The truth is out there!

Untangling the evidence around the anticancer effects of heparins.

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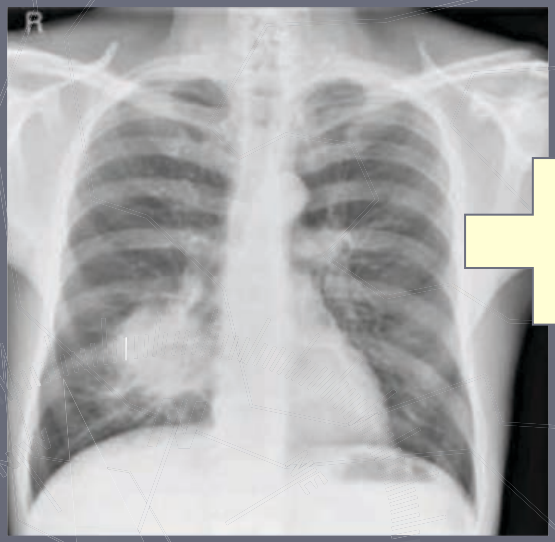
The ultimate quest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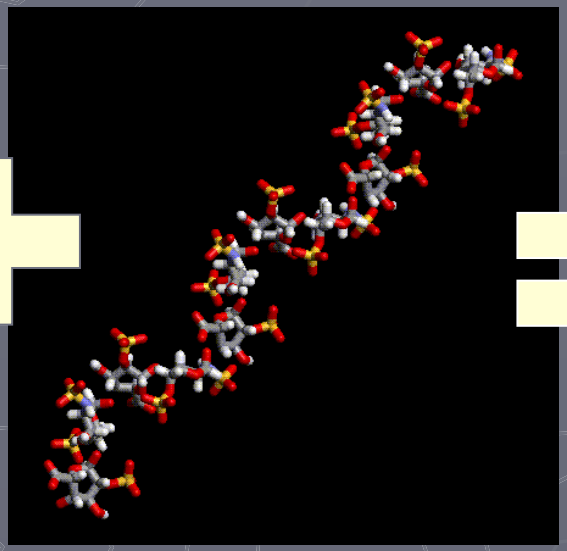

