Reproducing Graham et al. 2014 using the CohortMethod package

Martijn Schuemie

R code for reproducing the study

```
library(CohortMethod)
library(SqlRender)
connectionDetails <- createConnectionDetails(dbms = "pdw",
                    server = "JRDUSAPSCTL01",
                    port = 17001)

cdmDatabaseSchema <- "CDM_Truven_MDCR_V415.dbo"
resultsDatabaseSchema <- cdmDatabaseSchema
exposureTable <- "cohort"
outcomeTable <- "cohort"
cdmVersion <- "5"

options('fftempdir' = 's:/fftemp')
workFolder <- "s:/temp/GrahamStudy"

excludedConcepts <- c()
includedConcepts <- read.csv("inst/csv/GrahamIncludedConcepts.csv")$Concept.ID
covariateSettings <- createCovariateSettings(useCovariateDemographics = TRUE,
                    useCovariateDemographicsGender = TRUE,
                    useCovariateDemographicsRace = TRUE,
                    useCovariateDemographicsEthnicity = TRUE,
                    useCovariateDemographicsAge = TRUE,
                    useCovariateDemographicsYear = FALSE,
                    useCovariateDemographicsMonth = FALSE,
                    useCovariateConditionOccurrence = TRUE,
                    useCovariateConditionOccurrence365d = TRUE,
                    useCovariateConditionOccurrence30d = TRUE,
                    useCovariateConditionOccurrenceInpt180d = TRUE,
                    useCovariateConditionEra = FALSE,
                    useCovariateConditionEraEver = FALSE,
                    useCovariateConditionEraOverlap = FALSE,
                    useCovariateConditionGroup = TRUE,
                    useCovariateConditionGroupMeddra = TRUE,
                    useCovariateConditionGroupSnomed = FALSE,
                    useCovariateDrugExposure = FALSE,
                    useCovariateDrugExposure365d = FALSE,
                    useCovariateDrugExposure30d = FALSE,
                    useCovariateDrugEra = TRUE,
                    useCovariateDrugEra365d = TRUE,
                    useCovariateDrugEra30d = FALSE,
                    useCovariateDrugEraOverlap = FALSE,
                    useCovariateDrugEraEver = FALSE,
                    useCovariateDrugGroup = TRUE,
                    useCovariateProcedureOccurrence = FALSE,
                    useCovariateProcedureOccurrence365d = FALSE,
                    useCovariateProcedureOccurrence30d = FALSE,
                    useCovariateProcedureGroup = FALSE,
                    useCovariateObservation = FALSE,
                    useCovariateObservation365d = FALSE,
                    useCovariateObservation30d = FALSE,
                    useCovariateObservationCount365d = FALSE,
                    useCovariateMeasurement = FALSE,
                    useCovariateMeasurement365d = FALSE,
                    useCovariateMeasurement30d = FALSE,
                    useCovariateMeasurementCount365d = FALSE,
                    useCovariateMeasurementBelow = FALSE,
                    useCovariateMeasurementAbove = FALSE,
                    useCovariateConceptCounts = FALSE,
                    useCovariateRiskScores = TRUE,
                    useCovariateRiskScoresCharlson = FALSE,
                    useCovariateRiskScoresDCSI = FALSE,
                    useCovariateRiskScoresCHADS2 = TRUE,
                    useCovariateRiskScoresCHADS2VASc = FALSE,
                    useCovariateInteractionYear = FALSE,
                    useCovariateInteractionMonth = FALSE,
                    excludedCovariateConceptIds = excludedConcepts,
                    includedCovariateConceptIds = includedConcepts,
                    deleteCovariatesSmallCount = 100)

cohortMethodData <- getDbCohortMethodData(connectionDetails = connectionDetails,
                   cdmDatabaseSchema = cdmDatabaseSchema,
                   oracleTempSchema = resultsDatabaseSchema,
                   targetId = 2649,
                   comparatorId = 2650,
                   outcomeIds = 2651,
                   studyStartDate = "",
                   studyEndDate = "",
                   exposureDatabaseSchema = resultsDatabaseSchema,
                   exposureTable = exposureTable,
                   outcomeDatabaseSchema = resultsDatabaseSchema,
                   outcomeTable = outcomeTable,
                   cdmVersion = cdmVersion,
                   excludeDrugsFromCovariates = FALSE,
                   covariateSettings = covariateSettings)

saveCohortMethodData(cohortMethodData, file.path(workFolder, "cohortMethodData"))

studyPop <- createStudyPopulation(cohortMethodData = cohortMethodData,
               outcomeId = 2651,
               firstExposureOnly = FALSE,
               washoutPeriod = 0,
               removeSubjectsWithPriorOutcome = TRUE,
               minDaysAtRisk = 1,
               riskWindowStart = 1,
               addExposureDaysToStart = FALSE,
               riskWindowEnd = 0,
               addExposureDaysToEnd = TRUE)

saveRDS(studyPop, file.path(workFolder, "studyPop.rds"))

drawAttritionDiagram(studyPop, treatmentLabel = "Target", comparatorLabel = "Comparator")
ps <- createPs(cohortMethodData = cohortMethodData,
       population = studyPop,
       control = createControl(cvType = "auto",
                 startingVariance = 0.01,
                 noiseLevel = "quiet",
                 tolerance  = 2e-07,
                 cvRepetitions = 10,
                 threads = 20))
saveRDS(ps, file.path(workFolder, "ps.rds"))
computePsAuc(ps)
plotPs(ps, treatmentLabel = "Dabigatran", comparatorLabel = "Warfarin", fileName = file.path(workFolder, "ps.png") )
propensityModel <- getPsModel(ps, cohortMethodData)
head(propensityModel)

matchedPop <- matchOnPs(ps, caliper = 0.25, caliperScale = "standardized", maxRatio = 1)
plotPs(matchedPop, ps)
drawAttritionDiagram(matchedPop)

balance <- computeCovariateBalance(matchedPop, cohortMethodData)
plotCovariateBalanceScatterPlot(balance)
plotCovariateBalanceOfTopVariables(balance)

outcomeModel <- fitOutcomeModel(cohortMethodData = cohortMethodData,
              population = matchedPop,
              stratified = FALSE,
              modelType = "cox",
              useCovariates = FALSE)
outcomeModel
plotKaplanMeier(matchedPop, treatmentLabel = "Dabigatran", comparatorLabel = "Warfarin", includeZero = FALSE, fileName = file.path(workFolder, "kaplanMeier.png"))
```

Step 1: Getting the necessary data from the database

- Target and comparator cohorts of interest
  - Index date
  - End of cohort eligibility (e.g. end of exposure)
  - End of observation
- Outcome(s) of interest
  - Dates of occurrence
- Covariates

Take as-is from ATLAS

Covariates (Graham et al.)

Graham et al. used several covariates, including

- Demographics
- Medical history
  - Various conditions
  - CHADS
  - HAS-BLED
- Medication use

These were hand-picked for this study

Loading the list of selected covariate concept IDs

```
includedConcepts <- read.csv("inst/csv/GrahamIncludedConcepts.csv")$Concept.ID
```

Covariate settings

```
covariateSettings <- createCovariateSettings(useCovariateDemographics = TRUE,
                                             useCovariateDemographicsGender = TRUE,
                                             useCovariateDemographicsRace = TRUE,
                                             useCovariateDemographicsEthnicity = TRUE,
                                             useCovariateDemographicsAge = TRUE,
                                             useCovariateDemographicsYear = FALSE,
                                             useCovariateDemographicsMonth = FALSE,
                                             …
                                             useCovariateRiskScores = TRUE,
                                             useCovariateRiskScoresCharlson = FALSE,
                                             useCovariateRiskScoresDCSI = FALSE,
                                             useCovariateRiskScoresCHADS2 = TRUE,
                                             useCovariateRiskScoresCHADS2VASc = FALSE,
                                             excludedCovariateConceptIds = c(),
                                             includedCovariateConceptIds = includedConcepts,
                                             deleteCovariatesSmallCount = 100)
```

