Parc Sanitari Sant Joan de Déu

HEPARINAS DE BAJO PESO MOLECULAR EN EL TRATAMIENTO A LARGO PLAZO EN PACIENTES CON CÁNCER

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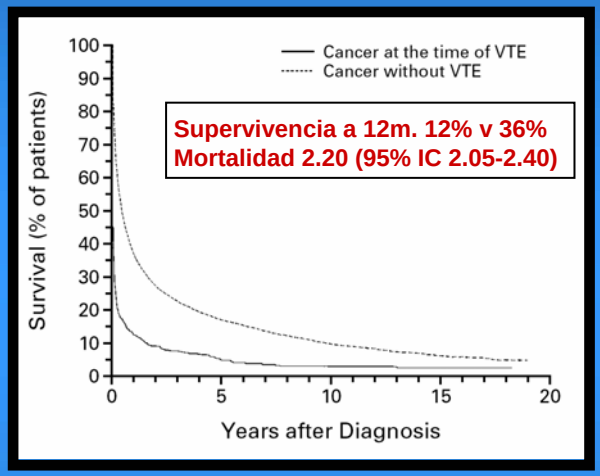
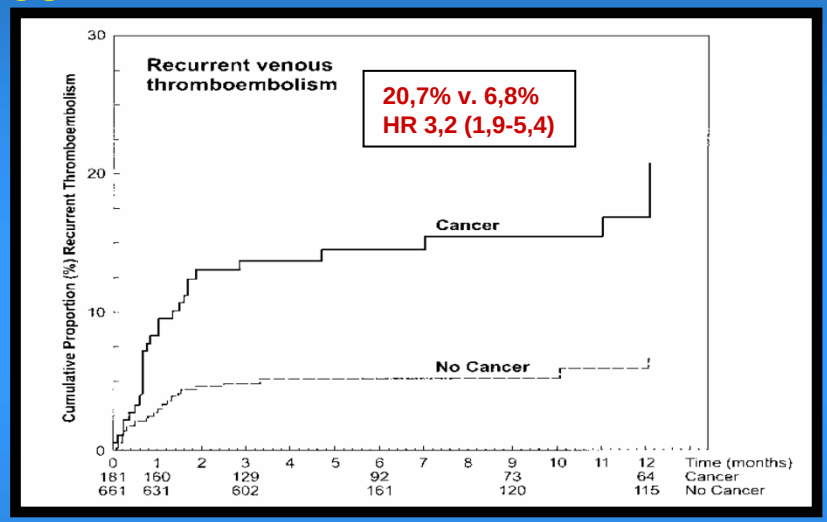
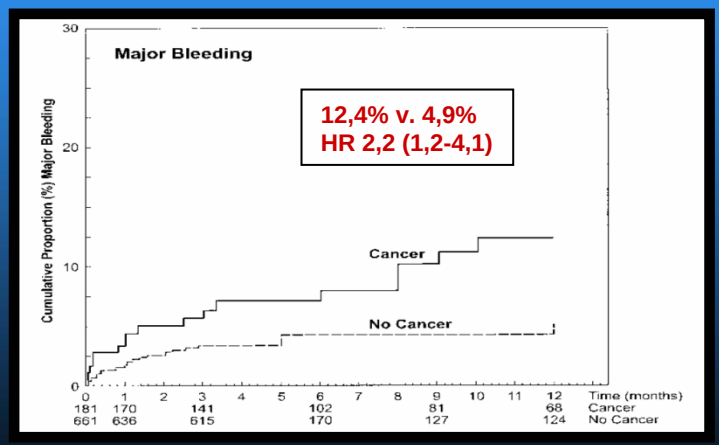
Introducción

- Los paciente con ETEV y cáncer se mueren más, recurren más y sangran más que los no oncológicos







Prandoni. Blood 2002; 100: 3484-8

Sorensen HT. NEJM 2000; 343: 1846-50.

Introducción

- 10-20% con ETEV idiopática desarrollan cáncer en los 3 próximos años
- Riesgo aumentado por las terapias del cáncer
- Riesgo aumentado en las cirugías del cáncer
- Metástasis: predictoras de mayor mortalidad entre los que padecen ETEV
- AVK x 2-4 veces riesgo de recurrencias y sangrados mayores

Lyman. Cancer 2011

Factores de riesgo de ETEV en pacientes oncológicos

- > 65 años
- ETEV previa
- Obesidad
- Infección
- Insuficiencia renal
- Cirugía mayor pélvica o abdominal
- Hospitalización
- > 350000 plaquetas previa a la quimioterapia
- Trombofilia
- Aparición de entre 3-6 meses tras el diagnóstico del cáncer

- Localización tumor primario
  - Adenocarcinoma, pulmón y gástrico
- Más riesgo si metástasis que local
- Quimioterapia activa
- Tratamietno hormonal activo (tamoxifeno)
- Talidomida, lenalidomida, bevacizumab
- Estimulantes de la eritropoyesis
- Cateter venoso central

Lyman et al. J Clin Oncol 2007

8th ACCP
Tromboprofilaxis en cáncer

- *7.0 Cancer Patients*
  - **7.0.1. For cancer patients undergoing surgical procedures, we recommend routine thromboprophylaxis that is appropriate for the type of surgery** (Grade 1A)**. Refer to the recommendations in the relevant surgical subsections.**
  - **7.0.2. For cancer patients who are bedridden with an acute medical illness, we recommend routine thromboprophylaxis as for other high risk medical patients** (Grade 1A)**. Refer to the recommendations in Section 6.0.**
  - **7.0.3. For cancer patients with indwelling central venous catheters, we recommend that clinicians not use either prophylactic doses of LMWH** (Grade 1B)**. or minidose warfarin** (Grade1B) **to try to prevent catheter-related thrombosis**
  - **7.0.4. For cancer patients receiving chemotherapy or hormonal therapy, we recommend against the routine use of thromboprophylaxis for the primary prevention of VTE** (Grade 1C)**.**
  - **7.0.5. For cancer patients, we recommend against the routine use of primary thromboprophylaxis to try to improve survival** (Grade 1B)**.**

8th ACCP
Tratamiento y duración

- *1.4 LMWH for the Initial Treatment of DVT / PE*
  - **1.4.1. In patients with acute DVT, we recommend initial treatment with LMWH SC once or twice daily, as an outpatient if possible** (Grade1C), **or as an inpatient if necessary** (Grade 1A), **rather than treatment with IV UFH.**
  - **1.4.2. In patients with acute DVT treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements** (Grade 1A).
  - **1.4.3. In patients with acute DVT and severe renal failure, we suggest UFH over LMWH** (Grade 2C).

La ACCP aconseja el tratamiento inicial con HBPM y la profilaxis secundaria con AVK el tiempo que requiera

- *2.1 Duration of Anticoagulant Therapy*
  - **2.1.1. For patients with DVT secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods** (Grade 1A).
  - **2.1.2. For patients with unprovoked DVT, we recommend treatment with a VKA for at least 3 months** (Grade 1A). **We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked DVT should be evaluated for the risk-benefit ratio of long-term therapy** (Grade 1C). **For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment** (Grade 1A).
  - **For patients with a second episode of unprovoked VTE, we recommend long-term treatment** (Grade 1A). **For patients with a first isolated distal DVT that is unprovoked, we suggest that 3 months of anticoagulant therapy is sufficient rather than indefinite therapy** (Grade 2B).
  - **2.1.3. For patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A). For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (also, see Section 2.4) [Grade 1C].**
  - **2.1.4. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals** (Grade 1C).

¿Por qué HBPM a largo plazo ?

¿Tratamos pacientes con HBPM a largo plazo?

HBPM	AVK	Sin tto a largo plazo	Otros
7015 (24.62%)	19989 (70.23%)	1221 (4.28%)	237 (0.83%)

N=28462 (Nov 2009)

¿A quién tratamos con HBPM?