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LeBeau et al 1994

- 277 SCLC randomized to standard care +/- UFH for 5 weeks

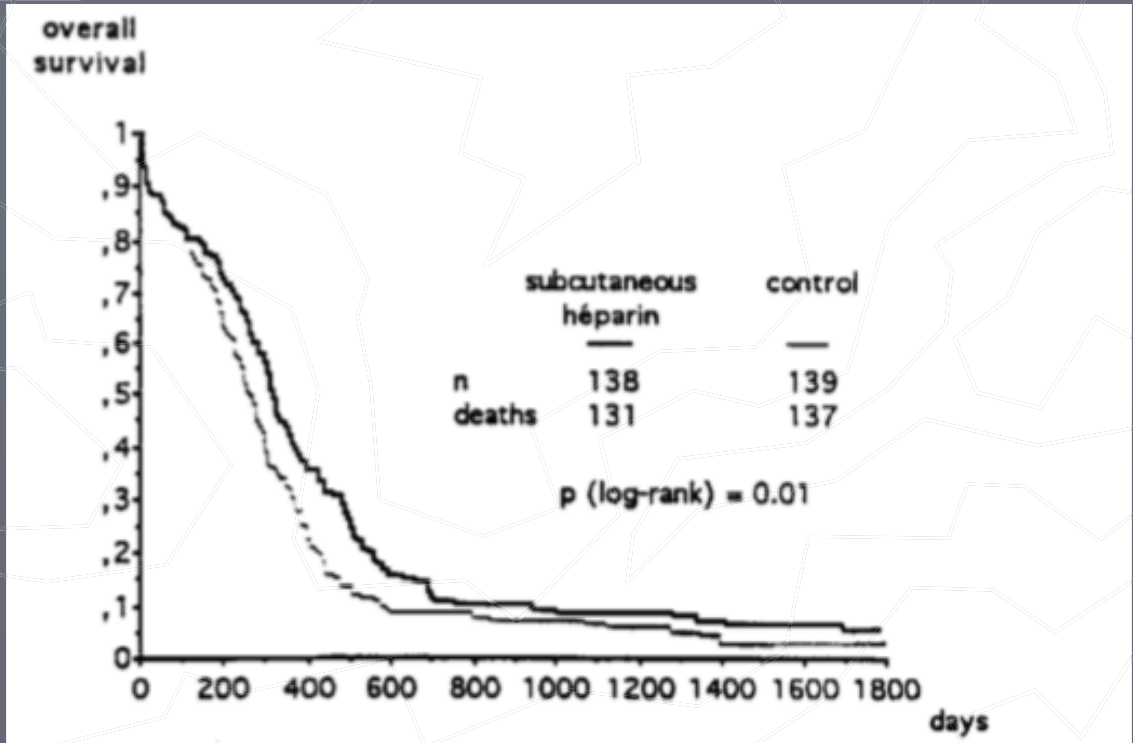


Figure 1. Overall population survival according to the subcutaneous heparin treatment randomization. Group 1 (heparin) is black line and Group 2 (control) is gray line.

Cochrane Review: Akl et al (2007)

'Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation'

- 5 RCTs (LeBeau, Altinbas, Kakkar, Klerk, Sideras)
- 1174 patients
- Conclusions:
  - 'Overall, heparin therapy was associated with a statistically and clinically significant survival benefit (hazard ratio (HR) = 0.77; 95% CI: 0.65 to 0.91).' I^2 =48%
  - 'In subgroup analyses, patients with limited small cell lung cancer experienced a clear survival benefit (HR = 0.56; 95% CI: 0.38 to 0.83).'

Proposed Mechanisms of survival advantage

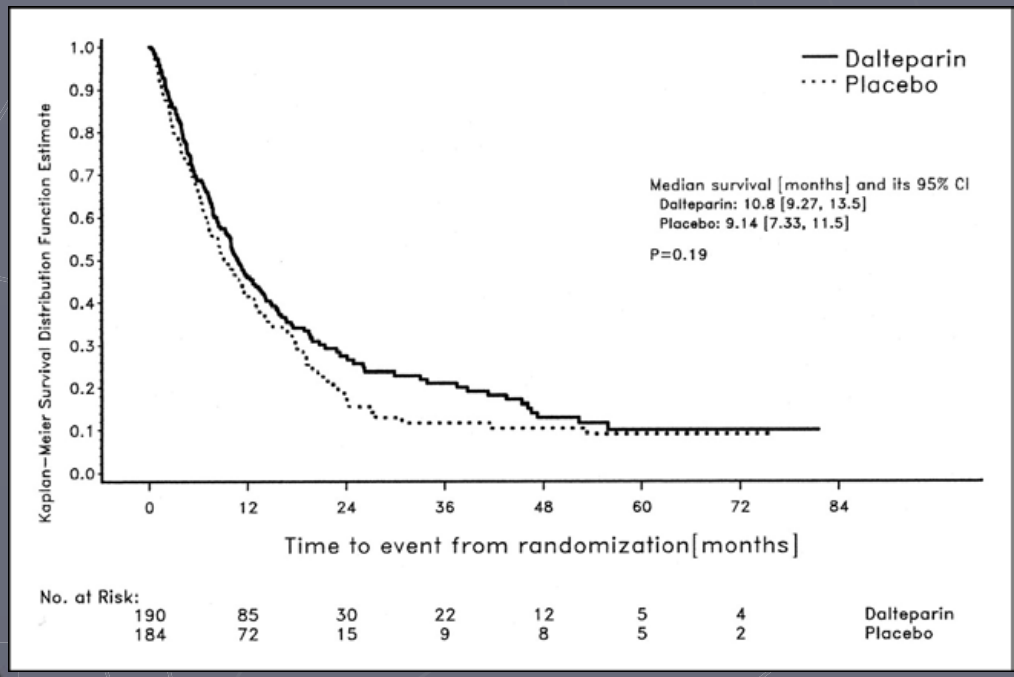
- 1. Anti VTE effects
  - Reduce number of fatal VTEs
- 2. Anticancer effects
  - ↑TFPI
  - ↓Seeding
  - Antiangiogenic
  - Inhibition of soluble P-selectin


