

A Bayesian Meta-Analysis approach to address the effectiveness of statins in preventing death after an initial myocardial Infarction

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Abstract: It is interesting to note that the effect of cholesterol lowering drugs such as statins and their ability to actually lower the cholesterol or some component such as the low density lipids (LDL) is fairly well established. The benefits appear to be present regardless of patient age, gender, or baseline cholesterol. However, the use of statins post myocardial infarction (MI) and their efficacy for reducing the likelihood of death can still be a topic of discussion. Despite the fact that they are an effective cardio event preventive therapy, the number of patients receiving statin therapy as a secondary prevention may remain suboptimal to some investigators. There are several retrospective cohort studies of patients discharged from the hospital following an acute myocardial infarction and many investigators have sought to look at the population impact of statin prescribing patterns.

There have been conflicting studies concerning the efficacy of this intervention and meta analyses have been performed to determine the benefits and risks of intervention for individuals with an initial MI. Basically the question considered concerns the reduction in mortality in MI subjects due to this type of intervention. The general results have produced some conflicting data. This, of course, is controversial. The controversy usually arises from the fact that the patient cohort in most studies include unselected consecutive survivors of a first recorded MI from a large number of different hospital or institution types. The only exclusion criterion used, for example, may be age, since the recorded information focuses on coronary artery disease and, therefore, data on other important comorbidities influencing survival in various populations may not be available. There are usually no exclusions due to presence or absence of specific risk factors, comorbidities, anticipated adverse effects, participation in clinical trials, or contraindications to certain medications. Many representative cohorts are also strengthened by the inclusion of all patients with MI from the general population at institutions or clinics with different levels of care within an entire country or various countries of the world.. Compared with the National Registry of Myocardial Infarction in the United States, for example, the Swedish registry does not focus on thrombolytic therapy but includes all types of MI patients and a wider selection of background characteristics and treatments, which allows for adjustment of a large number of confounding factors. Some investigators will even contend that the definitions and detection of non fatal MI and adjudication of cause of death are not always straight forward particularly in large multi center trials. One should try to be aware of as many of these contentions as possible. However, this may not be possible.

With these limitations in mind, the goal of this study is to examine the six known intervention trials which addressed this issue with conflicting results, combine the statistics in a rigorous Bayesian meta-analytic format with little or no bias and reach a conclusion concerning the efficacy of intervention in reducing post MI mortality. The approach here is to apply a Markov Chain Monte Carlo strategy to coherently combine prior diffuse information on the binary response (death versus alive) with the distribution of the logit of the response probability in the 6 studies and derive a posterior log odds of death for treatment (cholesterol lowering agents) versus no treatment (no intervention). We will examine the credible regions for the parameters and the convergence properties as well. The posterior values of the parameters of the six studies as well as the combined posterior parameters of the combined meta-analytic approach will be evaluated and examined. The interesting point is that results may conflict in part depending on the type of statin or population being treated. Our goal here is to investigate the models closely and determine the discrepancies and reasons for them. We then follow this process with another study to determine what consistency, if any, is there in studying the merits of statins after MI.

Key Words: *statins, cardiovascular disease, meta-analysis, Bayesian*

1. INTRODUCTION

The American Heart Association (Report, 2001) announces that each year, over 1 million individuals in the United States will have a new or recurrent acute MI . From this same report, it is estimated that there are 7.3 million individuals (4.5 million men and 2.8 million women) who have a history of acute MI . The cardiovascular risk after acute MI remains daunting. Within 1 year after an acute MI, 25% of men and 38% of women will die (Report, 2001). Within 6 years of a clinically evident event, 18% of men and 35% of women will have had a recurrent MI. During this time frame, approximately 22% of men and 46% of women will go on to develop congestive heart failure. Patients with a prior history of MI are five to seven times more likely to sustain a cardiovascular event when compared with individuals without clinically evident atherosclerotic vascular disease. These patients remain at risk for recurrent events even if they are without symptoms and have no demonstrated ischemia on conventional stress testing. This risk remains even if they have undergone complete revascularization. Patients after acute MI thus constitute a noticeably high-risk group for recurrent coronary events and cardiovascular mortality

