# Venous thromboembolism in advanced cancer

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Marie Curie
Care and support through terminal illness

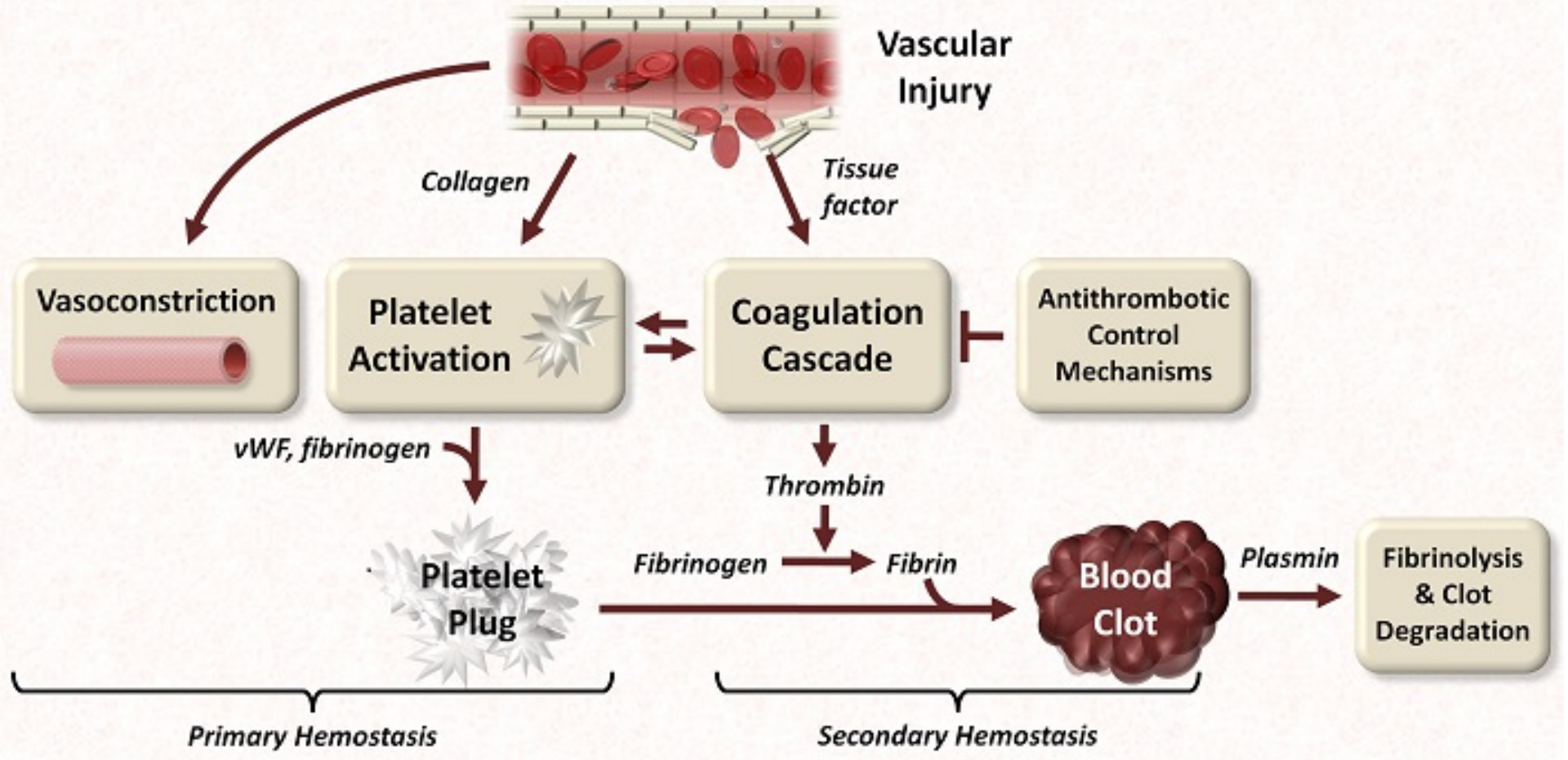
# Disclosures

1. Speakers bureau: Leo, Pfizer
2. Advisor Board: Bayer
3. Grant: HIDDEN was funded by NIHR (RfPB)

# To cover

1. Haemostasis oversight
2. The clinical trials informing practice non representative populations
3. Anticoagulants at the end of life
4. Thromboprophylaxis in the SPCU
5. Tranexamic and thrombotic risk

