- Likelihood: What the new data say
- Posterior: What you believe **after** combining both



Prior Knowledge: A Strength or Bias?

- Strength: Informs probabilistic inference, enables cumulative learning
- Criticism: “Subjective”
- Response:
  - All models involve assumptions
  - Assumptions can be tested
  - Bayesianism just makes assumptions (priors) explicit

Frequentist vs Bayesian Meta-analysis

Feature	Frequentist	Bayesian
Point estimate	Yes	Yes
Confidence/Credible Interval	CI (coverage probability)	CrI (posterior probability)
Interpretations	Long-run frequency: 95% of intervals cover true effect	95% chance the true effect lies within the interval
Probability Statements	Not valid for individual studies or patients	Directly answer “how likely” questions
Shrinkage	No	Yes (esp. in hierarchical models)
Predictive intervals	Limited (available in mixed models)	Yes (posterior predictive distribution)
Parameter interpretation	Fixed (unknown constant)	Random variable with probability
Prior inclusion	No	Yes
Tailored Inference	No	Yes (e.g., P(RR < 0.9), threshold-specific)

MA Predictive Thinking: The Next Study

Pooled average = typical effect across included studies
Predictive interval = likely next-study range (includes between-study heterogeneity, τ^2)

Frequentist

- Parameters are **fixed**, data are **random** -> probability statements about the true effect are **not defined**
- Prediction interval = future observation given fixed parameters
- Interpretation:
  > "There is a 95% chance that the next study's outcome falls within this interval, *if* the parameters are correct"

Bayesian

- Parameters are **random variables** with distributions, data is **fixed** → probability statements *about the effect* are **valid**
- Posterior predictive distribution integrates over parameter uncertainty
- Interpretation:
  > "There is a 95% probability that the next study's outcome lies in this range, *given our data and prior*."

Clinically Important Difference (CID)

CID probabilities only available with Bayesian approach

- Define a **CID** based on clinical context:
  - e.g., ARR ≥ **1.5%** over 3 years (RR ≤ **0.85** if baseline risk = **10%**)
- Report:
  - **P(RR < 1.0)** (any benefit)
  - **P(RR ≤ CID)** (clinically meaningful benefit)
  - **Predictive interval** for a new, comparable study
- Decision:
  - treat when **P(RR ≤ CID)** is high *and* the predictive interval lies mostly on the favorable side.

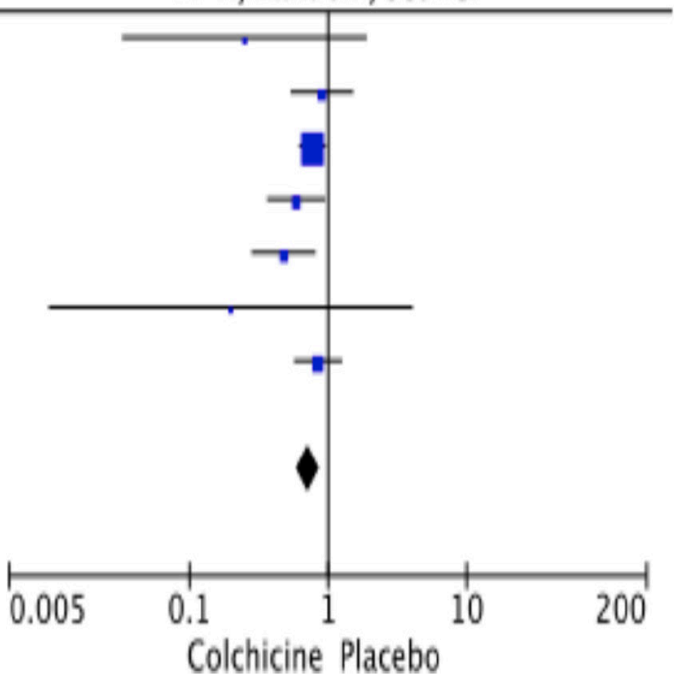
Colchicine in ACS

Colchicine's role in post-ACS care - a 2022 frequentist meta-analysis

Study or Subgroup	Colchicine Events	Colchicine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
CISR	1	30	8	60	0.7%	0.25 [0.03, 1.91]
COLCHICINE-PCI	24	206	25	194	10.6%	0.90 [0.53, 1.53]
COLCOT	131	2366	170	2379	48.3%	0.77 [0.62, 0.97]
COPS	24	396	41	399	12.3%	0.59 [0.36, 0.96]
Deftereos 2013	16	100	32	96	10.3%	0.48 [0.28, 0.82]
Lodoco-MI	0	119	2	118	0.3%	0.20 [0.01, 4.09]
O'Keefe 1992	41	130	25	67	17.5%	0.85 [0.57, 1.26]
Total (95% CI)		**3347**		**3313**	**100.0%**	**0.73 [0.61, 0.87]**
Total events	237		303			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.37$, df = 6 (P = 0.38); $I^2 = 6\%$

Test for overall effect: Z = 3.58 (P = 0.0003)



Conclusion: Colchicine "significantly" reduced the risk of MACE in CAD patients

Is the colchicine / ACS story over, or is further research justified or even ethical?

Not so fast...

- No prediction interval (PI) for next study provided
- Frequentist PI (0.60 - 0.90) assumes study parameters & statistical model are known without uncertainty -> overconfident conclusions
- Bayesian PI for next study accounts for parameter variability -> CI 0.35 - 1.29
- Providing more realistic heterogeneity estimate and justification for future studies

CLEAR Trial: Colchicine in ACS

These investigators obviously didn't believe the colchicine story was over

CLEAR Trial (2025) published in NEJM 2025

- 7062 patients randomized at 104 centers in 14 countries
- Primary outcome: CV death, MI, stroke, or urgent revascularization
- Results: RR = 0.99 (95% CI 0.85–1.16, p=0.93)

Conclusion: "Treatment with colchicine, when started soon after MI and continued for a median of 3 years, did not reduce theincidence of the composite primary outcome."

