Supplemental Appendix

Likelihood

Similar to the calculation for the prior distribution, we need to set $y_m = log_e(OR_n) = \hat{\theta}$, and $\sigma^2/n = V(\hat{\theta})$, given by

$$\hat{\theta} = log\left[\frac{(a + \frac{1}{2})(d + \frac{1}{2})}{(b + \frac{1}{2})(c + \frac{1}{2})}\right], \qquad (Appendix\ 1a)$$

where $\hat{\theta}$ represents an estimate of θ and, from the FREEDOM results (Table I bottom), a=83, b=114, c=761–83, and d=699–114. The estimator has an approximate variance

$$V(\hat{\theta}) = \frac{1}{a + \frac{1}{2}} + \frac{1}{b + \frac{1}{2}} + \frac{1}{c + \frac{1}{2}} + \frac{1}{d + \frac{1}{2}}. \qquad (2a)$$

The likelihood is described by y_n = 0.629, estimated $log_e(OR)$ = -0.463 (from Eq. 1a) and standard error $\sigma/\sqrt{171} = 0.153$, and variance V of 0.023 = 0.153^2 (Eq. 4a). The 95% CI for y_n of -0.463 are given by $\pm 1.96 \times \sigma/\sqrt{171} = \pm 0.300$, which gives rise to values extending from -0.763 to -0.163. Exponentiation of y_n and its 95% CI leads to the values given in the text.

Conjugate Normal Model

Given that the normal prior $\theta \sim N[\mu_m, \sigma_m^2/m_0]$ (MS Eq. 2) and the normal likelihood $y_n \sim N[\mu_n, \sigma_n^2/n_0]$ (Eq. 7) belong to the same family of mathematical functions, we have thus defined a "conjugate normal model":

$$p(\theta|y_n) \propto p(y_n|\theta)p(\theta) \propto \exp\left[-\frac{(y_n - \theta)^2 n}{2\sigma_n^2}\right] \times \exp\left[-\frac{(\theta - \mu_m^2)m_0}{2\sigma_m^2}\right],$$

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

$$(y_n - \theta)^2 m + (\theta - \theta_0)^2 m_0 = \left(\theta - \frac{m_0\theta_0 + ny_n}{m_0 + n}\right)^2 (m_0 + n) + (y_m - \mu_m)^2 \left(\frac{1}{n} + \frac{1}{m_0}\right),$$

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

$$p(\theta|y_n) = N\left[\theta \mid \frac{m_0\mu_m + ny_n}{m_0 + n}, \frac{\sigma^2}{m_0 + n}\right]. \qquad (3a)$$

This equation states that the posterior mean $(m_0\mu + ny_n)/(m_0 + n)$ is an average of the prior mean μ and parameter estimate y_m, which equals $log_e(OR_m)$, weighted by their respective number of observations n_0 and m, and is thus a compromise between the 2.

The posterior distribution, which is based on the equivalent number of observations in the posterior of $m_0 + n = 397$ $(227 + 171)$, yields a value for θ of -0.593, obtained by using Equation 7 $(m_o\mu + ny_n)/(m_0 + n)$ = -0.593 and solving (227 · [-0.70] + 171 · [-0.46])/397). The standard error is given by $\sigma/\sqrt{m_0 + n} = 2/\sqrt{397} = 0.100$ (Eq. 7). The 95% posterior Bayesian credible intervals (BCI) for θ of -0.593 are given by $\pm 1.96 \times \sigma/\sqrt{397} = \pm 0.196$, which gives rise to values extending from -0.396 to -0.789. Exponentiation of θ and its 95% BCI leads to an estimated OR of 0.55 presented in the text.

