A Bayesian Approach to Left Main Disease – How has the Excel Trial moved the needle?

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Combined JGH-MUHC Cardiovascular Rounds

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Conflicts of Interest

- I have no known conflicts associated with this presentation and to the best of my knowledge, am equally disliked by all pharmaceutical and device companies

- As a non-interventionalist cardiologist, I have no direct skin in the PCI or CABG techniques

- But I do have a lot of skin in choosing the right revascularization technique for my patients

Before statistical inference

- Before statistical inference is considered, there are plenty of places where **study design** and **data collection** can go wrong
  - Is the **sample representative** of the population that we'd like to draw inferences about?
  - Is there a **pre-specified protocol** & has it been followed?
  - Are there **systematic biases** created by **selection**, **misclassification** or **missing data**?
  - Are there known and observed, known and unobserved or unknown and unobserved **confounding variables** that contaminate our conclusions, **unlikely** in well conducted RCT

Before statistical inference – a few buts (EXCEL)

- Designed non-inferiority trial **BUT** reported as a superiority trial @ 5 years
- Protocol listed 3rd Universal Definition MI (UDMI) as a secondary endpoint **BUT** not reported initially & claimed unavailable before finally releasing it 1 year after the original publication
- Independent authors **BUT** home institution of 8 (Cardiovascular Research Foundation) received $1 million donation from stent sponsor during study

Back to the beginning SYNTAX (2009)

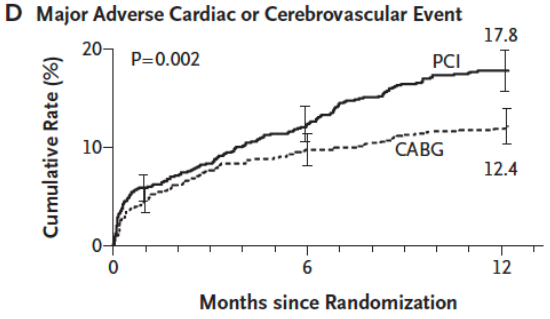
The NEW ENGLAND JOURNAL of MEDICINE

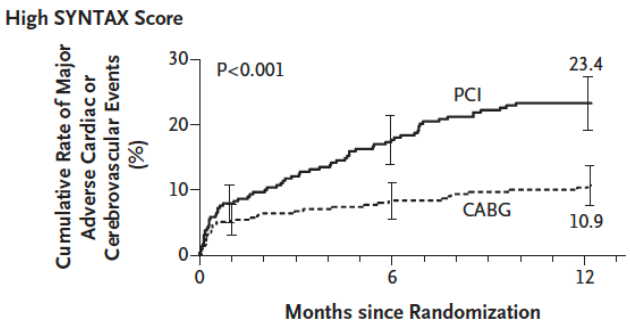
ESTABLISHED IN 1812 MARCH 5, 2009 VOL. 360 NO. 10

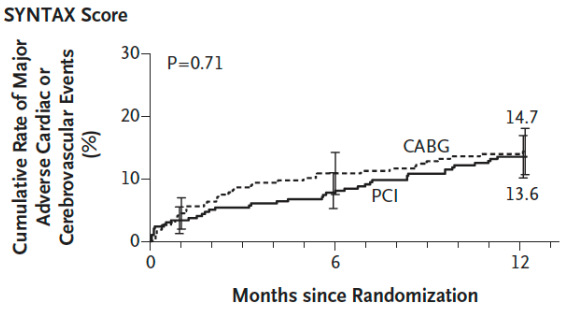
Randomized 1800 pt, 3VD or LM (705) to PCI or CABG

Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease

NI trial. If the one-sided 95% upper confidence limit for the difference was less than the prespecified delta value (6.6%), PCI with the drug-eluting stents would be considered to be noninferior to CABG in the overall randomized cohort. **Δ 5.4 95% CI (2.5-8.3)**







CONCLUSIONS

CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events at 1 year. (ClinicalTrials.gov number, NCT00114972.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2016 VOL. 375 NO. 23

Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

Prospective
SYNTAX < 32

margin 4.2%

RESULTS

At 3 years, a primary end-point event had occurred in 15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group (difference, 0.7 percentage points; upper 97.5% confidence limit, 4.0 percentage points; P=0.02 for non-

CONCLUSIONS

In patients with left main coronary artery disease and low or intermediate SYNTAX scores by site assessment, PCI with everolimus-eluting stents was noninferior to CABG with respect to the rate of the composite end point of death, stroke, or myocardial infarction at 3 years. (Funded by Abbott Vascular; EXCEL ClinicalTrials.gov number, NCT01205776.)

