Supplemental Appendix:

Bayesian Analysis: A Practical Approach to Interpret Clinical Trials and

Create Clinical Practice Guidelines

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**Supplemental Appendix A: Bayesian Analysis of Diagnostic Testing**

To understand how conditional probability in Bayesian analysis adds more details than ordinary probability, we start with a familiar example. A common question is: What is the predictive value of an abnormal screening stress test that is accurate 85% of the time? But, it is arguably more relevant to ask: What is the predictive value of an abnormal stress that is accurate 85% of the time in a healthy 40-year old person? The answer is 5%, which may seem surprisingly low and is based on a straightforward application of Bayes theorem1, 2:

where *H1* is the presence of obstructive CAD, *H0* the absence of disease, *y* is an abnormal stress test, and *p*(*H1|y*) is the posterior probability of having CAD, given the presence of an abnormal stress test *y*. In this application of Bayes’ rule, we calculate the positive predictive value of an abnormal test (*y*) for the presence of disease (*θ*) by dividing the rate of true positives (*y1*|*θ*) by the sum of true (*y1*|*θ*) and false positives (*y2*|*θ*).

If the prior probability of having CAD *p*(*H1*) equals 0.01, the sensitivity *p*(*y|H1*) of stress testing equals 0.85, and *p*(*y|H0*) is the false positive rate of stress testing and equals 0.15 (1 – specificity), for every 10,000 low-risk patients undergoing screening stress tests, 100 will have obstructive CAD (0.01**.**10,000), 85 with CAD will have a true positive stress test (0.85**.**100), and 1485 without CAD will have a false positive test (0.15**.**9900). The posterior probability *p*(*H1*|*y*) is calculated by dividing the number of true positives by all the positives *p*(*y*) and found to be 5% (85/1570). The same solution, which in this example involved the numerical approach that clinicians use without needing a calculator, is obtained by substituting the values of 0.01, 0.85, 0.99, and 0.15 into Bayes’ formula above. Using more nuanced prognostic information, such as the degree of ST depression and maximum exercise time, improves the diagnostic accuracy of exercise treadmill testing more than a simple binary positive-negative outcome.3, 4

Bayesian inference allows practitioners to see that the predictive value of an abnormal test is conditional on the pretest probability of disease,3, 4 and during the revision of the 2011 PCI guideline,5 allowed members of the writing committee to consider that, if there is only a 5% risk of restenosis after DES implantation,6 then the positive predictive value of an abnormal stress test in an asymptomatic individual after PCI could be as low as 23%. This is based on realizing that the chance of restenosis is 5%, which is equivalent to a prior probability *p*(*H1*) of 0.05. The positive predictive value of an abnormal stress test can be calculated from a theoretical sample of 1000 patients, 50 of whom (0.05**.**1000) will have restenosis (*H1*), 950 (1000 – 50) will not have restenosis (*H0*), 43 (0.85·50) will have a true positive test result, and 143 (0.15·950) will have a false positive test result. The posterior probability *p*(*H1*|*y*) of 0.23 is calculated from dividing the true positives by the sum of true and false positives (43/186), which yields the positive predictive value of an abnormal stress test. As a result, the writing committee reached consensus for a Class III recommendation (“no benefit”): “Routine periodic stress testing of asymptomatic patients after PCI without specific clinical indications should not be performed (Level of Evidence: C).”5

**Supplemental Appendix B: Running Bayesian Analyses on Your Computer Using Open-Source Software**

**Running OpenBUGS and [R] On a Macintosh Computer Using a Native Windows Platform (Preferred)2:**

1. You will need to download and open WINE (Windows Not an Emulator). Get the file WineBottlerCombo\_1.6.1.dmg, or latest version compatible with your operating system (OS), from winebottler.kronenberg.org.
2. To run WINE in an older Mac OS environment such as OS X El Capitan version 10.11.6 or earlier, download and run XQuartz 2.7.11. Get the file from xquartz.org. To run WINE in OS X Sierra version 10.12.1, you do not need XQuartz.
3. If you have trouble loading WINE, you may need to modify the security settings on your Mac. Under the , select **System Preferences…** and click on **Security and Privacy**. Under the **General** menu, select 🞉Allow apps downloaded from … App store and identified developers. If this fails, go to the **Applications** folder, open the **Utilities** folder, and double-click on **Terminal.** At the prompt, type sudo spectl –master-disable, and then find under the **General** pane in **Security and Privacy,** a new radio button for 🞉**Anywhere.** After you successfully open WINE, remember to go back into **Terminal** and reset the security settings by typing sudo spctl –master-enable.
4. To perform statistical analyses using [R], you will need to load R-3.0.3-win.exe. To run [R] using WINE on your Mac, download the Windows version of the file from cran.r-project.org. You can get any of the previous versions by clicking on the “Old” button and scrolling, for example, to R-3.0.3.pkg 2014-03-06 16:47 66M.
5. To edit code in [R], you should obtain a code editing program like Tinn-R. You can get Tinn-R\_3.0.3.6\_setup.exe from [https://sourceforge.net/projects/tinn-r/files/Tinn-R setup/3.0.3.6/](https://sourceforge.net/projects/tinn-r/files/Tinn-R%20setup/3.0.3.6/). To get the [R] code in this Supplemental Appendix to work, you will need to copy it to Tinn-R or similar program, save it as a file to your computer and access it directly from [R]. Copy and pasting from the Supplemental Appendix to [R] may not work.
6. To find [R] on your Mac, click on the Wine icon, which may be in your applications folder but should be moved to the task bar for easier accessibility. In the Wine submenu on the menu bar, scroll down to **File Manager**. Double click on the folder **Program Files**, double click on the folder **R**, double click on the folder **R 3.0.3**, double click on folder **bin**, double click on folder **i386**, double click on file **Rgui.exe**, and watch [R] start.
7. To run Markov chain Monte Carlo modeling, get and run OpenBUGS323setup.exe or latest version compatible with your OS. Download the file from [www.openbugs.net/w/**Downloads**](http://www.openbugs.net/w/Downloads)**.** In the Wine submenu on the menu bar, scroll down to **File Manager**. Double click on the folder **Program Files**, double click on the folder **OpenBUGS**, double click on the folder **OpenBUGS323**, double click on file **OpenBUGS.exe**, and watch OpenBUGS start.
8. In [R], scroll down from **File** to **Change dir…** to browse for a folder that you intend to use for data files, code files and figures.
9. To run OpenBUGS in the background with [R], you must install the package BRugs. To do this, open both [R] and OpenBUGS. In [R], scroll down from the **Packages** to **Install package(s)…** and select CRAN mirror **USA (CA 1)** or any other familiar source. Then, scroll down from **Packages** to **Load package…** and select **BRugs.** In [R], type install.packages(“BRugs”) and then type library(BRugs). In future [R] sessions, simply type **library(BRugs)**.
10. To run meta-analyses, type install.packages(“meta”) and then type library(meta). In future [R] session, simply type library(meta).
11. This seemingly incoherent combination of computer and software is recommended, because the Mac is arguably the most reliable computer for the consumer, and the Windows versions of BUGS and [R] are discussed more extensively than any other approach in the recommended textbooks.7-10