# Major Components of Hemostasis

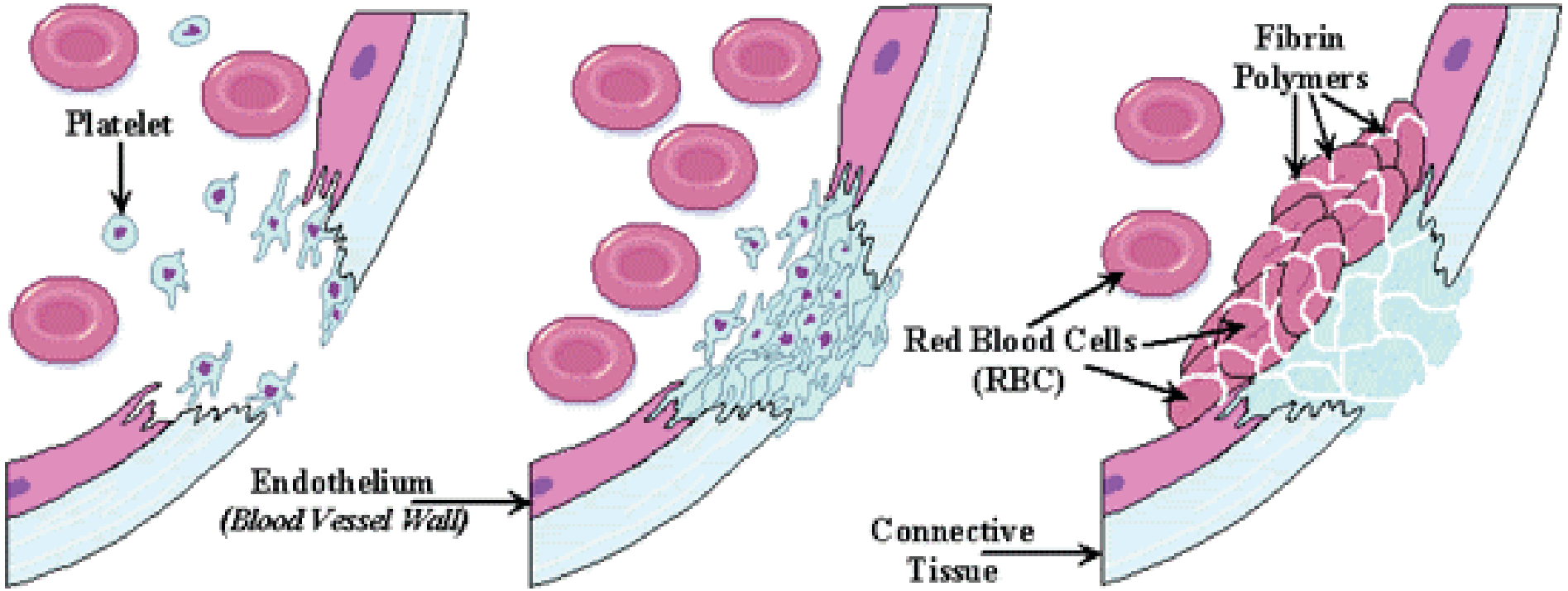


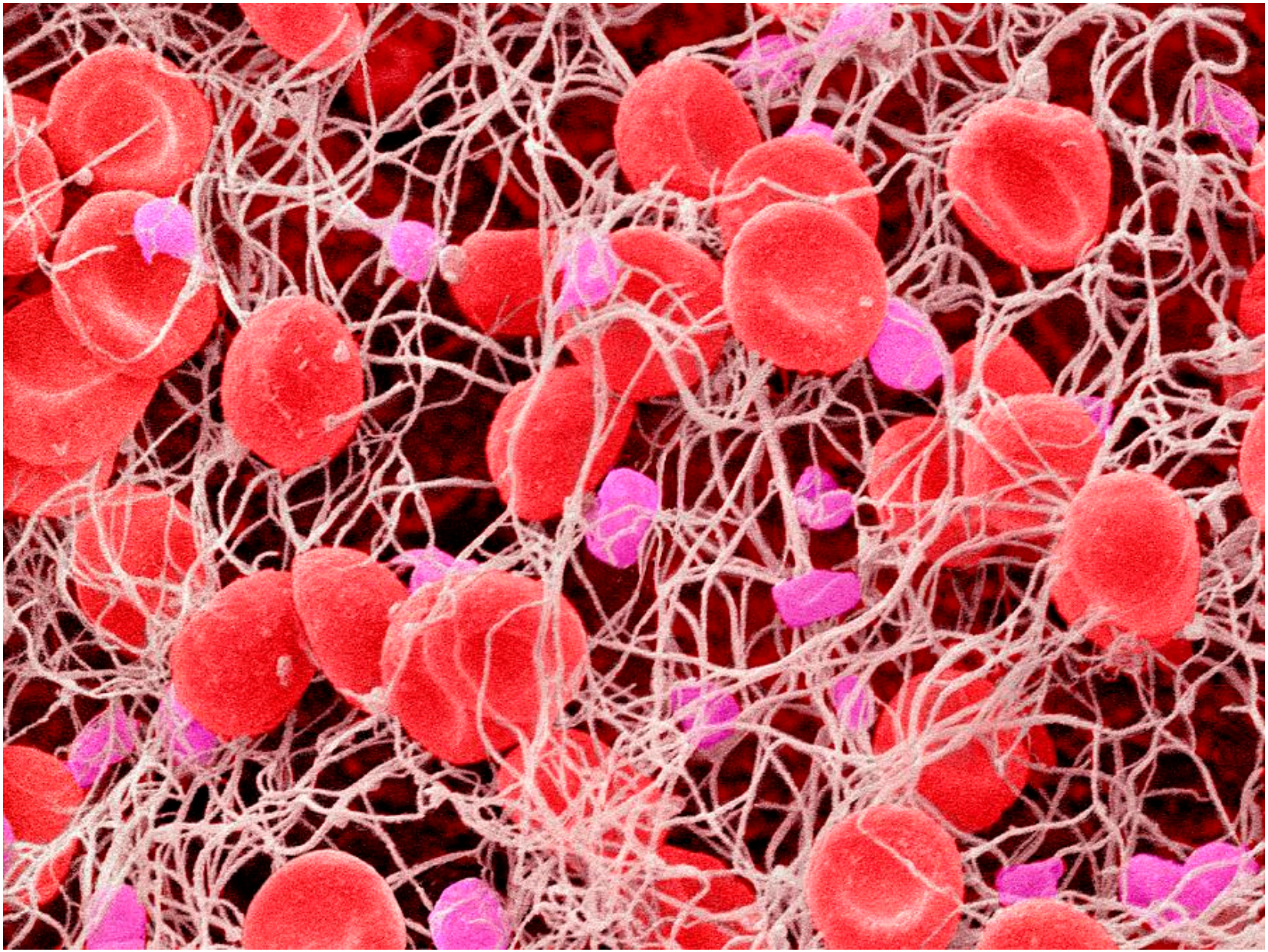
# *COAGULATION*: The Formation of a Blood Clot

**Stage I:**
*Platelets attach to the endothelium (blood vessel wall)*

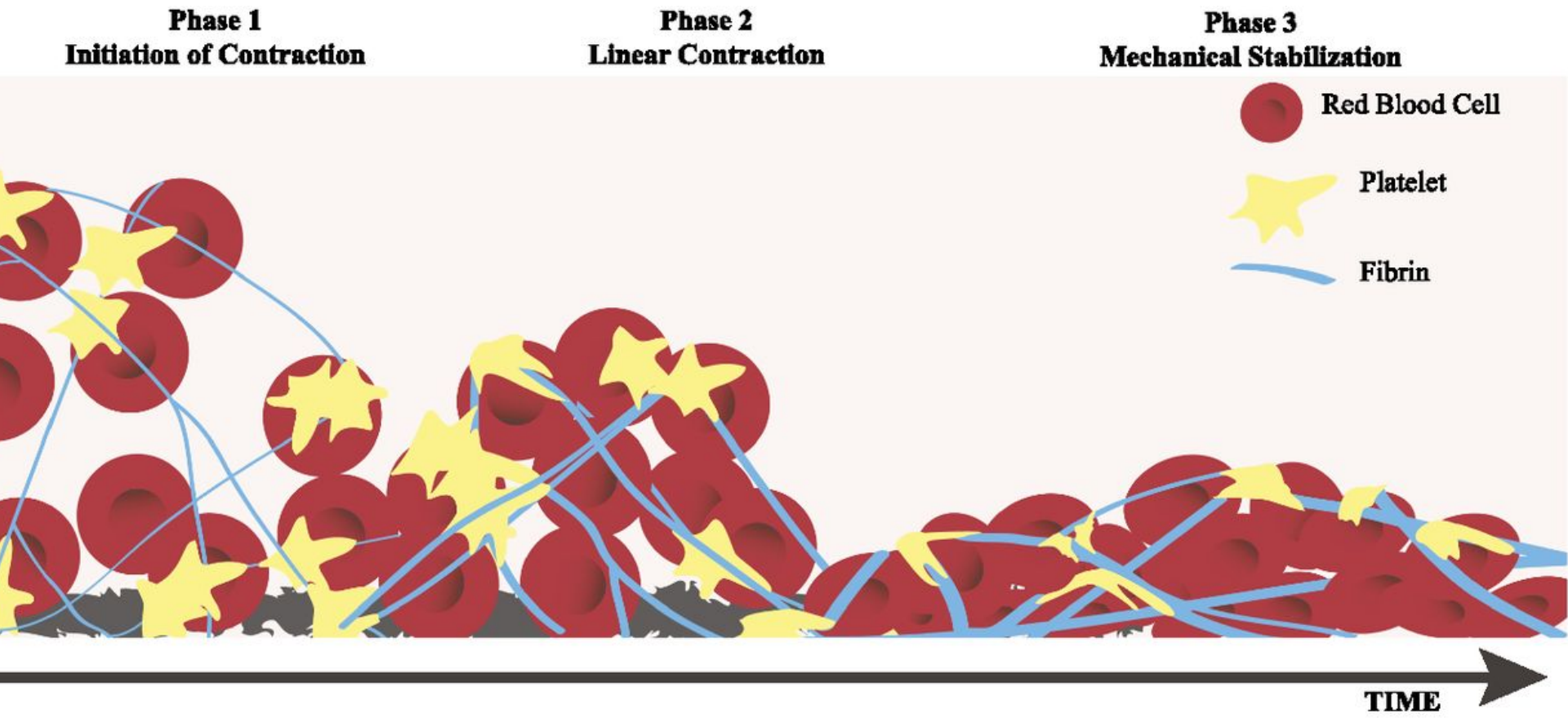
**Stage II:**
*Platelets start to release fibrin and begin to seal the endothelium*

