Heparin induced thrombocytopoenia in dialysis patients

Indranil Dasgupta
Consultant Nephrologist, Birmingham Heartlands Hospital
Honorary Senior Lecturer, School Clinical and Experimental Medicine, University of Birmingham

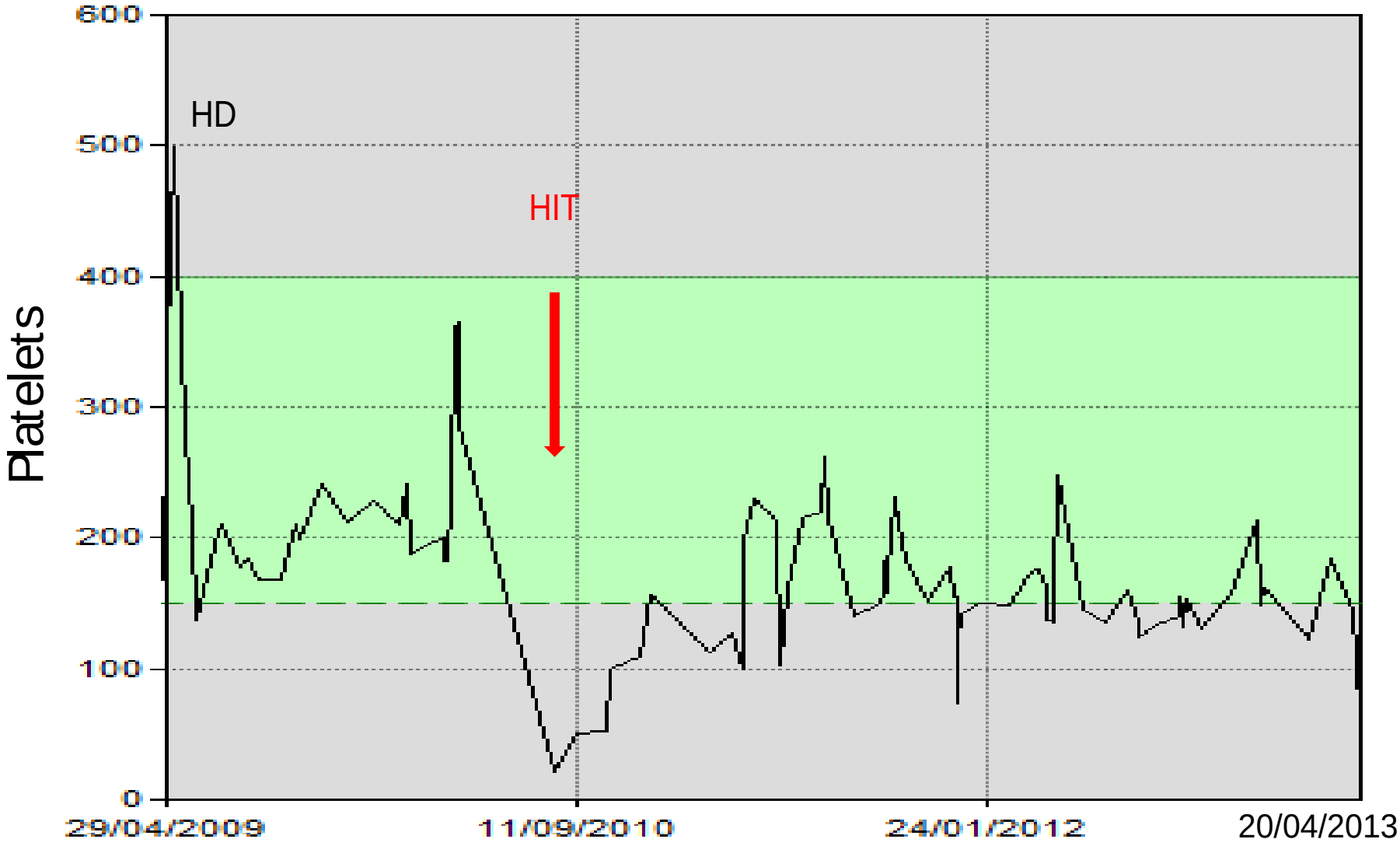
What this presentation covers

- Case histories
- Brief review of world literature
- Unusual features of HIT in dialysis patients
- UK national survey
- The possible reasons for the difference
- Therapeutic options

