Cancer associated thrombosis

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• **Cancer associated thrombosis becoming more complex**
  • Systemic anti cancer therapies
  • Patients living longer with metastatic disease
  • Increasing number of anticoagulants with CAT data

• **Individualised approach**
  • One size does not fit all

• **Advanced cancer different beast?**
  • Increased bleeding risk
  • VTE manifestation of advanced disease
  • ?biomarker of impending death?
Patient 1

- 58 year old male
- T3 N2 M0 carcinoma oesophagus
- Neoadjuvant chemotherapy: cisplatin/ 5FU
- 2nd cycle sudden onset SOB
- CTPA: multiple moderate volume pulmonary emboli
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

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Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D.,
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Michale F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D.,
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ABSTRACT

BACKGROUND
Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulants agents is unclear.

METHODS
In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS
Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio: 0.97; 95% confidence interval [CI], 0.70 to 1.36; P = 0.006 for noninferiority; P = 0.87 for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, -2.4 percentage points; 95% CI, -7.0 to 2.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

CONCLUSIONS
Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. *(Rounded by Daichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02053682.)

*Complete list of Hokusai VTE Cancer Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Edoxaban for the Treatment of Venous Associated Venous Thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is common in patients with cancer. Long-term anticoagulation therapy with low-molecular-weight heparin (LMWH) is standard of care for patients with cancer and VTE. Edoxaban, a direct factor Xa inhibitor, has been shown to be noninferior to LMWH in patients with VTE, but it is not approved for this indication. In this randomized, open-label, noninferiority trial, we compared the efficacy and safety of edoxaban with that of LMWH in patients with VTE and cancer.

Methods

Patients were randomized 1:1 to receive either edoxaban (20 mg once daily) or fondaparinux (2.5 mg subcutaneously once daily) for 3 months. The primary endpoint was the time to first thrombotic event or recurrent VTE at 1 month. A 2-sided noninferiority margin of 20% was used.

Results

A total of 500 patients were randomized: 250 to edoxaban and 250 to fondaparinux. The median duration of follow-up was 158 days. The primary endpoint occurred in 14 (5.6%) of 246 patients treated with edoxaban and in 14 (5.6%) of 254 patients treated with fondaparinux (hazard ratio, 1.00; 97.5% CI, 0.43 to 2.25; P = 0.999). The incidence of major bleeding was similar in the 2 groups (3.2% [10 patients] in the edoxaban group and 3.6% [9 patients] in the fondaparinux group).

Conclusions

Edoxaban is noninferior to fondaparinux for the prevention of recurrent VTE in patients with cancer and VTE.

J Clin Oncol 2017;35:2017-2025. © 2018 by American Society of Clinical Oncology.

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Vogel, Andrea Marshall, Julie Thwaites, Oliver Chapman, Anand Lokesh, Catherine Hill, Danielle Hall, Janet A. Hancox, Gary H. Liman, Charles Hutchinson, Peter McCullum, Ajay Kakkar, E.D. Richard Gibbins, Sunoo Farooq, Jeremy Dale, Christopher J. Peto, Anthony Manary, and Mark Levine.

ABSTRACT

Venous thromboembolism (VTE) is common in patients with cancer. Long-term anticoagulation therapy with low-molecular-weight heparin (LMWH) has been standard treatment for VTE in patients with cancer. In cancer-associated thrombosis, there is limited evidence on the duration of antithrombotic therapy beyond 6 months. Guidelines recommend treatment continue as long as the cancer is active.

Over the last decade, a new class of anticoagulants, which directly inhibits a direct factor Xa inhibitor, has been developed. In this multicenter, randomized, double-blind, placebo-controlled trial, we compared the efficacy and safety of edoxaban, an oral direct factor Xa inhibitor, with that of LMWH in patients with cancer and VTE.

Methods

Patients were randomized 1:1 to receive either edoxaban (20 mg once daily) or LMWH (enoxaparin, 1 mg/kg subcutaneously twice daily) for 6 months. The primary endpoint was the time to first occurrence of recurrent VTE at 6 months. Secondary endpoints included the time to first occurrence of major bleeding, nonmajor bleeding, and death.

Results

A total of 400 patients were randomized: 200 to edoxaban and 200 to LMWH. The median duration of follow-up was 6 months. The primary endpoint occurred in 10 (5.0%) of 200 patients treated with edoxaban and in 11 (5.5%) of 200 patients treated with LMWH (hazard ratio, 0.92; 97.5% CI, 0.43 to 2.02; P = 0.89). The incidence of major bleeding was similar in the 2 groups (2.0% [4 patients] in the edoxaban group and 0.0% [0 patients] in the LMWH group).

