Assessing treatment effect using registry data

Brice Ozenne

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UNIVERSITY OF COPENHAGEN

Motivation

OBJECTIVE: decide whether a treatment is beneficial
→ for a give time horizon `1 year`

MATERIAL: registry data

- observational data (i.e. non-randomized)
- long term follow-up
- large number of patients

What do we mean by beneficial:

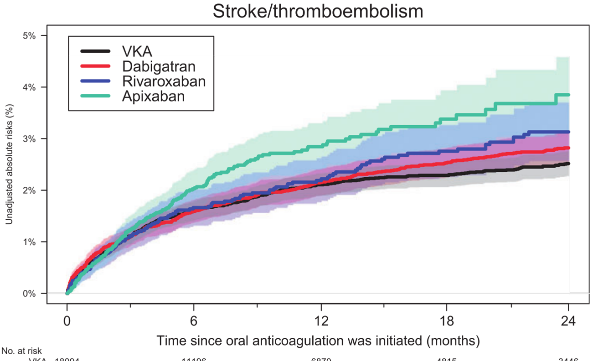
- does the treatment reduce the 1-year risk of developing the disease ?

Plan

1. Estimating a 1-year risk of a disease using registry data
   → model checking [Cox]

2. Estimating a treatment effect using registry data
   → model checking [new strategy]

   e.g. Staerk et al. 2016:

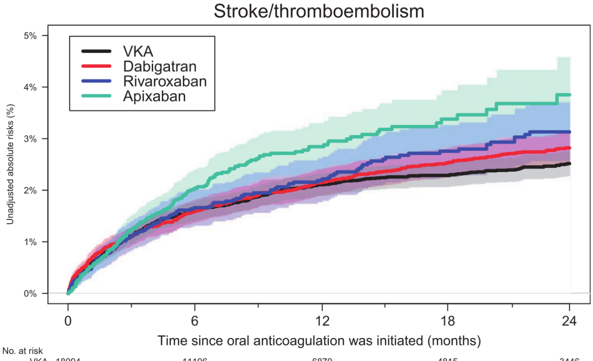


Plan

1. Estimating a 1-year risk of a disease using registry data
   → model checking [Cox]

2. Estimating a treatment effect using registry data
   → model checking [new strategy]

   e.g. Staerk et al. 2016:



Absolute risk

Definition

1-year absolute risk:

- chance that a person will be diagnosed with the event in 1 year
  $\rightarrow$ depends on the risk of the event λ_{event}
  $\rightarrow$ depends on the risk of death λ_{death}

$$r_{event}(t|X) = \underbrace{\int_0^t}_{\text{addition over time}} \underbrace{S_0(s|X)}_{\text{survival at to time s}} \underbrace{\lambda_{event}(s|X)}_{\substack{\text{immediate risk of} \\ \text{the event at time s}}} ds$$

X: covariates like age, gender ...

Considering registry data, are involved:

- the event of interest
- competing risks, e.g. death
  $\rightarrow$ will prevent the observation of the event

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X: covariates like age, gender ...

Considering registry data, are involved:

- the event of interest
- competing risks, e.g. death
  $\rightarrow$ will prevent the observation of the event

Cause specific Cox model

One Cox regression for each competing risk:

$$\lambda_{event}(t|X) = \lambda_{0,event}(t)\exp(X\beta_{event})$$
$$\lambda_{death}(t|X) = \lambda_{0,death}(t)\exp(X\beta_{death})$$

We can then estimate the overall survival.

Cause specific Cox model

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We can then estimate the overall survival.

- no event
- not dead

Cause specific Cox model

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$$\lambda_{event}(t|X) = \lambda_{0,event}(t)\exp(X\beta_{event})$$
$$\lambda_{death}(t|X) = \lambda_{0,death}(t)\exp(X\beta_{death})$$

We can then estimate the overall survival.

$$S_0(t|X) = \exp\left(-\int_0^t \lambda_{death}(s|X) + \lambda_{event}(s|X)ds\right)$$

