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Efficacy of Colchicine in Coronary Disease: Bayesian Analysis and Null-Hypothesis Testing

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Abstract

Background: Colchicine has emerged as an effective therapy for coronary artery disease (CAD). Existing evidence relies on frequentist methods for statistical inferences. However, Bayesian statistics offer a complementary and alternative approach that enhances understanding of the evidential strength, thereby facilitating clinical decision-making.

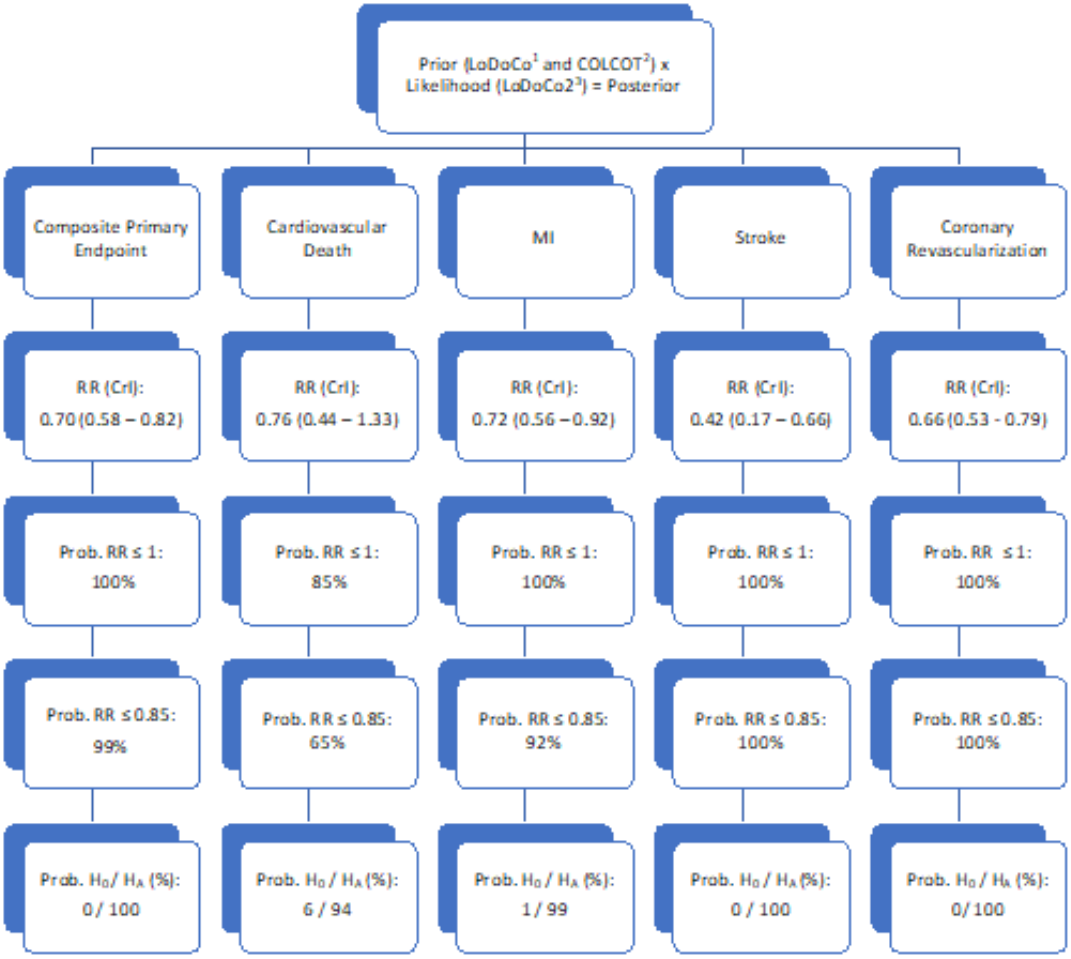
Objectives: To use Bayesian methods to analyze the efficacy of colchicine compared to placebo in patients with CAD

Methods: We analyzed LoDoCo2 trial's primary composite and individual endpoints using an informative prior derived from the LoDoCo and COLCOT trials. We employed a conjugate normal analysis to integrate prior and likelihood information, sensitivity analyses to assess the impact of various prior weights on posterior probability distributions and Bayes factor to quantify the strength of evidence against H0.

Results: The Bayesian analysis of LoDoCo2 primary endpoint estimated a mean posterior RR (95% credible interval) of 0.70 (0.58 - 0.82), a 100% probability of colchicine reducing this outcome compared with placebo and a 99% probability of at least 15% reduction. High probabilities (100%) of reduced risk (RR ≤ 1) with colchicine were observed for most individual endpoints, while the probability was 85% for cardiovascular death. Bayes factor analyses showed strong support for differences between colchicine and placebo for most endpoints, with low posterior probabilities (0% to 2%) supporting the null hypothesis (H0). The posterior probability of H0 being true for cardiovascular death ranged from 6% to 9%.

Conclusions: Bayesian analyses confirm substantial risk reductions and high probabilities of benefit with colchicine, underscoring its compelling efficacy in the secondary prevention of cardiovascular events in patients with CAD.