Bayesian hierarchical model

It is reasonable to model such a problem hierarchically with observable outcomes OR_i modeled conditionally on certain parameters θ_i, which themselves are given probabilistic specification in terms of an additional parameters θ

$$\begin{aligned} \theta_i|\theta,\tau^2 &\overset{independent}{\sim} N(\theta,\tau^2), \\ (\theta,\tau^2) &\sim p(\theta,\tau^2), \end{aligned} \qquad (4a)$$

where OR_i denotes the odds ratio for mortality after CABG compared with PCI in the i-th (i =1, ... 9) study (Table I), θ_i the unknown study-level treatment effect, s_i^2 the (asymptotic) variance of $log_e(OR_i)$, θ the population-average treatment effect, and τ^2 the between-study variance of study-level effects.

In a Bayesian meta-analysis, there is a separate parameter for mean treatment effect in each trial θ_i, though a structured prior can be formulated to state that these treatment effects should not be too different from each other in a hierarchical model, where a common underlying mean efficacy is postulated and each trial effect is independently distributed around this mean.[20] Thus, $log_e(OR_i)$ and s_i^2 can be calculated using the number of cases and mortalities from the summary data (Report Table I).

Compared with the fixed-effects approach to meta-analysis (i.e., assuming $\theta_1 = \theta_2 = \cdots = \theta$), the random-effects meta-analysis model can acknowledged the existence of between-study variation and incorporated it explicitly into the estimation process. The prior belief about the summary effect size θ and between-study heterogeneity can be incorporated into the prior distribution $p(\theta, \tau^2)$.

In the absence of strong quantifiable beliefs about the magnitude or ranges of θ and τ^2 before the publication of the BARI substudy results, we impose non-informative (or vague) priors so that the posterior inference would be dominated by the likelihood of the data. The aim is to emulate the Peto fixed-effect meta-analysis of 9 trials, comparing CABG with PCI for diabetic patients with multivessel CAD, and to incorporate prior information through the use of a prior distribution on the common odds ratio. We choose independent priors (mu.theta) for θ and τ^2 as $\theta \sim N(0, 10^3)$. A normal likelihood with a large variance is sometimes referred to as "non-informative" distribution.

[R] codes

```
#Export data from Excel in comma-separated format
dmdat<-read.csv("Z:/Users/jabittl/Dropbox/BayesDM/DMDeath.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$n.pci)
m.theta<-c(dmdat$m.theta)
logOR<-c(dmdat$logOR)
#Convert to data frame with all variables listed as col heads
mdmdat<-data.frame(study,m.theta,logOR)
mdmdat
#Split dataframe "mbleeddat" into subsets, separated by year of report
old<-subset(mdmdat,n.cabg<=500)
new<-subset(mdmdat,n.cabg>=500)
#calculate m.0 for prior distribution
m.0<-sum(c(old$m.theta))
#sum log odds weighted by m/m.0
```

```
# 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 n.0 for likelihood
n.0 <- sum(c(new$m.theta))
likeLogSD<-2/(sqrt(n.0))
#To provide trial weighting by proportion of radial cases
#radWt <- sum(highradial$radial)
#FREEDOM
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)
```

```
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=2,col="skyblue")
axis (4, pos=0.0, tck = 0, labels=FALSE, col="black")
text (-0.8,3,"Prior (8 trials)",col="skyblue", cex= 1.4, font=3)
text (-0.12,2.5,"Likelihood (FREEDOM)",col="red",cex = 1.4, font =3)
#text (-0.12,4.0,"NAPLES 3, BRIGHT,",col="red",cex = 1.4, font =3)
#text (-0.12, 3.3, "HEAT PPCI & BRAVE 4)",col="red",cex = 1.4, font=3)
#text (-0.24, 0.5, "0.78 (0.61-1.01)")
text (-0.35, 3.5, "Posterior", cex = 1.4, font=3)
text (-0.95, 4,"Death",cex = 1.6)
#text (-0.85, 7, "by Study Age", cex = 1.6)
#text (PostLogOR, 1.1, round(PostOR,2))
#text (PostLower-0.034, 1.1, round(PostLowerCI,2))
```

```
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))
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=2,col="red")
lines(x,y3,type="l", lwd=2,col="black")
mar.default <- c(5,4,4,2) + 0.1
par(mar = mar.default + c(0, 4, 0, 0))
dev.copy2eps(file="CIbyFREEDOMDMDeath.eps")
dev.copy2pdf(file="CIbyFREEDOMDMDeath.pdf")
```

