U.S. FOOD & DRUG ADMINISTRATION

Statistical Analysis of Heplisav-B AMI Risk

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Overview

- Discussion of confidence interval approaches for relative risk of AMI for Heplisav-B vs. Engerix-B
- Alternative Bayesian analyses

Confidence Interval Approaches

- Several different possible methods for calculating relative risk confidence intervals
- Applicant's calculations use Wald method
  - Computationally simple
  - Conservative and perform poorly with very low event counts
- FDA calculated Koopman score intervals
  - Perform better here based on literature and simulations
  - Better in terms of coverage and power

Confidence Intervals for AMI Relative Risk

Study HBV-23	Events		RR	95% CI[A]	95% CI[B]
	Heplisav-B (N = 5587)	Engerix-B (N = 2781)			
MACE	28 (0.50%)	6 (0.22%)	2.32	(0.96, 5.60)	(0.99, 5.46)
CV death	3 (0.05%)	1 (0.04%)	1.49	(0.16, 14.35)	(0.21, 10.42)
AMI	14 (0.25%)	1 (0.04%)	6.97	(0.92, 52.97)	(1.17, 41.44)
Non-fatal stroke	11 (0.20%)	4 (0.14%)	1.37	(0.44, 4.30)	(0.46, 4.07)

A. Wald confidence interval (applicant's analysis)
B. Koopman score confidence interval (FDA analysis)

Confidence Interval Interpretation

- With prespecified safety outcomes:
  - Typically evaluated based on upper confidence limit
  - Level of risk “ruled out” by data
  - Lower confidence limit less relevant
  - Tests of the null hypothesis of no difference are underpowered with low event rates
- This is an unexpected safety finding
  - CIs difficult to interpret in this setting
  - Multiple testing
  - Regression to the mean

Overview of Bayesian Alternative

- We performed a simple Bayesian analysis of relative risk (RR) of AMI for Heplisav-B vs. Engerix-B
- Alternative to confidence interval analysis
- Advantages:
  - Can explore different levels of borrowing information from previous studies
  - Allows direct probability interpretations of what true RR is likely to be

Basics Of Bayesian Analysis

- Bayesian approaches synthesize existing data with new data to form updated probability distributions of the likely values of quantities of interest
- Existing data summarized in a *prior distribution*
- Result expressed as a *posterior distribution*
  - Posterior distributions are always a form of compromise between prior distribution and new data