Keywords: Bayesian Analysis; Colchicine; Secondary Prevention; Coronary Artery Disease



[1]LoDoCo: Low-dose colchicine for secondary prevention of cardiovascular disease; [2]COLCOT: Efficacy and safety of low- do se colchicine after myocardial infarction; [3]LoDoCo2: Colchicine in patients with chronic coronary diseaseCAD: coronary artery disease; Crl: credible interval; H_0: null hypothesis, H_A: alternative hypothesis; MI: myocardial infarction: Prob.: probability; RR: risk ratio

Graphical Illustration

Introduction

Inflammation is a critical factor in atherosclerosis, contributing to ischemic complications in cardiovascular diseases [1-3]. Colchicine, an established anti-inflammatory drug used for gout [4-6] and rheumatic diseases [7,8], has shown promise in cardiovascular therapy by suppressing specific cytokines associated with inflammation [9]. Randomized controlled trials (RCTs) demonstrated this anti-inflammatory effect to reduce the incidence of adverse cardiovascular events in patients with acute coronary syndrome and stable coronary disease [10-12].

In the Colchicine Cardiovascular Outcomes Trial (COLCOT, 4745 participants) [10] and the Low Dose Colchicine trial-2 (LoDoCo2, 5522 participants) [11], the incidence of the primary endpoint was lower with colchicine 0.5 mg once daily than with placebo. The hazard ratio in COLCOT [10] was 0.77 (95% confidence interval [CI], 0.61 – 0.96), and in LoDoCo2 [11] was 0.69 (95% CI: 0.57 – 0.83). The incidence of all the individual endpoints was also lower with colchicine compared to placebo. Using a traditional statistics line of thought, the difference between colchicine and placebo was statistically significant for the primary and most of the individual endpoints, to the exception of myocardial infarction (MI) and cardiovascular (CV) death in COLCOT [10] and ischemic stroke and CV death in LoDoCo2 [11].

Like most medical research, these trials were analyzed using frequentist methods, which rely on p-value and null hypothesis testing (HT) for statistical inference. However, the p-value and HT have increasingly become subjects of criticism in the medical literature [13-20]. Commonly dis-

cussed issues include: 1) the misinterpretation of the p-value as equivalent to the chance of a false-positive error, 2) the arbitrary cut-off value of p ($0.05 \leq p < 0.05$) to determine the validity of the null hypothesis (H_0), 3) the tendency to use the p-value to estimate the effect size or as a probability of H_0 being true. These problems contribute to a profound misunderstanding of RCT data, potentially harming clinical decision-making.

Confidence intervals (CIs) have been proposed as a potential remedy for these challenges. CIs represent the measure of uncertainty around effect estimates [21-25]. However, they, too, have been the object of misinterpretations. They are often misconstrued as a surrogate for HT, which hinders a proper discussion on the interval's values, precision, and practical implications. Nonetheless, CIs are seen as a step in the right direction as they offer a more informative perspective on the range of effects.

Bayesian methods are promoted as an alternative or supplement to the frequentist paradigm. These approaches offer a probabilistic interpretation of data and hypothesis testing that aligns more closely with medical reasoning. Several studies [26-32] on Bayesian methods for statistical inference in medical research have been published to guide researchers and demonstrate their use for analyzing a new trial or the reanalysis of completed trials. Here we have analyzed the primary endpoint of LoDoCo2 [11] and its components while accounting for prior evidence from LoDoCo [12] (Low-dose colchicine for secondary prevention of cardiovascular disease) and COLCOT [10]. Additionally, we derived probabilities associated with various benefit thresholds for each endpoint. We also utilized Bayes factor calculations to obtain a quantitative evaluation of the evidence for and against the hypothesis of independence. This multifaceted analysis aimed to offer a thorough and comprehensive perspective on the robustness of the evidence regarding the efficacy of colchicine in coronary artery disease (CAD).

Methods

Key Points on Bayesian Methods

Bayesian methods are based on Bayes' rule, a mathematical expression defining the relationship between conditional probabilities. In Bayesian statistics, the prior distribution represents what is known or assumed about a parameter before considering the current data. It is an essential component of Bayes' theorem, which updates this prior belief in light of new evidence to form the posterior distribution. In notation: "prior odds x likelihood = posterior odds" or in probabilities: $p(A|B) = p(B|A) \times p(A)$.

The prior can be based on previous studies, expert knowledge, or any other relevant information. The choice of prior strongly influences the calculation of posterior odds. It can be informative or non-informative. A non-informative or vaguely informative prior may be modelled when no prior knowledge is available. In such instances, the posterior estimates will align with those obtained through traditional statistical methods. Varying the prior's mean and SD allows for the representation of different beliefs in data strength. When prior knowledge of the parameters' value exists, an informative prior may be mathematically defined and integrated into the calculations of posterior probability densities of effect size.

In Bayesian methods, credible intervals are the Bayesian equivalent of confidence intervals in frequentist statistics. They provide a range of values within which the parameter is believed to lie with a certain probability and are derived from the posterior distribution, which combines the prior distribution and the likelihood of the observed data.

Another concept of Bayesian inference is the Bayes factor. It is a measure used to compare how well two competing hypotheses predict the data. It is the likelihood ratio of the probability of the data under the null hypothesis to the probability of the data under the alternative hypothesis.

If the Bayes factor is structured such as the likelihood of the null hypothesis is in the numerator and the likelihood of the alternative hypothesis is in the denominator then a smaller Bayes factor means less support for the null hypothesis. When the evidence for the best-supported hypothesis is put in the denominator the resulting ratio is the smallest possible Bayes factor with respect to the null hypothesis. This minimum Bayes factor or minimum likelihood ratio may serve as a benchmark against which to compare the P value.

Data Sources and Outcomes Measures

We utilized findings from previously published systematic literature reviews and meta-analyses [33,34] to identify relevant prior evidence. We excluded Deftereos [35] (2013) due to its focus on a distinct patient population (diabetic patients undergoing percutaneous coronary). Additionally, we omitted COPS [36] due to notable limitations, including lack of statistical power, possible reporting bias, post hoc analysis of CV mortality, and lack of complete patient's data over the planned 365 days after randomization.