Including only the concept IDs we just loaded

Loading all data

```
cohortMethodData <- getDbCohortMethodData(connectionDetails = connectionDetails,
                                          cdmDatabaseSchema = cdmDatabaseSchema,
                                          targetId = 2649,
                                          comparatorId = 2650,
                                          outcomeIds = 2651,
                                          exposureTable = "cohort",
                                          outcomeTable = "cohort",
                                          cdmVersion = cdmVersion,
                                          excludeDrugsFromCovariates = FALSE,
                                          covariateSettings = covariateSettings)

saveCohortMethodData(cohortMethodData, “s:/GrahamStudy/cohortMethodData")
```

Loading all data

```
cohortMethodData <- getDbCohortMethodData(connectionDetails = connectionDetails,
                                          cdmDatabaseSchema = cdmDatabaseSchema,
                                          targetId = 2649,
                                          comparatorId = 2650,
                                          outcomeIds = 2651,
                                          exposureTable = "cohort",
                                          outcomeTable = "cohort",
                                          cdmVersion = cdmVersion,
                                          excludeDrugsFromCovariates = FALSE,
                                          covariateSettings = covariateSettings)

saveCohortMethodData(cohortMethodData, “s:/GrahamStudy/cohortMethodData")
```

Using the cohorts generated by ATLAS

Loading all data

```
cohortMethodData <- getDbCohortMethodData(connectionDetails = connectionDetails,
                                          cdmDatabaseSchema = cdmDatabaseSchema,
                                          targetId = 2649,
                                          comparatorId = 2650,
                                          outcomeIds = 2651,
                                          exposureTable = "cohort",
                                          outcomeTable = "cohort",
                                          cdmVersion = cdmVersion,
                                          excludeDrugsFromCovariates = FALSE,
                                          covariateSettings = covariateSettings)

saveCohortMethodData(cohortMeth
```

The covariate settings we specified earlier

Inspecting the data

```
summary(cohortMethodData)
```

```
CohortMethodData object summary

Treatment concept ID: 2649
Comparator concept ID: 2650
Outcome concept ID(s): 2651

Treated persons: 19046
Comparator persons: 50918

Outcome counts:
     Event count Person count
2651        8063         8063

Covariates:
Number of covariates: 827
Number of non-zero covariate values: 2428813
```

Step 2: Defining the study population

```
studyPop <- createStudyPopulation(cohortMethodData = cohortMethodData,
                                  outcomeId = 2651,
                                  removeSubjectsWithPriorOutcome = TRUE,
                                  minDaysAtRisk = 1,
                                  riskWindowStart = 1,
                                  addExposureDaysToStart = FALSE,
                                  riskWindowEnd = 0,
                                  addExposureDaysToEnd = TRUE)
```

Step 2: Defining the study population

```
studyPop <- createStudyPopulation(cohortMethodData = cohortMethodData,
                                  outcomeId = 2651,
                                  removeSubjectsWithPriorOutcome = TRUE,
                                  minDaysAtRisk = 1,
                                  riskWindowStart = 1,
```

Remove subjects with outcomes prior to index date

Step 2: Defining the study population

```
studyPop <- createStudyPopulation(cohortMethodData = cohortMethodData,
                                  outcomeId = 2651,
                                  removeSubjectsWithPriorOutcome = TRUE,
                                  minDaysAtRisk = 1,
                                  riskWindowStart = 1,
                                  addExposureDaysToStart = FALSE,
                                  riskWindowEnd = 0,
                                  addExposureDaysToEnd = TRUE)
```

Define risk window: start on day after index date, end at end of cohort eligibility (end of exposure)

Graham: “Follow-up began on the day after the first qualifying anticoagulant prescription fill”

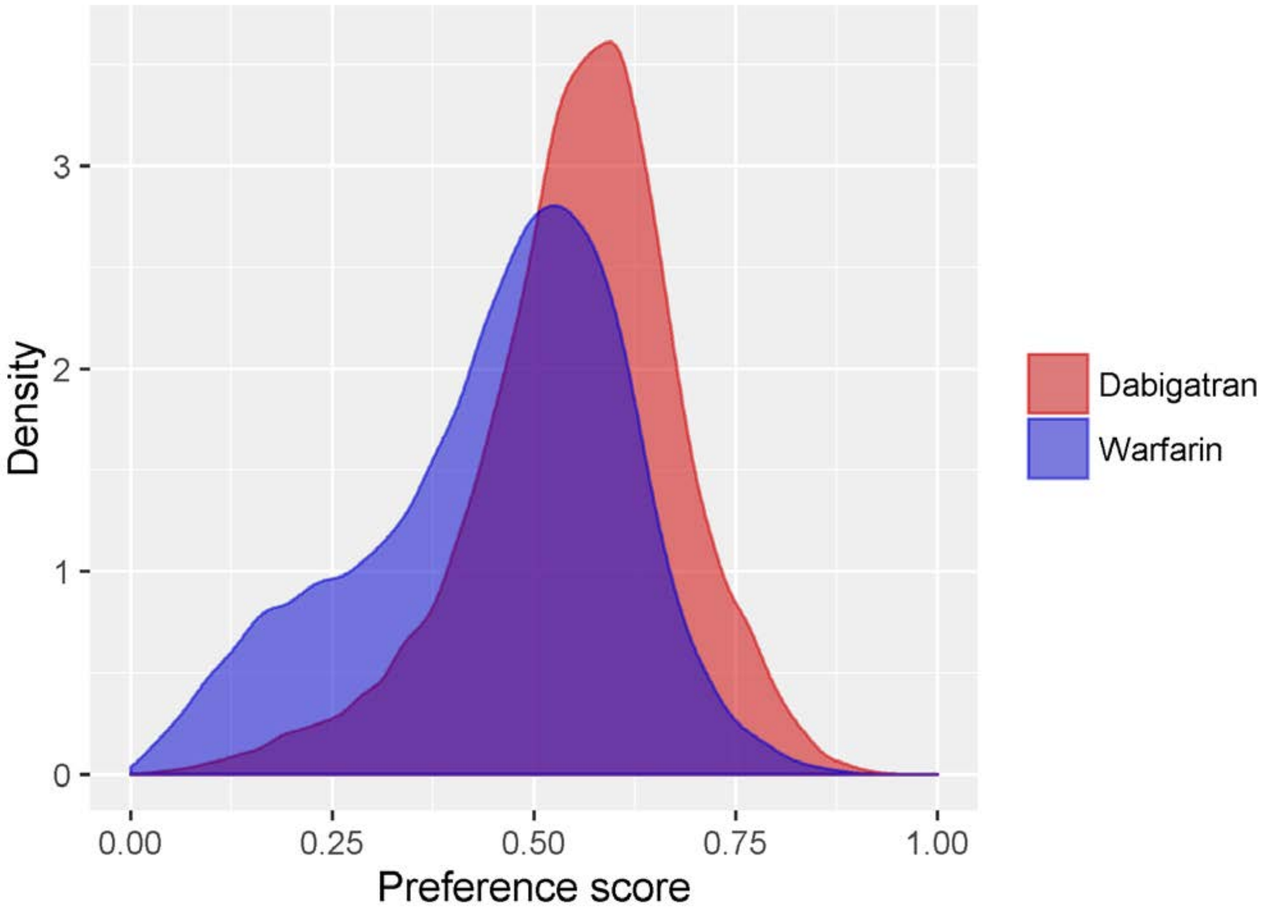
Step 3: Creating a propensity model

```
ps <- createPs(cohortMethodData = cohortMethodData,
               population = studyPop)


saveRDS(ps, “s:/GrahamStudy/ps.rds")
```

Plot propensity score distribution

```
plotPs(ps , treatmentLabel = "Dabigatran", comparatorLabel = "Warfarin")
```



Step 4: Matching

```
matchedPop <- matchOnPs(ps,
                        caliper = 0.25,
                        caliperScale = "standardized",
                        maxRatio = 1)
```