- Cáncer
- Embarazadas
- Insuficiencia renal
- Situaciones especiales:
  - Contraindicación o dificultad para control de AVK
  - Alto riesgo de sangrado
  - Ancianos: deterioros cognitivos, dificultad a la movilidad

Embarazadas

6.1.1. For pregnant women with acute VTE, we recommend initial therapy with either adjusted dose subcutaneous LMWH or adjusted-dose UFH (IV bolus, followed by a continuous infusion to maintain the aPTT within the therapeutic range or subcutaneous therapy adjusted to maintain the aPTT 6 h after injection into the therapeutic aPTT range) for at least 5 days (Grade 1A)**.**

6.1.2. For pregnant women with acute VTE, after initial therapy, we recommend that subcutaneous LMWH or UFH should be continued throughout pregnancy (Grade 1B)**.**

6.1.3. For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 6 months) [Grade 2C]**.**

6.1.4. For pregnant women receiving adjusted dose LMWH or UFH therapy, we recommend discontinuation of the heparin at least 24 h prior to elective induction of labor (Grade 1C)**.**

ACCP 8th

Ancianos

- Dificultad de controles de AVK
- Polifarmacia
- En la mayoría de ancianos existe un cierto grado de insuficiencia renal
- Mayor riesgo de sangrados

Insuficiencia renal

- Mayor riesgo de sangrado por acumulación
- Mayor acumulación por mayor proporción de efecto antiXa vs anti-IIa (menor peso molecular)
- FG < 30 ml/min → HNF
- Reducir la dosis inicial terapéutica (ACCP→ 50%) y monitorizar antiXa.
- Medición de factor antiXa con HBPM a las 4 horas:
  - Intervalo terapéutico de actividad antiXa:
    - 0.6-1 UI/ ml para HBPM cada 12 horas
    - > 1 UI/ ml para HBPM cada 24 horas

Cáncer y HBPM

¿Beneficios de la HBPM en los pacientes oncológicos?

Ventajas de HBPM a largo plazo

- Efecto inhibidor de la trombina, disminuyendo la carga protrombótica del tumor
- Efecto antineoplásico que influye en la supervivencia
- Tratamiento indefinido si cáncer activo, metástasis o QT
- Más eficaz previniendo recidivas sin más sangrados que AVK
- Mucositis, vómitos que dificultan la vía oral
- Procedimientos invasivos se manejan mejor con HBPM
- Mejor recanalización venosa
- No necesita monitorización
- Menos interacciones
- Mejor calidad de vida

Piccioli et al. Curr Treat Option Cardiovasc Med 2011

Louzada et al. Blood Coagulation & fibrinolysis 2011

Lee A. Thromb Resarh 2010

Pranadoni. Intern Emerge Med 2010

Louzada et al. Thromb Reseach 2009

Lee A. Thromb Research 2007

Ensayos tromboprofilaxis

ENSAYOS FASE II Y III

				Reference
Phase 3				
Bemiparin vs placebo	LMWH	SC	CANBESURE Study (Cancer, Bemiparin and Surgery Evaluation)	NCT00219973
Dalteparin vs SOC	LMWH	SC	A Study of Dalteparin Prophylaxis in High-Risk Ambulatory Cancer Patients	NCT00876915
Dalteparin vs SOC	LMWH	SC	Dalteparin in Preventing Blood Clots in Patients With Lung Cancer	NCT00519805
Dalteparin vs placebo	LMWH	SC	Dalteparin Low Molecular Weight Heparin for Primary Prophylaxis of Venous Thromboembolism in Brain Tumour Patients	NCT00135876
Gemcitabine with or without dalteparin	LMWH	SC	Gemcitabine With or Without Dalteparin in Treating Patients With Unresectable or Metastatic Pancreatic Cancer	NCT00031837
Gemcitabine or capecitabine with or without dalteparin	LMWH	SC	Gemcitabine With or Without Capecitabine and/or Dalteparin in Treating Patients with Metastatic Pancreatic Cancer	NCT00662688
Chemotherapy with or without enoxaparin	LMWH	SC	Chemotherapy With or Without Enoxaparin in Pancreatic Cancer (PROSPECT)	NCT00785421
Enoxaparin	LMWH	SC	Enoxaparin Thromboprophylaxis in Cancer Patients With Elevated Tissue Factor Bearing Microparticles	NCT00908960
Enoxaparin vs intermittent pneumatic compression	LMWH	SC	Japanese Efficacy and Safety Study of Enoxaparin in Patients With Curative Abdominal Cancer Surgery	NCT00723216
Chemotherapy with or without enoxaparin	LMWH	SC	Overall Survival of Inoperable Gastric/GastroOesophageal Cancer Subjects on Treating With LMWH + Chemotherapy (CT) vs Standard CT (GASTRANOX)	NCT00718354
Fondaparinux with or without inferior vena cava filter	Indirect factor Xa inhibitor	SC	Anticoagulation and Inferior Vena Cava Filters in Cancer Patients With a Venous Thromboembolism	NCT00423683
Semuloparin vs placebo	ULMWH	SC	Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy (SAVE-ONCO)	NCT00694382
Tinzaparin	LMWH	SC	Effect of Low Molecular Weight Heparin: Tinzaparin in Lung Tumours (TILT)	NCT00475098
Tinzaparin vs warfarin	LMWH/VKA	SC	Long-Term innohep® Treatment Versus a Vitamin K Antagonist (Warfarin) for the Treatment of Venous Thromboembolism (VTE) in Cancer	NCT01130025
Phase 2				
Apixaban vs placebo	Direct factor Xa inhibitor	Oral	A Phase 2 Pilot Study of Apixaban for the Prevention of Thromboembolic Events in Patients With Advanced (Metastatic) Cancer	NCT00320255
Combination chemotherapy with wafarin	VKA	Oral	Combination Chemotherapy Plus Warfarin in Treating Patients With Prostate Cancer	NCT00014352
Gemcitabine with or without dalteparin	LMWH	SC	Gemcitabine With or Without Dalteparin in Treating Patients With Locally Advanced or Metastatic Pancreatic Cancer	NCT00462852
Dalteparin and warfarin	LMWH/VKA	SC/Oral	The Catheter Study: Central Venous Catheter Survival in Cancer Patients Using Low Molecular Weight Heparin (Dalteparin) for the Treatment of Deep Vein Thrombosis	NCT00216866
Dalteparin	LMWH	SC	Fragmin in Ovarian Cancer: Utility on Survival (FOCUS)	NCT00239980
Dalteparin	LMWH	SC	Treatment of Blood Clots in Children With Cancer	NCT00952380
Enoxaparin	LMWH	SC	Identification and Treatment of Clinically Silent Catheter-Related Deep Vein Thrombosis in Children With Cancer	NCT00633061
Fondaparinux	Indirect factor Xa inhibitor	SC	Fondaparinux in Preventing Blood Clots in Patients Undergoing Surgery for Gynecologic Cancer	NCT00381888
Tinzaparin	LMWH	SC	Tinzaparin for Primary Treatment and Extended Secondary Prophylaxis of Venous Thromboembolism in Patients with Cancer	NCT00981903
Tinzaparin	LMWH	SC	Tinzaparin in Treating Patients with Metastatic Kidney Cancer That Cannot Be Removed by Surgery	NCT00293501

MOA indicates mechanism of action; NCT, National Clinical Trial; LMWH, low molecular-weight heparin; SC, subcutaneous; SOC, standard of care; ULMWH, ultra-low molecular weight heparin; VKA, vitamin K antagonist.

*Search of www.clinicaltrials.gov Web site on August 21, 2009. Search terms used were: "venous thromboembolism," "thromboprophylaxis," "thrombosis," "phase II," and "phase III." Conditions searched for: cancer. Completed studies and studies actively recruiting participants were included.