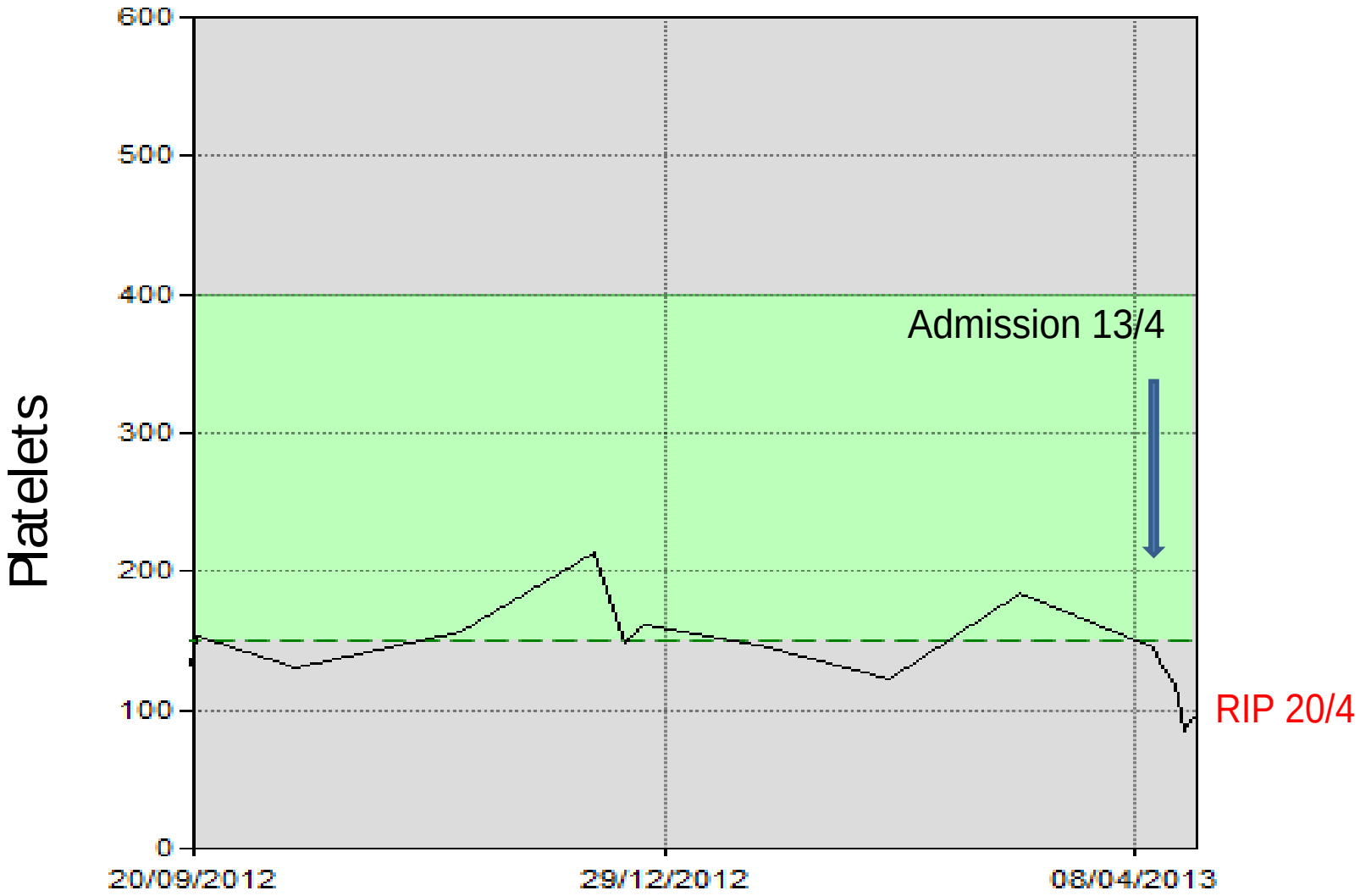
What this presentation does not cover

- General features of HIT
- Pathophysiology of HIT
- Diagnosis of HIT

67 year SA lady, T2D, AKI on CKD started HD 24.04.09

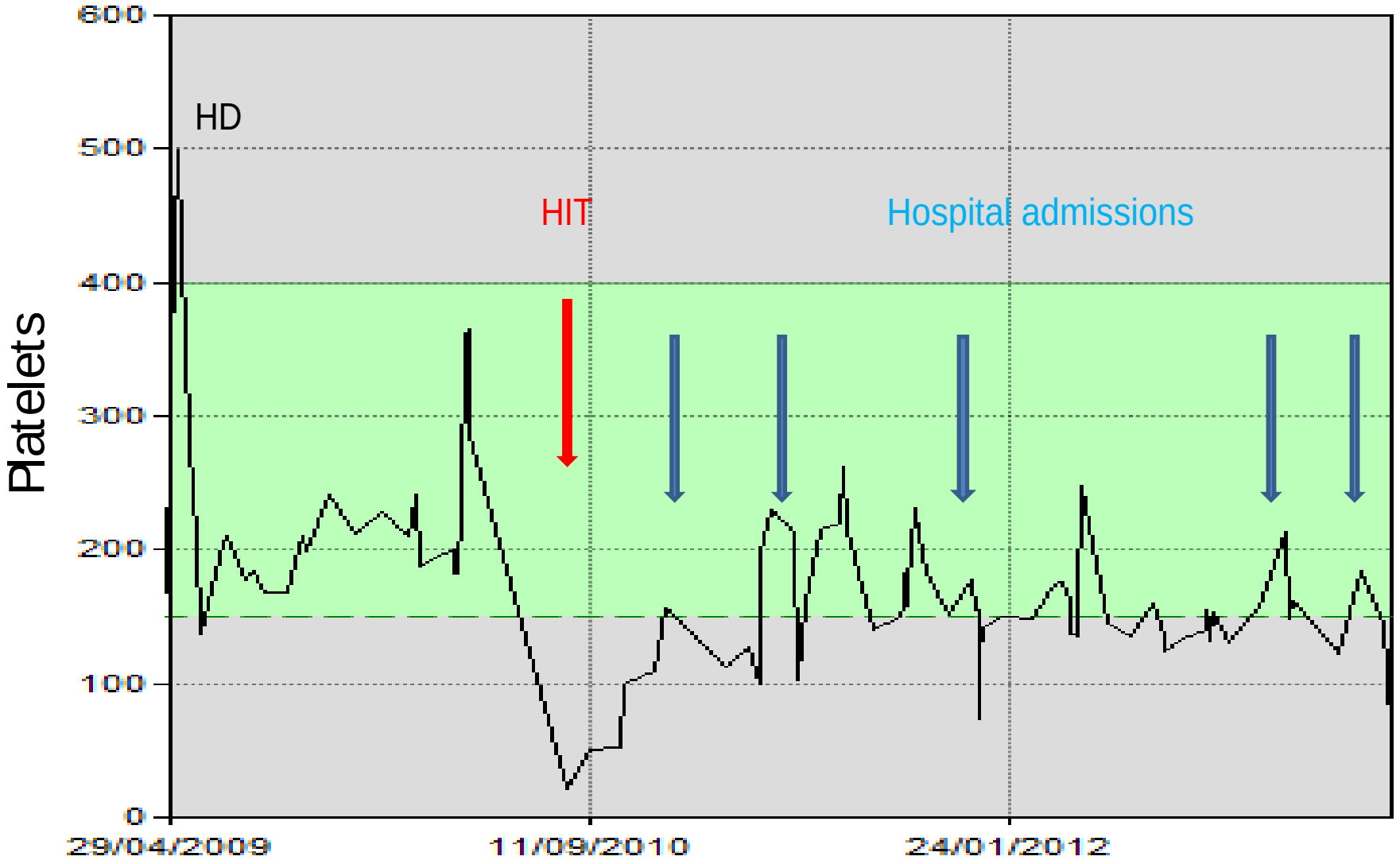


Unfractionated heparin <----------Tinzaparin ---------->



- Admitted with pneumonia 13/04
- Received UFH for VTE prophylaxis
- Sudden death 20/4