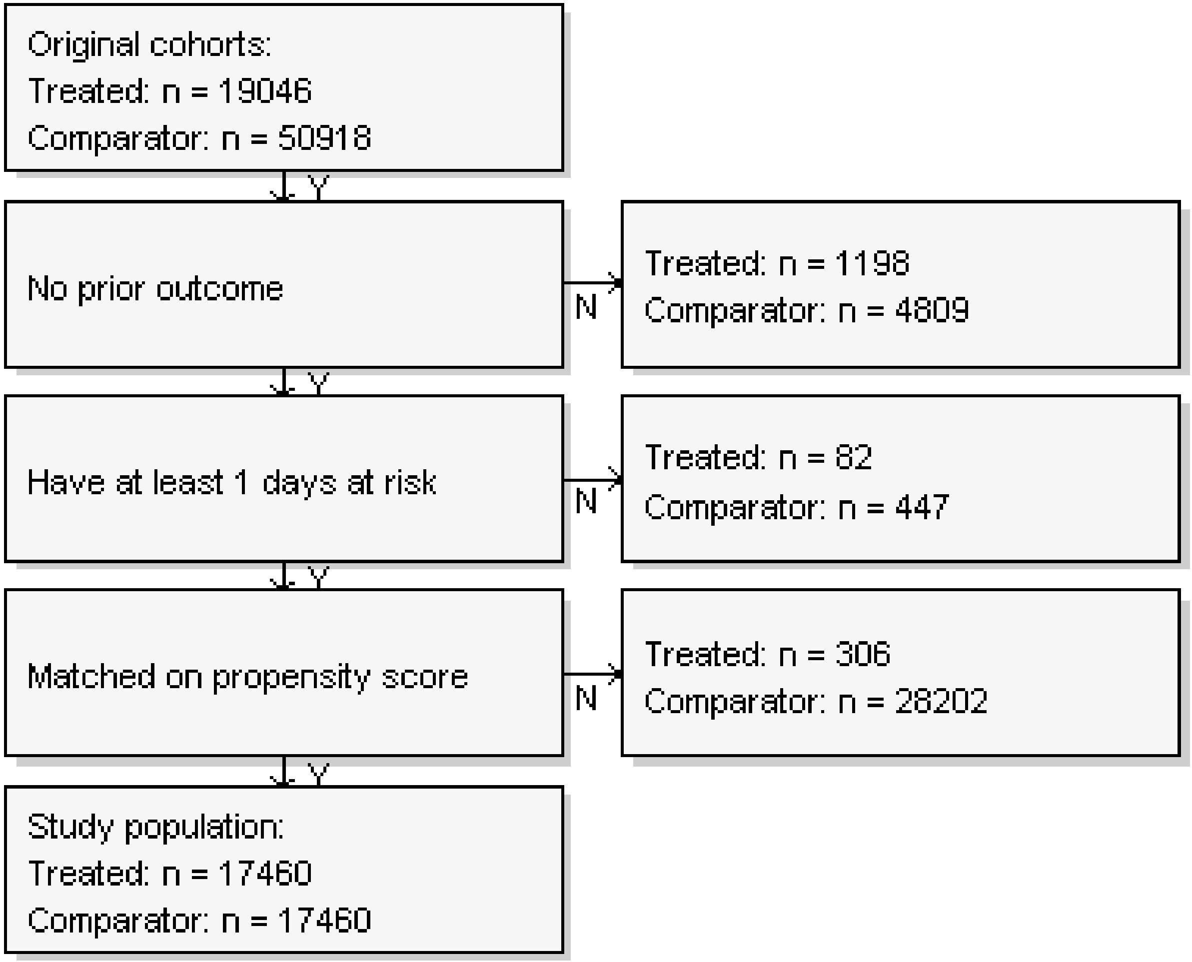
Select up to 1 comparator per target subject (1-on-1 matching)

Graham: “Dabigatran users were propensity score matched to warfarin users in a 1:1 ratio with the use of a greedy matching algorithm.”

No caliper was mentioned, but it is probably a good idea to use one

Attrition

```
drawAttritionDiagram(matchedPop , treatmentLabel = "Dabigatran", comparatorLabel = "Warfarin")
```



Original cohorts:
Treated: n = 19046
Comparator: n = 50918

No prior outcome

Treated: n = 1198
Comparator: n = 4809

Have at least 1 days at risk

Treated: n = 82
Comparator: n = 447

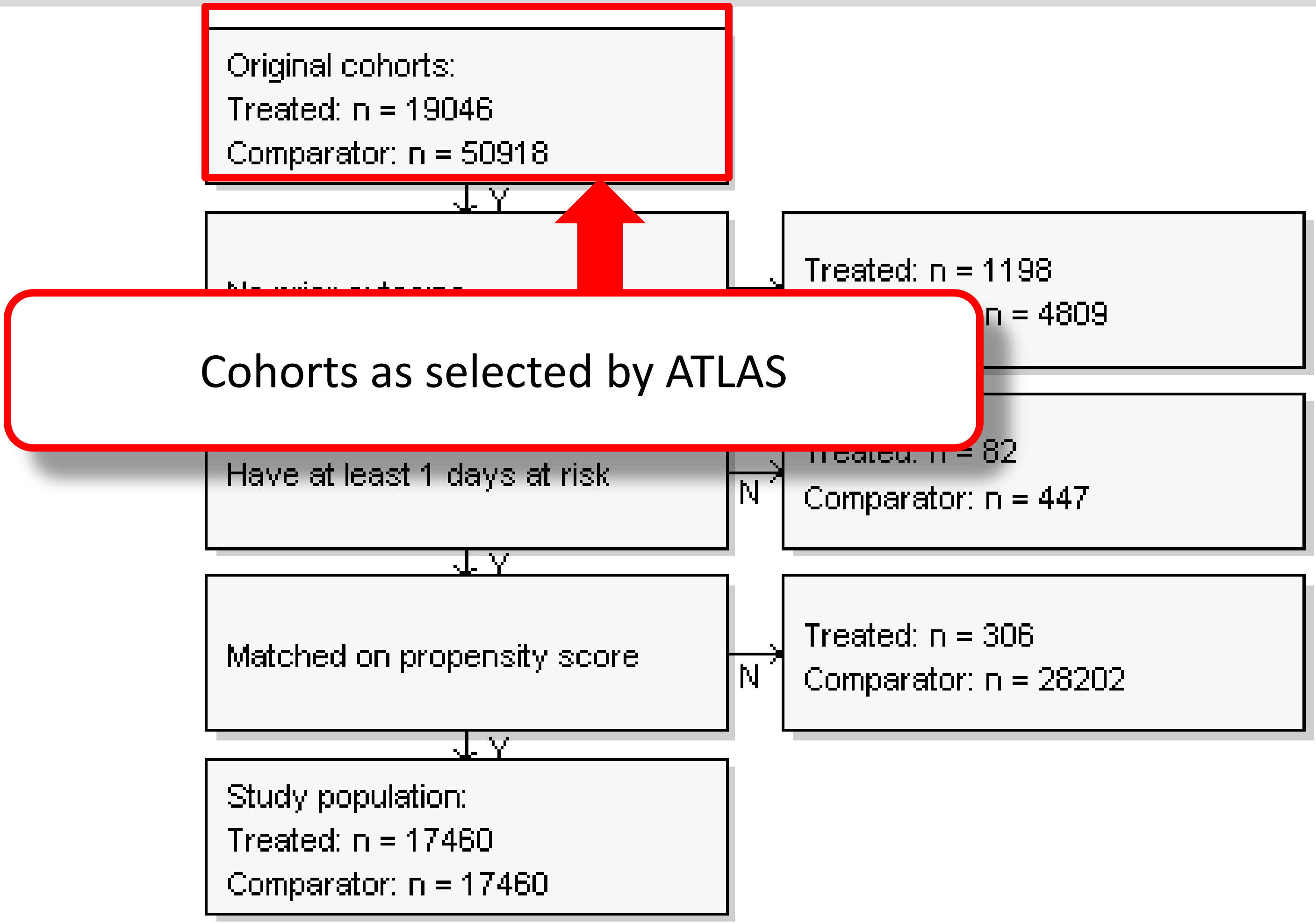
Matched on propensity score

Treated: n = 306
Comparator: n = 28202

Study population:
Treated: n = 17460
Comparator: n = 17460

Attrition

```
drawAttritionDiagram(matchedPop , treatmentLabel = "Dabigatran", comparatorLabel = "Warfarin")
```



