Supplementary data 4: Code for analysis

```
## Load the libraries we will be using
library(tidyverse)
library(metafor)
library(rms)
library(Hmisc)
library(readr)

citation(package="rms")
citation(package="ggplot2")

#Analysis with code based on refs 9-11

fd <- function(x){
  return(c(sum(!is.na(x)),mean(x),sd(x),as.numeric(quantile(x,seq(0,1,0.25)))))
}

df <- read_csv("BBvsPlacebofull.csv")
df<-df[1:19,]
dim(df)
colnames(df)
df$N_study    <- (df$N_Outcome_BB + df$N_Ouctome_Control)
df$logBasVR <- log(df$Bas_VR)

TableS2 <- with(df,matrix(c(fd(log(df$SD_HVPG_baseline_control)),
                            fd(log(df$SD_HVPG_outcome_control)),
                            fd(log(df$SD_HVPG_baseline_BB)),
                            fd(log(df$SD_HVPG_outcome_BB)),
fd(log(df$SD_HVPG_outcome_BB)-log(df$SD_HVPG_baseline_BB)),
fd(log(df$SD_HVPG_outcome_BB)-log(df$SD_HVPG_outcome_control)),
fd(log(df$SD_HVPG_outcome_BB)-log(df$SD_HVPG_baseline_BB)-
(log(df$SD_HVPG_outcome_control)-log(df$SD_HVPG_baseline_control)))),
                          nrow=7,byrow=TRUE))


rownames(TableS2) <-
paste0('log',paste0('SD_',c('BasalC','FinalC','BasalT','FinalT','DifT','DifO','DifDif'
)))
colnames(TableS2) <- c('n','mean','sd','P0%','P25%','P50%','P75%','P100%')
TableS2

# calculate VR

rdat <- escalc(measure = "VR",
               m1i = HVPG_outcome_BB, n1i = N_Outcome_BB, sd1i = SD_HVPG_outcome_BB,
               m2i = HVPG_outcome_control, n2i = N_Ouctome_Control,
               sd2i = SD_HVPG_outcome_control,
               data = df)

# fit random-effects models
m1    <- rma(yi = yi, vi = vi, data = rdat, method = "REML",
             slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)

summary(m1)
coef(summary(m1))
m1_back <- round(exp(coef(summary(m1))), digits = 2)

summary(m1_back)

# transform values back to relative scale through exponentiation
```

```
srdat <- summary(rdat, trans = exp, digits = 2)
srdat

#forest plots

forest(m1, atransf = exp, xlim=c(-8,12), at=log(c( .25,0.5, 1,2, 4)),
       ilab=cbind(rdat$N_Ouctome_Control,
                  rdat$N_Outcome_BB,
                  rdat$time_between_measurements_days,
                  rdat$type_BB,
                  rdat$Route_administration),
       ilab.xpos=c(-4,-3,3.5,6,8),
       cex=.75, header="Author and Year")
text(c(-4,-3), 21, c("nCont", "nBB"), cex=.8, font=2)
text(c(3.5,6,8), 21, c("Days", "Type of BB", "Route"), cex=.8, font=2)
text(c(-1.5,1.3), 21, c("Control", "BB"), cex=.8, font=2)
text(c(-1.5,1.3), 22, c("Greater", "Greater"), cex=.8, font=2)

# Moderator analysis
## Baseline logVR
mmod5    <- rma(yi = yi, vi = vi,mods = ~logBasVR, data = rdat,
                method = "REML",
                slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)
summary(mmod5)

coef(summary(mmod5))
m5back <- round(exp(coef(summary(mmod5))), digits = 2)
m5back

# Route
mmod1    <- rma(yi = yi, vi = vi,mods = ~ Route_administration, data = rdat,
                method = "REML",
                slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)
summary(mmod1)
coef(summary(mmod1))
m1back <- round(exp(coef(summary(mmod1))), digits = 2)
m1back

# Type
mmod2    <- rma(yi = yi, vi = vi,mods = ~type_BB, data = rdat,
                method = "REML",
                slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)
summary(mmod2)
coef(summary(mmod2))
m2back <- round(exp(coef(summary(mmod2))), digits = 2)
m2back

# TIme
mmod3    <- rma(yi = yi, vi = vi,mods = ~time_between_measurements_days, data = rdat,
                method = "REML",
                slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)
