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CURSO DE ACTUALIZACIÓN EN URGENCIAS (PROGRAMA)

Luis Jara-Palomares
Neumología. Unidad Médico Quirúrgica de Enfermedades Respiratorias.
Instituto de Biomedicina de Sevilla (IBiS)
Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES)
Hospital Universitario Virgen del Rocío, Sevilla.

AGENDA

- **TRATAMIENTO DE LA ETV EN PACIENTES ONCOLÓGICOS**
- **TEP INCIDENTAL**
- **MANEJO DE LA ETV RECURRENTE**

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Tratamiento de la ETV en pacientes oncológicos.

Luis Jara-Palomares
Neumología. Unidad Médico Quirúrgica de Enfermedades Respiratorias.
Instituto de Biomedicina de Sevilla (IBiS)
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Hospital Universitario Virgen del Rocio, Sevilla.

INTRODUCCION

El cáncer asociado a la ETV tiene más riesgo de recurrencias, hemorragias y muerte

- A.Y. Lee, et al. Venous thromboembolism and cancer: risks and outcomes, Circulation 107 (23 Suppl. 1) (2003) I17–I21, http://dx.doi.org/10.1161/01.CIR. 0000078466.72504.AC.
- A.Y. Lee, et al. Treatment of cancer-associated thrombosis, Blood 122 (14) (2013) 2310–2317, http://dx.doi.org/10.1182/blood-2013-04-460162.
- J.F. Timp, et al. Epidemiology of cancer-associated venous thrombosis, Blood 122 (10) (2013) 1712–1723, http://dx.doi.org/10.1182/blood-2013-04-460121.
- G. Gussoni, et al. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry, Thromb. Res. 131 (1) (2013) 24–30, http://dx.doi.org/10.1016/j.thromres.2012.10.007.

Tratamiento Anticoagulante

AVK

- Acenocumarol
- Warfarina

HBPM

- Enoxaparina
- Tinzaparina
- Bemiparina
- Dalteparina
- Fraxiparina

DOAC

- Rivaroxaban
- Apixaban
- Edoxaban
- Dabigatran

Ensayos clínicos comparando HBPM vs. AVK

	Number of patients	LMWH	Dosage and duration
Patients with cancer			
CLOT; Lee et al (2003)[25]	672	Dalteparin	200 IU/kg once per day for 1 month, 150 IU/kg per day for 5 months
CATCH; Lee et al (2015)[26]	900	Tinzaparin	175 IU/kg once per day for 6 months
LITE; Hull et al (2006)[42]	200	Tinzaparin	175 IU/kg once per day for 3 months
CANTHANOX; Meyer et al (2002)[43]	146	Enoxaparin	1·5 mg/kg once per day for 3 months
ONCENOX; Deitcher et al (2006)[44]	122	Enoxaparin	1 mg/kg twice per day for 5 days, 1·0 mg/kg or 1·5 mg/kg once per day for 6 months
Unselected patients			
Lopez-Beret et al (2001)[45]	158	Nadroparin	0·1 mL/10 kg twice per day for 3 to 6 months
Romera et al (2009)[46]	241	Tinzaparin	175 IU/kg once per day for 6 months

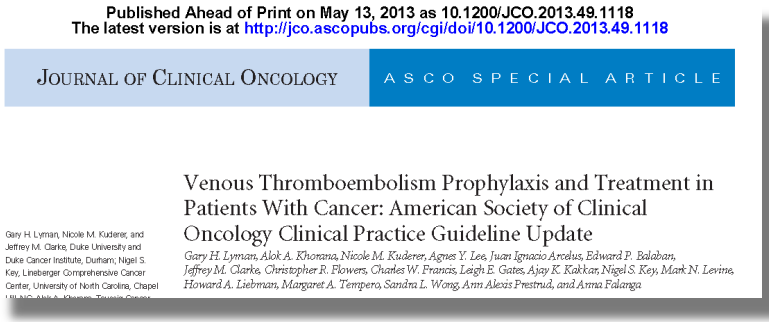
Early maintenance was 10 days to 3 months. Long-term treatment was more than 3 months. LMWH=low-molecular-weight heparin.