Original cohorts:
Treated: n = 19046
Comparator: n = 50918

Cohorts as selected by ATLAS

Treated: n = 1198
n = 4809

Have at least 1 days at risk

Treated: n = 82
Comparator: n = 447

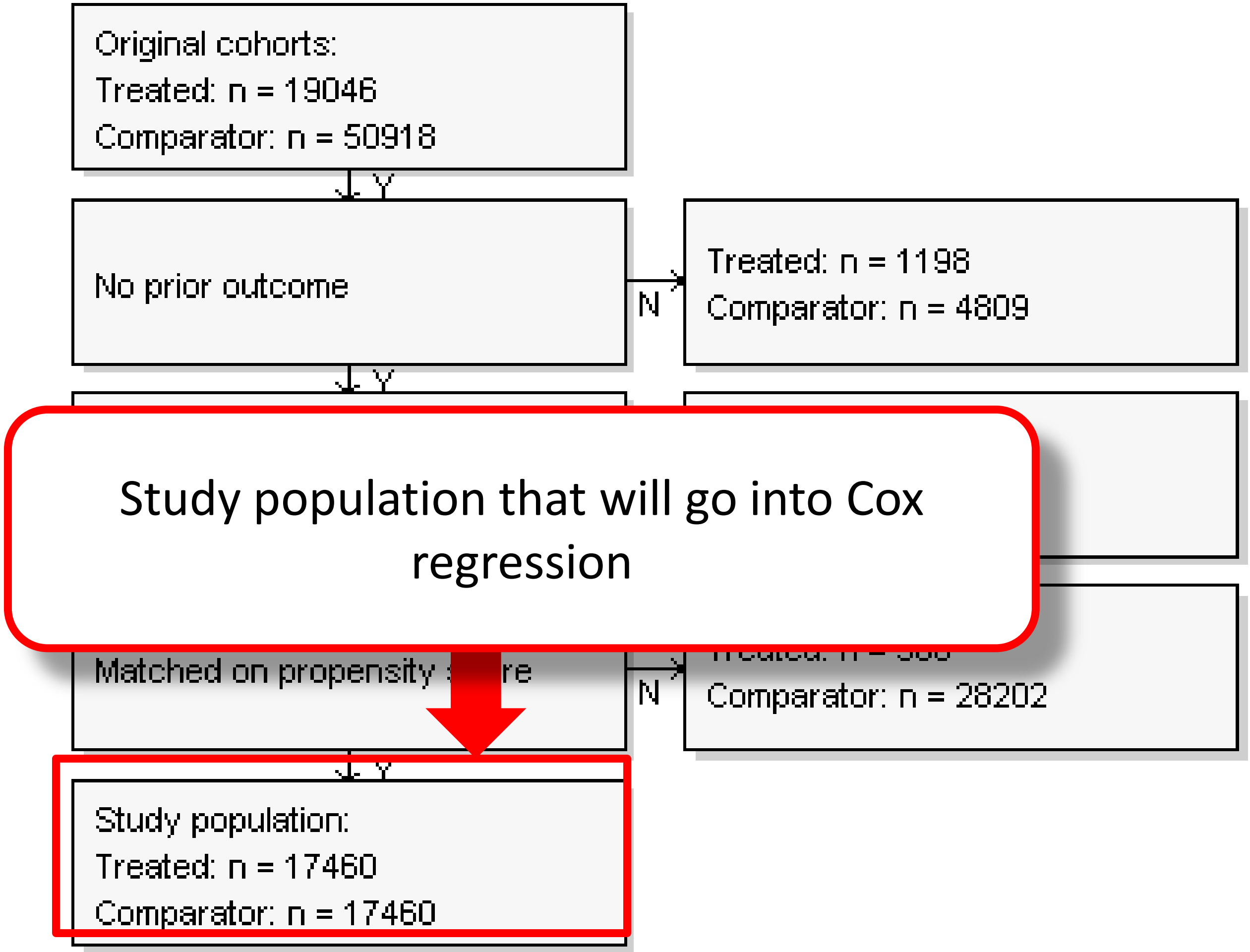
Matched on propensity score

Treated: n = 306
Comparator: n = 28202

Study population:
Treated: n = 17460
Comparator: n = 17460

Attrition

`drawAttritionDiagram(matchedPop , treatmentLabel = "Dabigatran", comparatorLabel = "Warfarin")`



Original cohorts:
Treated: n = 19046
Comparator: n = 50918

No prior outcome

Treated: n = 1198
Comparator: n = 4809

Matched on propensity s re

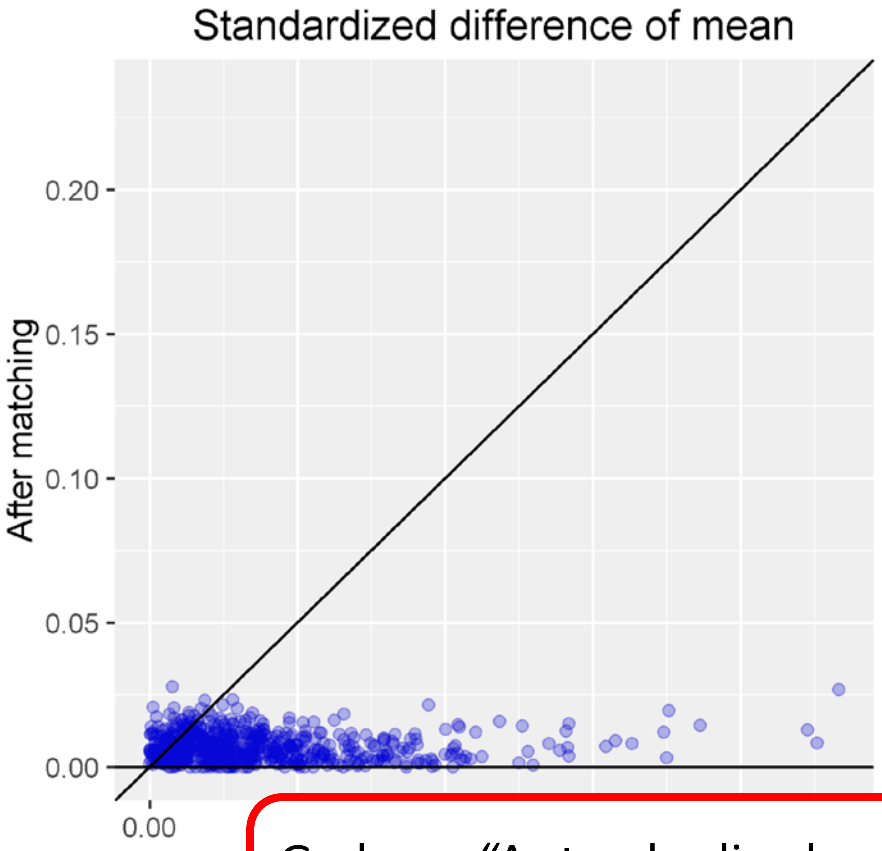
Comparator: n = 28202

Study population:
Treated: n = 17460
Comparator: n = 17460

Study population that will go into Cox regression

Covariate balance

```
balance <- computeCovariateBalance(matchedPop, cohortMethodData)
plotCovariateBalanceScatterPlot(balance)
```



Standardized difference of mean

Most covariates are binary:

$$\frac{\mathrm{abs}(P_{\text{target group}} - P_{\text{comparator group}})}{\text{standard deviation}}$$

Graham: “A standardized mean difference of ≤0.1 indicates a negligible difference.”

Step 5: Fitting the outcome model

```
outcomeModel <- fitOutcomeModel(population = matchedPop,
                                modelType = "cox",
                                stratified = FALSE,
                                useCovariates = FALSE)
```

Graham: “Cox proportional hazards regression was used to compare time to event in dabigatran compared with warfarin (reference) cohorts.

Ambiguous: Did they condition the model on the matched set (recommended)?