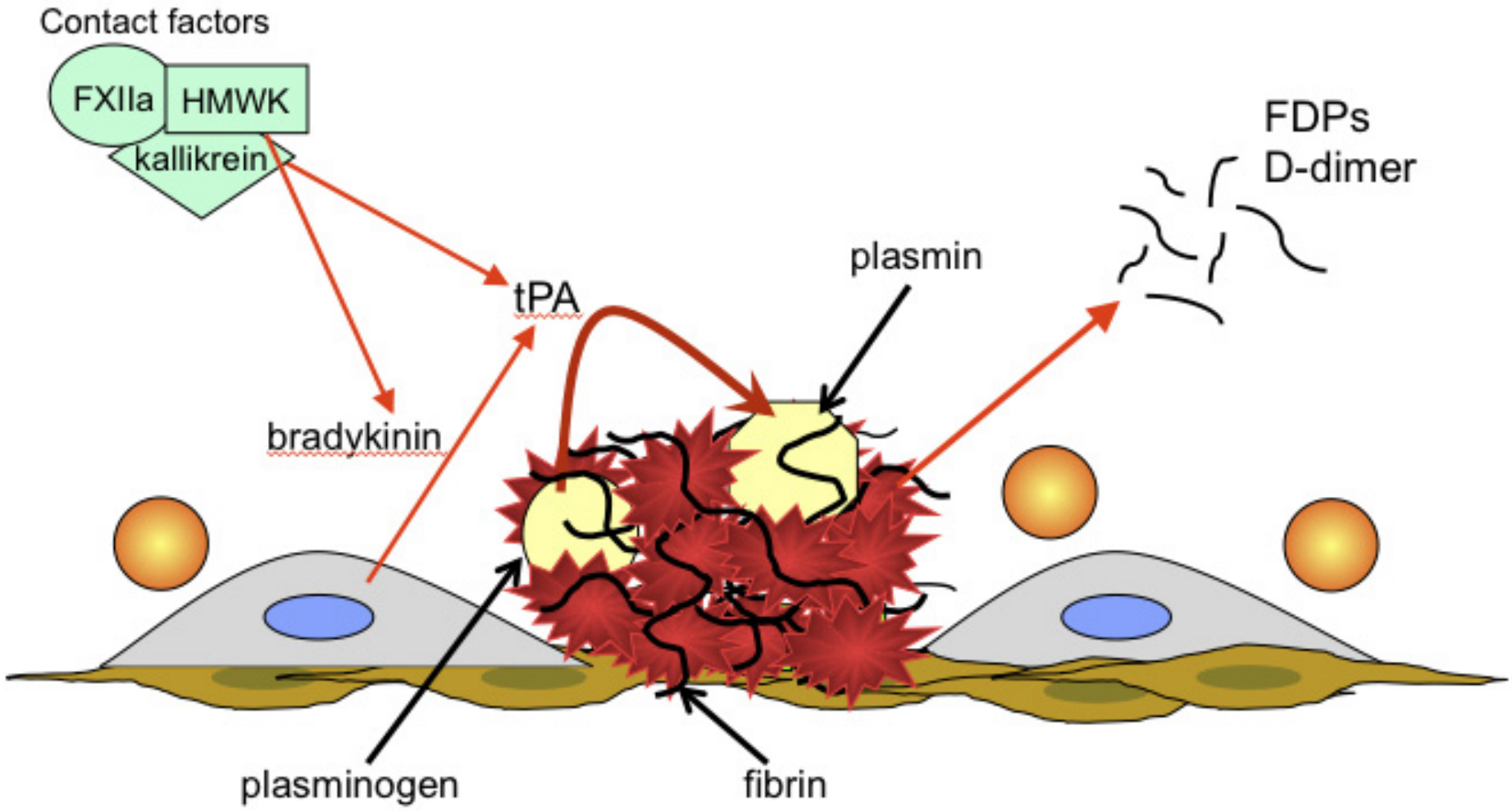
**Stage III:**
*The fibrin network traps the RBC, and completely seal the endothelium*





**Schematic of the phase dynamics of blood clot contraction.**




Contact factors
FXIIa
HMWK
kallikrein
tPA
bradykinin
plasmin
FDPs
D-dimer
plasminogen
fibrin

# Clot presentation

- DVT: 7-14 days
- PE: 21 days

# Clot stabilization and resorption

1. Initial stabilization: 5-14 days
2. Stable clot: 6 weeks
3. Resorption  4- 12 weeks

# Exclusion criteria to VTE clinical trials

1. ECOG>2
2. Prognosis < 3 months
3. Weight < 40kg
4. Deranged biochemistry

# Anticoagulants and Hospices

# RHESO study

- 22 SPCUs, 1199 patients
- CRB 9.8% (95% CI 8.3-11.6)