Thus, it is well known that after acute myocardial infarction, patients remain at substantial risk for recurrent cardiovascular events and mortality. Despite what may be deemed as compelling scientific and clinical trial evidence that lipid-lowering medications reduce mortality in patients after acute myocardial infarction, many believe this life-saving therapy continues to be underutilized (Fonarow, 2002). A number of studies in a variety of clinical settings have documented that a significant proportion of patients after myocardial infarction are not receiving treatment with lipid-lowering medications when guided by conventional care. Some will contend that it has recently been demonstrated that implementation of a hospital-based system for initiation of statins prior to hospital discharge results in a marked increase in treatment rates, improved long-term patient compliance, more patients reaching low density lipoprotein levels of less than 100 mg/dL, and improved clinical outcomes (Fonarow, 2002).. Following the administration of in-hospital initiation of lipid-lowering medications as the standard of care for patients hospitalized with acute myocardial infarction may dramatically improve treatment rates and thus impact positively to reduce the risk of future coronary events and prolong life in the large number of patients hospitalized each year. The overwhelming scientific evidence that lipid-lowering therapy reduces the risk of recurrent cardiovascular events and improves survival in patients after MI is seen in the literature (Rossouw, Lewis and Rifkind, 1990, Smith, Blair, Bono, et al, 2001 and LaRosa, He, and Vupputuri, 1999). Prospective, randomized clinical trials, including the Scandinavian Simvastatin Survival Study (4S) (Rossouw, Lewis, and Rifkind, 1990) and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID, 1998) trials, demonstrate a significant reduction in mortality with statins in post-MI patients.

The role of cholesterol in coronary health is not new and there have been numerous studies and publications to confirm this association. In the late 1980's and early 1990's the emphasis was not only on primary prevention, but on the role of cholesterol in that population already having cardiac events or difficulties (Siegal et al, 1988). It remains a common belief that those who survive a myocardial infarction (MI) the extent of myocardial damage is the factor of choice on further prognosis and that cholesterol is not a major risk factor to consider (Lancet, 1989). Further there is the belief that modifiable risk factors after an MI are unchanged and require treatment (Evans, 1986). Much of the data from observational and prospective clinical trials has been reviewed in the hope that cholesterol lowering strategies should be pursued in most patients with coronary disease where it had not been done so in the past (Rossouw, Lewis and Rifkind, 1990). As a matter of fact since the 1990's (Fonarow, 2002), applying hospital-based systems to ensure initiation of lipid lowering medications and other cardio protective therapies has been demonstrated by several sources to improve treatment rates, long term patient compliance, and clinical outcomes. The national guidelines have been reviewed and revised to recommend that, in addition to diet and exercise counseling, lipid-lowering medications be initiated prior to hospital discharge in patients hospitalized with a cardiovascular event. Thus it appears that widespread application of hospital-based treatment programs may increase lipid-lowering treatment rates considerably with this proven, cost-effective (Fonarow, 2002) therapy, and thus allow an increased reduction in the risk of recurrent events and death in the large number of high-risk patients hospitalized each and every year.

In light of all this history it is the goal of this study is to reevaluate the six known intervention trials (Rossouw, Lewis and Rifkind, 1990) which addressed this issue with some conflicting results, combine the statistics in a rigorous Bayesian meta-analytic format and reach a conclusion concerning the efficacy of intervention in reducing post MI mortality when a body of studies are considered under one analytic examination. The approach here is to apply a Markov Chain Monte Carlo strategy to coherently combine prior diffuse information on the binary response (death versus alive) with the distribution of the logit of the response probability in the 6 studies and derive a posterior log odds of death for treatment (cholesterol lowering agents) versus no treatment (no intervention).