Colchine Meta-Analyses in 2025

CLEAR acknowledged previous COLCOT RCT (n = 4725, HR 0.77, 95% CI 0.61 - 0.96) No effort to quantitatively incorporate or explain this, or any other, study results
Simply stated CLEAR was a larger trial, with an improved precision

7 meta-analyses have been published in the 3-6 months following CLEAR!

All concluded colchicine is beneficial in post-ACS patients

PubMed: Search: colchicine AND coronary disease Filters: Meta-Analysis, from 2025/1/1 - 2025/7/24

References:

1. Younas et al. Curr Probl Cardiol 2025;50(1):102878. (In eng). DOI: 10.1016/j.cpcardiol.2024.102878.

2. Wang et al. Medicine (Baltimore) 2025;104(22):e42650. (In eng). DOI: 10.1097/md.0000000000042650.

3. Shaikh et al. Int J Cardiol 2025;425:133045. (In eng). DOI: 10.1016/j.ijcard.2025.133045.

4. Samuel et al. Eur Heart J 2025;46(26):2552-2563. (In eng). DOI: 10.1093/eurheartj/ehaf174.

5. Jaiswal et al.Am J Cardiovasc Drugs 2025;25(1):83-93. (In eng). DOI: 10.1007/s40256-024-00689-7.

6. Ballacci et al.J Cardiovasc Med (Hagerstown) 2025;26(7):359-368. (In eng). DOI: 10.2459/jcm.0000000000001744.

7. d'Entremont et al. Eur Heart J 2025;46(26):2564-2575. (In eng). DOI: 10.1093/eurheartj/ehaf210.

Colchicine Meta-Analyses in 2025

EHJ - IF 36.4

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

Marc-André d'Entremont [1,2,3,†], Michiel H.F. Poorthuis[4], Aernoud T.L. Fiolet[5,6], Pierre Amarenco[1,7], Kevin Emery Boczar[8], Ian Buysschaert[9], Noel C. Chan [10], Jan H. Cornel[6,11,12], Jalina Jannink[13], Shirley Jansen[14], Sasko Kedev[15], Anthony C. Keech[16,17], Jamie Layland[18], Nathan Mewton[19], Gilles Montalescot[20], Domingo A. Pascual-Figal[21,22], Alfredo E. Rodriguez[23], Binita Shah[24,25], Martin Teraa [26], Aimee van Zelm[26], Yongjun Wang[27], Arend Mosterd [6,13], Peter Kelly[28,29], John Eikelboom[1,30], and Sanjit S. Jolly[1,2,*]; on behalf of the Colchicine Cardiovascular Trialists Collaboration

- In 2^o prevention, colchicine reduced the composite outcome by 12%
- Includes CLEAR authors and published only 3 months after CLEAR trial
- Apparently frequentist statistics allows investigators to declare both that the treatment does not, and simultaneously does work, all with same evidence base!!!