summary(mmod3)

coef(summary(mmod3))
m3back <- round(exp(coef(summary(mmod3))), digits = 2)
m3back

# N
mmod4    <- rma(yi = yi, vi = vi,mods = ~N_study, data = rdat,
                method = "REML",
                slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)
summary(mmod4)
```

```
coef(summary(mmod4))
m4back <- round(exp(coef(summary(mmod4))), digits = 2)
m4back

# Baseline HVPG
df$meanbaseline <- (df$HVPG_baseline_BB+df$HVPG_baseline_control)/2
mmod6    <- rma(yi = yi, vi = vi,mods = ~df$meanbaseline, data = rdat,
                method = "REML",
                slab = paste(df$Study, df$Year,sep=" "), weighted = TRUE)
summary(mmod6)
coef(summary(mmod6))
m6back <- round(exp(coef(summary(mmod6))), digits = 2)
m6back


# function for funnel plot with VR (ratio of SDs) (modified from Cortes et al)

myFunnel <- function(data,comparison,model,subgroup=NA,zoom=TRUE,xlab,...){

  ##-- Parameters according tipe of graphic
  if(comparison=='Between arms'){
    x=data$yBetweenArmsRatioSD
    y=data$seBetweenArmsRatio
    tit='Funnel plot'
    lab.11 <- 'Greater Treated'; lab.12 <- 'Greater Control'
    lab.21 <- 'Arm Variability'; lab.22 <- 'Arm Variability'
  }
  if(comparison=='Over time'){
    x=data$yOverTimeRatioT
    y=data$seOverTimeRatioT
    tit='Over time'
    lab.11 <- 'Greater Outcome';lab.12 <- 'Greater Baseline'
    lab.21 <- 'Variability';     lab.22 <- 'Variability'
  }
  if(comparison=='Baseline between arms'){
    x=data$yBaselineRatio
    y=data$seBaselineRatio
    tit='Baseline between arms'
    lab.11 <- 'Greater Treated'; lab.12 <- 'Greater Control'
    lab.21 <- 'Arm Variability'; lab.22 <- 'Arm Variability'
  }

  ##-- Plot region
  #graphics.off()
  #windows()
  xmax <- 1.75
  ymax <- 1.02
  ymin <- 0.05
  par(las=1)

plot(x,y,pch=19,xlab='',col=0,xaxt='n',xlim=log(c(1/xmax,xmax)),ylim=c(ymax,ymin),main
=tit,...)
  mtext(xlab,1,at=0,line=4,adj=0.5)
  rect(-10,-10,300,100,col='grey85')
  ticksy <- seq(0,1,0.2)
  abline(h=ticksy,lwd=2,col='white')
  x0 <- c(2,0,-2,2)
  y0 <- c(2,0,2,2)
  polygon(x0,y0,col='white',lty=3)
  abline(v=0)
  abline(v=coef(model)[1],lwd=2,lty=2,col=4)
  ticksx <- c(0.66,0.80,1,1.25,1.50)
  axis(1,at=log(ticksx),lab=ticksx)
```

```
  ##-- Point colors
  if(is.na(subgroup)){
    co <- 1
    pc <- 1
  }else{
    if(subgroup=='variance'){
      ##-- Significant studies regarding to variance
      sign1 <- x < (-2*y)
      sign2 <-  x > 2*y
      sign <- sign1 | sign2

      ##-- Point colors
      co1 <- rgb(1,0,0,0.5)
      co2 <- rgb(0,0,0,0.5)
      co <- ifelse(sign,co1,co2)
      cat(sum(sign1),'studies with lower variance in experimental group\n')
      cat(sum(sign2),'studies with greater variance in experimental group\n')
      cat(length(x)-sum(sign1)-sum(sign2),'studies with no significant differences in
variance\n')
      pc <- 19
      legend('topright',c('Different variances','Non different variances'),
             pch=19,text.font = 2,pt.cex=1.3,
             co=c(co1,co2))
    }
    if(subgroup=='effect'){
      co <- with(data,ifelse(pvalue>=0.05 | significant=='No',rgb(0,0,0,0.8),
                             ifelse(pvalue>0.001,rgb(227,66,52,255/2,maxColorValue =
255),
                                    rgb(128,0,0,255/2,maxColorValue =
255))))#'#E34234','#800000'))))
      pc <- with(data,ifelse(significant=='No',1,19))
      co[is.na(co)] <-
ifelse(data$significant[is.na(co)]=='No',rgb(0,0,0,0.8),rgb(128,0,0,255/2,maxColorValu
e = 255))
      legend('topright',c('p > 0.05','0.001 < p < 0.05','p < 0.001'),
             pch=c(1,19,19,19),pt.lwd = 2,text.font = 2,pt.cex=1.3,
