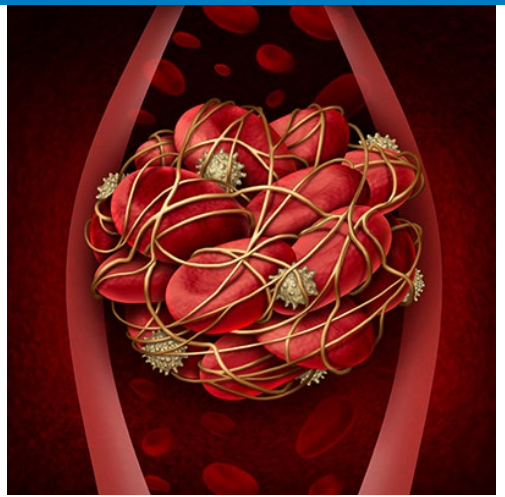
Leiden University
Medical Center

# Glucocorticoids treatment and coagulation parameters in patients with a first venous thromboembolism

## Data from the MEGA study



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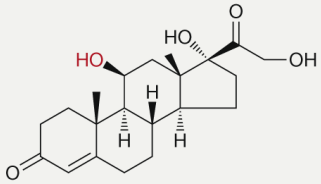
# Glucocorticoid

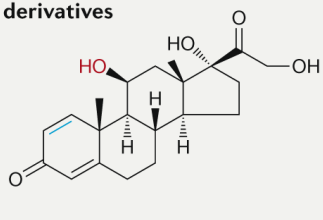
**Short acting**

**Endogenously derived**

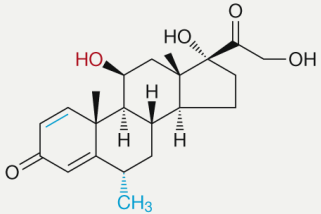


Cortisol (hydrocortisone)