Weighted Meta-Analysis by use of Drug-Eluting Stents (DES)

```
#Export data from Excel in comma-separated format
dmdat<-read.csv("Z:/Users/jabittl/Dropbox/BayesDM/DMDeath.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$n.pci)
a.LIMA<-c(dmdat$a.LIMA)
a.DES<-c(dmdat$a.DES)
a.age<-c(dmdat$a.age)
m.theta<-c(dmdat$m.theta)
logOR<-c(dmdat$logOR)
#Convert to data frame with all variables listed as col heads
mdmdat<-data.frame(study,m.theta,logOR,a.LIMA,a.DES,a.age)
mdmdat
#Split dataframe "mdmdat" into subsets, separated by FREEDOM
free<-subset(mdmdat,n.cabg>=500)
old<-subset(mdmdat,n.cabg<500)
#calculate m.0 for prior distribution and apply weights
m.0<-sum(c(old$m.theta)*(old$a.DES))
#sum log odds weighted by m/m.0
for (k in 1:8)
{
# calculate weighted log odds ratios, alpha = by DES;
PriorLogOdds <- (old$a.DES)*((old$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)
```

```
UpperCI <- exp(PriorUpper)
#To get the SD of the backtransformed data in a normal distribution
#---------------------------------------------------------------------------
#calculate n.0 for likelihood for FREEDOM
n.0 <- sum(c(free$m.theta))
likeLogSD<-2/(sqrt(n.0))
# calculate weighted log odds ratios;
#FREEDOM
for (k in 1:1)
{
# calculate weighted log odds ratios;
LikeLogOdds <- ((free$m.theta)/n.0)*(free$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)
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 <-
```