You never listen to me, you only hear what you want to hear
Sure, I'll have a beer

FAMOUS

Kakkar et al (2004)

- RCT 382 patients with advanced solid tumours, LMWH vs placebo for 1 year
- In those surviving >17 months significant survival advantage for LMWH (log rank, p=0.03)



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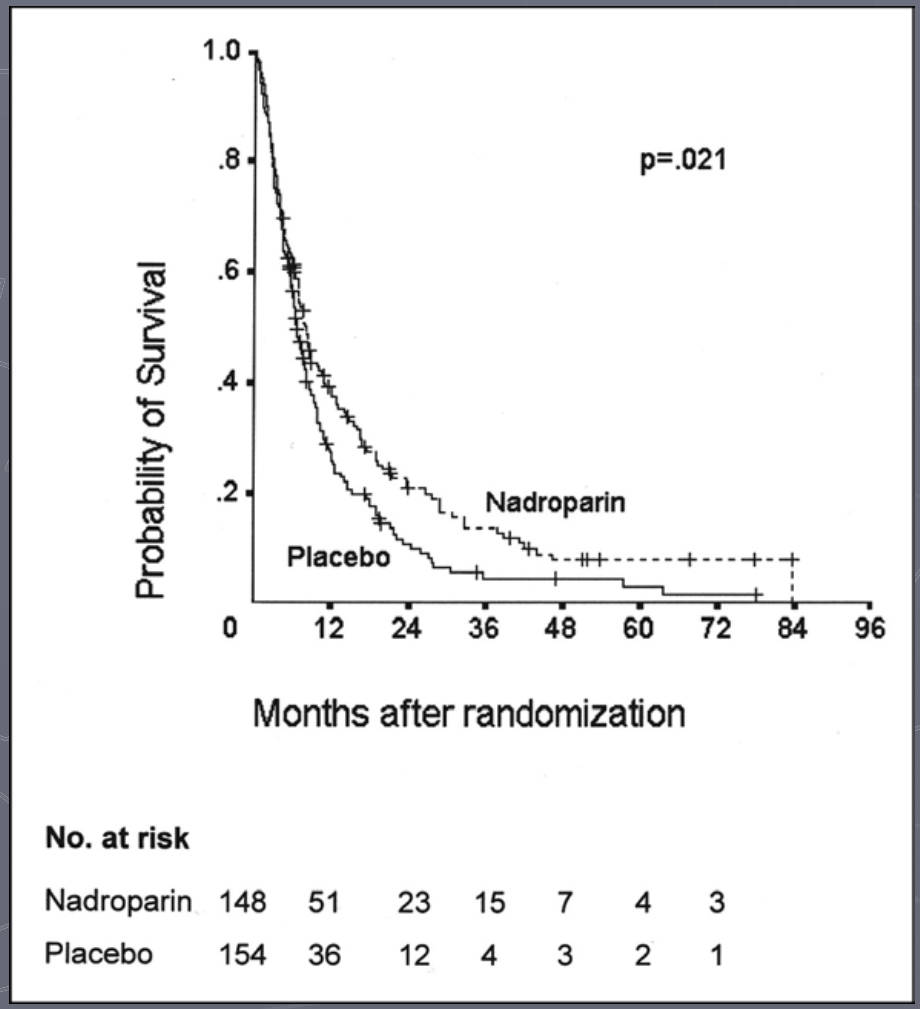
Non stratified

- Pancreas
  - 9.5% in LMWH vs (13% control)
- Breast
  - 21% in LMWH (14% control)
- Stage
  - Stage III 37% in LMWH (28% in control)
- Any point in the disease
- No restriction on treatment

MALT

Klerk et al (2005)

- RCT: 148 pts with advanced solid tumours (11% lung cancer), LMWH for 6w vs. placebo
- Survival by estimated prognosis (> or <6m);
  - 'good prognosis': HR 0.64 (95% CI: 0.45-0.90; p=0.01)
  - 'poor prognosis': HR 0.88 (95% CI; 0.62-1.25)



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- Breast
  - 21% nadroparin vs 12% control
- Are we over interpretating?
  - Can we explain the mechanism?
  - How does 6 weeks of LMWH impact on survival 12 months later?