ESTUDIOS PROFILAXIS

Table 4. Recent Studies of Pharmacologic Anticoagulants in Medical Patients With Cancer

Study	Patient Population	Treatments	Primary Outcome	Result	Significance Level	Bleeding Rates	Significance Level	Length of Treatment	Setting
Hull 2010[31]	Acutely ill medical patients	Enoxaparin, 40 mg QD or placebo	VTE	Enoxaparin, 2.5% (45/1818); Placebo, 4.2% (78/1867)	$P < .042$	Major bleeding: enoxaparin, 0.8%; placebo, 0.3%	$P < .05$	28 d	Prophylaxis
De Cicco 2009[32]	Cancer patients with a central vein catheter	Acenocumarine, 1 mg QD or dalteparin, 5000 IU QD or no anticoagulant therapy	Central vein catheter-related thrombosis	Acenocumarine, 21.9% (25/114); dalteparin, 40.0% (48/120); no treatment, 52.6% (60/114)	Acenocumarine vs no treatment: $P < .01$; dalteparin vs no treatment: $P = .05$; acenocumarine vs dalteparin: $P = .01$	Major bleeding: none observed	NR	Acenocumarine: 11 d; dalteparin, 8 d	Prophylaxis
Young 2009[33]	Cancer patients receiving chemotherapy via central venous catheters	Fixed-dose warfarin, 1 mg QD or INR-adjusted warfarin QD or no warfarin	Catheter-related thrombotic events	Fixed-dose warfarin, 7% (34/471); INR-adjusted warfarin, 3% (13/473); no warfarin, 6% (24/404)	Warfarin vs no warfarin: $P = .98$; fixed-dose warfarin vs INR-adjusted warfarin: $P = .002$	Major bleeding: fixed-dose warfarin, 1%; INR-adjusted warfarin, 3%; no warfarin, <1%	Warfarin vs no warfarin: $P = .07$; INR-adjusted warfarin vs fixed-dose warfarin: $P = .09$	Treatment continued until catheter removal or occurrence of thrombosis	Prophylaxis
Weber 2008[34]	Terminal cancer	Nadroparin, 2850–3800 IU/kg QD or no treatment	VTE	Nadroparin, 10% (1/10); no treatment, 0% (0/10)	$P = 1.00$	Major bleeding: nadroparin, 10%; no treatment, 0%	$P = 1.00$	Treatment continued until death	Prophylaxis
Robins 2008[35]	Glioblastoma multiforme	Dalteparin, 5000 IU QD with conventional radiotherapy vs control cohort	Survival time	Median survival time in dalteparin-treated patients: 11.9 mo	$P = .47$ vs control cohort	Major bleeding: none reported	NR	≤24 mo	Prophylaxis
Niers 2007[36]	Hematologic malignancy	Nadroparin, 2850 IU QD vs placebo	Catheter-related thrombosis	Nadroparin, 17% (7/41); placebo, 9% (4/46)	$P = .49$	Major bleeding: none reported	NR	3 wk	Prophylaxis
Meister 2008[37]	Acute lymphoblastic leukemia	Antithrombin alone vs antithrombin plus enoxaparin, 0.75–1.2 mg/kg QD	VTE	Antithrombin alone, 12.7% (9/71); antithrombin plus enoxaparin, 0%	$P = .02$	Major bleeding: none reported	NR	1–2 wk during chemotherapy induction and reinduction phases	Prophylaxis
Icli 2007[38]	Advanced pancreatic cancer	Combination chemotherapy plus nadroparin, 2850 IU QD vs combination chemotherapy alone	Treatment response rate; survival	Response rate: nadroparin, 58.8% (20/34); no nadroparin, 12.1% (4/33). Median overall survival time: nadroparin, 13.0 mo; no nadroparin, 5.5 mo	Response rate: $P = .0001$; survival time: $P = .0001$	Treatment-related bleeding: none reported	NR	Until disease progression	Prophylaxis
Miller 2006[39]	Patients with multiple myeloma or chronic lymphocytic leukemia treated with thalidomide-based therapies	Warfarin 1 or 2 mg QD vs historical studies with similar chemotherapy regimens	VTE	Warfarin, 5.9% (4/68); thalidomide plus doxorubicin, 27%; thalidomide plus epirubicin, 26%	Warfarin regimen vs thalidomide plus doxorubicin: $P = .034$; warfarin regimen vs thalidomide plus epirubicin: $P = .009$	Treatment-related bleeding: none reported	NR	4 mo	Prophylaxis

(Continued)

ESTUDIOS PROFILAXIS

Table 4. (Continued)

Study	Patient Population	Treatments	Primary Outcome	Result	Significance Level	Bleeding Rates	Significance Level	Length of Treatment	Setting
Deitcher 2006[40]	Patients with active cancer and acute VTE	Enoxaparin, 1 mg/kg BID × 5 d, then 1 mg/kg QD thereafter *or* enoxaparin, 1 mg/kg BID × 5 d, then 1.5 mg/kg QD thereafter vs enoxaparin, 1 mg/kg BID × 5 d or until INR target achieved, then INR-adjusted warfarin thereafter	Recurrent VTE	Enoxaparin at 1 mg/kg, 3.4% (1/29); enoxaparin at 1.5 mg/kg, 3.1% (1/32); warfarin, 6.7% (2/30)	NR	Major bleeding: enoxaparin at 1 mg/kg, 6.5%; enoxaparin at 1.5 mg/kg, 11.1%; warfarin, 2.9%	NR	180 d	Treatment
Ruud 2006[41]	Children with active cancer and central venous lines	INR-adjusted warfarin QD vs no prophylaxis	Central vein catheter-related VTE	Warfarin, 48% (14/29); no prophylaxis, 36% (12/33)	$P = .44$	Bleeding rates NR	NR	6 mo	Prophylaxis
Ikhlaque 2006[42]	Patients receiving thalidomide therapy	Low-dose warfarin (1–2 mg/d) or high-dose warfarin (adjusted to INR 2–3) vs no prophylaxis	DVT	Low-dose warfarin, 2.7% (1/37); high-dose warfarin, 11.1% (2/18); no warfarin, 23.7% (18/76)	$P = .01$ for any dose of warfarin vs no warfarin	Clinical bleeding: low-dose warfarin, 0%; high-dose warfarin, 22.2%; no warfarin, 0%	NR	≤14 mo	Prophylaxis
Baz 2005[43]	Multiple myeloma	Aspirin, 81 mg QD initiated at the start of chemotherapy or aspirin, 81 mg QD initiated after the start of chemotherapy vs no aspirin	VTE	Aspirin initiated at the start of chemotherapy, 19% (11/58); aspirin initiated after the start of chemotherapy, 15% (4/26); no aspirin, 58% (11/19)	$P \leq .002$ for both aspirin groups vs no aspirin	Significant bleeding complications: none reported	NR	Median, 2 y	Prophylaxis
Karthaus 2006[44]	Cancer patients with central venous catheters	Dalteparin, 5000 IU QD vs placebo	Catheter-related complications	Dalteparin, 3.7% (11/294); placebo, 3.4% (5/145)	$P = .88$	Any bleeding event: dalteparin, 17.5%; placebo, 15%	NR	16 wk	Prophylaxis
Verso 2005[45]	Cancer patients with central venous catheters	Enoxaparin, 40 mg QD vs placebo	DVT or clinically overt PE	DVT: enoxaparin, 14.1% (22/155); placebo, 18.0% (28/155)	$P = .35$	Major bleeding: none reported	NR	6 wk	Prophylaxis
Couban 2005[46]	Cancer patients with central venous catheters	Warfarin, 1 mg QD vs placebo	Central venous catheter-related thrombosis	Warfarin, 4.6% (6/130); placebo, 4.0% (5/125)	HR 1.20 (95% CI, 0.37–3.94)	Major bleeding: warfarin, 0%; placebo, 2%	$P = .07$	Until catheter removal, death, or catheter-related thrombosis	Prophylaxis

QD indicates every day; VTE, venous thromboembolism; NR, not reported; INR, international normalized ratio; BID, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; HR, hazard ratio; 95% CI, 95% confidence interval.