**On a PC (Easier)2:**

1. To perform statistical analyses using [R], get and run R-3.0.3-win.exe. Download the Windows version of the file from cran.r-project.org. You can get any of the previous versions by clicking on the “Old” button and scrolling, for example, to R-3.0.3.pkg 2014-03-06 16:47 66M.
2. To edit code in [R], run Tinn-R\_3.0.3.6\_setup.exe. Download the file from [https://sourceforge.net/projects/tinn-r/files/Tinn-R setup/3.0.3.6/](https://sourceforge.net/projects/tinn-r/files/Tinn-R%20setup/3.0.3.6/). To get the [R] code in this Supplemental Appendix to work, you will need to copy it to Tinn-R or similar program, save it as a file to your computer and access it directly from [R]. Copy and pasting from the Supplemental Appendix to [R] may not work.
3. To run Markov chain Monte Carlo modeling, get and run OpenBUGS323setup.exe or latest version compatible with your OS. Download the file from [www.openbugs.net/w/**Downloads**](http://www.openbugs.net/w/Downloads)**.** In the Wine submenu on the menu bar, scroll down to **File Manager**. Double click on the folder **Program Files**, double click on the folder **OpenBUGS**, double click on the folder **OpenBUGS323**, double click on file **OpenBUGS.exe**, and watch OpenBUGS start.
4. In [R], scroll down from **File** to **Change dir…** to browse for a folder that you intend to use for data files, code files and figures.
5. To run OpenBUGS in the background with [R], you must install the package BRugs. To do this, open both [R] and OpenBUGS. In [R], scroll down from the **Packages** to **Install package(s)…** and select CRAN mirror **USA (CA 1)** or any other familiar source. Then, scroll down from **Packages** to **Load package…** and select **BRugs.** In [R], type install.packages(“BRugs”) and then type library(BRugs). In future [R] sessions, simply type **library(BRugs)**.
6. To run meta-analyses, type install.packages(“meta”) and then type library(meta). In future [R] session, simply type library(meta).

**On a Mac using JAGS and [R] for Mac (An Emerging Approach)11:**

1. Go to the Sourceforge.net site and follow instructions for downloading and installing JAGS that is compatible with your OS.
2. To perform statistical analyses using [R], get and run R for Mac from https://cran.r-project.org/bin/macosx/.
3. To run JAGS in [R], you must download and rjags\_4-3 from Sourceforge.net and install.
4. To run meta-analyses, type install.packages(“meta”) and then type library(meta). In future [R] session, simply type library(meta).
5. This combination of hardware and software is gaining wider use,12-14 but is not as widely cited as the Windows-based approaches.

**Supplemental Appendix C: Conjugate Normal Analysis of Revascularization Choices in Diabetic Patients with Multivessel Coronary Artery Disease**

 **Bayesian Inference:** If we suppose that *θ* is a parameter governing mortality rates after CABG or PCI in diabetic patients with multivessel CAD, the “prior probability” of *θ* is given by *p*(*θ*), which represents what is known about the parameter from older trials like the Bypass Angioplasty Revascularization Investigation.15 In this context, the function *p*(*θ*) takes the form of a bell-shaped curve to show that some values of *θ* are more probable than others. When we observe some new trial evidence *y* from FREEDOM,16 which we also presume to be conditional on *θ*, we represent the relation by *p*(*y|θ*) and call it the “likelihood,” to denote the probability of *y* for each possible value of *θ*.

 What we want to know, however, is how the probability of *θ* is altered by the new trial evidence *y*,a parameter that is denoted by *p*(*θ|y*). This is the conditional probability of *θ* based on the new trial data *y*, which is called the “posterior probability,”and is calculated from Bayes theorem:

In other words, Bayes’ theorem expresses how the new evidence *y* from FREEDOM changes the probability of *θ*.

 For a series of clinical trials *i=*1, 2, …, *n*, we have the general form of Bayes’ equation:

In summary, the posterior probability for the hypothesis *θ* given the new evidence is proportional to the new data FREEDOM *y* times the prior probability for the hypothesis *θ* independent of the evidence, divided by the evidence from all trials.

 **Basic definitions**. In the present analysis, we used odds ratios (*OR*s) as the measure of the effect size between treatments. As a convention, if *yi* observations in the *i*th trial have been cross classified by treatment after CABG or PCI in a 2 x 2 table, and the odds of, say, death after CABG was a/c (the number of deaths divided by the number of survivors) and the odds of death after PCI b/d, then the OR describing the trial results would be given by (a/c)/(b/d). Because some trials had small numbers of events, we added 0.5 to the numerator and denominator, and the trial result *ORi* on the loge scale would become *θi*, to represent the treatment effect of the *i*th trial,7

The estimator has an approximate variance

 **Conjugate Normal Model**: A Bayesian approach presumes that efficacy outcome for each RCT is exchangeable and that the ‘true’ treatment effect ***θi*** for the *i*th trial is considered to be a random quantity drawn from a population distribution.7 For the purposes of this report, ***θi*** is represented by a normal distribution and generates an estimate for the global treatment effect ***θ*** that governs, for example, the underlying hypothesis that CABG is associated with reduced mortality compared with PCI in diabetic patients with multivessel CAD. If we let *p*(***θ***) denote the prior probability distribution of *θ*, which for the purposes of this analysis is not subjective opinion but rather is derived empirically from 8 previous trials, each of which has an outcome described by the summary statistic *ORold*, and we have observed some new trial evidence from FREEDOM, *ORFREEDOM*, then the probability of occurrence of *ORFREEDOM* is conditional on *θ* and is denoted by *p*(*ORFREEDOM*|*θ*). The conditional probability of *ORFREEDOM* for each possible value of *θ* is called the likelihood. What we are looking for, however, is the probability distribution of *θ*, which takes into account the trial evidence *ORFREEDOM* and is denoted by p(*θ*|*ORFREEDOM*). This is the conditional probability of *θ* conditional on the trial data *ORFREEDOM*, called the posterior probability, and is calculated from Bayes theorem:

In words, the posterior probability for the hypothesis *θ* given the evidence *ORFREEDOM* is proportional to the likelihood times the prior probability for the hypothesis *θ* independent of the evidence.17 In summary, Bayes theorem expresses how the new evidence *ORFREEDOM* changes the probability of *θ*, and incorporates it with what is already known based on *ORold*.

In older studies,15, 18-24 we have data *OR1*, …, *OR8*, each of which is assumed to have a normal distribution, governed by an underlying treatment parameter *θh* and its variance for *h* = 1,2, …, 8 trials. In order to put the variance into a workable form for the prior distribution, some experts recommend calculating the standard error for each study using a term m to reflect the “effective number of events” in balanced trials,7 which is obtained from setting the variance of the loge(*OR*) to *σ2/m* and a normal likelihood with In a 2 x 2 table for a balanced randomized trial, it can be assumed that the sample sizes for each treatment are approximately equal, the number of events a ≈ b are very small compared with the number of enrolled patients c ≈ d in each treatment group, so that:

where m = a + b is the number of events, allowing *σ* = 2 to be an appropriate choice.7

 After calculating *mh* for each trial, we can obtain the “pooled” results by summing the *m*s for the *h* = 1, 2, …, 8 trials. The summed *m*s can be relabeled to represent the overall “effective number of events” in the prior distribution. We can use this value to calculate a pooled loge(*ORold*) for the prior distribution by weighting the individual loge(*ORh*)s by their respective *m*s divided by the sum *m0*,25 using the standard approach:

 **Likelihood**. In the context of prematurely stopped clinical trials, it is reasonable to assume that the data can likewise be summarized by a statistic, , after *i* observations and will assume a normal distribution containing *θ* as the underlying treatment effect that governs the trial observation with its variance . The study-specific trial result *yi* can estimate the true underlying treatment effect with standard error .7 Similar to the prior discussion, we need to set , and 7 The summed *n*s can be relabeled to represent the overall “effective number of events” in the likelihood.