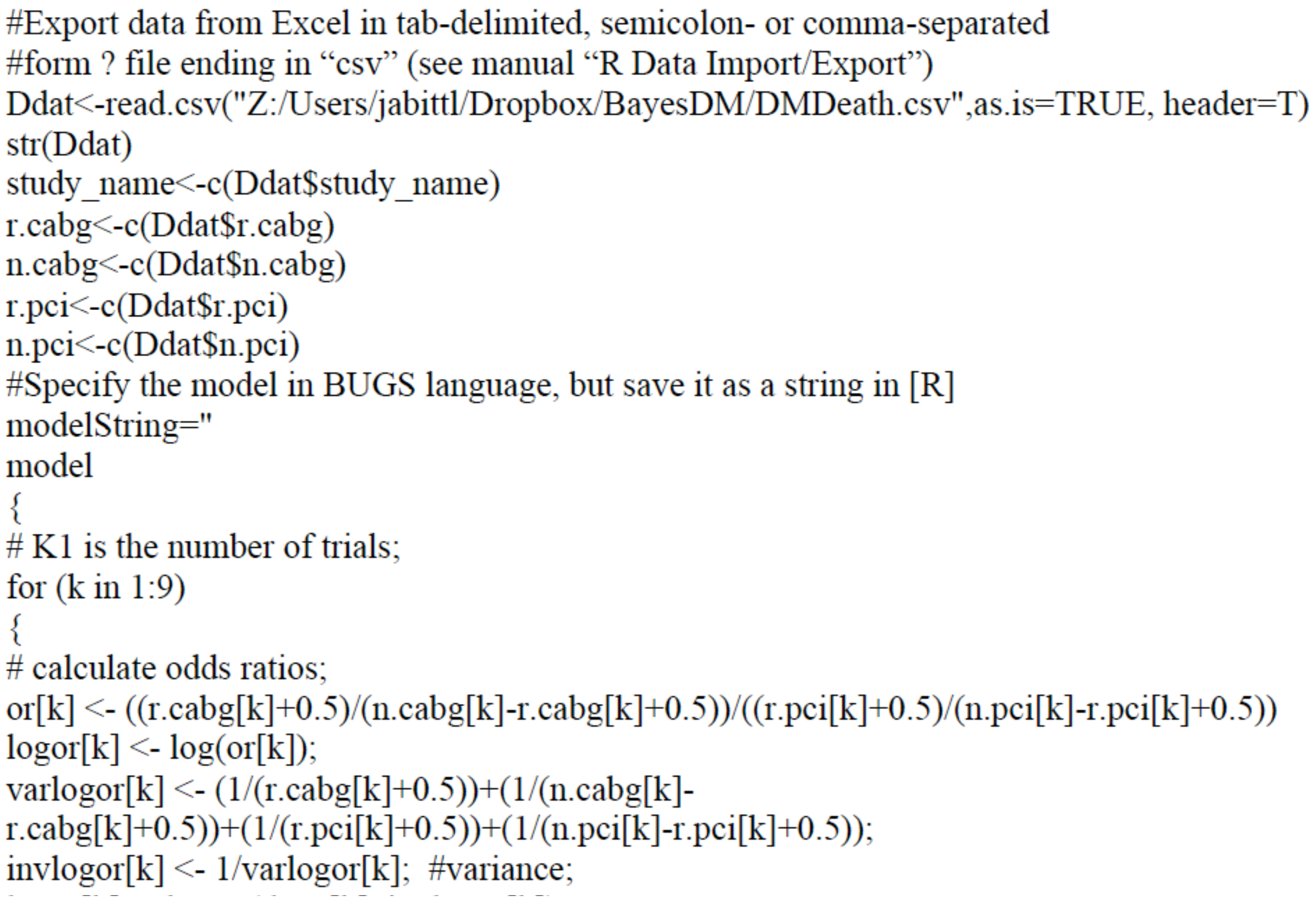
```
like <- data.frame (likeData)
print (like)
PostLogVariable <- c("PostLogOR", "PostLower", "PostUpper", "PostLogSD")
PostLogResult <- c(PostLogOR, PostLower, PostUpper, PostLogSD)
PostLog <- data.frame(PostLogVariable, PostLogResult)
PostVariable <- c("PostOR", "PostLowerCI", "PostUpperCI")
PostResult <- 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=2,col="skyblue")
axis (4, pos=0.0, tck = 0, labels=FALSE, col="black")
text (-0.8,2,"Prior (8 trials)",col="skyblue", cex= 1.4, font=3)
text (-0.08,2.2,"Likelihood (FREEDOM)",col="red",cex = 1.4, font =3)
#text (-0.12, 3.3, "BRIGHT, HEAT PPCI)",col="red",cex = 1.2, font=3)
text (-0.3, 3.0, "Posterior", cex = 1.4, font=3)
text (-0.95, 3.25, "DES", cex = 1.6)
text (PostLogOR, 0.5, round(PostOR,2))
text (PostLower-0.05, 0.5, round(PostLowerCI,2))
text (PostUpper+0.05, 0.5, round(PostUpperCI,2))
text(-0.9,1,"CABG better",cex=1.2, font=3)
text(0.2,1,"PCI better",cex=1.2, font=3)
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=2,col="red")
lines(x,y3,type="l", lwd=2,col="black")
mar.default <- c(5,4,4,2) + 0.1
par(mar = mar.default + c(0, 4, 0, 0))
dev.copy2eps(file="byFREEDOMConjNormalAlphaDES.eps")
dev.copy2pdf(file="byFREEDOMConjNormalAlphaDES.pdf")
```

