Investigate washout

Some studies have washout, which can mean different things for different studies.

These are all the studies that are labeled as having washout:

```
pander(df %>% filter(WashOut == 'Y') %>%
  select(JournalVolumePage, Author, Year, subtype))
```

JournalVolumePage	Author	Year	subtype
JCRS, 36(407-412)	Fea et. al	2010	OAG
AAO, 118(459-467)	Samuelson et al.	2011	OAG
AAO, 122(1283-1293)	Pfeiffer et al.	2015	OAG
Lancet, 388(1389-1397)	Azuara-Blanco et al.	2016	ACG
Ophthalmol, 123(2103-2112)	Vold et al.	2016	OAG

This study has pre- and post-washout and no measurements without washout. This is equivalent to setting the pre and post op meds to 0:

```
pander(df %>% filter(Washoutbaseline == PreOpIOPMean, !is.na(WashoutIOP)) %>%
  select(JournalVolumePage, Author, Year))
```

JournalVolumePage	Author	Year
AAO, 122(1283-1293)	Pfeiffer et al.	2015
Ophthalmol, 123(2103-2112)	Vold et al.	2016

This study has preop washout and no washout in the post period. Virgin patients were enrolled, and had 0 pre-op meds; only after were they put on meds:

```
pander(df %>% filter(Washoutbaseline == PreOpIOPMean, is.na(WashoutIOP)) %>%
  select(JournalVolumePage, Author, Year))
```

JournalVolumePage	Author	Year
Lancet, 388(1389-1397)	Azuara-Blanco et al.	2016

These studies had both washout and regular measurements in the pre-period. That tells us about the relationship between meds and IOP:

```
pander(df %>% filter(Washoutbaseline != PreOpIOPMean) %>%
  mutate(mm.Hg.per.med = (Washoutbaseline - PreOpIOPMean)/RxPreOpMean,
         rel.p = 100*(1-(Washoutbaseline - PreOpIOPMean)/Washoutbaseline),
         rel.p.drop.per.med =
           100*(1-exp(log(rel.p / 100) / RxPreOpMean))) %>%
  select(Author, Year, PreOpIOPMean, RxPreOpMean, mm.Hg.per.med,
         rel.p, rel.p.drop.per.med), digits = 2)
```

Table 4: Table continues below

Author	Year	PreOpIOPMean	RxPreOpMean	mm.Hg.per.med	rel.p
Samuelson et al.	2011	18	1.5	5	71

Author	Year	PreOpIOPMean	RxPreOpMean	mm.Hg.per.med	rel.p

rel.p.drop.per.med
21

Most commonly, 1 med corresponds to about a 15-20% drop in IOP; or a 4-5 mmHg drop.

Note: Pfeiffer has washout in the pre-periods and the post-periods. It also has a baseline measurement (with meds).

This study has washout only in the last period; we can also use this to estimate the drop in IOP per med:

```
pander(df %>% filter(regexpr("Fea", Author)==TRUE) %>%
  mutate(mm.Hg.per.med = (WashoutIOP - LastPeriodIOPMean)/RxPostOpMean,
         rel.p = 100*(1-(WashoutIOP - LastPeriodIOPMean)/WashoutIOP),
         rel.p.drop.per.med = 100*(1-exp(log(rel.p / 100) / RxPostOpMean))) %>%
  select(Author, Year, LastPeriodIOPMean, RxPostOpMean, mm.Hg.per.med,
         rel.p, rel.p.drop.per.med), digits = 2)
```

Table 6: Table continues below

Author	Year	LastPeriodIOPMean	RxPostOpMean	mm.Hg.per.med	rel.p
Fea et. al	2010	16	1.3	2.7	82

rel.p.drop.per.med
14

This study is also in line with the estimate of 4-5mmHg, 15-20% drop in IOP per med.

Study classifications

I went back and classified the studies depending on the washout type:

```
pander(df %>% filter(washout.type != 'None') %>%
  select(JournalVolumePage, Author, Year, subtype, washout.type))
```

JournalVolumePage	Author	Year	subtype	washout.type
JCRS, 36(407-412)	Fea et. al	2010	OAG	Partial
AAO, 118(459-467)	Samuelson et al.	2011	OAG	Partial
AAO, 122(1283-1293)	Pfeiffer et al.	2015	OAG	Both
Lancet, 388(1389-1397)	Azuara-Blanco et al.	2016	ACG	Pre
Ophthalmol, 123(2103-2112)	Vold et al.	2016	OAG	Both