 Given that the normal prior and the normal likelihood belong to the same family of mathematical functions, we have thus defined a “conjugate normal model”7:

ignoring irrelevant terms that do not include θ. By matching terms in θ it can be shown that:

*,*

indicating that the term involving θ is arising from the posterior distribution

Data table “DMDeathCABGvPCI.csv” for Figure 2:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| study | n.cabg[]  | n.pci[]  | r.cabg[] | r.pci[]  |
| BARI | 180 | 173 | 16 | 47 |
| ARTS | 96 | 112 | 8 | 15 |
| ERACI II | 39 | 39 | 4 | 4 |
| MASS II | 59 | 56 | 9 | 9 |
| SoS | 74 | 68 | 1 | 7 |
| CARDia | 248 | 254 | 32 | 37 |
| SYNTAX | 202 | 226 | 26 | 44 |
| VA CARDS | 97 | 101 | 5 | 21 |
| FREEDOM | 761 | 699 | 83 | 114 |

where: n.cabg = number of patients undergoing CABG, n.pci = number of patients undergoing PCI, r.cabg = number of deaths in the CABG group, and r.pci = number of deaths in the PCI group.

[R] code for Figure 2: Conjugate Normal Analysis.

The file is entitled, “ConjugateNormalDMDeathM” and can be found at: <https://www.dropbox.com/sh/0pziu9ct6qzrnge/AABdt3VDr2IJUdDvz6W_-7kXa?dl=0>

*#Export data from Excel in comma-separated format containing a csv suffix, which is the best way to input data into [R}. Remember that "Z:" is a common designation of the hard disk on a Mac running Windows, but "C:" is used on a PC. Remember also to replace "johnbittl" with your user name on your computer, "Dropbox" and "BayesVFreq" with your folder names, and "DMDeath.csv" with your file name:*

dmdat<-read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/DMDeathCABGvPCI.csv",as.is=TRUE, header=T)

str(dmdat)

study<-c(dmdat$study)

r.cabg<-c(dmdat$r.cabg)

n.cabg<-c(dmdat$n.cabg)

r.pci<-c(dmdat$r.pci)

n.pci<-c(dmdat$n.pci)

*#Calculate ORs, log(OR)s, variance, and effective number of events, m:*

for (k in 1:9)

{

or <- ((r.cabg+0.5)/(n.cabg-r.cabg+0.5))/((r.pci+0.5)/(n.pci-r.pci+0.5))

logor <- log(or);

varlogor <- (1/(r.cabg+0.5))+(1/(n.cabg-r.cabg+0.5))+(1/(r.pci+0.5))+(1/(n.pci-r.pci+0.5))

m.theta<-4/varlogor

}

*#Convert to data frame with all variables listed as col heads*

mdmdat<-data.frame(study,m.theta,logor)

mdmdat

*#Split dataframe "mdmdat" into subsets, FREEDOM ("new" = likelihood) vs. non-FREEDOM ("old" = prior), separated by size of report*

old<-subset(mdmdat,n.cabg<=500)

new<-subset(mdmdat,n.cabg>=500)

*#calculate total number of events m.0 for prior distribution*

m.0<-sum(c(old$m.theta))

*#sum log odds weighted by m/m.0*

for (k in 1:8)

{

*# calculate weighted log odds ratios;*

PriorLogOdds <- ((old$m.theta)/m.0)\*(old$logor)

}

*#sum log odds*

PriorPooledLogOR<-sum(c(PriorLogOdds))

PriorPooledLogSD <- 2/(sqrt(m.0))

PriorPooledLogCI <- 1.96\*4/(sqrt(m.0))

*#calculate 95% CIs for the prior distribution*

PriorLower <- PriorPooledLogOR-(PriorPooledLogCI/2)

PriorUpper <- PriorPooledLogOR+(PriorPooledLogCI/2)

*#exponentiate to get Prior ORs and 95% CIs*

PriorPooledOR <- exp(PriorPooledLogOR)

LowerCI <- exp(PriorLower)

UpperCI <- exp(PriorUpper)

*#To get the SD of the backtransformed data in a normal distribution*

*#-----------------------------------------------------------------------------*

*#calculate effective number of events n.0 for likelihood from FREEDOM*

n.0 <- sum(c(new$m.theta))

likeLogSD<-2/(sqrt(n.0))

for (k in 1:1)

{

*# calculate "weighted" log odds ratios;*

LikeLogOdds <- ((new$m.theta)/n.0)\*(new$logor)

}

likeLogOR<-  sum(c(LikeLogOdds))

likeLogCI <- 1.96\*4/(sqrt(n.0))

likeSD<- exp(likeLogSD)

likeOR<-exp(likeLogOR)

*#calculate the 95%CIs for the likelihood*

likeLogLower <- likeLogOR-(likeLogCI/2)

likeLogUpper <- likeLogOR+(likeLogCI/2)

*#exponentiate*

likeLowerCI <- exp(likeLogLower)

likeUpperCI <- exp(likeLogUpper)

*#-----------------------------------------------------------------------------*

*#calculate posterior*

PostLogOR<-(((m.0\*PriorPooledLogOR)+(n.0\*(likeLogOR)))/((m.0+n.0)))

PostLogSD<-2/(sqrt(m.0+n.0))

PostCI <- 1.96\*4/(sqrt(m.0+n.0))

PostLower<-PostLogOR-(PostCI/2)

PostUpper<-PostLogOR+(PostCI/2)

*#exponentiate*

PostOR<-exp(PostLogOR)

PostLowerCI<-exp(PostLower)

round(PostLowerCI,2)

PostUpperCI<-exp(PostUpper)

*#To get the SD of the backtransformed data in a normal distribution*

*#----------------------------------------------------------------------*

*#print all*

PriorLogVariable <- c("PriorPooledLogOR","PriorPooledLogCI","PriorLower","PriorUpper","PriorPooledLogSD")

PriorLogResult <- c(PriorPooledLogOR,PriorPooledLogCI,PriorLower,PriorUpper,PriorPooledLogSD)

PriorLog <- data.frame(PriorLogVariable, PriorLogResult)

PriorVariable <- c("PriorPooledOR","LowerCI","UpperCI")

PriorResult <- c(PriorPooledOR,LowerCI,UpperCI)