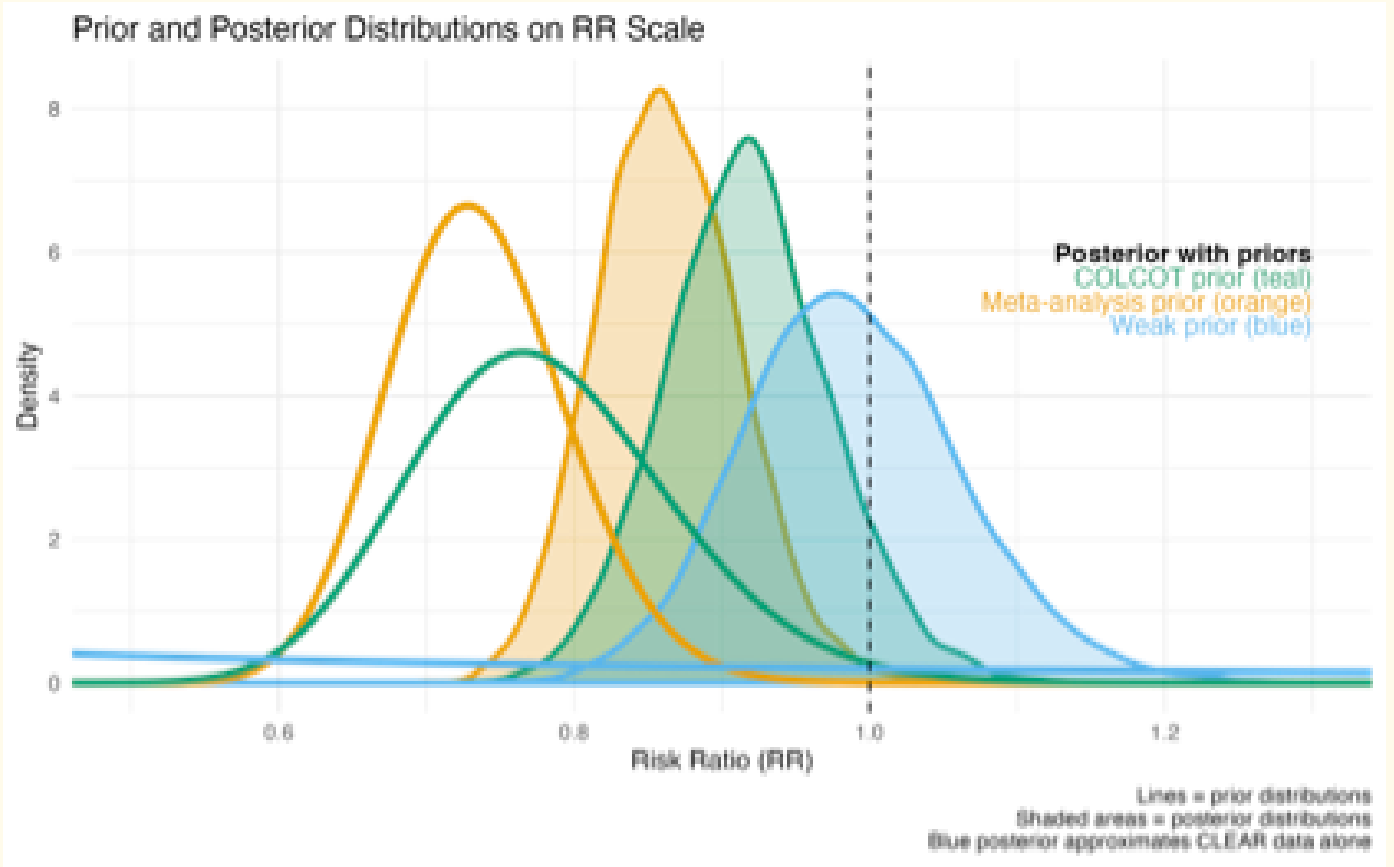
Anatomy of a Bayesian Meta-Analysis

1. Standard difficulties - searching for relevant studies & critical assessment of their quality and appropriateness
2. Additional difficulty - define the priors
3. Specify model (random or fixed effects)
4. Combine likelihood from all studies to compute posterior (via MCMC)
5. Interpret full distribution, not just point estimate

```r
# brms example for Bayesian meta-analysis
library(brms)
brm(r | trials(n) ~ 0 + treatment + (1 | Study),
    family = binomial(),
    data = nma_data,
    prior = prior(normal(0, 2), class = b),
    chains = 4, cores = 4)
```

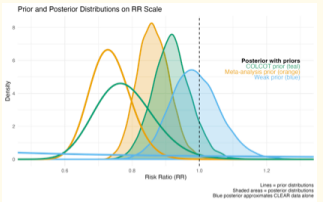
Colchicine Prior Beliefs: Three Perspectives

- Use a community of prior beliefs to assess conclusions' robustness
- Vague prior: N(0, 2) → allows CLEAR data to dominate
- Focused prior: Based on major pre-CLEAR trial – COLCOT as acknowledged by CLEAR
- Comprehensive prior: Based on 2022 meta-analysis (pre-CLEAR)



- Posterior mean RR:
  - Vague: 0.99 (95% CrI 0.85–1.14)
  - Focused (COLCOT): 0.92 (0.81–1.03)
  - Comprehensive (2022 MA): 0.86 (0.78–0.96)

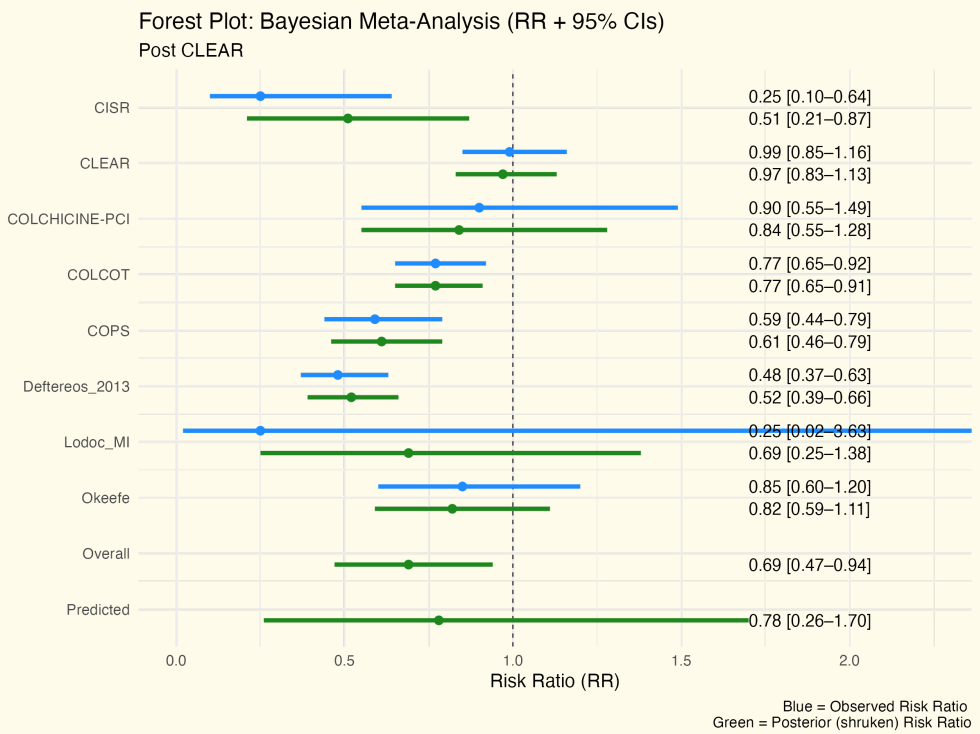
Probabilities for Clinical Thresholds



Prior	P(RR < 0.8)	P(RR < 0.85)	P(RR < 0.9)	P(RR < 1.0)	P(RR < 1.15)
Weak (N(0,2))	0%	3%	11%	58%	98%
COLCOT-based	1%	11%	38%	92%	100%
Meta-analysis	9%	40%	78%	100%	100%

1. CLEAR & weak prior-> modest 58% probability of some benefit (RR < 1.0)
2. COLCOT & meta-analysis priors -> higher probability of some benefit (92-100%) but only modest probability (11-40%) of clinical significance (RR < 0.85).
3. **Predictive spread** across settings is wide — the **next study could differ**.
4. More informed than frequentist 12% reduction with no uncertainty measure

Bayesian forest plot



- Partial pooling with shrinkage of extreme trials
- Bayesian models pull extreme estimates toward the mean
- Particularly helpful in small trials or sparse data
- Hierarchical model accounts for heterogeneity
- Colchicine example - Bayesian next study: RR 0.78, 0.26–1.70 (wider, more realistic than frequentist PI)

What this means for practice today

- CLEAR (RR ~0.99, p = 0.93) ≠ proof of no effect; Absence of evidence ≠ evidence of absence
- Frequentist meta-analysis conclusion: 12% reduction but no measure of uncertainty
- Bayesian analysis: ~60–100% probability of some benefit RR < 1 but only modest (~11-40%) probability of ≥15% benefit
- The evidence does not completely reject the colchicine hypothesis — but does rule out high probability of any very strong benefit
- **Reasonable**: more evidence, especially if your CID is ≥15% relative reduction
- **Reasonable**: targeted use in higher-risk groups + honest discussion of uncertainty

AVR for early asymptomatic patients with severe AS?