EXCEL 2019 – 5 year follow-up

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease

RESULTS

At 5 years, a primary outcome event had occurred in 22.0% of the patients in the PCI group and in 19.2% of the patients in the CABG group (difference, 2.8 percentage points; 95% confidence interval [CI], −0.9 to 6.5; P=0.13). Death from any cause occurred more frequently in the PCI group than in the CABG group (in 13.0% vs. 9.9%; difference, 3.1 percentage points; 95% CI, 0.2 to 6.1). In the PCI and CABG

CONCLUSIONS

In patients with left main coronary artery disease of low or intermediate anatomical complexity, there was no significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or myocardial infarction at 5 years. (Funded by Abbott Vascular; EXCEL ClinicalTrials.gov number, NCT01205776.)

Analyzed as a **superiority** trial
Ho: no difference between the 2 techniques
p > 0.05 -> Ho can't be rejected -> no Δ

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Analyzed as designed - **non-inferiority** (margin 4.2%)

Ho for NI: there is a meaningful difference (Δ) between the 2 techniques

p > 0.05 -> Ho can't be rejected –> **PCI is inferior to CABG**

P values < .05 ≠ true Δ

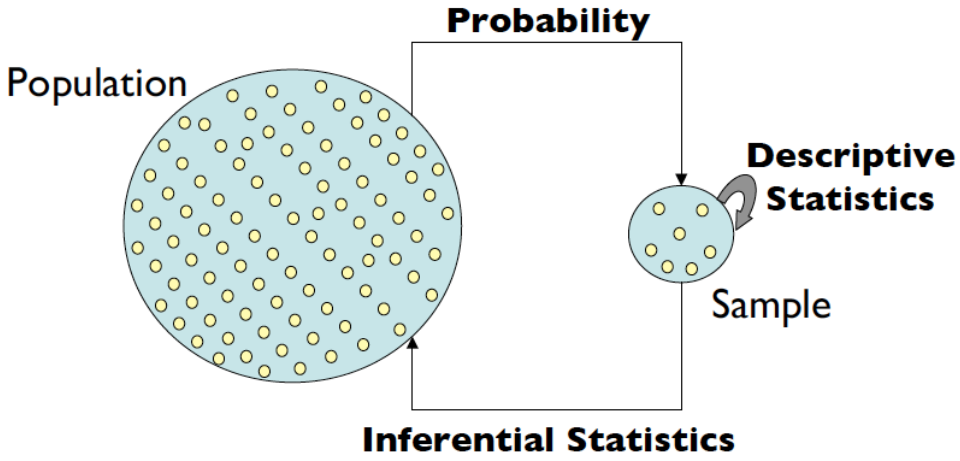
- Not very strong evidence (4 heads on 4 coin tosses)
- Dichotomization (binary) loses information -> incorrect decisions
- Puts excessive weight on null
- Doesn't consider effect size (confuses clinical vs. statistical significance)
- No consideration of prior information

P values > .05 ≠ absence of true Δ

- "Absence of evidence is not evidence of absence", could be power issue

Statistical Inference - Central Dogma of Statistics

- The process of generating conclusions about a study population from a sample, without it we're left simply within our data



- Inference should acknowledge
  - the "noise" or uncertainty in the sample
  - past or prior beliefs

Frequentist versus Bayesian

- Standard frequentist fix the working hypotheses &, by deduction, make inference on the observed data:
  - **Pr(Observed data | Hypothesis)** – drawbacks i) cannot use it to expand our knowledge beyond what is in the null hypothesis ii) can't make probabilistic statements about the hypotheses (as they are considered fixed elements of nature and do not possess probability distributions)

- Bayesian fixes the value of the observed data & by induction, make inference on unobservable hypotheses
  - **Pr(Hypothesis | Observed data)** - provides broader view of nature by allowing calculations of the probability of other competing hypotheses but drawback can't be sure that what we conclude about nature is actually true (David Hume & the problem of induction)