Prior <- data.frame(PriorVariable, PriorResult)

print (PriorLog)

print (Prior)

likeVariable <- c("likeLogSD","likeLogOR","likeSD","likeOR","likeLowerCI","likeUpperCI")

likeResult <- c(likeLogSD,likeLogOR,likeSD,likeOR,likeLowerCI,likeUpperCI)

likeData <- data.frame(likeVariable,likeResult)

like <- data.frame (likeData)

print (like)

PostLogVariable <- c("PostLogOR", "PostLower", "PostUpper", "PostLogSD")

PostLogResult <- c(PostLogOR, PostLower, PostUpper, PostLogSD)

PostLog <- data.frame(PostLogVariable, PostLogResult)

PostVariable <- c("PostOR", "PostLowerCI", "PostUpperCI")

round(PostLowerCI,2)

PostResult <- c(PostOR, PostLowerCI, PostUpperCI)

Post <- data.frame(PostVariable, PostResult)

print (PostLog)

print (Post)

*#------------------------------------------------------------------------*

*#triplot*

x<-seq(from=-1,to=0.3,by=0.01)

*#Prior*

y1=dnorm(x,mean<-PriorPooledLogOR,sd<-PriorPooledLogSD)

*#Likelihood*

y2=dnorm(x,mean<-likeLogOR,sd<-likeLogSD)

*#Posterior*

y3=dnorm(x,mean<-PostLogOR, sd<-PostLogSD)

maxY = max( c(y1,y2,y3) )

plot(x,y1,type="l", ylim = c(0,maxY), cex.axis=1.0, xlab=bquote(theta), cex.lab=1.6, ylab="Probability Density", axes=TRUE, lwd=3,col="blue")

axis (4, pos=0.0, tck = 0, labels=FALSE, col="black")

text (-0.8,3,"Prior (8 trials)",col="blue", cex= 1.4, font=3)

text (-0.12,2.5,"Likelihood (FREEDOM)",col="red",cex = 1.4, font =3)

text (-0.35, 3.5, "Posterior", cex = 1.4, font=3)

text (-0.90, 3.9,"A. All-cause",cex = 1.6)

text (-0.90, 3.6,"mortality",cex = 1.6)

text(-0.9,1.5,"CABG better",cex=1.2, font=3)

text(0.2,1.5,"PCI better",cex=1.2, font=3)

text (PostLogOR, 0.55, round(PostOR,2))

text (PostLower-0.05, 0.55, round(PostLowerCI,2))

text (PostUpper+0.05, 0.55, round(PostUpperCI,2))

text (PriorPooledLogOR, max(y1)/7, col="blue",round(PriorPooledOR,2))

text (PriorLower-0.04, max(y1)/7, col="blue",round(LowerCI,2))

text (PriorUpper+0.04, max(y1)/7, col="blue",round(UpperCI,2))

text (likeLogOR, max(y2)/7.5, col="red", round(likeOR,2))

text (likeLogLower-0.04, max(y2)/7.5, col="red", round(likeLowerCI,2))

text (likeLogUpper+0.04, max(y2)/7.5, col="red", round(likeUpperCI,2))

segments(PostLower, max(y3)/7, PostLogOR-0.04, max(y3)/7, lty=1, col="black", lwd=2)

segments(PostUpper, max(y3)/7, PostLogOR+0.04, max(y3)/7, lty=1, col="black", lwd=2)

segments(PriorLower, max(y1)/7, PriorPooledLogOR-0.04, max(y1)/7, lty=1, col="blue", lwd=2)

segments(PriorUpper, max(y1)/7, PriorPooledLogOR+0.04, max(y1)/7, lty=1, col="blue", lwd=2)

segments(likeLogLower, max(y2)/7.5, likeLogOR-0.04, max(y2)/7.5, lty=1, col="red", lwd=2)

segments(likeLogUpper+0.005, max(y2)/7.5, likeLogOR+0.04, max(y2)/7.5, lty=1, col="red", lwd=2)

mtext ("Odds Ratio",3, line =2, cex = 1.6)

axis (3, at=c(-0.91,-0.69, -0.51, -0.35, -0.22, -0.105, 0.0, 0.095, 0.262), labels=c(0.4,0.5, 0.6, 0.7, 0.8, 0.9, "1.0", 1.1, 1.3))

lines(x,y2,type="l",lwd=3,col="red")

lines(x,y3,type="l", lwd=3,col="black")

*#To create good margins*

mar.default <- c(5,4,4,2) + 0.1

par(mar = mar.default + c(0, 4, 0, 0))

*#To copy in eps and pdf formats to your original folder. (Change the date each time or you will overwrite.)*

dev.copy2eps(file="DMDeathMar25.eps")

dev.copy2pdf(file="DMDeathMar25.pdf")

**Bayes factors.** The use of Bayes factors (BFs) is a potentially superior approach to quantifying evidence than is the potentially conflicting mix of approaches based on *P* values and hypothesis testing.7, 26 The BF is defined as a likelihood ratio (LR) or relative likelihood of two different hypotheses and can range from 0 to ∞, with small values close to 0 simultaneously providing strong evidence against the null hypothesis and for the alternative hypothesis.7, 26, 27

Bayes factors were derived from the relation:

where the Bayes factor =

Using data from Figure 5, we obtain:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Comparison** | **Bayes Factor** | **Prior Probability (%)** | **Prior Probability** | **Prior Odds** | **Posterior Odds** | **Posterior Probability** | **Posterior Probability (%)** |
| FREEDOM | 1.19E-02 | 2.70E-04 | 2.70E-06 | 2.70E-06 | 3.22E-08 | 3.22E-08 | 3.22E-06 |

Calculations as follows26: Odds = Prob/(1-Prob). Posterior odds = Bayes factor prior odds.

Minimum Bayes factors (BF) can also be calculated from26:

using 2-tailed outputs for Z from [R] functions “pnorm” and “qnorm,” which in this case produced a value of 1.09E-02, in good agreement with the previous calculation.

**Supplemental Appendix D: Left Main Coronary Artery Disease (Not presented in text)**

 **Mixed Treatment Comparisons for Left Main Coronary Artery Disease:** A network meta-analysis allows practitioners to compare treatments indirectly when direct comparisons do not exist. No clinical-trial evidence exists to show that PCI compared with medical therapy (MT) alone improves mortality in patients with unprotected left main CAD (ULMCAD) and stable ischemic heart disease (SIHD), but the 2011 ACC/AHA revascularization guidelines5, 28 contained a Class IIa recommendation for percutaneous coronary intervention (PCI) to improve survival in selected patients with ULMCAD. The recommendation was based on the reasoning that:

 • CABG confers a survival advantage over MT for ULMCAD

 • PCI is equivalent to CABG for ULMCAD

 ∴ PCI confers a survival advantage over MT for ULMCAD

Evidence for the first premise came from subgroup analyses of 7 trials performed 30 years ago,29-35 and evidence for the second came from 4 randomized trials36-39 and 8 cohort studies,40-47 all reported during the past 10 years.