Inspect the outcome model

```
summary(outcomeModel)
```

```
Model type: cox
Stratified: FALSE
Use covariates: FALSE
Status: OK

          Estimate   lower .95   upper .95              logRr       seLogRr
treatment 0.89626    0.71863     1.11829                -0.10952    0.1128

Population counts
          treatedPersons         comparatorPersons    treatedExposures      comparatorExposures
Count     17460                  17460                17460                 17460

Outcome counts
          treatedPersons         comparatorPersons    treatedExposures      comparatorExposures
Count     164                    155                  164                   155

Time at risk
          treatedDays            comparatorDays
Days      4912947                3954046
```

Inspect the outcome model

```
summary(outcomeModel)
```

```
Model type: cox
Stratified: FALSE
Use covariates: FALSE
Status: OK

          Estimate   lower .95   upper .95          logRr      seLogRr
treatmen  0.89626    0.71863     1.11829            -0.10952   0.1128

Population counts
          treatedPersons          comparatorPersons    treatedExposures     comparatorExposures
C                                                                           17460

C
                                                       edExposures          comparatorExposures
Count     164                     155                  164                  155

Time at risk
          treatedDays             comparatorDays
Days      4912947                 3954046
```

Point estimate and 95% confidence interval

Inspect the outcome model

```
summary(outcomeModel)
```

```
Model type: cox
Stratified: FALSE
Use covariates: FALSE
Status: OK

          Estimate  lower .95  upper .95            logRr      seLogRr
treatment 0.89626   0.71863    1.11

Population counts
          treatedPersons     com                                        es
Count     17460              1746

Outcome counts
          treatedPersons     comparatorPersons  treat  Exposures    comparatorExposures
Count     164                155                164                 155

Time at risk
          treatedDays        comparatorDays
Days      4912947            3954046
```

Target group (dabigatran) has more outcomes, but also more time at risk

Inspect the outcome model

```
summary(outcomeModel)
```

```
Model type: cox
Stratified: FALSE
Use covariates: FALSE
Status: OK

          Estimate   lower .95   upper .95
treatment 0.89626    0.71863     1.11829

Population counts
          treatedPersons        comparatorPers
Count     17460                 17460

Outcome counts
          treatedPersons        comparatorPersons   treat   Exposures      comparatorExposures
Count     164                   155                 164                    155

Time at risk
          treatedDays           comparatorDays
Days      4912947               3954046
```

Graham:

$IR_{dabigatran}$ = 11.3

$IR_{warfarin}$ = 13.9

$HR_{adjusted}$ = 0.80 (0.67–0.96)

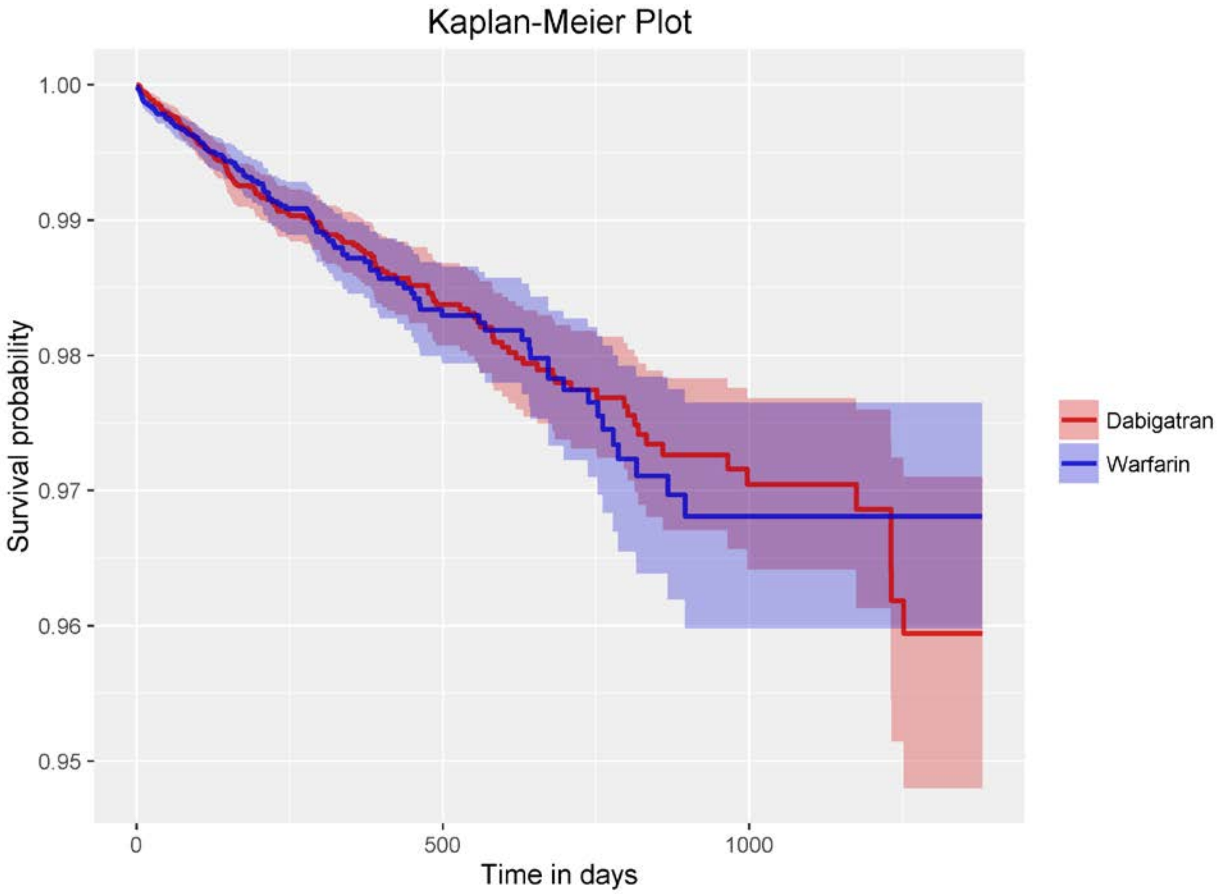
$IR_{dabigatran}$ = 12.2

$IR_{warfarin}$ = 14.3

$HR_{adjusted}$ = 0.90 (0.72 – 1.12)

Kaplan Meier plot

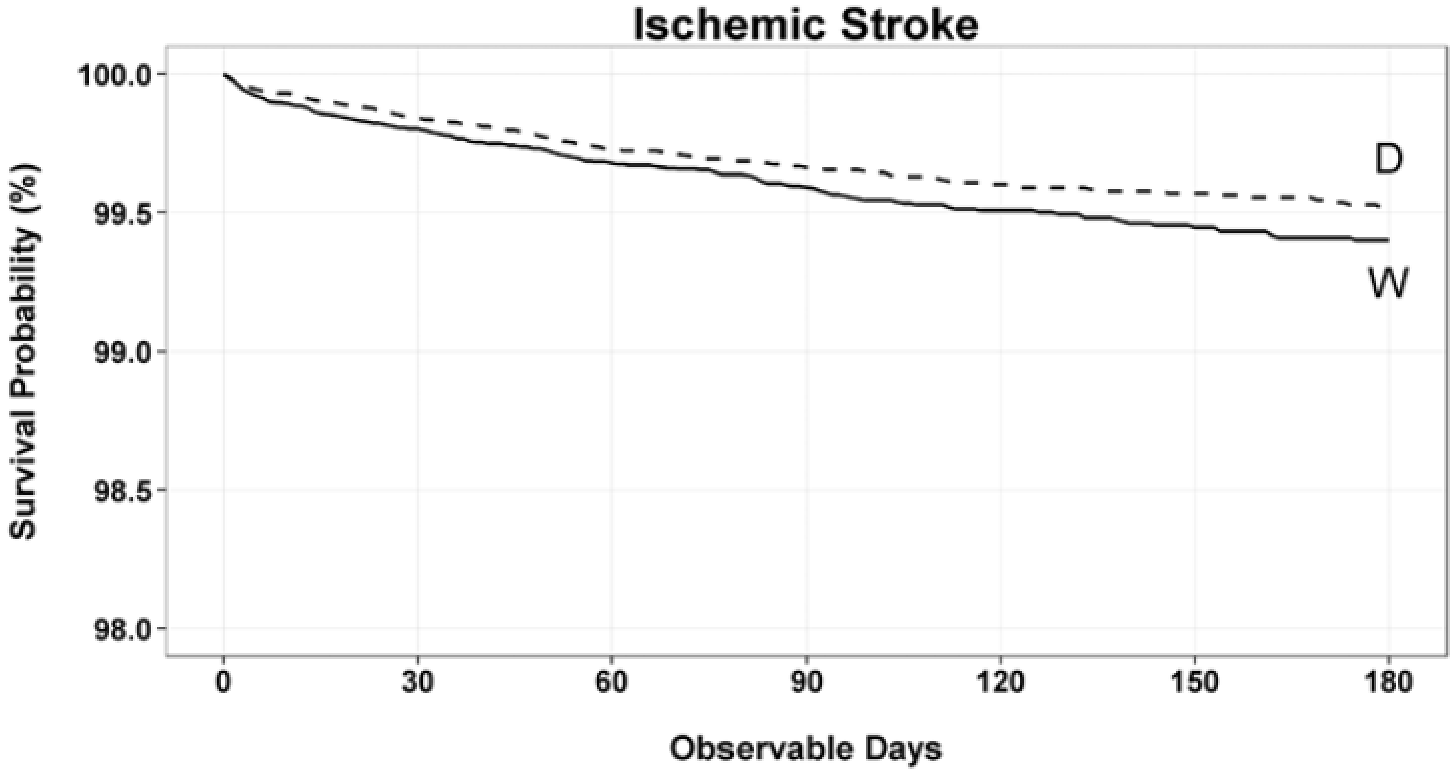
```
plotKaplanMeier(matchedPop,
                treatmentLabel = "Dabigatran",
                comparatorLabel = "Warfarin“,
                includeZero = FALSE)
```