Hence, LoDoCo [12] and COLCOT [10] formed the prior for our Bayesian re-analysis of LoDoCo2 [11] (likelihood). While these trials varied in certain aspects, notably in the timing of enrollment (30 days after an acute MI vs. six months after), they uniformly assessed the low dose of colchicine (0.5 mg od) effect in secondary prevention of CV complications.

Given the absence of individual site data and time--to-event data, we used the pooled number of events of the primary composite outcome and its component in each arm of the trials. These proportions enabled the calculations of risk ratios (RR) and their credible intervals (CrI) or their Gaussian transform on a logarithmic scale. The analysis excluded cardiac arrest as it was not a shared endpoint. Despite differing definitions of coronary revascularization and stroke, we deemed them similar enough to justify a joint analysis.

Data Analysis

Given the normal distribution of both the prior and the likelihood, we employed a conjugate normal model to integrate the estimates from the prior with those derived from LoDoCo2 [11]. This process enabled the creation of weighted posterior inferences [37] for the primary endpoint and its components. We conducted sensitivity analyses by assigning weights to the prior, ranging from 50%, 25%, and 10%. These allocations corresponded to a spectrum of beliefs in LoDoCo [12] and COLCOT [10] data —neutral, skeptical, or pessimistic—reflecting different degrees of acceptance, with 100% indicating complete endorsement. These analyses yielded posterior distributions for the effect size and probabilities across various benefit thresholds.

Bayesian Hypothesis Testing

We evaluated the strength of H_0 using Bayes factors (BF) [38,39], defined as the ratio of the probability of the observed data under one hypothesis to its probability under another hypothesis. The minimum BF (min BF = $e^{-Z2/2}$), indicating the smallest evidence supporting H_0 based on the data, was computed for the likelihood, and analyzed with prior odds of H_0. Two regions of practical equivalence (ROPE) were tested in the model: $0.85 \leq RR \leq 1.15$ and $0.90 \leq RR \leq 1.10$. These intervals were selected based on the concept of clinical meaningfulness, wherein an effect size within these ranges would have negligible or minimal clinical significance. The posterior probabilities of H_0 and the alternative hypothesis (H_A) were generated considering the min BF and prior odds of H_0 within a ROPE. The discrete categories table proposed by Jeffrey [39] was used to interpret min BF values.

Software

All computations were made using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). We used the "rma" function in the R "metafor" package [40] to conduct a random-effects meta-analysis of the prior with a restricted estimation of maximum likelihood. The computation of weighted posterior RR means and variances of the conjugate analysis were programmed in R, as was that of min BF using the formula: min BF = $e^{-Z2/2}$. The "pnorm" function was used to generate data for the probability density functions.

Results

As highlighted in the methods section, modelling a non-informative prior in conjunction with LoDoCo2 [11] data yields estimates that closely align with traditional statistics. It is essential to emphasize that the focus of this report was the analysis of LoDoCo2 [11] data in light of existing evidence.

A key strength of Bayesian methods lies in their ability to integrate new trial data with prior knowledge, enabling the generation of a posterior probability distribution for the effect size. Table 1 provides the mean posterior RR, the 95% CrI, and risk probabilities for the primary com-

posite and the individual endpoints.

For the primary composite endpoint, the conjugate analysis of the prior with LoDoCo2 [11] data yielded a mean posterior RR (95% CrI) of 0.70 (0.58 - 0.82). There was a 100% probability that the primary endpoint was decreased with colchicine compared to placebo. Moreover, there was a 99% probability that this reduction was at least 15%.

Likewise, the mean posterior RRs for individual endpoints consistently fell below 1, indicating a lower risk with colchicine compared to placebo. Notably, there was a 100% probability that each endpoint was decreased with colchicine. The exception was an 85% probability of a reduced risk of CV death. Furthermore, there was a 100% probability that the risk reduction of stroke and coronary revascularization was at least 15% (Table 1).

Table 1: Mean posterior RR (CrI) and probabilities of risk for the primary composite and individual endpoints

Endpoint	RR (CrI)	Prob. (%) risk null	Prob. (%) risk reduction of at least 10%	Prob. (%) risk reduction of at least 15%
Primary	0.70 (0.58 - 0.82)	100	100	99
CV Death	0.76 (0.44 – 1.33)	85	73	65
MI	0.72 (0.56 – 0.92)	100	97	92
Stroke	0.42 (0.17 – 0.66)	100	100	100
Coronary Revascularization	0.66 (0.53 - 0.79)	100	100	100