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P(T+ I D+) – Sensitivity of a test

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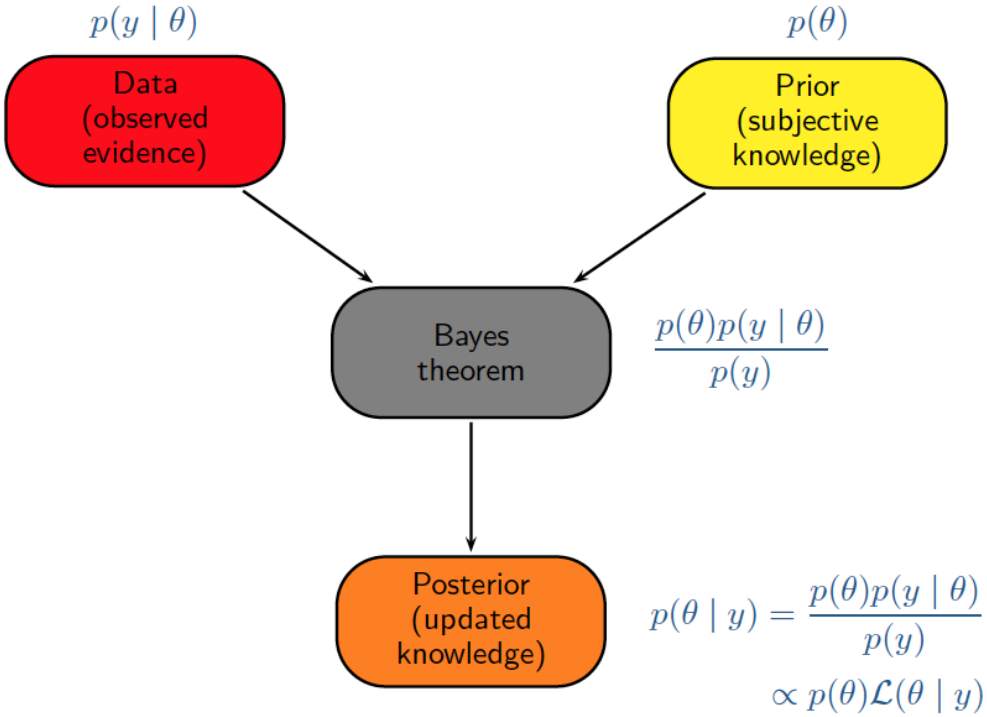
P(D+ I T+) – Predictive value of a test

Bayesian Benefits

- Provides desired answers
- Fundamentally sound, follows the rules of probability
- Intellectually coherent & intuitive -> clear and direct inferences
- Makes use of all available information -> allows flexible, allows complex models
- Emphasis on parameter estimation & uncertainty measures -> avoids inferential problems with p values
- Readily computed with modern computers
- My personal, but not universally shared, belief Bayesian perspective may provide additional insights into understanding a study & decision making