Kaplan Meier plot

```
plotKaplanMeier(matchedPop,
```

Graham:



Time in days

Execution steps

1. Getting the necessary data from the database
2. Defining the study population
3. Creating a propensity model
4. Matching
5. Fitting the outcome model

+ generating various diagnostics

Handpicking covariates is not recommended!

- Might miss an important confounder (proxy)
- Subjective (non-reproducible)

Better:

- Include all pre-defined covariates
- Let data (and regularization) decide which ones are important
- Bonus: more work for the computer, but less work for you!

Covariate settings

```
covariateSettings <- createCovariateSettings(useCovariateDemographics = TRUE,
                                             useCovariateConditionOccurrence = TRUE,
                                             useCovariateConditionOccurrence365d = TRUE,
                                             useCovariateConditionOccurrence30d = TRUE,
                                             useCovariateConditionOccurrenceInpt180d = TRUE,
                                             …
                                             useCovariateRiskScores = TRUE,
                                             useCovariateRiskScoresCharlson = TRUE,
                                             useCovariateRiskScoresDCSI = TRUE,
                                             useCovariateRiskScoresCHADS2 = TRUE,
                                             useCovariateInteractionYear = FALSE,
                                             useCovariateInteractionMonth = FALSE,
                                             excludedCovariateConceptIds = excludeConceptIds,
                                             deleteCovariatesSmallCount = 100)
```

Covariate settings

```
covariateSettings <- createCovariateSettings(useCovariateDemographics = TRUE,
                     useCovariateConditionOccurrence = TRUE,
                     useCovariateConditionOccurrence365d = TRUE,
                     useCovariateConditionOccurrence30d = TRUE,
                     useCovariateConditionOccurrenceInpt180d = TRUE,
                     …
                     useCovariateRiskScores = TRUE,
                     useCovariateRiskScoresCharlson = TRUE,
                     useCovariateRiskScoresDCSI = TRUE,
                     useCovariateRiskScoresCHADS2 = TRUE,
                     useCovariateInteractionYear = FALSE,
                     useCovariateInteractionMonth = FALSE,
                     excludedCovariateConceptIds = excludeConceptIds,
                     deleteCovariatesSmallCount = 100)
```

Constructing covariates for

- Demographics
- All drugs & classes
- All conditions & groups
- All procedures
- All measurements
- All observations
- Risk scores

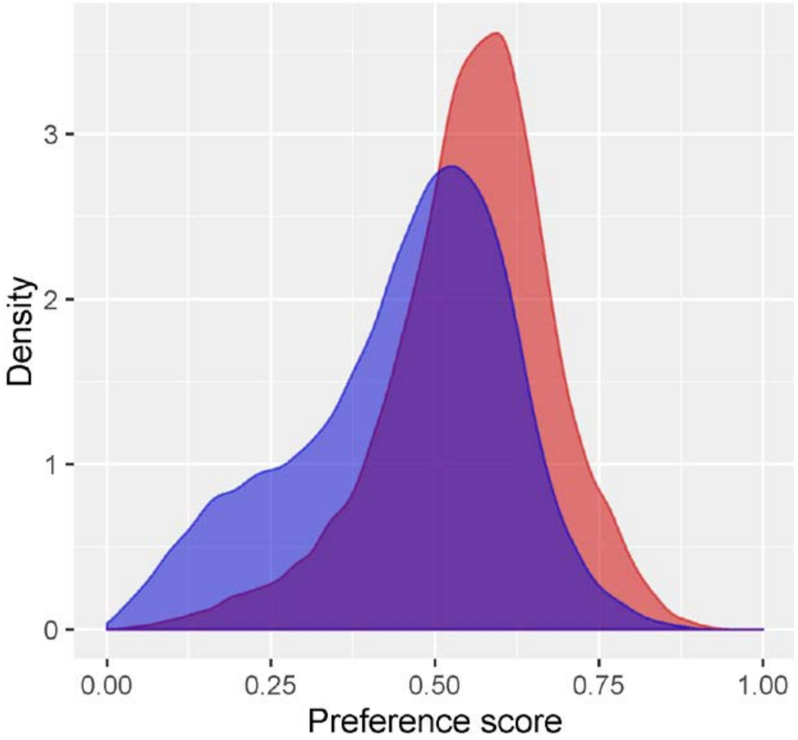
Covariate settings

```
covariateSettings <- createCovariateSettings(useCovariateDemographics = TRUE,
                                             useCovariateConditionOccurrence = TRUE,
                                             useCovariateConditionOccurrence365d = TRUE,
                                             useCovariateConditionOccurrence30d = TRUE,
                                             useCovariateConditionOccurrenceInpt180d = TRUE,
                                             …
                                             useCovariateRiskScores = TRUE,
                                             useCovariateRiskScoresCharlson = TRUE,
                                             useCovariateRiskScoresDCSI = TRUE,
                                             useCovariateRiskScoresCHADS2 = TRUE,
                                             useCovariateInteractionYear = FALSE,
                                             useCovariateInteractionMonth = FALSE,
                                             excludedCovariateConceptIds = excludeConceptIds,
                                             deleteCovariatesSmallCount = 100)
```

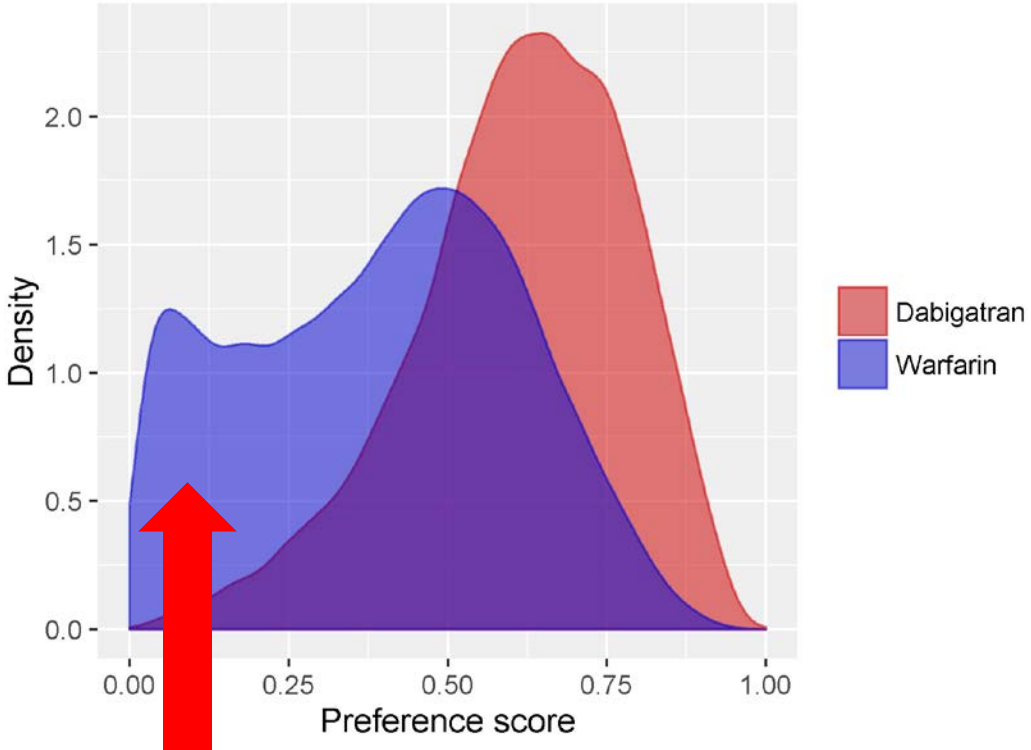
Have to explicitly exclude dabigatran and warfarin

