Supplemental Online Content

Alexander M, Harris S, Underhill C, et al. Risk-directed ambulatory thromboprophylaxis in lung and gastrointestinal cancers: the TARGET-TP randomized clinical trial. *JAMA Oncol*. Published online September 21, 2023. doi:10.1001/jamaoncol.2023.3634

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Methods: Inclusion and Exclusion Criteria

Inclusion criteria
All of the following must apply at the time of enrollment:

1. Patient is 18 years of age or older
2. Patient has a confirmed histological diagnosis of any gastrointestinal or lung cancer
3. Patient is newly diagnosed treatment-naïve or is previously treated with newly relapsed or progressive disease
4. Patient is being considered for, but has not commenced anticancer therapy including chemotherapy and/or radiotherapy and/or immunotherapy and/or targeted therapies, within neoadjuvant, adjuvant, curative, or palliative treatment settings.
5. Patient has expected life expectancy of at least six months, as estimated by their treating clinician
6. Patient has provided written confirmation of informed consent on participant information and consent form.

Exclusion criteria
Patients who meet any of the following criteria will be excluded from participation in this study:

1. Patients who have already commenced anticancer therapy
2. Patients with a clinical indication for therapeutic anticoagulation (antiplatelet agents such as clopidogrel and aspirin are permitted)
3. Patients with a contraindication to anticoagulation and/or specifically LMWH (Appendix 2)
4. Cancer diagnosis other than those specified in inclusion criteria.

Methods: Definition of primary endpoint

Objectively confirmed symptomatic or asymptomatic TE (DVT, PE, ATE) at 6 months after randomisation.

DVT must be confirmed by ultrasonography, venography, or magnetic resonance angiography (cerebral events). PE must be confirmed by spiral CT, CT pulmonary angiography (CTPA) or lung ventilation/perfusion scan. ATE must be confirmed by relevant radiologic imaging, or specifically for myocardial infarct (MI) must meet criteria outlined in the universal definition of MI considering biomarker changes, ischemic symptoms, ECG changes, cardiac imaging abnormalities, and cardiac death.

Superficial Vein Thrombosis (SVT) will not be considered a TE event, but will be documented if they occur. All TE events will be adjudicated by a committee unaware of randomisation (Clinical Event Committee – CEC).

Methods: Definition of bleeding events

Major bleeding was defined as clinically overt bleeding meeting at least one of the following criteria: fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells.

Clinically overt was defined as new onset visible bleeding or signs and symptoms suggestive of bleeding which in the absence of visible bleeding were confirmed by relevant imaging techniques.

Clinically relevant non-major (CRNM) bleeding was defined as bleeding not meeting criteria for major bleeding but that would be considered relevant and not trivial by a patient and physician.

Methods: Enoxaparin duration

Patients classified at high-risk were randomized 1:1 to enoxaparin 40mg subcutaneously daily for a minimum of 90 days, however could extend up to 180 days according to ongoing risks, at discretion of the treating clinician. For systemic anticancer treatments with planned duration beyond 90-180 days, the protocol specified that prophylaxis continue at least until the end of treatment. For systemic anticancer treatments with planned duration beyond 180 days (i.e. until disease progression), the protocol specified that prophylaxis may be ceased

after 90 days if the patient was considered to have stable or responding disease and was continuing on the same regimen.

Methods: Randomization details

If high-risk at baseline [criteria (a) or (b)], randomisation was performed and thromboprophylaxis initiated (month one assessments conducted but do not impact risk-categorisation). If low-risk at baseline anticancer treatment was initiated without thromboprophylaxis. If high-risk at month one with profile change from low- to high-risk after initiating anticancer treatment [criteria (c)], randomization was performed and thromboprophylaxis initiated. If low-risk at month one (profile low-risk baseline and month one), anticancer treatment continued without thromboprophylaxis (observational cohort). Final risk categorisation was applied at month one to define analysis cohorts. In all cohorts time-at-risk commenced at baseline risk-assessment.

Randomization was performed using the randomization module (blinded) created in advance of patient recruitment by an independent statistician. After randomization the study team, treating clinician and patient were unblinded to treatment allocation.

