

SUPPLEMENT 2: Sample Code

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#Sample codes

#####
### propensity score model-GBM ###
library(twang)
require(gbm)
set.seed(100)

mnps1<- mnps(med_class~ age + gender +race +income +A1c + comorbidity_1 +
comorbidity_2 + ... + comorbidity_n,
  data=cohort,
  n.trees=25000,
  interaction.depth = 3,
  shrinkage=0.01,
  perm.test.iters=0,
  stop.method=c("es.mean", "es.max"),
  estimand="ATE",
  verbose=FALSE,
  n.keep = 100)

#Stabilized weights
drug.pct = prop.table(table(cohort$med_class))
head(drug.pct)

ps.scores.cana = mnps1$psList$canagliflozin$ps[,1]
stab.weights.cana = drug.pct[1] / ps.scores.cana

ps.scores.glim = mnps1$psList$glimepiride$ps[,1]
stab.weights.glim = drug.pct[2] / ps.scores.glim

ps.scores.lira = mnps1$psList$liraglutide$ps[,1]
stab.weights.lira = drug.pct[3] / ps.scores.lira

ps.scores.sita = mnps1$psList$sitagliptin$ps[,1]
stab.weights.sita = drug.pct[4] / ps.scores.sita
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stab.weights = data.frame(stab.weights.cana, stab.weights.glim, stab.weights.lira,
  stab.weights.sita, cohort$med_class)
stab.weights$sweight = ifelse(stab.weights$cohort.med_class=='canagliflozin',
  stab.weights$stab.weights.cana,
    (ifelse(stab.weights$cohort.med_class=='glimepiride',
  stab.weights$stab.weights.glim,
    ifelse(stab.weights$cohort.med_class=='liraglutide',
  stab.weights$stab.weights.lira, stab.weights$stab.weights.sita))))))

# weighted cohort
cohort_weighted = data.frame(cohort, stab.weights$sweight)

#construct table 1
library(survey)
library(tableone)

vars<-c("age", "gender", "race", "income", "A1c", "comorbidity_1", "comorbidity_2",
"comorbidity_n")

# #unweighted table
tabUnweighted<- CreateTableOne(vars=vars, strata="med_class", data=cohort, test=FALSE)
# #show table with SMD and pairwise SMD
print(tabUnweighted, smd=TRUE)
ExtractSmd(tabUnweighted)

#weighted table
cohort_weighted<-svydesign(ids=~1, data=cohort_weighted, weight=~ stab.weights.sweight)
tabweighted<- svyCreateTableOne(vars=vars, strata="med_class", data=cohort_weighted,
test=FALSE)
#show table with SMD and pairwise SMD
print(tabweighted, smd=TRUE)
ExtractSmd(tabweighted)

#####
##### Kaplan-Meier estimate of time to censoring #####
library(survminer)
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library(survival)
library(ggplot2)

fit_censor_itt <- survfit(Surv(time_to_A1C, 1-outcomeA1C) ~ med_class, data =
cohort_weighted, weights = sweight)
fit_censor_itt #median time to censor

g <- ggsurvplot(fit_censor_itt, risk.table = TRUE, fun = 'event',
break.x.by = 180, conf.int = TRUE, xlim = c(0, 1092),
legend.labs = c("canagliflozin", "glimepiride", "liraglutide", "sitagliptin"),
xlab = "Time (month)", ylab = "Cumulative incidence rate", legend.title = "Group",
xscale="d_m")
g

#####
####Cumulative incident curve for primary A1C outcome #####
fit_iptw <- survfit(Surv(time_to_A1C, outcomeA1C) ~ med_class, data = cohort_weighted,
weights = sweight)
fit_iptw #median time to primary metabolic failure

g_m <- ggsurvplot(fit_iptw, risk.table = TRUE, fun = 'event',
break.x.by = 180, conf.int = TRUE, xlim = c(0, 1092),
legend.labs = c("canagliflozin", "glimepiride", "liraglutide", "sitagliptin"),
xlab = "Time (months)", ylab = "Cumulative incidence rate",
legend.title = "Group", xscale="d_m", surv.median.line = "hv", title="Primary
Metabolic Failure")
g_m

#####
#####Cox PH model #####
library(survminer)
library(survival)
library(ggplot2)
library(splines)

tmp<-cohort_weighted
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# create indicator variables for treatment groups
tmp$med_canagliflozin <- ifelse(tmp$med_class == "canagliflozin", 1, 0)
tmp$med_glimepiride <- ifelse(tmp$med_class == "glimepiride", 1, 0)
tmp$med_liraglutide <- ifelse(tmp$med_class == "liraglutide", 1, 0)
tmp$med_sitagliptin <- ifelse(tmp$med_class == "sitagliptin", 1, 0)

# Split data into 3 time periods (within 40 days after index date, 40-365 days after index_date
and >365 days after index date);
# For the best model fit, we used 2 time period for med_class and 3 time periods for A1c
tmp_split3 <- survSplit(Surv(time_to_A1C, outcomeA1C) ~ ., data=tmp, cut=c(40, 365), episode
= "tgroup", id="id")
tmp_split3$tgroup2 <- ifelse(tmp_split3$tgroup <= 2, 1, 2)
table(tmp_split3$tgroup, tmp_split3$tgroup2)

#The best model fit after testing multiple model fits
fit_adj6 <- coxph(Surv(tstart, time_to_A1C, outcomeA1C) ~ med_canagliflozin:strata(tgroup2)
+ med_glimepiride:strata(tgroup2) + med_liraglutide:strata(tgroup2) + ns(A1C, df =
5):strata(tgroup), data=tmp_split3, weights = sweight)
fit_adj6
cox.zph(fit_adj6)
plot(cox.zph(fit_adj6), resid = FALSE)

