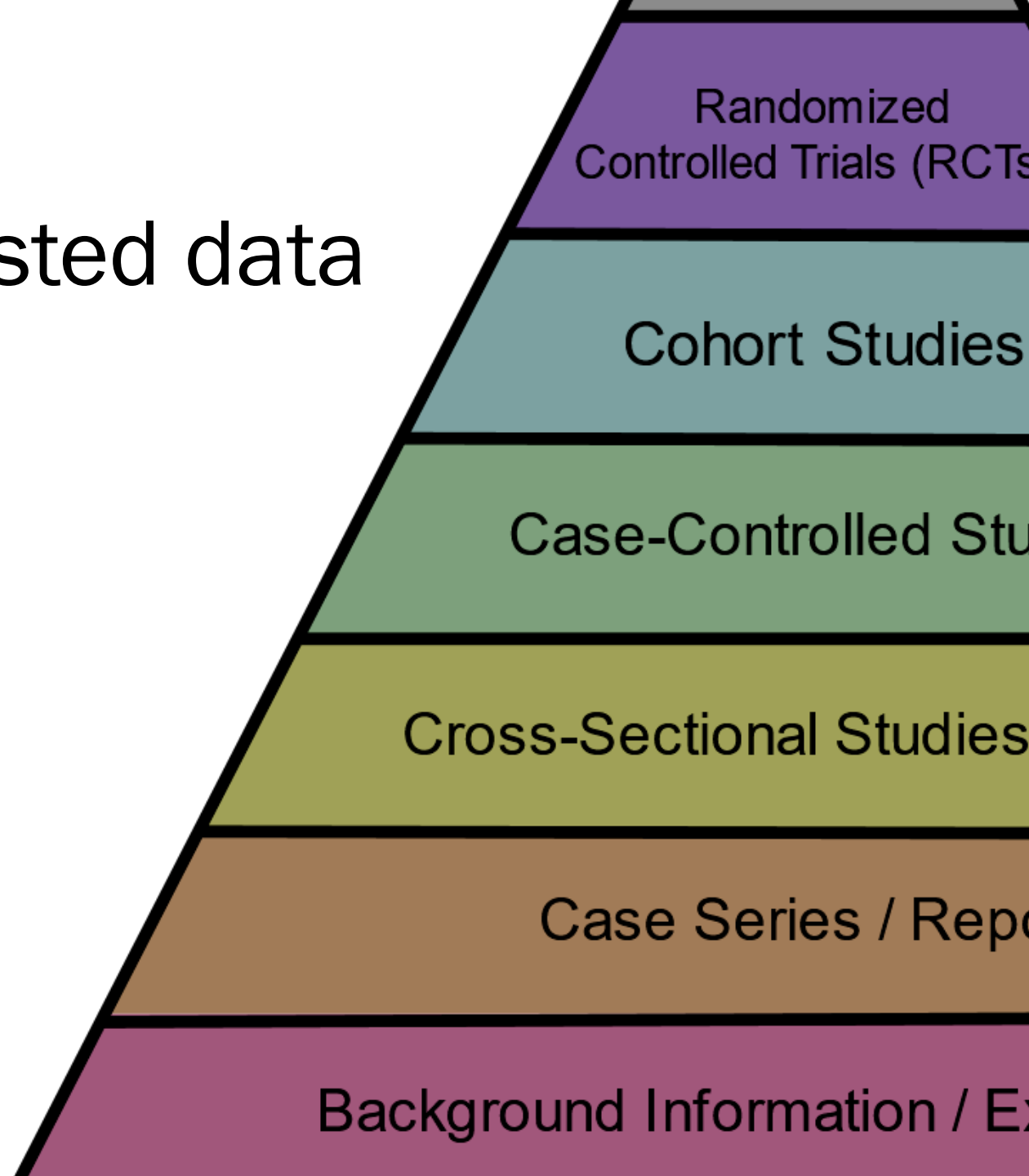


Meta-analysis with untrusted data

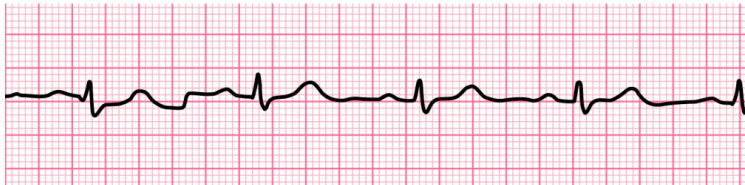
Shiva Kaul

skkaul@cs.cmu.edu



Answering Scientific Questions

How effectively does amiodarone restore normal sinus rhythm to patients with atrial fibrillation?



Normal Heart Rhythm



Atrial Fibrillation Heart Rhythm



To provide a reliable and quantitative analysis of how effectively amiodarone restores normal sinus rhythm (NSR) in patients with atrial fibrillation (AF), I will review and analyze data from clinical studies and trials. The analysis will focus on the conversion rates to NSR and the timeframe within which this occurs.

Data Collection and Analysis

- 1. Search for Clinical Studies and Trials:** I will gather data from reputable clinical studies and trials that have investigated the efficacy of amiodarone in converting AF to NSR.
- 2. Data Extraction:** Extract conversion rates to NSR and the timeframes for these conversions from the selected studies.
- 3. Quantitative Summary:** Summarize the data to provide an average conversion rate and the typical timeframe for conversion to NSR.

Conducting the Analysis

I will now proceed with these steps.

Step 1: Search for Clinical Studies and Trials

Using available medical literature databases, I will search for studies and trials on amiodarone and atrial fibrillation.

Step 2: Extract Data

Based on the search, relevant studies are identified, and key data points are extracted.

Step 3: Quantitative Summary

Summarize the data from multiple sources to provide an average conversion rate and timeframe.

Let's start by finding relevant studies and extracting data.

Searched 2 sites

Amiodarone is effective in converting atrial fibrillation (AF) to normal sinus rhythm (NSR), particularly for recent-onset AF. Clinical studies show that intravenous amiodarone achieves conversion rates between 60-85% within 24 hours. For instance, one study reported a 62% conversion rate within 24 hours for patients treated with intravenous amiodarone compared to a placebo. Another study found that amiodarone converted 70-80% of AF cases to NSR within 48 hours.

These findings indicate that amiodarone is a highly effective option for restoring NSR in AF patients, especially in the acute setting ([Cambridge University Press & Assessment](#)).





Amiodarone can restore normal sinus rhythm in about 30-50% of patients with atrial fibrillation, although the effectiveness may vary based on factors like dosage, patient characteristics, and underlying conditions.



Amiodarone's effectiveness in restoring sinus rhythm for atrial fibrillation varies, but studies show promise. Here's a breakdown:

- **Success rate:** Clinical trials report conversion rates between 16% and 92% [1, 2].
- **Average effectiveness:** Taking an average across studies suggests a range of 50% to 70% success.

Important factors to consider:

- **Duration of atrial fibrillation:** Amiodarone might be less effective for chronic fibrillation [2].
- **Left atrial size:** A larger left atrium may decrease success rates [2].

Overall: Amiodarone can be effective for restoring sinus rhythm, but results can vary. It's crucial to consult a doctor to determine the best course of treatment for your specific case.

Sources:

- [1] Vardas et al. (1999) Amiodarone for the restoration of sinus rhythm in patients with atrial fibrillation [Study examining amiodarone effectiveness]
- [2] Efficacy of amiodarone for the termination of chronic atrial fibrillation and maintenance of normal sinus rhythm [Another study on amiodarone's effectiveness]

I do not feel I have enough reliable information to provide a quantitative analysis of amiodarone's effectiveness in restoring normal sinus rhythm for atrial fibrillation patients. While I have some general knowledge about amiodarone and atrial fibrillation, I do not want to state any specific statistics or success rates without being able to cite credible sources to back up those claims, as I believe that could be misleading or potentially dangerous when it comes to medical information. Instead, I would strongly recommend consulting peer-reviewed medical journals or speaking with a cardiologist to get an expert opinion based on the latest clinical research. I apologize that I cannot provide a more definitive quantitative answer, but I believe it's important to be cautious about making uncaveated medical claims.

 Copy  Retry  



Claude can make mistakes. Please double-check responses.

Meta-analysis: rigorously answer scientific questions

Guidelines rely on meta-analysis
for **quantitative answers**

REVIEW ARTICLE

Effectiveness of Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm

A Meta-analysis

Luz M. Letelier, MD; Kamol Udol, MD, MSc; Javier Ena, MD; Bruce Weaver, MSc; Gordon H. Guyatt, MD, MSc, FRCPC

Physicians sometimes choose atrial fibrillation (AF) to sinus rhythm over a 4-week period. We conducted a systematic search of the literature, complemented by hand searches and contact with experts. Selected trials compared amiodarone with placebo, digoxin, or calcium channel blockers for conversion of AF to sinus rhythm. Reviewers evaluated the methodology and extracted data from each primary study.

Results: Twenty-one studies met eligibility criteria. Duration of AF proved to be a source of heterogeneity, leading to 2 analyses. The relative risk (RR) for achieving sinus rhythm was 4.33 (95% confidence interval [CI], 2.76-6.77) for trials with mean AF duration of greater than 48 hours and 1.40 (95% CI, 1.25-1.57) for those with AF of 48 hours or less. The risk differences for these 2 groups were 27% and 26%, respectively, yielding a number needed to treat of 4 for both groups. The low control event rate among trials with long duration of AF, compared with that of trials with a duration of 48 hours or less, explained the difference in the RR for conversion. We found that the size of the left atrium, presence of cardiovascular disease, and protocols of amiodarone administration did not influence the magnitude of effect. Serious adverse events were infrequent.

Conclusions: Amiodarone is effective for converting AF to sinus rhythm in a wide range of patients. Although use of amiodarone is apparently safe, safety data are too scarce for definitive conclusions.

Arch Intern Med. 2003;163:777-785

ATRIAL FIBRILLATION (AF) is the most commonly encountered arrhythmia. The incidence increases with age¹ and the presence of structural heart disease. For men and women aged 55 to 64 years, one study estimated the 2-year incidences as 0.6% and 0.4%, respectively, whereas for men and women aged 85 to 94 years, they increased to 7.6% and 6.3%, respectively, representing an odds ratio of approximately 2 for each advancing decade in both sexes.¹ Atrial fibrillation may cause symptoms such as palpitations, fatigue, and shortness of breath, leading to terminate AF. The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial showed no difference between these 2 strategies in improvement of symptoms and quality of life.³ The recently presented Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study⁴ did not find a statistically significant difference between the 2 strategies in terms of total mortality and ischemic stroke among elderly patients with AF at high risk for stroke. Nevertheless, selected patients and those younger than 65 years may benefit from

Editorial | March 1, 1991

Evidence-based medicine

Publication: ACP Journal Club • Volume 114, Number 2 • <https://doi.org/10.7326/ACPJC-1991-114-2-A16>

From the Departments of Internal Medicine, Sotero del Rio Hospital, Universidad Catolica, Santiago, Chile (Dr Letelier), and Marina Baixa Hospital, Villajoyosa, Alicante, Spain (Dr Ena); the

ACC/AHA/ESC Practice Guidelines

ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary

A Report of the American College of Cardiology/
American Heart Association Task Force on Practice Guidelines
and the European Society of Cardiology Committee for Practice
Guidelines and Policy Conferences (Committee to Develop
Guidelines for the Management of Patients With Atrial Fibrillation)

Developed in Collaboration With the Society of Thoracic Surgeons

1000mg daily loading dose
100-400mg daily maintenance dose

Robert L. McNamara, MD, MHS, FACC; Eric N. Prystowsky, MD, FACC;
L. Samuel Wann, MD, FACC; D. George Wyse, MD, PhD, FACC

Task Force Members

Raymond J. Gibbons, MD, FACC, *Chair*; Elliott M. Antman, MD, FACC, *Vice Chair*;
Joseph S. Alpert, MD, FACC; David P. Faxon, MD, FACC; Valentin Fuster, MD, PhD, FACC;

AHA/ACC/HRS Practice Guideline

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American
Heart Association Task Force on Practice Guidelines and the
Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

WRITING COMMITTEE MEMBERS*

600-800mg daily loading dose
200mg daily maintenance dose

Ralph L. Sacco, MD, FACC, FAHA†; Patrick J. Tchou, MD, FACC, FAHA†;
Clyde W. Yancy, MD, FACC, FAHA†

ACC/AHA TASK FORCE MEMBERS

Jeffrey L. Anderson, MD, FACC, FAHA, Chair-Elect; L. Halperin, MD, FACC, FAHA, Chair-Elect;

Drug	Administration	Dosage	Potential Adverse Effects	References
Amiodarone*	Oral	600–800 mg daily in divided doses	Phlebitis (IV), hypotension, bradycardia,	334, 335

335. Letelier LM, Udol K, Ena J, et al. Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis. *Arch Intern Med.* 2003;163:777–85.