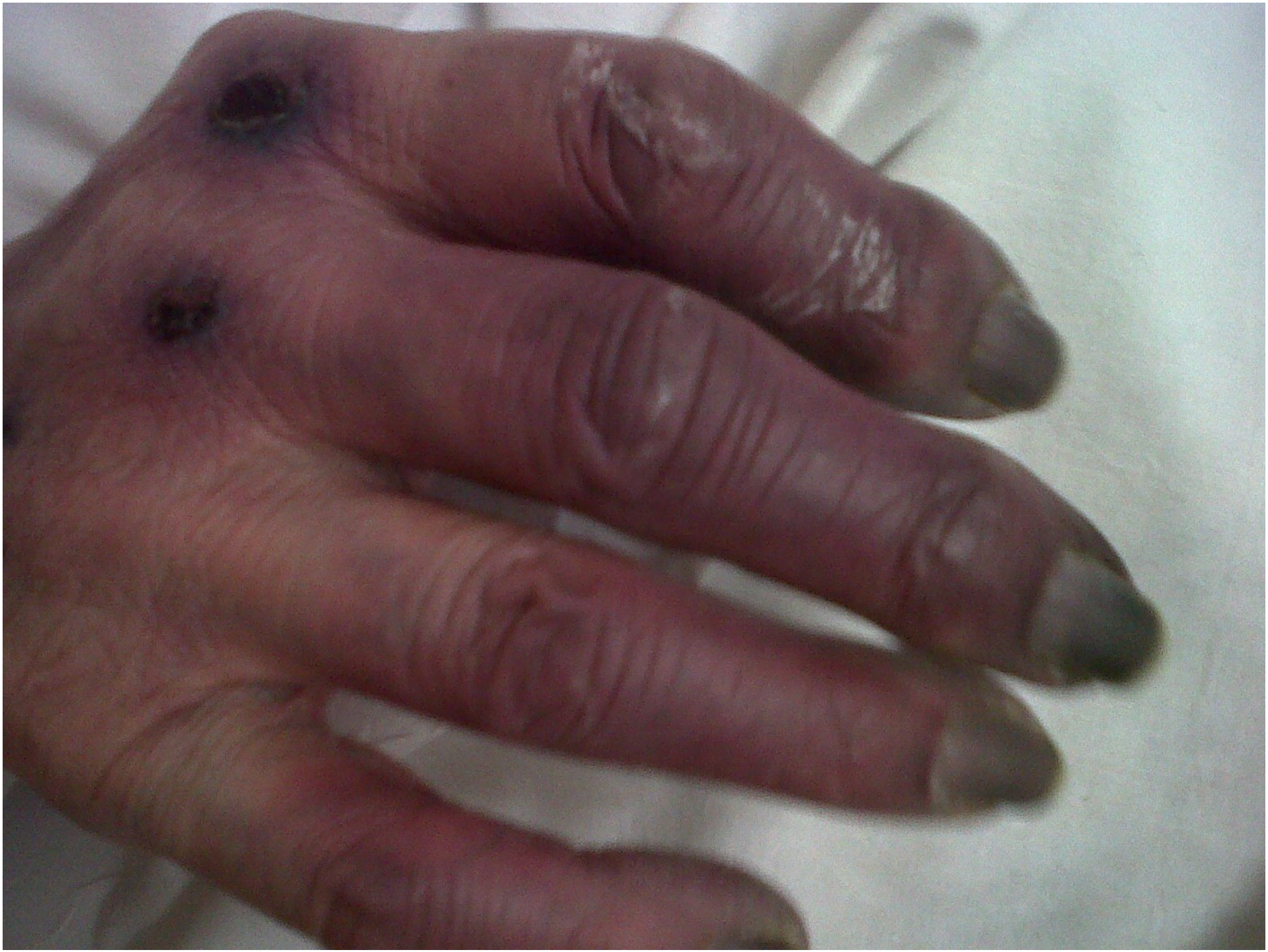
67 year SA lady, T2D, AKI on CKD started HD 24.04.09