Altinbas et al JTH 2004 2: 1266- 1271

- Chemo + Fragmin 18 weeks vs Chemo alone for SCLC
- 84 patients
- Flat dose 5000U sc od
- Response 70% Fragmin vs 43% without
- Median survival 13/12 vs 8/12 without

Altinbas et al JTH 2004 2: 1266- 1271

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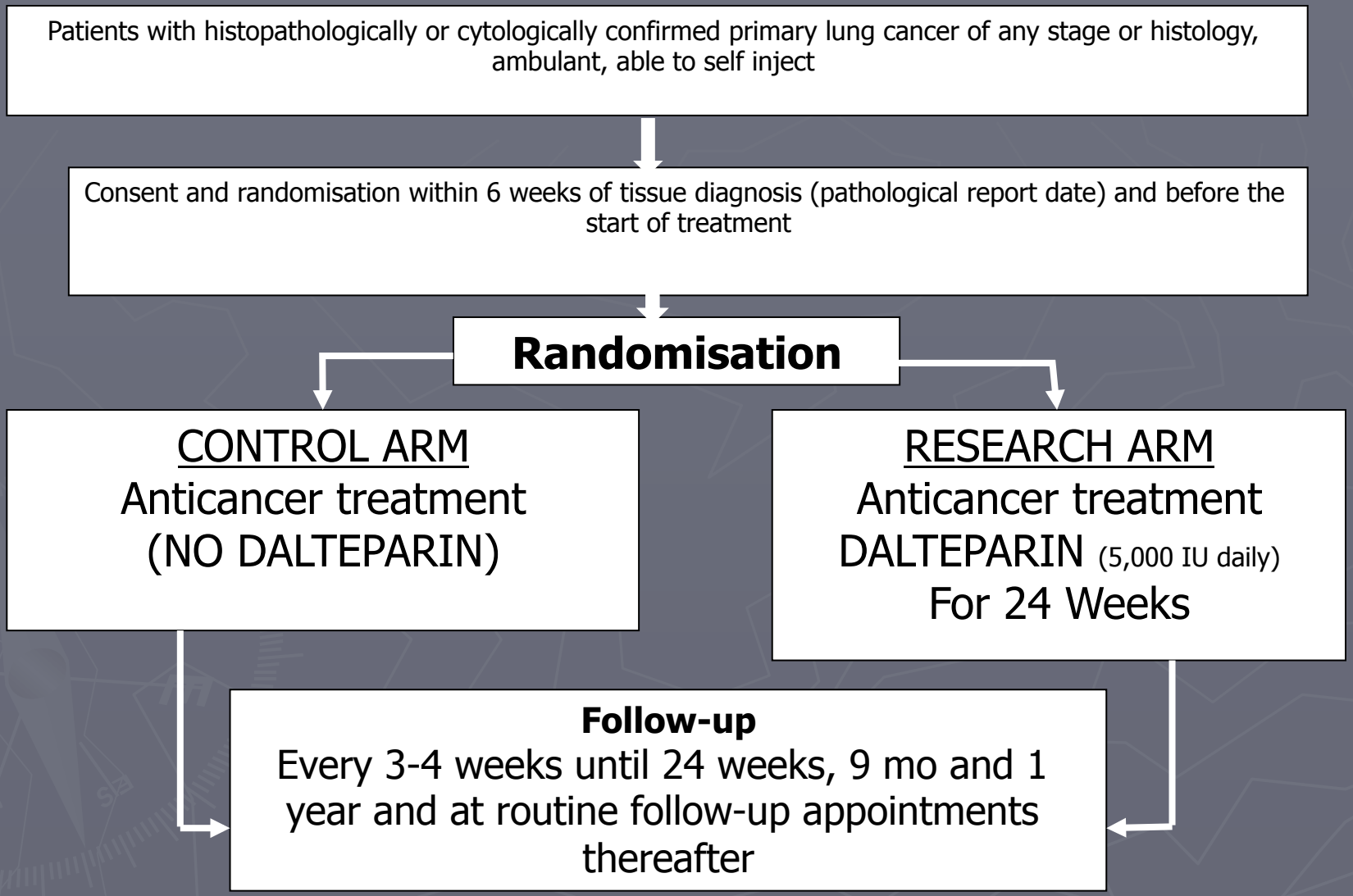
The problem