In R

```
> library(riskRegression)
> data(Melanoma)
> fit1 <- CSC(formula=Hist(time,status)~sex+invasion+age,
+              data=Melanoma)
fit1$models$`Cause 1`
Call:
survival::coxph(...)
                     coef exp(coef) se(coef)    z       p
sexMale           0.66338   1.94135  0.26632 2.49 0.01274
invasionlevel.1 1.03717   2.82122  0.32824 3.16 0.00158
invasionlevel.2 1.40323   4.06830  0.38074 3.69 0.00023
age               0.00982   1.00987  0.00834 1.18 0.23884
```

In R

```
> head(Melanoma[1:2,c("sex","invasion","age")])
      sex invasion age
    1 Male  level.1  76
    2 Male  level.0  56
> predictRisk(fit1, newdata = Melanoma[1:2,],
                  cause = 1, time = 365.25)
         365.25
[1,] 0.06441670
[2,] 0.01992289
```

Summary

We can easily compute the absolute risk

- using one Cox model for the event of interest
- using another Cox model for the competing events

But now we have to check the assumptions for each Cox model !

Cox model assumptions

Assumptions:

1. proportional hazard (PH) assumption
2. (linear) functional form
3. (absence of) interaction

[Not covered] non-informative censoring, influential observations

Checking Cox model assumptions

Model checking is more complex compared to a linear regression

- several types of residuals
- many different diagnostic tools
    - validity of the null hypothesis

      `e.g. PH vs. non PH`
    - against a specific alternative hypothesis

      `e.g. quadratic vs. linear effect age`

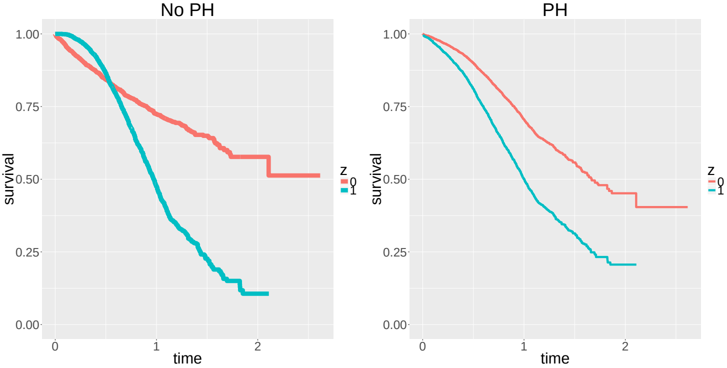
(1) Checking Proportional hazard assumption

Cox model:

$$\lambda(t|X) = \lambda_0(t)e^{\beta X}$$

Here we assume $\beta \perp\!\!\!\perp t$

- Visual checking with Kaplan Meier



(1) Checking Proportional hazard assumption

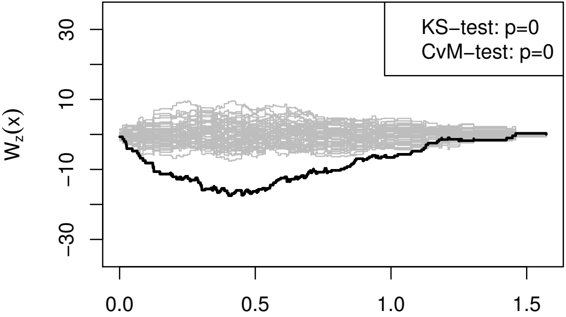
Cox model:

$$\lambda(t|X) = \lambda_0(t)e^{\beta X}$$

Here we assume $\beta \perp\!\!\!\perp t$

- Statistical test: $(\mathcal{H}_0)$ the PH assumption holds, i.e. the cumulative score process follows a brownian bridge

```
> plot(gof::cumres(coxph))
```

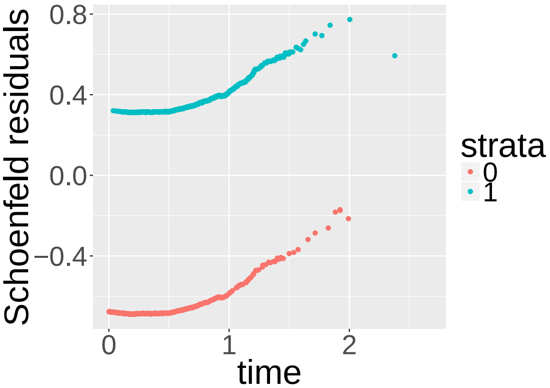


(1) Remedies for non proportional hazard

Strategy 1: find the problematic variable and the type of time dependency

- Display of the Schoenfeld residuals (Grambsch et al. 1994)