In the absence of clinical trials directly comparing PCI with MT for this indication, a Bayesian network was constructed to perform the indirect comparison.48, 49 In the Bayesian models, the treatment advantage of PCI over MT was represented as ∆PCI-MT=∆PCI­-CABG – ∆MT-CABG and inferred from summary data. Using an approach presented in Supplemental Appendix D and prior reports,48, 49 we used MCMC modeling8, 9 to draw a large simulated sample from the posterior distribution to identify accurate estimates for relative mortality rates after PCI, CABG and MT. As shown in figure below, the indirect comparison suggested a beneﬁt of PCI over MT (*OR*, 3.21; 95% BCI 2.12–5.00) and of CABG over MT (*OR*, 3.29; 95% BCI, 2.37–4.47) for 1-year mortality. There was no difference in mortality after PCI compared with CABG (*OR*, 1.03; 95% BCI 0.76–1.35).



Mortality Rates after Treatment of Left Main Coronary Artery Disease. A Bayesian network meta-analysis of 19 trials produced posterior median odds ratios and 95% credible intervals (data labels) for 1-year mortality after percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or medical therapy (MT). The distributions are plotted on the OR and *θ* (logeOR) scales. The indirect comparisons suggest that mortality rates were no different after CABG or PCI but more than 3-fold higher after MT than after PCI, and after MT than after CABG. Original caterpillar plot was created using procedures outlined below.

Because not all studies comparing PCI with CABG were randomized or matched, and many of the trials in the network analysis were published more than 30 years ago but arguably still relevant today,50 the writing committee assigned a level of evidence (LOE) B to the recommendation.5, 28 No classical statistical approach exists to directly quantify the probability of outcomes using indirect comparisons.

 To compare PCI with medical therapy (MT) for unprotected left main (LM) CAD, we have individual studies that have compared CABG with MT and CABG with PCI. Suppose that the probability of dying after CABG, MT, and PCI is *Pc*, *PM*, and *PP*. The treatment of each of these trials can be assessed through *OR*s:

The summary *OR* of indirect comparison of PCI vs. MT can be computed by the ratio of the *OR*s from the studies comparing CABG vs. MT and CABG vs. PCI:

To allow for parametric hypothesis testing (*H0*: *ORPM* = 1), a natural log transformation of the above equation yields:

.

From the model presented in Table D1 below, we obtained the posterior distribution of *exp(PC)* and *exp(MC)*, which were the summary odds ratios of PCI vs. CABG and PCI vs. MT, respectively. We also obtained *exp(PM)*, the indirect summary odds ratio of PCI vs. MT. Although the original analysis48 and details of methods can be found in original reports,49 practitioners interested in replicating the network meta-analysis can follow the methods outlined here by inputting the model, data and initial values directly into OpenBUGs or WinBUGS, using procedures in Tables D1 and D2, or by using data in Table D3 and running commands directly in [R] linked to OpenBUGS, using procedures outlined in Table D4.

**Supplement Table D1: How to Enter the Model, Data and Initial Values Directly into OpenBUGS or WinBUGS**

1. Under File, click New 3 times to open 3 new files.
2. Copy and paste the model, data and inits from Table D2 below into each of the 3 windows.
3. Under Model, click Specification, and a new window opens.
4. Place the cursor anywhere in open model window, and then click the **check model** box. At the bottom of the model window, you should see the message, model is syntactically correct.
5. Place the cursor anywhere in open data window, and then click the **load data** box. At the bottom of the model window, you should see the message, data loaded.
6. Click compile. You should see the message model compiled.
7. Place the cursor anywhere in open inits window, and then click the **load inits** box. At the bottom of the model window, you should see the message, initial values loaded...
8. Click the box **gen inits.**
9. Under Inferences, click Samples…
10. A new window opens. Enter the term lor into the node space. Click set.
11. Under Model, click Update… and change 1000 to 10000 in the updates tool. Click the update box.
12. Under Inferences, click Samples… if it is not open and review history. Enter an \* into the node and click on stats to get your results, which compare present the loge(OR) for the comparisons of CABG (1), PCI (2), and MT (3).

**Table D2: Direct-Entry Commands for WinBUGS or OpenBUGS**

#model

model

{ # i counts the two arms of all 19 studies

for (i in 1:38)

{

r[i] ~ dbin(p[i], n[i]);

logit(p[i]) <- mu[s[i]]+delta[i]\*(1-equals(t[i],b[i]));

delta[i] ~ dnorm(md[i], prec);

md[i] <- d[t[i]]-d[b[i]];

}

# j represents the CABG arm

for (j in 1:19)

{

mu[j] ~ dnorm(0, .001);

}

prec ~ dgamma(0.001, 0.001);

d[1] <- 0;

# K represents the relative treatment comparator: k=2 is PCI, k=3 is MT

for (k in 2:3)

{

d[k] ~ dnorm(0, .001)

}

for (c in 1:2)

{

for (k in (c+1):3)

{

lor[c,k] <- d[k]-d[c];

log(or[c,k]) <- lor[c,k];

}

}

}

**#data (from table**

**list(s=c(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19),t=c(1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,3,1,3,1,3,1,3,1,3,1,3,1,3),r=c(15,15,4,1,5,2,20,26,7,9,12,3,18,20,25,2,19,21,20,5,8,22,12,7,3,10,59,46,16,6,5,4,16,12,2,2,61,93),n=c(348,357,53,52,101,100,300,300,67,67,142,107,542,542,238,49,154,157,245,96,135,135,190,97,48,43,1183,309,141,24,40,17,89,32,28,31,899,440),b=c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1))**

**#inits**

**list(d=c(NA,0,0), prec=1, mu=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0))**

**Table D3. Data Format for Indirect Inference “LMNetworkData.csv”**

 s[] t[] r[] nn[] b[]

SYNTAX36 1 1 15 348 1

 1 2 15 357 1

LEMANS37 2 1 4 53 1

 2 2 1 52 1

Boudriot38 3 1 5 101 1

 3 2 2 100 1

PRECOMBAT39 4 1 20 300 1

 4 2 26 300 1

Cedars-Sinai40 5 1 7 67 1

 5 2 9 67 1

Chieffo44 6 1 12 142 1

 6 2 3 107 1

MAIN-COMPARE51 7 1 18 542 1

 7 2 20 542 1

Mäkikallio45 8 1 25 238 1

 8 2 2 49 1

Palmerini46 9 1 19 154 1

 9 2 21 157 1

Sanmartín47 10 1 20 245 1

 10 2 5 96 1

Wu42 11 1 8 135 1

 11 2 22 135 1

Brener43 12 1 12 190 1

 12 2 7 97 1

Takaro29, 52 13 1 3 48 1

 13 3 10 43 1

Chaitman30 14 1 59 1183 1

 14 3 46 309 1

Oberman31 15 1 16 141 1

 15 3 6 24 1

Cohen32 16 1 5 40 1

 16 3 4 17 1

Talano33 17 1 16 89 1

 17 3 12 32 1

European34 18 1 2 28 1

 18 3 2 31 1

Dzavik53 19 1 61 899 1

 19 3 93 440 1

**Supplemental Appendix E: Network Meta-Analysis of Mortality with Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation**

 **Network Meta-Analysis and Absolute Event Rates:** The methods presented here describe how weights obtained from the random-effects model are used to calculate annual rates for each endpoint in the group after receiving 3-6 months of DAPT and how the posterior mean *OR* and 95% BCI are used to calculate the event rates for group treated with 18-48 months of DAPT. Placing the results in the Bayesian framework seemed preferable to simply adding all the events as if they came from a single study.

