BRIEF COMMUNICATION

Mortality Benefit of Alirocumab: A Bayesian Perspective

Christopher Labos, MDCM, MSc; James M. Brophy, MD, PhD; Allan Sniderman, MD; George Thanassoulis, MD, MSc

***Background*—**The ODYSSEY OUTCOMES (Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome) trial demonstrated that alirocumab reduced major cardiovascular events. However, because of the hierarchical testing strategy used for the multiple outcomes examined, the observed reduction in all-cause mortality was labeled "nominally significant" which has clouded its interpretation.

***Methods and Results*—**We re-analyzed data from ODYSSEY OUTCOMES using Bayesian methods and generated various prior probabilities by incorporating mortality data from previous similar PCSK9 (proprotein convertase subtilisin–kexin type 9) inhibitor trials. We first used data from the ODYSSEY OUTCOMES trial with a non-informative prior, then sequentially added data from ODYSSEY LONG TERM and the FOURIER trial, giving FOURIER full weight, 50% weight and 10%. The posterior probability of a mortality reduction using only the ODYSSEY OUTCOMES data was hazard ratio 0.85 (95% CI 0.74–0.99) which corresponded to a 98.4% probability of a mortality benefit. When the ODYSSEY LONG TERM data were added to the analysis, the posterior probability was hazard ratio 0.84 (95% CI 0.72–0.97) with a 99.9% probability of mortality reduction, and when the FOURIER data were added to the analysis the posterior probability was hazard ratio 0.94 (95% CI 0.85–1.04) with an 89.1% probability of a mortality reduction. When the FOURIER trial was given only 50% or 10% weight, the probability of a mortality reduction rose 95.4% and 98.7%, respectively. We estimate that the probability of >1% absolute risk reduction ranges from 8% to 24%, while the probability of >0.5% absolute risk reduction ranges from 66% to 89%.

***Conclusions*—**Our analysis demonstrates a high likelihood that alirocumab confers a reduction in all-cause mortality, despite the equivocal interpretation of the data in the original ODYSSEY OUTCOMES publication. **(*J Am Heart Assoc*. 2019;8:e013170. DOI: 10.1161/JAHA.119.013170.)**

Key Words: Bayesian • cholesterol • mortality • PCSK9

The publication of the ODYSSEY OUTCOMES (Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome) trial[1] demonstrated that the PCSK9 (proprotein convertase subtilisin–kexin type 9) inhibitor (PCSK9i) alirocumab reduced major cardiovascular events. However, because of the hierarchical testing strategy used for the multiple outcomes examined, the observed reduction in all-cause mortality was labeled "nominally significant" which has clouded its interpretation.

Bayesian analysis allows direct estimation of the probability of a given outcome and is not encumbered by concerns about null hypothesis testing (eg, type 1 errors). By updating prior data (ie, prior probability) with current results (ie, likelihood), Bayesian methods naturally and intrinsically permit synthesis of all available evidence allowing more precise and potentially less biased effect estimates (ie, posterior probability).[2] Importantly, the posterior probability allows clinicians to directly determine not only the probability of any mortality benefit, but also the probability that this exceeds any clinically interesting difference, for example a 0.5% or 1% absolute mortality difference.

Methods

To cover the range of varying prior probabilities, we generated various prior probabilities using mortality data from previous similar PCSK9i trials. We first used data from the ODYSSEY OUTCOMES trial with a non-informative before generate a posterior probability and the probability of a mortality reduction. Non-informative priors provide little a priori information and consequently a Bayesian posterior probability using a non-informative prior will yield a result that is numerically similar to the frequentist analysis, ie, the published result from the ODYSSEY OUTCOMES trial. However, with Bayesian statistics one can determine the actual probability of the result being true, whereas with frequentist statistics one can only establish, if the

From the McGill University Health Center, Montreal, Canada.

Correspondence to: Christopher Labos, MDCM, MSc, Preventive and Genomic Cardiology, McGill University Health Center, 1001 Decarie Blvd, D5-5120 Montreal, QC H4A 3J1, E-mail: christopher.labos@mail.mcgill.ca

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Table. Posterior Probability of Mortality Benefit Given 4 Different Prior Probabilities

Source of Data	Mortality Data		Posterior Probability	Probability Mortality Treatment < Control	Probability Mortality Reduction >1%	Probability Mortality Reduction >0.5%
	Treatment Arm	Control Arm				
ODYSSEY outcomes	334/9462	392/9462	HR 0.85 (95% CrI 0.74–0.99)	98.4%	8%	66%
+ ODYSSEY LONG TERM	8/1542	10/778	HR 0.84 (95% CrI 0.72–0.97)	99.2%	24%	89%
+ FOURIER	444/13 784	426/13 780	HR 0.94 (95% CrI 0.85–1.04)	89.1%	<0.1%	8.2%
+ FOURIER (50% weight of trial)			HR 0.91 (95% CrI 0.81–1.02)	95.4%	0.01%	38%
+ FOURIER (10% weight of trial)			HR 0.85 (95% CrI 0.74–0.98)	98.7%	11%	81%

HR indicates hazard ratio; CrI, Credible Interval.

hypothesis being tested were false, what would be the probability of observing the data obtained.