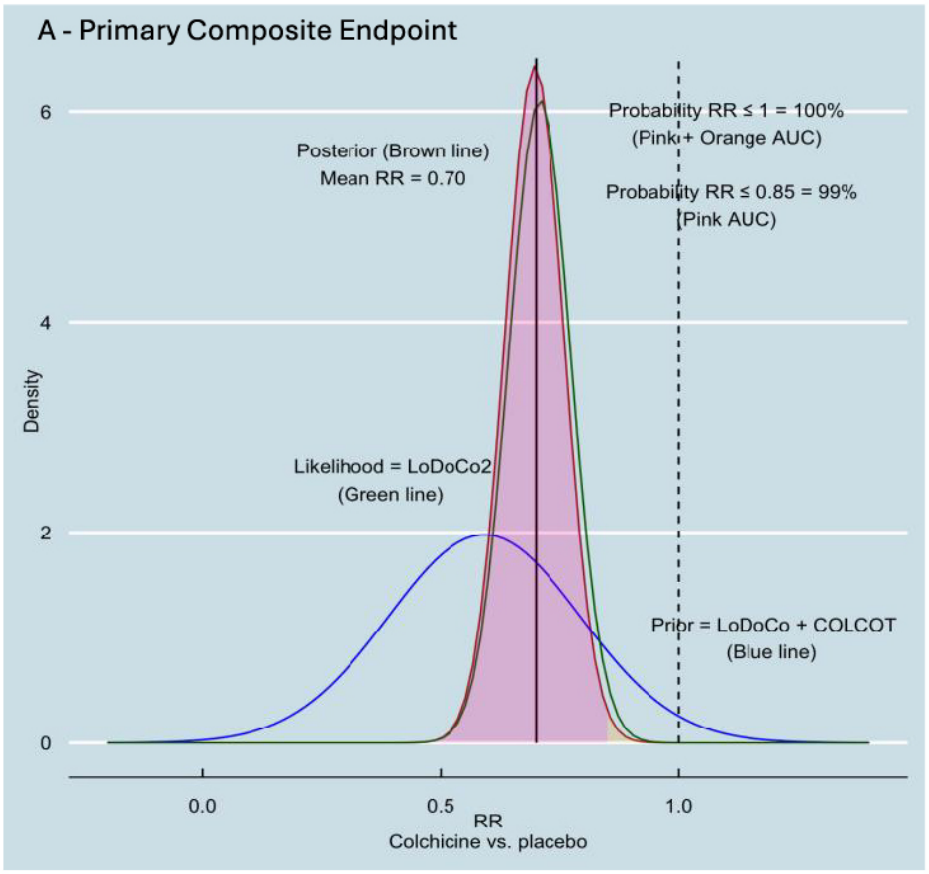
CrI: credible interval; CV: cardiovascular; MI: myocardial infarction; Prob.: probability; RR: risk ratio

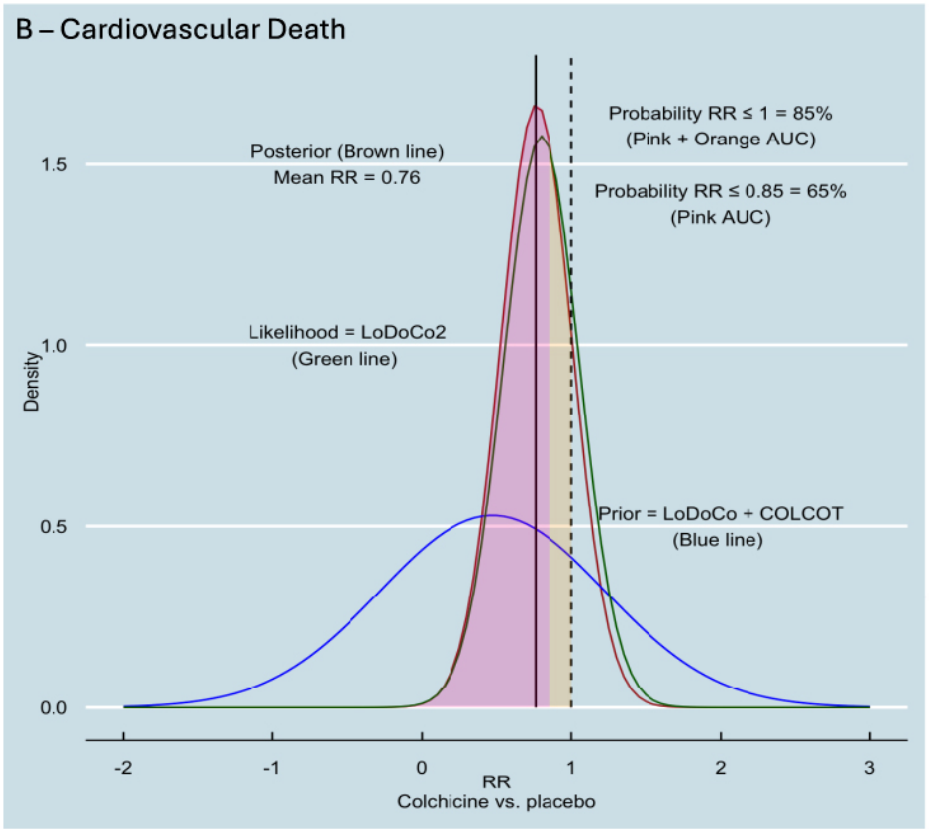
Influence of the Prior and Likelihood on the Posterior Distributions