**Synthetic derivatives**

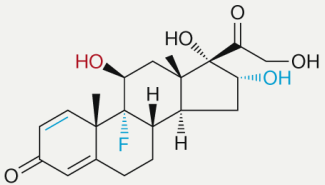


Prednisolone



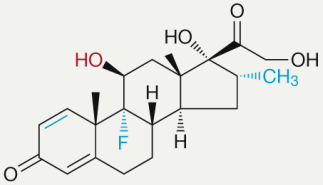
Methylprednisolone

**Intermediate acting**

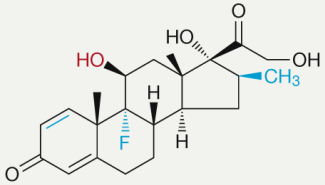


Triamcinolone

**Long acting**



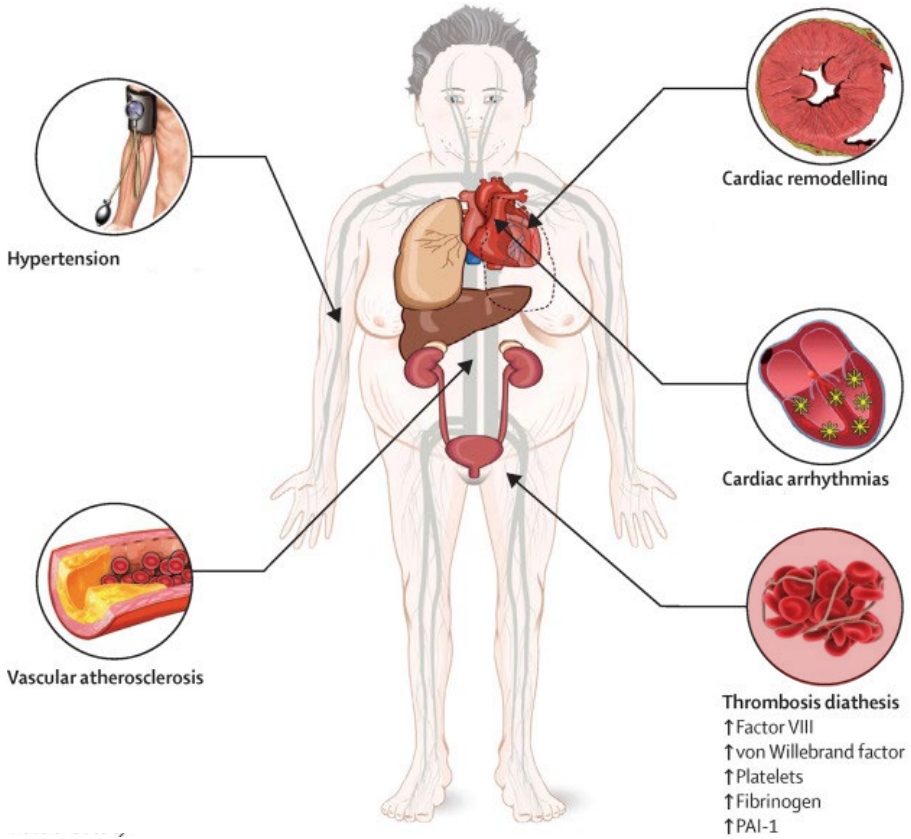
Dexamethasone



Betamethasone

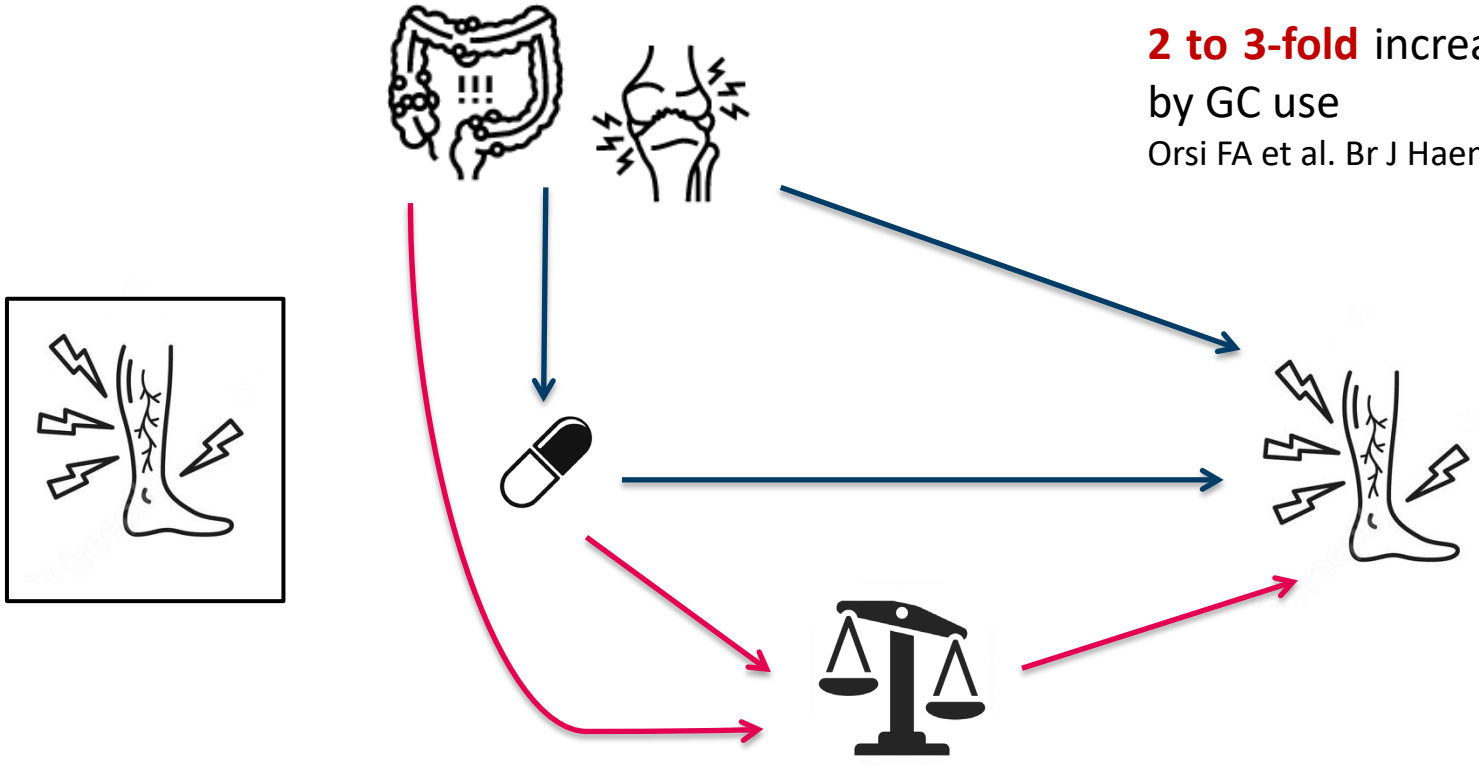
Hardy RS *et al.* Nat Rev Rheumatol 2020

# Glucocorticoid: adverse effects




Buttgereit F *et al.* Lancet 2005; Pivonello R *et al.* Lancet Diabetes Endocrinol 2016; Orsi FA *et al.* Br J Haematol 2021

# Mechanism of increased risk of VTE



**2 to 3-fold** increased risk of VTE by GC use

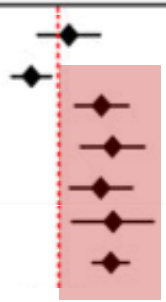
Orsi FA et al. Br J Haematol 2021

# Haemostatic changes during GC use

In patients with endogenous Cushing's syndrome: ↑ FVIII, IX, vWF and PAI-1

For exogenous GC:

| | Studies N | Low quality N | Medium quality N | High quality N | Exposed N | Unexposed N | Standardized mean difference, IV, random, 95% CI |
|---|---|---|---|---|---|---|---|
| Factor VIII: C | 1 | 1 | 0 | 0 | 26 | 23 | 0.17 [–0.39; 0.73] |
| VWF: Ag | 10 | 8 | 2 | 0 | 195 | 177 | –0.50 [–0.85; –0.15] |
| ATIII | 2 | 2 | 0 | 0 | 37 | 36 | 0.74 [0.27; 1.22] |
| Protein C | 1 | 1 | 0 | 0 | 27 | 26 | 0.94 [0.37; 1.51] |
| Protein S (total) | 1 | 1 | 0 | 0 | 27 | 26 | 0.73 [0.18; 1.29] |
| PAI-1: Ag | 2 | 2 | 0 | 0 | 38 | 35 | 0.95 [0.22; 1.67] |
| PAI-1: C | 4 | 4 | 0 | 0 | 86 | 85 | 0.91 [0.59; 1.23] |



Zaane B *et al.* J Thromb Haemost 2010; Isidori A.M. *et al.* Eur J Endocrinol 2015

# Aims

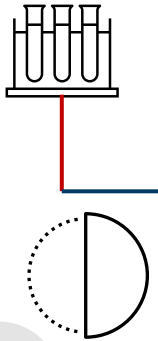
1) Differences in coagulation associated with GC treatment in patients with first VTE

2) Role of coagulation in mediating the risk of recurrent VTE in patients treated with GC

# Study population: MEGA study

Case-control study into causes of VTE (1999-2004)