$$\mathbb{E}\left[r_{ij}\right] \approx \beta_j(t_i) - \hat{\beta}_j$$

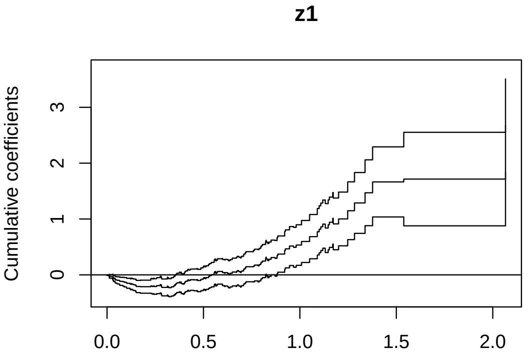


(1) Remedies for non proportional hazard

Strategy 1: find the problematic variable and the type of time dependency

- Use a Cox model with time varying effects

$$\lambda(t|X) = \lambda_0(t)e^{\beta(t)X}$$



```
> plot(timereg::timecox(Surv(time,status) ∼ z,
```

(1) Remedies for non proportional hazard

Strategy 1: find the problematic variable and the type of time dependency

Strategy 2: stratification
Cox model:

$$\lambda(t|X, treatment) = \lambda_0(t)e^{\beta X+\gamma treatment}$$

Stratified Cox model:

$$\lambda(t|X, treatment) = \lambda_{0,treatment}(t)e^{\beta X}$$

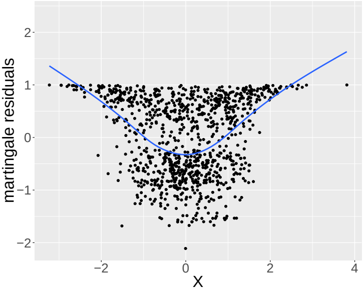
(2) Checking the functional form

$$\lambda(t|X, T) = \lambda_0 e^{\beta X}$$

Here we assume the log of the risk increase linearly with X, e.g. with age.

Diagnostic tools:

- Display martingale residuals
- Comparison with model including a quadratic term or spline



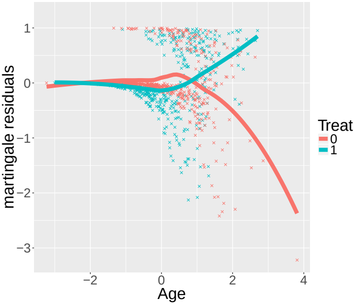
(3) Checking possible interactions

$$\lambda(t|X, T) = \lambda_0 e^{\beta X + \gamma \mathit{treatment}}$$

Here we assume that the risk increase independently with X and with *treatment*

Diagnostic tools:

- Display martingale residuals
- Comparison with a model with interactions



Limits

In practice model validation is tedious:

- large number of tests
  - at least 2 per variables + PH
    (i.e. linearity and interaction with treatment)
  - competing risks: two Cox models to check
- unclear alternative hypothesis
  - residual plot can be hard to interpret
- large *n* small *p*
  - overpowered tests (Grøn et al. 2016)
    → may detect unimportant deviations to hypothesis

Average treatment effect

Observational vs. randomized study

Randomized experiment

- eliminates confounding
- balances all risk factors: known **AND** unknown

→ causal interpretation

Observational studies

- can **ONLY** account for known and measured risk factors

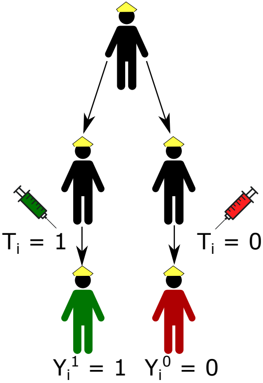
→ establish associations

Causal inference theory:

- causal interpretation (under hypothesis) in observational studies

Counterfactual outcomes

$\mathcal{H}$ypothetical world



Counterfactual outcomes

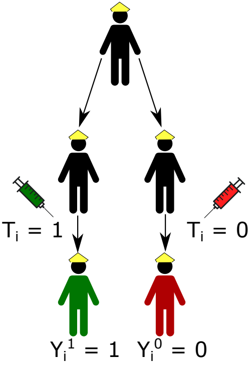
$\mathcal{H}$ypothetical world

We can measure for individual i at time t:
${Y_i}^{T=1}(t)$, outcome using intervention 1
${Y_i}^{T=0}(t)$, outcome using intervention 0