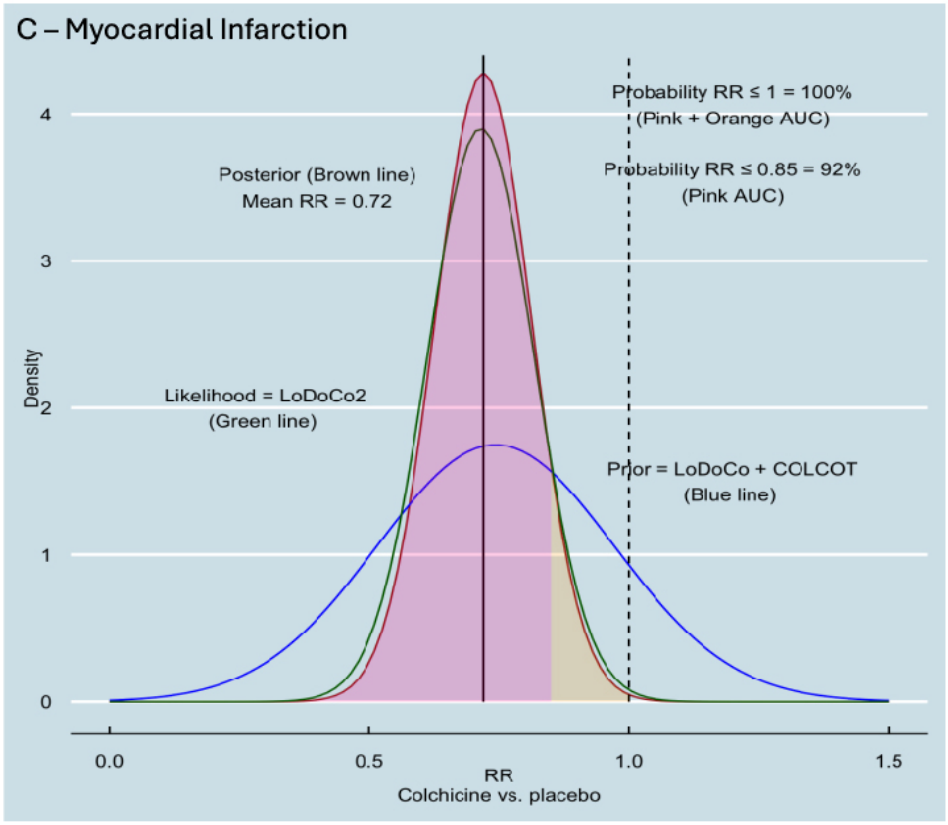
To assess the impact of the prior and likelihood on the posterior probability distribution of the effect size, we evaluated the information contributed by each component in our analysis. Given that the posterior distribution is a weighted average of the prior and likelihood, understanding each component's precision (inverse of variance) is crucial. However, as there was a lack of detailed event data by site, our analyses utilized variances derived from aggregated data from the LoDoCo2 [11], LoDoCo [12] and COLCOT [10] trials, leading to potential underestimation of between-studies heterogeneity.

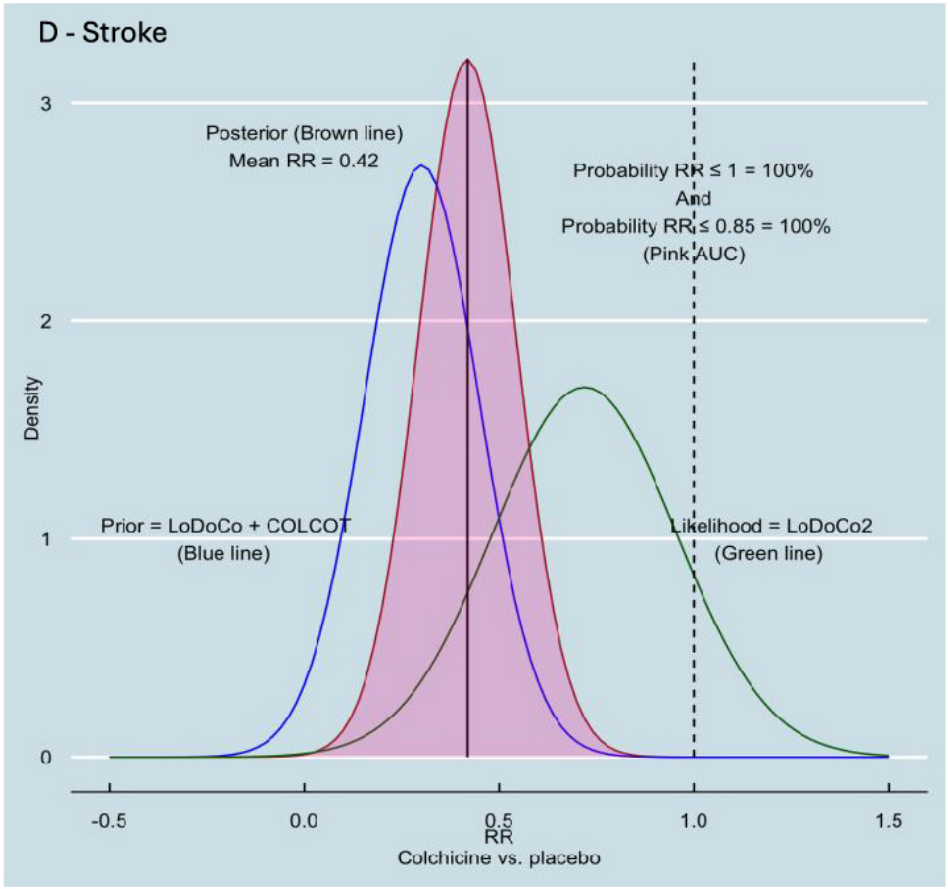
Graphical representations in Figure 1 (A to E) offer a visual insight into the influence of the prior and likelihood on the probability density functions of the primary composite and individual endpoints. Notably, for the primary endpoint (Figure 1A), the likelihood held ten times (1/ 0.004) the weight of the prior (1/ 0.04), resulting in a more pronounced shift in the posterior distribution towards the likelihood, hence underscoring its predominant influence on the posterior outcomes.

Similar patterns were observed for CV death and MI (Figure 1B and 1C) where the likelihood information held more weight than the prior exerting predominant influence over the posterior outcomes. Conversely, for stroke (Figure 1D), the posterior distribution shifted closer to the prior, which held more significant influence than the likelihood, while for coronary revascularization (Figure 1E), both the prior and likelihood exerted comparable impact, positioning the posterior distribution of effect size centrally.