For ODYSSEY OUTCOMES we generated a normal distribution centered on the log-transformed point estimate published in the trial, namely the hazard ratio 0.85 (95% CI 0.78–0.93). The non-informative prior in this case was a normal distribution with a wide variance of 1 000 000. Using the properties of conjugate priors, these 2 distributions were combined into the posterior distribution.

Subsequent steps followed the same pattern. We sequentially added data from ODYSSEY LONG TERM[3] and the FOURIER trial,[4] which used evolocumab, giving FOURIER full weight, a 50% and then a 10% weight. Using partial weights allows for a statistical compromise: the prior data from FOURIER are not given full weight when applied to the current trial (since this trial used a different molecule) nor is it dismissed entirely.[5] This weighting was achieved by multiplying the variance of the data distribution. For example, doubling the variance provides a 50% weight.

We were able to calculate the absolute risk reduction by using the number of deaths in each of the treatment and controls arms reported trials. By generating a beta distribution using these data, we used the same sequential Bayesian process described above. We started with a beta (1,1) non-informative prior which was added to the ODYSSEY OUTCOMES data, and then sequentially added data from ODYSSEY LONG TERM and the FOURIER trial at full, 50%, and 10% weighting.

Using the beta distributions in this way allowed us to calculate the probability of a 1% and 0.5% mortality reduction on the absolute scale, equivalent to a number needed to treat of 1 in 100 or 1 in 200, respectively.

Results

In the ODYSSEY OUTCOMES trial, all-cause mortality was 3.5% for alirocumab versus 4.1% for placebo. The probability of a mortality reduction using only the ODYSSEY OUTCOMES data was 98.4% and rises to >99% when data from the ODYSSEY LONG TERM were sequentially added to the analysis. The probability of >1% absolute risk reduction ranged from 8% to 24%, while the probability of >0.5% absolute risk reduction ranged from 66% to 89% (Table).

Discussion

This Bayesian analysis demonstrates a high likelihood that alirocumab confers a reduction in all-cause mortality, despite the equivocal interpretation of the data in the original ODYSSEY OUTCOMES publication.[1] When considering the data from both molecules on the market, the probability of a mortality reduction with PCSK9 inhibition is high. Although there remains considerable uncertainty for >1% absolute mortality difference in mortality, the probability of >0.5% mortality difference (number needed to treat, 1 in 200) is high and potentially clinically relevant. Further research will be needed to determine the economic relevance of these benefits.

An advantage of Bayesian analysis is that it allows us to incorporate data from multiple trials and use different priors and weights to simulate how different clinicians might weigh the data. For example, some clinicians, citing the similar mechanism of action between alirocumab and evolocumab, would give the FOURIER data more weight, whereas others may give them less weight since they are similar but distinct molecules. This difference in opinion can be formally expressed in a Bayesian analysis, as performed here, and represents an advantage of such an approach. It is also consistent with how individuals naturally incorporate new information, using the totality of the available evidence.

Bayesian analysis also allows us to directly estimate the probability that alirocumab reduces all-cause mortality without concern for multiple testing and type 1 error. Therefore, Bayesian analysis overcomes the potential confusion caused by the hierarchical testing strategy used in the ODYSSEY OUTCOMES trials to limit type 1 error (ie, false positives), which involves testing multiple end points in a predetermined

sequence and stopping when the first non-significant result appeared. In our opinion, this non-standard approach, which may not adequately control for type 1 error, is prone to misinterpretation.

In summary, we demonstrate that although Bayesian analysis requires additional inputs (ie, prior data) and different assumptions than frequentist methods, it also provides additional clarity to the interpretation of the ODYSSEY OUTCOMES mortality data and avoids some of the interpretation problems that can arise with frequent analysis. Our Bayesian estimates of the probability that alirocumab reduces total mortality provide an answer to one of the more important clinical questions that concerns the majority of practitioners and payers.

Disclosures

Dr Thanassoulis has received personal fees as part of advisory boards and speaker bureaus for Sanofi/Regeneron, Amgen, Boehringer-Ingelheim, and Servier and has received research grants from Servier and Ionis. The remaining authors have no disclosures to report.

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