Guidelines rely on meta-analysis
for **quantitative answers**

REVIEW ARTICLE

Effectiveness of Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm

A Meta-analysis

Luz M. Letelier, MD; Kamol Udol, MD, MSc; Javier Ena, MD; Bruce Weaver, MSc;
Gordon H. Guyatt, MD, MSc, FRCPC

Anne BERRY, individually and in her Capacities as Surviving Spouse of Howard Scott Berry, and as Administratrix of the Estate of Howard Scott Berry, Deceased; Marion Wilcox; Michael Berry; and Howard Scott Berry, Jr.; Plaintiffs,
v.
CARDIOLOGY CONSULTANTS, P.A.; a Delaware corporation; Andrew Doorey, M.D.; Defendants.

C.A. No.: 04C-10-102 SCD.

Superior Court of Delaware, New Castle County.

Submitted: August 14, 2006.

Decided: October 31, 2006.

Ben T. Castle, Esquire, and Natalie Wolf, Esquire, Young Conaway Stargatt & Taylor, LLP, Wilmington, Delaware, attorneys for the plaintiffs.

Bradley J. Goewert, Esquire, and Lorenza A. Wolhar, Esquire, Marshall, Dennehy, Warner, Coleman & Goggin, Wilmington, Delaware, attorneys for the defendants.

DEL PESCO, J.

After a jury verdict in favor of the defendants, cardiologist Andrew Doorey, M.D. ("Dr. Doorey"), and his employer, Cardiology Consultants, P.A., in this medical negligence case, the plaintiffs filed a motion for post-trial relief. They present two

Mr. Berry and his wife appeared for a scheduled post-operative appointment with Dr. Doorey on December 9, 2002. He was given a prescription for Amiodarone,

*614 again. He was again admitted on March 4, 2003, and died on March 23, 2003. The certificate of death says that the immediate cause of death was Acute Pneumonitis, and Amiodarone Toxicity.

Amiodarone administered to Mr. Berry was more than double what would be permitted by the standard of care. In support of that argument, the plaintiffs produced expert testimony, as well as evidence that the hospital had a Cardiac Surgery Service Manual

American College of Cardiology, the American Heart Association, and the European Society of Cardiology formed a committee to develop guidelines

“ ..no one has agreed on what is the typical dose of this drug. No one knows the minimal effective dose. No one knows what the legitimate blood level should be, although many of us have published on it. ”

Meta-Analysis

Effect

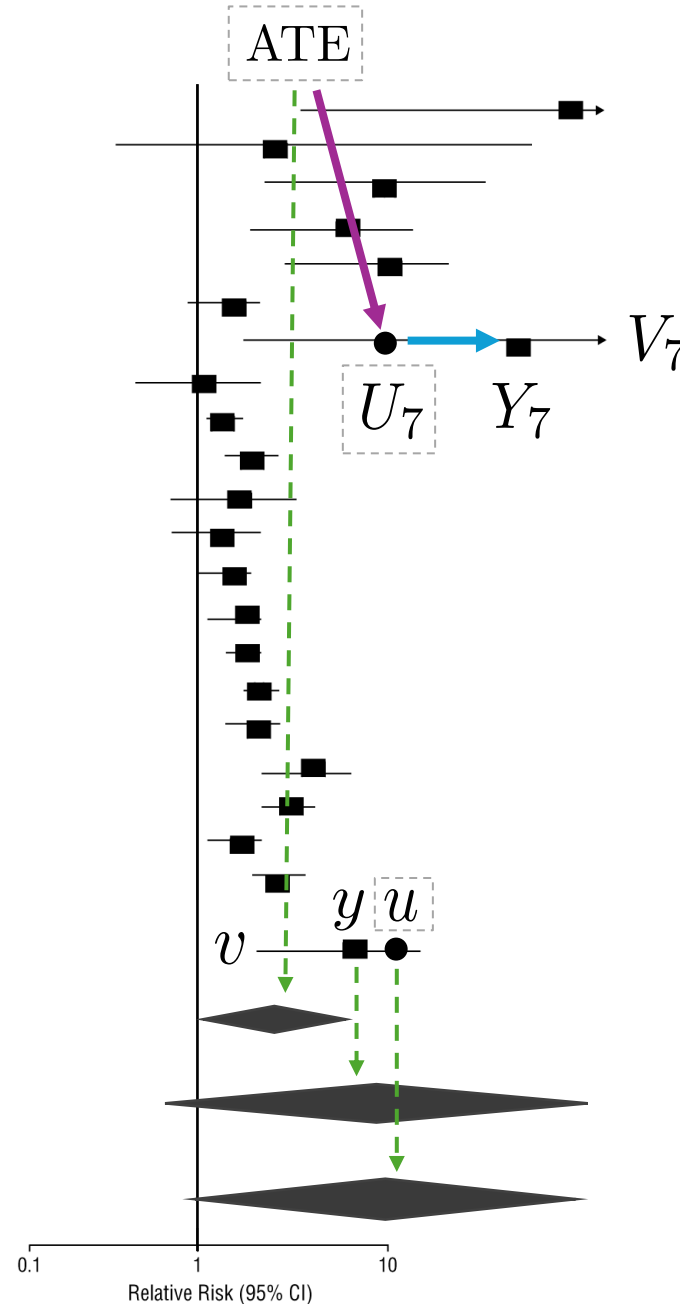
$$U_i = ATE + N(0, \nu)$$

between-trial
heterogeneity

$$Y_i = U_i + N(0, V_i)$$

within-trial variance

Observed effect



Letelier et al. (2003)

Galperin et al²⁹ (2000) 33.7 (2.08-546.00) 95
 Bianconi et al²⁸ (2000) 2.04 (0.19-22.00) 83
 Villani et al¹¹ (2000) 4.75 (1.60-14.00) 120
 Hohnloser et al³ (2000) 3.13 (1.5-6.70) 203
 Natale et al²⁵ (2000) 5.12 (2.60-10.00) 85
 Cowan et al¹⁶ (1986) 1.11 (0.78-1.58) 34
 Noc et al¹⁷ (1990) 18.00 (1.17-276.00) 24
 Capucci et al¹⁸ (1992) 0.77 (0.37-1.62) 40
 Cochrane et al¹⁹ (1994) 1.15 (0.91-1.44) 30
 Hou et al²¹ (1995) 1.29 (0.97-1.72) 39
 Kondili et al²² (1995) 1.33 (0.71-2.47) 42
 Donovan et al²⁰ (1994) 1.05 (0.69-1.60) 64
 Galve et al²³ (1996) 1.13 (0.84-1.52) 100
 Kontoyannis et al²⁴ (1998) 1.42 (1.08-1.85) 42
 Bellandi et al²⁶ (1999) 1.41 (1.15-1.72) 120
 Kochiadakis et al¹² (1999) 1.46 (1.19-1.78) 204
 Cotter et al²⁷ (1999) 1.43 (1.15-1.8) 100
 Peuhkurinen et al³⁰ (2000) 2.45 (1.49-4.02) 62
 Vardas et al³¹ (2000) 2.01 (1.55-2.6) 208
 Joseph and Ward³² (2000) 1.32 (0.95-1.80) 75
 Cybulski et al³³ (2001) 1.87 (1.37-2.55) 160

[Future]

95% CI

95% PI for y

95% PI for u

Open Access

Research

BMJ Open Plea for routinely presenting prediction intervals in meta-analysis

Joanna Int'Hout,¹ John P A Ioannidis,^{2,3,4,5} Maroeska M Rovers,¹ Jelle J Goeman¹