**Cases**
4956 1st VTE

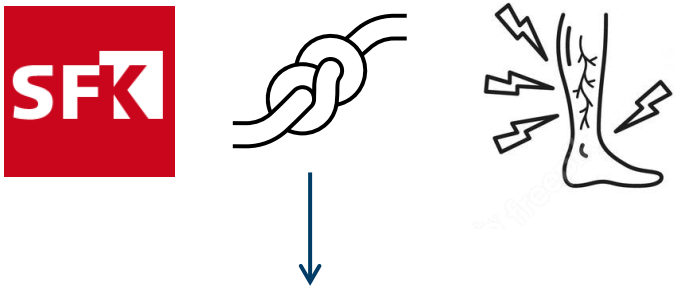


4731
Consented
to f-up

**Controls**
3000 RDD
3297 Partners

# Exposure: GC treatment

**Stichting Farmaceutische Kengetallen** (SFK)

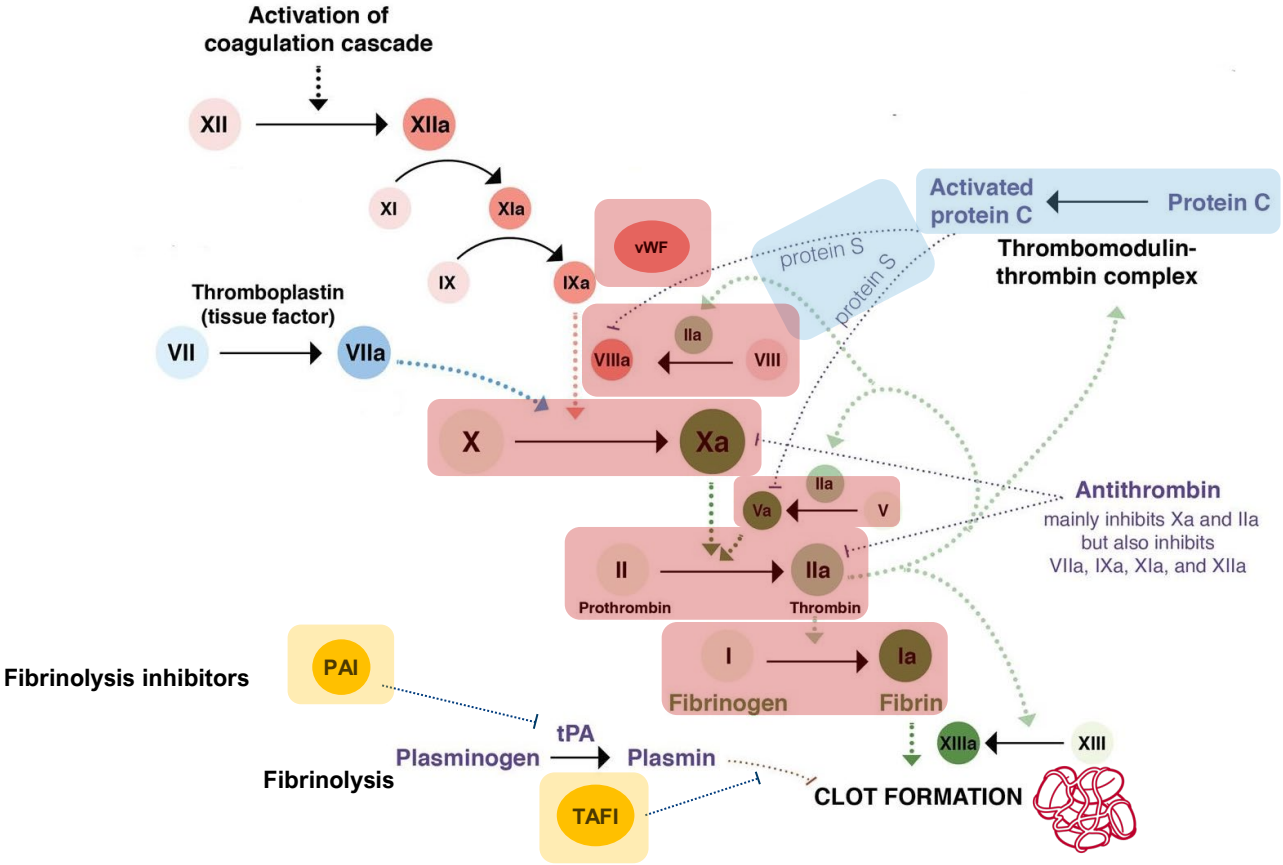


2547 (54%) uniquely linked

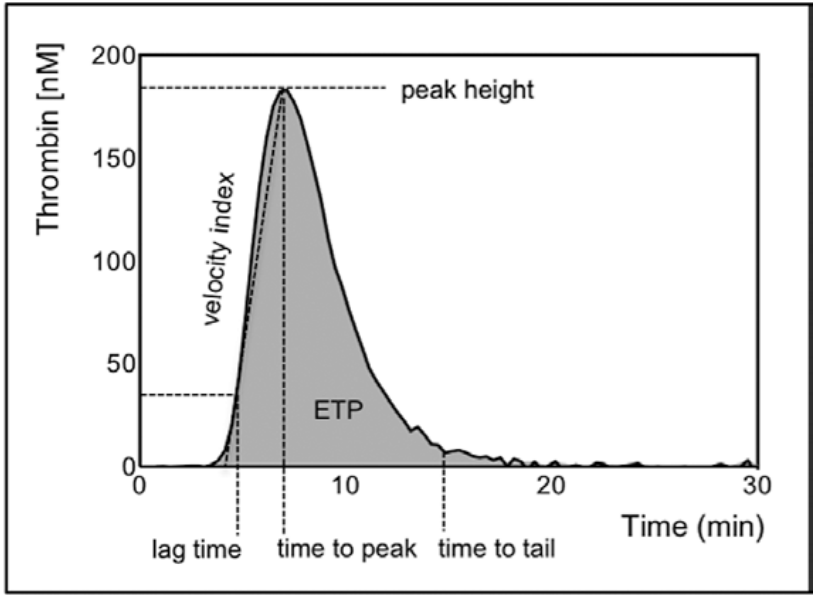
1155 (45%) blood sample