**Clinically relevant bleeding = Major Bleeding**

**+**

**Clinically Relevant Non Major Bleeding**

Tardy B, et al J Thromb Haemost. 2017 Mar;15(3):420-428

# Characteristics of patients

| | | |
|---|---|---|
| Reason for admission to the palliative unit | 0/1199 | |
| Cancer | | 1091 (91.0) |
| Metastatic cancer | | 929 (77.5) |
| Neurologic disease | | 52 (4.3) |
| Cardiac or respiratory disease | | 49 (4.1) |
| AIDS* | | 7 (0.6) |

| | | |
|---|---|---|
| Treatments received within 4 weeks prior to admission | | |
| Cancer treatment | 0/1199 | |
| Chemotherapy | | 257 (21.4) |
| Targeted cancer therapy | | 35 (2.9) |
| Radiotherapy | | 91 (7.6) |
| Growth factors | 0/1199 | 32 (2.7) |
| Anticoagulant therapy | | |
| At prophylactic (low) dose** | 0/1199 | 527 (44.0) |
| At therapeutic (high) dose†† | 0/1199 | 69 (5.7) |
| Antiplatelet therapy | 3/1196 | 167 (14.0) |
| Corticosteroids | 6/1193 | 620 (52.0) |
| Antidepressive agents | 0/1199 | 304 (25.4) |
| Serotonin reuptake inhibitors | | 208 (17.3) |

# Risk factors for bleeding

**Table 4** Univariate and multivariate analyses of potential risk factors for clinically relevant bleeding at 3 months

| Patient factor | With bleeding ($n$ = 116) | Without bleeding ($n$ = 1075) | Multivariate analysis* | |
|---|---|---|---|---|
| | | | HR (95% CI) | $P$ value |
| Male sex | 63 (54.3) | 479 (44.6) | 1.31 (0.91–1.90) | 0.15 |
| Cancer | 114 (98.3) | 970 (90.2) | 5.65 (1.40–22.9) | 0.01 |
| Previous surgery† | 2 (1.7) | 67 (6.2) | 0.21 (0.05–0.87) | 0.03 |
| Previous bleeding† | 38 (32.8) | 134 (12.5) | 3.36 (2.28–4.97) | < 0.0001 |
| Anticoagulant prophylaxis | 69 (59.5) | 561 (52.2) | 1.48 (1.02–2.15) | 0.04 |
| Antiplatelet therapy‡ | 44 (37.9) | 288 (26.9) | 1.67 (1.15–2.44) | 0.007 |

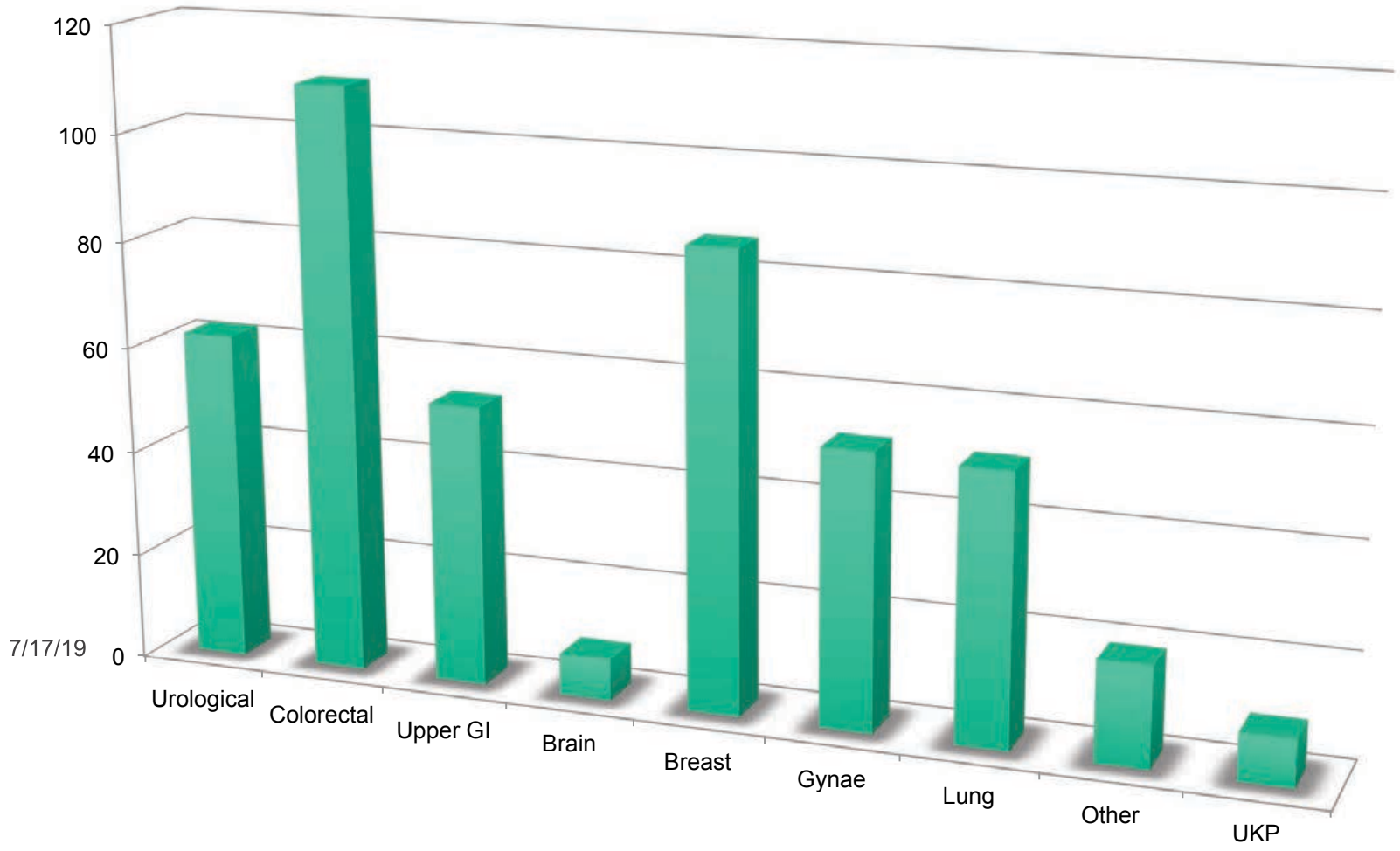
Only factors with a $P$ value ≤ 0.15 in the univariate analysis are presented. Because data were available in less th
index (univariate Hazard Ratio, HR = 2.38 [1.05–5.40]) and moderate or severe renal insufficiency (univariate H
included in the multivariate analysis. *According to the Fine and Gray method. †Within 4 weeks prior to incl
4 weeks prior to inclusion or during hospitalization in the palliative care unit.