2. METHODS

The six trials from which we gathered the data for our analyses have been published, outlined, (Rossouw, Lewis and Rifkind, 1990) and examined individually for their ability to lower the risk of death with statins. We describe them briefly here. They are; the Coronary Drug Project(CDP), the Newcastle (NC) study, Edinburgh (ED), Stockholm (STOCK), Oslo and the Medical Research Council (MRC). The Coronary Drug Project was conducted between 1966 and 1975 to assess the long-term efficacy and safety of five lipid-influencing drugs in 8,341 men aged 30 to 64 years with electrocardiogram-documented previous myocardial infarction. The Newcastle study was a 5 year study of clofibrate by a group of physicians in the Newcastle upon Tyne Region. The Edinburgh trial was a secondary prevention trial using clofibrate by a research committee of the Scottish Society of physicians. The Stockholm study examined the reduction of mortality in ischaemic heart disease in a secondary prevention trial of combined treatment with clofibrate and nicotine acid. The Oslo investigators examined the effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. The MRC group studied a low fat diet in MI as well as a controlled trial of soya bean oil. The control therapy in each case was "no treatment. Table 1 lists the number treated or active subjects as well as the number of controls and the percent failures (died) in each group. One can see that all had a higher percent failure on the control arm except the ED study with equality of failures in each. The task is to apply a binomial sampling model to the data. From the model we derive the logit of the response (failure) and compute the posterior odds ratio of response for each study and then derive the overall odds ratio for the six trials using meta-analysis. Once this is done then we derive the posterior predicted odds ratio for the group. The authors have utilized the MCMC procedure for deriving the posterior parameters of the model which include the posterior odds and predicted posterior odds. We let rc_i and ra_i denote the number of failures in the control group and active group, respectively in each of the six studies, $i=1, \dots, 6$. For the remainder of our presentation the subscripting is; $i=1$ for the CDP study, $i=2$ for the NC study, $i=3$ for ED, etc until $i=6$ for the MRC study which is the order of studies as they appear in Table 1. Likewise we let nc_i and na_i be the total number of subjects in the control and active groups respectively, $i=1, \dots, 6$. We further define,

Table 1 The Six Lipid Studies

Trial	Active	Died %	Control	Died %
CDP	2224	0.18	2789	0.19
NC	244	0.10	253	0.17
ED	350	0.10	367	0.10
STOCK	279	0.17	276	0.26
Oslo	206	0.18	206	0.24
MRC	322	0.11	323	0.12

$$\begin{aligned} rc_i &\sim \text{binomial}(pc_i, nc_i), \\ ra_i &\sim \text{binomial}(pa_i, na_i) \end{aligned} \quad (1)$$

and,

$$\begin{aligned} \text{logit}(pc_i) &= \mu_i \\ \text{logit}(pa_i) &= \mu_i + \delta_i \end{aligned} \quad (2)$$

where

$$\mu_i \sim \text{normal}((0.0, 1.0E-5)) \quad (3)$$

One can see that logit functions will have a vague normal prior distribution and that the δ_i represents the log odds of failure in each of the six studies, $i=1, \dots, 6$. Also we let δ_i have the prior distribution,

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$$\text{delta}_i \sim t(d, \tau, 4) \tag{4}$$

which is a t distribution which hyper prior mean d , inverse variance, τ , variance $\sigma^2=1/\tau$, and degrees of freedom, 4. One can see that this is a rather flat distribution with only 4 degrees of freedom. The mean, d , is actually the overall mean of the six studies combined and d and τ have the hyper prior vague distributions,

$$\begin{aligned} d &\sim \text{normal}(0.0, 1.0E-6) \\ \tau &\sim \text{gamma}(0.001, 0.001) . \end{aligned} \tag{5}$$

The odds ratio or odds of failure for the treated group versus the control group for each of the six studies is,

$$\text{odds}_i = \exp(\text{delta}_i) , \tag{6}$$

with overall odds for the six studies combined having the value,

$$\text{odd}_R = \exp(d) . \tag{7}$$

We define one more parameter, or the predicted value of the odds, which is simply,

$$\text{Odd_Pred} = \exp(\text{delta.new}) . \tag{8}$$

3 RESULTS

We shall examine each of these parameters in Table 2 which gives the value of the posterior odds for each of the six studies, $i=1, \dots, 6$, and the overall odds for the combined six studies in the last row. One can see from the second column that all of the odds ratios are less than one which indicates a favorable outcome for the treatment participants on average. However as we examine the last two columns of Table 2, we see that four of the studies, CDP, ED, Oslo and MRC have a 95% posterior credible interval which cover the value ,1, indicating no superiority for these four studies. It is thus interesting that the overall treatment superiority is evident when doing the meta-analysis, but two of the smaller studies, NC and Stockholm are the ones alone exhibiting some superiority. Also note in all cases how the upper limit of the interval is very close to one.