A - Primary Composite Endpoint
Probability RR ≤ 1 = 100%
(Pink + Orange AUC)
Posterior (Brown line)
Mean RR = 0.70
Probability RR ≤ 0.85 = 99%
(Pink AUC)
Likelihood = LoDoCo2
(Green line)
Prior = LoDoCo + COLCOT
(Blue line)
Density
RR
Colchicine vs. placebo


B – Cardiovascular Death
Probability RR ≤ 1 = 85%
(Pink + Orange AUC)
Posterior (Brown line)
Mean RR = 0.76
Probability RR ≤ 0.85 = 65%
(Pink AUC)
Likelihood = LoDoCo2
(Green line)
Prior = LoDoCo + COLCOT
(Blue line)
Density
RR
Colchicine vs. placebo


C – Myocardial Infarction
Probability RR ≤ 1 = 100%
(Pink + Orange AUC)
Posterior (Brown line)
Mean RR = 0.72
Probability RR ≤ 0.85 = 92%
(Pink AUC)
Likelihood = LoDoCo2
(Green line)
Prior = LoDoCo + COLCOT
(Blue line)
Density
RR
Colchicine vs. placebo


D - Stroke
Posterior (Brown line)
Mean RR = 0.42
Probability RR ≤ 1 = 100%
And
Probability RR ≤ 0.85 = 100%
(Pink AUC)
Prior = LoDoCo + COLCOT
(Blue line)
Likelihood = LoDoCo2
(Green line)
Density
RR
Colchicine vs. placebo

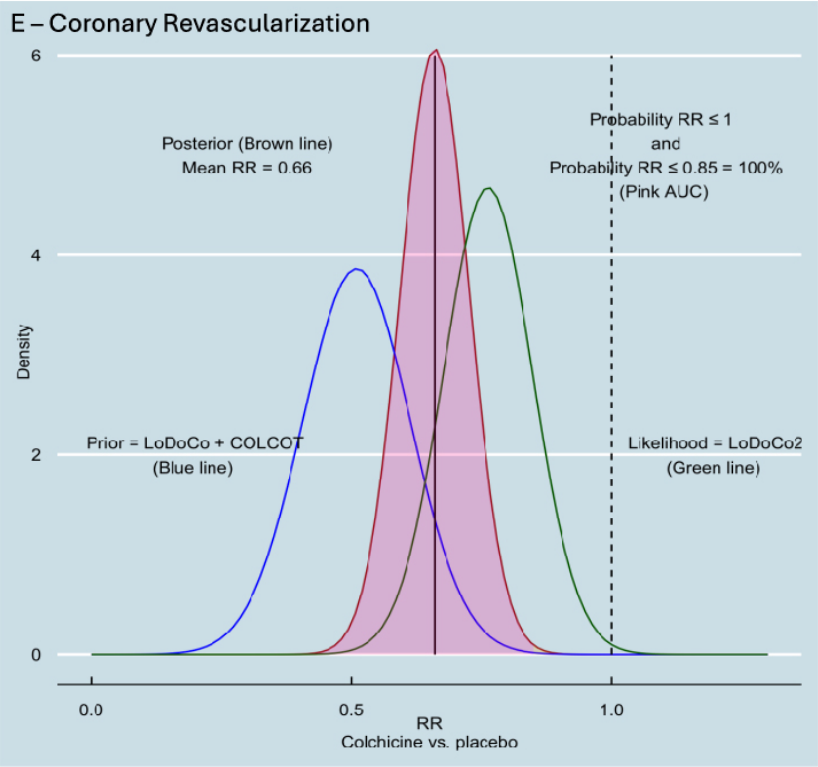


Figure 1: Bayesian triplots of probability density functions of the primary composite and individual endpoints for the prior derived from LoDoCo and COLCOT, the likelihood representing the results from the LoDoCo2 trial and the posterior distributions of effect size.

AUC: area under the curve; RR: risk ratio

The objectivity and validity of the prior are often subject to criticism in the context of Bayesian statistics. In our analysis, the prior exerted minimal influence on the computations of the posterior distributions for the primary endpoint, CV death and MI. Varying the prior weight of these endpoints would have had negligible effects on the results. Consequently, we performed sensitivity analyses for stroke and coronary revascularization, which involved deliberate reductions in the prior weight by 50%, 25%, and 10% (Table 2). For stroke, adjusting the prior weight led to an increase in the mean posterior RR, peaking at 0.63 with a 10% reduction in the prior weight. Notably, the likelihood of a decreased risk with colchicine remained consistently high, ranging from 96% to 100%, while the probability of at least a 15% reduction in risk varied from 85% to 99%. Regarding coronary revascularization, the rates of risk reduction with colchicine ranged between 25% and 30%, accompanied by probabilities of risk reduction at 100%, and probabilities of at least a 15% reduction ranging from 90% to 98%. These findings emphasize the strength of the evidence and the consistent tendency of colchicine to exert a protective effect on cardiovascular outcomes.

Null Hypothesis Testing

In contrast to the dichotomous statistical significance assessment ($0.05\ p < 0.05$) used in traditional statistics, the Bayes factor can quantify the strength of evidence in terms of probability against H_0 or in support of H_A. The min BF for the primary endpoint in LoDoCo2 [11] was 0.0008, indicating robust evidence against H_0 [39]. With a prior odds of H_0 set at 0.11, derived from the prior probability of the primary endpoint's RR falling within a ROPE ($0.85 \leq RR \leq 1.15$), the resulting posterior odds of H_0 were 0 (0.0008 x 0.11), indicating a 100% probability favouring a non-null effect (Table 3). When adopting a reduced prior odds of H_0 at 0.06, indicative of a more stringent ROPE ($0.90 \leq RR \leq 1.10$), similar posterior probabilities favouring H_A were observed at 100% (Table 3). These results suggested that a null effect was highly unlikely after observing the LoDoCo2 [11] data and confirmed the presence of a difference in the primary outcome between colchicine and placebo.