# Study to identify current practice in patients with cancer associated thrombosis at the end of life

- Setting: Patients attending a regional cancer associated thrombosis clinic
- Follow up over two years
- Notes review of patients at end of life
- Demographics, when anticoagulation stopped, bleeding/ thrombotic complications,
- Place of death

16 Noble S, Banerjee S, Pease N. Anticoagulation for Cancer Associated Thrombosis at the End of Life: Review of a Case Series of 214 Patients. *Palliative Medicine* 32(1S) 47-48

# Cancer diagnoses: n=450



# Patient spread at initial review

- 44% metastatic
- 60% during chemotherapy (majority palliative)
- 59% known to specialist palliative care services

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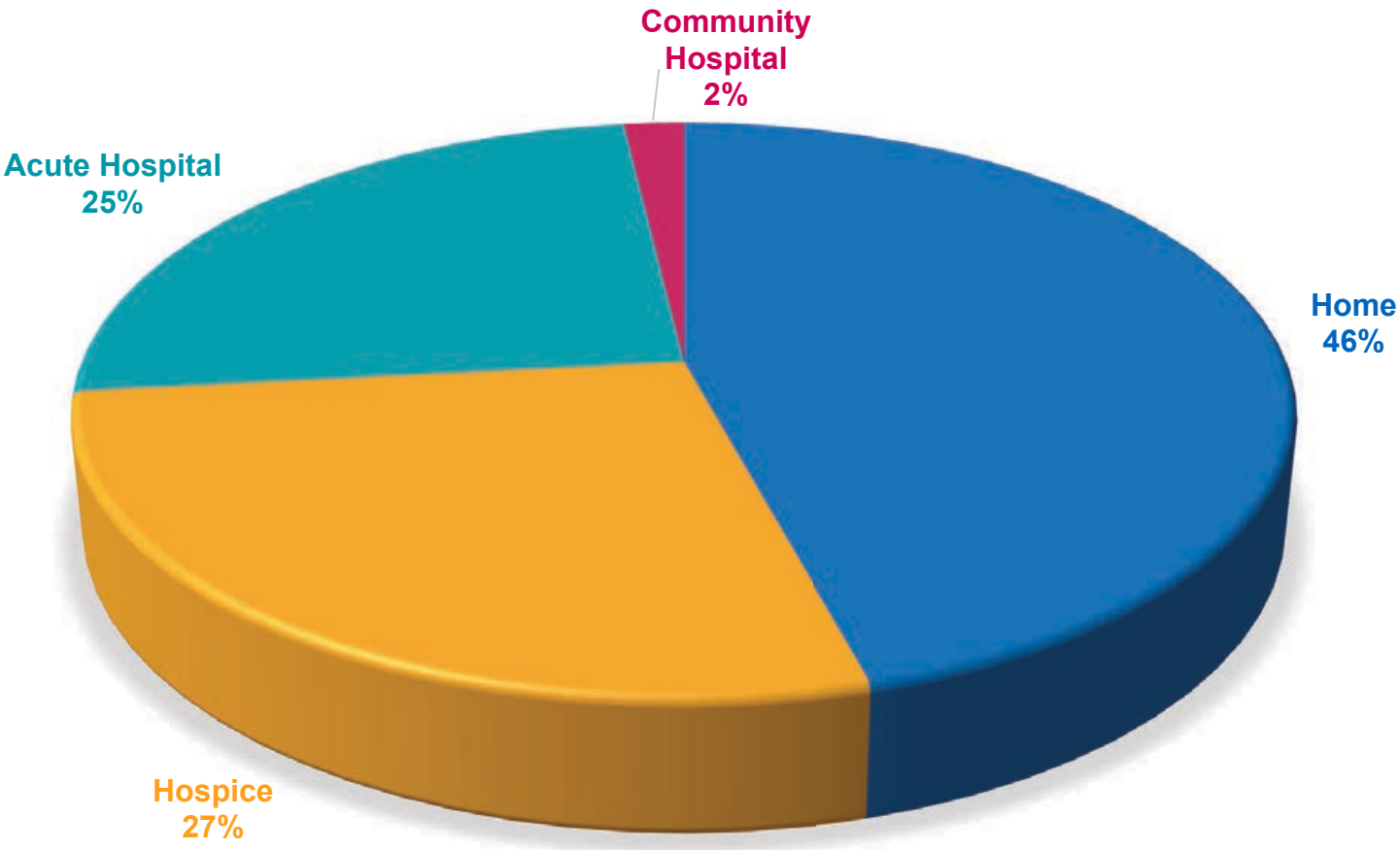
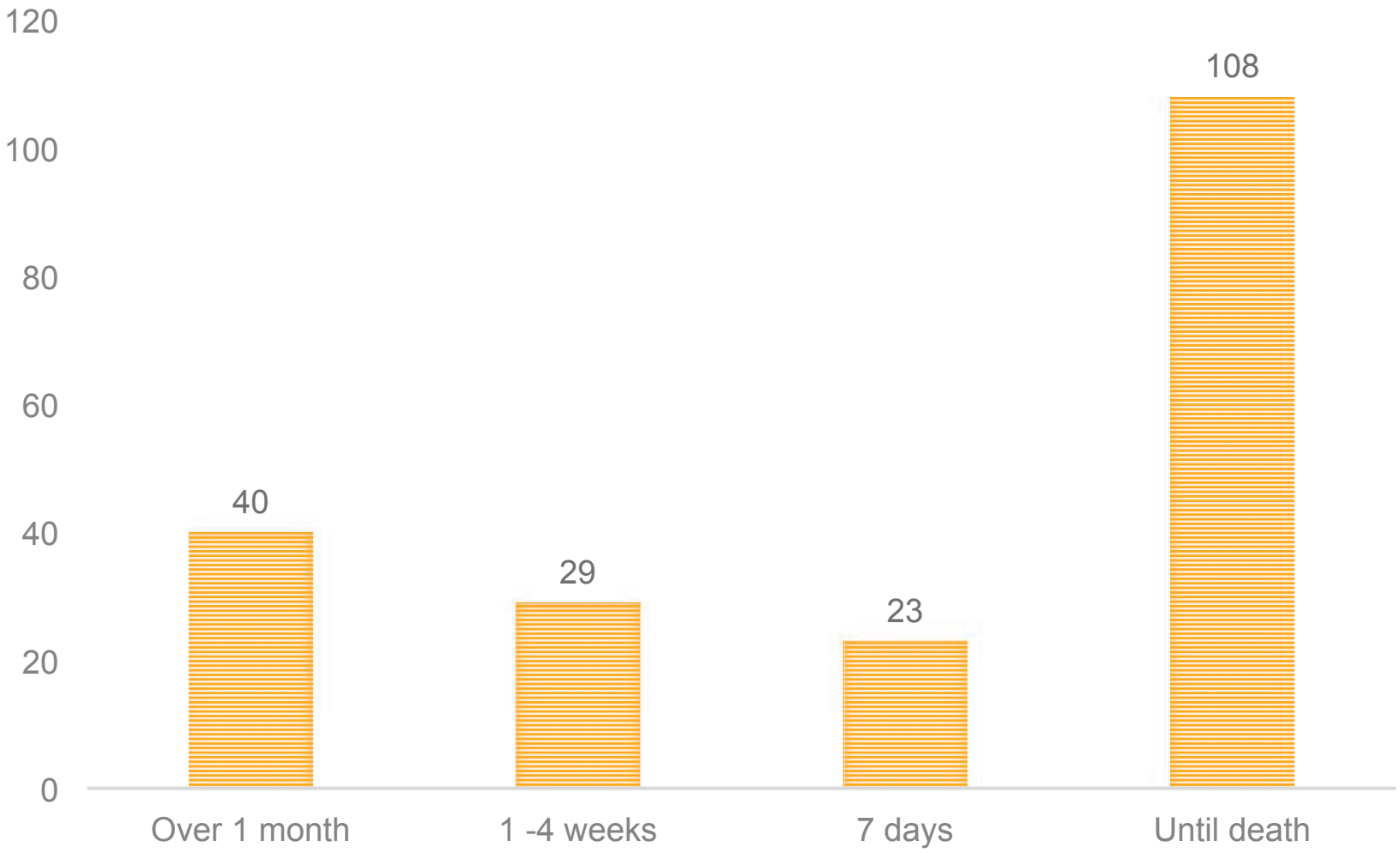
Noble S, Banerjee S, Pease N. Anticoagulation for Cancer Associated Thrombosis at the End of Life: Review of a Case Series of 214 Patients. *Palliative Medicine* 32(1S) 47-48