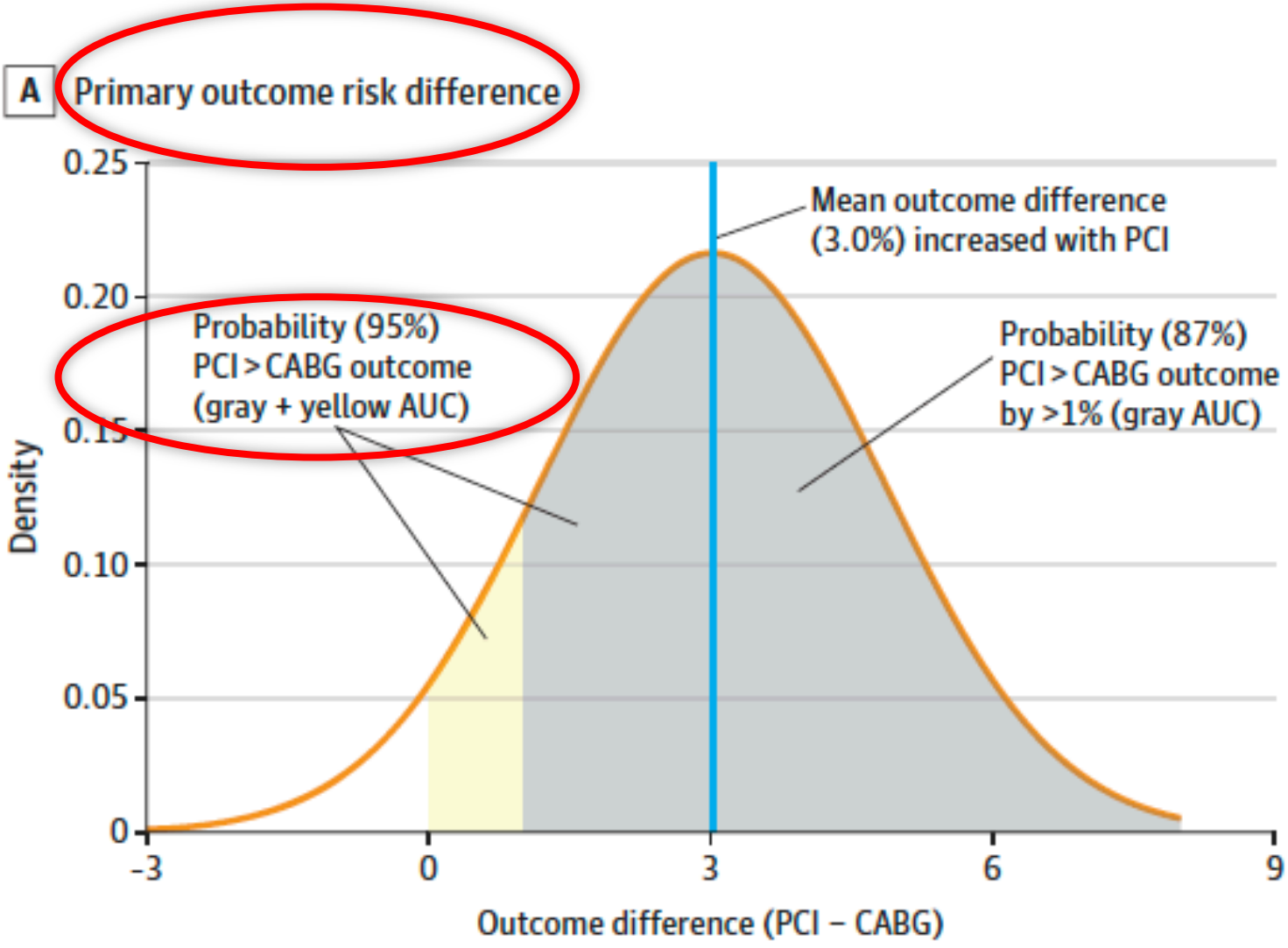
Bayesian Inference



- In identifiable problems as more data accumulates the subjective component diminishes and divergent opinions converge
- Patterns our sequential learning processes

"Today's posterior is tomorrow's prior"

Bayesian analysis – EXCEL alone (vague non informative prior)



JAMA Intern Med. doi:10.1001/jamainternmed.2020.1647
Published online June 1, 2020.