We can estimate

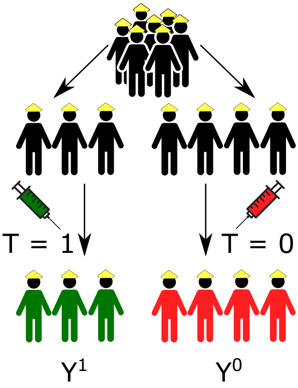
$${Y_i}^{T=1}(t) - {Y_i}^{T=0}(t)$$

the individual causal effect at t



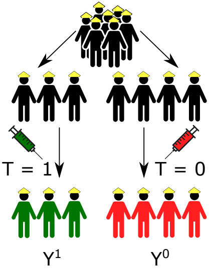
Counterfactual outcomes

$\mathcal{R}$eal world



Counterfactual outcomes

$\mathcal{R}$eal world



We only can measure :
$Y_i^{T=1}(t)$ OR $Y_i^{T=0}(t)$

We can infer the average causal effect:

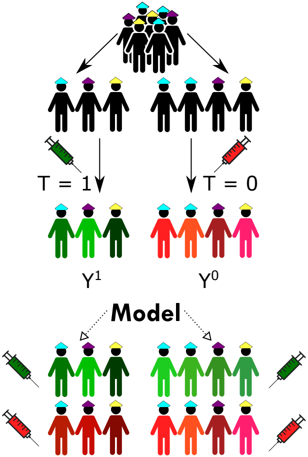
$$\begin{aligned} ACE(t) &= \mathbb{E}\left[Y^{T=1}(t) - Y^{T=0}(t)\right] \\ &= \mathbb{E}\left[Y^{T=1}(t)\right] - \mathbb{E}\left[Y^{T=0}(t)\right] \end{aligned}$$

e.g. (no confounder)

$$\widehat{ACE}(t) = \sum_{i=1}^{n_1} Y_i^{T=1}(t) - \sum_{j=1}^{n_2} Y_j^{T=0}(t)$$

G formula

$\mathcal{R}$eal world: confounders



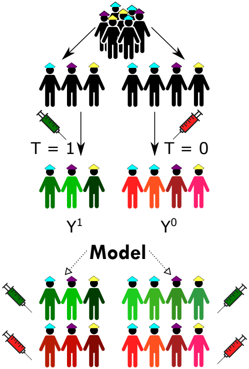
G formula

$\mathcal{R}$eal world: confounders

Statistical model: $\mathbb{E}[Y|X,T]$

$$ACE(t) = \sum_{i=1}^{n} \mathbb{E}[Y_i(t)|X_i, T=1] \\ -\mathbb{E}[Y_i(t)|X_i, T=0]$$

Here $Y(t)|X,T$ is the absolute risk



Workflow (Christiansen et al. 2015)

1. Define the population of interest

   `Patients with first-time ischemic stroke (n=19223)`

   `Exclusion criteria: atrial fibrillation ...`
2. Define the intervention (T)
3. Define the event of interest (Y)
4. Identify the possible competing events (D)
5. Identify the possible confounders/pronostic variable (X)
6. Define a statistical model for relating Y, T, and X

Workflow (Christiansen et al. 2015)

1. Define the population of interest
2. Define the intervention (T)

```
e.g.: antiplatelet regimens for secondary stroke prevention
      T=0:  ASA
      T=1:  Clopidogrel
      T=2:  ASA+Clopidogrel
```

3. Define the event of interest (Y)
4. Identify the possible competing events (D)
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Workflow (Christiansen et al. 2015)

1. Define the population of interest
2. Define the intervention (T)
3. Define the event of interest (Y)

   `e.g.: fatal or non fatal ischemic stroke`
4. Identify the possible competing events (D)
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Workflow (Christiansen et al. 2015)

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2. Define the intervention (T)
3. Define the event of interest (Y)
4. Identify the possible competing events (D)

   `e.g.: death not related to a stroke event`
5. Identify the possible confounders/pronostic variable (X)
6. Define a statistical model for relating Y, T, and X

Workflow (Christiansen et al. 2015)