- Heterogenity
- Post hoc analyses
- Non balanced arms
- Not powered for survival

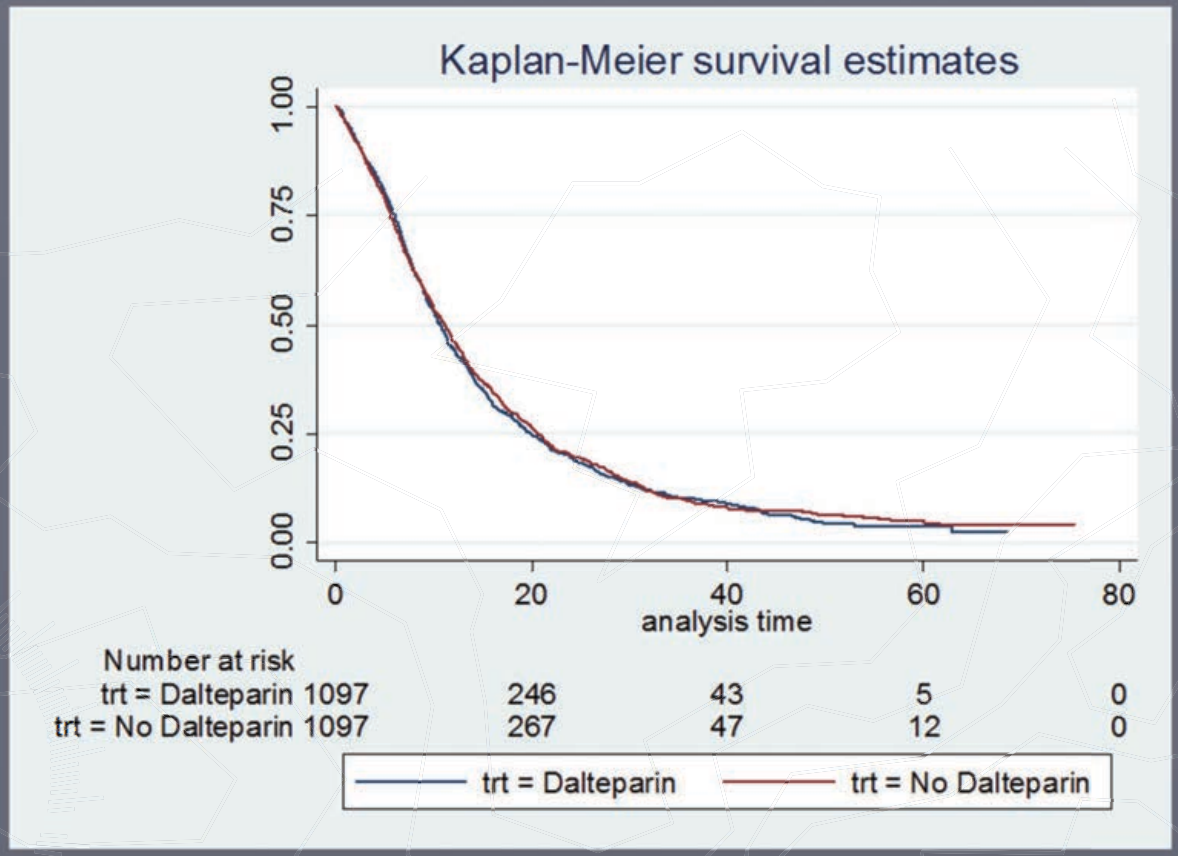
Macbeth F, Noble SIR et al 2016



Demographics

	Dalteparin	No Dalteparin
Number	1102	1100
Male	60.1%	59.6%
Female	39.9%	40.4%
Median Age	65	64
SCLC	17.8%	17.8%
NSCLC	82.2%	82.2%
PS 0-1	85.1%	85.2%
PS 2-3	14.9%	14.8%
SCLC Lim	37.2%	36.7%
SCLC Ext	62.8%	63.3%
NSCLC I-II	4.3%	5.5%
NSCLC III	37.5%	38.5%
NSCLC IV	57.2%	56.0%
CHEMO	89%	92%