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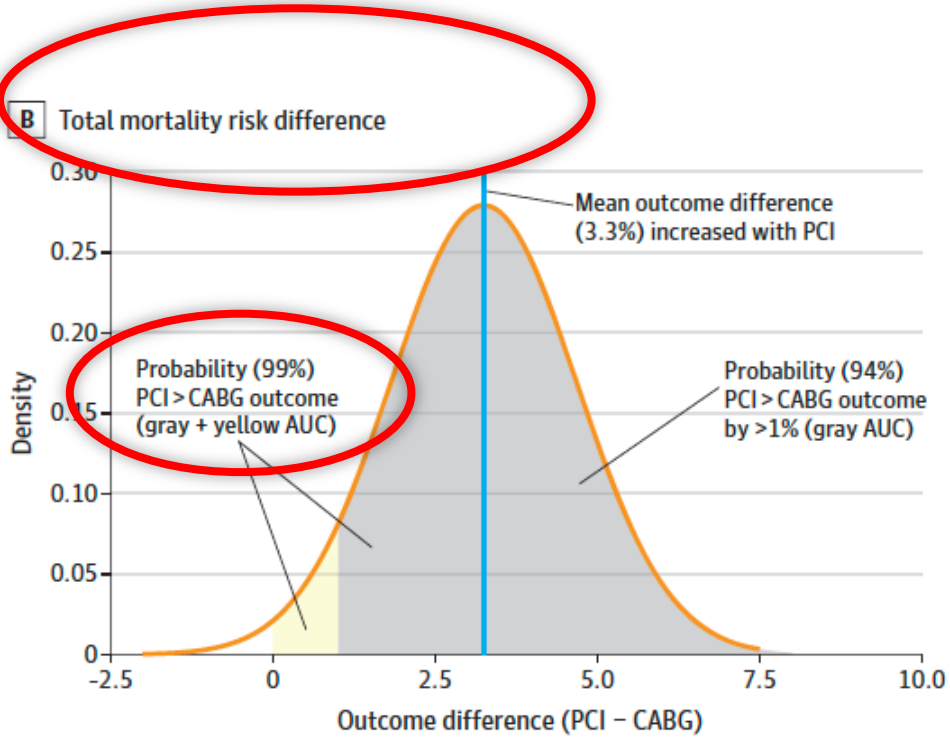
