Supplementary data 1

Increased variability in the final HVPG with heterogeneous treatment effect: A simulation

To illustrate the main concept behind out approach to assess if the effects of beta-blockers are homogeneous or heterogeneous we simulated trials comparing 30 patients treated with placebo and 30 patients with an active drug, in which at baseline patients had a mean HVPG of 15 mmHg, with a SD of 3 mmHg. This was done by adapting code described in our previous study (Bai et al, Hepatology 2021; 74:3301-3315) (https://github.com/mathesong/HVPG_TRT), and reported in full at the end of this file.

In the placebo group we assumed no change over time. In the treatment group we assumed that the drug decreased HVPG, in mean, by 2 mmHg. This would equate to a 13.3%, and it reflects what has been described for propranolol.

To model the impact of the variability in HVPG measurements, we used a within-subject coefficient of variation (wscv) of 0.10, derived from our previous publication (Bai et al, Hepatology 2021; 74:3301-3315). In the case of a homogeneous treatment effect, we assumed that the treatment decreased HVPG by 2 mmHg in all patients. To model the heterogeneous effect, we assumed a coefficient of variation of the response of 1.4, which resulted in different patient-to-patient decreases in HVPG (figure).

The figure 1 in the main manuscript shows the theoretical underlying true values of HVPG, and what would be the observed (measured) values of HVPG, before and after placebo and treatment. An homogeneous effect assumes the same effect occurred in all patients and hence the parallel lines when looking at the "true" effects. By applying the expected measured variability these lines are not parallel anymore, but there is not an increase in the variability of the final HVPG (table 1). When modeling a heterogeneous effect, the "true" lines are not parallel anymore since there are different effects for different patients. This results in higher variability in the final HVPG (Table 1).

As shown in the table, while modeling a homogeneous effect resulted in a variability ratio (VR) close to 1 (no differences in final standard deviations of HVPG between treatment and placebo), modeling a heterogeneous treatment effect resulted in larger VR of 1.58 in this simulation.

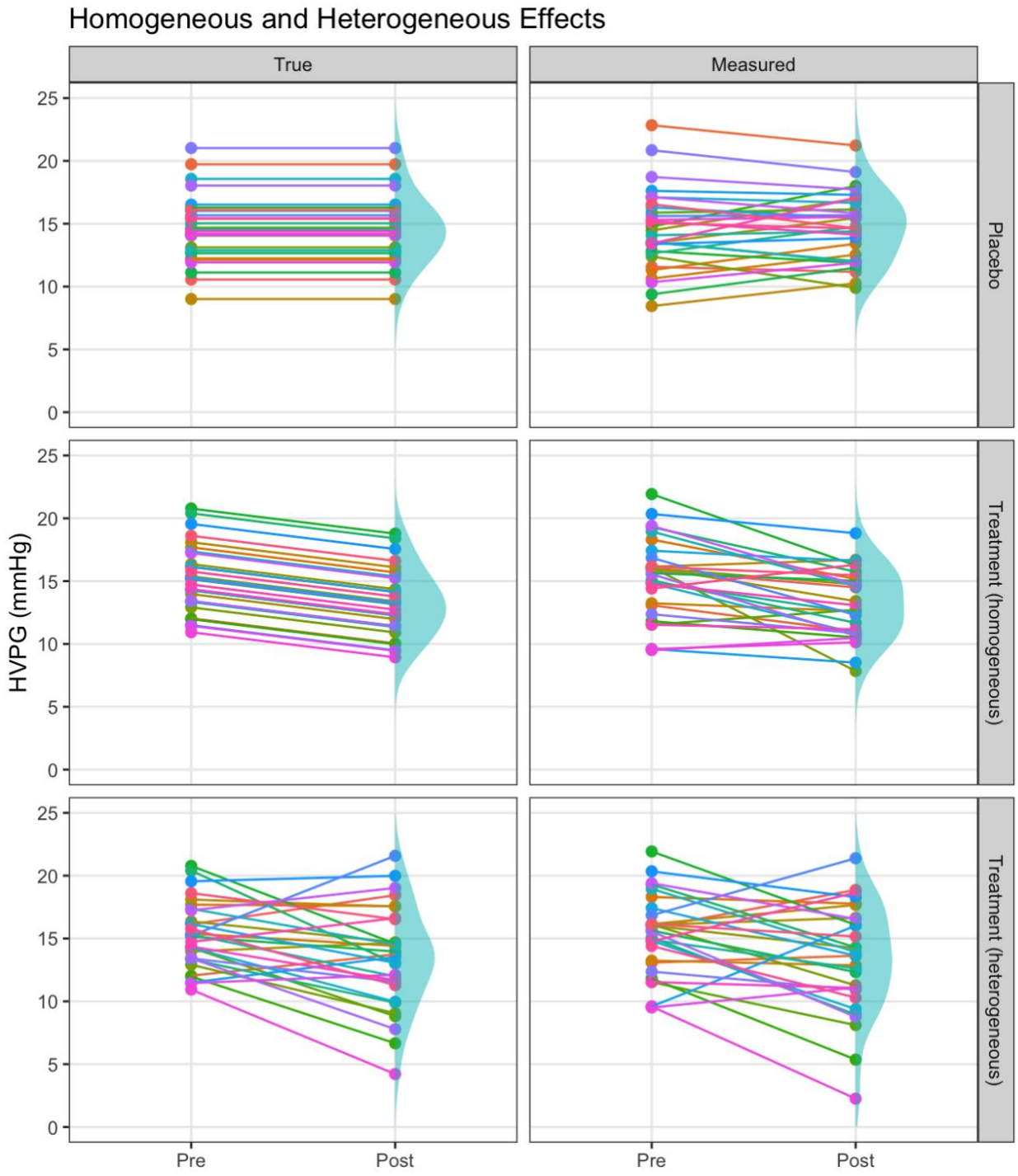
Homogeneous and Heterogeneous Effects
True
Measured
Placebo
Treatment (homogeneous)
Treatment (heterogeneous)
HVPG (mmHg)
25
20
15
10
5
0
Pre
Post

Table 1: Final mean HVPGs, SDs and VRs.