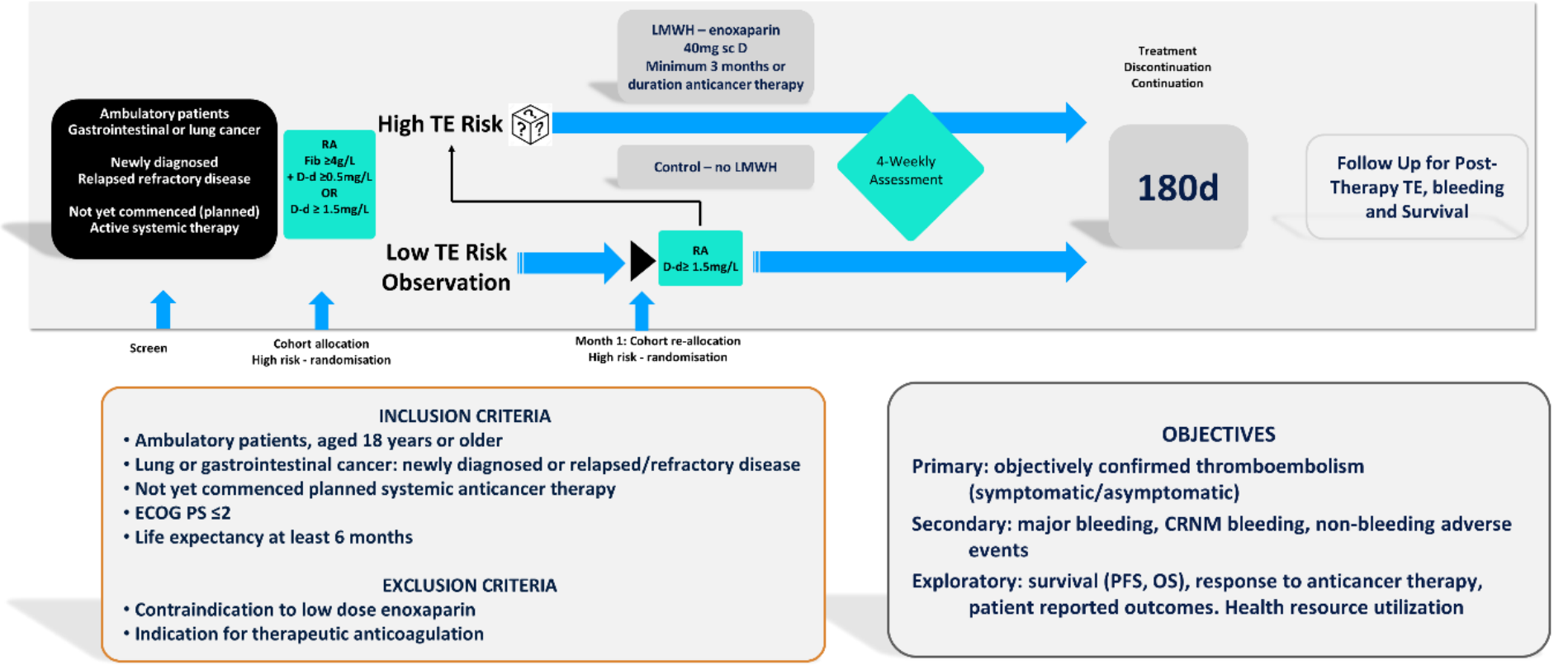
Methods: Networked Teletrial methodology

The trial was conducted using the networked teletrial methodology. Under this networked model, participants enrolled at regional satellite sites had shared care between their enrollment site and the primary site, facilitated by digital technologies. The primary site was an Australian metropolitan specialist cancer centre, with four regional satellite sites across the state of Victoria. Trial operation and governance was managed according to site specific Supervision Plans, factoring individual capabilities of each satellite site and trial conduct requirements. Trial oversight meetings were conducted to ensure open communication and facilitate shared responsibilities between primary and satellite sites. Data collected at sites were entered into an encrypted web-based database. Principal Investigators were responsible for data completeness and accuracy at their sites.

Methods: Sensitivity and Specificity

Sensitivity was defined as the number of individuals with thromboembolism classified as high-risk (control arm), as a proportion of all individuals with thromboembolism. Specificity was defined as the number of individuals without thromboembolism classified as low-risk (observational arm), as a proportion of all individuals without thromboembolism. Analysis included events occurring up to 180 days after randomisation, as per primary endpoint definitions.

eFigure 1. Trial Schema[(a)]



RA= risk assessment; Fib=fibrinogen; D-d = D-dimer; D=Daily; LMWH = low molecular weight heparin. ECOG PS=Eastern Cooperative Oncology Group Performance Status; CRNM = clinically relevant non-major bleeding
TARGET-TP: Clinicaltrials.gov ANZCTR number, ACTRN12618000811202. Accessed June 2019.