ESTUDIOS PROFILAXIS

Table 5. Recent Studies of Pharmacologic Anticoagulants in Surgical Patients With Cancer

Study	Patient Population	Treatments	Primary Outcome	Result	Significance Level	Bleeding Rates	Significance Level	Length of Treatment	Setting
Einstein 2008[47]	Gynecologic cancer surgery	Dual prophylaxis with sequential compression devices alone or compression devices plus heparin, 5000 U Q 12 h or Q 8 h	VTE	Dual prophylaxis with prolonged prophylaxis in high-risk patients resulted in a significant reduction in VTE rate from 6.5% (19/294) in 2005 to 1.9% (6/311) in 2006	OR, 0.33 (95% CI, 0.12–0.88)	Median blood loss: 2005: 250 mL; 2006: 200 mL	$P = .22$	Until hospital discharge, extended to 2 wk after hospital discharge in high-risk patients	Prophylaxis
Shukla 2008[48]	Colorectal cancer surgery	Dalteparin, 2500 IU QD × 6 d or no prophylaxis	DVT	No DVT occurred in either group	NR	Not specified	NR	6 d	Prophylaxis
Simonneau 2006[49]	Colorectal cancer surgery	Nadroparin, 2850 IU QD vs enoxaparin, 40 mg QD	VTE	Nadroparin, 15.9% (74/464); enoxaparin, 12.6% (61/486)	$P = NS$	Major bleeding: nadroparin, 7.3%; enoxaparin, 11.5%	$P = .012$	7–11 d	Prophylaxis
Perry 2009[50]	Patients with brain tumors	Tinzaparin, 4500 IU QD	Safety outcomes	CNS hemorrhage in 5% (2/40)	NR	CNS hemorrhage: grade 1: 2.5%; grade 2: 2.5%	NR	12 mo	Prophylaxis

UFH indicates unfractionated heparin; Q, every; VTE, venous thromboembolism; OR, odds ratio; 95% CI, 95% confidence interval; QD indicates every day; DVT, deep vein thrombosis; NR, not reported; NS, not significant; CNS, central nervous system.

ESTUDIOS PROFILAXIS

Table 6. Recent Studies of Pharmacologic Anticoagulants in Ambulatory Cancer Patients

Sudy	Patient Population	Treatments	Primary Outcome	Result	Significance Level	Bleeding Rates	Significance Level	Length of Treatment	Setting
Cini 2010[51]	Multiple myeloma	Thalidomide and dexamethasone or thalidomide and dexamethasone plus warfarin	VTE	No prophylaxis, 26.3% (5/19); warfarin, 10.6% (26/246)	$P = .095$	Major bleeding: none recorded	Not specified	120 d	Prophylaxis
Agnelli 2009[52]	Lung, GI, pancreatic, breast, ovarian, or head and neck cancer	Nadroparin, 3800 IU QD or placebo	Composite of symptomatic venous or arterial thromboembolic events	Nadroparin, 2.0% (15/769); placebo, 3.9% (15/381)	$P = .02$	Major bleeding: nadroparin, 0.7%; placebo, 0%	$P = .18$	≤4 mo	Prophylaxis
Lee 2005[53]	Patients with solid tumors and VTE	Dalteparin, 200 U/kg QD × 1 mo then 150 U/kg QD × 5 mo or dalteparin, 200 U/kg × 7 d then INR-adjusted coumarin derivative × 6 mo	All-cause mortality at 12 mo	Dalteparin, 20% (15/75); warfarin, 36% (26/75) in patients with no metastases	$P = .03$	Not specified	Not specified	6 mo	Prophylaxis
Hull 2006[54]	Patients with cancer and VTE	Tinzaparin, 175 U/kg QD vs usual care (UFH plus warfarin)	Recurrent VTE or death at 3 mo	Recurrent VTE: tinzaparin, 6% (6/100); usual care, 10% (10/100); death: tinzaparin, 20% (20/100); usual care, 19% (19/100)	Recurrent VTE: P = NS; death: P = NS	Major bleeding: tinzaparin, 7%; usual care, 7%	P = NS	3 mo	Treatment
Romera 2009[55]	Patients with VTE including 28.6% (69/241) with cancer	Tinzaparin, 175 IU/kg QD or INR-adjusted acenocoumarol	Recurrent VTE at 6 mo and 1 y	Cancer population: 6 mo: tinzaparin, 5.5% (2/36); warfarin, 9.1% (3/33); 1 y: tinzaparin, 5.5% (2/36); warfarin, 21.2% (7/33)	6 mo: $P = .58$; 1 y: $P = .06$	Major bleeding in total population: tinzaparin, 0.8%; warfarin, 2.5%	$P = .6$	6 mo	Treatment

VTE indicates venous thromboembolism; GI, gastrointestinal; QD, every day; INR, international normalized ratio; UFH, unfractionated heparin; NS, not significant.

HBPM y cáncer
Tromboprofilaxis quirúrgica

- ARISTOS project
  - 81.7% cirugias cáncer tromboprofilaxis intrahospitalaria vs 31% al alta a pesar de que la ETEV se producía más allá del día 21 postquirúrgico en el 40% de los pacientes con una media de 17 días.
- ENOXACAN
  - Enoxaparina vs HNF en cirugía abdominal y pélvica neoplásica
  - 18% vs 14% reducción de ETEV
  - Sin aumento del riesgo de sangrado
- ENOXACAN II
  - Enoxaparina 27-31 días vs Enoxaparina 6-10 días
  - Reducía la incidencia de ETEV en las cirugías abdominales y pélvicas oncológicas (4.8% vs 12%)
  - Sin aumento del riesgo de sangrado
- CANBESURE
  - Bemiparina 3500 UI vs placebo durante 4 semamas cirugía pélvica y abdominal
  - 0.4 % vs 3.3% incidencia de ETEV

Agnelli et al. Ann Surg 2006, 243:89-98
ENOXACAN study group Br J Surg 1997 84:1099-1103
Bergqvist et al. NEJM 2002 346:975-980
Kakkar et al. Abstract LB-MO-002 ISTH 2009. Boston

HBPM y cáncer
Tromboprofilaxis médica

- MEDENOX (enoxaparina)
  - Incidencia 5.5% ETEV vs 14% placebo (reducción riesgo relativo 63%)
    - **Samana, NEJM 1999**
- FRAISSE (nandroparina)
  - Incidencia 15.5% TVP vs 28.2% placebo en EPOC con ventilación mecánca (reducción riesgo relativo 45%)
    - **Fraisse,Am J Respr Crit Care Med 2000**
- PREVENT (dalteparina)
  - Incidencia 2.77% ETEV vs 5% placebo (reducción riesgo relativo 45%)
    - **Leizorovicz, Circulation 2004**
- ARTEMIS (fondaparinux)
  - Incidencia 5.6% ETEV vs 10.5% placebo (reducción riesgo relativo 47%)
    - **Cohen, BMJ 2006**

HBPM y cáncer
Tromboprofilaxis ambulatoria

- PROSPECT-CONKO 004: Neoplasia páncreas en tratamiento QT
  - Enoxaparina 1 mgr/Kg/ día → reducción 65% ETEV a las 12 semanas sin más sangrados
    - » Riess H et al. Abstract LBA 4506, ASCO 2009
- FAMOUS: Neoplasias avanzadas
  - 5000 UI dalterapina → no diferencias supervivencia a un año pero sí más allá
    - » Kakkar AK et al. J. Clin. Oncol 2004
- PROTECHT: QT en cáncer avanzado.
  - Nandroparina reducía eventos ETEV.
    - » Agnelli et al. Lancet Oncol 2009

HBPM y cáncer
Tromboprofilaxis ambulatoria

- PRODIGE: Gliomas de reciente diagnóstico tras cirugías
  - Dalteparina 5000 UI: → no diferencias
    - » Perry et al. J Thromb Haemost 2010
- UK FRAGMEN study: páncreas avanzado
  - Dalteparina ajustada al peso por 12 semanas y con reducción de dosis a las 4 semanas → reducción del riesgo de ETEV.
    - » Maraveyas et al. Abastract O-6503 ECCO 2009

HBPM y cáncer
Tromboprofilaxis ambulatoria

- TOPIC -1 y TOPIC-2
  - Mama avanzada o no células pequeñas
  - Certoparina 3500 vs placebo
  - Objetivo: ETEV asociado a la QT
  - En la rama de certoparina se mostraba una reducción de la trombosis sobre todo en los casos de estadíos avanzados

    » Haas et al. Abstract 1707 ISTH 2005. Sydney

Ensayos tratamineto

Canthanox

- Enoxaparina (1.5 mg/Kg/d v. warfarina * 3 meses)
- Reducción eventos (ETEV recurrentes + sangrados) 21.1% → 10.5%. RR 2.02 (0.88-4.65)
- Tendencia reducción mortalidad 22.7% → 11.3%