Conclusions

Edoxaban is noninferior to LMWH for the prevention of recurrent VTE in patients with cancer and VTE.

J Clin Oncol 2017;35:2017-2025. © 2018 by American Society of Clinical Oncology.
DOAC Pharmacology

Dabigatran etexilate
- Hydrolysis
- Bioavailability: 3-7%
- $t_{1/2} = 12-17h$
- CrCl < 30 mL/min: Contraindicated/not recommended:

Rivaroxaban
- Cyp3A4, Cyp2J2
- Bioavailability: 66% without food, >80% with food
- Healthy/young: $t_{1/2} = 5-9h$
- Elderly: $t_{1/2} = 11-13h$
- Severe hepatic disease: contraindicated
- CrCl < 30 mL/min: not recommended:

Apixaban
- Cyp3A4: minor
- Bioavailability: 50%
- $t_{1/2} = 12h$
- CrCl < 30 mL/min: use with caution

Edoxaban
- Cyp3A4: minor
- Bioavailability: 62%
- $t_{1/2} = 9-11h$
- CrCl 15–30 mL/min: half treatment dose
- CrCl < 15 mL/min: not recommended

Adapted from: Heidbuchel H et al. Europace 2013; U.S., Canadian Prescribing Information
CrCl = creatinine clearance
DOACs and the jobbing oncologist
DOACs are only as safe as the stupidest person allowed to prescribe them
Current practice and recommendations
The CLOT Trial

Primary outcome: VTE recurrence

Risk reduction = 52%
HR 0.48 (95% CI 0.30, 0.77)
log-rank $p = 0.002$

NNT = 13

Lee AY et al. *N Engl J Med* 2003;349(2):146–153
### LMWH vs warfarin meta analysis

| Study ID | RR (95% CI) | Intervention Events | VKA Events | Weight % |
|----------|-------------|---------------------|------------|----------|
| CLOT    | 0.51 (0.33, 0.79) | 27/336             | 53/336     | 41.31    |
| LITE    | 0.60 (0.23, 1.59)  | 6/100               | 10/100     | 8.37     |
| Romera  | 0.61 (0.11, 3.43)  | 2/36                | 3/33       | 2.66     |
| ONCENOX | 0.66 (0.16, 2.74)  | 4/61                | 3/30       | 3.87     |
| CATCH   | 0.69 (0.45, 1.07)  | 31/449              | 45/451     | 41.24    |
| CANTHANOX | 0.70 (0.12, 4.09) | 2/71                | 3/75       | 2.56     |
| Subtotal (I-squared = 0.0%, p = 0.963) | 0.60 (0.45, 0.79)  | 72/1053             | 117/1025   | 100.00   |

Florian Posch et al, Thrombosis Research 136 (2015) 582–589
Guideline recommendations:

Standard of treatment for cancer-associated thrombosis is three to six months LMWH  
(Grade A)

In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference.  
(Grade D)
Recent data challenges us to think about the needs and desires of individual patients

**Hokusai VTE Cancer**

*Primary outcome:* composite of recurrent VTE or major bleeding regardless of duration of therapy

Secondary outcomes: VTE, PE, DVT, major bleeding, CRNMB, all cause death, EFS

**SELECT-D pilot study**

*Primary outcome:* VTE recurrence at 6 months

Secondary outcomes: major bleeding, CRNMB

Adapted from Raskob GE et al. *N Engl J Med* 2017.

Adapted from Young A et al. *ASH* 2017; Abstract 625.
Hokusai VTE-Cancer: Primary endpoint

Recurrent VTE or major bleeding

Hazard ratio 0.97 (95% CI: 0.70, 1.36)  
$p = 0.006$ for non-inferiority

Raskob GE et al. *N Engl J Med* 2017; [Epub ahead of print].

CI = confidence interval; VTE = venous thromboembolism
Hokusai VTE-Cancer: Secondary outcomes

Recurrent VTE and major bleeding

### Recurrent VTE

|               | Edoxaban N = 522 | Dalteparin N = 524 | p-value (HR, 95% CI) |
|---------------|------------------|-------------------|----------------------|
| **VTE, n (%)** | 41 (7.9)         | 59 (11.3)         | 0.09 (0.71, 0.48–1.06) |
| **PE, n (%)**  | 27 (5.2)         | 28 (5.3)          | (0.56, 0.59–1.69)     |
| **DVT, n (%)** | 19 (3.6)         | 35 (6.7)          | (0.56, 0.32–0.97)     |