Table 2: Mean posterior RR (CrI) and probabilities of risk for the primary composite and individual endpoints using various prior weight

Endpoint	RR (CrI)	Prob. (%) risk null	Prob. (%) risk reduction of at least 10%	Prob. (%) risk reduction of at least 15%
Stroke				
50% of prior weight	0.48 (0.18 – 0.79)	100	100	99
25% of prior weight	0.56 (0.20 – 0.92)	99	97	95
10% of prior weight	0.63 (0.22 – 1.04)	96	90	85
Coronary Revascularization				
50% of prior weight	0.70 (0.55 – 0.84)	100	100	98
25% of prior weight	0.73 (0.57 – 0.88)	100	99	94
10% of prior weight	0.75 (0.58 – 0.91)	100	97	90

CrI: credible interval; Prob.: probability; RR: risk ratio

Table 3: Null Hypothesis testing using Bayes factor

Endpoints	Minimum Bayes Factor	Prior Prob. of H_0(Null interval: 0.85 < RR < 1.15)	Posterior Prob. (%) (H_0 / H_A)	Prior Prob. of H_0(Null interval: 0.90 < RR < 1.10)	Posterior Prob. (%) (H_0 / H_A)
Primary	0.0008	0.10	0 / 100	0.06	0 / 100
CV Death	0.76	0.12	9 / 91	0.08	6 / 94
MI	0.06	0.28	2 / 98	0.19	1 / 99
Stroke	0.45	0	0 / 100	0	0 / 100
Coronary Revascularization	0.05	0	0 / 100	0	0 / 100

CV: cardiovascular; H_0: null hypothesis; H_A: alternative hypothesis; MI: myocardial infarction; Prob.: probability; RR: risk ratio

In the case of CV death, the min BF was 0.76 in the LoDoCo2 [11] trial. Combining the min BF with prior odds of H_0, derived from the probability of the prior's RR within a ROPE (set at either 0.12 or 0.08), yielded a posterior probability of H_0 ranging from 6% to 9% (Table 3). These results provide an estimate of the residual posterior probability of no effect after considering the LoDoCo2 [11] data.

The min BF values for MI and coronary revascularization were 0.05 and 0.06, respectively, indicating moderate to strong support for a non-null effect. Combined with prior odds of H_0, derived from the probability of the prior's RR within a ROPE, it yielded posterior probabilities of H_A ranging from 98% to 99% for MI and 100% for coronary revascularization (Table 3). These results reinforced the improbability of the null hypothesis for these two endpoints after observing the LoDoCo2 [11] data and the discernible difference in the effects of colchicine and placebo on the incidence of MI and coronary revascularization.

Regarding stroke, the min BF of 0.45, when combined with prior odds of H_0, derived from the probability of the prior's RR within a ROPE, resulted in a posterior probability of H_0 of 0. Consequently, the posterior probability of H_A was 100% (Table 3). These probabilities indicate that the null hypothesis is unlikely to remain true after observing the LoDoCo2 data, supporting the alternative hypothesis of a difference in this outcome between colchicine and placebo.

Discussion

To our knowledge, this study represents the first Bayesian analysis of the primary composite and individual endpoints of the LoDoCo2 [11] trial, integrating prior evidence from LoDoCo [12] and COLCOT [10]. Aligned with findings from colchicine RCTs, our results showed compelling evidence of colchicine's efficacy in reducing cardiovascular complications, with posterior probabilities consistently favouring a protective effect. Furthermore, our Bayesian approach provided probabilities of benefit associated with colchicine at various thresholds. Additionally, the Bayes factor calculations provided quantitative measures of the strength of evidence, indicating strong support for a non-null effect in the primary and most individual endpoints. A small residual probability of a null effect remained between colchicine and placebo for CV death (6% - 9%).

Implications for Clinical Practice and Decision--Making

The Bayesian results and probabilities derived from this reanalysis of colchicine data hold practical implications for clinical decision-making. First, the Bayesian results present the mean posterior risk ratios and probabilities associated with various benefit thresholds for the composite and individual endpoints. This nuanced information provides clinicians with a comprehensive understanding of the likelihood of risk reduction with colchicine, aiding in assessing the treatment's clinical relevance for specific cardiovascular outcomes.

Second, Bayesian methods inherently incorporate uncertainty into their analyses, providing a more realistic representation of the variability in clinical trial data. The credible intervals generated in this study offer clinicians a range within which the true effect size is likely to fall without the hypothesized repeat of experiments underlying traditional statistics.

Third, by incorporating prior evidence from relevant trials, Bayesian methods provide a contextually rich analysis that aligns with the cumulative knowledge in the field. This integration allows clinicians to assess the robustness of the findings in the context of existing evidence, contributing to a more informed decision-making process.

Fourth, the Bayes factor calculations depart from the traditional binary significance testing, offering a continuous measure of the strength of evidence for or against the null hypothesis. Clinicians can appreciate the gradient of evidence strength, allowing for an enhanced interpretation of the data's reliability and relevance to clinical practice.