 **Standard meta-analysis:** Traditional forest plots can becreated with the open-source statistical program [R] 3.0.354 and library package “meta” 3.8-0.55 For example:



The forest plot was created using data table D1 and [R] code below:

**Table E1: Major Bleeding after Prolonged or Short DAPT in Trials with a Control Group Treated with 3-6 Months of Therapy. (Table saved as “bleed3-6.csv”.)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| study | f.u | n.prolonged[] | n.short[] | b.prolonged[] | b.short[] |
| PRODIGY (24 vs. 6 mo) | 24 | 750 | 751 | 13 | 5 |
| EXCELLENT (12 vs. 6 mo) | 12 | 721 | 722 | 4 | 2 |
| RESET (12 vs. 3 mo) | 12 | 1058 | 1059 | 6 | 2 |
| OPTIMIZE (12 vs. 3 mo) | 12 | 1556 | 1563 | 14 | 10 |
| SECURITY (12 vs. 6 mo) | 12 | 717 | 682 | 8 | 4 |
| ITALIC (24 vs. 6 mo) | 12 | 910 | 912 | 3 | 0 |
| ISAR-SAFE (12 vs. 6 mo) | 12 | 2003 | 1997 | 5 | 4 |
| I-LOVE-IT 2 (12 vs. 6 mo) | 18 | 920 | 909 | 6 | 12 |
| IVUS-XPL (12 vs. 6 mo) | 12 | 701 | 699 | 7 | 5 |

where: n.prolonged = number of patients receiving prolonged dual antiplatelet therapy (DAPT), n.short = number of patients receiving 3-6 months of DAPT, r.prolonged = number of bleeds in the prolonged DAPT group, r.short = number of bleeds in the short DAPT group, and W(random) = weights from random-effects model.

**[R] code for the creating forest plot and for calculating weighted bleeding rates using data in Table E1:** The [R] code is in a file entitled, “MetaDAPTBleed3-6.R” and can be found at:

<https://www.dropbox.com/sh/0pziu9ct6qzrnge/AABdt3VDr2IJUdDvz6W_-7kXa?dl=0>

Remember in [R] to load the following packages:

> library(meta)

Loading 'meta' package (version 4.1-0).

> library(BRugs)

Welcome to BRugs connected to OpenBUGS version 3.2.3

*#Export data from Excel in tab-delimited, semicolon- or comma-separated*

*#form ? file ending in “csv” (see manual “R Data Import/Export”) into file called bdat*

ddat<-read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/DAPT3-6.csv",as.is=TRUE, header=T)

str(ddat)

study<-c(ddat$study)

b.prolonged<-c(ddat$b.prolonged)

n.prolonged<-c(ddat$n.prolonged)

b.short<-c(ddat$b.short)

n.short<-c(ddat$n.short)

f.u<-c(ddat$f.u)

mddat<-data.frame(study,n.prolonged,n.short,b.prolonged,b.short,f.u)

mddat

md1 = metabin(b.prolonged, n.prolonged, b.short, n.short, sm = "OR", data = mddat, studlab = study)

str(md1)

class(md1)

md1

summary(md1)

forest(md1,col.square="red",col.diamond="red",col.i.inside.square="white",rightcols=c("effect", "ci","w.random"),title="test",smlab="Bleeds in 3-6 mo RCTs",pooled.events=TRUE,lab.e="Prolonged",lab.c="Short",xlim=c(0.1,10),xlab="Prolonged better        Short better")

*#text("Title", .5, .75, gp=gpar(cex=2))*

mar.default <- c(5,4,4,2) + 0.1

par(mar = mar.default + c(0, 4, 0, 0))

*#store image files as eps and pdf formats*

dev.copy2eps(file="WeightsDAPTBleed3-6Dec23.2016.eps")

dev.copy2pdf(file="WeightsDAPTBleed3-6Dec23.2016.pdf")

*#######################################################*

*#Calculate weighted absolute event rates for the control group (short DAPT)*

*#get meta outputs, which includes random-effects weights*

bweights<-data.frame(md1)

*#get random-effects weights from meta output*

bweight<-subset(bweights,select=c(w.random))

*#normalize weights to total 1.00*

bsum.weight<-sum(bweight$w.random)

weight100<-bweight/bsum.weight

*#calculate event rates*

r.short<-b.short/n.short

*#calculate annual event rates*

r12.short<-12\*r.short/f.u

*#Calculate weighted annual event rates*

w.short<-r12.short\*weight100

ShortDAPTBleedRate<-sum(w.short)

print("Weighted Bleed Rate after short DAPT =")

print(ShortDAPTBleedRate)

The output is a forest plot and weighted annual bleeding rate during follow-up in the groups treated with 3-6 months of DAPT. Using the OR and 95% Bayesian confidence intervals from the network meta-analysis (Fig. 3 in the main MS) and standard methods,56 one obtains the corresponding bleeding rate from the Bayesian model for the group treated with 18-48 months of DAPT, absolute differences, and numbers needed to treat to harm.

**Table E2: Data Table for DAPT Network Meta-Analysis: Mortality**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | s[] | t[] | r[] | nn[] | b[] |
| DES-LATE (36 vs. 12 mo) | 1 | 2 | 32 | 2514 | 1 |
| DES-LATE (36 vs. 12 mo) | 1 | 3 | 46 | 2531 | 1 |
| PRODIGY (24 vs. 6 mo) | 2 | 1 | 45 | 751 | 1 |
| PRODIGY (24 vs. 6 mo) | 2 | 3 | 49 | 750 | 1 |
| EXCELLENT (12 vs. 6 mo) | 3 | 1 | 4 | 722 | 1 |
| EXCELLENT (12 vs. 6 mo) | 3 | 2 | 7 | 721 | 1 |
| RESET (12 vs. 3 mo) | 4 | 1 | 5 | 1059 | 1 |
| RESET (12 vs. 3 mo) | 4 | 2 | 8 | 1058 | 1 |
| OPTIMIZE (12 vs. 3 mo) | 5 | 1 | 43 | 1563 | 1 |
| OPTIMIZE (12 vs. 3 mo) | 5 | 2 | 45 | 1556 | 1 |
| ARCTIC (18 vs. 12 mo) | 6 | 2 | 9 | 624 | 1 |
| ARCTIC (18 vs. 12 mo) | 6 | 3 | 7 | 635 | 1 |
| SECURITY (12 vs. 6 mo) | 7 | 1 | 8 | 682 | 1 |
| SECURITY (12 vs. 6 mo) | 7 | 2 | 8 | 717 | 1 |
| DAPT (30 vs. 12 mo) | 8 | 2 | 74 | 4941 | 1 |
| DAPT (30 vs. 12 mo) | 8 | 3 | 98 | 5020 | 1 |
| ITALIC (24 vs. 6 mo) | 9 | 1 | 8 | 912 | 1 |
| ITALIC (24 vs. 6 mo) | 9 | 3 | 7 | 910 | 1 |
| ISAR-SAFE (12 vs. 6 mo) | 10 | 1 | 8 | 1997 | 1 |
| ISAR-SAFE (12 vs. 6 mo) | 10 | 2 | 12 | 2003 | 1 |
| OPTIDUAL (48 vs. 12 mo) | 11 | 2 | 24 | 690 | 1 |
| OPTIDUAL (48 vs. 12 mo) | 11 | 3 | 16 | 695 | 1 |
| I-LOVE-IT 2 (12 vs. 6 mo) | 12 | 1 | 11 | 909 | 1 |
| I-LOVE-IT 2 (12 vs. 6 mo) | 12 | 2 | 14 | 920 | 1 |
| IVUS-XPL (12 vs. 6 mo) | 13 | 1 | 5 | 699 | 1 |
| IVUS-XPL (12 vs. 6 mo) | 13 | 2 | 10 | 701 | 1 |