### Major bleeding

|               | Edoxaban N = 522 | Dalteparin N = 524 | p-value (HR, 95% CI) |
|---------------|------------------|-------------------|----------------------|
| **All, n (%)**  | 36 (6.9)         | 21 (4.0)          | 0.04 (1.77, 1.03–3.04) |
| **Gr 2, n (%)** | 21 (4.0)         | 5 (0.1)           |                      |
| **Gr 3/4, n (%)** | 12 (2.3)         | 12 (2.3)          |                      |
| Appendix: page 16/32 |
GI cancers: 13.1% major bleeding
Urothelial cancers 8% major bleeding
ISTH definition major bleeding

Major bleeding event
A major bleeding event will be confirmed when it is a clinically overt bleeding event that meets at least one of the following:

a) Fatal bleeding

b) Bleeding in a critical area or organ such as:
   - Retroperitoneal
   - Intracranial
   - Intraocular
   - Intraspinal
   - Intra-articular
   - Pericardial
   - Intramuscular with compartment syndrome

c) A clinically overt bleeding event
   - that is associated with a fall in hemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or
   - leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood.
## Classification of clinical presentation

| Category | Description |
|----------|-------------|
| 1        | Bleeding events presenting without any clinical emergency |
| 2        | All bleeding events that could not be classified to any of the other three |
| 3        | Bleeding events presenting with great medical emergency |
| 4        | Bleeding events already fatal before or almost immediately upon entering the hospital |
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Stroke, Systemic or Venous Thromboembolism

Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists

An individual patient data meta-analysis

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430 patients randomized.
A protocol change was implemented to exclude patients with esophageal and gastro-esophageal cancer by the safety committee due to excessive bleeding in the rivaroxaban arm.
Second randomization was deemed not feasible.
Will not proceed to large study.

| Six-month outcomes            | Rivaroxaban (N = 203) | Dalteparin (N = 203) |
|-------------------------------|------------------------|----------------------|
| Recurrent VTE, n (%)          | 8 (4)                  | 18 (11)              |
| Major bleeding, n (%)         | 11 (5)                 | 6 (3)                |
| CRNMB, n (%)                  | 25 (12)                | 6 (3)                |
| Major and CRNMB, n (%)        | 36 (17)                | 12 (6)               |

Young A et al. Presented at ASH 2017; Abstract 625.

ASH = American Society of Hematology; CRNMB = clinically-relevant non-major bleeding; VTE = venous thromboembolism
SELECT-D

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Young A et al. Presented at ASH 2017; Abstract 625.

ASH = American Society of Hematology; CRNMB = clinically-relevant non-major bleeding; VTE = venous thromboembolism
Similar outcomes in Hokusai and SELECT-D
Six-month results

Recurrent VTE

| Study or Subgroup | DOAC Events | Total | LMWH Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|-------|-------------|-------|--------|---------------------------------|
| Raskob 2017       | 34          | 522   | 46          | 524   | 73.4%  | 0.74 [0.48, 1.14]              |
| Young 2017        | 8           | 203   | 18          | 203   | 26.6%  | 0.44 [0.20, 1.00]              |
| Total (95% CI)    | 42          | 725   | 64          | 727   | 100.0% | 0.65 [0.42, 1.01]              |

Heterogeneity: $\hat{\tau}^2 = 0.02; \text{Chi}^2 = 1.21, df = 1 (P = 0.27); I^2 = 17%$
Test for overall effect: $Z = 1.92 (P = 0.06)$

Major bleeding

| Study or Subgroup | DOAC Events | Total | LMWH Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|-------|-------------|-------|--------|---------------------------------|
| Raskob 2017       | 29          | 522   | 17          | 524   | 73.5%  | 1.71 [0.95, 3.08]              |
| Young 2017        | 11          | 203   | 6           | 203   | 26.5%  | 1.83 [0.69, 4.86]              |
| Total (95% CI)    | 40          | 725   | 23          | 727   | 100.0% | 1.74 [1.05, 2.88]              |

Heterogeneity: $\hat{\tau}^2 = 0.00; \text{Chi}^2 = 0.01, df = 1 (P = 0.91); I^2 = 0%$
Test for overall effect: $Z = 2.17 (P = 0.03)$

Li A et al. Thromb Res 2018; [in press].