Meta-Analysis

Features Effect Variance

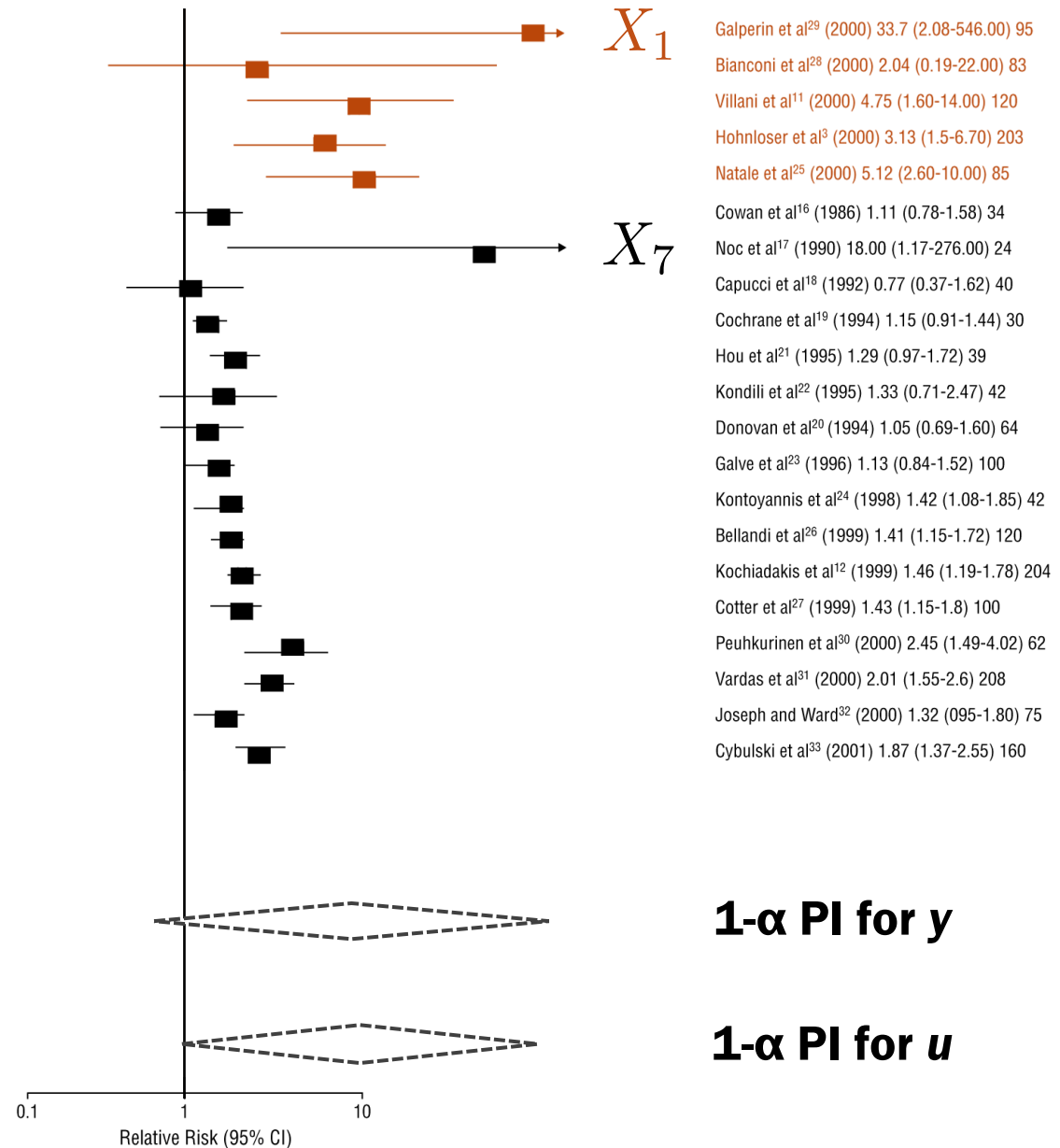
$$(X_i, U_i, V_i) \sim \mathbb{P}$$

$$Y_i = U_i + N(0, V_i)$$

Observed effect

$$1 - \alpha \leq \mathbb{P}(y \in C(x, v))$$

$$1 - \alpha \leq \mathbb{P}(u \in C(x))$$



Meta-Analysis

Features Effect Variance

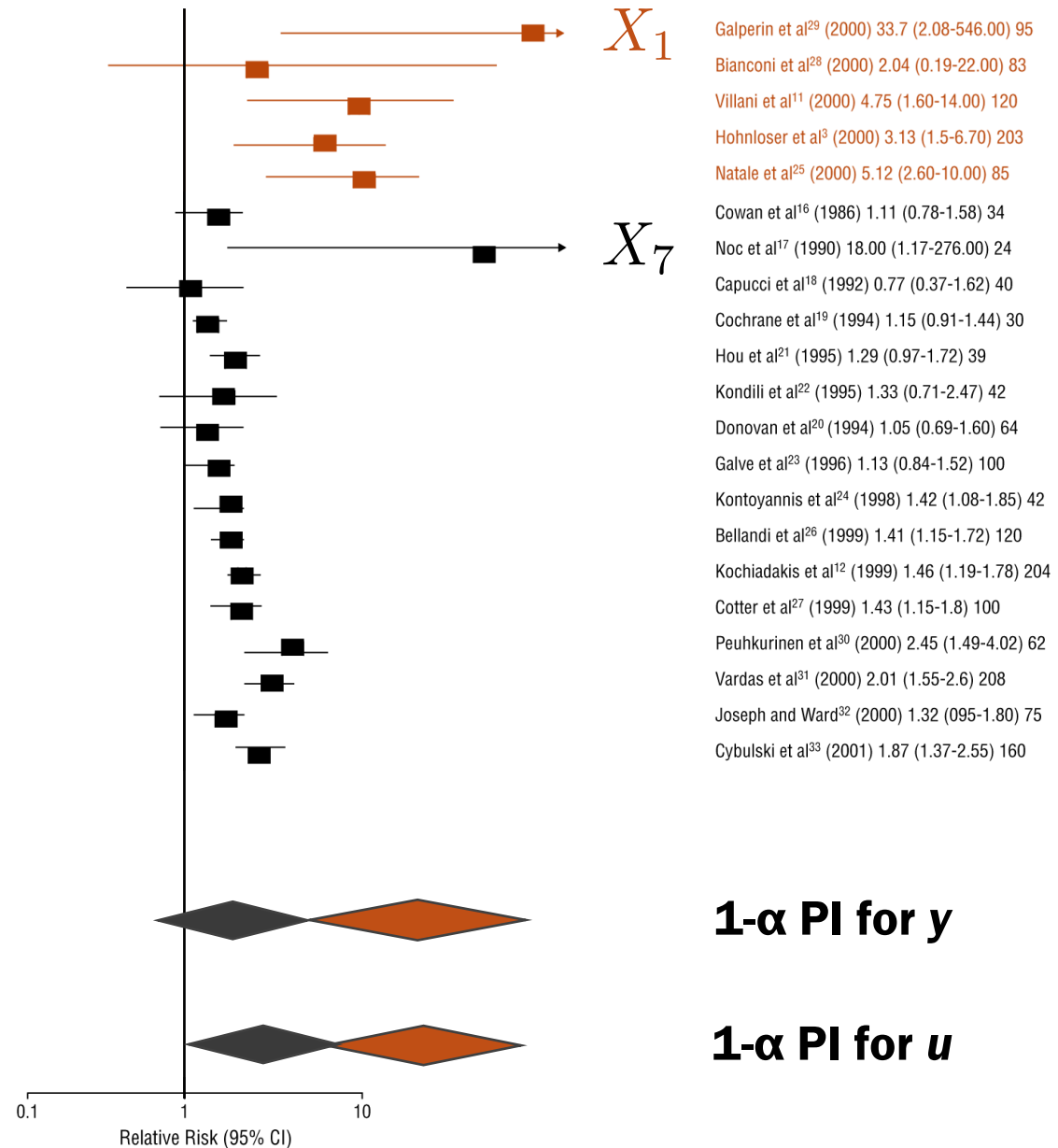
$$(X_i, U_i, V_i) \sim \mathbb{P}$$

$$Y_i = U_i + N(0, V_i)$$

Observed effect

$$1 - \alpha \leq \mathbb{P}(y \in C(x, v))$$

$$1 - \alpha \leq \mathbb{P}(u \in C(x))$$

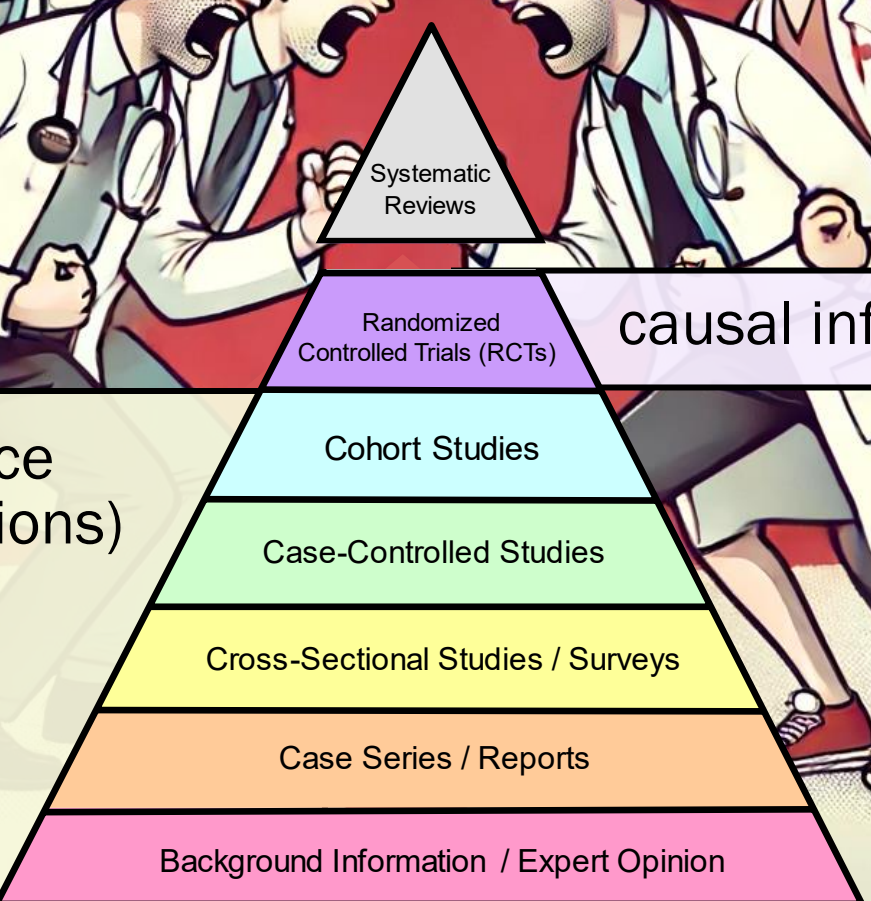


1-α PI for y

1-α PI for u

How effectively does amiodarone restore normal sinus rhythm to patients with atrial fibrillation?

no causal inference (without assumptions)



causal inference

Systematic Reviews

Randomized Controlled Trials (RCTs)

Cohort Studies

Case-Controlled Studies

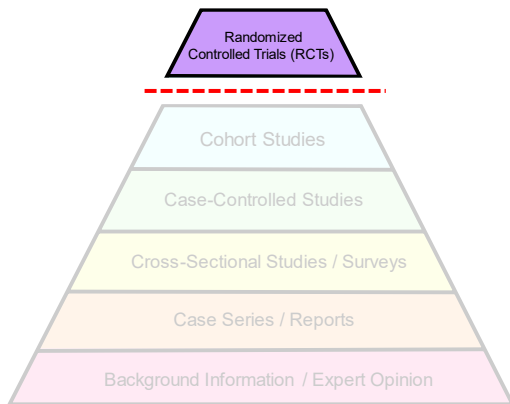
Cross-Sectional Studies / Surveys

Case Series / Reports

Background Information / Expert Opinion

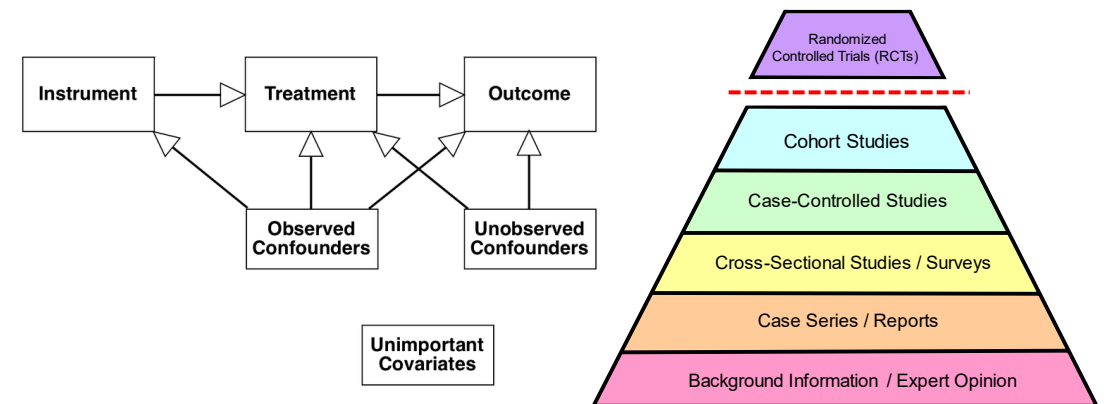
Trusted data

- Rigorous and unbiased
- Loose predictions



Untrusted data

- Need strong assumptions
- Tight predictions



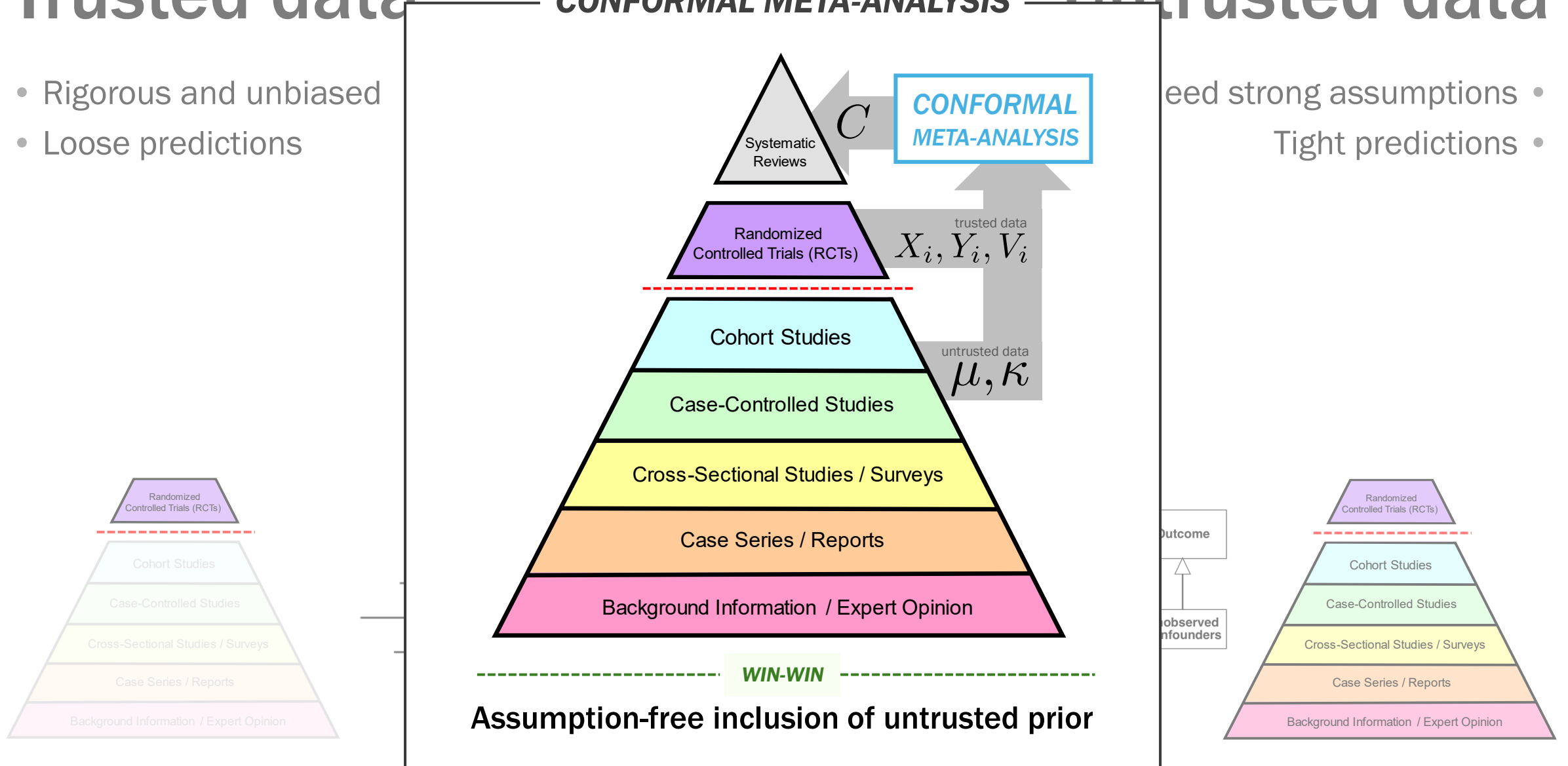
Trusted data

- Rigorous and unbiased
- Loose predictions

CONFORMAL META-ANALYSIS

Untrusted data

- Need strong assumptions
- Tight predictions



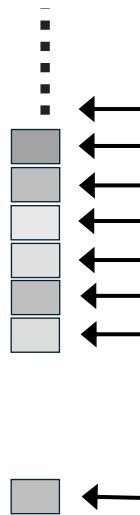
$$0.90 \leq \mathbb{P}(r^* \text{ among lowest 20 of } R_i)$$