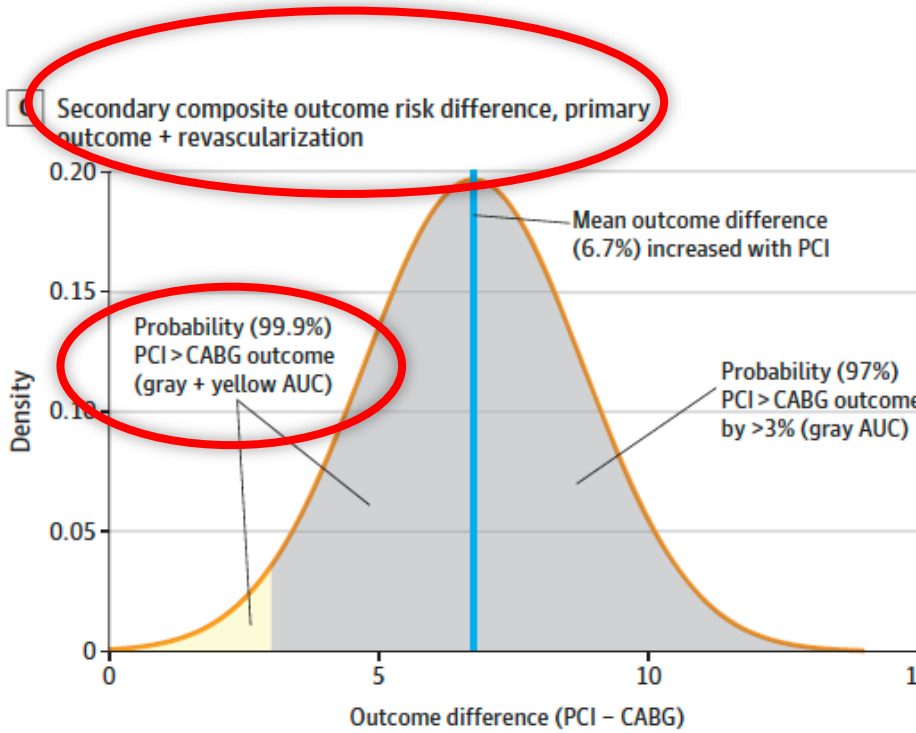
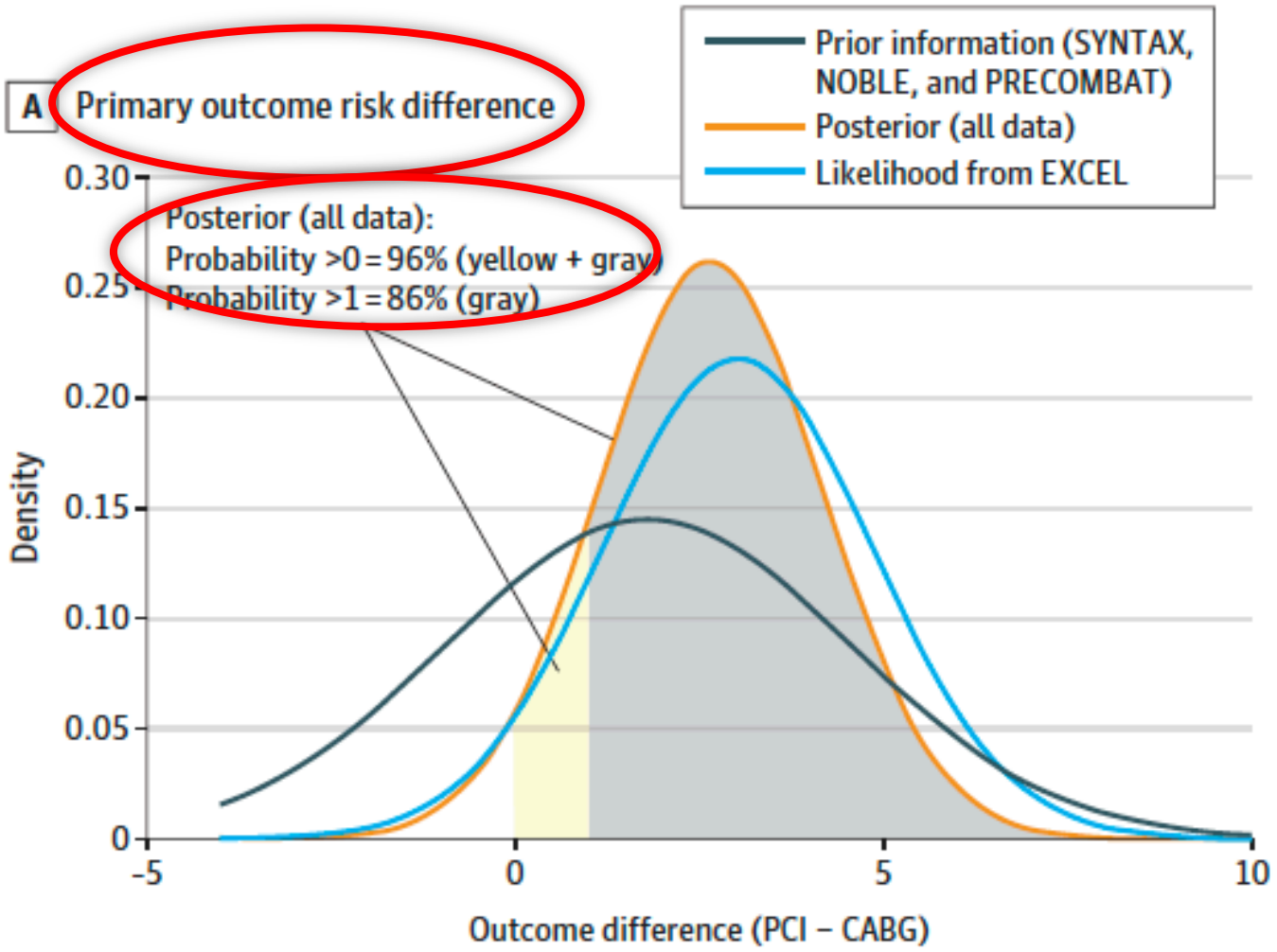