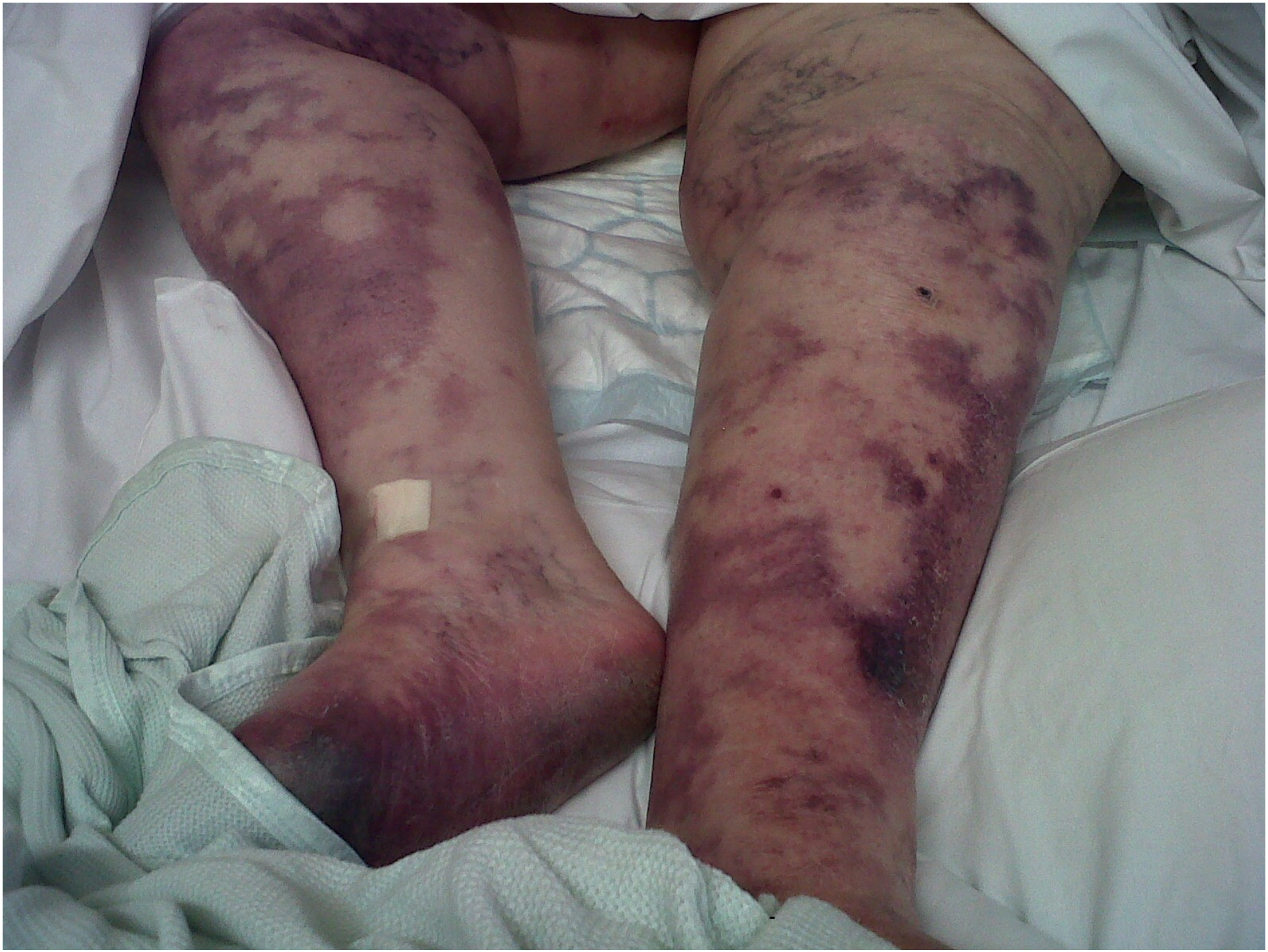


Admitted with pneumonia on 13.04.13, Sudden death 20.04.13

Case 2

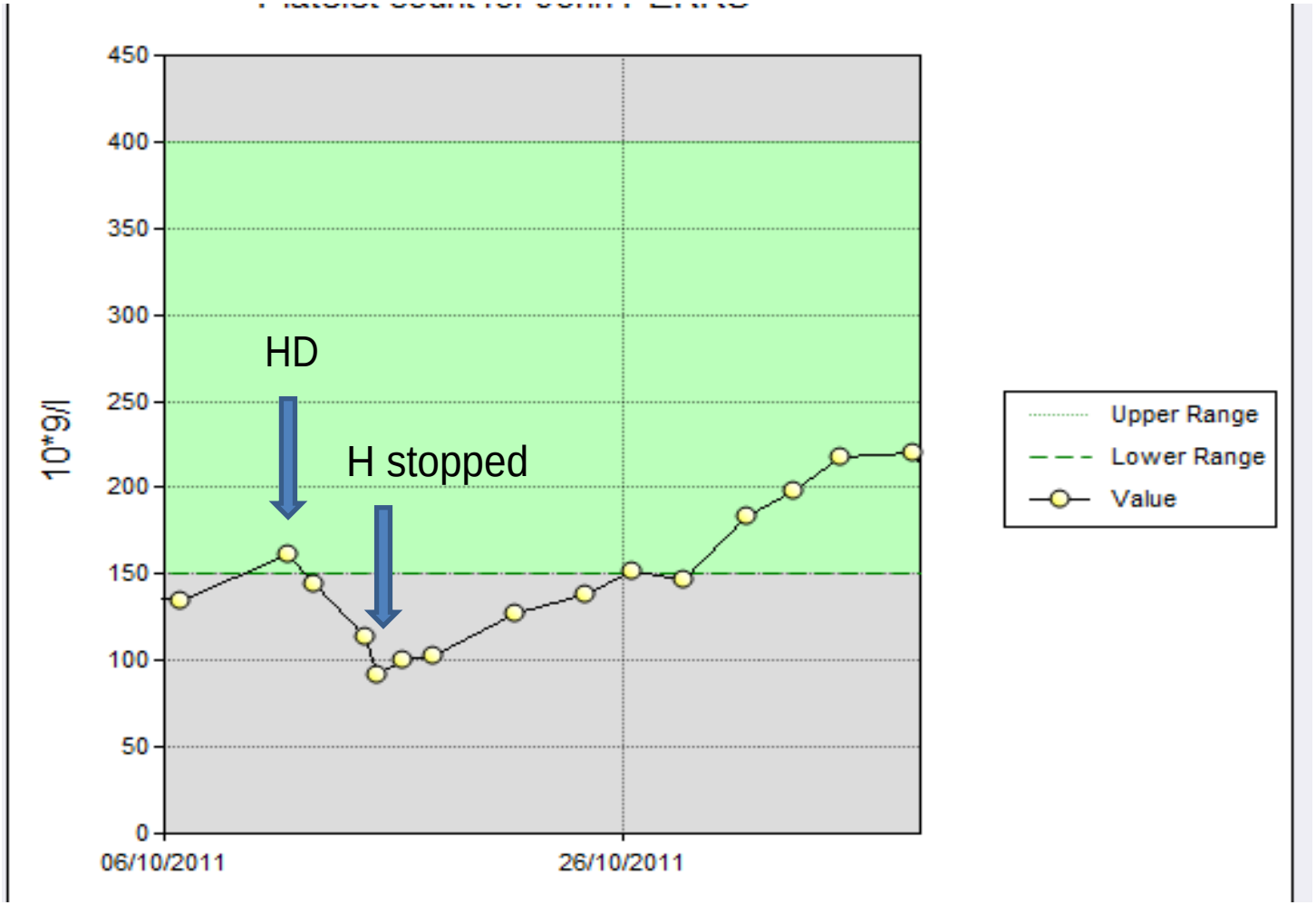
- 76 year old Caucasian lady
- Had been on haemodialysis for >5 years
- Receiving unfractionated heparin
- Platelets 150 to 200 through out
- Admitted with severe chest infection requiring prolonged admission
- Was put on unfractionated heparin for VTE prophylaxis
- Platelets dropped to 20
- HIT confirmed by ELISA