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2. Define the intervention (T)
3. Define the event of interest (Y)
4. Identify the possible competing events (D)
5. Identify the possible confounders/pronostic variable (X)
   `e.g. age, hypertension, ...`
6. Define a statistical model for relating Y, T, and X

Workflow (Christiansen et al. 2015)

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A two-cause specific Cox model:

$$\begin{aligned}\lambda^Y(t|X,T) &= \lambda_0^Y e^{\beta^Y X+\gamma^Y T}\\ \lambda^D(t|X,T) &= \lambda_0^D e^{\beta^D X+\gamma^D T}\end{aligned}$$

Computation of the G-formula - in R

Package: riskRegression https://github.com/tagteam/riskRegression
Function: ate

Arguments

- `object`: outcome model which describes how event risk depends on treatment and covariates
- `data`
- `treatment`: name of the treatment variable in `data`
- `times`: time points at which to evaluate risks
- `cause`: the cause of interest
- B: the number of bootstrap replications used to compute the confidence interval.

G-formula (software)

No competing risks:

```
> head(dtSurv)
         time strokeEvent Treatment      Age
1:   4.901849       FALSE        T0 59.78796
2:   4.555159        TRUE        T0 60.66406
3:   6.681136       FALSE        T1 58.76296
> mCox <- coxph(Surv(time,strokeEvent)~ Treatment + Age,
+               data = dtSurv)

> ate(mCox, data = dtSurv, treatment = "Treatment",
+     times = 12, B = 1000)
```

G-formula (software)

Competing risks:

```
> head(dtCR)
   time eventtype eventtypeNum Treatment      Age
1:  2.9    stroke            1        T0 58.96060
2:  9.3 censoring            0        T0 59.37469
3:  2.0     death            2        T0 59.36296
```

```
> mCSC <- CSC(
+           list(Hist(time,eventtypeNum)~ Treatment + Age,
+           Hist(time,eventtypeNum)~ Age),
+             data = dtCR
+ )

> ate(mCSC,data = dtCR, treatment = "Treatment",
+     times = 12, cause = 1, B = 1000)
```

G-formula (software output)

Absolute risk of stroke relapse

```
   Treatment meanRisk  meanRiskBoot lower upper n.boot
1:        T0    0.111         0.111 0.101 0.123 1000
2:        T1    0.080         0.080 0.071 0.090 1000
3:        T2    0.078         0.078 0.073 0.082 1000
```

Difference in absolute risk of stroke between treatments:

```
  Treatment.A  Treatment.B  time diff
1:          T1           T0    12 0.032
2:          T2           T0    12 0.034
3:          T2           T1    12 0.002
   diffMeanBoot diff.lower  diff.upper n.boot
1:        0.032      0.017       0.046   1000
2:        0.033      0.022       0.046   1000
3:        0.002      0.002       0.013   1000
```

Assumptions

- no unmeasured confounders
- positivity
- well-defined intervention
- **correctly specified model**
  - ▷ proportional hazard assumption
  - ▷ (linear) functional form
  - ▷ (absence of) interaction

[Not covered] non-informative censoring, influential observations

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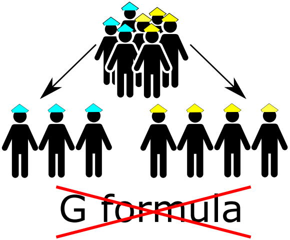
[Not covered] non-informative censoring, influential observations



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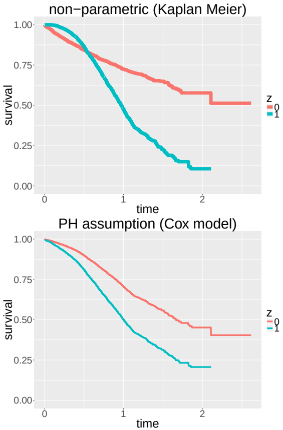

$$\widehat{ATE} : -0.513[-0.571; -0.441] \text{ vs } -0.244[-0.281; -0.206]$$

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  - ▷ proportional hazard assumption
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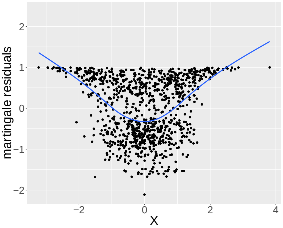