(a) Pragmatic open label design adopted to improve participant experience (avoid placebo injection), and given previously established safety/efficacy of low-molecular weight heparin (LMWH),[3-5] and objectively confirmed endpoints of thromboembolism and all-cause mortality.

eResults

Results: Thromboembolism by race

Among 93 participants who reported White/Caucasian race at enrollment, 6/93 (6%) high-risk enoxaparin, 21/92 (23%) high-risk control, and 9/118 (8%) low-risk developed thromboembolism. Among 18 participants who reported Asian race at enrollment, 1/5 high-risk enoxaparin, 0/4 high-risk control, and 1/9 low-risk developed thromboembolism. Race was not a significant predictor of thromboembolism, with small numbers limiting interpretation.

Results: Thromboembolism by cancer diagnosis

There was no evidence of differing treatment effect, with the applied risk-directed strategy, between lung and gastrointestinal subtypes (interaction model P=0.10), with a comparable reduction in thromboembolic events (enoxaparin versus control) for both tumour groups(Table 2). Across both tumour groups there was a comparable increased thromboembolic risk in the designated high-risk control, versus low-risk observational cohorts. Specifically, among patients with lung cancer assigned high-risk, thromboembolism occurred in 2/46 (4%) randomized to enoxaparin and 13/46 (28%) randomized to control: hazard ratio, HR 0.13, 95%CI 0.03 to 0.58, P=0.01. Thromboembolism occurred in 3/35 (9%) low-risk lung cancer patients: high-risk control vs. low-risk: HR 3.79, 95% CI 1.08 to 13.33, P=0.04. Similarly, among patients with gastrointestinal cancers, thromboembolism occurred in 6/54 (9%) randomized to enoxaparin and 10/54 (19%) randomized to control: hazard ratio, HR 0.29, 95%CI 0.21 to 1.59, P=0.29. Thromboembolism occurred in 7/93 (8%) low-risk gastrointestinal.

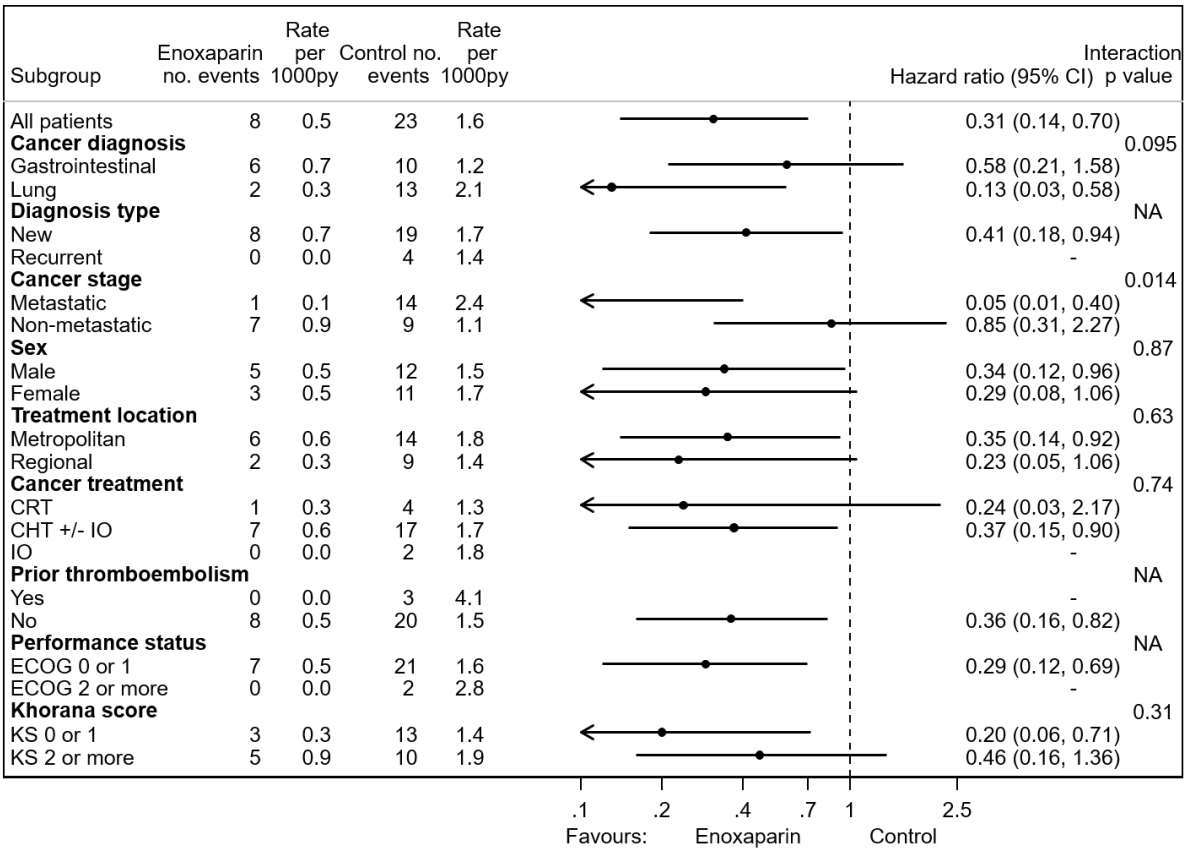
Results: Thromboembolism in the intervention cohort