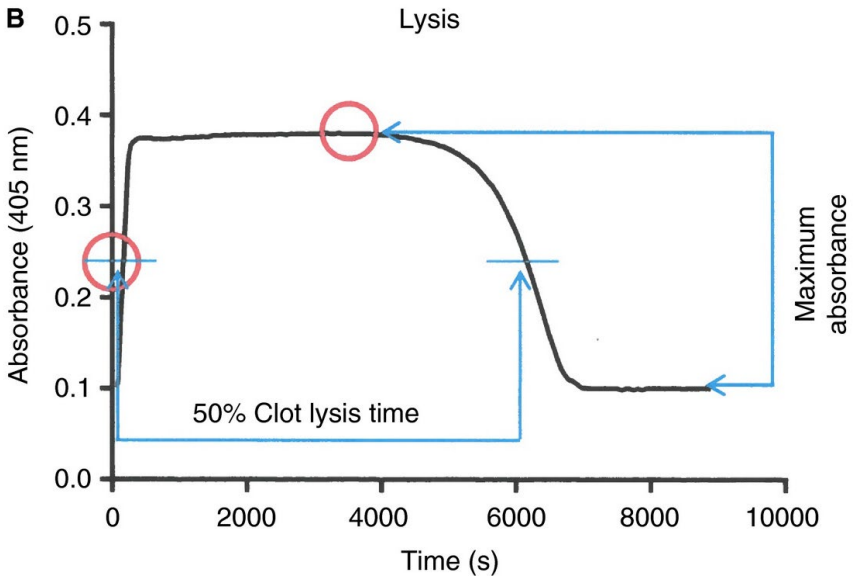
# 1st aim: methods & results

# 1st aim: outcome - coagulation & fibrinolysis

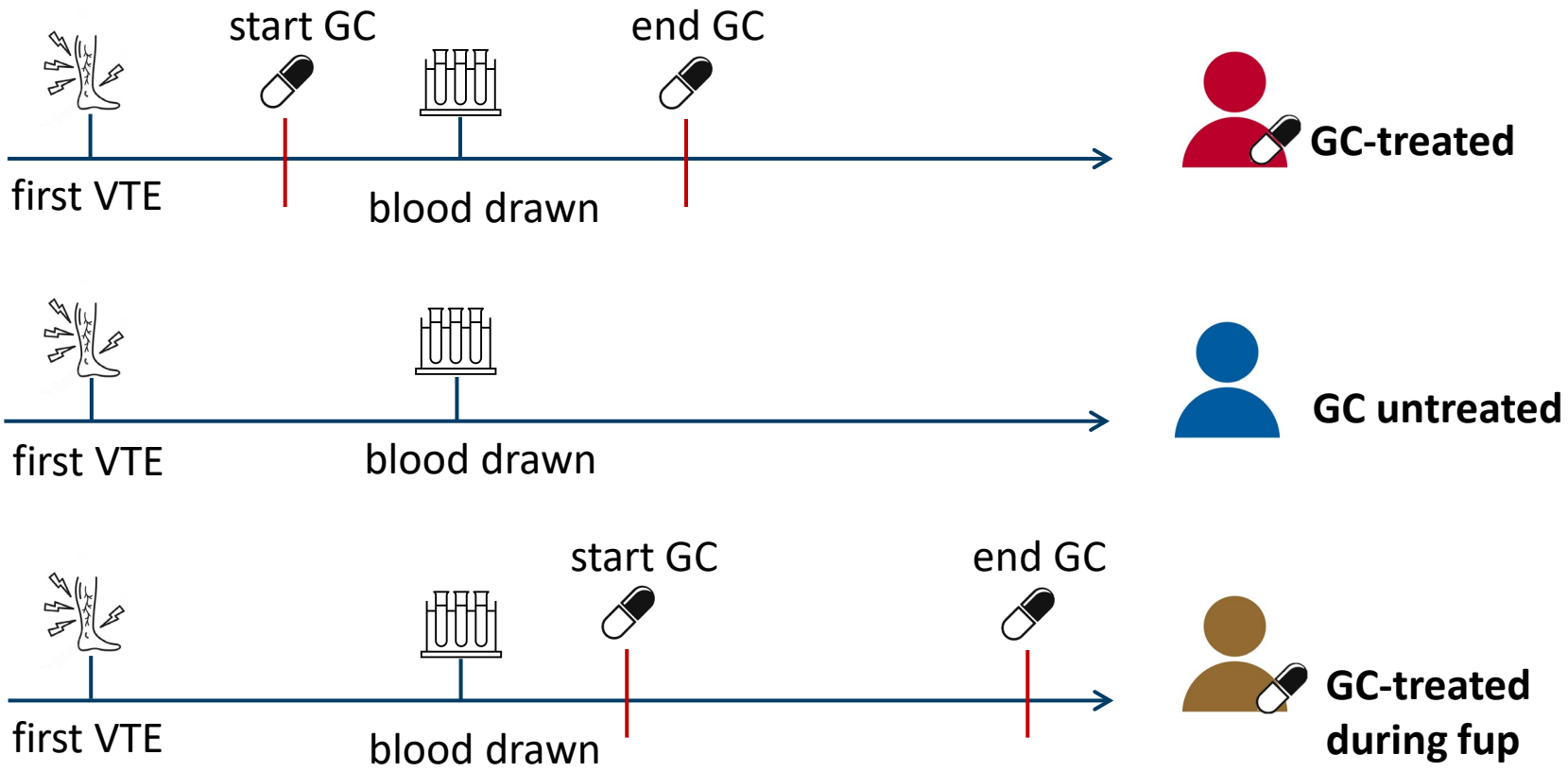


# 1st aim: global tests of coagulation and fibrinolysis

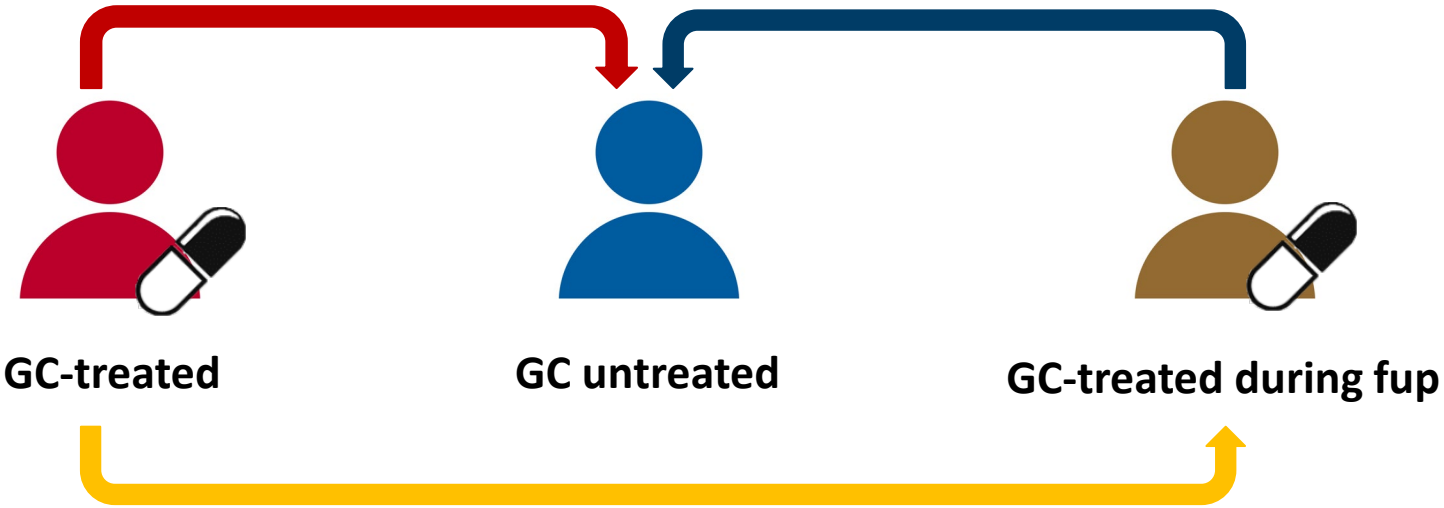


# 1st aim: study design



# 1st aim: statistical analysis




adjusted for age, sex, BMI, comorbidities