Meyer G. Arch Intern Med 2002: 162: 1729-35

ONCEROX

- Enoxaparina inicial +
  - AVK→ 180 días
  - Enoxaparina 1 mgr/Kg
  - Enoxaparina 1.5 mgr/Kg

  → 175 días
- No diferencias significativas en referencia a los sangrados

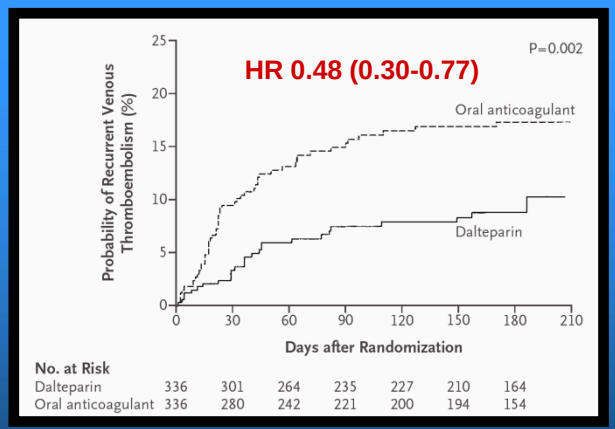
Deitcher SR. Clin Appl Thromb Hemost 2006: 12 (4): 389-96

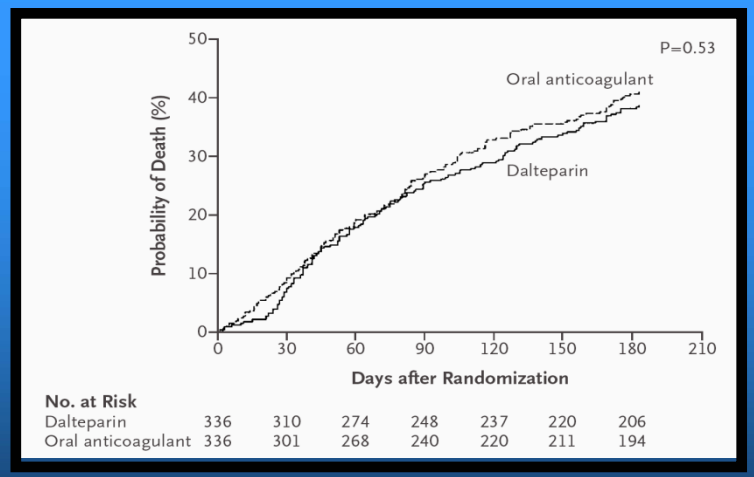
CLOT

- Dalteparina (200 UI/Kg/d * 1 mes + 150 UI/Kg/d * 5 meses v. warfarina * 6 meses)
- Menores eventos con dalteparina

Table 3. Primary Efficacy Outcome Events.

Event	Dalteparin (N=336)	Oral Anticoagulant (N=336)
	no. of patients	
Deep-vein thrombosis alone	14	37
Nonfatal pulmonary embolism	8	9
Fatal pulmonary embolism	5	7
Total	27	53





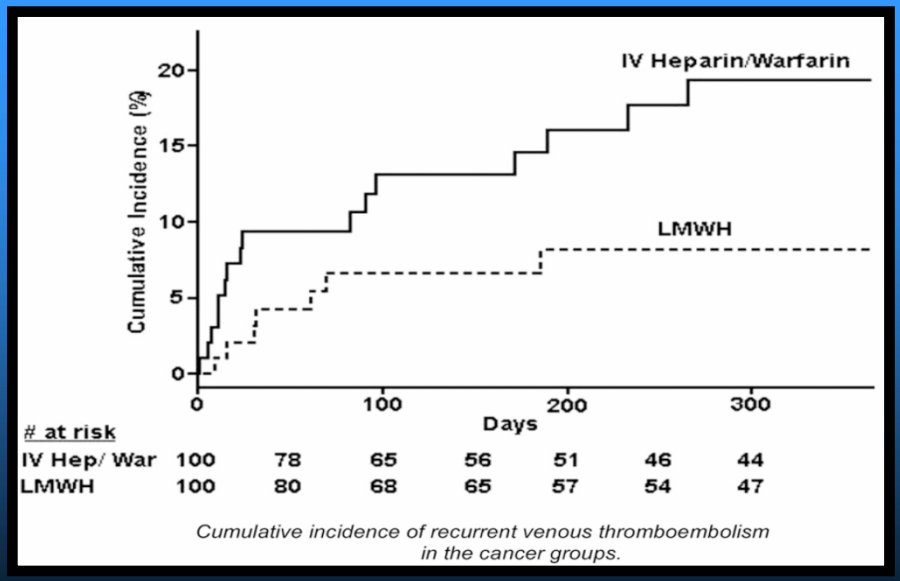
-Menores recurrencias

- Misma mortalidad

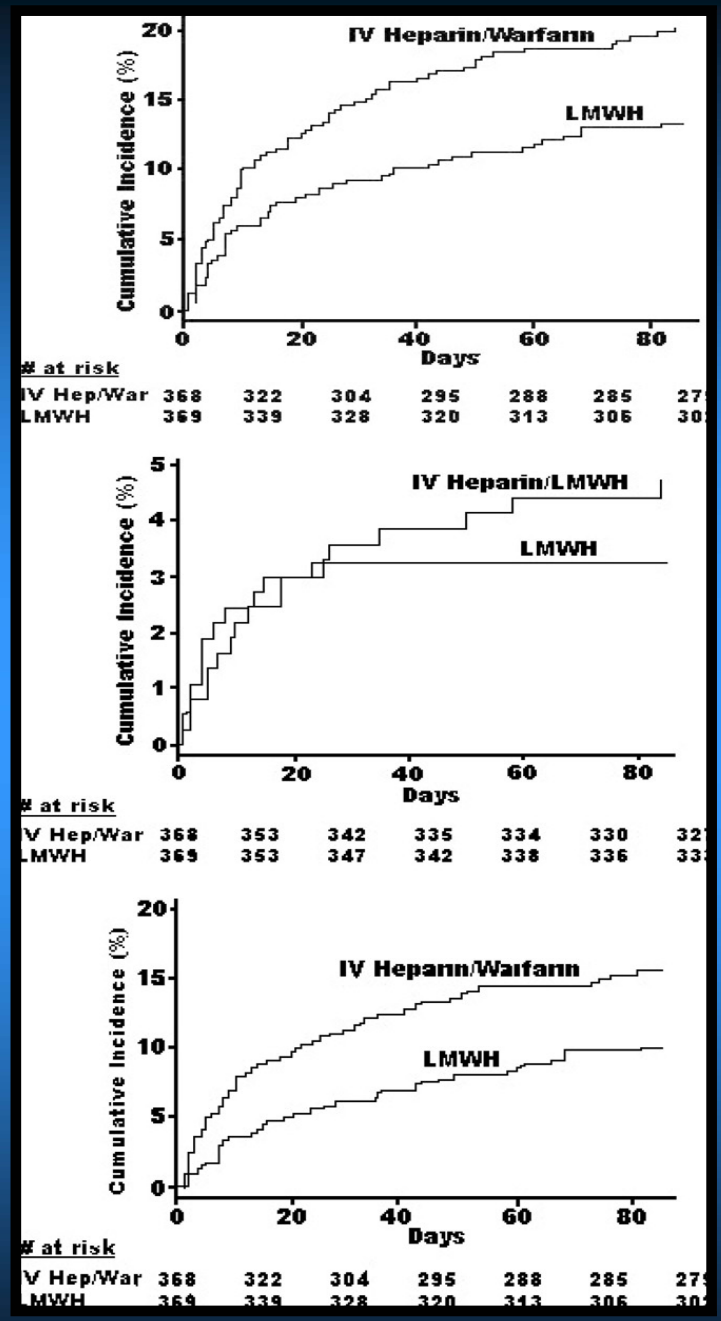
Lee AY. N Engl J Med 2003; 349: 146-53.

Main- LITE

- Tinzaparina vs AVK 3 meses
- Menores recurrencia
- Menores sangrados



Cumulative incidence of recurrent venous thromboembolism in the cancer groups.