**R Code for Network Meta-Analysis for DAPT Mortality and Caterpillar Plot:** The [R] code is in a file entitled, “NetworkDAPTDeathReadDataCaterpillar” and can be found at:

<https://www.dropbox.com/sh/0pziu9ct6qzrnge/AABdt3VDr2IJUdDvz6W_-7kXa?dl=0>

Remember in [R] to load the following packages:

> library(meta)

Loading 'meta' package (version 4.1-0).

> library(BRugs)

Welcome to BRugs connected to OpenBUGS version 3.2.3

*#Export data from Excel in comma-separated format containing a csv suffix:*

DDdat<read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/NetworkDAPTDeath.csv",as.is=TRUE, header=T)

str(DDdat)

s<-c(DDdat$s)

t<-c(DDdat$t)

r<-c(DDdat$r)

nn<-c(DDdat$nn)

b<-c(DDdat$b)

*#Specify the model in BUGS language, but save it as a string in [R]*

modelString="

model

{ # i counts the two arms of all 11 studies

for (i in 1:26)

{

r[i] ~ dbin(p[i], nn[i]);

logit(p[i]) <- mu[s[i]]+delta[i]\*(1-equals(t[i],b[i]));

delta[i] ~ dnorm(md[i], prec);

md[i] <- d[t[i]]-d[b[i]];

}

# j represents the CABG arm

for (j in 1:13)

{

mu[j] ~ dnorm(0, .001);

}

prec ~ dgamma(0.001, 0.001);

d[1] <- 0;

# K represents the relative treatment comparator: k1 = Short, k=2 is 12 mo, k=3 is Long

for (k in 2:3)

{

d[k] ~ dnorm(0, .001)

}

for (c in 1:2)

{

for (k in (c+1):3)

{

lor[c,k] <- d[k]-d[c];

log(or[c,k]) <- lor[c,k];

}

}

}

  "

*# Write the modelString to a file*

writeLines (modelString,con="model.txt")

*# Use BRugs to check model*

modelCheck ("model.txt")

*#load data*

dataList = list(s=c(s),

     t=c(t),

     r=c(r),

     nn=c(nn),

     b=c(b)

)

*#Use BRugs commands to put the data into a file and ship the file to BUGS*

modelData(bugsData(dataList))

*#Initialize the chains*

nChain=1

modelCompile(numChains = nChain) *#Compile the model*

initsList = list(d=c(NA,0,0), prec=1, mu=c(0,0,0,0,0,0,0,0,0,0,0,0,0))

modelInits(bugsData(initsList))

modelGenInits()

*#R defines a new variable to specify an arbitrary chain length*

chainLength1 = 5000

*#BRugs tells BUGS to generate a MCMC chain*

modelUpdate (chainLength1)

*#BRugs keeps a record of parameters*

samplesSet(c("lor"))

*#BRugs asks BUGS for summary statistics*

chainLength2 = 10000

thinStep = 2

modelUpdate (chainLength2)

thetaSummaryObs = samplesStats (c("lor")); thetaSummaryObs

thetaSummaryObs<-thetaSummaryObs[order(thetaSummaryObs$mean),]

expTheta<-exp(thetaSummaryObs)

print(thetaSummaryObs)

print(expTheta)

*#forest plot*

x<-seq(from=-0.8,to=0.6,by=0.01)

*#Short vs. 12 mo*

x<-thetaSummaryObs$mean

y<-c(1,2,3)

plot(x,y,xlim=c(-0.7,0.6),ylim=c(3.5,0),pch=23,cex=4,ylab="",yaxt="n",col="black",bg="lightblue", cex.axis=1.0, xlab="log(e)OR", cex.lab=1.6)

axis (4, pos=0.0, tck = 0, labels=FALSE, col="black")

text (-0.555,1,"3-6 months vs. 12 months", cex= 1.4)

text (-0.53,3,"3-6 months vs. 18-48 months",cex = 1.4)

text (-0.54,2, "12 months vs. 18-48 months", cex = 1.4)

text (-0.55, 0,"All-Cause Mortality",cex = 1.6,font =2)

text (-0.55, 0.2,"With Prolonged DAPT",cex = 1.6,font =2)

text (thetaSummaryObs$mean[3], 3.2, font=2, round(expTheta$mean[3],2))

text (thetaSummaryObs$val2.5pc[3], 3.2, font=2,round(expTheta$val2.5pc[3],2))

text (thetaSummaryObs$val97.5pc[3], 3.2, font=2,round(expTheta$val97.5pc[3],2))

text (thetaSummaryObs$mean[1],1.2,font=2,round(expTheta$mean[1],2))

text (thetaSummaryObs$val2.5pc[1], 1.2, font=2,round(expTheta$val2.5pc[1],2))

text (thetaSummaryObs$val97.5pc[1], 1.2, font=2,"1.40")

text (thetaSummaryObs$mean[2], 2.2,  font=2,round(expTheta$mean[2],2))

text (thetaSummaryObs$val2.5pc[2], 2.2,  font=2,round(expTheta$val2.5pc[2],2))

text (thetaSummaryObs$val97.5pc[2], 2.2,  font=2,round(expTheta$val97.5pc[2],2))

segments(thetaSummaryObs$val2.5pc[3], 3, thetaSummaryObs$mean[3]-0.025, 3, lty=1, col="black", lwd=3)

segments(thetaSummaryObs$val97.5pc[3], 3, thetaSummaryObs$mean[3]+0.025, 3, lty=1, col="black", lwd=3)

segments(thetaSummaryObs$val2.5pc[1], 1, thetaSummaryObs$mean[1]-0.025, 1, lty=1, lwd=3)

segments(thetaSummaryObs$val97.5pc[1], 1, thetaSummaryObs$mean[1]+0.025, 1, lty=1,  lwd=3)

segments(thetaSummaryObs$val2.5pc[2], 2, thetaSummaryObs$mean[2]-0.025, 2, lty=1,  lwd=3)

segments(thetaSummaryObs$val97.5pc[2], 2, thetaSummaryObs$mean[2]+0.025, 2, lty=1,  lwd=3)

mtext ("Posterior Odds Ratio (OR)",3, line =2, cex = 1.6)

axis (3, at=c(-0.91,-0.69, -0.51,-0.35, -0.22, -0.105,0.0, 0.095,0.182, 0.262,0.336, 0.405,0.47,0.531,0.588,0.693, 0.833, 0.956, 1.10,1.19, 1.281,1.386,1.46,1.53,1.61,1.67,1.72,1.79), labels=c(0.4,0.5,0.6, 0.7, 0.8,0.9, "1.0", 1.1,1.2, 1.3,1.4,1.5, 1.6,1.7, 1.8, "2.0", 2.3, 2.6, "3.0", 3.3,3.6,"4.0",4.3,4.6,"5.0",5.3,5.6,"6.0"))