(cancer, rheumatic disease, diabetes) and previous GC use

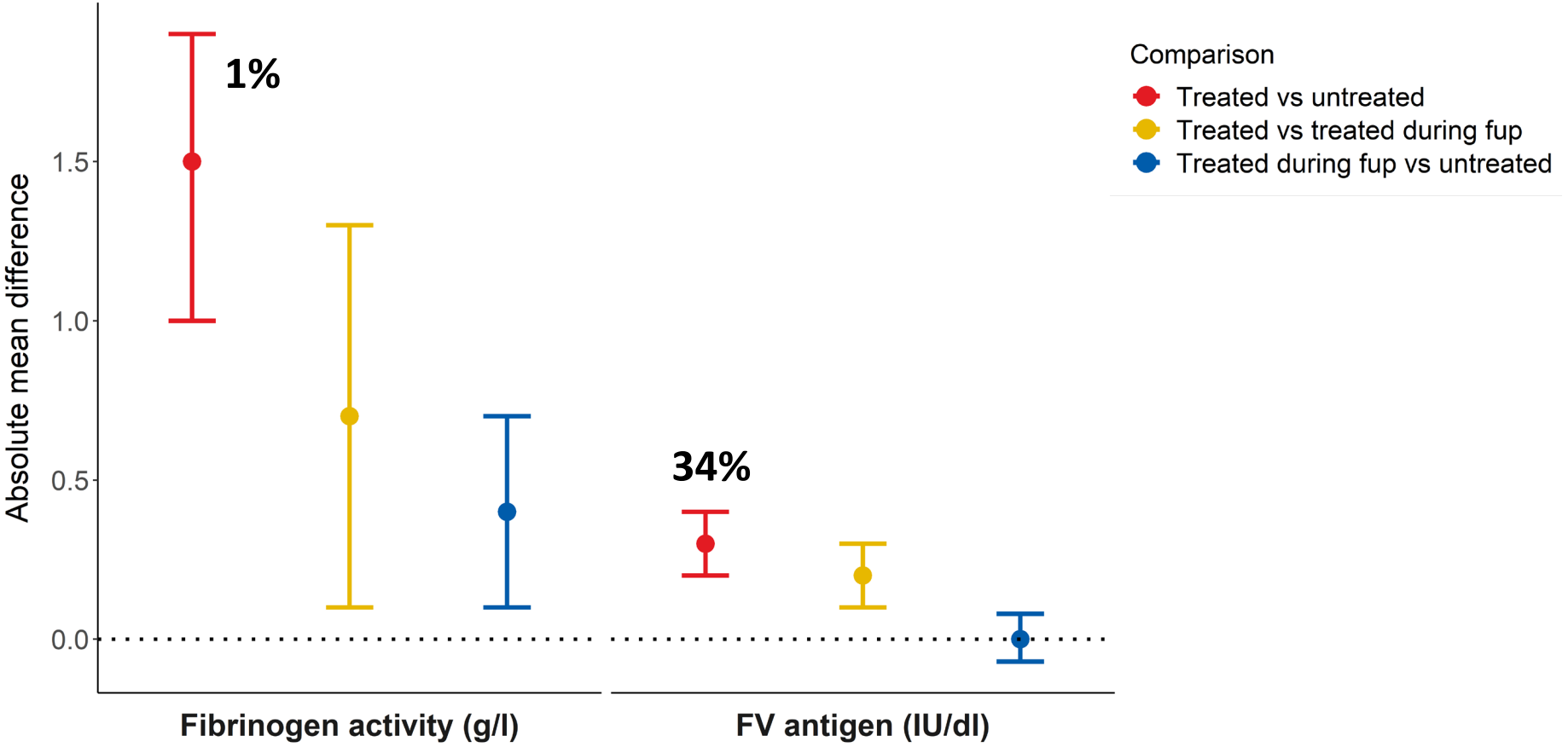
# Baseline characteristics

| | 31 | 890 | 40 |
|---|---|---|---|
| years | 57 (42-64) | 50 (39-58) | 58 (47-66) |
| ♂ | 12 (39%) | 418 (47%) | 19 (48%) |
| kg/m² | 27 (23-29) | 26 (24-29) | 25 (23-27) |
| **First VTE** | | | |
| | 13 (42%) | 538 (60%) | 22 (55%) |