- Historically AVR has been restricted to symptomatic patients

> "operative treatment is the most common cause of sudden death in asymptomatic patients with AS" - Braunwald, 1990

- More recently, four RCTs & four MAs have all concluded early AVR reduces mortality and morbidity

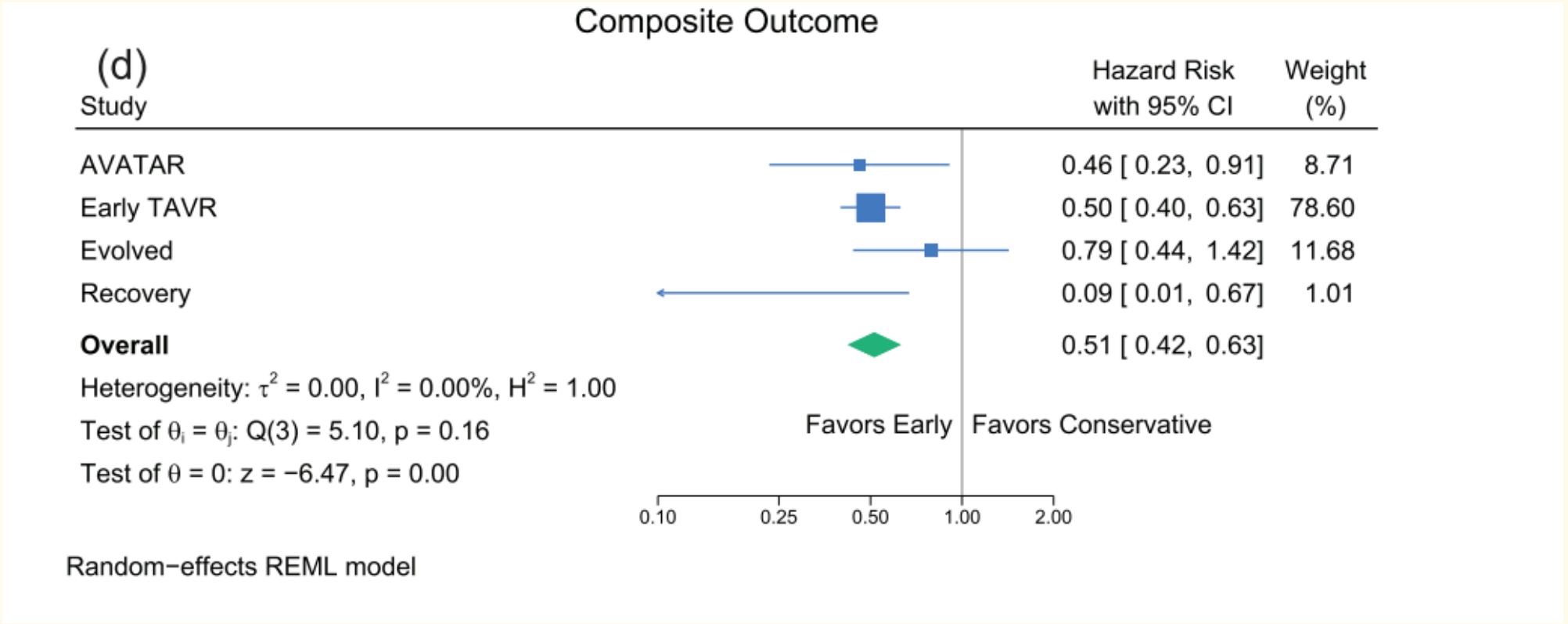
> "… the time has come to recommend AVR for asymptomatic patients with severe AS" - Braunwald, 2025

Google scholar: Braunwald E - Citations 436,176; h-index 280

Do we have the temerity to question this opinion & these findings?

Meta-analyses of early AVR in asymptomatic AS

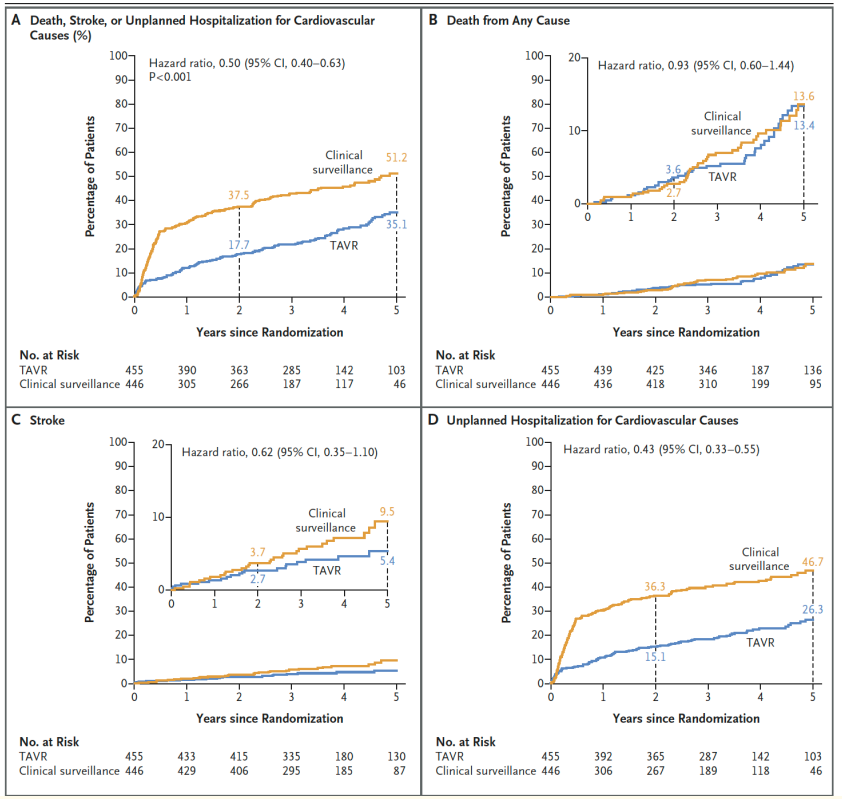
Typical MA -> early AVR reduces mortality and morbidity in asymptomatic AS patients