Bayesian analysis (informative prior)



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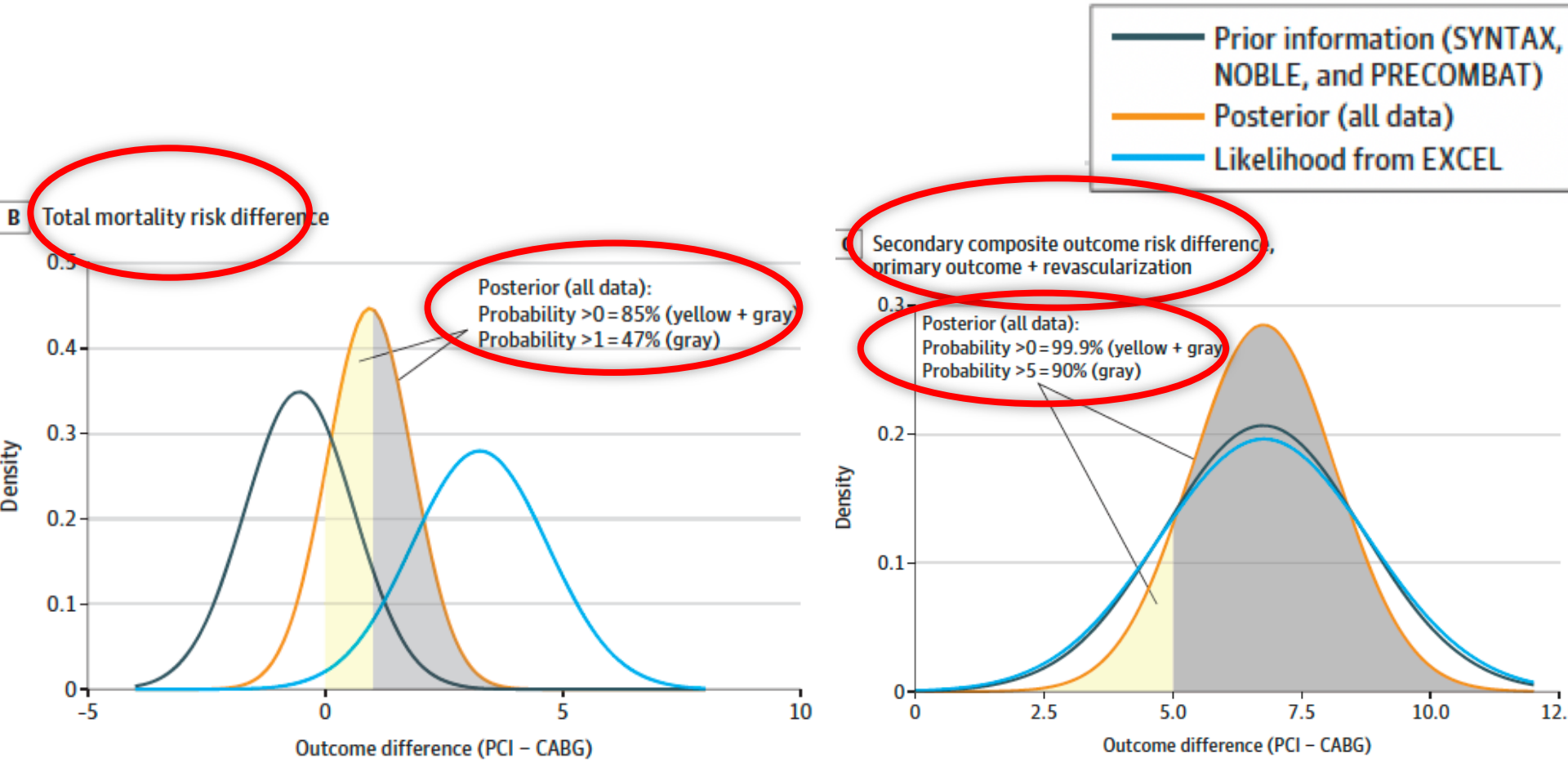


EXCEL – UDMI (July 2020)

NEJM July 16 2020

Table 1. Cumulative Incidence of Myocardial Infarction at 5 Years, According to Two Definitions.*

Outcome	PCI (N=948)		CABG (N=957)		Difference (95% CI)†
	Patients	Event Rate	Patients	Event Rate	
	no.	%	*no.*	%	*percentage points*
Protocol definition					
Procedural myocardial infarction	37	3.9	57	6.0	−2.1 (−4.1 to −0.2)
All myocardial infarction	95	10.2	84	9.0	1.2 (−1.5 to 3.9)
Third universal definition					
Procedural myocardial infarction	31	3.3	13	1.4	1.9 (0.5 to 3.3)
All myocardial infarction	89	9.6	43	4.7	4.9 (2.6 to 7.2)

- Protocol def'n **11** more MI with PCI
- UDMI definition **46** more with PCI

EXCEL 2020 – Standard Analysis (with 3rd UDMI data)