Effect on propensity score distribution

Using hand-picked covariates



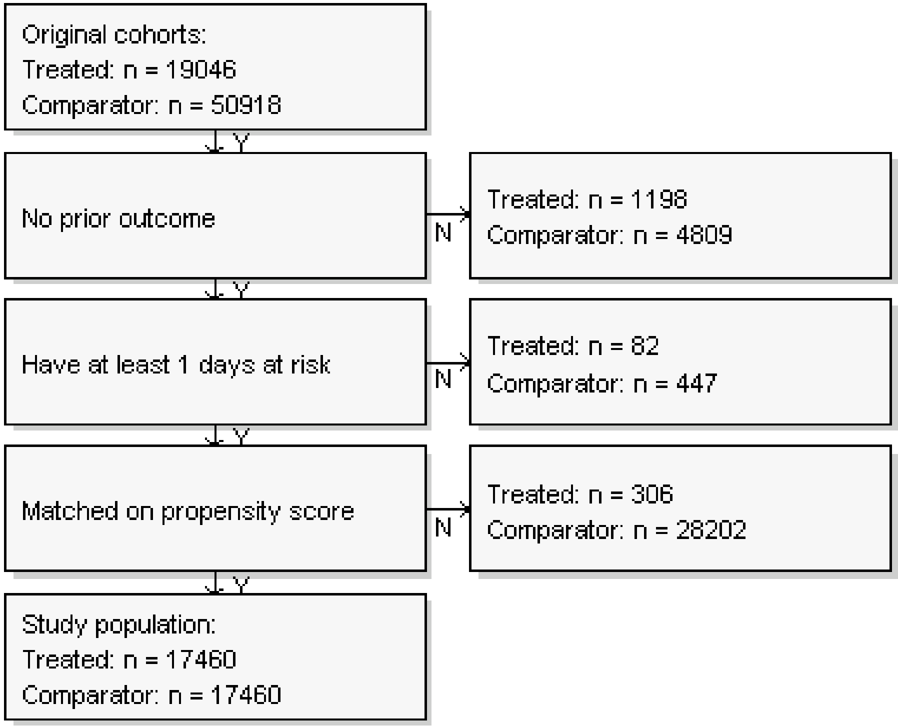
Using all covariates



Whole subgroup of people likely to get warfarin was not identified by Graham

Effect on matching

Using hand-picked covariates



Original cohorts:
Treated: n = 19046
Comparator: n = 50918

No prior outcome

Treated: n = 1198
Comparator: n = 4809

Have at least 1 days at risk

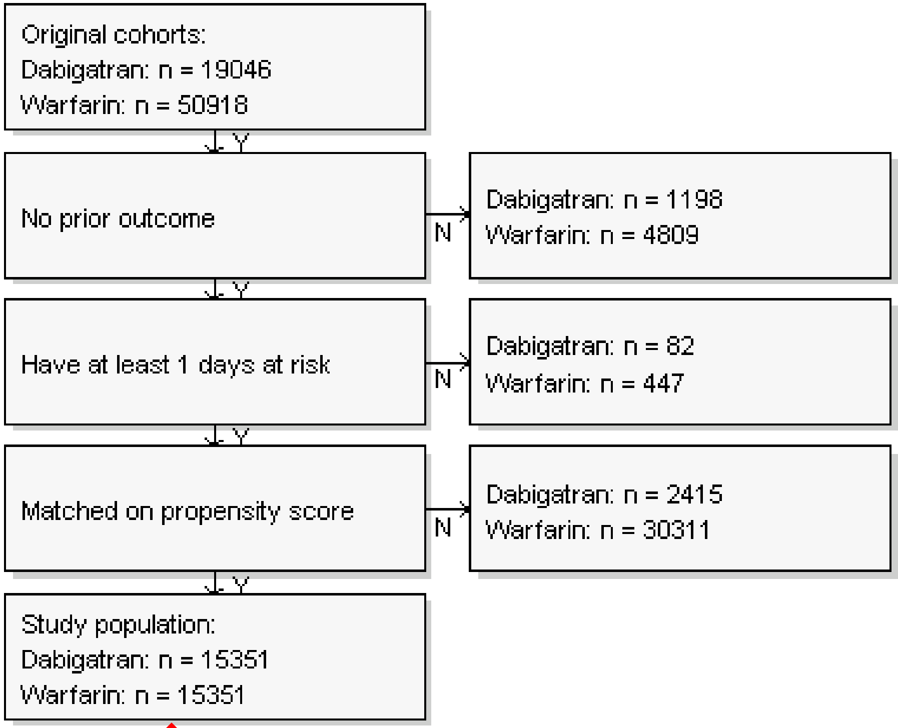
Treated: n = 82
Comparator: n = 447

Matched on propensity score

Treated: n = 306
Comparator: n = 28202

Study population:
Treated: n = 17460
Comparator: n = 17460

Using all covariates



Original cohorts:
Dabigatran: n = 19046
Warfarin: n = 50918

No prior outcome

Dabigatran: n = 1198
Warfarin: n = 4809

Have at least 1 days at risk

Dabigatran: n = 82
Warfarin: n = 447

Matched on propensity score

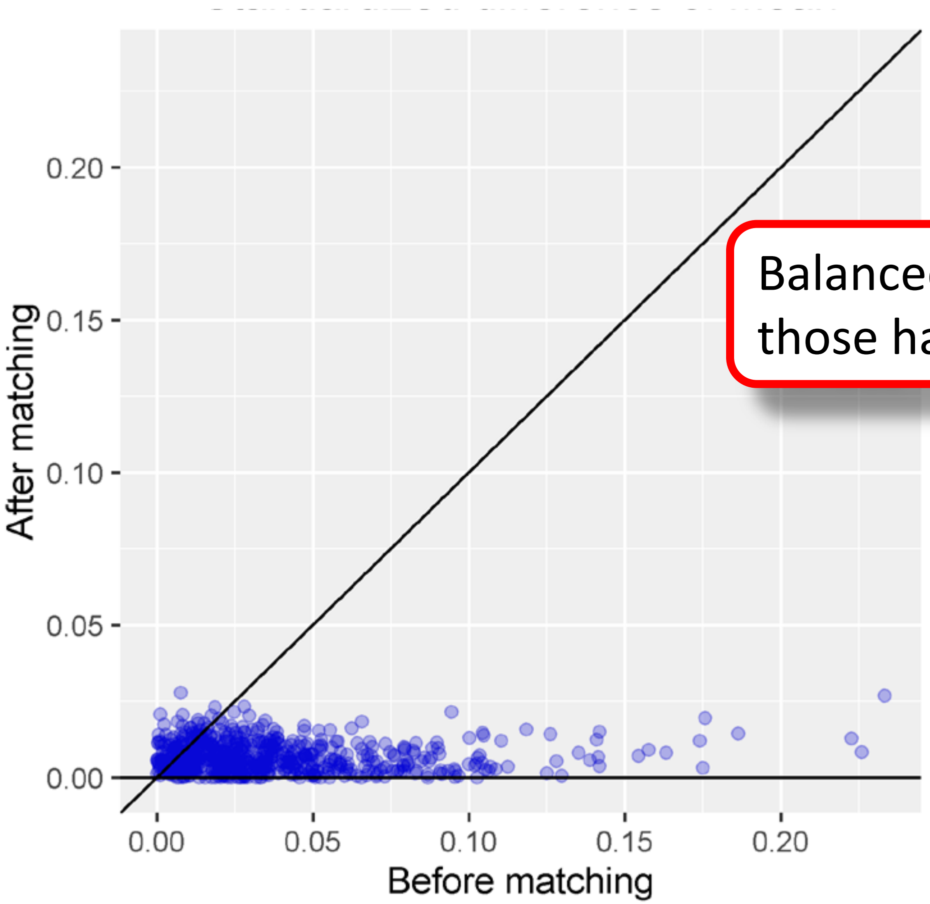
Dabigatran: n = 2415
Warfarin: n = 30311