# Place of death



# When anticoagulation stopped



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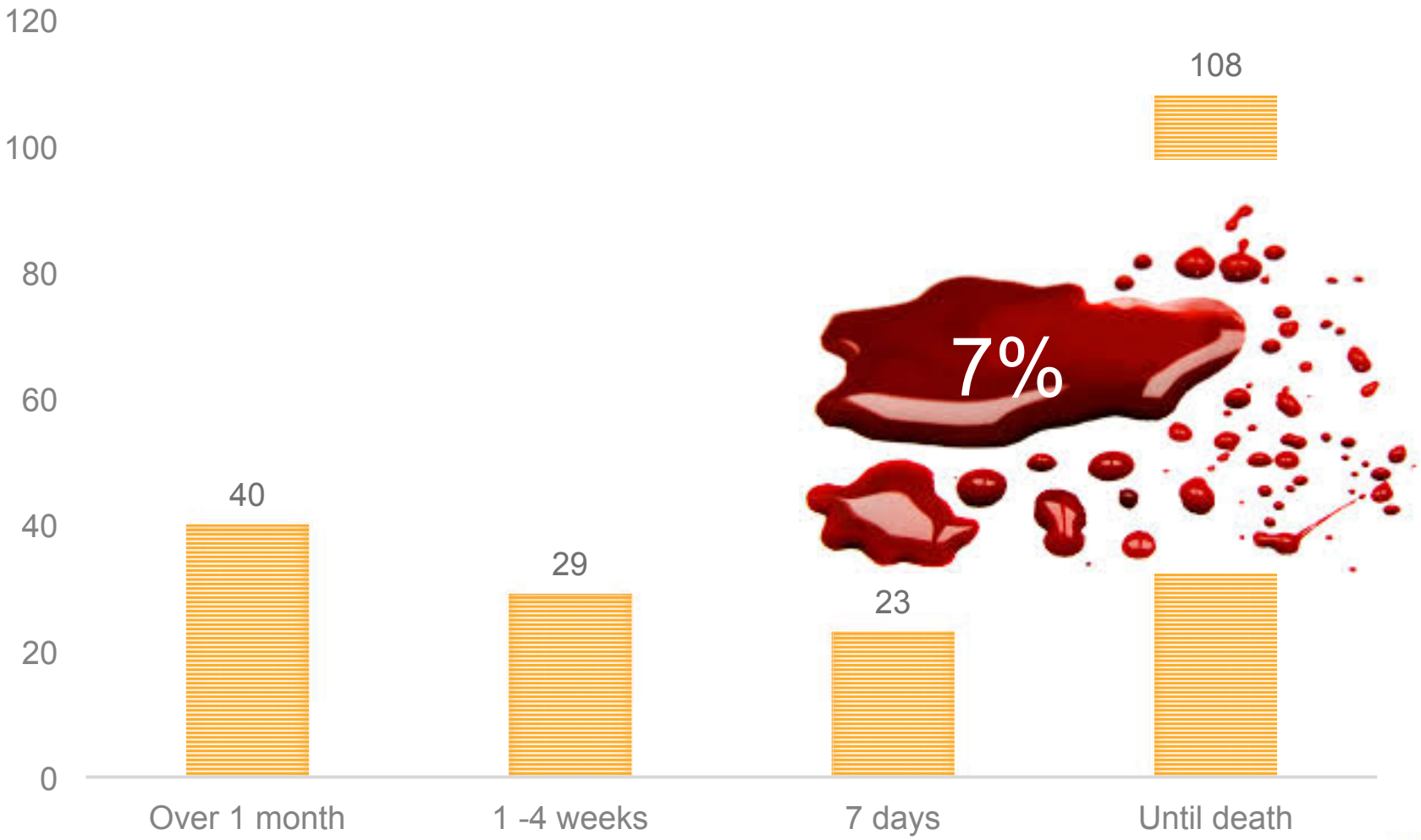

# Primary Thromboprophylaxis

# Thromboprophylaxis: Hospice Inpatient DVT Detection Study (HIDDEN)

- Setting: Patients admitted to UK hospice/ SPCU
- Compression ultrasonography on admission and weekly
- Screened for symptoms attributable to VTE
- Primary outcome
  - Prevalence of radiological apparent DVT
- Secondary outcomes
  - Attributable symptoms
  - Incidence of VTE and symptoms
  - Associated variables
  - Survival



