Supplemental Appendix

Likelihood

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

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

(Appendix 1a)

where \( \hat{\theta} \) represents an estimate of \( \theta \) 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

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

(2a)

The likelihood is described by \( y_n = 0.629 \), estimated \( \text{log}_e(OR) = -0.463 \) (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 \( \theta \sim N[\mu_m, \sigma^2/m_0] \) (MS Eq. 2) and the normal likelihood \( y_n \sim N[\mu_n, \sigma^2/n_0] \) (Eq. 7) belong to the same family of mathematical functions, we have thus defined a “conjugate normal model”:

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

ignoring irrelevant terms that do not include \( \theta \). By matching terms in \( \theta \) it can be shown that:

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

indicating that the term involving \( \theta \) is arising from the posterior distribution

\[
p(\theta | y_n) = N \left[ \theta \mid \frac{m_0 \theta_0 + n y_n}{m_0 + n}, \frac{\sigma^2}{m_0 + n} \right].
\]

(3a)

This equation states that the posterior mean \( (m_0 \theta_0 + n y_n)/(m_0 + n) \) is an average of the prior mean \( \mu \) and parameter estimate \( y_m \), which equals \( \text{log}_e(OR_m) \), weighted by their respective number of observations \( n \) and \( m_0 \), and is thus a compromise between the 2.

The posterior distribution, which is based on the equivalent number of observations in the posterior of \( m_0 + n = 397 \), yields a value for \( \theta = -5.93 \), obtained by using Equation 7 \( (m_0 \theta_0 + n y_n)/(m_0 + n) = -0.593 \) and solving \( 227 \cdot [-0.70] + 171 \cdot [-0.46]/397 \). 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 \( \theta \) of -5.93 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 \( \theta \) 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 \( \theta_i \), which themselves are given probabilistic specification in terms of an additional parameters \( \theta \).
\[ \theta_i | \theta, \tau^2 \sim \text{independent} \quad N(\theta, \tau^2), \quad (\theta, \tau^2) \sim p(\theta, \tau^2), \quad (4a) \]

where \( OR_i \) denotes the odds ratio for mortality after CABG compared with PCI in the \( i \)-th (\( i = 1, \ldots, 9 \)) study (Table I), \( \theta_i \) the unknown study-level treatment effect, \( s_i^2 \) the (asymptotic) variance of \( \log_{e}(OR_i) \), \( \theta \) the population-average treatment effect, and \( \tau^2 \) 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 \( \theta_i \), 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.\(^2\) 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 acknowledge the existence of between-study variation and incorporate it explicitly into the estimation process. The prior belief about the summary effect size \( \theta \) 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 \( \theta \) and \( \tau^2 \) 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 (\( m.\theta \) and \( m.\tau \)) for \( \theta \) and \( \tau^2 \) as \( \theta \sim N(0, 10^2) \). A normal likelihood with a large variance is sometimes referred to as “non-informative” distribution.

[R] codes

```r
#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 <- ((oldSm.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$m.theta))
likeLogSD<-2/(sqrt(n.0))
# To provide trial weighting by proportion of radial cases
# radWt <- sum(high$radial$radial)
# FREEDOM
for (k in 1:1)
{
  # calculate weighted log odds ratios;
  LikeLogOdds <- ((new$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( (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 (-0.83,"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 PPC1 & 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))
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)

# 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$theta)*(old$DES))

# Sum log odds weighted by m/m.0
for (k in 1:8)
{
  # calculate weighted log odds ratios, alpha = by DES:
  PriorLogOdds <- (old$DES)*((old$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 <-
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 <-
Hierarchical Model: The posterior variance (1/precision) is based on an implicit sample size equivalent to the sum of the prior “sample size” $n_0$ 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
\[ p(\theta | y_n) = N \left[ \frac{\mu}{\tau^2} \frac{y_n}{\sigma_n^2} + \frac{1}{\tau^2} \frac{1}{\sigma_n^2} \right]. \]

#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/jabitll/Dropbox/BayesDM/DMDDeath.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
\[
p(\theta | y_n) = N \left[ \theta \mid \frac{\mu}{\tau^2} + \frac{\gamma_n}{\sigma_n^2}, \frac{1}{\frac{1}{\tau^2} + \frac{1}{\sigma_n^2}} \right].
\]

#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;"