Hull RD. AM J Med 2006; 119: 1062-72

A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis

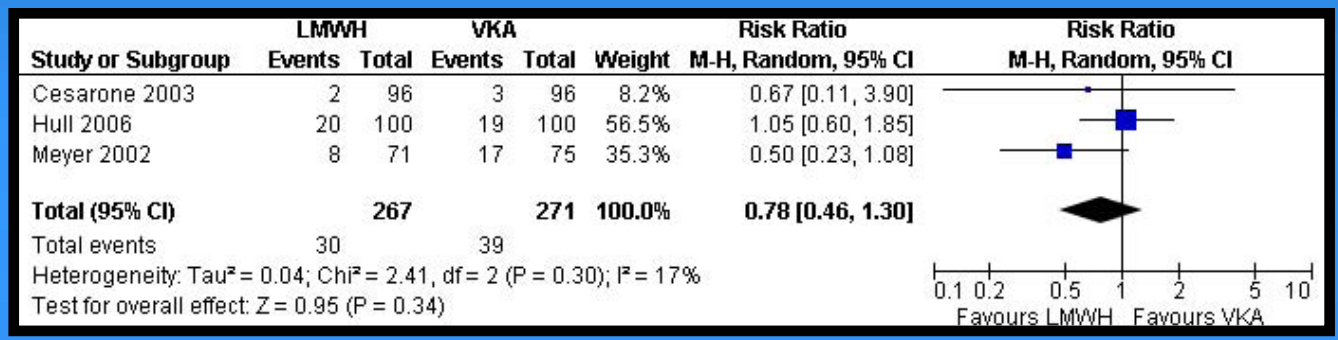
Evento	***HBPM N=119***	***AVK N=122***
Hemorragia	0.84%	2.67%
Recurrencia	5%	10.7%
Recurrencia con cáncer	5.5%	21.2%
Recanalización vena 6m/12m	73.1% / 91.5%	47.5% / 69.2%

Romera A et al. Eur J Vasc Endovasc Surg. 2009 ;37(3):349-56

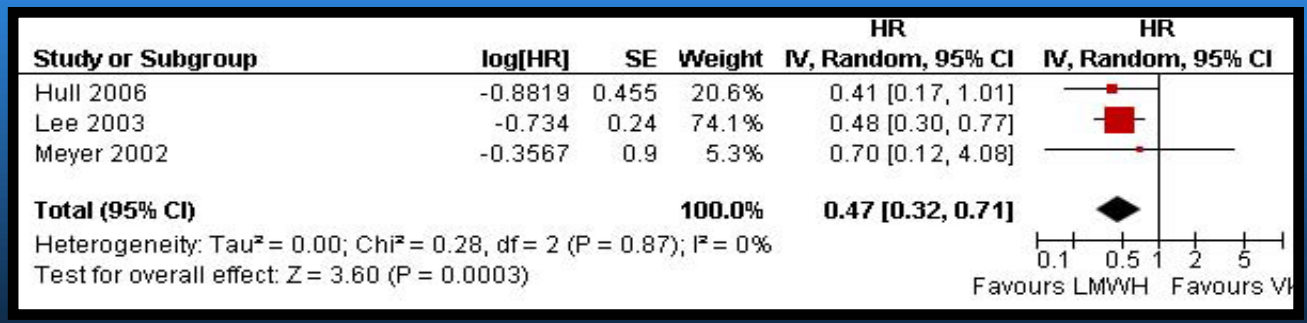
Low-molecular-weight heparins are superior to vitamin K antagonists for the long term treatment of venous thromboembolism in patients with cancer: a cochrane systematic review

Elie A Akl, Maddalena Barba, Sandeep Rohilla, Irene Terrenato, Francesca Sperati, Paola Muti and Holger J Schünemann

Comparison of the effects of LMWHs and vitamin K anatomists on survival (time to event analysis) in patients with cancer and venous thromboembolism.



Comparison of the effects of LMWHs and vitamin K anatomists on recurrent venous thromboembolism (survival analysis) in patients with cancer and venous thromboembolism.



Journal of Experimental & Clinical Cancer Research 2008, **27**:21 doi:10.1186/1756-9966-27-21

¿ Qué dosis de HBPM a largo plazo en pacientes con cáncer?

Recomendaciones

- ***ESMO (Sociedad Europea de Oncología Médica) Ann Oncol 2009; 20: (suplemento 4): iv 182-iv 184***

  El tratamiento recomienda en fase aguda con HBPM a dosis ajustadas al peso (200 UI/ Kg / día o 100 mgr /Kg / 12 horas basada en dalteparina) a dosis plenas durante los 5 primeros días y después AVK con INR entre 2-3 como tratamiento estándad. Los AVK tienen problemas en los pacientes con cáncer (recurren más y sangrán más) además de interacciones con otros fármacos. Por tanto y en función de de los ensayos clínicos randomizados (CLOT y LITE-Main/ LITE-Cancer +/- Canthanox) se recomienda que en los pacientes con cáncer se administre tras la fase aguda, un 75-80% de la dosis inicial hasta completar 6 meses de tratamiento (profilaxis secundaria) .

  En ningún caso se puede saber que pasa más allá de esos 6 meses si bien estaría indicada la anticoagulación mientras hubiera evidencia de actividad maligna.

- ***Italian Guidelines Clin Rev Oncol Hemol 2006; 59: 194-204***

- ***French national guidelines for the treatment of venous thromboembolism in patients with cancer: Report from the working group. Crit Rev Oncol Hematol 2010; 73: 31-46.***

- ***ASCO GUIDELINE (Sociedad Americana de Oncología) J Clin Oncol 2007; 25: 5490-5505***

  Basándose nuevamente en los tres ensayos clásicos, la ASCO recomienda la aplicación de HBPM para el tratamiento inicial y para el tratamiento crónico al menos 6 meses con reducción de dosis. Se basa en dalteparina (única HBPM aprobada por la FDA para el tratamiento a largo plazo en paciente con cáncer : 200 UI Kg/Kg/ día durante un mes y después 150 UI / Kg/ día los 5 meses restantes. El LITE se basa en aplicar tinzaparina 175 UI/ Kg/ día los 3 meses del ensayo en la rama de HBPM y el Canthanox lo hace con enoxaparina 1.5 mgr/Kg / día durante los tres meses sin reducción de dosis.

- ***NCCN Guideline (2009)***

  El tratamiento inicial se hará con dalteparina (200 UI/Kg/ día) , tinzaparina (175 UI/ Kg/ día) y enoxaparina (1 mgr /Kg / 12 horas). Cuando esté indicado el tratamiento a largo plazo con HBPM éste se realizará con disminución de dosis (que no especifica) . Por otra parte y aunque es un estudio de supervivencia el FAMOUS, aplica a la rama de HBPM 5000 UI fijas de dalteparina que en un análisis inicial, no logra más supervivencia en estudios posteriores en paciente con mejor pronóstico vital, la rama de HBPM tiene mejor supervivencia al año. De toda formas no está recomendado la aplicación de HBPM para mejorar la supervivencia.