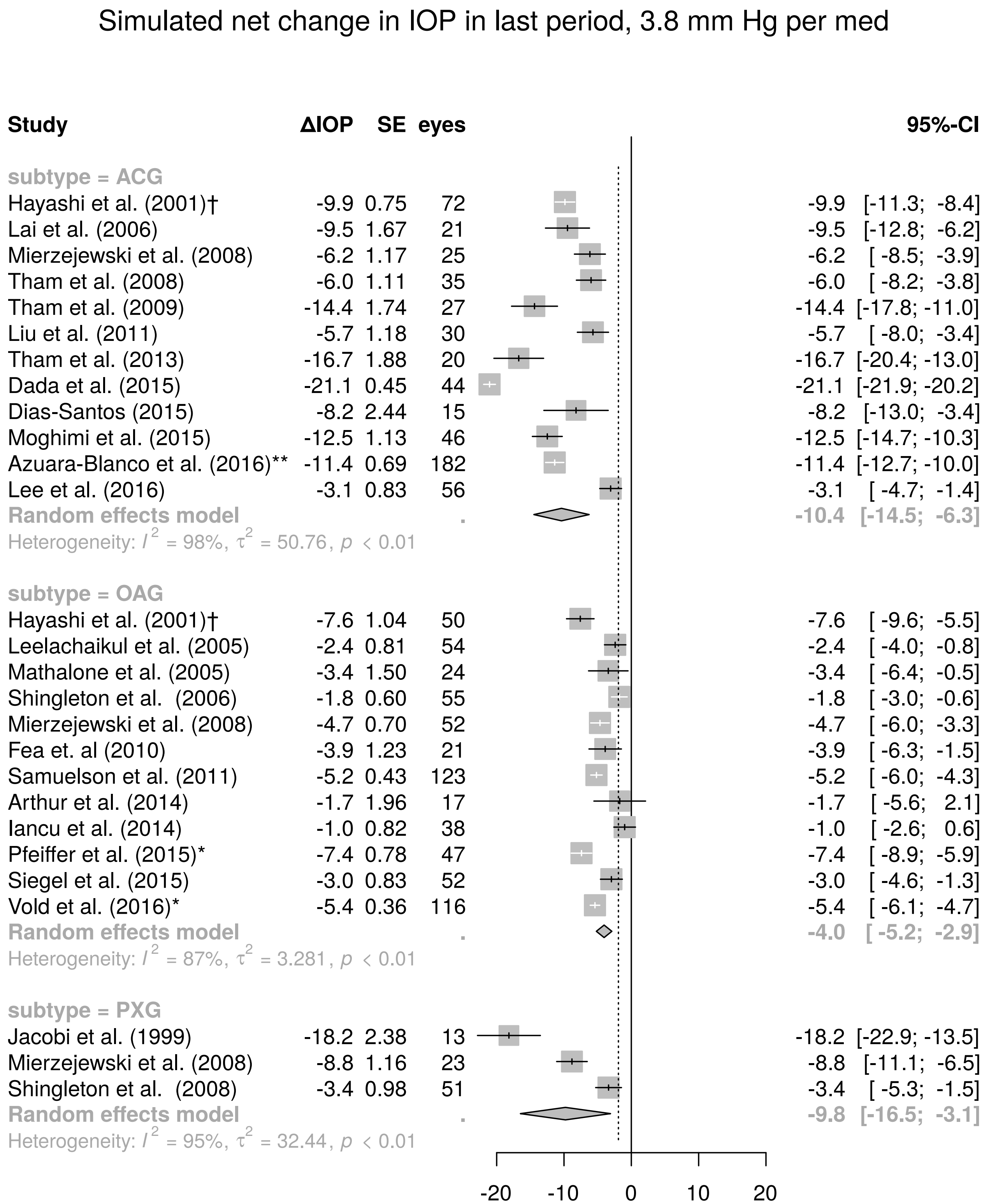
Net effect - including IOP and meds

Let's see what happens when we add the IOP drop effect to the Rx drop effects. We try different values of the translation value between meds and mmHg drop: 0, 2, 3, 4, or 5 mm Hg per Rx.

Last period

```
mmhg.per.meds <- c(3.8)
for(mmhg.per.med in mmhg.per.meds) {

  df_ <- df %>%
    filter(!is.na(RxChangeMean),
           df$subtype != "AACG",
           MIGsYorN == 'N',
           !is.na(LastPeriodAbsIOPChangeStdDev),
           !is.na(RxChangeStdDev)) %>%
    mutate(subtype=factor(subtype),
           net.effect=LastPeriodAbsIOPChangeMean +
             mmhg.per.med * RxChangeMean * (washout.type %in% c('None', 'Partial')) +
             mmhg.per.med * RxPostOpMean * (washout.type %in% c('Pre')),
           net.sem=sqrt(LastPeriodAbsIOPChangeStdDev ** 2 +
             (mmhg.per.med * (washout.type %in% c('None', 'Partial', 'Pre')) * RxChangeStdDev) ** 2) / s
  m <- metagen(net.effect,
               net.sem,
               study.name,
               data=df_,
               byvar=subtype,
               n.e=LastPeriodEyes)
  forest(m,
         comb.fixed=FALSE,
         digits=1,
         digits.se = 2,
         overall=FALSE,
         leftcols=c("studlab", "TE", "seTE", "n.e"),
         leftlabs=c("Study", "ΔIOP", "SE", "eyes"),
         refline=0)
  grid.text(
    paste0("Simulated net change in IOP in last period, ", mmhg.per.med, " mm Hg per med"), .5, .97, gp=
  grid.lines(c(1, 1)*.5952, c(.11, .86), gp = gpar(lty=3))
  print(" ")
}
```




```
## [1] " "
```

```
mmhg.per.meds <- c(3.8)
for(mmhg.per.med in mmhg.per.meds) {

  df_ <- df %>%
```