Of patients randomised to enoxaparin, 6/8 thromboembolic events occurred without active enoxaparin therapy. All 6 patients had gastrointestinal cancer, two events occurred shortly after completing the protocol-planned prophylaxis, two had ceased due to bleeding events, one ceased for end of life care, and one event occurred shortly after randomisation, prior to starting anticancer and enoxaparin therapy – median time to event 128 days (range 7-158 days). Among two patients with lung cancer, events occurred on enoxaparin; one patient with metastatic disease undergoing systemic chemo/immunotherapy and one patient with locally advanced disease undergoing curative intent chemo/radiotherapy – time to event 70 days (57-83 days).

Discussion: impact of race on generalisability

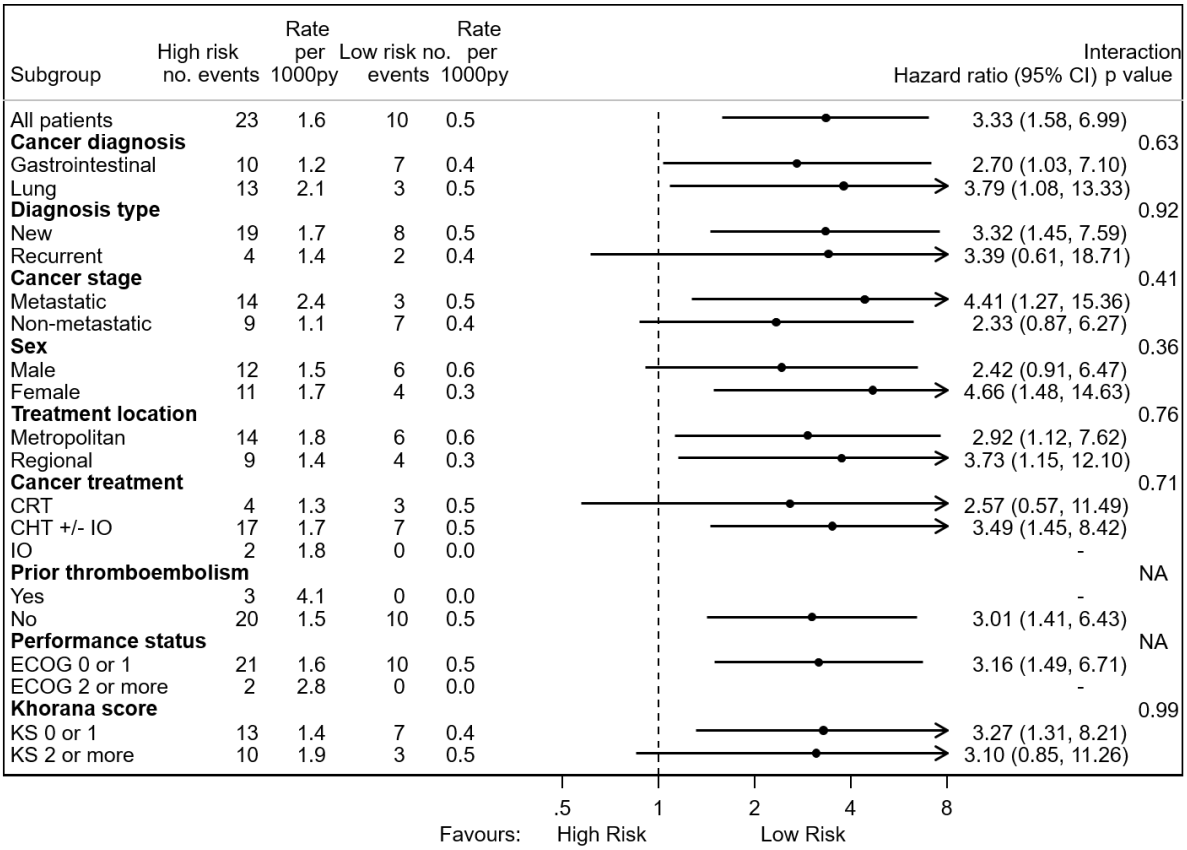
The cohort included small (n=18) but higher proportion of Asian participants compared to similar Western trials (6% vs 1% CASSINI; not reported AVERT). Whilst evidence suggests lower thromboembolism risk compared to whites, this may be limited to earlier stage disease,30 and small numbers in this cohort limit further interpretation on generalizability of findings.