LONG-TERM USE OF DIFFERENT DOSES OF LMWH VS AVK IN THE TREATMENT OF VTD

- Metanálisis 17 ensayos clínicos
  - 7 estudios : rebajaron la dosis hasta dosis profilácticas
  - 5 estudios: continuaron a dosis plenas
  - 3 estudios: redujeron 25% la dosis
  - 2 estudios: redujeron entre 25-50%
- Dosis plenas son igual que las reducidas en términos de hemorragias y recidivas en tratamientos 3-6 meses.
- En los pacientes con cáncer hay más recurrencias con dosis reducidas que con dosis plenas sin más hemorragias

Romera et al. Ann Vasc Surg 2009

Pacientes con cáncer

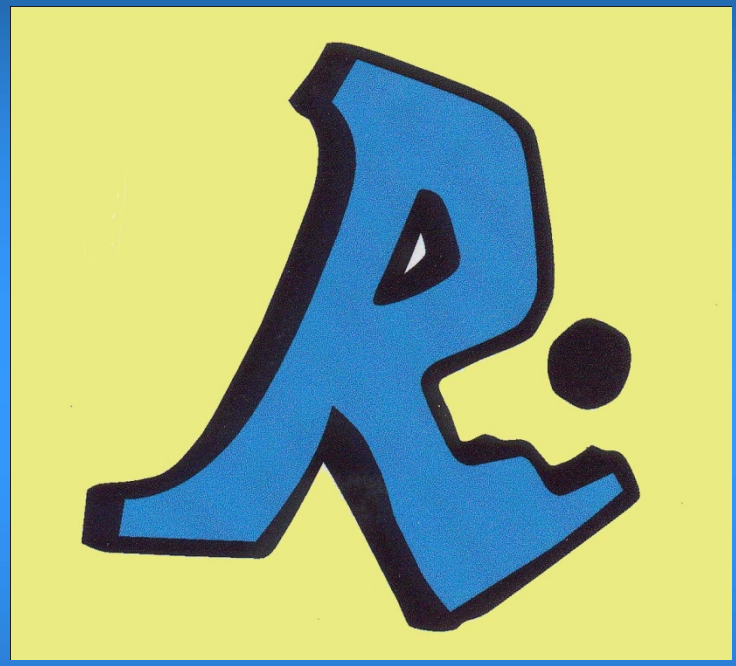
Estudios	HBPM dosis plenas / AVK	HBPM dosis reducidas /AVK
Recurrencias en tratamiento	6.5 % / 17.9 % (p= 0.005)	7.1% / 13.4% (p= 0.002)
Recurrencias tras fin de tratamiento	1.6% / 9.5% (RR 0.25 (IC 0.06-1.1)	12% / 7.4% (RR 1.49 (IC 0.3-7.48)
Hemorragias	5.1%	6.3%

Romera et al. Ann Vasc Surg 2009

Recurrencias en tratamiento con HBPM

- Hasta un 9% recurren a pesar de estar con tratamiento con HBPM
- Reajuste de HBPM, HNF o filtro de cava

Retrombosis con	***Recomendación***
Dosis subóptima	Aumentar hasta dosis terapéutica
Dosis adecuada	Aumentar 20-25% al menos 4 semanas
Dosis de mantenimiento	Aumentar a dosis terapéuticas de 6-12 semanas
Dosis bajas	Volver a dosis terapéuticas al menos durante un mes



Long-term therapy with low-molecular-weight heparin in cancer patients with venous thromboembolism.

Findings from the RIETE Registry.

- Usando la base de datos del RIETE (observacional, multinacional y multicéntrica) se analizan el número y el tipo de eventos clínicos definidos como recidivas de ETEV, hemorragias y defunciones en el subgrupo de pacientes con cáncer en función de la dosis de HBPM a largo plazo dividida en dos grupos de 150 UI/Kg /día

- Se define tratamiento a largo plazo aquel que comprende desde el día 8 del inicio del tratamiento hasta al menos tres meses.

- Propensity score matching para comparación de grupos

Clinical characteristics of 2,538 cancer patients with VTE who received long-term therapy with fixed doses of LMWH, after propensity score matching (only cases with delta <0.1).

	LMWH doses ≥150 IU/kg/d	LMWH doses <150 IU/kg/d	p value
Patients, N	*1,269*	*1,269*	
Clinical characteristics,			
Gender (males)	711 (56%)	680 (54%)	0.23
Age (mean years±SD)	67±13	67±14	0.41
Age ≥65 years	491 (39%)	509 (40%)	0.49
Body weight (mean kg±SD)	72± 12	72±15	0.001
Body weight <65 kg	321 (25%)	359 (28%)	0.10
Underlying conditions,			
Chronic heart failure	47 (3.7%)	49 (3.9%)	0.92
Chronic lung disease	105 (8.3%)	96 (7.6%)	0.56
Recent major bleeding	36 (2.8%)	41 (3.2%)	0.64
Abnormal creatinine levels	190 (15%)	201 (16%)	0.55
Anemia	840 (66%)	768 (61%)	0.003
Risk factors for VTE,			
Surgery	225 (18%)	166 (13%)	0.001
Immobility ≥4 days	244 (19%)	277 (22%)	0.12
Prior VTE	166 (13%)	155 (12%)	0.55
Initial VTE presentation,			
Pulmonary embolism	557 (44%)	518 (41%)	0.12
If only DVT signs,			
Proximal DVT	524 (74%)	556 (74%)	0.95
Upper-extremity DVT	105 (15%)	106 (14%)	0.77
Cancer characteristics,			
Metastatic cancer	669 (53%)	663 (52%)	0.84
Diagnosis >3 months earlier	735 (58%)	771 (61%)	0.16

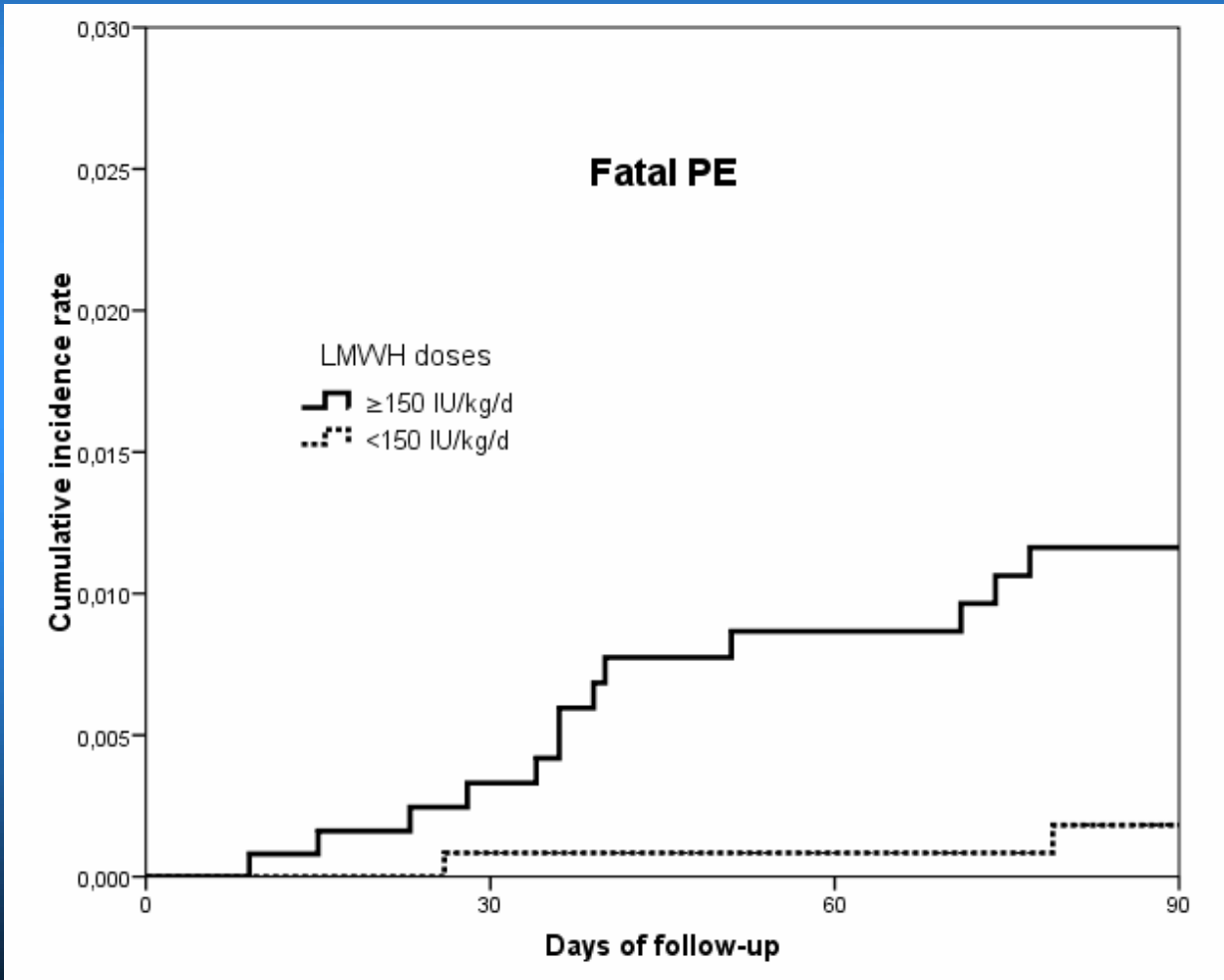
Initial therapy and 3-month outcome (After propensity score matching, with 2,538 cases with delta < 0.1).