Study population:
Dabigatran: n = 15351
Warfarin: n = 15351

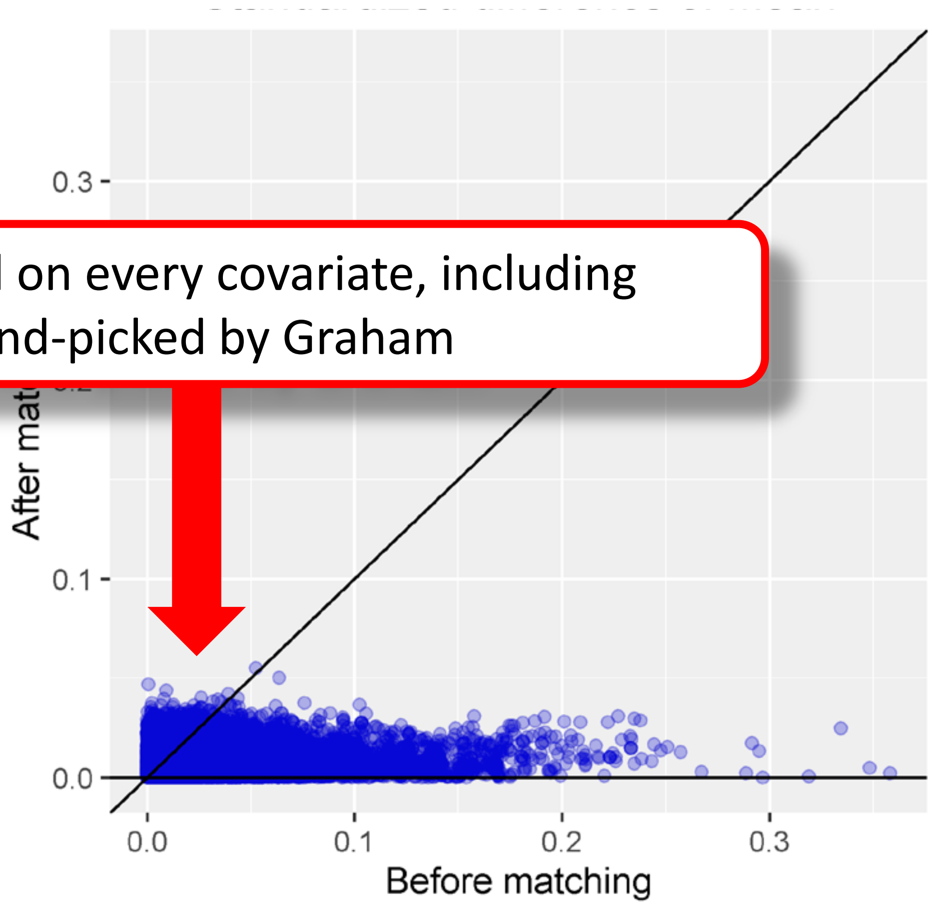
Fewer people left after matching

Effect on balance

Using hand-picked covariates



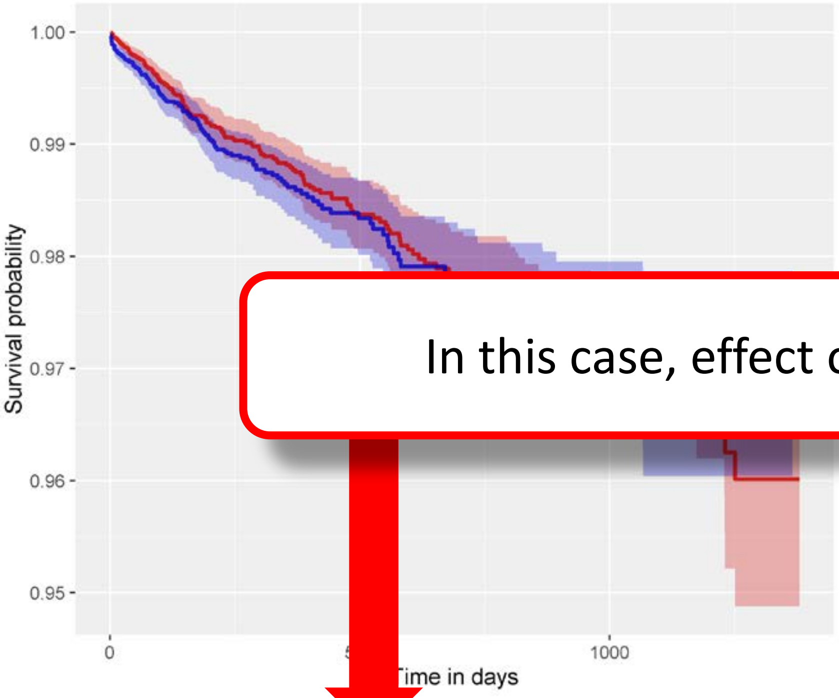
Using all covariates



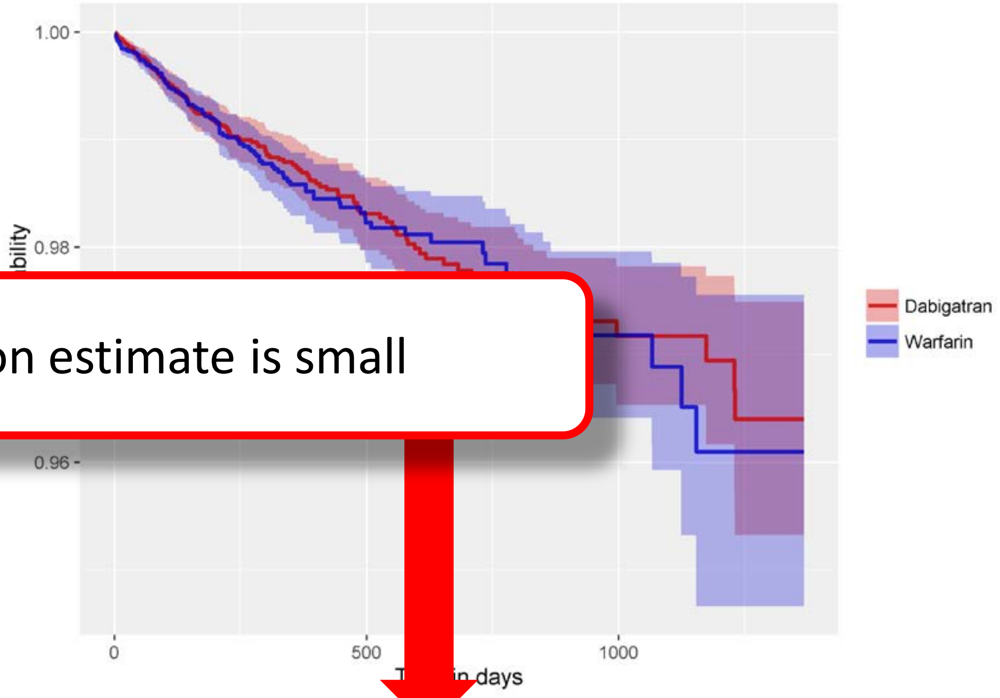
Balanced on every covariate, including those hand-picked by Graham

Effect on hazard ratio

Using hand-picked covariates



Using all covariates



In this case, effect on estimate is small

HR = 0.90 (0.72 – 1.12)

HR = 0.95 (0.75 - 1.21)

Conclusions

- OHDSI tools can replicate the Graham study
- Diagnostics are an important part of both design and execution
  - Show impact of adjustments: lots of inbalance before matching
  - Lot of attrition: how generalizable are our results?
- Hand picking covariates is not recommended
- Including negative controls is recommended