| ± | 18 (58%) | 352 (40%) | 18 (45%) |

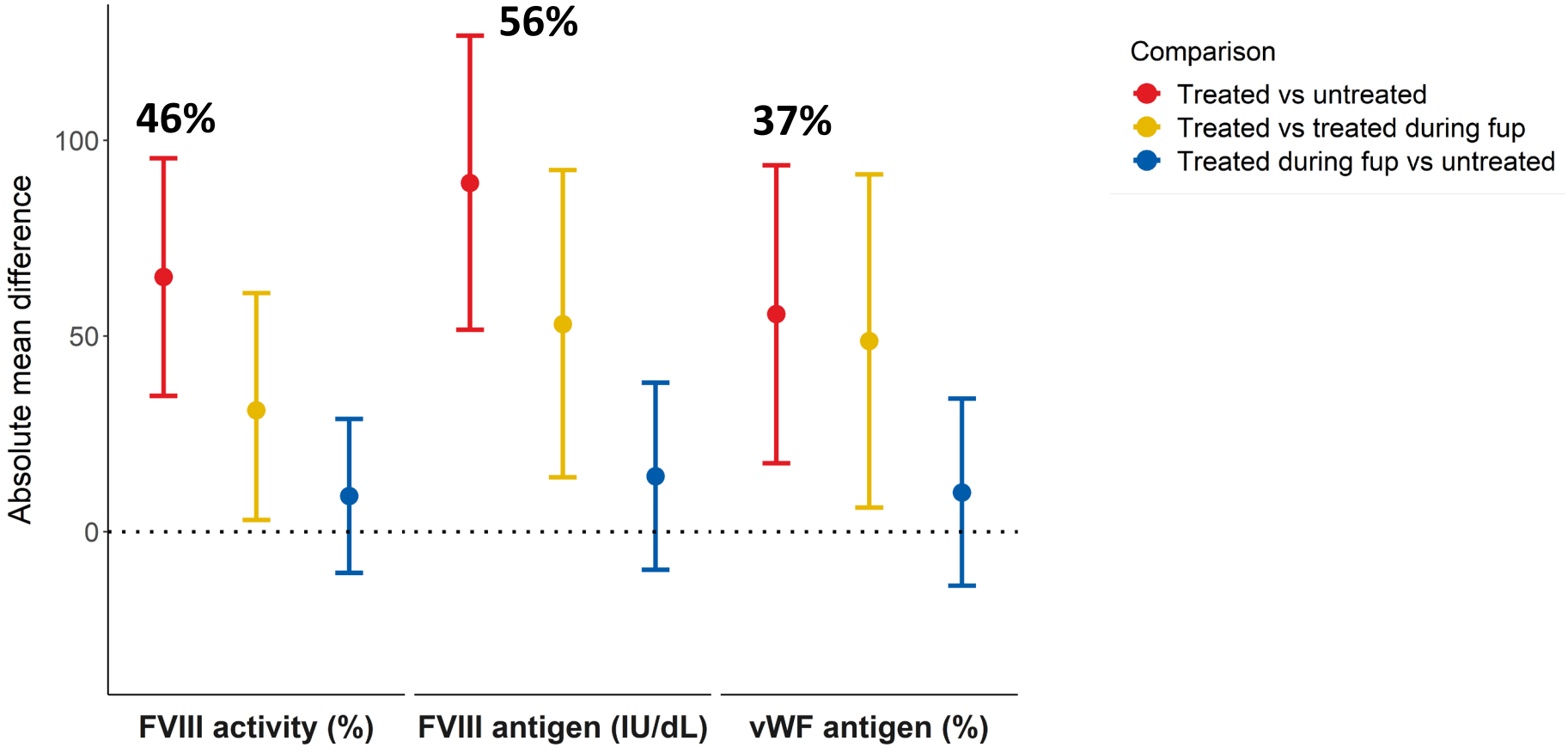
# Information on GC prescription

| | | |
|---|---|---|
| **Day GC use** | 44 (16-80) | 57 (27-71) |
| **Type GC** | | |
| Prednison | 17 (55%) | 14 (35%) |
| Prednisolon | 8 (25%) | 16 (40%) |
| Betamethason | 3 (10%) | 4 (10%) |
| Other | 3 (10%) | 6 (15%) |