The last row of the Table 2 contains the information from the meta-analytic application of the six studies and indicates treatment superiority. Figure 1 is the posterior density of the odds denoted odd_R . One can see on both Figures 1 and 2 (Figure 2 discussed later) that using the MCMC approach we utilized about a 10,000 burn iteration and the convergence to all our solutions was fairly rapid. We actually could have achieved similar results with about a third or less of this effort. The predicted value for the overall odds is 0.7917 with posterior interval (0.4083, 1.366). Here the upper limit of the interval is above the value,1 and thus covers the possibility of no significant predicted treatment effect. We tried a range of prior hyper parameters on the log odds, delta and d and the results were fairly robust.

Table 2 Posterior Parameters for the Six Studies

Trial	Odds	2.5%	97.5%
CDP	0.8902	0.7734	1.025
NC	0.7241	0.4430	0.9674
ED	0.8761	0.6382	1.263
STOCK	0.7081	0.4730	0.9336
Oslo	0.7698	0.5243	1.008
MRC	0.8555	0.6262	1.199
All	0.7994	0.6022	0.995

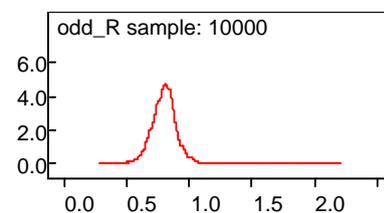


Figure 1. Posterior Density of Overall Odds

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The Swedish 4S was a study (Scandinavian Simvastatin Survival Trial group,1994) that was conducted after the six studies that we have discussed so far with markedly different frequencies of coronary deaths in either group. This was a trial that had many side studies including the effect of other risk factors on death such as diabetes. An interesting side consequence of this trial was also the cost effective considerations of administering lipids in the long term. It was believed from this trial that the overall cost of hospitalization was reduced by about 32%. There were 4444 entries onto this new study with 2221 on the treatment and 2223 on the control. The percent failures on the treated were 5% and the percent failures on the control were 9%. Note that this much reduced from the percents from the previous studies given in Table 1. Also note in Table 3 that the odds of failure on the 4S study is fairly close to the meta-analysis summarized above for the six studies. The sample size of the 4S study yields a narrower posterior interval for the mean odds, but with an upper bound of the interval still very close to 1. Figure is the density of the posterior odds including the 4S study The interesting consequence of all this is that this study does not change the prediction status. The predicted odds from the seven studies is now 0.6762 with posterior interval (0.3814, 1.3518). It is not much changed from the previous prediction analysis from the six studies.

Table 3 Posterior Parameters for the Six Studies and the 4S study added

Trial	Odds	2.5%	97.5%
All Six	0.7994	0.6022	0.995
With 4S	0.7318	0.5606	0.9243

We attempted a sensitivity analysis for the prior hyper parameters based on the reports of authors who have also investigated these studies (Stangl, D.K. and Berry, R.A., 2000) but using sharper less diffuse hyper parameters and our results are the same which lends this problem to fairly robust interpretations. Of course, the sample sizes are rather large in all the trials thus perhaps dominating the interpretation of the results.

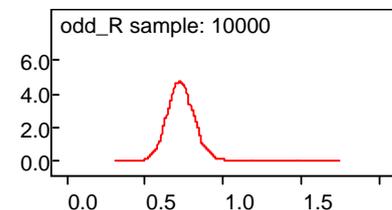


Figure 2. Posterior Density of Overall Odds +4S

The above results show that the combining of the results do in fact demonstrate that there may be an advantage to administering cholesterol lowering drugs after an initial MI. Obviously not all studies are going to agree in the same direction, that is to say an odds ratio greater than one or an odds ratio less than one for all of the studies. As seen above there was heterogeneity in our results as several of the studies had posterior credible intervals which covered the value of one or no effect and others were to the contrary. However, combining the results in a legitimate meta-analytic way with some vague expression in the form of the prior distributions demonstrated some superiority to administering of statins after the first MI.