66 year man, endovascular repair of AAA, AKI needing dialysis

Platelet count

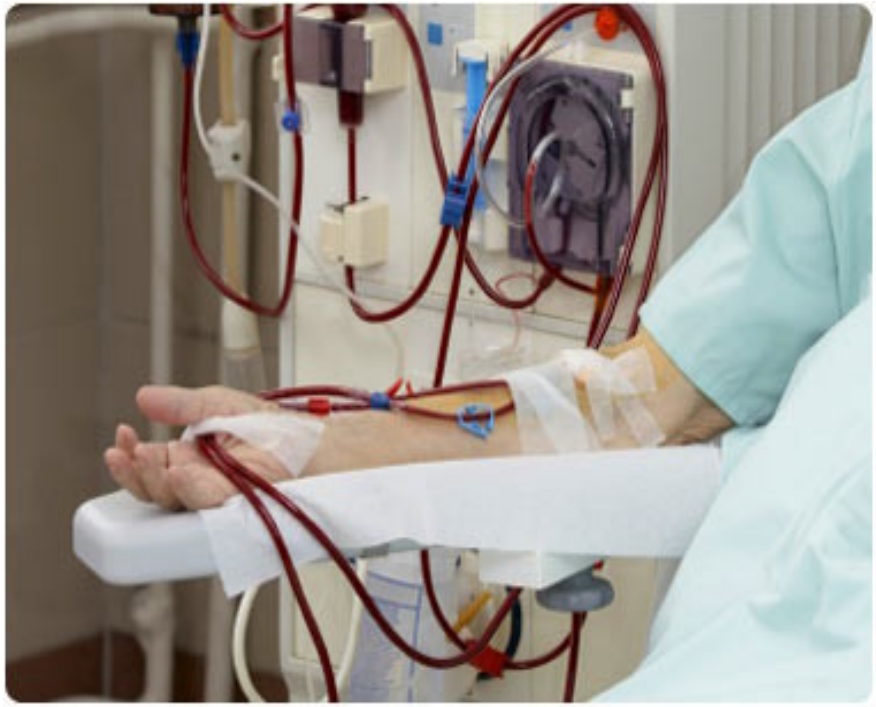


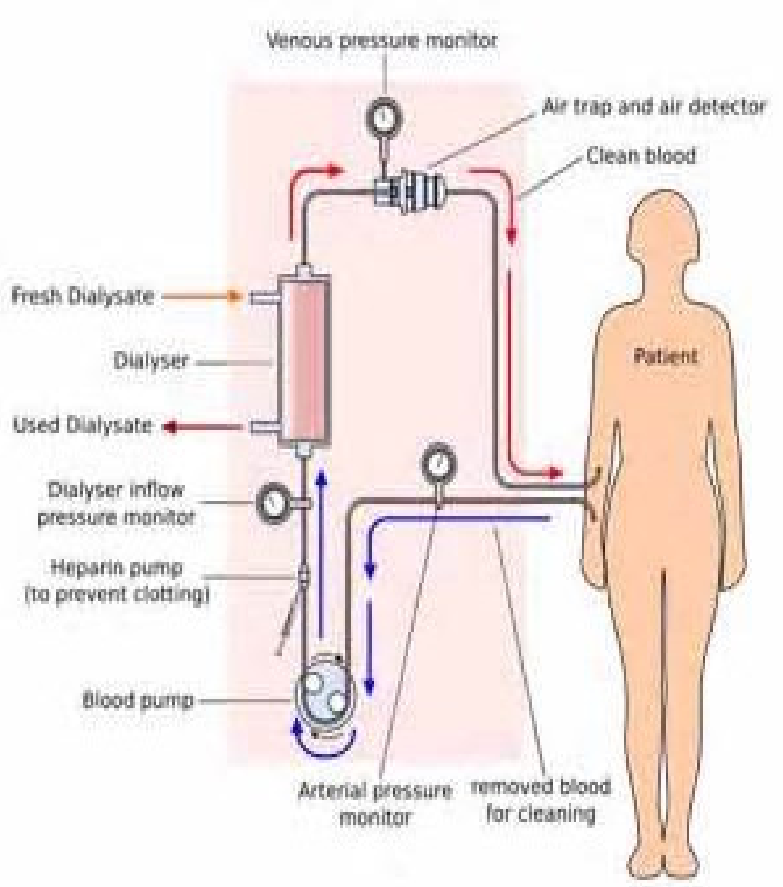
HIT antibody in HD patients

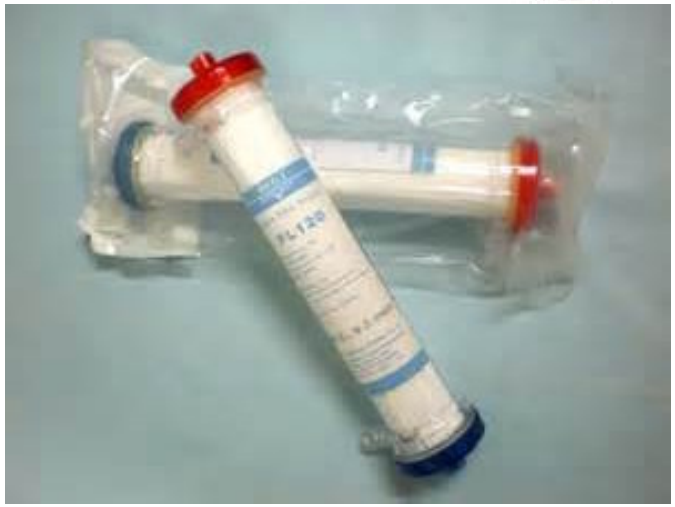
- PF4-Heparin complex
- HIT antibodies are present in 0 to 17.4% patients on HD (15 studies, n = 3818)
- In those reported type of heparin used
  - 8.1% with UFH by ELISA, n = 1450
  - 1.8% with LMWH, n = 218
  - 3.7% by functional assays, n= 730
- Prevalence of clinical HIT is much lower

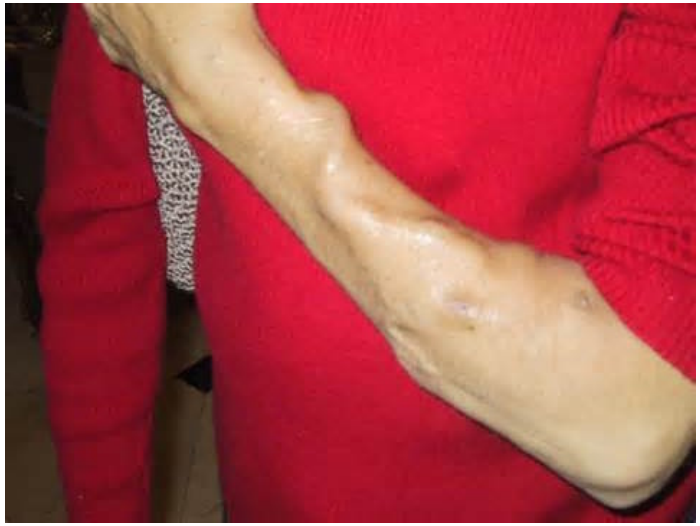
Clinical manifestations

- Thrombocytopoenia – rarely <100
- Arterial or venous thrombosis distinctly rare
- Clots in the dialyser
- Clotting of dialysis circuit
- Failure of AV fistula
- All cross-sectional or short follow up
- Prevalent patients




Venous pressure monitor
Air trap and air detector
Clean blood
Fresh Dialysate
Dialyser
Used Dialysate
Patient
Dialyser inflow pressure monitor
Heparin pump (to prevent clotting)
Blood pump
Arterial pressure monitor
removed blood for cleaning





HIT and clot in extracorporeal circuit

- One study – 154 patients starting HD
- Suspicion of HIT if clotting of circuit, increase circuit pressure, clot in drip chamber, clotted dialyser fibres and acute drop in platelet count of >20%
- 6 patients had clot in the circuit – all had low platelet count
- 5 positive ELISA for IgG antibody, 4 positive functional assay
- Heparin stopped, argatroban started
- All safely continued HD
- 2 other studies associated clot in circuit with HIT but very few had positive antibody
- Unclear whether EC clot is a manifestation of HIT in HD

Yamamoto et al,Am J Kidney Dis 1996

Clotting of filter in CVVH

- Continuous veno-venous haemofiltraion is treatment of AKI in ICU setting
- Repeated clotting of filter (≥ 2 episodes) within 24 to 48 hours with no obvious cause
- 28 out of 87 patients over 2 years – only 8 had positive HIT antibodies
- No difference in platelet counts
- Those with positive antibody – shorter duration of CVVH and lower clearance