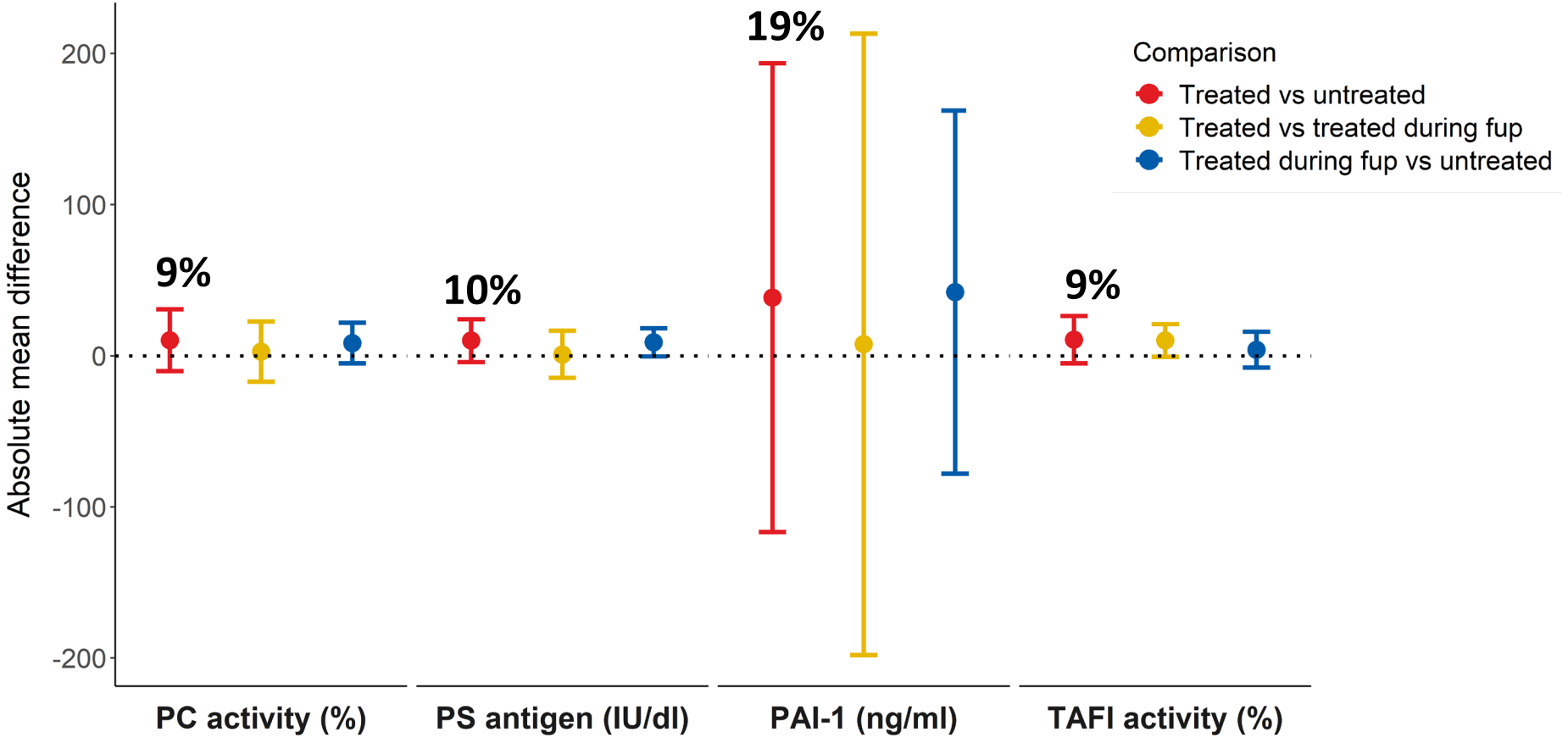
# Absolute mean difference – procoagulant



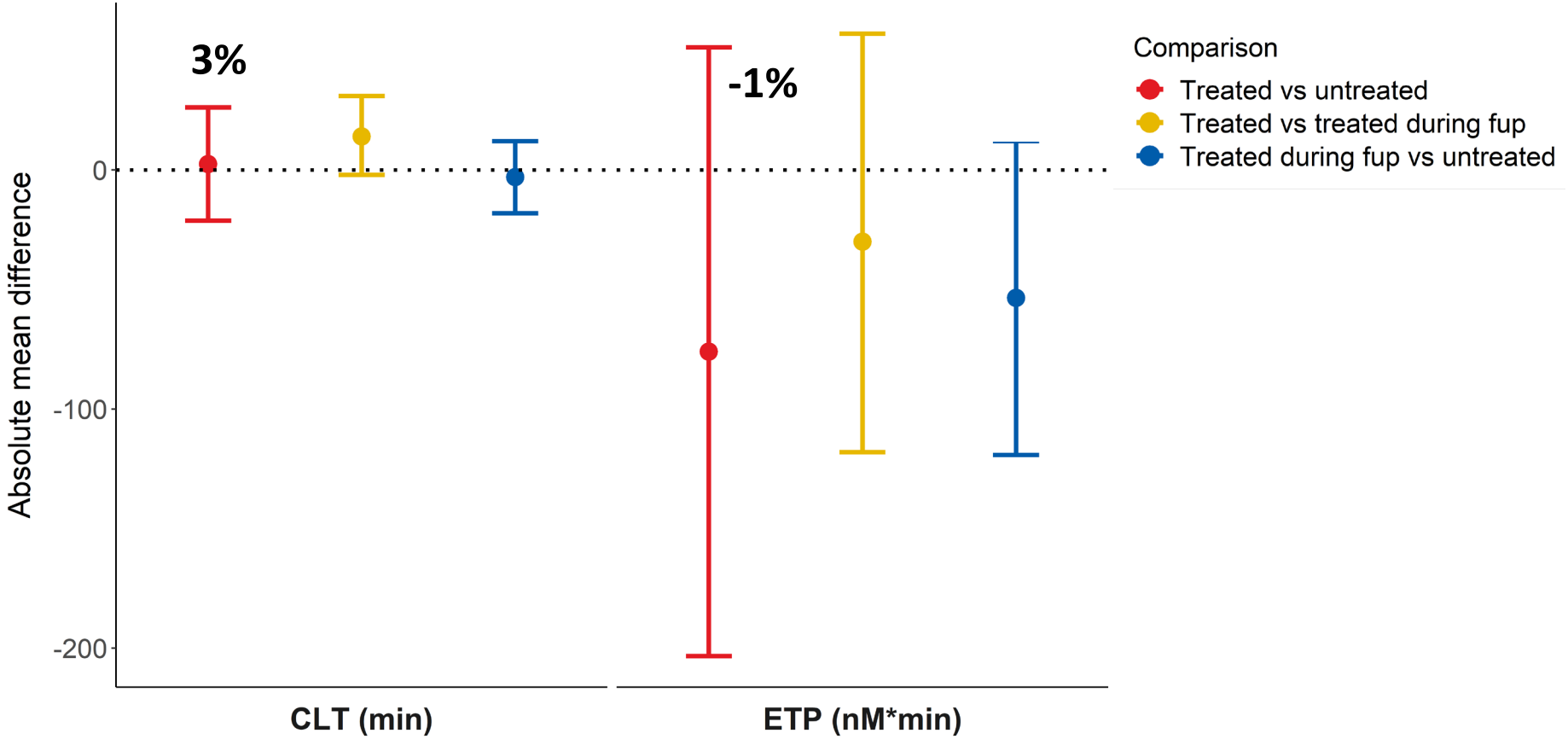
# Absolute mean difference – procoagulant