AJC; Volume 245, 15 June 2025, Pages 11-16

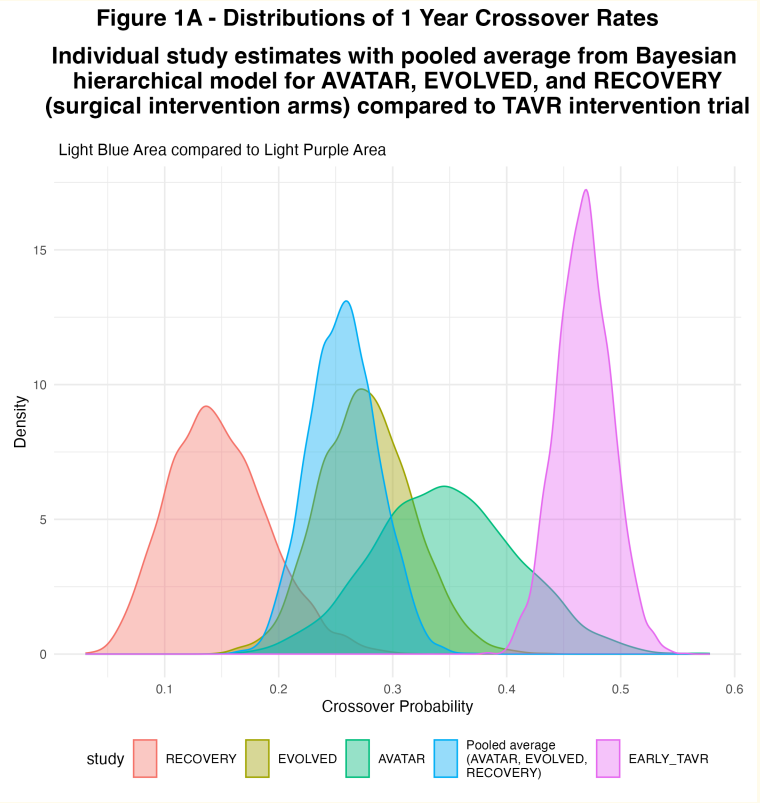
Observations from Early TAVR Trial

1. Meta-analysis results driven by most recent Early TAVR trial
2. Only trial with TAVR for intervention, others used SAVR
3. **No** mortality /stroke benefit
4. **Significant** ↑ hospitalizations in CS group 2^{o} later AVR