[Not covered] non-informative censoring, influential observations

$\widehat{ATE}$: $-0.164[-0.221; -0.107]$ vs $-0.200[-0.264; -0.132]$

Assumptions

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- positivity
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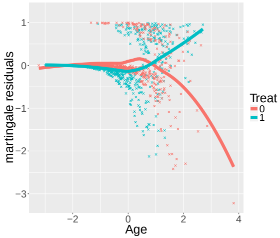
  - ▷ proportional hazard assumption
  - ▷ (linear) functional form
  - ▷ (absence of) interaction



[Not covered] non-informative censoring, influential observations

$\widehat{ATE}$: $-0.110[-0.169; -0.049]$ vs $-0.267[-0.302; -0.228]$

Assumptions

- no unmeasured confounders
- positivity
- well-defined intervention
- **correctly specified model**
  - proportional hazard assumption
  - (linear) functional form
  - (absence of) interaction

[Not covered] non-informative censoring, influential observations

Proposed approach

- Compare alternative modelling strategies to the Cox model
  → check result sensitivity to model assumptions

Alternative models:

✓ increased flexibility:
→ less biased

✗ increased complexity:
→ harder to interpret
→ increased variance of the estimates

Extensions/alternatives to Cox model

- relax PH assumption:

-Cox strata	stratified Cox model
-Others	Cox model with time varying effects
	logistic risk regression

- include non-linear relationships/interactions

-Cox spline	regression spline in Cox model
-RF	random survival Forest

Simulation study

Investigate the bias/variance trade-off

Three scenari:

(I) violation of proportional hazard assumption

(II) mispecification of the functional form of a risk factor

(III) missing interaction with the treatment variable

Results - proportional hazard

Scenario I	Non proportional effect of treatment		
$OR_T(t \leq 5)$	0.8	1.7	7.4
$OR_T(t \geq 5)$	0.4	0.4	0.4
ATE	0.181	-0.002	-0.068
Cox	-0.049 (0.05)	-0.082 (0.083)	-0.062 (0.062)
Cox strata	0.001 (0.011)	0 (0.01)	-0.01 (0.013)
Random Forest	0.001 (0.01)	0 (0.009)	0.005 (0.007)

Table: last three rows:
bias (root mean square error) of the ATE estimated by the models
OR_T odd ratio for the treatment effect

Results - functional form

Scenario II	Non linear effect of covariate		
OR_T	0.4	0.4	0.4
OR_{Age}	0.8	2.7	7.4
ATE	0.338	0.338	0.338
Cox	0.001 (0.01)	0 (0.01)	0 (0.01)
Cox strata	0.001 (0.011)	-0.001 (0.011)	-0.001 (0.011)
Random Forest	-0.003 (0.011)	-0.004 (0.012)	-0.004 (0.012)

Table: last three rows:
bias (root mean square error) of the ATE estimated by the models
OR_T odd ratio for the treatment effect
OR_{Age} odd ratio for the non linear effect of the risk factor
(increased risk after 50 years)

Results - interaction

Scenario III	Interaction between treatment and covariate		
OR_T	0.4	0.4	0.4
$OR_{T*gender}$	1.6	2.7	7.4
ATE	0.075	-0.011	-0.097
Cox	-0.01 (0.014)	-0.04 (0.041)	-0.146 (0.146)
Cox strata	0.001 (0.011)	0 (0.011)	0.001 (0.01)
Random Forest	0.001 (0.011)	0 (0.011)	0 (0.01)

Table: last three rows:
bias (root mean square error) of the ATE estimated by the models
OR_T odd ratio for the treatment effect
$OR_{T*gender}$ odd ratio for interaction between gender and treatment

Discussion

Alternative models:

- ✓ No noticeable increase of the variance of the estimates
- ✓ For categorical variables, a fully stratified Cox model is robust against:
  - non PH
  - interaction between variables
- ✓ For dealing with continuous variables, use random Forests
  - ✗ extra-parameters to be tuned (e.g. number of trees)

✗ Increased computation time

Application

Objective:

- to compare 3 antiplatelet regimens using the danish registry
- n = 19223 patients
- time horizon: 1 year

Outcome:

- date of first stroke event (n=1610, 8.4%)

Competing event:

- death (n=677, 3.5%)