4. DISCUSSION AND CONCLUSIONS

There had been some discussion (Stangl, D.K. and Berry, R.A., 2000) that perhaps the 4S study did not support the meta-analysis of the six prior studies. Examining the data in Table 1 and the facts and all the results of the studies prior to any Bayesian treatment, this may be due mainly from the fact that the results from the 4S study differed in per cent failures of treated versus controls compared to the six studies involved in the original meta-analysis that we performed. As a matter of a quick calculation the six studies had an un weighted combined failure rate of about 14% on the treated group and the 4S study had a failure rate of 5% on the treated group which is rather striking given the sizes of the samples. We also got a hint that in turn the results if the six study meta-analysis may not be so impressive due to the fact that the predicted distribution of the odds based on the data yielded a 95% posterior interval that did cover the value, 1. The final meta-analysis involving the seven studies confirmed the possible positive effect of lowering lipids on survival outcome, but still not convincing in some circles as the prediction from that updated result still confirmed the possibility of a non clinically significant result in a future study.

Upon further investigation of the studies involved in this meta-analysis, one should ask if there are possible sources of heterogeneity in the data. Obviously there is as several of the studies that we examined had odds ratio posterior intervals that covered one and others had posterior intervals that did not cover one. The ultimate disadvantage of not being able to examine all the raw data is that it may be difficult to pin down the sources of heterogeneity. However, random effects meta-analyses do take into account the heterogeneity (Dersomonian and Laird, 1986). Our Bayesian

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approach is certainly a random effects treatment of the parameters of interest in our meta-analysis. The issue of heterogeneity is precisely one of the reasons why we have taken this approach.

We are aware of the limitations of meta-analyses and the fact that to attempt to combine data from various sources must be done with the greatest statistical rigor, which we have attempted. Nevertheless, with these limitations in mind, the goal of this study which was to examine the six known intervention trials which addressed this issue of statins after MI with conflicting results and combine the statistics in a rigorous Bayesian meta-analytic format with little or no bias and reach a conclusion concerning the efficacy of intervention in reducing post MI mortality was met in this short presentation. The approach here was to apply a Markov Chain Monte Carlo strategy to coherently combine prior diffuse information on the binary response (death versus alive) with the distribution of the logit of the response probability in the 6 studies and derive a posterior log odds of death for treatment (cholesterol lowering agents) versus no treatment (no intervention). We dealt with rather well behaved distribution functions which facilitated convergence to estimates which certainly made sense. We examined the credible regions for the parameters and the convergence properties as well. The posterior values of the parameters of the six studies as well as the combined posterior parameters of the combined meta-analytic approach were evaluated and examined. The interesting point is that results may conflict in part depending on the study or underlying heterogeneity. Our goal was to investigate the studies closely and determine if we could the discrepancies between them and reasons for them. One of our thoughts on this was the different regimens and perhaps differing populations of the studies. We then followed this process with another study, the 4S, to determine what consistency, if any, is there in studying the merits of statins after MI. Results were similar but certainly not exact. Our results were somewhat convincing, but certainly not overwhelming as some authors may claim (Fonarow, 2002).

We have attempted here to give an overview of the major statistical approaches in Bayesian format to the issue of statins in MI. We consider the broader issue of meta-analysis. Advantages of meta-analyses are seen from the ability to address a controversial issue statistically that may not have been conclusively addressed in single studies. The ability to integrate results from diverse sources and address the relevant issues have been demonstrated many times in the literature through the publication of meta-analyses. One would want to certainly take advantage of the wealth of information published and have a rational way of synthesizing that information. There are certainly controversies involved when one attempts to integrate information from various published works or different databases. (Dersimonian, R. and Laird, N., 1986). Meta-analysis is prone to that controversy. However, every attempt is made to guard against bias through examination of topics such as heterogeneity and publication bias which we did not discuss here and to at least expose them and explain them. Limitations obviously result from selection of studies, choice of relevant outcome, methods of analysis, interpretation of heterogeneity and generalization and application of results. The statistical tools at hand are certainly adequate for addressing these issues. However, one should keep in mind that meta-analyses should not be a replacement for well designed large scale randomized studies (Bartolucci, A., 1999) nor a justification for conducting small underpowered studies. It is a tool when properly utilized helps one to arrive at a reasonable and defensible decision from the scientific information already presented.

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