Lasocki et al. Crit Care 2008

Increased mortality in hemodialysis patients having specific antibodies to the platelet factor 4-heparin complex

M Carrier, M A Rodger, D Fergusson, S Doucette, M J Kovacs, J Moore, J G Kelton and G A Knoll

Table 2. Cox regression analysis examining the risk of death associated with PF4-H antibodies

Previous table | Figure and tables index

Model	Hazard ratio	95% Confidence interval	*P*-value
Nonspecific PF4-H antibodies			
Univariate	0.87	0.50–1.52	0.64
Multivariate[a]	0.65	0.36–1.15	0.14
IgG-specific PF4-H antibodies			
Univariate	2.40	0.98–5.89	0.06
Multivariate[a]	2.68	1.08–6.63	0.03
IgG-specific PF4-H antibodies and indeterminate serotonin release assay			
Univariate	3.61	1.14–11.43	0.02
Multivariate[a]	6.32	1.68–23.7	0.01

IgG, immunoglobulin G; PF4-H, platelet factor 4-heparin.

No significant association with major CV events

Asymptomatic patients on HD, n = 419,
Tested by IgG PF4-H antibody and platelet serotonin release assay
Prospectively followed up, median 2.5 years

Kidney International 2008

Heparin-induced antibodies and cardiovascular risk in patients on dialysis (CHOICE Study cohort, n = 740, FU ≈ 3 years)

Table 3: Adjusted risk of adverse events by the presence of HIA at baseline.

	Hazard ratio	95% CI	No. of events
Arterial cardiovascular events*	0.98	0.70 – 1.37	372
Venous thromboembolism	1.39	0.17 – 11.5	7
Vascular access occlusion	0.82	0.40 – 1.71	86
Mortality†	1.18	0.85 – 1.64	448

CI: confidence interval; *adjusted for age, sex, race, dialysis modality, and smoking status; †adjusted for age, race, albumin and comorbidity score (ICED).

Asmis et al, Thromb. Haemost. 2008

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doi:10.1093/ndt/gfm055
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Original Article

NDT
Nephrology Dialysis Transplantation

National survey of heparin-induced thrombocytopenia in the haemodialysis population of the UK population

Colin A. Hutchison[1,2] and Indranil Dasgupta[1]

[1]Birmingham Heartlands Hospital, Heart of England NHS Foundation Trust, Birmingham, Warwickshire, UK and [2]Division of Medical Sciences, University of Birmingham, Birmingham, UK

National survey of heparin-induced thrombocytopenia in the haemodialysis population of the UK population

Table 1.
Demographics for UK renal units, the study population and haemodialysis patients with HIT type II

	UK renal units*	Responding renal units*	Patients with HIT type II (*n* = 28)
HD population	14041	10564	–
Age	56.4	58.1	62.4
Ethnicity			
Caucasian	84[a]	N/A	92
Indo-Asian	9[a]	N/A	4
Afro-Caribbean	4[a]	N/A	4
Others	3[a]	N/A	–

*Details were taken from the UK Renal Registry 2005 report [9].

[a]A poor return of ethnicity details, from UK renal units limits these results to only approximate percentages.

N/A, not available.

52% female

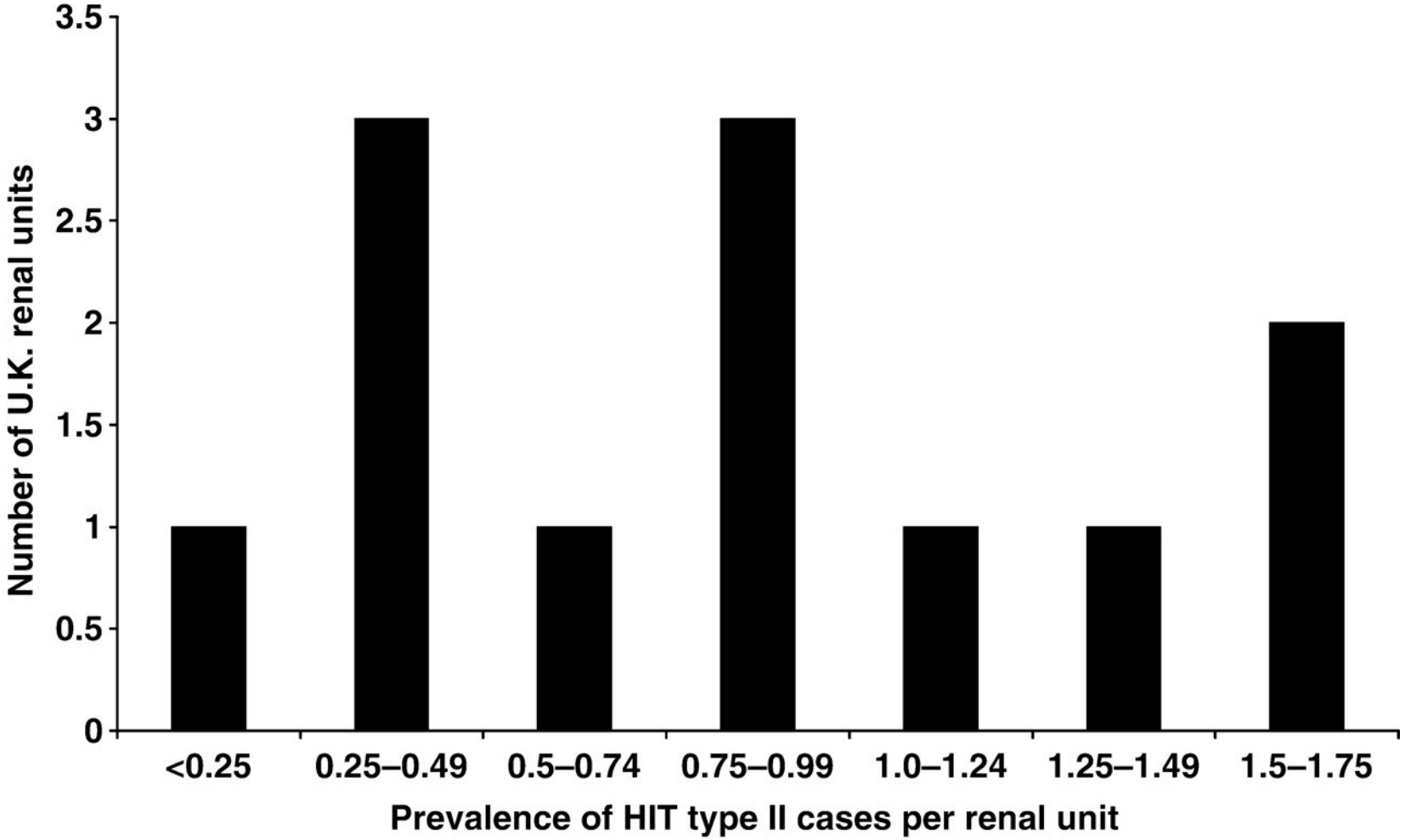
Hutchison C A , and Dasgupta I Nephrol. Dial. Transplant. 2007;22:1680-1684