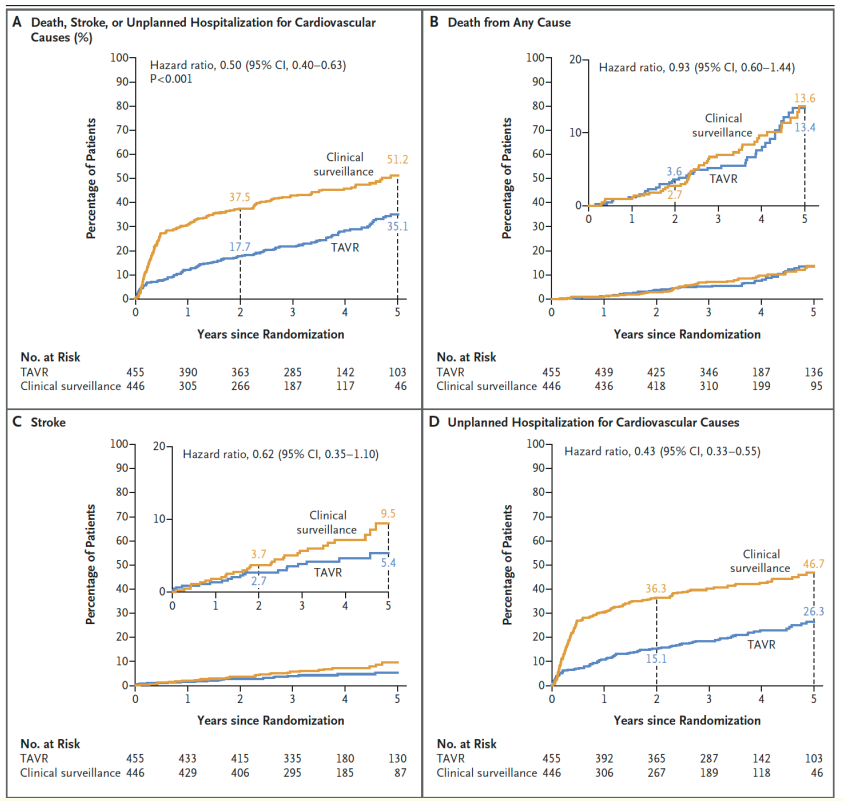
Observations from Early TAVR Trial

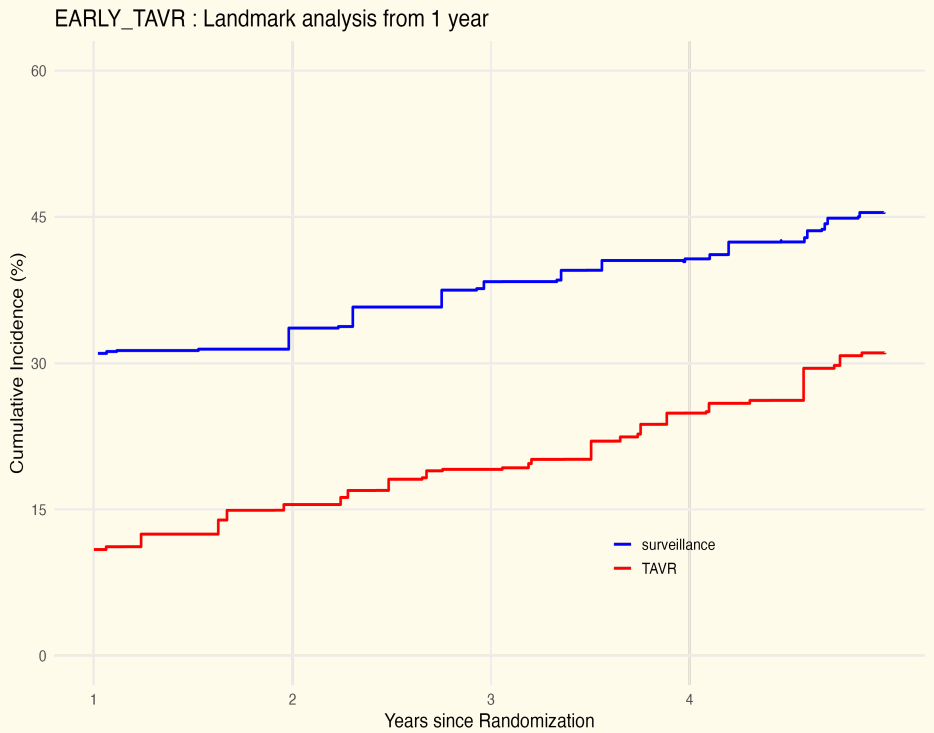
5. Xovers ≈ **2X** other trials, 95% probability of absolute Δ > 15%!



Observations from Early TAVR Trial

6. Timing of events??? Despite confirmed baseline asx, majority Xovers in first 6 months
7. Landmark analysis of Early TAVR after first year - no difference in any outcomes BTW early TAVR and CS groups





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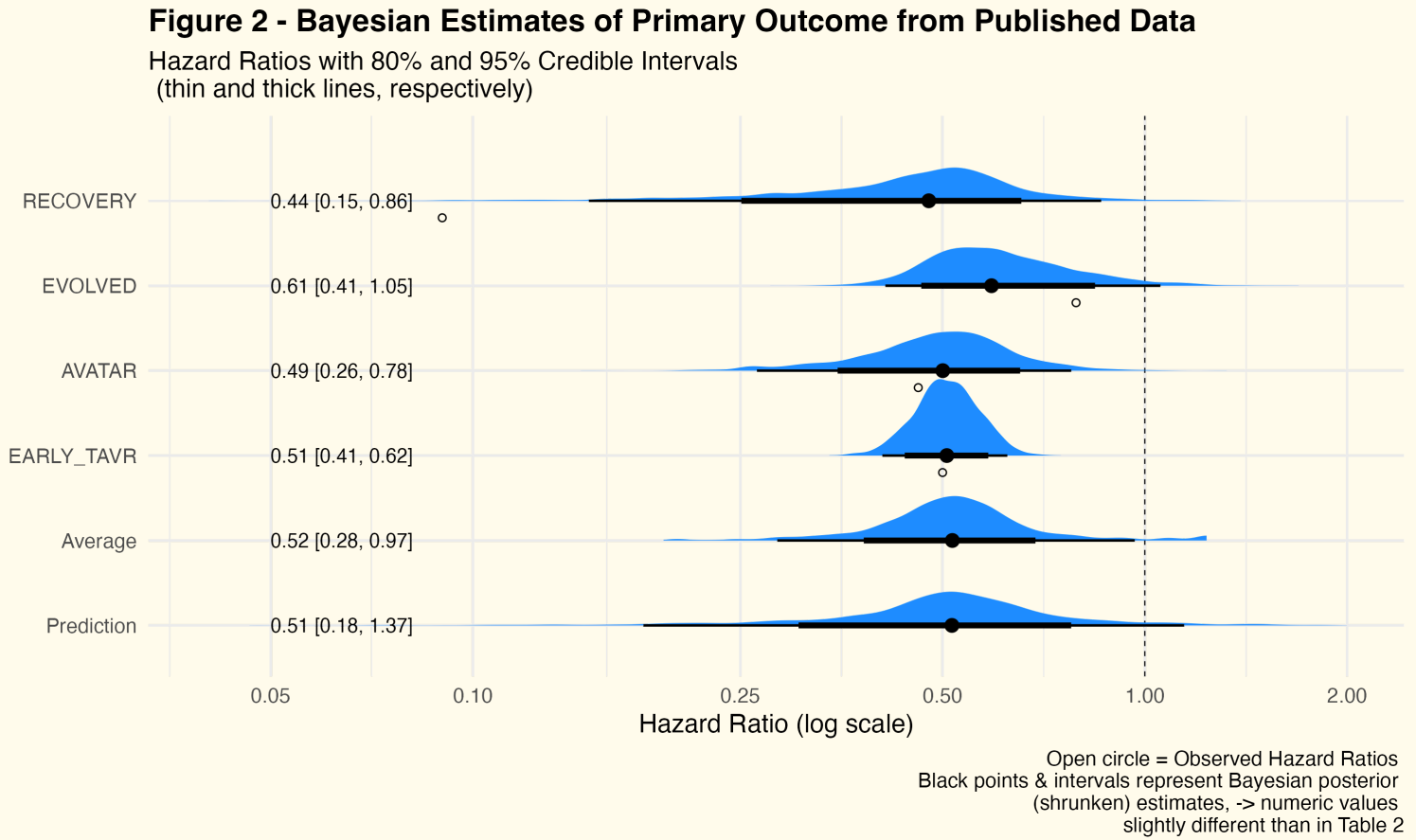
What to expect in the next study (predictive)