Overall Survival

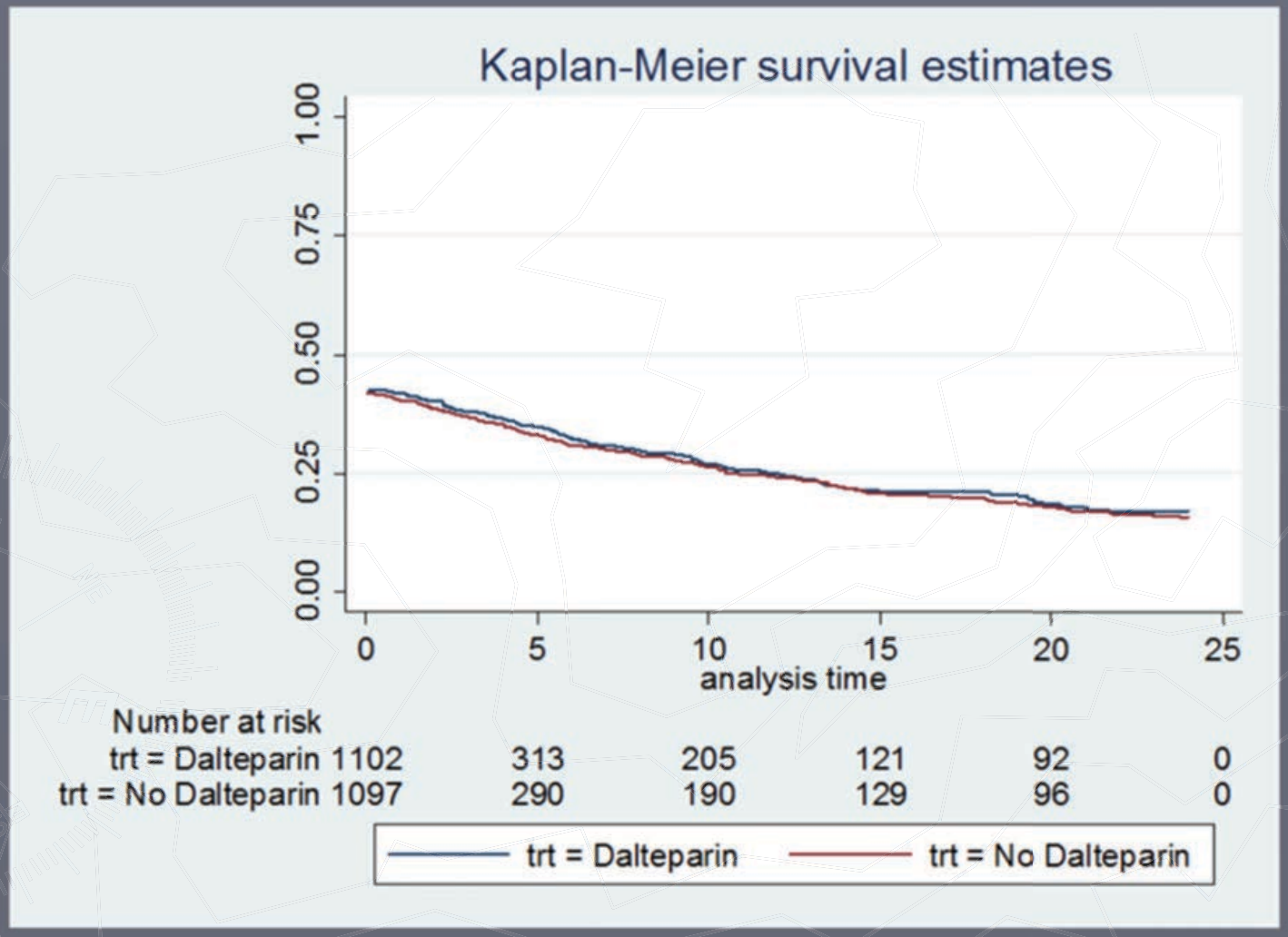


- Hazard ratio 0.98 (95% CI 0.893 to 1.069)
- Median survival: Dalteparin: 10.6 m, No Dalteparin: 11.11 m
- 1 year survival rate: Dalteparin: 44.4%, No Dalteparin: 46.3%