Finally, Bayesian methods provide a robust framework for enhancing various aspects of clinical research and practice. They enable adaptive designs, where data is continuously updated and analyzed, allowing for real-time modifications to trials. This improves trial efficiency and ethics by potentially reducing the number of participants exposed to less effective treatments. Bayesian models, when applied to patient-level data, can predict individual responses to treatments, facilitating personalized medical interventions tailored to each patient’s unique characteristics. Furthermore, by integrating data from multiple sources, including real-world evidence and post-marketing surveillance data, Bayesian methods enhance drug safety monitoring and regulatory decision-making. Additionally, Bayesian techniques, when used to model the cost-effectiveness of different interventions, assist policymakers in making informed decisions and optimizing resource allocation in healthcare.

Limitations

This study has limitations that warrant consideration. One limitation is the use of aggregate data, which averages out individual differences and masks the variability and heterogeneity present in patient-level data. This can lead to biased estimates due to inadequate control for confounding variables and interaction effects, as well as reduced statistical power and less precise parameter estimates compared to patient-level data.

The use of aggregate data in medical research is common because of the significant challenges associated with obtaining patient-level data. These challenges include privacy concerns, data access restrictions, and the logistical complexity of collecting detailed individual data across large populations. Consequently, researchers often rely on aggregate data as a more feasible alternative, despite its limitations in capturing variability and providing precise estimates.

In our study, the absence of detailed event data by site in the analysis led to the utilization of variances derived from aggregated data, potentially underestimating between-studies heterogeneity. In an analysis of the primary endpoint of LoDoCo2 [11] by country, Brophy obtained a variance vastly higher than the one reported by the authors [29]. His Bayesian analysis of this endpoint in context with prior evidence from COLCOT [10] assumed a prior variance equal to the likelihood. His results showed lower probabilities than the ones we are reporting, specifically a 92% probability of a decreased composite endpoint with colchicine and a 75% probability that this reduction is at least 15% [29]. Our results, on the other hand, were 100% and 99%, respectively. As data by site were unavailable for the individual endpoints, we opted for a consistent approach of analyzing all the endpoints using the reported aggregated data instead of making assumptions regarding the between-study heterogeneity. Both approaches have their downfalls, underscoring the importance of individual patient data for more accurate assessments.

We addressed the potential biases associated with using aggregate data by conducting sensitivity analyses. These analyses involved varying the weight of the prior for posterior distribution calculations and considering two ROPE intervals for Bayes factor calculations. This approach generated posterior probabilities of effect and quantified the support for or against the null hypothesis, thereby helping to assess the strength of our inferences.

Another limitation is related to the choice of prior. Our selection of prior may have impacted the outcomes, potentially not aligning with others' perspectives, and thereby limiting the generalizability of our findings. However, an in-depth examination of the influence of the prior on the posterior distributions revealed a predominantly minimal effect. In instances where the prior held significant (stroke) or equal sway (coronary revascularization) over the posterior distributions, we conducted sensitivity analyses to offer a more comprehensive evaluation of the fluctuations in the posterior estimates.

Conclusion

The Bayesian reanalysis of the LoDoCo2 [11] trial, integrating prior evidence from the LoDoCo [12] and COLCOT [10] trials, yielded compelling positive results for the efficacy of colchicine in secondary prevention of cardiovascular complications. With substantial risk reduction, high probabilities of benefit, and continuous evidence strength, colchicine emerged as a reliable intervention for clinicians seeking effective strategies to mitigate cardiovascular risks. These findings underscore the potential for colchicine to optimize patient outcomes and warrant its consideration in evidence-based therapies for cardiovascular medicine.

In addition, our findings contribute to the ongoing discussion regarding the optimal approach for statistical analysis in clinical research, emphasizing the importance of considering both frequentist and Bayesian methods for a more comprehensive interpretation of trial data.

Author Statement

Gisèle Nakhlé: Conceptualization, methodology, formal analysis, writing – original draft, writing - review and editing; Jean-Claude Tardif: Conceptualization, writing – review and editing, funding acquisition; Marie-Pierre Dubé: Writing – review and editing; Anick Dubois: Writing – review and editing, funding acquisition; Jacques LeLorier: Conceptualization, writing – review and editing, supervision, funding acquisition.

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Competing Interests

Drs. G. Nakhlé and J. LeLorier have received grants from the Montreal Heart Institute for this project. The Montreal Heart Institute received funding from the Health Collaboration Acceleration Fund (FACS) from the Government of Quebec.

Dr. J-C.Tardif reports grant from Amarin, grant from AstraZeneca, grant from Ceapro, grants, personal fees and minor equity interest from Dalcor, grant from Esperion, fees from HLS Pharmaceuticals, grant from Ionis, grant

from Merck, grants from Novartis, fees from Pendopharm, and grant and fees from Pfizer, outside the submitted work; in addition, Dr. Tardif has a patent “Genetic markers for predicting responsiveness to therapy with hdl-raising or hdl mimicking agent” pending, a patent “Methods for using low dose colchicine after myocardial infarction” pending, a patent “Methods of treating a coronavirus infection using colchicine” pending, and a patent “Early administration of low-dose colchicine after myocardial infarction" pending; Dr. Tardif has waived his rights in the colchicine patents and do not stand to gain financially.

Dr. M-P Dubé reports minor equity interest in Dalcor Pharmaceuticals. She has a patent Methods for Treating or Preventing Cardiovascular Disorders and Lowering Risk of Cardiovascular Events issued to Dalcor Pharmaceuticals, no royalties received; a patent Genetic Markers for Predicting Responsiveness to Therapy with HDL-Raising or HDL Mimicking Agent issued to Dalcor Pharmaceuticals, no royalties received; and a patent Methods for using low dose colchicine after myocardial infarction, assigned to the Montreal Heart Institute.

Dr. A. Dubois has no relevant financial or non-financial interests to disclose.

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