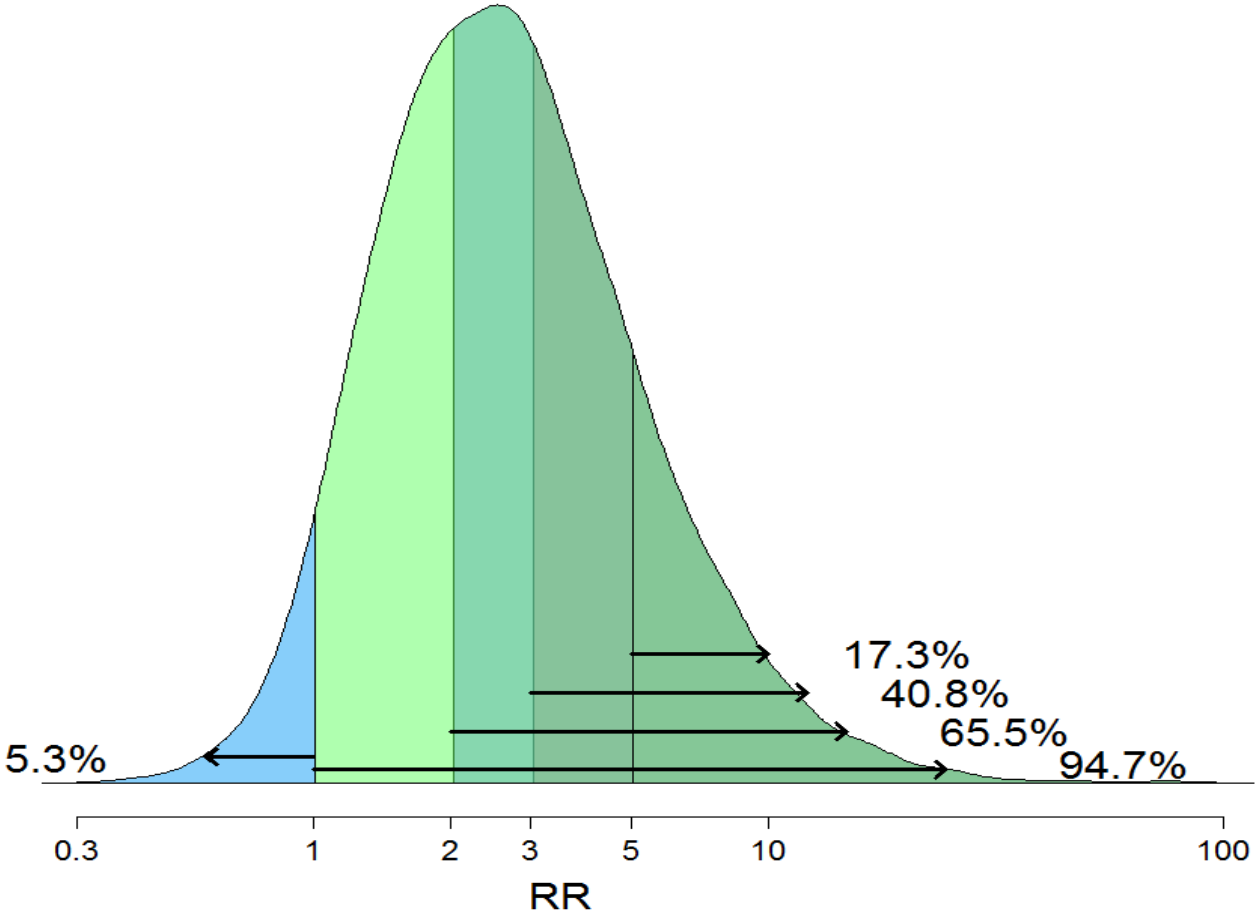
Heplisav-B Analysis

- We used studies HBV-10 and HBV-16 to form prior distributions of the risk of AMI for Heplisav-B and Engerix-B
- We updated the distributions using the data from study HBV-23 to form posterior distributions of the RR of AMI
- We are presenting two scenarios:
  - Full borrowing (equivalent to pooling all three studies)
  - No borrowing (i.e., only HBV-23 data contributes)
  - Other potential borrowing scenarios would fall in between