eFigure 2. Thromboembolism in the Intention-to-Treat Randomized Population, According to Subgroup



Footnote: The hazard ratio and 95% confidence intervals for time to first occurrence of thromboembolism within 180 days in the enoxaparin compared to control group are shown. The intention-to-treat population included all eligible patients classified high-risk of thromboembolism who underwent randomization. Arrow heads signal that the confidence interval has been truncated for display purposes. For the subgroups treated with immunotherapy and with ECOG 2 or more, no events occurred in the enoxaparin arm and the hazard ratios could not be calculated (and corresponding interaction p value is NA for not available).

eFigure 3. Thromboembolis in the Intention-to-Treat Untreated Population, According to Subgroup



Footnote: The hazard ratio and 95% confidence intervals for time to first occurrence of thromboembolism within 180 days in the high risk control group compared to the low risk observation group. The intention-to-treat population included all eligible patients classified high-risk of thromboembolism who were randomized to control, and all eligible patients classed low-risk. Arrow heads signal that the confidence interval has been truncated for display purposes. For the subgroups treated with immunotherapy, prior thromboembolism, and with ECOG 2 or more, no events occurred in the high or low risk group, and the hazard ratios could not be calculated (and corresponding interaction p value is NA for not available).

eTable 1. Efficacy and Safety Outcomes Within 180 Days According to Thromboembolism Risk Classification and Randomization: Univariable and Multivariable Analyses