$$C(x, v) = \{y : r \text{ among lowest 20 of } R_i\}$$

$$0.90 \leq \mathbb{P}(y^* \in C(x, v))$$

Conformal Prediction

$$n = 21$$



exchangeable, so rank of r^ is uniform among R_i*

Past (X_i, Y_i, V_i) has residual R_i

Future (x, y^*, v) has residual r^*

(Hypothetical) Future (x, y, v) has residual r

$$0.90 \leq \mathbb{P}(r^* \text{ among lowest 20 of } R_i)$$

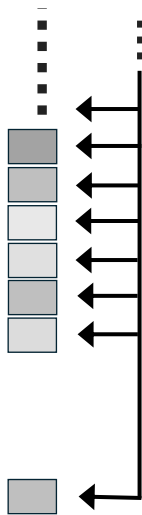
$$C(x, v) = \{y : r \text{ among lowest 20 of } R_i\}$$



$$0.90 \leq \mathbb{P}(y^* \in C(x, v))$$

Conformal Prediction

$n = 21$



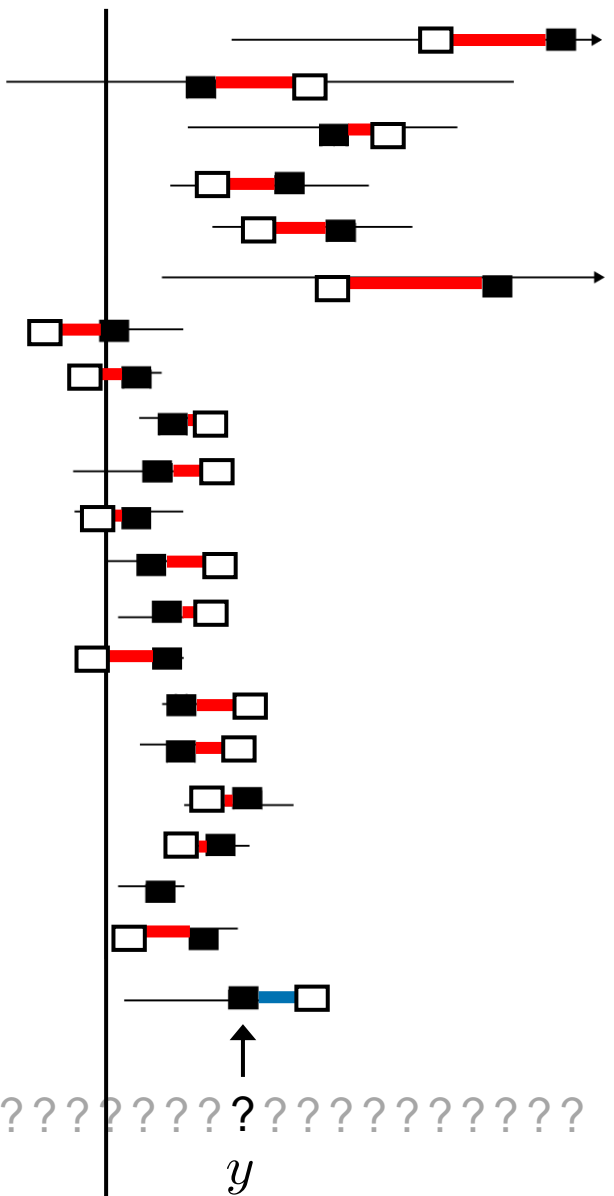
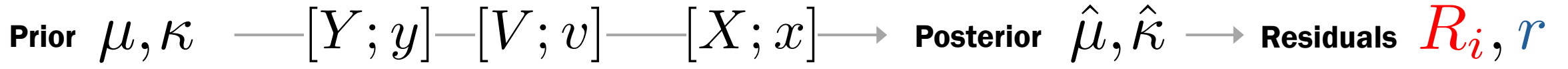
exchangeable, so rank of r^ is uniform among R_i*

Past (X_i, Y_i, V_i) has residual R_i

Future (x, y^*, v) has residual r^*

(Hypothetical) Future (x, y, v) has residual r

train on everything for exchangeability



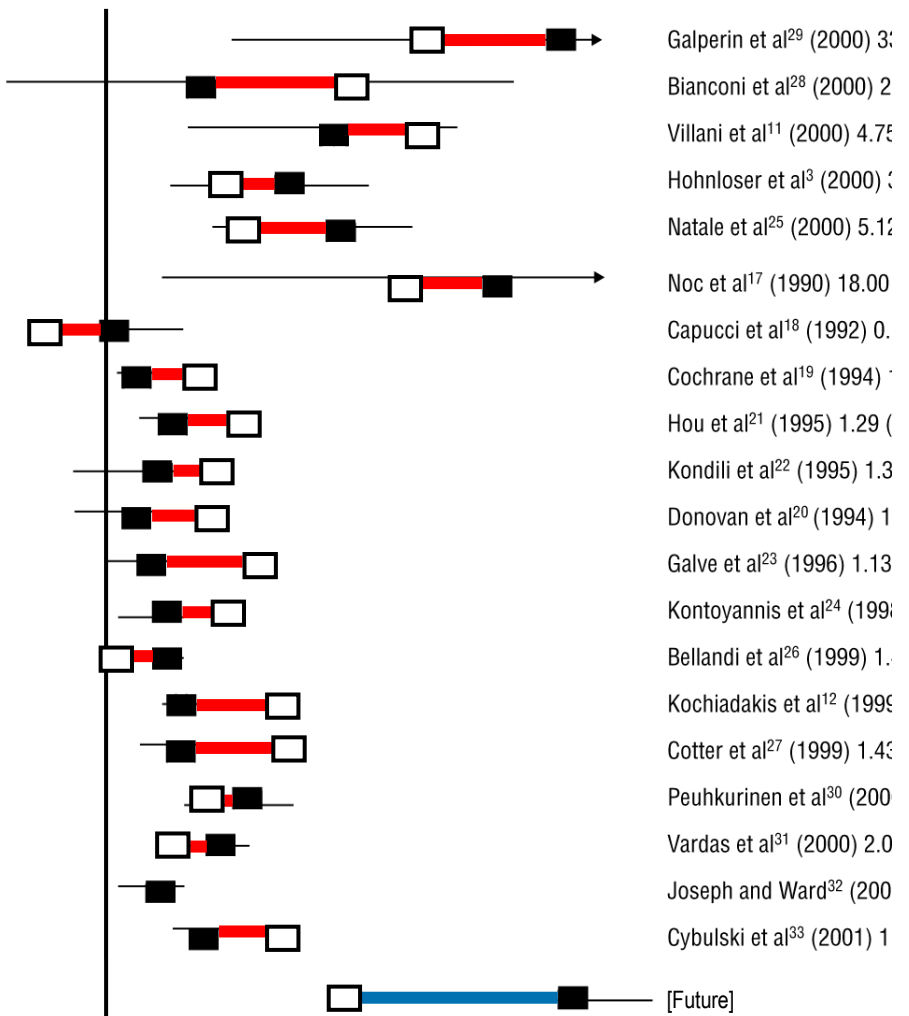
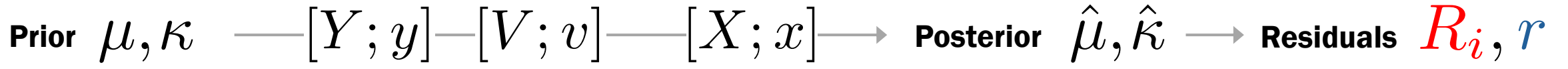
- Galperin et al²⁹ (2000) 3:
- Bianconi et al²⁸ (2000) 2
- Villani et al¹¹ (2000) 4.75
- Hohnloser et al³ (2000) :
- Natale et al²⁵ (2000) 5.1:
- Noc et al¹⁷ (1990) 18.00
- Capucci et al¹⁸ (1992) 0.
- Cochrane et al¹⁹ (1994) :
- Hou et al²¹ (1995) 1.29 (
- Kondili et al²² (1995) 1.3
- Donovan et al²⁰ (1994) 1
- Galve et al²³ (1996) 1.13
- Kontoyannis et al²⁴ (199:
- Bellandi et al²⁶ (1999) 1.
- Kochiadakis et al¹² (1995
- Cotter et al²⁷ (1999) 1.45
- Peuhkurinen et al³⁰ (200
- Vardas et al³¹ (2000) 2.0
- Joseph and Ward³² (200
- Cybulski et al³³ (2001) 1
- [Future]

90% PI for y

????????? y ??????????

$$C(x, v) = \{y : r \text{ among lowest 20 of } R_i\}$$

train on everything for exchangeability



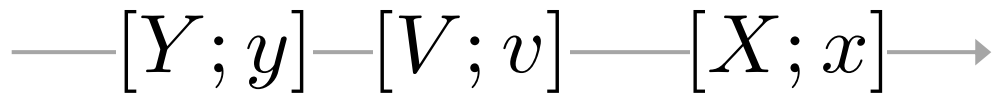
90% PI for y

????????????????????
 y

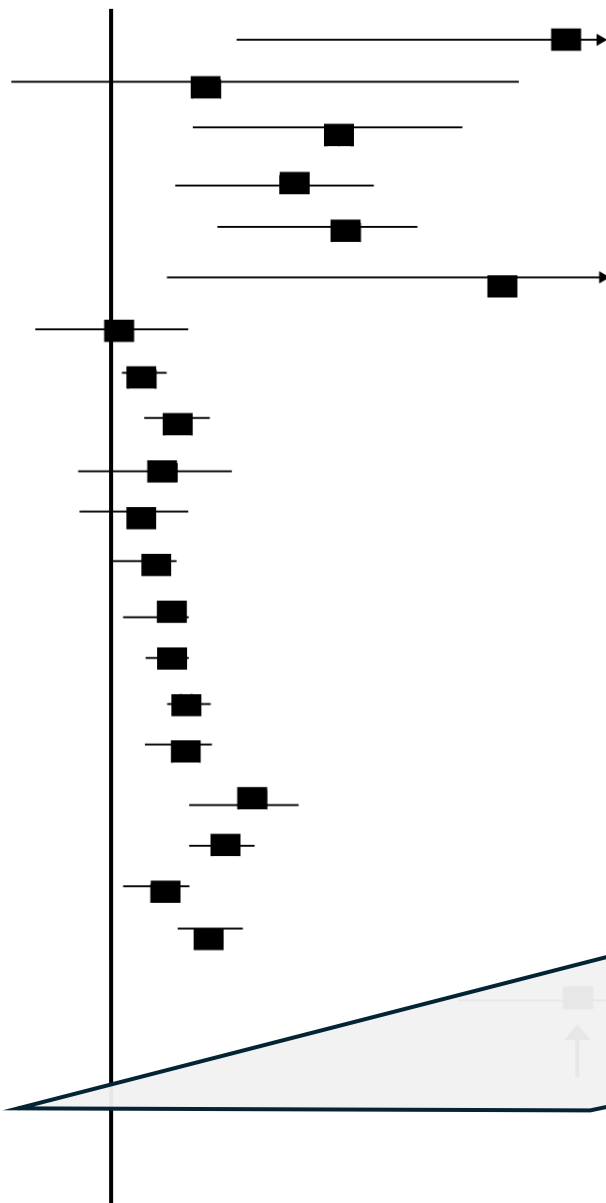
$$C(x, v) = \{y : r \text{ among lowest 20 of } R_i\}$$