	LMWH doses ≥150 UI/kg/d	LMWH doses <150 UI/kg/d	p value
Patients, N	*1,269*	*1,269*	
Initial therapy,			
LMWH	1,208 (95%)	1,234 (97%)	0.009
Mean LMWH dose (IU/kg/day)	190±65	187±60	0.19
LMWH dose (median, IQR)	184 (67)	181 (76)	-
Unfractionated heparin	61 (4.8%)	35 (2.8%)	0.009
Inferior vena cava filter	41 (3.2%)	61 (4.8%)	0.054
Long-term therapy,			
Mean LMWH dose (IU/kg/day)	182±25	111±27	<0.001
LMWH dose (median, IQR)	177 (30)	118 (40)	-
Outcome from Day 0 to Day 7,			
Recurrent DVT	0	1 (0.1%)	1.0
Recurrent PE	3 (0.2%)	0	0.25
Recurrent VTE	3 (0.2%)	1 (0.1%)	0.63
Major bleeding	2 (0.2%)	0	0.5
Outcome from Day 8 to Day 90,			
Recurrent DVT	13 (1.0%)	34 (2.7%)	0.003
Recurrent PE	24 (1.9%)	15 (1.2%)	0.20
Major bleeding	31 (2.4%)	24 (1.9%)	0.41
Overall death	290 (23%)	264 (21%)	0.23
Causes of death:			
Pulmonary embolism	13 (1.0%)	2 (0.2%)	0.004
Respiratory insufficiency	13 (1.0%)	12 (0.9%)	0.844
Sudden, unexpected	1 (0.1%)	3 (0.2%)	0.375
Bleeding	7 (0.6%)	13 (1.0%)	0.188
Disseminated cancer	171 (13%)	167 (13%)	0.816
Other	85 (6.7%)	67 (5.3%)	0.133

Multivariate analysis after propensity score matching

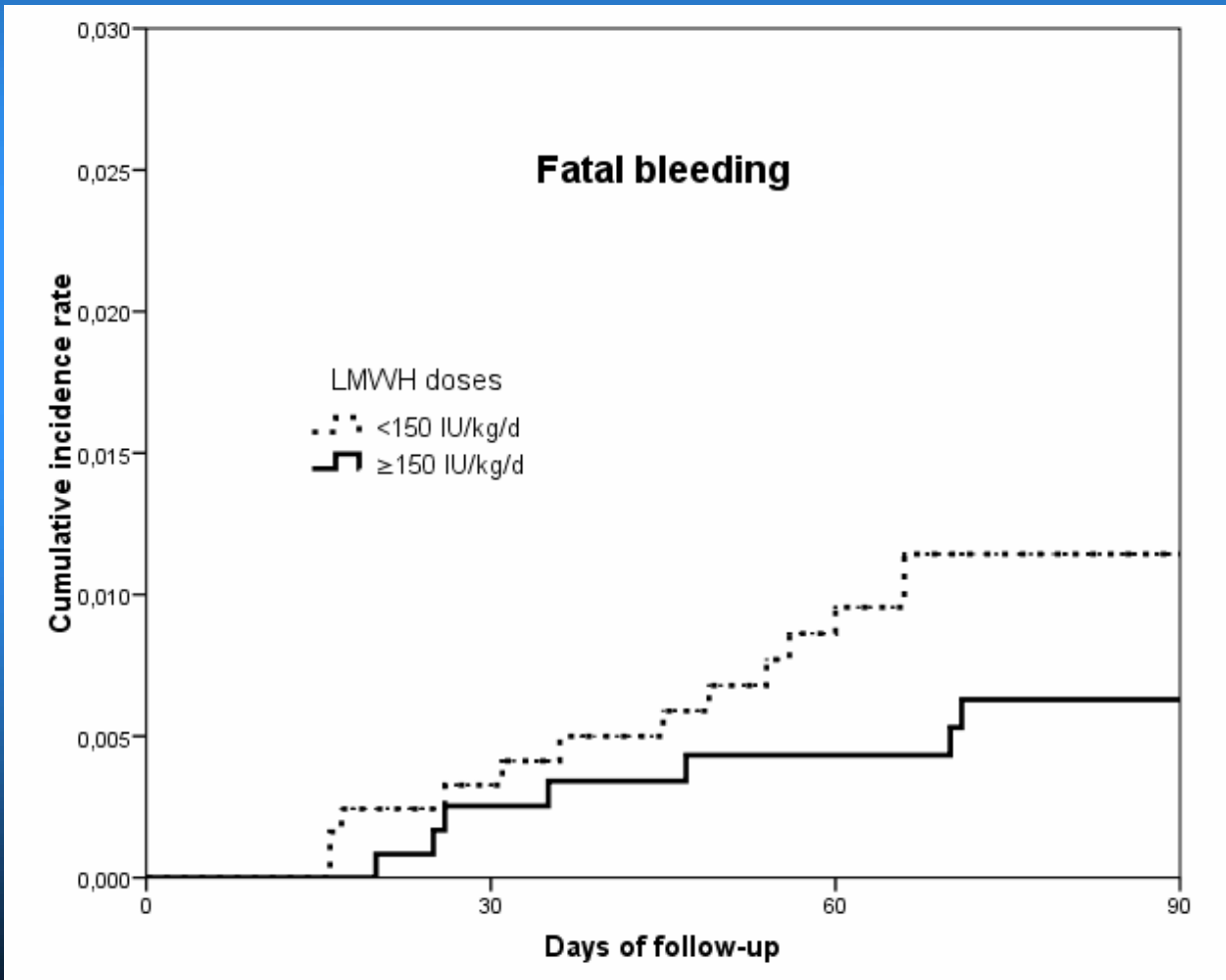
Patients, N	Fatal PE OR (95% CI)	p value	Fatal bleeding OR (95% CI)	p value
Chronic lung disease	3.9 (1.2-12.7)	0.02	-	
Abnormal creatinine levels	2.8 (0.9-8.4)	0.06	-	
Initial presentation as PE	2.5 (0.8-7.3)	0.10	-	
Metastases	2.6 (0.8-8.3)	0.10	2.4 (0.8-6.6)	0.10
Lung cancer	-	-	2.4 (0.9-6.1)	0.07
LMWH dose <150 IU/kg/d	0.2 (0.04-0.7)	0.015	2.0 (0.7-5.0)	0.19

Cumulative incidence of fatal pulmonary embolism according to the doses of LMWH during long-term therapy.



p = 0.015

Cumulative incidence of fatal bleeding according to the doses of LMWH during long-term therapy.



p = 0.19

Conclusiones

Dosis < 150 UI/ Kg / día a largo plazo:

- **Presentan menos EP fatales.**
- **Pero más recurrencias de TVP**
- **Menos mortalidad en general (sin propensity)**
- **Mortalidad por la propia EP y no por sangrados**
- **Más portadores de filtros de cava**
- **Más sangrados fatales (p=ns)**

¿HBPM es una alternativa segura y eficaz a los anticoagulantes orales en el tratamiento a largo plazo de la ETEV?

Sí

¿Beneficios de la HBPM en los pacientes oncológicos?

Sí

Para acabar…

- Heparinas Bajo Peso Molecular:
  - Ejercen efectos beneficiosos sobre los pacientes con cáncer
    - Efecto antineoplásico que mejora supervivencia
    - Mejor calidad de vida
    - Eficacia aumentada con mayor seguridad
  - Dosis menores a largo plazo parecen mejorar la supervivencia por menos mortalidad del TEP (RIETE)
  - Reducción de dosis respecto de las de la fase aguda asumiendo el riesgo de recurrencia de TVP (RIETE)

Parc Sanitari Sant Joan de Déu

MUCHAS GRACIAS POR SU ATENCIÓN