CI = confidence interval; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; VTE = venous thromboembolism.
## Inducers and inhibitors of CYP3A4 and P-gp

### Kinase inhibitors

| Kinase inhibitors | CYP3A4 | P-gp |
|-------------------|--------|------|
| Afatinib          | ↓      | ↓    |
| Alectinib         | ↓      | ↓    |
| Ceritinib         | ↓      |      |
| Crizotinib        | ↓      |      |
| Dasatinib         | ↓      |      |
| Ibrutinib         | ↓      | ↓    |
| Idelalisib        | ↓      | ↓    |
| Imatinib          | ↓      |      |
| Lapatinib         | ↓      | ↓    |
| Nilotinib         | ↓      | ↓    |
| Osimertinib       | ↓      |      |
| Vemurafenib       | ↑      | ↓    |
| Lenvatinib        | ↑      | ↑    |

### Chemotherapy

| Chemotherapy       | CYP3A4 | P-gp |
|--------------------|--------|------|
| Doxorubicin        | ↓      |      |
| Topotecan          | ↓      |      |
| Vinblastine        | ↓      |      |
| Mitotane           | ↑      |      |
| Venetoclax         | ↓      |      |

### Supportive care

| Supportive care    | CYP3A4 | P-gp |
|--------------------|--------|------|
| Aprepitant         | ↓      |      |
| Methylpred         | ↓      |      |
| Dexamethasone      | ↑      | ↑    |
ISTH SSC DOACS

1. We recommend individualized treatment regimens after shared decision-making with patients.

2. We suggest the use of specific DOACs for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy. LMWHs constitute an acceptable alternative.

3. We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis.

Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, Carrier M. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018 Jun 29. doi: 10.1111/jth.14219
Patient 2

- 68 year old female
- Metastatic ovarian cancer
- Last scan showed disease progression on post chemo scan
- General deterioration past 3 months
- Reduced mobility due to weakness/ pain
- Poor appetite, constipation
- Admitted to optimize symptom control

- What about thromboprophylaxis?
Thromboprophylaxis in hospices and specialist palliative care units

- Variable practice across UK hospices
- “not a big problem”
- “population in thromboprophylaxis studies not representative”
- “large PE a nice way to go”
- “clinical outcomes not appropriate”
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 et al 2019 Lancet Haem
Thromboprophylaxis: Hospice Inpatient DVT Detection Study (HIDDEN

1390 screened

841 (60.5%) ineligible
- Likely to die within 5 days: 397
- Physical limitations to perform ultrasonography: 85
- Lacking capacity to consent/ no proxy: 48
- Consultee or patient too distressed: 22
- Insufficient English/ Welsh: 8
- Outside of consent timeframe: 245
- Non-cancer: 44

Declined participation 206 (30% of those eligible)

Recruited 343 (70% of those eligible)
Demographics

- Average AKPS = 49
- Mean survival = 44 days

White C et al 2019 Lancet Haem
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)
  - lower limb oedema (p=0.009)

No significant attributable symptom burden difference

White C et al 2019 Lancet Haem
No association with

- Serum albumin ($p = 0.430$),
- Thromboprophylaxis ($p = 0.173$) and

No impact on survival ($p = 0.473$)
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

| Reason                        | Count | Percentage |
|-------------------------------|-------|------------|
| 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

| Treatment                               | Count | Percentage |
|-----------------------------------------|-------|------------|
| Cancer treatment                        | 0     | 0.0        |
| Chemotherapy                            | 257   | 21.4       |
| Targeted cancer therapy                 | 35    | 2.9        |
| Radiotherapy                            | 91    | 7.6        |
| Growth factors                          | 0     | 0.0        |
| Anticoagulant therapy                   | 32    | 2.7        |
| At prophylactic (low) dose**            | 527   | 44.0       |
| At therapeutic (high) dose††            | 69    | 5.7        |
| Antiplatelet therapy                    | 167   | 14.0       |
| Corticosteroids                         | 620   | 52.0       |
| Antidepressive agents                   | 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* |
|---------------------------------|-------------------------|-----------------------------|------------------------|
| 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 than 10% of patients with an elevated risk index (univariate Hazard Ratio, HR = 2.38 [1.05–5.40]) and moderate or severe renal insufficiency (univariate HR = 2.13 [0.61–7.56]), these factors were not included in the multivariate analysis. *According to the Fine and Gray method. †Within 4 weeks prior to inclusion. ‡4 weeks prior to inclusion or during hospitalization in the palliative care unit.
Anticoagulation at the end of life

In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference.
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

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)
Place of death

- Home: 46%
- Hospice: 27%
- Acute Hospital: 25%
- Community Hospital: 2%
When anticoagulation stopped

- Over 1 month: 40
- 1-4 weeks: 29
- 7 days: 23
- Until death: 108
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- Over 1 month: 40
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7%
To conclude

- **Cancer associated thrombosis becoming more complex**
  - Systemic anti cancer therapies
  - Patients living longer with metastatic disease
  - Increasing number of anticoagulants with CAT data
- **Individualised approach**
  - One size does not fit all
- **Advanced cancer different beast?**
  - Increased bleeding risk
  - VTE manifestation of advanced disease
  - ?biomarker of impending death?