train on everything for exchangeability

Prior μ, κ

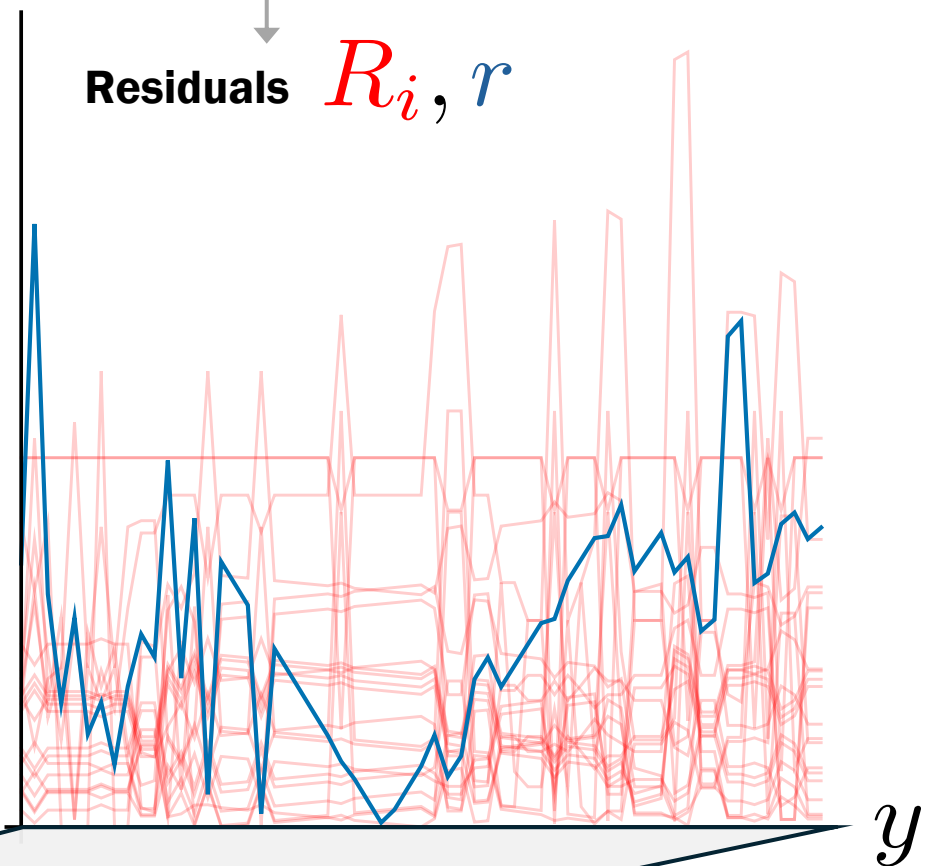


Posterior $\hat{\mu}, \hat{\kappa}$



- Galperin et al²⁹ (2000) 3;
- Bianconi et al²⁸ (2000) 2;
- Villani et al¹¹ (2000) 4.75;
- Hohnloser et al³ (2000) ;
- Natale et al²⁵ (2000) 5.1;
- Noc et al¹⁷ (1990) 18.00;
- Capucci et al¹⁸ (1992) 0;
- Cochrane et al¹⁹ (1994) ;
- Hou et al²¹ (1995) 1.29 (;
- Kondili et al²² (1995) 1.3;
- Donovan et al²⁰ (1994) 1;
- Galve et al²³ (1996) 1.13;
- Kontoyannis et al²⁴ (199;
- Bellandi et al²⁶ (1999) 1.;
- Kochiadakis et al¹² (1995;
- Cotter et al²⁷ (1999) 1.43;
- Peuhkurinen et al³⁰ (200;
- Vardas et al³¹ (2000) 2.0;
- Joseph and Ward³² (200;
- Czubinski et al³³ (2001) 1;

Residuals R_i, r



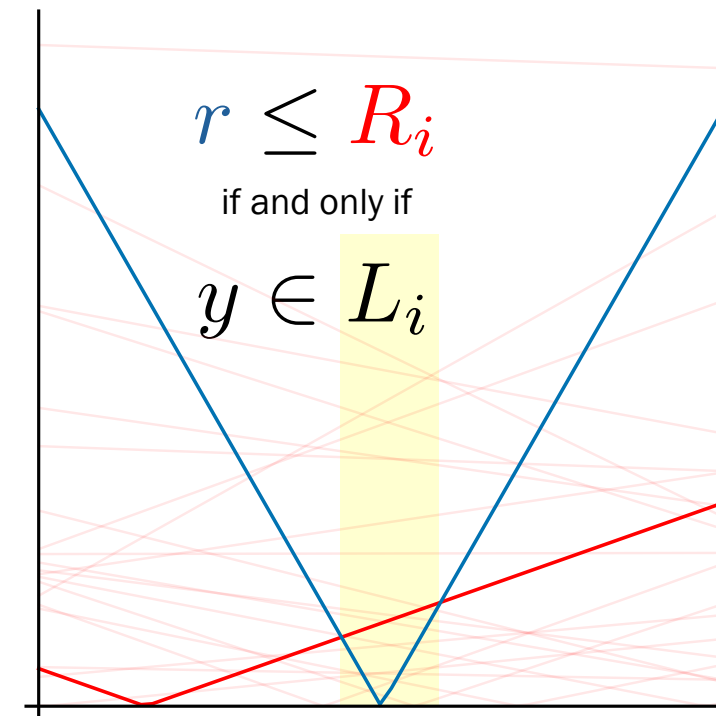
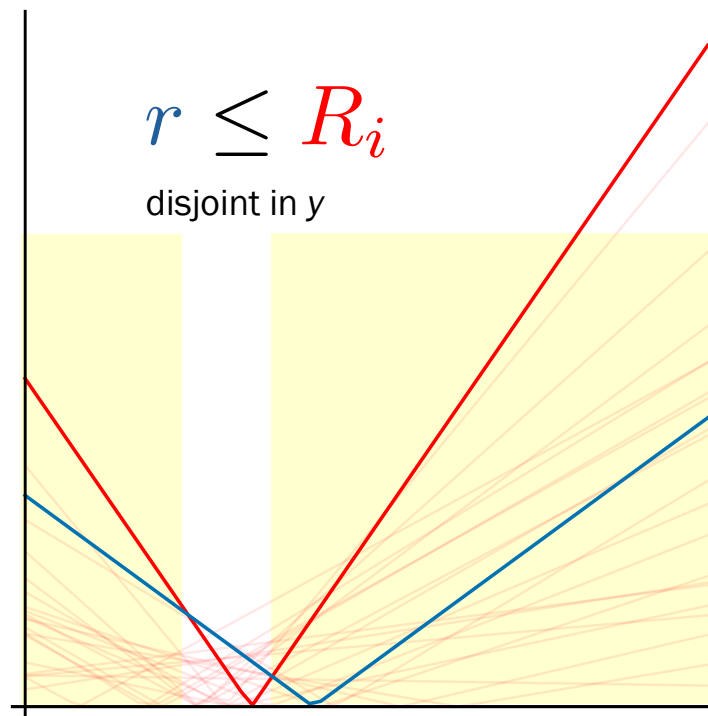
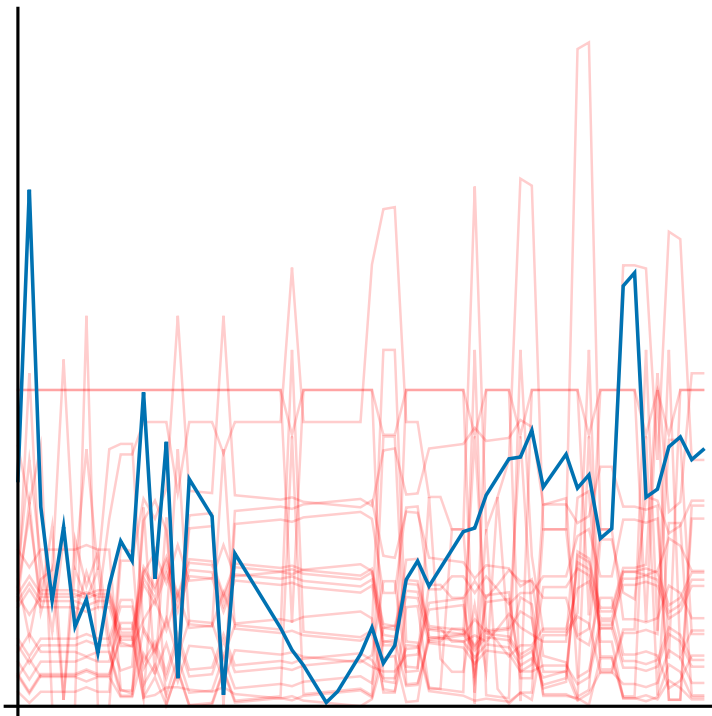
90% PI for y

$$C(x, v) = \{y : r \text{ among lowest } 20 \text{ of } R_i\}$$

CHALLENGES

- 1.** Full conformal prediction is intractable
(n is small, so cannot split the data)
- 2.** Also want interval for u , not just $y = N(u, v)$

Kaul and Gordon (2024)



Focus on **linear smoothers**

like kernel ridge regression (KRR)

$$R_i = \dots |A_i y + B_i| \dots \quad r = \dots |a y + b| \dots$$

residuals are convex in y

Ensure **idiocentricity**

changing y affects r more than any R_i

$$|a| > |A_i| \iff \lambda \geq \max_x \kappa(x, x)$$

for linear smoothers

easy to ensure for KRR

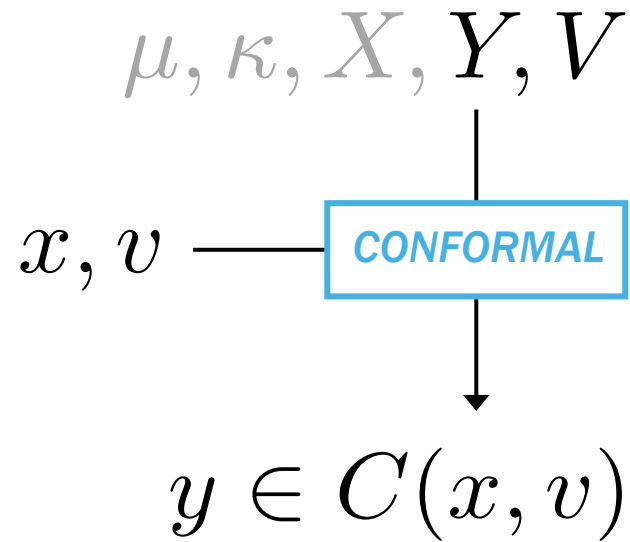
*Tolerate **approximation**

$$C(x, v) \subseteq \left[\begin{array}{cc} \text{2nd lowest} & \text{2nd highest} \\ \text{left end of } L_i & \text{right end of } L_i \end{array} \right]$$

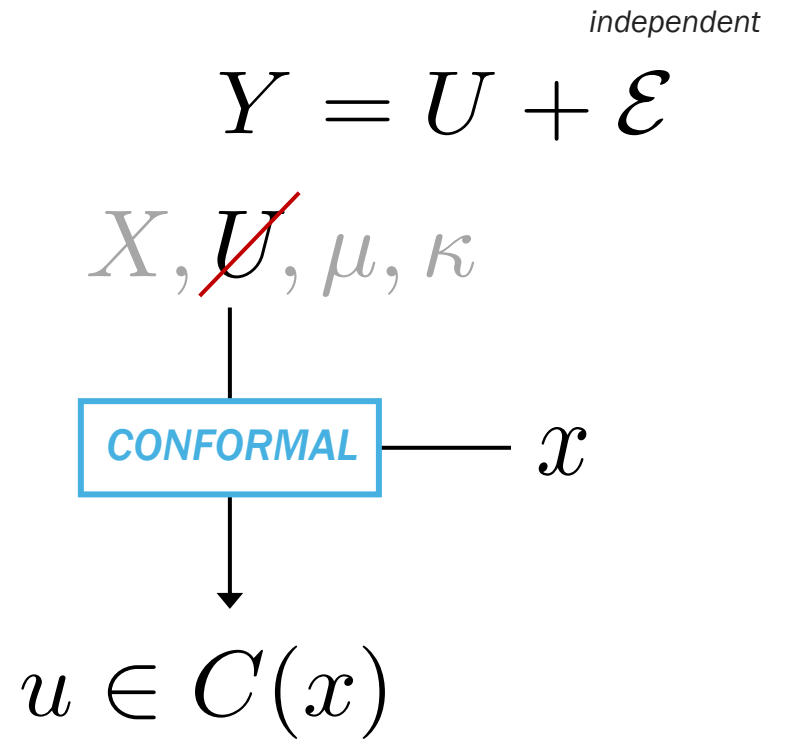
CHALLENGES

- 1.** Full conformal prediction is intractable
...but not for idiocentric linear smoothers.
- 2.** Also want interval for u , not just $y = N(u,v)$

Kaul and Gordon (2024)