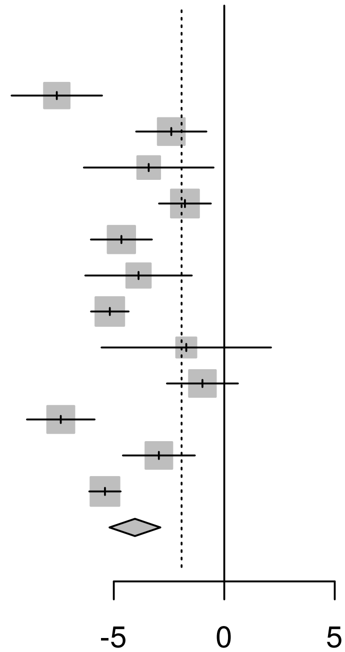
```r
    filter(!is.na(RxChangeMean),
           df$subtype == "OAG",
           MIGsYorN == 'N',
           !is.na(LastPeriodAbsIOPChangeStdDev),
           !is.na(RxChangeStdDev)) %>%
    mutate(subtype=factor(subtype),
           net.effect=LastPeriodAbsIOPChangeMean +
             mmhg.per.med * RxChangeMean * (washout.type %in% c('None', 'Partial')) +
             mmhg.per.med * RxPostOpMean * (washout.type %in% c('Pre')),
           net.sem=sqrt(LastPeriodAbsIOPChangeStdDev ** 2 +
             (mmhg.per.med * (washout.type %in% c('None', 'Partial', 'Pre')) * RxChangeStdDev) ** 2) / s
  m <- metagen(net.effect,
               net.sem,
               study.name,
               data=df_,
               n.e=LastPeriodEyes,
                byvar=subtype
              )
  forest(m,
         comb.fixed=FALSE,
         digits=1,
         digits.se = 2,
         overall=FALSE,
         leftcols=c("studlab", "TE", "seTE", "n.e"),
         leftlabs=c("Study", "ΔIOP", "SE", "eyes"))
  grid.text(
    paste0("Simulated net change in IOP in last period, ", mmhg.per.med, " mm Hg per med"), .5, .97, gp=

  # Stupid hack to get a reference line at -2: set ref=-2 in forest, and mess with the number
  # until the two lines overlap.
  # TODO(Patrick): Banish this hack to the fiery pits of hell.
  grid.lines(c(1, 1)*.5807, c(.23, .75), gp = gpar(lty=3))
  print(" ")
}
```

Simulated net change in IOP in last period, 3.8 mm Hg per med

Study	ΔIOP	SE	eyes	95%-CI
subtype = OAG				
Hayashi et al. (2001)†	-7.6	1.04	50	-7.6 [-9.6; -5.5]
Leelachaikul et al. (2005)	-2.4	0.81	54	-2.4 [-4.0; -0.8]
Mathalone et al. (2005)	-3.4	1.50	24	-3.4 [-6.4; -0.5]
Shingleton et al. (2006)	-1.8	0.60	55	-1.8 [-3.0; -0.6]
Mierzejewski et al. (2008)	-4.7	0.70	52	-4.7 [-6.0; -3.3]
Fea et. al (2010)	-3.9	1.23	21	-3.9 [-6.3; -1.5]
Samuelson et al. (2011)	-5.2	0.43	123	-5.2 [-6.0; -4.3]
Arthur et al. (2014)	-1.7	1.96	17	-1.7 [-5.6; 2.1]
Iancu et al. (2014)	-1.0	0.82	38	-1.0 [-2.6; 0.6]
Pfeiffer et al. (2015)*	-7.4	0.78	47	-7.4 [-8.9; -5.9]
Siegel et al. (2015)	-3.0	0.83	52	-3.0 [-4.6; -1.3]
Vold et al. (2016)*	-5.4	0.36	116	-5.4 [-6.1; -4.7]
Random effects model			.	**-4.0 [-5.2; -2.9]**

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 3.281$, $p < 0.01$




```
## [1] " "
```

Conclusion

If you take into account the drop in number of meds in each study, you get an additional ~1mmHg drop in the OAG group. That's a net effect around 4 mmHg drop at 12 months and in the last period: quite a bit larger than the uncorrected estimates we had previously.

There's another source of bias we can't correct for here: in some studies, less potent medicines with better side effect profiles might have replaced more potent medicines in the post period, in response to better control of IOP after surgery. That would be measured as a net change of 0 between RxPreOp and RxPostOp, and it would result in an apparent increase in IOP, even though that's a net positive for the patient. I'll leave it to the clinician to determine how likely this is.