Exploratory Analyses

	HR (95% CI)
NSCLC	0.97 (0.88-1.07)
SCLC	0.92 (0.74-1.14)
Lim SCLC	0.98 (0.67-1.43)
Ext SCLC	0.88 (0.68-1.15)

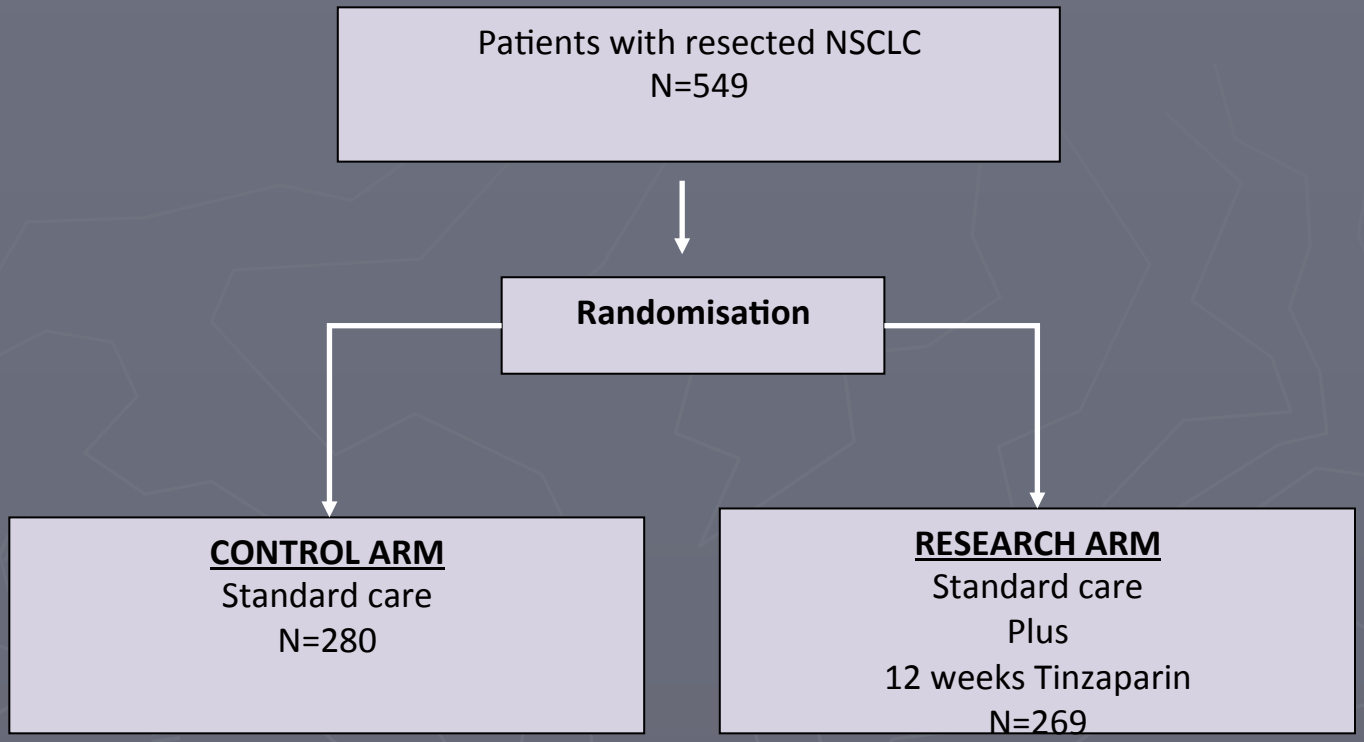
Metastasis Free Survival



What does it tell us?

- Giving Dalteparin 5000IU sc od to all lung cancer patients does not improve overall survival
- However
  - Only 5% NSCLC early stage disease
  - Only one third limited stage SCLC
  - Those most likely to benefit (in theory) to LMWH under represented

Meyer et al 2018



Primary endpoint: overall survival

- Median follow up 5.7 years
- No significant difference in overall survival between groups (hazard ratio (HR) 1.24, 95% CI 0.92-1.68; p=0.17).