Primary outcome: all-cause mortality, stroke or CV hospitalization



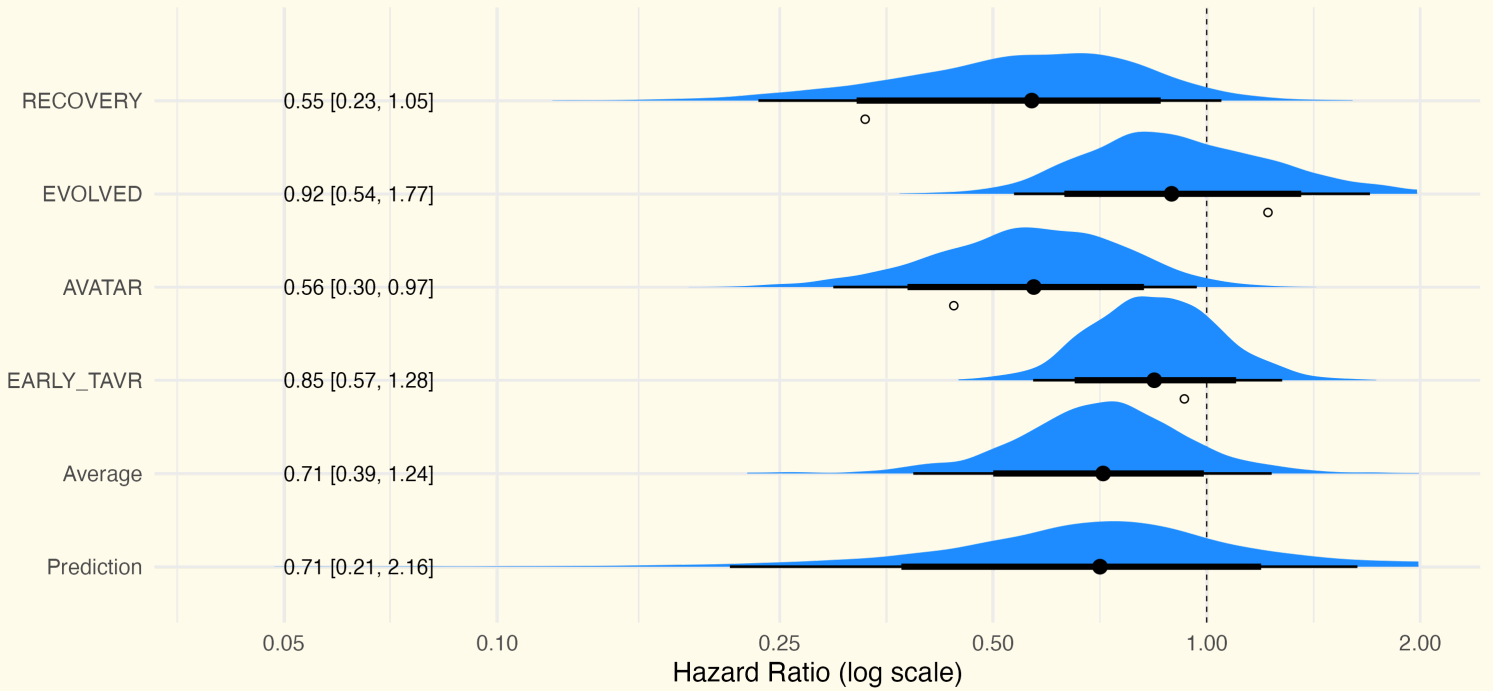
- Frequentist average 0.51 (0.42 - 0.63)
- Bayesian average 0.52 (0.28 - 0.97)
- Bayesian PI (next study) 0.51 (0.18 - 1.37)

What to expect in the next study (predictive)

Primary outcome: all-cause mortality

Figure 4 - Bayesian Estimates of Total Mortality from Published Data

Hazard Ratios with 80% and 95% Credible Intervals
(thin and thick lines, respectively)



Open circle = Observed Hazard Ratios
As black points and intervals represent Bayesian posterior (shrunken) estimates, values are slightly different than in Table 2