Data

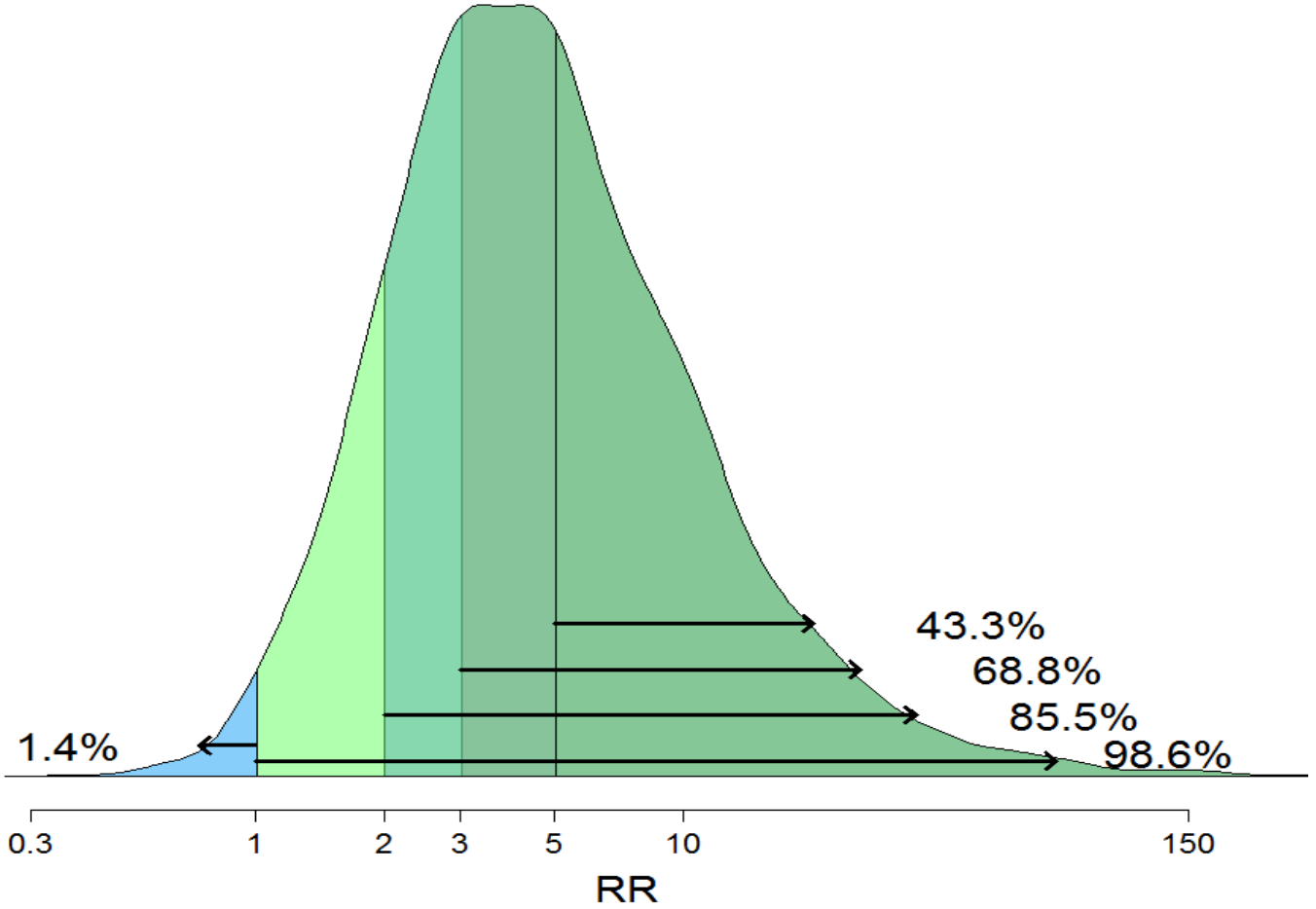
	HBV-23		HBV-16		HBV-10	
	Heplisav-B	Engerix-B	Heplisav-B	Engerix-B	Heplisav-B	Engerix-B
N	5587	2781	1968	481	1810	605
AMI events	14 (0.25%)	1 (0.04%)	2 (0.10%)	1 (0.21%)	0	0
Composite 3-point MACE events	28 (0.50%)	6 (0.22%)	3 (0.15%)	2 (0.42%)	0	0
Age (mean)	50.4	50.4	54.0	53.8	39.9	39.8
Type 2 Diabetes	13.6%	13.7%	8.0%	6.9%	2.4%	1.8%
Hypertension	36.2%	35.2%	29.4%	29.7%	11.7%	9.4%

Results From Full-Borrowing Scenario



Based on HBV-23, HBV-16 and HBV-10 data. The posterior probabilities that the RR is greater than 1, 2, 3, or 5 are 94.7%, 65.5%, 40.8%, and 17.3%, respectively.

Results From No-Borrowing Scenario



Based on HBV-23 data only. The posterior probabilities that the RR is greater than 1, 2, 3, or 5 are 98.6%, 85.5%, 68.8%, and 43.3%, respectively.

Posterior Probability Interpretation

- Results based on cumulative incidence data only
  - Similar to confidence interval analysis
- Does not take into account additional external factors
  - Temporality and other causal criteria
  - Regression to the mean
- Provides range of possible relative risk probabilities within the scope of what the event rates from the three pivotal studies provide in isolation from other considerations