Possible confounders:

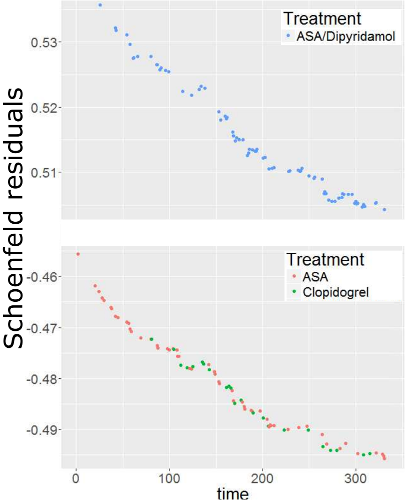
- many (p=10) including age, gender, . . .

Checking Proportional hazard assumption

Tests:[1]

- not significant
  except for one treatment modality

We can stratify on treatment!

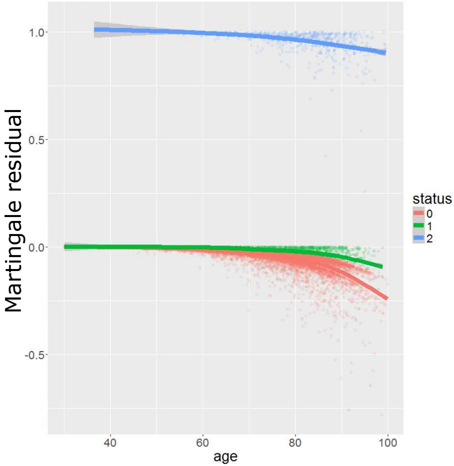


[1] based on the score process

Checking functional form

Variable age

- additional risk after 75 years
- approx. linear



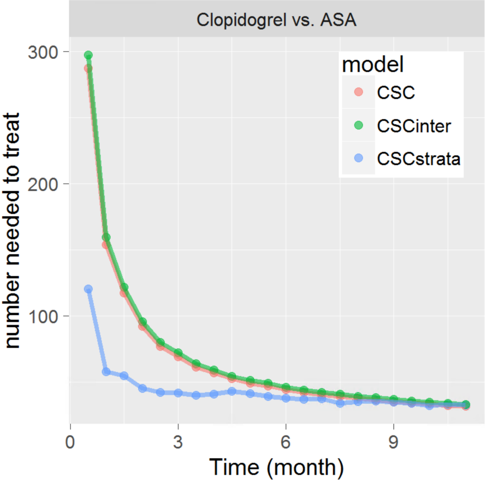
Models

Variables:

- Continuous: age
- Categorical: treatment, gender, year

CSC	Two cause specific Cox model
CSC inter	CSC + interactions between treatment and gender, age, year + cubic spline on age
CSC strata	stratified CSC on treatment, gender, year

naive Cox model vs. alternatives



- violation of PH assumption impacts the estimate of NTT at early times

Summary

Cox models can be used to assess :

- disease incidence (absolute risk)
- average treatment effect

Relies on several assumptions, e.g.:

- proportional hazard
- linear effect, no interaction between variables

Model checking:

- **Hope**: no unmeasured confounders
- usual diagnostic tools are of limited interest for large p or n
- *proposal*: assess the impact of Cox model assumptions using alternative models

Bibliography I

Christiansen, C. B. et al. (2015). ‘Comparison of antiplatelet regimens in secondary stroke prevention: a nationwide cohort study’. In: *BMC Neurology* 15.1, p. 225. ISSN: 1471-2377. URL: http://www.biomedcentral.com/1471-2377/15/225.

Grambsch, P. M. et al. (1994). ‘Proportional hazards tests and diagnostics based on weighted residuals’. In: *Biometrika* 81.3, pp. 515–526. ISSN: 00063444.

Grøn, R. et al. (2016). ‘Misspecified poisson regression models for large-scale registry data: inference for 'large n and small p'.’ In: *Statistics in medicine* 35.7, pp. 1117–29. ISSN: 1097-0258. URL: http://www.ncbi.nlm.nih.gov/pubmed/26423319.

Staerk, L. et al. (2016). ‘Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study’. In: *European Heart Journal*. URL: http://eurheartj.oxfordjournals.org/content/early/2016/10/12/eurheartj.ehw496.abstract.