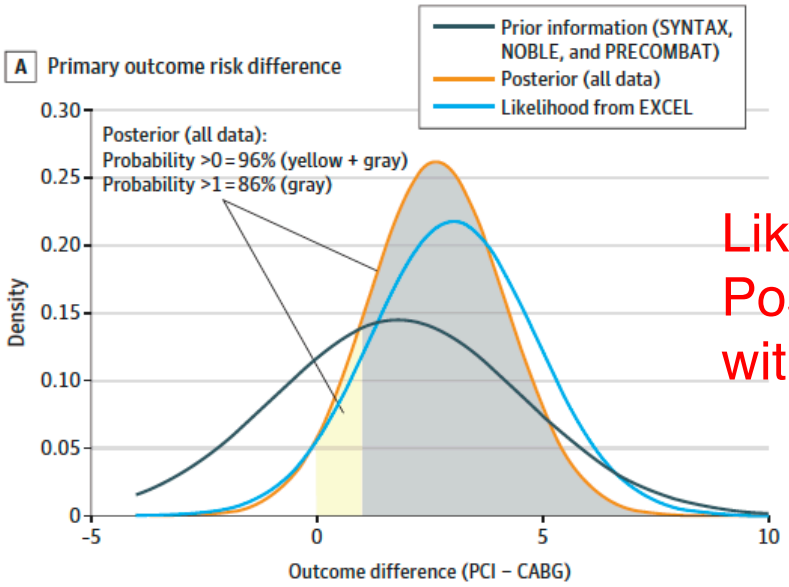
Table 1. Primary and Secondary Clinical Outcomes at 5 Years.*

Outcome	PCI (N=948)		CABG (N=957)		Difference in Event Rates (95% CI)	Odds Ratio (95% CI)
	Events	Event Rate	Events	Event Rate		
	no.	%	*no.*	%	*percentage points*	
Primary outcome	197	20.8	135	14.1	6.7 (3.1-10.2)	1.60 (1.26, 2.03)
Death, stroke, or myocardial infarction	~~203~~	~~22.0~~	~~176~~	~~19.2~~	~~2.8 (−0.9 to 6.5)~~	~~1.19 (0.95 to 1.50)~~
Secondary outcomes						
Death, stroke, myocardial infarction, or ischemia-driven revascularization	~~290~~	~~31.3~~	~~228~~	~~24.9~~	~~6.5 (2.4 to 10.6)~~	~~1.39 (1.13 to 1.71)~~
	284	30.0	187	19.5	10.5 (6.5-14.4)	1.76 (1.43, 2.18))

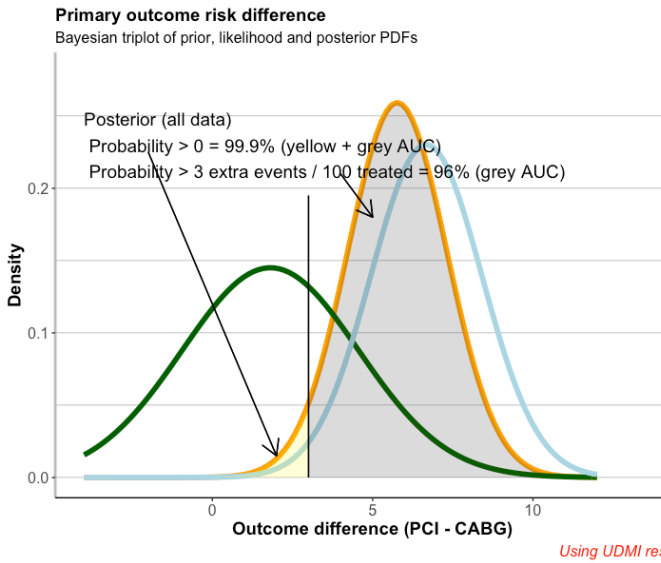
CONCLUSIONS

In patients with left main coronary artery disease of low or intermediate anatomical complexity, there was ~~no~~ significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or myocardial infarction at 5 years. (Funded by Abbott Vascular; EXCEL ClinicalTrials.gov number, NCT01205776.)

Bayesian primary outcome (with 3rd UDMI data)



Likelihood (EXCEL) & Posterior right shifted with UDMI data



96% probability more composite events (deaths, strokes or MIs) with PCI / 100 treated → 96% probability at least 3 more events

Conclusion

- EXCEL – certainly moved the "needle" (**shifted the curve**) but in the opposite direction that the authors have suggested!

CONCLUSIONS AND RELEVANCE Bayesian analysis assisted in RCT data interpretation and specifically suggested, whether based on EXCEL results alone or on the totality of available evidence, that PCI was associated with inferior long-term results for all events, including mortality, compared with CABG for patients with left main coronary artery disease.

- The above conclusion holds, **paribus ceteris**

- Individualization is still required & high surgical risk or with poor prognosis due to non-modifiable, non-cardiac causes may benefit from PCI choice

Thank you

- Slides available at
- https://www.brophyj.com/files/joint_rounds_sept30.pdf