White C, Noble S et al *Lancet Haematology* 2019

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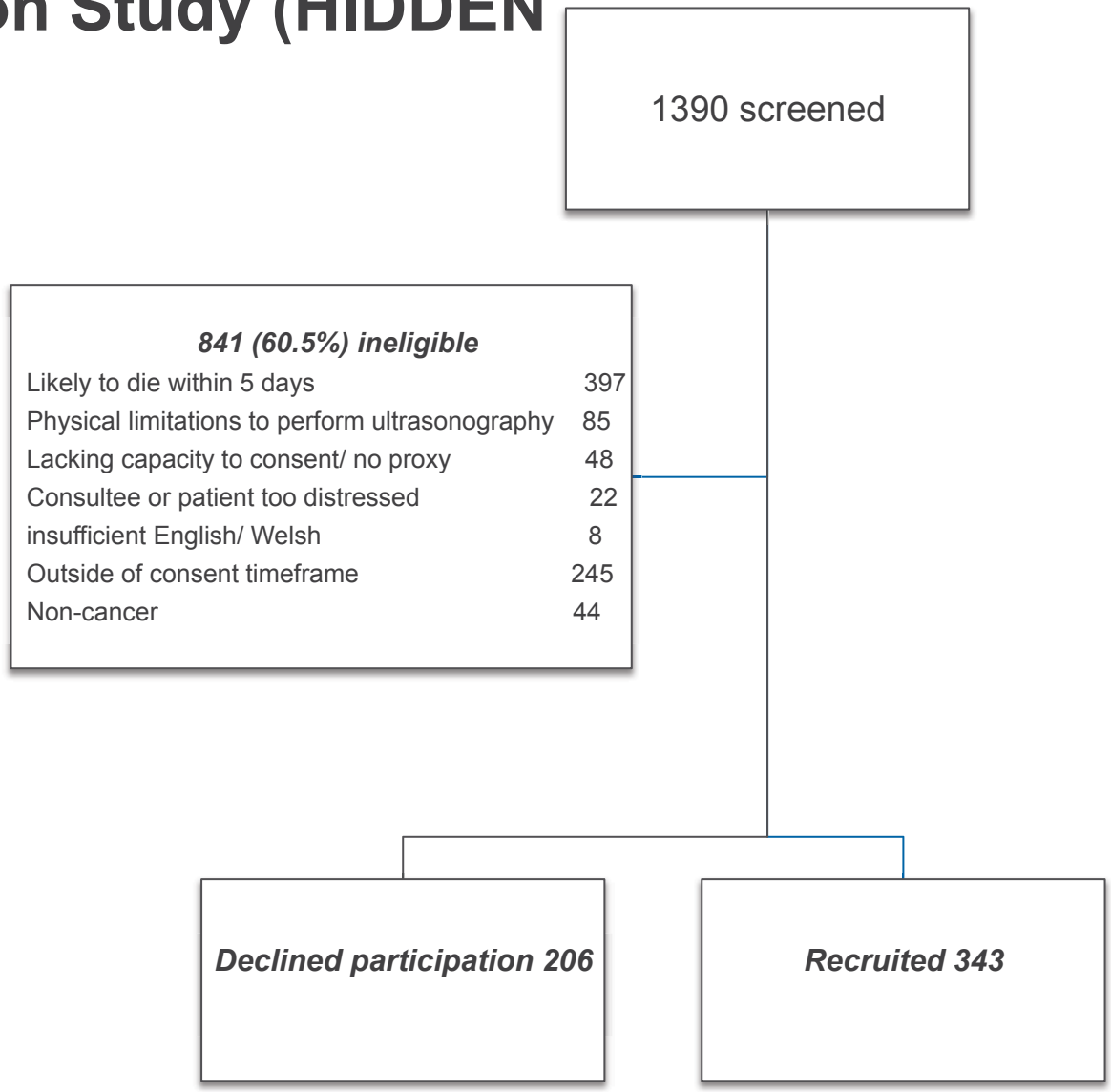

# Demographics

- Average AKPS =49
- Mean survival = 44 days

White C, Noble S et al *Lancet Haematology* 2019

# Results: 273 evaluable scans

- **92/273 (34%, CI 28% to 40%) showed DVT.**
- **Excluding early scans, 64/232 (28%, 22% to 34%)**

- **Associated with**
  - Previous thromboembolism,
  - bedbound ≤12 weeks for any reason (p=0·003)