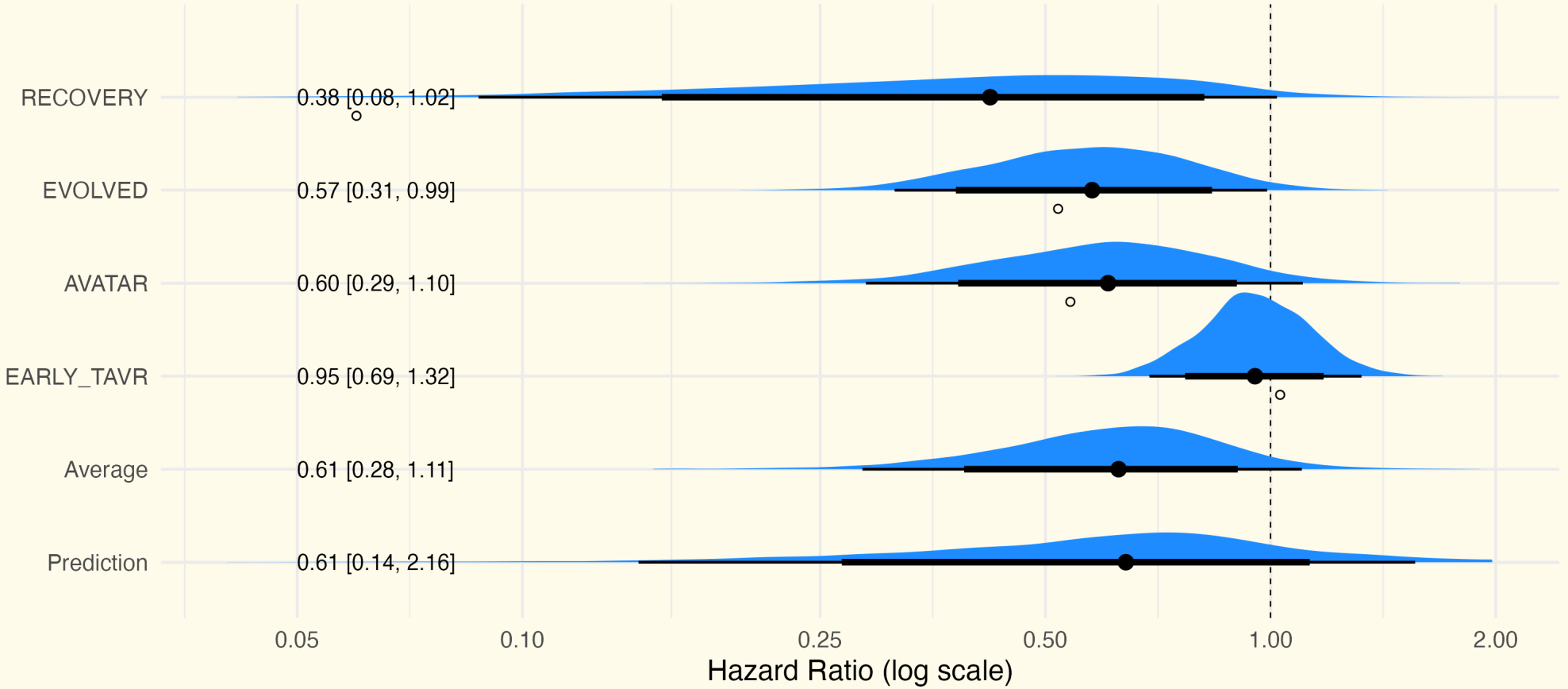
- Frequentist average 0.68 (0.40 - 1.17)
- Bayesian average 0.71 (0.39 - 1.24)
- Bayesian PI (next study) 0.71 (0.21 - 2.16)

Bayesian landmark analyses

Primary outcome: all-cause mortality, stroke or CV hospitalization after 1 year

Figure 3- Bayesian (Posterior) Estimates of Landmark Analysis for Primary Outcome from IPD

Hazard Ratios with 80% and 95% Credible Intervals
(thin and thick lines, respectively)



Open circle = Observed Hazard Ratios
As black points and intervals represent Bayesian posterior (shrunken) estimates, values are slightly different than in Table 2

True benefit vs bias

Meta-analysis driven by Early TAVR events - ↑ CV hospitalization 2^o early crossovers (no mortality Δ, no long term benefit with landmark analysis)

In asx pts with negative baseline exercise testing, which scenario is more likely?

Scenario 1 - benefit of decrease hospitalization occurs immediately following randomization, i.e. in first 6-12 months, with no longer term benefits

Scenario 2 - benefit is perhaps small initially but potentially increasing over time.

Logic says Scenario 2 is more likely if TAVR has a true beneficial impact on decreased hospitalizations & death

But landmark analysis compatible with Scenario 1

Existential question: When is an outcome not an outcome?

Answer: When it is an **intervention**!

True benefit vs bias

Empirical evidence effects from unblinded ≈ ↑ 30% over blinded trials

1. Untreated subjects knew they had severe disease and left untreated -> anxiety and possible conversion to symptomatic status — even in the absence of true progression of cardiac symptoms.
2. Researchers are likely TAVR “believers” knew who was untreated -> increasing probability of attributing any symptoms, whether of cardiac or not, in the untreated to the underlying AS
3. Early treatment group knew they were “fixed” and less likely to consult for any symptoms, whether cardiac or not.
4. Researchers knowing the treated might also be less inclined to attribute any future symptoms to the cardiac condition

All scenarios → ↑ differential hospitalizations btw early treatment and CS contributing to a spurious, rather than true, early TAVR benefit.

Don’t generalize early TAVR as standard of care; instead prioritize shared decision-making and further robust evidence.

Take-Home Messages

- Meta-analysis is powerful, but not infallible
- Bayesian meta-analysis:
  - ↑ flexibility
  - ↑transparency
  - ↑ acknowledgement & understanding of uncertainty
  - makes model assumptions explicit
  - respects the full evidence stream
  - avoids availability bias, dichotomous thinking
  - provides direct answers to questions like:
    - *What's the probability RR < clinical meaningful effect?*
    - *What's the probability absolute benefit > clinical meaningful effect?*
  - ↑ meta-cognition -> ↑ better decisions via enhanced statistical reasoning

Thank You

Let's keep thinking critically
Questions?

Slides available at https://www.brophyj.com/talks

Bayesian References

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- Heuts, S, Kawczynski MJ, Sayed A, Urbut SM, Albuquerque AM, Mandrola JM, Kaul S, Harrell FE, Gabrio A, and **Brophy JM.** 'Bayesian Analytical Methods in Cardiovascular Clinical Trials: Why, When, and How', Can J Cardiol, 41: 30-44 (2025)

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In memory of Dr. Maurice McGregor (1920 -2025)

mentor, colleague, friend, and critical thinker

Tools for Bayesian Meta-Analysis

- **R packages**:
  - `brms`, `rstanarm`, `bayesmeta`, `metaBMA`
- **Workflow**:
  - Visualize priors, run diagnostics, report predictive intervals
- **Resources**:
  - McElreath's *Statistical Rethinking*
  - Spiegelhalter's work on Bayesian evidence synthesis