# Absolute mean difference – anticoagulant & antifibrinolytic



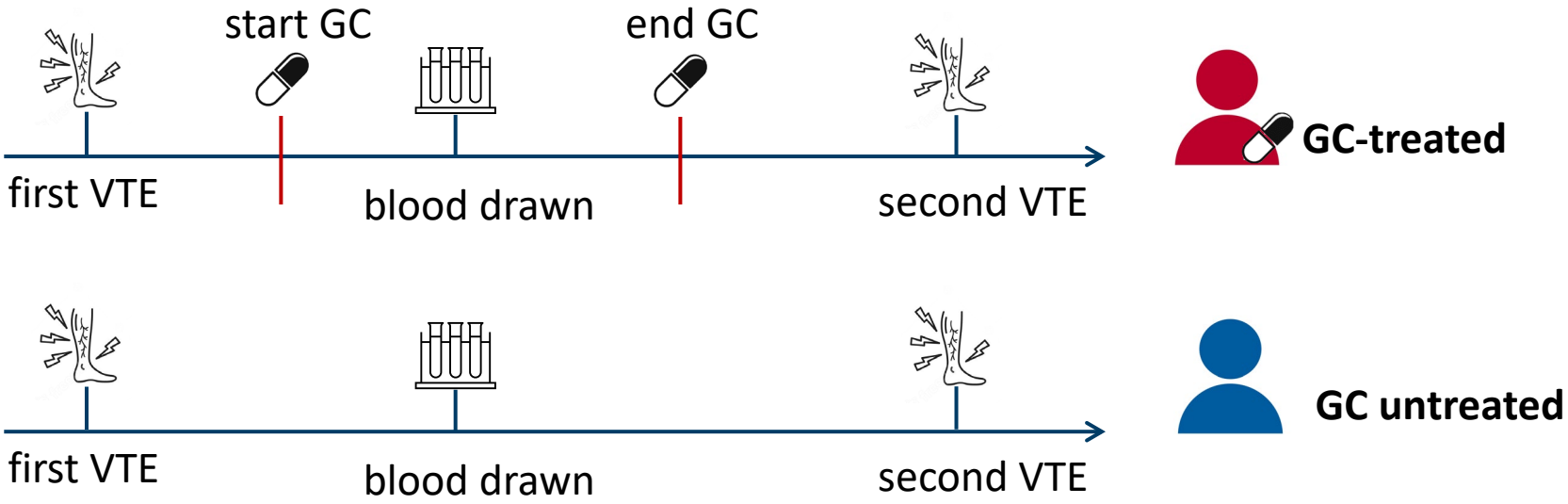
# Absolute mean difference – Global tests



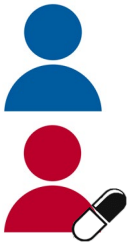
# 2nd aim: methods & results

# 2nd aim: study population and statistical analysis

Hazard ratios and 95% CIs for recurrent VTE adjusted for procoagulant



# Mediation analysis



| **Person years** | **Recurrent VTE** | **IR per 100 PYs** (95% CI) | **HR model 1** (95% CI) | **HR model 2** (95% CI) | **HR model 3** (95% CI) |
|---|---|---|---|---|---|
| **4649** | 143 | 3.1 (2.6-3.6) | 1.00 | 1.00 | 1.00 |
| **143** | 9 | 6.3 (3.1-11.6) | 2.0 (1.0-3.9) | 2.4 (1.2-4.8) | 1.7 (0.8-3.6) |

- Model 1: unadjusted model
- Model 2: adjusted for age, sex, BMI, comorbidities
- Model 3L adjusted for age, sex, BMI, comorbidities, fibrinogen, FV, FVIII, FX, vWF

# Strength and limitations

**Strength**

- Limited literature on GC in VTE patients
- Global measure of coagulation and fibrinolysis

**Limitations**

- Limited sample size of GC-treated
- No information on GC indication
- Linkage failure (46%)
- PAI-1 and TAFI measured in 40%

# Conclusions

- Mean levels of all parameters (except FX) **higher** in GC-treated
- ETP and CLT **not different**

Findings in line with those in patients with endogenous Cushing's disease

- Risk of recurrent VTE partially **mediated** by increase in procoagulant factors

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# Thank you for listening! Questions?

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