## Collect the pairwise comparisons and statistical tests
OUT <- data.frame(trt1 = NA, trt2 = NA, chisq = NA, overall_pValue = NA, HR1 = NA,
HR1_lower = NA, HR1_upper = NA, HR1_pValue = NA, HR2 = NA, HR2_lower = NA,
HR2_upper = NA, HR2_pValue = NA)

# full model, sitagliptin as reference group
fit_adj_full <- coxph(Surv(tstart, time_to_A1C, outcomeA1C) ~
med_canagliflozin:strata(tgroup2) + med_glimepiride:strata(tgroup2) +
med_liraglutide:strata(tgroup2) + ns(A1C, df = 5):strata(tgroup), data=tmp_split3, weights =
sweight, robust = FALSE)
# canagliflozin vs. sitagliptin
fit_reduced <- coxph(Surv(tstart, time_to_A1C, outcomeA1C) ~
med_glimepiride:strata(tgroup2) + med_liraglutide:strata(tgroup2) + ns(A1C, df =
5):strata(tgroup), data=tmp_split3, weights = sweight, robust = FALSE)
test_tmp <- anova(fit_reduced, fit_adj_full)
OUT <- rbind(OUT, data.frame(trt1 = "canagliflozin", trt2 = "sitagliptin", chisq =
test_tmp$Chisq[2], overall_pValue = test_tmp$"P(>|Chi|)"[2],
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HR1 =
sum_fit_adj_full$coefficients["med_canagliflozin:strata(tgroup2)tgroup2=1", "exp(coef)"],
HR1_lower =
sum_fit_adj_full$conf.int["med_canagliflozin:strata(tgroup2)tgroup2=1", "lower .95"],
HR1_upper =
sum_fit_adj_full$conf.int["med_canagliflozin:strata(tgroup2)tgroup2=1", "upper .95"],
HR1_pValue =
sum_fit_adj_full$coefficients["med_canagliflozin:strata(tgroup2)tgroup2=1", "Pr(>|z|)"],
HR2 =
sum_fit_adj_full$coefficients["med_canagliflozin:strata(tgroup2)tgroup2=2", "exp(coef)"],
HR2_lower =
sum_fit_adj_full$conf.int["med_canagliflozin:strata(tgroup2)tgroup2=2", "lower .95"],
HR2_upper =
sum_fit_adj_full$conf.int["med_canagliflozin:strata(tgroup2)tgroup2=2", "upper .95"],
HR2_pValue =
sum_fit_adj_full$coefficients["med_canagliflozin:strata(tgroup2)tgroup2=2", "Pr(>|z|)"])
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# glimepiride vs. sitagliptin
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fit_reduced <- coxph(Surv(tstart, time_to_A1C, outcomeA1C) ~
med_canagliflozin:strata(tgroup2) + med_liraglutide:strata(tgroup2) + ns(A1C, df =
5):strata(tgroup), data=tmp_split3, weights = sweight, robust = FALSE)
test_tmp <- anova(fit_reduced, fit_adj_full)
OUT <- rbind(OUT, data.frame(trt1 = "glimepiride", trt2 = "sitagliptin", chisq =
test_tmp$Chisq[2], overall_pValue = test_tmp$"P(>|Chi|)"[2]),
HR1 =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=1:med_glimepiride", "exp(coef)"],
HR1_lower =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=1:med_glimepiride", "lower .95"],
HR1_upper =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=1:med_glimepiride", "upper .95"],
HR1_pValue =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=1:med_glimepiride", "Pr(>|z|)"],
HR2 =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=2:med_glimepiride", "exp(coef)"],
HR2_lower =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=2:med_glimepiride", "lower .95"],
HR2_upper =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=2:med_glimepiride", "upper .95"],
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HR2_pValue =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=2:med_glimepiride", "Pr(>|z)"]])

# liraglutide vs. sitagliptin
fit_reduced <- coxph(Surv(tstart, time_to_A1C, outcomeA1C) ~
med_canagliflozin:strata(tgroup2) + med_glimepiride:strata(tgroup2) + ns(A1C, df =
5):strata(tgroup), data=tmp_split3, weights = sweight, robust = FALSE)
test_tmp <- anova(fit_reduced, fit_adj_full)
OUT <- rbind(OUT, data.frame(trt1 = "liraglutide", trt2 = "sitagliptin", chisq =
test_tmp$Chisq[2], overall_pValue = test_tmp$"P(>|Chi)"[2],
HR1 =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=1:med_liraglutide", "exp(coef)"],
HR1_lower =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=1:med_liraglutide", "lower .95"],
HR1_upper =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=1:med_liraglutide", "upper .95"],
HR1_pValue =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=1:med_liraglutide", "Pr(>|z)"],
HR2 =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=2:med_liraglutide", "exp(coef)"],
HR2_lower =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=2:med_liraglutide", "lower .95"],
HR2_upper =
sum_fit_adj_full$conf.int["strata(tgroup2)tgroup2=2:med_liraglutide", "upper .95"],
HR2_pValue =
sum_fit_adj_full$coefficients["strata(tgroup2)tgroup2=2:med_liraglutide", "Pr(>|z)"]])

# add adjusted p-values
OUT$Holm_overall_pValues <- p.adjust(OUT$overall_pValue, method = "holm")
OUT$Holm_HR1_pValues <- p.adjust(OUT$HR1_pValue, method = "holm")
OUT$Holm_HR2_pValues <- p.adjust(OUT$HR2_pValue, method = "holm")
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