NDT Nephrology Dialysis Transplantation

Main results

- Of the 81 renal units 50 responded
- Base population 13682 (77% HD)
- Prevalent cases 28 – 0.26 per 100 HD patients
- Incident cases 17 – 0.32 per 100 HD patients
- All confirmed by antibody assay
- 14 out of 50 units had HIT - ? Clustering
- Prevalence 0.22 – 1.74/ 100, incidence 0.58 – 4.3/ 100 HD patients

The number of renal units with different prevalence rates of HIT type II in their haemodialysis populations, for the 14 UK renal units with cases.



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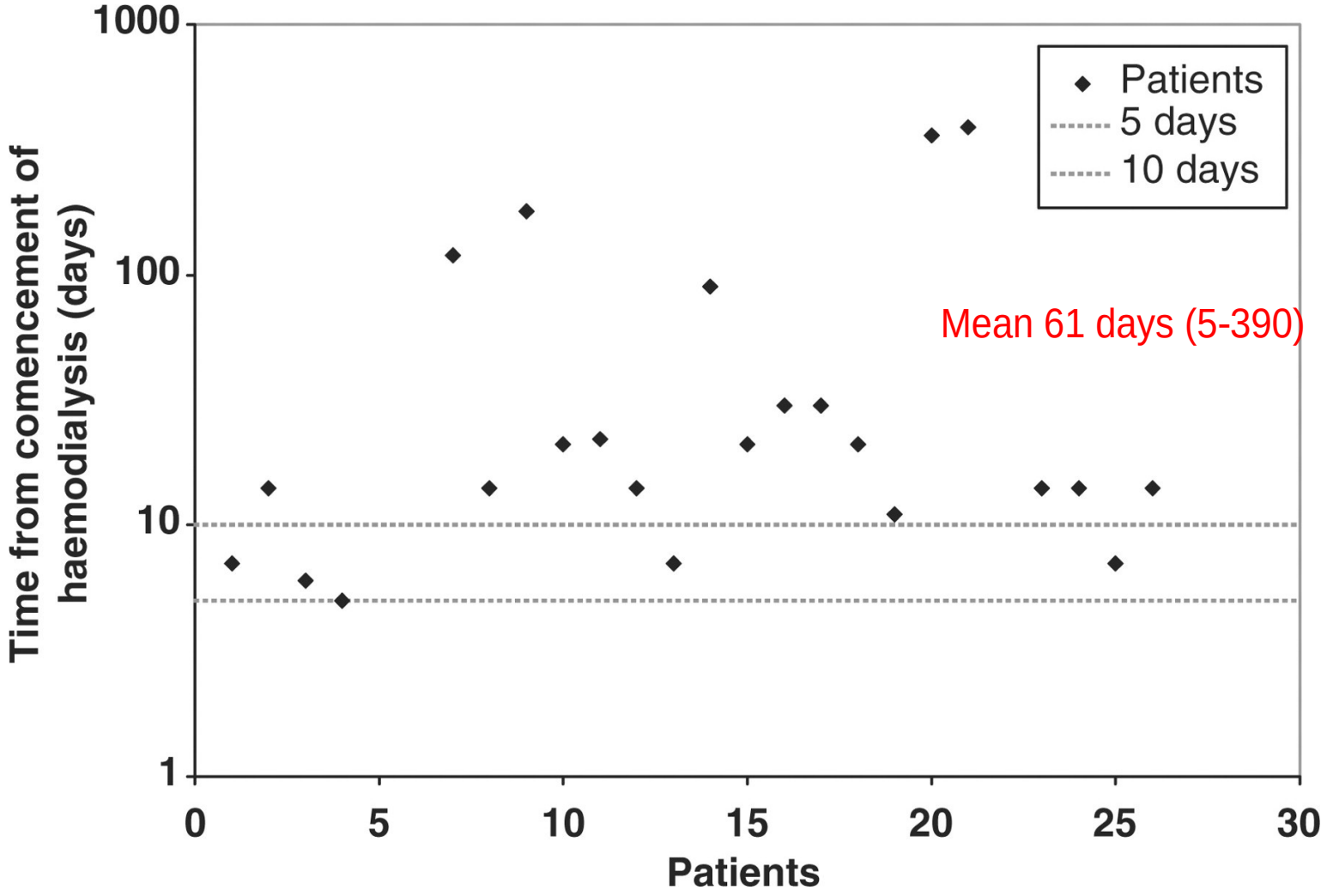
Time from commencement of haemodialysis to diagnosis of HIT type II. Dotted lines represent normal window of presentation of HIT type II of 5–10 days.



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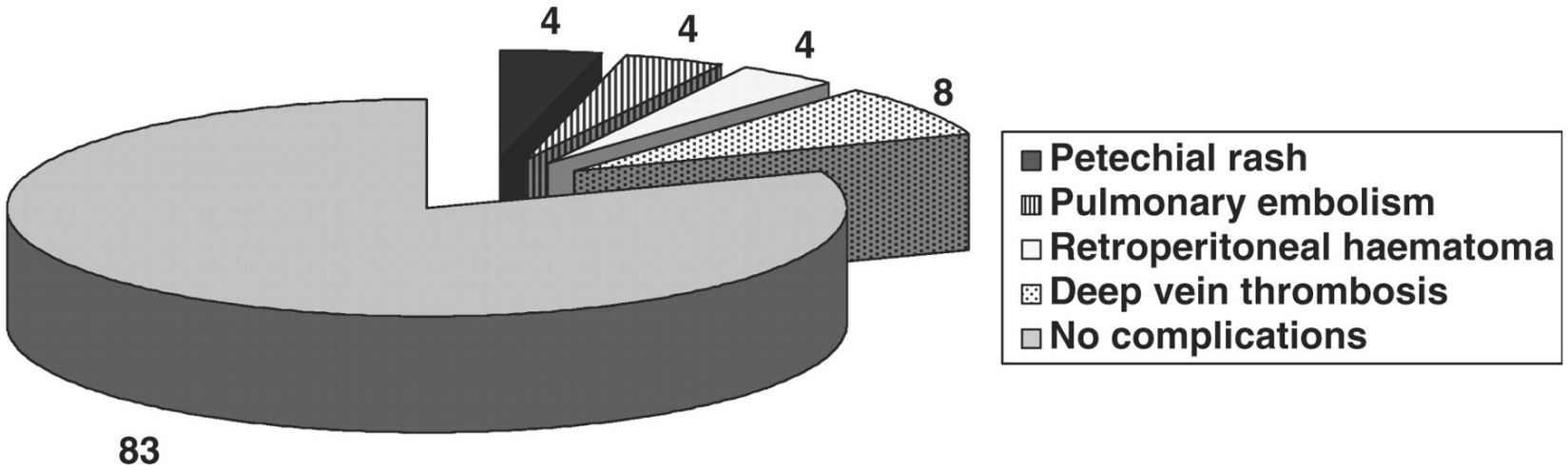
Complications of HIT type II syndrome in haemodialysis patients.