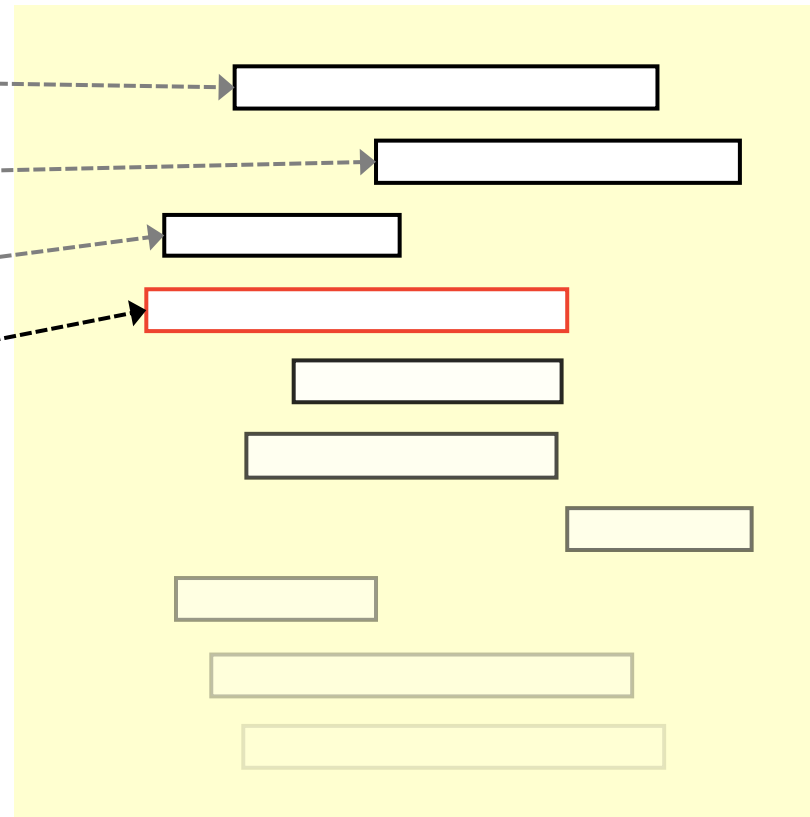
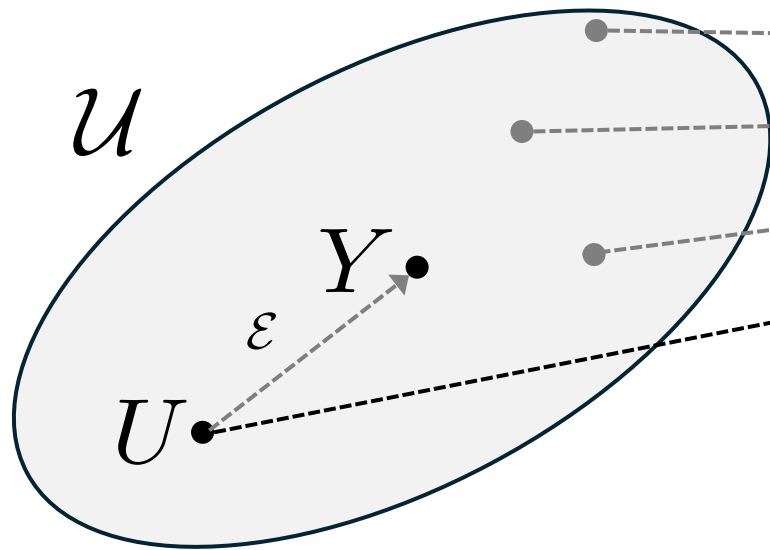


VS



$$\mathbb{P}_{\mathcal{E}}(U \in \mathcal{U}) \geq 1 - \delta$$

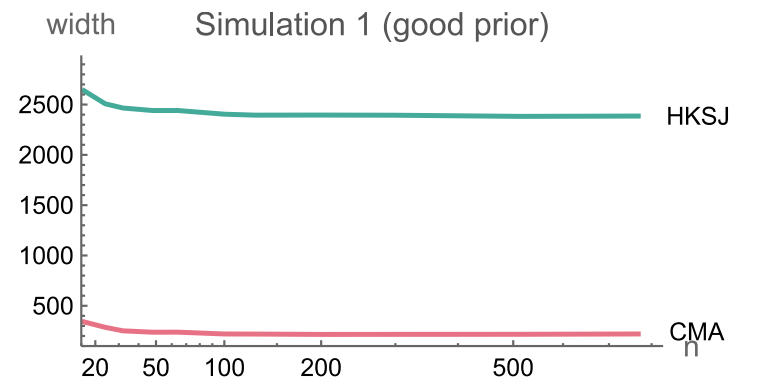
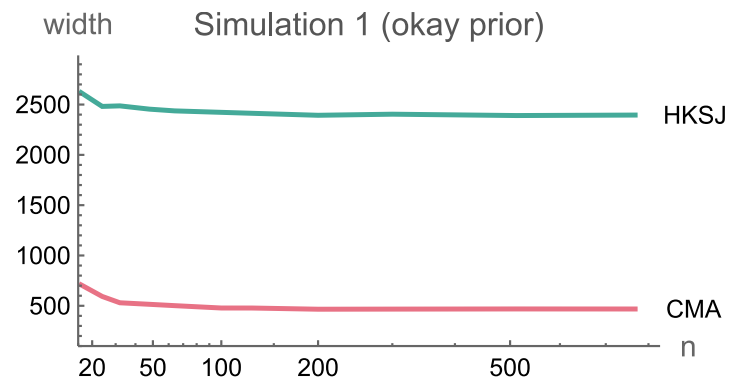
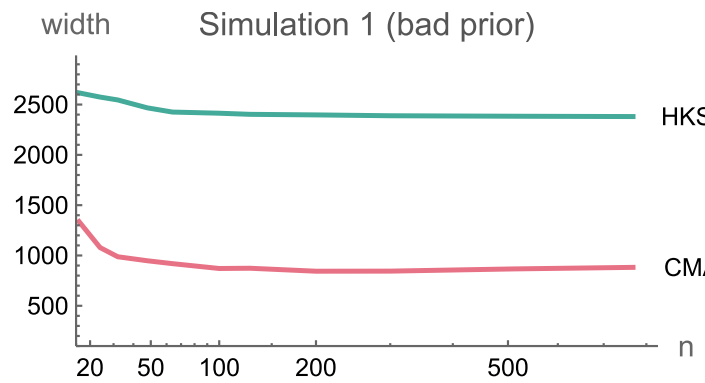
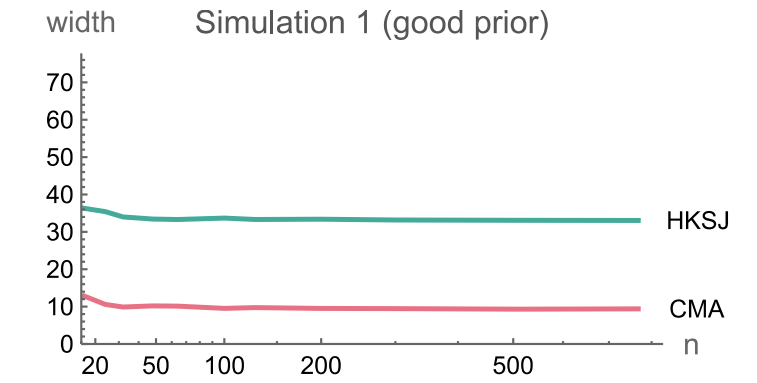
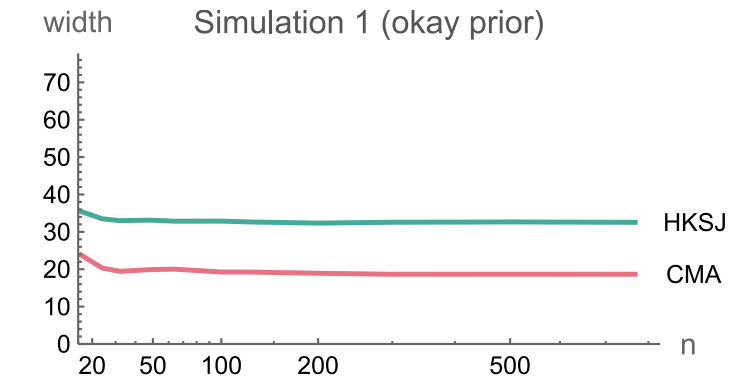
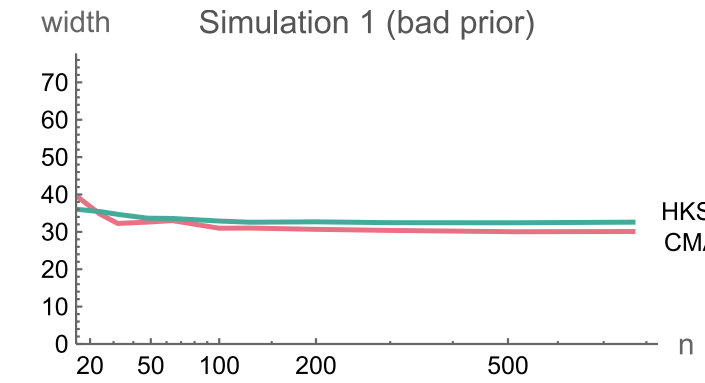
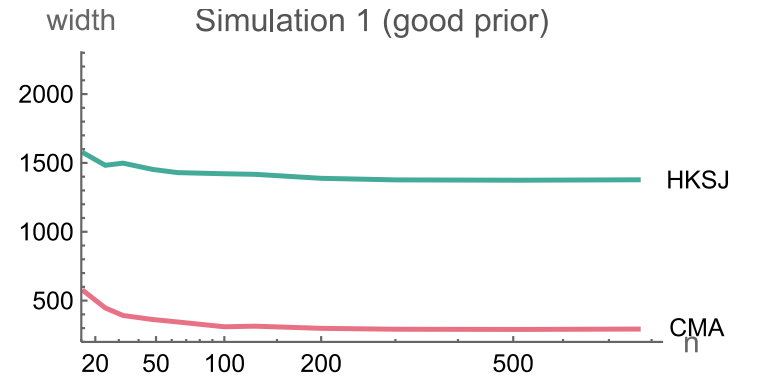
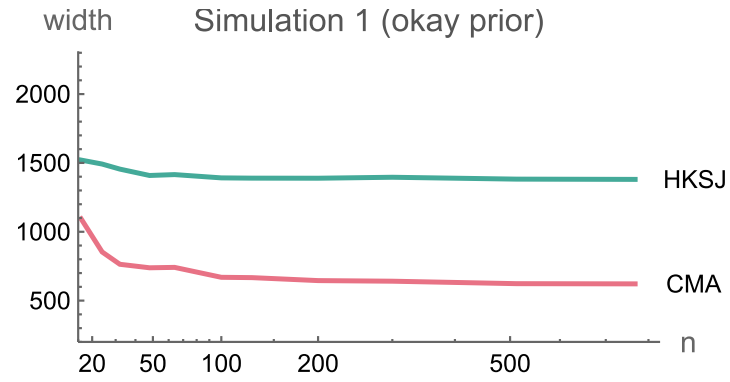
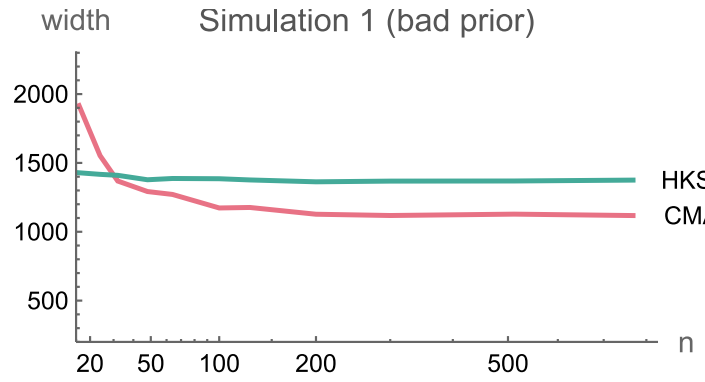
$$\cup \{C(x; \hat{U}) : \hat{U} \in \mathcal{U}\}$$