Hierarchical Model: The posterior variance (1/precision) is based on an implicit sample size equivalent to the sum of the prior “sample size” m_0 and sample size of the data m. If we recognize that $\tau^2 = 1/\sigma^2$, we can use the general notations for the prior $\theta \sim N[\mu, 1/\tau^2]$ from Eq. 2 and the likelihood $y_n \sim N[\theta, \sigma^2/n]$ from Eq. 6, and the posterior distribution

$$p(\theta|y_n) = N\left[\theta \mid \frac{\frac{\mu}{\tau^2}+\frac{y_n}{\sigma_n^2}}{\frac{1}{\tau^2}+\frac{1}{\sigma_n^2}}, \frac{1}{\frac{1}{\tau^2}+\frac{1}{\sigma_n^2}}\right].$$

```
#Export data from Excel in tab-delimited, semicolon- or comma-separated
#form ? file ending in “csv” (see manual “R Data Import/Export”)
Ddat<-read.csv("Z:/Users/jabittl/Dropbox/BayesDM/DMDeath.csv",as.is=TRUE, header=T)
str(Ddat)
study_name<-c(Ddat$study_name)
r.cabg<-c(Ddat$r.cabg)
n.cabg<-c(Ddat$n.cabg)
r.pci<-c(Ddat$r.pci)
n.pci<-c(Ddat$n.pci)
#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 1:9)
{
# calculate odds ratios;
or[k] <- ((r.cabg[k]+0.5)/(n.cabg[k]-r.cabg[k]+0.5))/((r.pci[k]+0.5)/(n.pci[k]-r.pci[k]+0.5))
logor[k] <- log(or[k]);
varlogor[k] <- (1/(r.cabg[k]+0.5))+(1/(n.cabg[k]-
r.cabg[k]+0.5))+(1/(r.pci[k]+0.5))+(1/(n.pci[k]-r.pci[k]+0.5));
invlogor[k] <- 1/varlogor[k];  #variance;
logor[k] ~ dnorm(theta[k], invlogor[k]);
or.est[k] <- exp(theta[k]);
theta[k] ~ dnorm(mu.theta, prec.theta); # random effects distribution;
}
mu.theta ~ dnorm(0, 0.001); # uninformative prior distribution
prec.theta ~ dgamma(0.001, 0.001);  # uninformative prior distribution;
or.theta <- exp(mu.theta);
# probability of mean effect greater than zero;
pmu0 <- equals(min(mu.theta,0),0);
theta.new ~ dnorm(mu.theta, prec.theta);  # predicted theta for a new study;
or.new <- exp(theta.new);  # calculate the new OR;
# 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
```

$$p(\theta|y_n) = N\left[\theta \mid \frac{\frac{\mu}{\tau^2}+\frac{y_n}{\sigma_n^2}}{\frac{1}{\tau^2}+\frac{1}{\sigma_n^2}}, \frac{1}{\frac{1}{\tau^2}+\frac{1}{\sigma_n^2}}\right].$$



```
#Export data from Excel in tab-delimited, semicolon- or comma-separated
#form ? file ending in “csv” (see manual “R Data Import/Export”)
Ddat<-read.csv("Z:/Users/jabittl/Dropbox/BayesDM/DMDeath.csv",as.is=TRUE, header=T)
str(Ddat)
study_name<-c(Ddat$study_name)
r.cabg<-c(Ddat$r.cabg)
n.cabg<-c(Ddat$n.cabg)
r.pci<-c(Ddat$r.pci)
n.pci<-c(Ddat$n.pci)
#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 1:9)
{
# calculate odds ratios;
or[k] <- ((r.cabg[k]+0.5)/(n.cabg[k]-r.cabg[k]+0.5))/((r.pci[k]+0.5)/(n.pci[k]-r.pci[k]+0.5))
logor[k] <- log(or[k]);
varlogor[k] <- (1/(r.cabg[k]+0.5))+(1/(n.cabg[k]-
r.cabg[k]+0.5))+(1/(r.pci[k]+0.5))+(1/(n.pci[k]-r.pci[k]+0.5));
invlogor[k] <- 1/varlogor[k];  #variance;
```