So where do we stand

- Compelling preclinical and invitro data
- Suggestions of survival benefit in some clinical studies
- Yet to have conclusive trial data to alter our practice

LeBeau et al 1994

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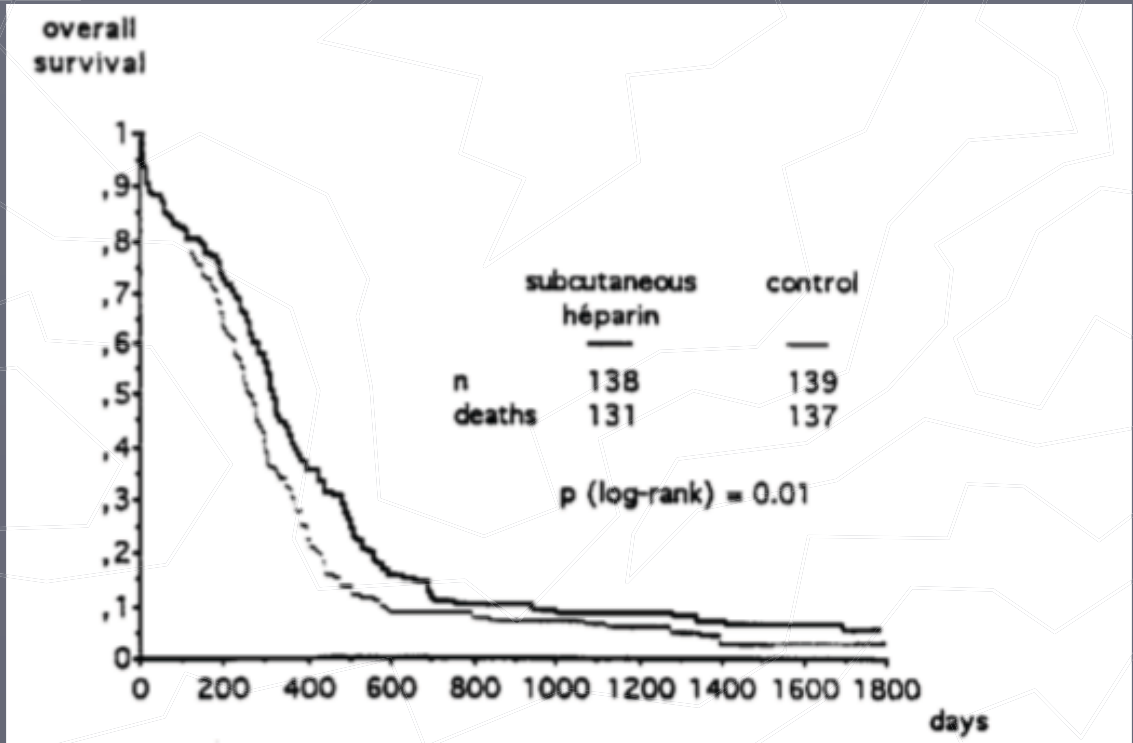

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LeBeau et al 1994

	Group 1 (Heparin)	Group 2 (Control)
No. of patients	138	139
Sex (male)	120 (87%)	132 (95%)
Age		
< 50 yr	21 (15%)	20 (14%)
50–59 yr	49 (36%)	55 (40%)
60–69 yr	49 (36%)	39 (28%)
70–81 yr	19 (14%)	25 (18%)
Karnofsky index		
90–100	51 (37%)	48 (35%)
70–80	61 (44%)	56 (40%)
60	11 (8%)	18 (13%)
≤ 50	15 (11%)	17 (12%)
Initial extent of disease		
Limited disease	64 (46%)	57 (41%)
Extensive disease	74 (54%)	82 (59%)
Chemotherapy		
Sequential	61 (44%)	68 (49%)
Alternating	62 (45%)	58 (42%)
Not randomized	15 (11%)	13 (9%)
Radiation therapy		
Randomized after 8 courses	15 (11%)	9 (6.5%)

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