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Anticoagulation used

- 36% used danaparoid
- 12% warfarin
- 12% hirudin
- 8% lepirudin
- 4% tinzaparin
- 12% saline flush
- 16% changed to peritoneal dialysis

- >1/3 units did not have a policy – sought haematology advice

Unusual features of HIT in HD patients

- Incidence is much lower than medical patients
- Milder – thrombotic complications rare
- Less drop in platelet count – rarely <100
- Takes longer to develop – 80% beyond the classical time frame, 20% beyond 90 days of exposure

- Possible explanations:
  - smaller dose of heparin used (5000 U/ HD)
  - intermittent use allowing platelets to recover
  - ?

Treatment options

- Traditionally UFH used for HD – 2000 u bolus followed by 1000 u/h infusion
- More recently, LMWH is being used in the UK

- Stop heparin including for flushing and locking
- Alternative anticoagulation for HD

Alternative anticoagulation for HD

- Danaparoid – indirect inhibitor Xa and lesser thrombin inhibition – easy to use in HD – initial anti-Xa monitoring –but is expensive (£2.5K a year)
- Argatroban – direct thrombin inhibitor – hepatic metabolism, no dose adjustment is required in ESRF – starting dose 2 mcg/kg/min infusion – APTT 1.5-3.0
- Fondaparinux – pentasaccharide, Xa inhibitor although not licensed for HIT – good renal data – easy to use – single dose at the beginning of HD, no monitoring required – popular in the UK currently

Summary

- Although prevalence of HIT antibody positivity is high among HD patients – clinical HIT is rare
- May be rarer in future as LMWH is being used
- Commonest manifestation is mild thrombocytopoenia
- Unusual features – late onset, rare thrombotic complications - ? because small dose & intermittent heparin
- HIT has been implicated in clotting of extracorporeal circuit and AV fistula – but jury is out
- Some studies suggest increased mortality associated with positive PF4-H antibody – need more research
- Danaparoid, Argatroban and Fondaparinux used in the UK – fondaparinux preferred for ease of use and cost

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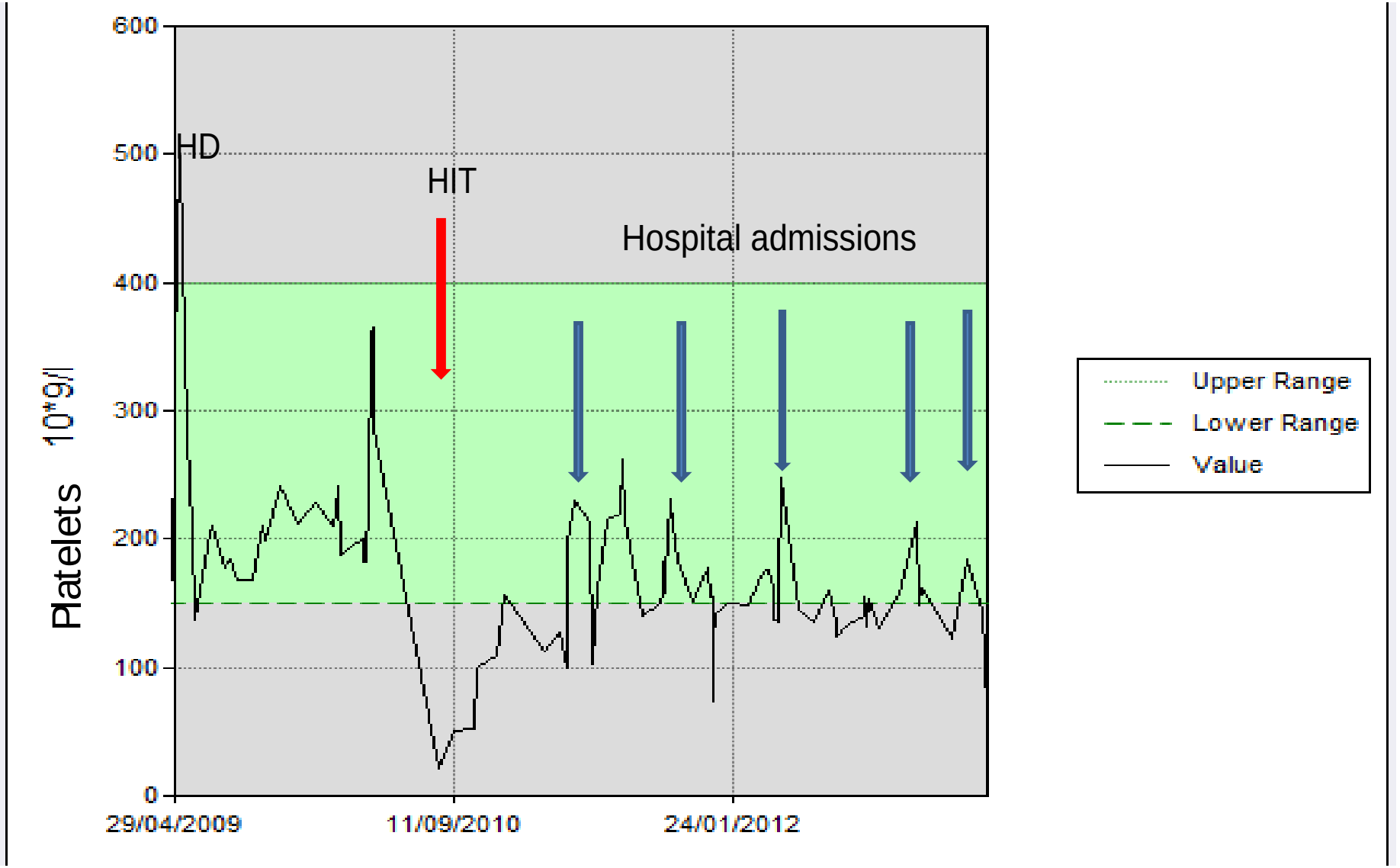

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