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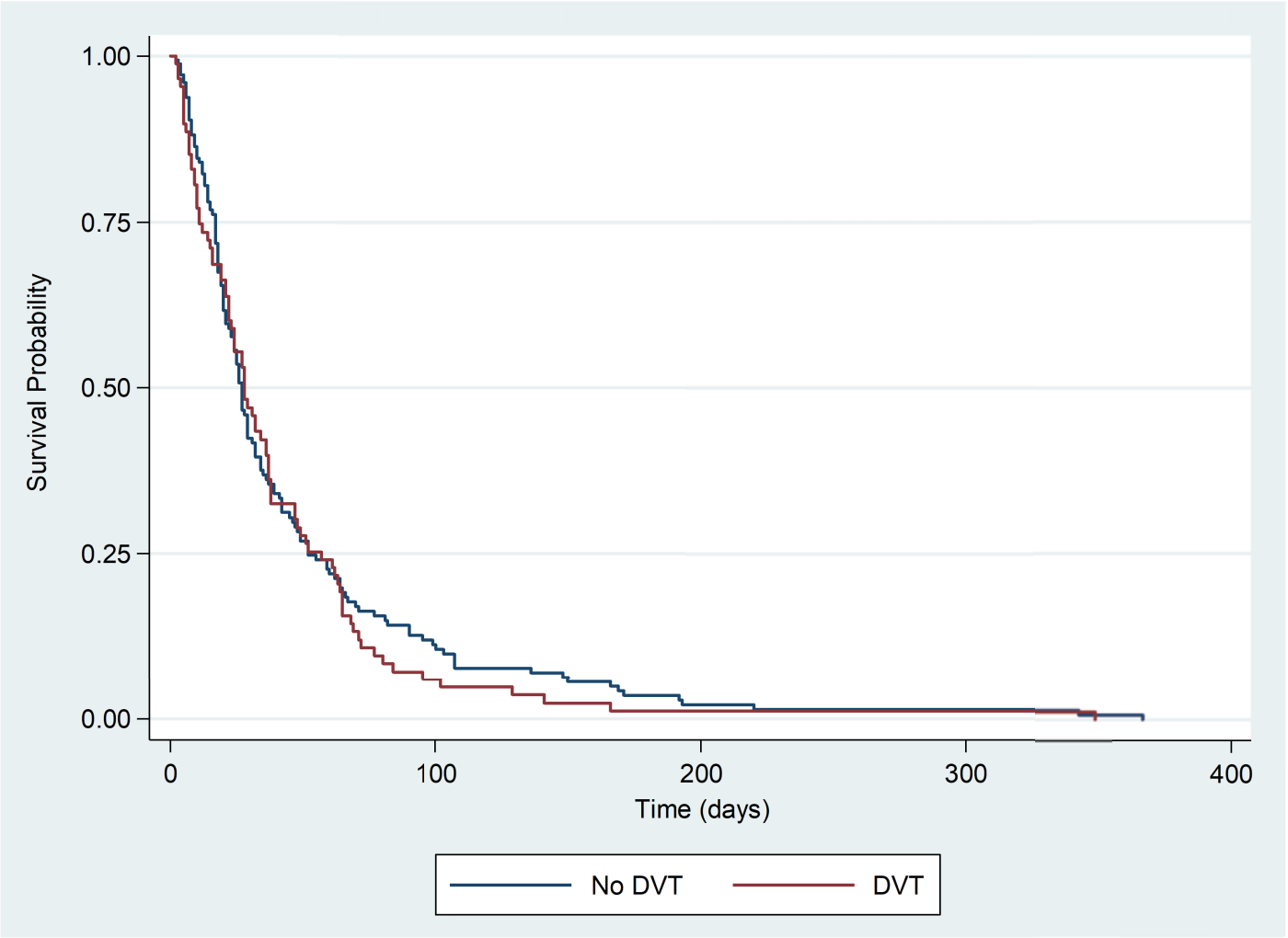
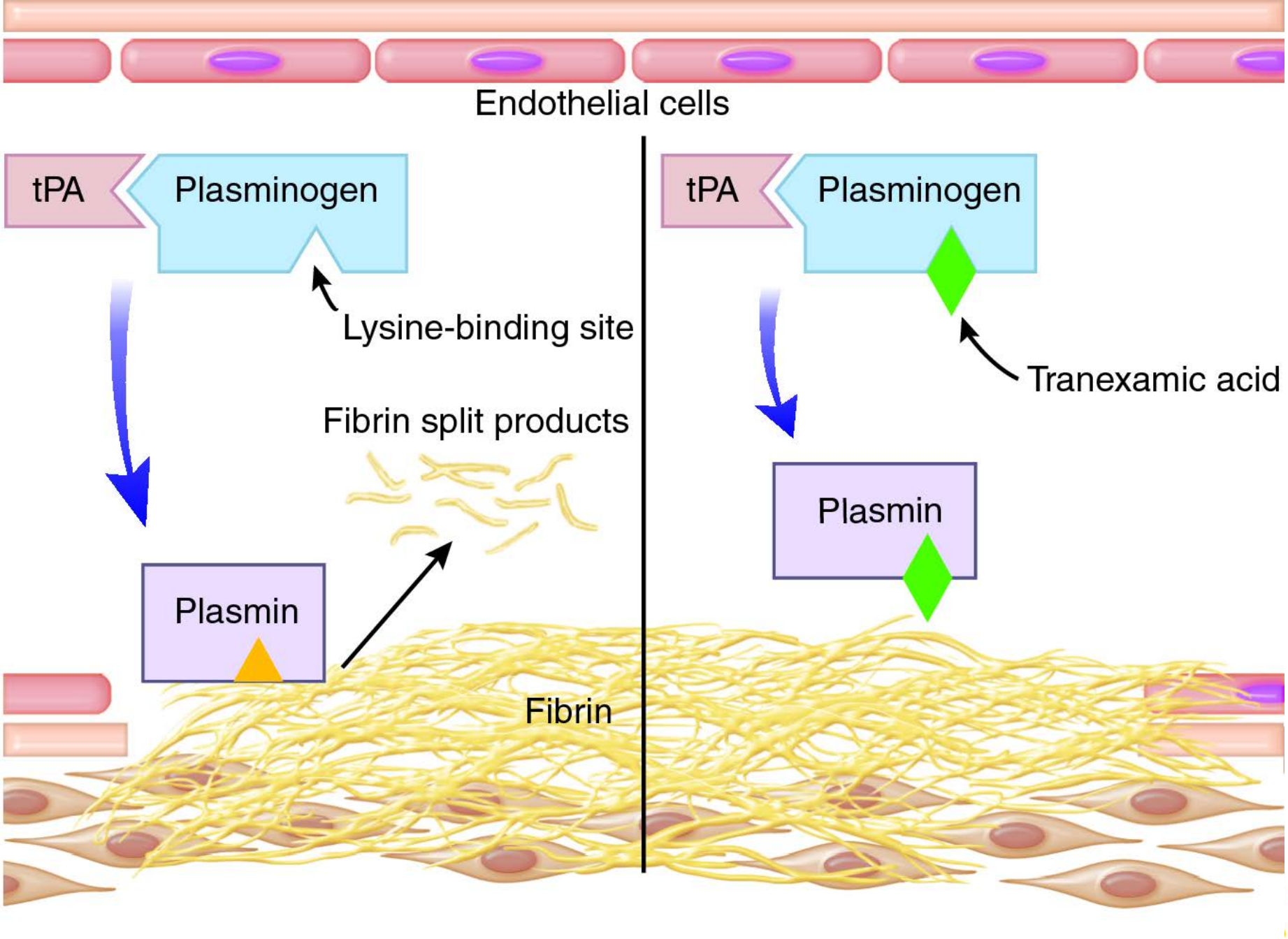
# No relationship with

- Serum albumin (p =0·430),
- Survival (p = 0·473)



# Tranexamic acid



# Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

*CRASH-2 trial collaborators**

## Summary

**Background** Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

**Methods** This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

**Findings** 10096 patients were allocated to tranexamic acid and 10115 to placebo, of whom 10060 and 10067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14·5%] tranexamic acid group *vs* 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). The risk of death due to bleeding was significantly reduced (489 [4·9%] *vs* 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077).

*Lancet* 2010; 376: 23–32

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See Comment page 3

*Members listed at end of paper

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# Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

*CRASH-2 trial collaborators**

| | Tranexamic acid (n=10 060) | Placebo (n=10 067) | RR (95% CI) | p value |
|---|---|---|---|---|
| **Vascular occlusive events*** | | | | |
| Any vascular occlusive event | 168 (1·7%) | 201 (2·0%) | 0·84 (0·68–1·02) | 0·084 |
| Myocardial infarction | 35 (0·3%) | 55 (0·5%) | 0·64 (0·42–0·97) | 0·035 |
| Stroke | 57 (0·6%) | 66 (0·7%) | 0·86 (0·61–1·23) | 0·42 |
| Pulmonary embolism | 72 (0·7%) | 71 (0·7%) | 1·01 (0·73–1·41) | 0·93 |
| Deep vein thrombosis | 40 (0·4%) | 41 (0·4%) | 0·98 (0·63–1·51) | 0·91 |

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## Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

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| | | |
|---|---|---|
| **Pulmonary embolism** | **72 (0.7%)** | **71 (0.7%)** |
| Deep vein thrombosis | 40 (0.4%) | 41 (0.4%) |

# Take home messages

1. Clots are cool
2. The clinical trials informing practice non representative populations
3. Consider stopping anticoagulants as death approaches
4. Do not give thromboprophylaxis if
   - Poor performance status (KPS<50)
   - Short prognosis
5. Tranexamic does not increase thrombotic risk


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