	Final measured HVPG (mmHg)	Standard deviation	Variability ratios (VRs)
Placebo	14.70	2.71	
Treatment (homogeneous effect)	13.17	2.67	0.99
Treatment (heterogeneous effect)	13.27	4.27	1.58

R code to reproduce the simulation and figure

```
library(tidyverse)

## Placebo group

set.seed(12)
n <- 30
delta <- 0

# Homogeneous
cv_delta <- 0

## Normal distribution of baseline HVPGs mean 15, SD 3
pre_true <- rnorm(n, 15, 3)

## Values after applying measurement variability (a wscv of 0.10 from our previous
paper)

pre_meas <- pre_true + rnorm(n, 0, 15*0.10)

## Same for post delta zero

post_true <- pre_true - rnorm(n, delta, cv_delta*delta)
post_meas <- post_true + rnorm(n, 0, 15*0.10)

pla_true <- tibble::tibble(
  ID = rep(1:n, times=2),
  Outcome = c(pre_true, post_true),
  PrePost = rep(c("Pre", "Post"), each=n),
  Effects = "Placebo",
  MeasuredTrue = "True"
)

pla_measured <- tibble::tibble(
  ID = rep(1:n, times=2),
  Outcome = c(pre_meas, post_meas),
```

```
  PrePost = rep(c("Pre", "Post"), each=n),
  Effects = "Placebo",
  MeasuredTrue = "Measured"
)

## treated groups homo / heter

delta <- 2

# Homogeneous
cv_delta <- 0

pre_true <- rnorm(n, 15, 3)
pre_meas <- pre_true + rnorm(n, 0, 15*0.10)

## we first apply a homogeneous decrease in portal pressure to all patients.

post_true <- pre_true - rnorm(n, delta, cv_delta*delta)

## and then we apply the measurement variability
post_meas <- post_true + rnorm(n, 0, 15*0.10)

hom_true <- tibble::tibble(
  ID = rep(1:n, times=2),
  Outcome = c(pre_true, post_true),
  PrePost = rep(c("Pre", "Post"), each=n),
  Effects = "Treatment (homogeneous)",
  MeasuredTrue = "True"
)

hom_measured <- tibble::tibble(
  ID = rep(1:n, times=2),
  Outcome = c(pre_meas, post_meas),
  PrePost = rep(c("Pre", "Post"), each=n),
  Effects = "Treatment (homogeneous)",
  MeasuredTrue = "Measured"
)

# Heterogeneous with a cv of delta of 1.4

cv_delta <- 1.4


post_true <- pre_true - rnorm(n, delta, abs(cv_delta*delta))
post_meas <- post_true + rnorm(n, 0, abs(15*0.10))

het_true <- tibble::tibble(
  ID = rep(1:n, times=2),
  Outcome = c(pre_true, post_true),
  PrePost = rep(c("Pre", "Post"), each=n),
  Effects = "Treatment (heterogeneous)",
  MeasuredTrue = "True"
)

het_measured <- tibble::tibble(
```

```
  ID = rep(1:n, times=2),
  Outcome = c(pre_meas, post_meas),
  PrePost = rep(c("Pre", "Post"), each=n),
  Effects = "Treatment (heterogeneous)",
  MeasuredTrue = "Measured"
)


## we create a dataframe with all values

effects <- bind_rows(pla_true, pla_measured, hom_true, hom_measured, het_true,
het_measured) %>%
  mutate(MeasuredTrue = fct_inorder(MeasuredTrue),
         Effects      = fct_inorder(Effects),
         PrePost      = fct_inorder(PrePost),
         ID           = as.factor(ID))


# mean HVPGs, mean SDs
HVPG <- aggregate(.~PrePost+MeasuredTrue+Effects,data=effects,mean)
HVPG
HVPGsd <-aggregate(.~PrePost+MeasuredTrue+Effects,data=effects,sd)
HVPGsd
subset(HVPGsd, PrePost=='Post' & MeasuredTrue=='Measured')$Outcome

## plot
library(ggridges)
ggplot(effects) +
  geom_point(aes(y=PrePost,x=Outcome,colour=ID, group=ID),size=2) +
  geom_line (aes(y=PrePost,x=Outcome,colour=ID, group=ID)) +
  geom_density_ridges(aes(x     = Outcome,
                          y     = PrePost,
                          alpha = PrePost,
                          fill  = PrePost),
                      color=NA,bandwidth = 1.7, scale = 0.25) +
  facet_grid(Effects~MeasuredTrue) +
  scale_x_continuous(minor_breaks = NULL,limits = c(0,25)) +
  coord_flip() +
  labs(x="HVPG (mmHg)",y="",
         colour="Values",
         x=NULL,
         title="Homogeneous and Heterogeneous Effects") +
  theme_bw()+
  scale_alpha_discrete(range = c(0, 0.5)) +
  guides(color="none", alpha="none", fill="none")
```