	Total (n=328)[a] no (%)	Low Risk (n=128) no (%)	Enoxaparin (n=100) no (%)	Control (n=100) no (%)	Unadjusted Hazard Ratio (95%CI) enoxaparin vs control	Adjusted[b] Hazard Ratio (95%CI) enoxaparin vs control	Unadjusted Hazard Ratio (95%CI) control vs low risk	Adjusted[b] Hazard Ratio (95%CI) control vs low risk
Thromboembolism								
Thromboembolism	41 (13)	10 (8)	8 (8) (c)	23 (23)	0.31 (0.14 to 0.70)	0.30 (0.13 to 0.68)	3.33 (1.58 to 6.99)	2.95 (1.39 to 6.24)
Thromboembolism gastrointestinal cancers	23/201 (11)	7/93 (8)	6/54 (9)[c]	10/54 (19)	0.58 (0.21 to 1.58)	0.64 (0.23 to 1.80)	2.70 (1.03 to 7.10)	2.66 (0.98 to 7.2)
Thromboembolism lung cancers	18/127 (14)	3/35 (9)	2/46 (4)[d]	13/46 (28)	0.13 (0.03 to 0.58)	0.11 (0.02 to 0.51)	3.79 (1.08 to 13.33)	5.33 (1.42 to 20.00)
Venous thromboembolism	38 (12)	9 (7)	7 (7)	22 (22)	0.29 (0.12 to 0.68)	0.28 (0.12 to 0.65)	3.56 (1.64 to 7.74)	3.14 (1.43 to 6.88)
Pulmonary embolism +/- deep vein thrombosis	17 (5)	3 (2)	4 (4)	10 (10)	0.29 (0.09 to 0.91)	0.27 (0.09 to 0.84)	6.10 (1.72 to 21.64)	4.80 (1.34 to 17.16)
Deep Vein Thrombosis incl. catheter events	21 (6)	6 (5)	3 (3)	12 (12)	0.22 (0.06 to 0.79)	0.21 (0.06 to 0.77)	2.99 (1.12 to 7.96)	2.87 (1.06 to 7.77)
Deep Vein Thrombosis excl. catheter events	17 (5)	3 (2)	3 (3)	11 (11)	0.24 (0.07 to 0.87)	0.23 (0.06 to 0.85)	5.44 (1.52 to 19.51)	4.97 (1.37 to 18.04)
Catheter related upper limb deep vein thrombosis	4 (1)	3 (2)	0 (0)	1 (1)	0.80 (0.05 to 12.87)	0.83 (0.05-14.29)	0.54 (0.06 to 5.20)	0.42 (0.04 to 4.34)
Arterial Thromboembolism (myocardial infarct)	3 (1)	1 (1)	1 (1)	2 (2)	0.82 (0.05 to 13.17)	0.78 (0.05 to 13.20)	1.52 (0.10 to 24.29)	1.13 (0.06 to 22.79)
Bleeding events								
Bleeding event								
Major bleeding	6 (2)	3 (2)	1 (1)	2 (2)	2.21 (0.20 to 24.44)	2.63 (0.23 to 29.71)	1.06 (0.18 to 6.34)	1.29 (0.21 to 8.03)
Clinically relevant non-major bleeding	36 (11)	11 (9)	16 (16)	9 (9)	0.70 (0.30 to 1.52)	0.68 (0.30 to 1.55)	0.69 (0.28 to 1.72)	0.96 (0.36 to 2.52)
Any bleeding[e]	40 (12)	13 (10)	17 (17)	10 (10)	0.70 (0.32 to 1.52)	0.71 (0.32 to 1.55)	0.77 (0.33 to 1.79)	1.13 (0.47 to 2.75)
Anticancer treatment response and survival								
Cancer progression	124/328 (38)	35 (27)	42 (42)	47 (47)	0.78 (0.51 to 1.19)	0.74 (0.49 to 1.14)	2.14 (1.38 to 3.32)	1.90 (1.21 to 2.98)
Progression gastrointestinal cancers	68/201 (34)	22/93 (24)	23/54 (43)	23/54 (43)	0.89 (0.50 to 1.60)	0.84 (0.46 to 1.53)	2.27 (1.27 to 4.08)	2.12 (1.14 to 3.94)
Progression lung cancers	56/127 (44)	13/35 (37)	19/46 (41)	24/46 (52)	0.68 (0.37 to 1.24)	0.70 (0.38 to 1.28)	1.61 (0.82 to 3.16)	1.62 (0.82 to 3.23)
Death, any cause	48/328 (15)	9 (7)	13 (13)	26 (26)	0.48 (0.24 to 0.92)	0.45 (0.23 to 0.87)	4.71 (2.13 to 10.42)	4.25 (1.90 to 9.51)
Death gastrointestinal cancers	26/201 (13)	7/93 (8)	7/54 (13)	12/54 (22)	0.56 (0.22 to 1.43)	0.50 (0.19 to 1.29)	3.87 (1.45 to 10.32)	3.61 (1.31 to 9.91)
Death lung cancers	22/127 (17)	2/35 (6)	6/46 (13)	14/46 (30)	0.39 (0.15 to 1.03)	0.42 (0.16 to 1.10)	6.01 (1.37 to 26.47)	6.25 (1.41 to 27.68)

Footnote: (a) All denominators are shown at top of the column except where specified in individual row (i.e. for tumour group analyses). (b) Adjusted for cancer diagnosis (lung versus gastrointestinal), cancer treatment (chemoradiotherapy, chemotherapy +/- immunotherapy, immunotherapy or targeted therapies), stage (metastatic versus non-metastatic), site (metropolitan versus regional). (c) 6/6 individuals with gastrointestinal cancer had stopped taking enoxaparin at the time of event. (d) 2/2 lung cancer patients were taking enoxaparin at time of event. (e) Two patients had both major and CRNM bleeding events.

eTable 2. Nonbleeding Adverse Events Among Patients Randomized to Enoxaparin

Event	No. (%) Patients
Grade 1-2	**13 (13)**
Bruising	11 (11)
Haematoma	2 (2)
Thrombocytopenia	1 (1)
Grade 3-4	0 (0)