*#To create good margins*

mar.default <- c(5,4,4,2) + 0.0

par(mar = mar.default + c(0, 2, 0, 0))

*#To copy in eps and pdf formats to your original folder. (Change the date each time or you will overwrite.)*

dev.copy2eps(file="NetworkDAPTDeathMar25Caterpillar.eps")

dev.copy2pdf(file="NetworkDAPTDeathMar25Caterpillar.pdf")

**Supplemental Appendix F: Hierarchical Model for Cross-Design Meta-Analysis**

 **Justification:** In this setting a hierarchical model is appropriate, because when we have uncertainty about a parameter such as *θ*, which reflects the overall treatment difference between the 2 PCI strategies, we make inferences about it. When other parameters such as , reflecting treatment differences from studies *i* = 1,…*n* of study type *k* = 1,…*n*, are also uncertain but dependent on an uncertain parameter such as *θ*, we have a chain of uncertainty, formalized in a hierarchical model.2Following the guidance of prior reports,57, 58 we chose some informative prior distributions for the model.

**[R] code for Bayesian cross-design meta-analysis using imbedded data:** The [R] code can be found in a file entitled, “CrossDesignBRugs18Studies.R” and can be found at:

<https://www.dropbox.com/sh/0pziu9ct6qzrnge/AABdt3VDr2IJUdDvz6W_-7kXa?dl=0>

Remember in [R] to load the following packages:

> library(meta)

Loading 'meta' package (version 4.1-0).

> library(BRugs)

Welcome to BRugs connected to OpenBUGS version 3.2.3

***#Specify the model in BUGS language, but save it as a string in [R]***

**modelString="**

**model**

**{**

**# K1 is the number of trials;**

**for (k in 1:18)**

**{**

**# calculate odds ratios;**

**or[k] <- ((r.multi[k]+0.5)/(n.multi[k]-r.multi[k]+0.5))/((r.culprit[k]+0.5)/(n.culprit[k]-r.culprit[k]+0.5))**

**logor[k] <- log(or[k]);**

**varlogor[k] <- (1/(r.multi[k]+0.5))+(1/(n.multi[k]-r.multi[k]+0.5))+(1/(r.culprit[k]+0.5))+(1/(n.culprit[k]-r.culprit[k]+0.5));**

**invlogor[k] <- 1/varlogor[k];**

**logor[k] ~ dnorm(theta[k], invlogor[k]);**

**or.est[k] <- exp(theta[k]);**

**# study-type level random-effects distributions**

**theta[k] ~ dnorm(mu.theta.study[study[k]], prec.theta.study[study[k]]);**

**}**

**# K2 is the number of study types**

**for (l in 1:3)**

**{**

**mu.theta.study[l] ~ dnorm(mu.theta, prec.theta);**

**or.theta.study[l] <- exp(mu.theta.study[l]);**

**prec.theta.study[l] <- 1/(tau.theta.study[l]\*tau.theta.study[l]);**

**# prior distribution for tau.theta.study based on HN[0.36^2], giving precision 7.72**

**tau.theta.study[l] ~ dnorm(0, 7.72)I(0,);**

**}**

**# prior distribution for mu.theta based on log(500)/1.96 = 3.17 for N[0,10], giving precision 0.1**

**mu.theta ~ dnorm(0, 0.1);**

**# prior distribution for tau.theta based on HN[0.18^2], giving precision 30.86**

**tau.theta ~ dnorm(0, 30.86)I(0,);**

**prec.theta <- 1/(tau.theta\*tau.theta);**

**# global summary odds ratio;**

**or.theta <- exp(mu.theta);**

**# K1 is the number of trials;**

**# DATA list(K1=21, K2=3);**

**# INITIAL VALUES list(mu.theta=0, tau.theta = 1);**

**# BUGS model specification ends**

**} .**

 **"**

***# Write the modelString to a file***

**writeLines (modelString,con="model.txt")**

***# Use BRugs to check model***

**modelCheck ("model.txt")**

***#load data***

**dataList = list(n.multi=c(52, 65, 234, 150, 79, 503, 403, 26, 95, 147, 3134, 70, 217, 419, 1108, 442, 77, 367),**

 **n.culprit=c(17, 84, 231, 146, 79, 503, 2418, 354, 25, 156, 25802, 707, 1984, 2118, 3833, 1467, 180, 706),**

 **r.multi=c(1, 6, 12, 4, 19, 59, 41, 5, 9, 12, 246, 11, 27, 6, 81, 12, 2, 26),**

 **r.culprit=c(0, 13, 16, 10, 13, 54, 164, 42, 2, 8, 1321, 57, 111, 72, 168, 40, 14, 127),**

 **study=c(1, 1, 1, 1, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)**

**)**

***#Use BRugs commands to put the data into a file and ship the file to BUGS***

**modelData(bugsData(dataList))**

***#Initialize the chains***

**nChain=1**

**modelCompile(numChains = nChain) *#Compile the model***

**initsList = list(mu.theta=0, tau.theta=1)**

**modelInits(bugsData(initsList))**

**modelGenInits()**

***#R defines a new variable to specify an arbitrary chain length***

**chainLength1 = 5000**

***#BRugs tells BUGS to generate a MCMC chain***

**modelUpdate (chainLength1)**

***#BRugs keeps a record of parameters***

**samplesSet(c("mu.theta","prec.theta","or.theta","tau.theta"))**

***#BRugs asks BUGS for summary statistics***

**chainLength2 = 10000**

**thinStep = 2**

**modelUpdate (chainLength2)**

**thetaSummary = samplesStats (c("mu.theta","prec.theta","or.theta","tau.theta"));**

**print(thetaSummary)**

**output**

> source("Z:\\Users\\jabittl\\Dropbox\\BayesCulpritCCI\\BRugs18StudiesCrossDesign.R")

model is syntactically correct

data loaded

model compiled

Initializing chain 1:

initial values loaded but chain contain uninitialized variables

initial values generated, model initialized

5000 updates took 0 s

monitor set for variable 'mu.theta'

monitor set for variable 'prec.theta'

monitor set for variable 'or.theta'

monitor set for variable 'tau.theta'

10000 updates took 0 s

 mean sd MC\_error val2.5pc median val97.5pc start sample

mu.theta **8.358e-02 1.803e-01** 6.970e-03 -0.301500 0.09143 4.089e-01 5001 10000

prec.theta 1.080e+05 2.844e+06 8.695e+04 6.367000 47.98000 2.273e+04 5001 10000

or.theta 1.105e+00 1.959e-01 7.564e-03 **0.739700 1.09600 1.505e+00** 5001 10000

tau.theta 1.579e-01 1.063e-01 3.704e-03 0.006652 0.14440 3.964e-01 5001 10000

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