             co=c(rgb(0,0,0,0.8),rgb(227,66,52,255/2,maxColorValue =
255),rgb(128,0,0,255/2,maxColorValue = 255)))
    }
  }

  ##-- plot points
  points(x,y,pch=pc,col=co,lwd=2,cex=1.1)

  ##-- Labels for both sides of x-axis
  if(zoom){
    mtext(lab.11,1,adj=1,at=log(xmax),line=2.7,cex=.8,font=2,las=0)
    mtext(lab.21,1,adj=1,at=log(xmax),line=3.5,cex=.8,font=2,las=0)
    mtext(lab.12,1,adj=0,at=log(1/xmax),line=2.7,cex=.8,font=2,las=0)
    mtext(lab.22,1,adj=0,at=log(1/xmax),line=3.5,cex=.8,font=2,las=0)
  }else{
    mtext(lab.11,1,adj=1,at=log(100),line=2.7,cex=.8,font=2,las=0)
    mtext(lab.21,1,adj=1,at=log(100),line=3.5,cex=.8,font=2,las=0)
    mtext(lab.12,1,adj=0,at=log(0.01),line=2.7,cex=.8,font=2,las=0)
    mtext(lab.22,1,adj=0,at=log(0.01),line=3.5,cex=.8,font=2,las=0)
  }
}

xl <- bquote(bold(frac(SD[OT],SD[OC])))
yl <- 'Standard error'

# Funnel plot
```

```
myFunnel(df,comparison='Between arms',model=m1,
         subgroup=NA, zoom=TRUE,xlab="",ylab=yl)
mtext(side=1, line=3.2, "VR", font=2,cex=1.4)

#########################
#########################
## Carv vs propr
#########################

df2 <- read_csv("Carve vs Prop.csv")
df2<-df2[1:6,]
dim(df2)
colnames(df2)
df2$N_study    <- (df2$N_Outcome_Carv + df2$N_Ouctome_Prop)

# calculate VR

rdat2 <- escalc(measure = "VR",
                m1i = HVPG_outcome_Carv,
                n1i = N_Outcome_Carv,
                sd1i = SD_HVPG_outcome_Carv,
                m2i = HVPG_outcome_Prop,
                n2i = N_Ouctome_Prop,
                sd2i = SD_HVPG_outcome_Prop,
                data = df2)


# fit random-effects models
m1Carv    <- rma(yi = yi, vi = vi, data = rdat2, method = "REML",
                 slab = paste(df2$Study, df2$Year,sep=" "), weighted = TRUE)

summary(m1Carv)
coef(summary(m1Carv))

# Forest plot

forest(m1Carv, atransf = exp, xlim=c(-7,7), at=log(c( .25,0.5, 1,2, 4)),
       ilab=cbind(rdat2$N_Ouctome_Prop,
                  rdat2$N_Outcome_Carv,
                  rdat2$time_between_measurements_days),
       ilab.xpos=c(-4,-3,3.5),
       cex=.75, header="Author and Year")
text(c(-4,-3), 8, c("nProp", "nCarv"), cex=.8, font=2)
text(3.5, 8, c("Days"), cex=.8, font=2)
text(c(-1.5,1.3), 8, c("Prop", "Carv"), cex=.8, font=2)
text(c(-1.5,1.3), 9, c("Greater", "Greater"), cex=.8, font=2)


###################
###################
### Statins
###################

df3 <- read_csv("Statinsdatabase.csv")
df3 <-df3[1:3,]
dim(df3)
colnames(df3)
df3$N_study    <- (df3$N_Outcome_statin + df3$N_Ouctome_Control)

# calculate VR

rdat2 <- escalc(measure = "VR",
                m1i = HVPG_outcome_statin,
```

```
                n1i = N_Outcome_statin,
                sd1i = SD_HVPG_outcome_statin,
                m2i = HVPG_outcome_control,
                n2i = N_Ouctome_Control,
                sd2i = SD_HVPG_outcome_control,
                data = df3)


# fit random-effects models
m1statin    <- rma(yi = yi, vi = vi, data = rdat2, method = "REML",
                   slab = paste(df3$Study, df3$Year,sep=" "), weighted = TRUE)

summary(m1statin)
coef(summary(m1statin))

# Forest plot
forest(m1statin, atransf = exp, xlim=c(-7,7), at=log(c( .25,0.5, 1,2, 4)),
       ilab=cbind(rdat2$N_Ouctome_Control,
                  rdat2$N_Outcome_statin,
                  rdat2$time_between_measurements_days),
       ilab.xpos=c(-4,-3, 3.5),
       cex=.75, header="Author and Year")
text(c(-4,-3), 5, c("nCont", "nStat"), cex=.8, font=2)
text(3.5, 5, c("Duration"), cex=.8, font=2)
text(c(-1.5,1.3), 5, c("Control", "Statin"), cex=.8, font=2)
text(c(-1.5,1.4), 5.5, c("Greater", "Greater"), cex=.8, font=2)
```