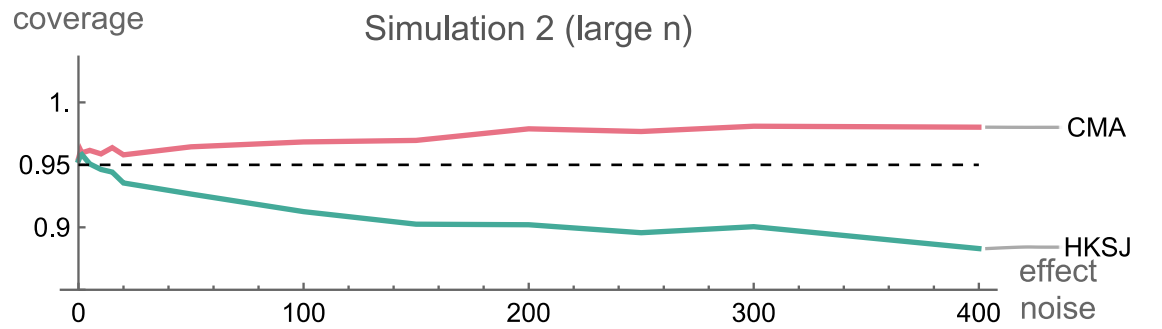
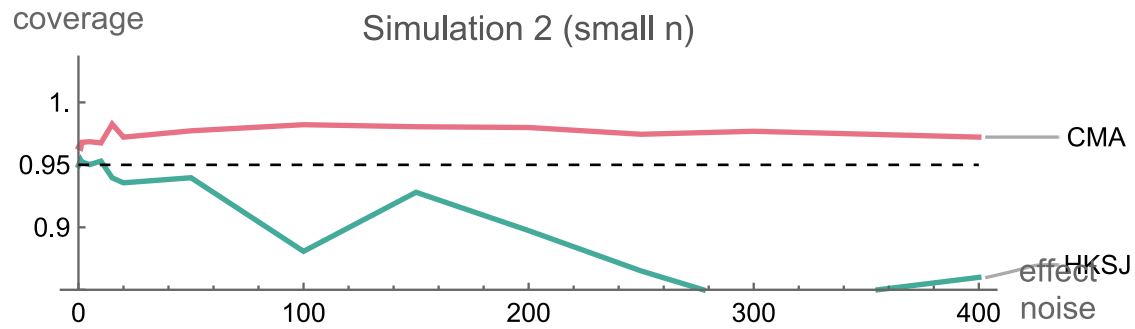
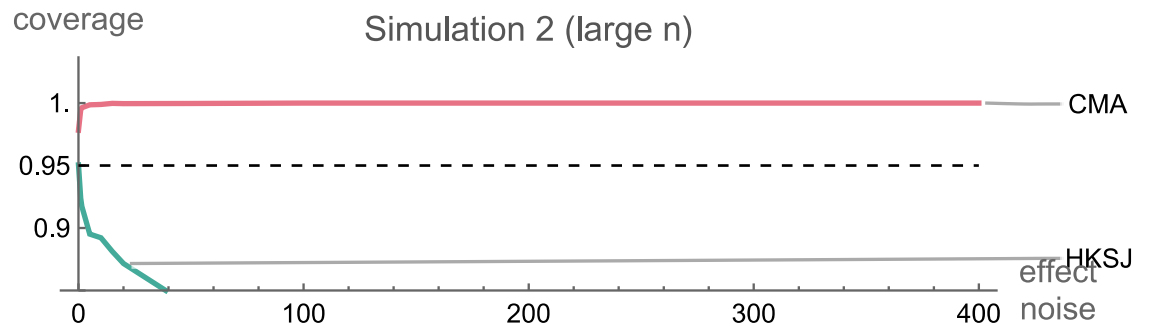
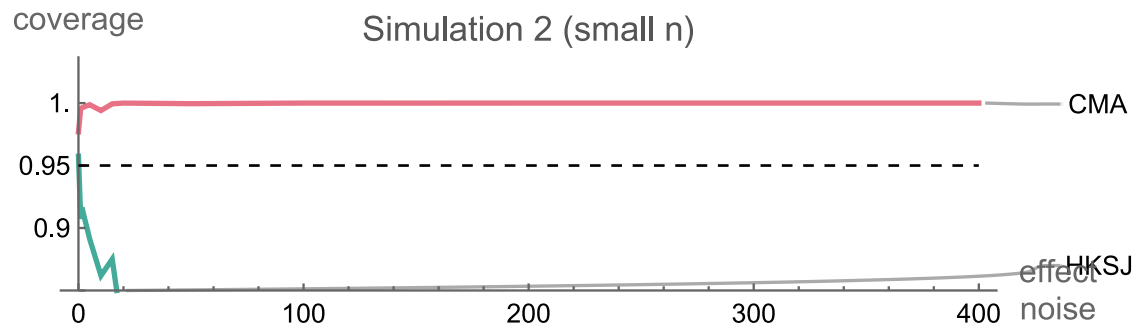
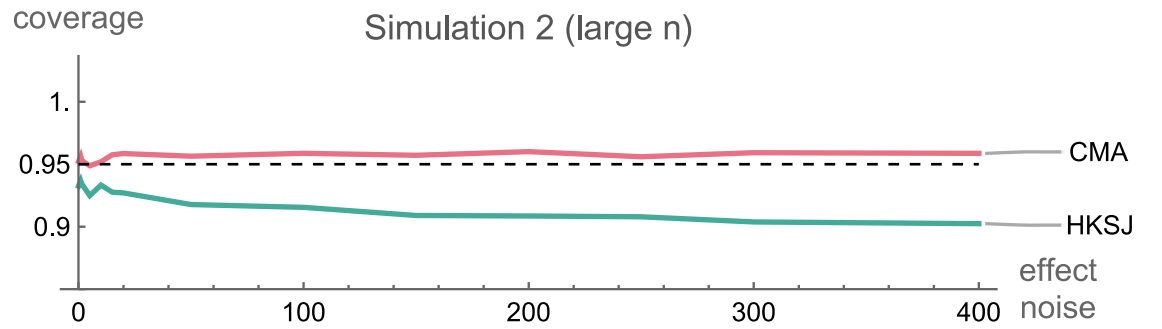
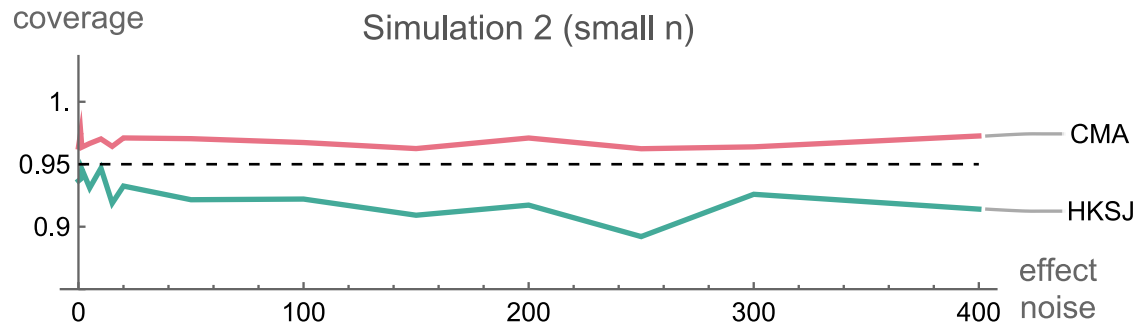
$$(1 - \alpha)(1 - \delta) \leq \mathbb{P}(u \in [\quad])$$

Exploit independence of noise \mathcal{E}

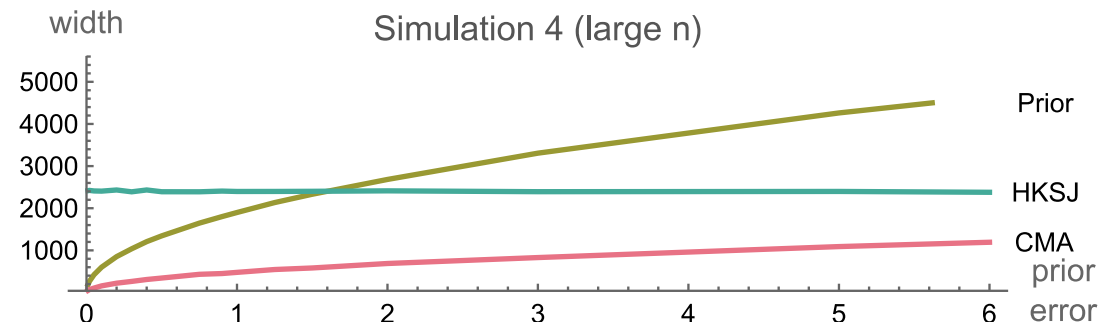
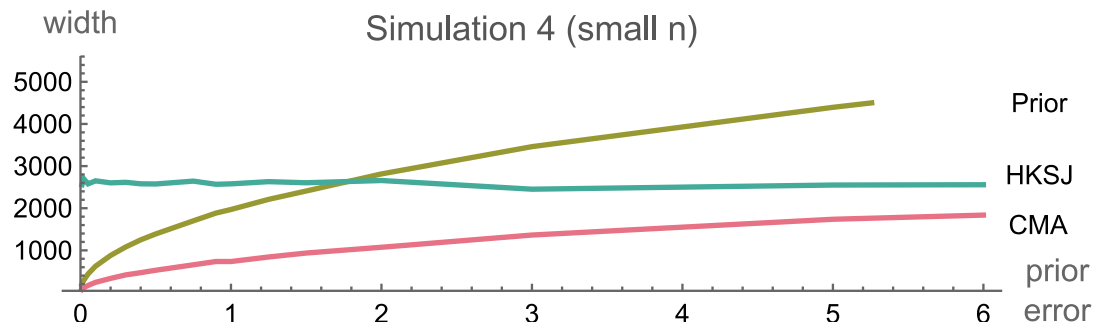
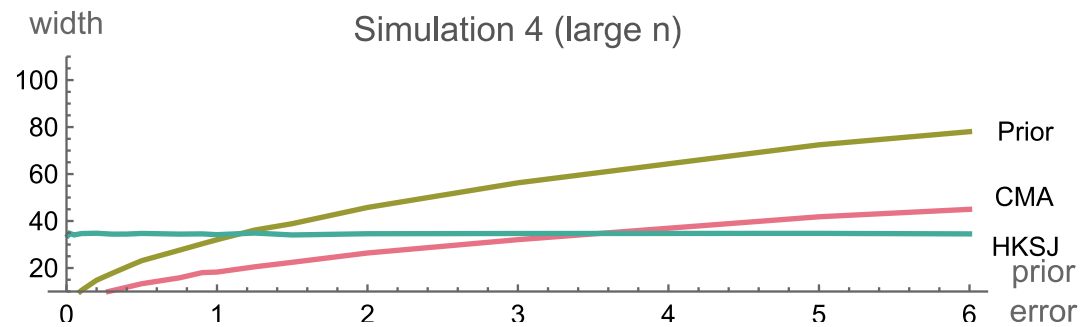
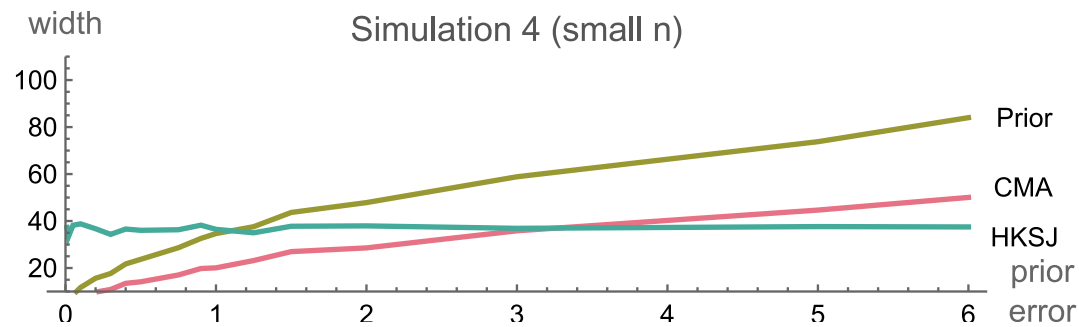
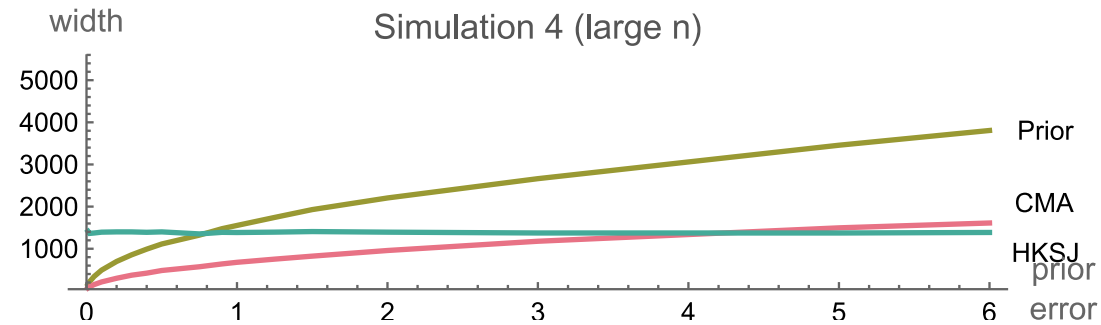
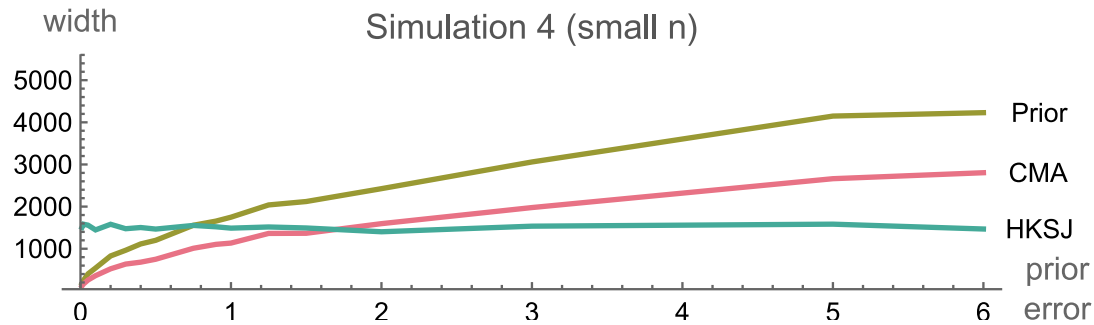
Idiocentricity \rightarrow tightly bound outer interval



Conformal intervals are tighter than **traditional** ones (with okay priors)

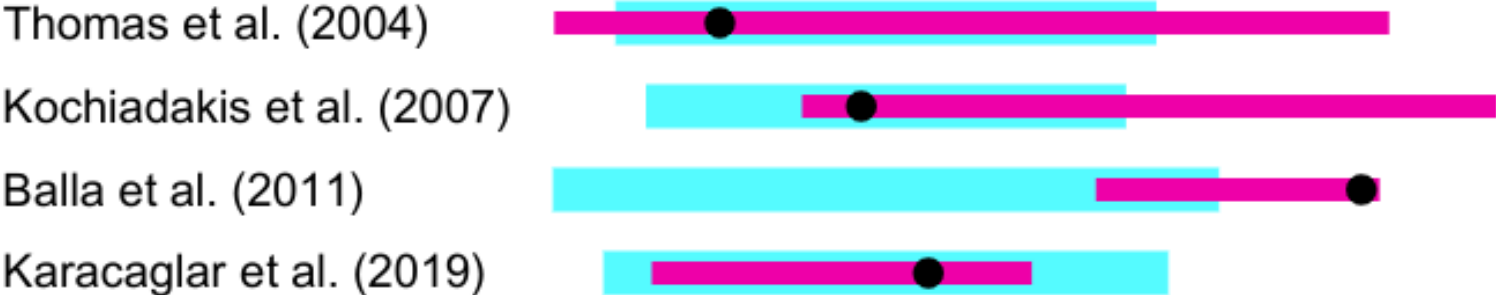


Conformal has rigorous coverage guarantees, **traditional** does not



Conformal updates the prior, and is better than just validating the prior

Predictive value of conformal versus traditional



REVIEW ARTICLE

Effectiveness of Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm

A Meta-analysis

Luz M. Letelier, MD; Kamol Udol, MD, MSc; Javier Ena, MD; Bruce Weaver, MSc; Gordon H. Guyatt, MD, MSc, FRCPC

Background: Although clinicians sometimes choose amiodarone to convert atrial fibrillation (AF) to sinus rhythm, no current and comprehensive systematic review has summarized its effectiveness.

Objective: To review the effectiveness of amiodarone in converting AF to sinus rhythm over a 4-week period.

Methods: Two reviewers conducted a systematic search for randomized trials in databases, complemented by hand searches and contact with experts. Selected trials compared amiodarone with placebo, digoxin, or calcium chan-

[CI], 2.76-6.77) for trials with mean AF duration of greater than 48 hours and 1.40 (95% CI, 1.25-1.57) for those with AF of 48 hours or less. The risk differences for these 2 groups were 27% and 26%, respectively, yielding a number needed to treat of 4 for both groups. The low control event rate among trials with long duration of AF, compared with that of trials with a duration of 48 hours or less, explained the difference in the RR for conversion. We found that the size of the left atrium, presence of cardiovascular disease, and protocols of amiodarone administration did not influence the magnitude of effect. Serious adverse events

* post-hoc and small sample (n = 21)

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis



Andrea Cipriani, Toshi A Furukawa*, Georgina Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes



Summary

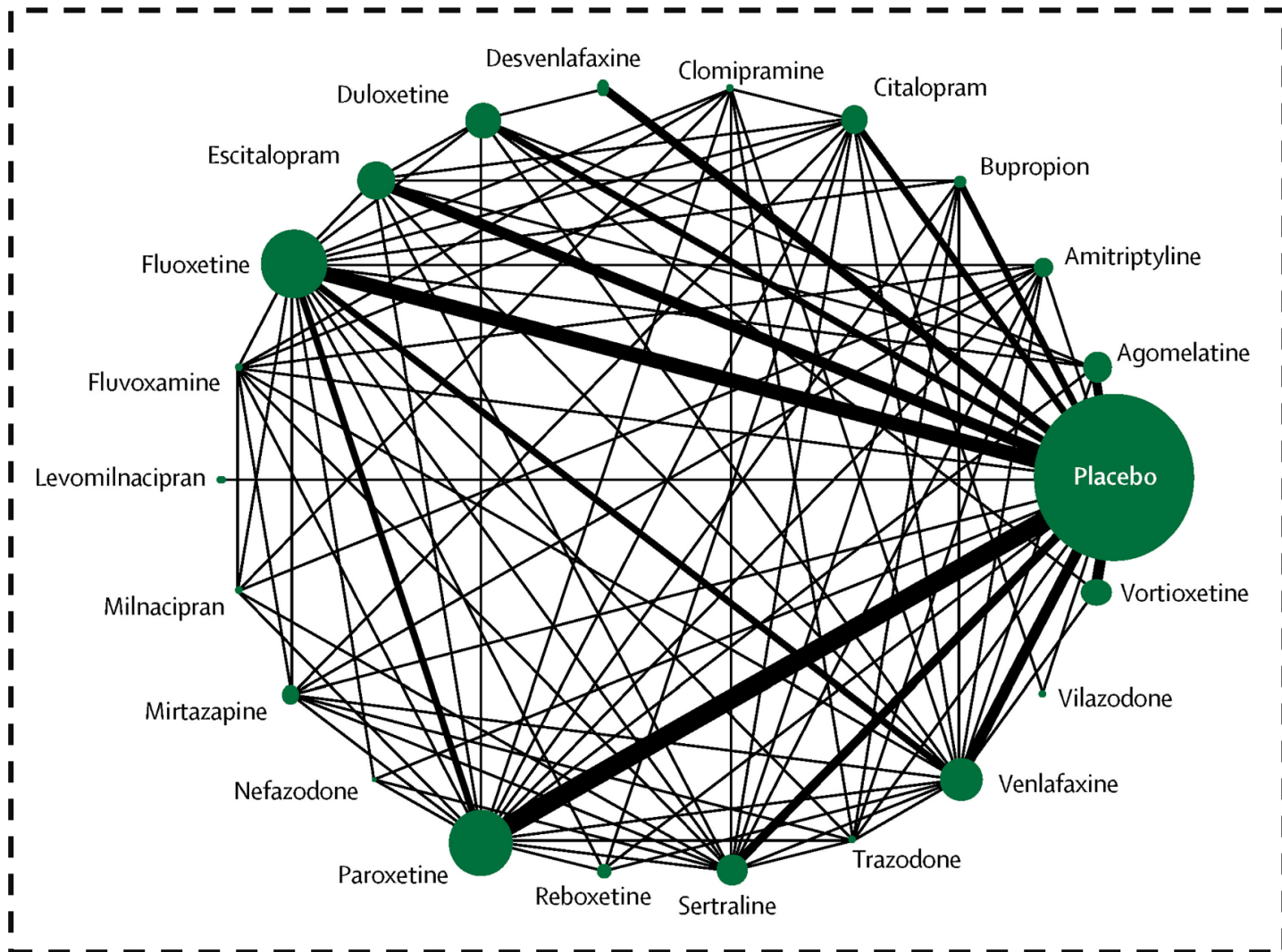
Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

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See [Comment](#) page 1333

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥ 18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the Cochrane Handbook for Systematic Reviews of Interventions, and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause). We estimated summary

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network meta-analysis (here, $n = 522$)



can make indirect inferences based on direct evidence, under the assumption of **transitivity**.

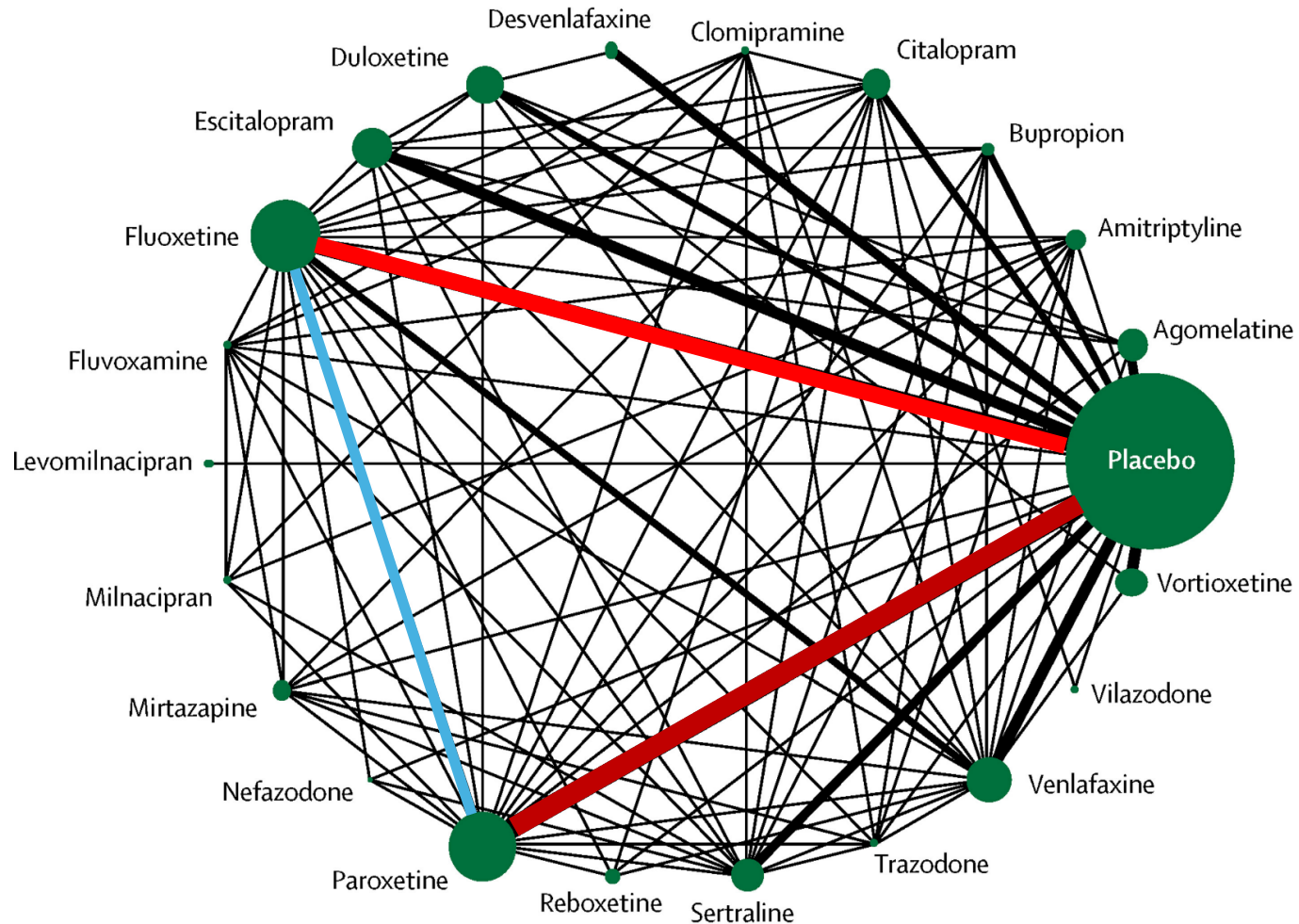
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network meta-analysis (here, $n = 522$)



can make indirect inferences based on direct evidence, under the assumption of **transitivity**.

this assumption is not needed by **conformal network meta-analysis**

$$\text{paroxetine} - \text{fluoxetine} = (\text{paroxetine} - \text{placebo}) - (\text{fluoxetine} - \text{placebo})$$