Table 1: **Trials comparing LMWH with LMWH plus vitamin K antagonists in early maintenance and long-term treatment of venous thromboembolism**

International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

www.thelancet.com/oncology **Vol 17 October 2016**

Dominique Farge, Henri Bounameaux, Benjamin Brenner, Francis Cajfinger, Philippe Debourdeau, Alok A Khorana, Ingrid Pabinger, Susan Solymoss, James Douketis, Ajay Kakkar

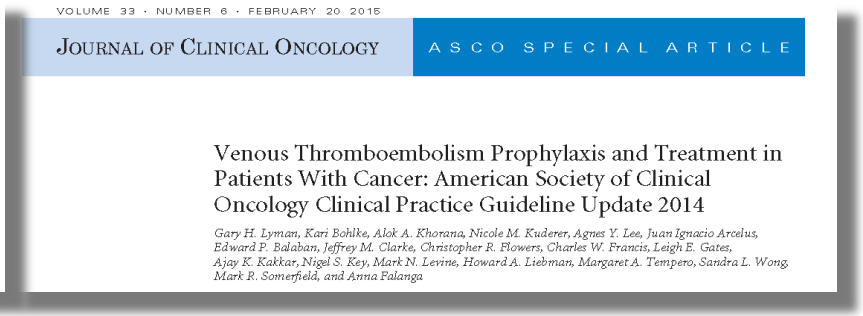

Published Ahead of Print on May 13, 2013 as 10.1200/JCO.2013.49.1118
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.49.1118

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Gary H. Lyman, Nicole M. Kuderer, and Jeffrey M. Clarke, Duke University and Duke Cancer Institute, Durham; Nigel S. Key, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel

Gary H. Lyman, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Ann Alexis Prestrud, and Anna Falanga


VOLUME 33 · NUMBER 6 · FEBRUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014

Gary H. Lyman, Kari Bohlke, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Mark R. Somerfield, and Anna Falanga

En cáncer asociado a la ETV: HBPM al menos 6 meses.

[Evidence-Based Medicine]

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

CHEST

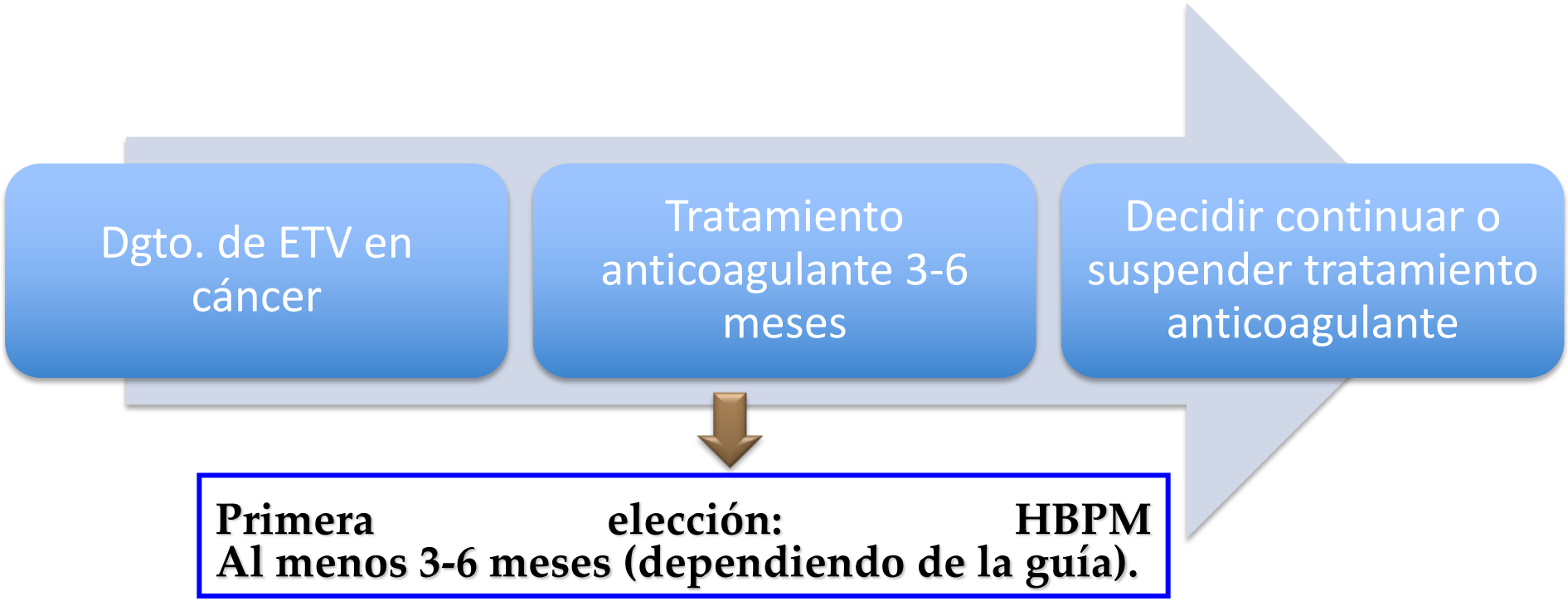
CrossMark

CHEST 2016; 149(2):315-352

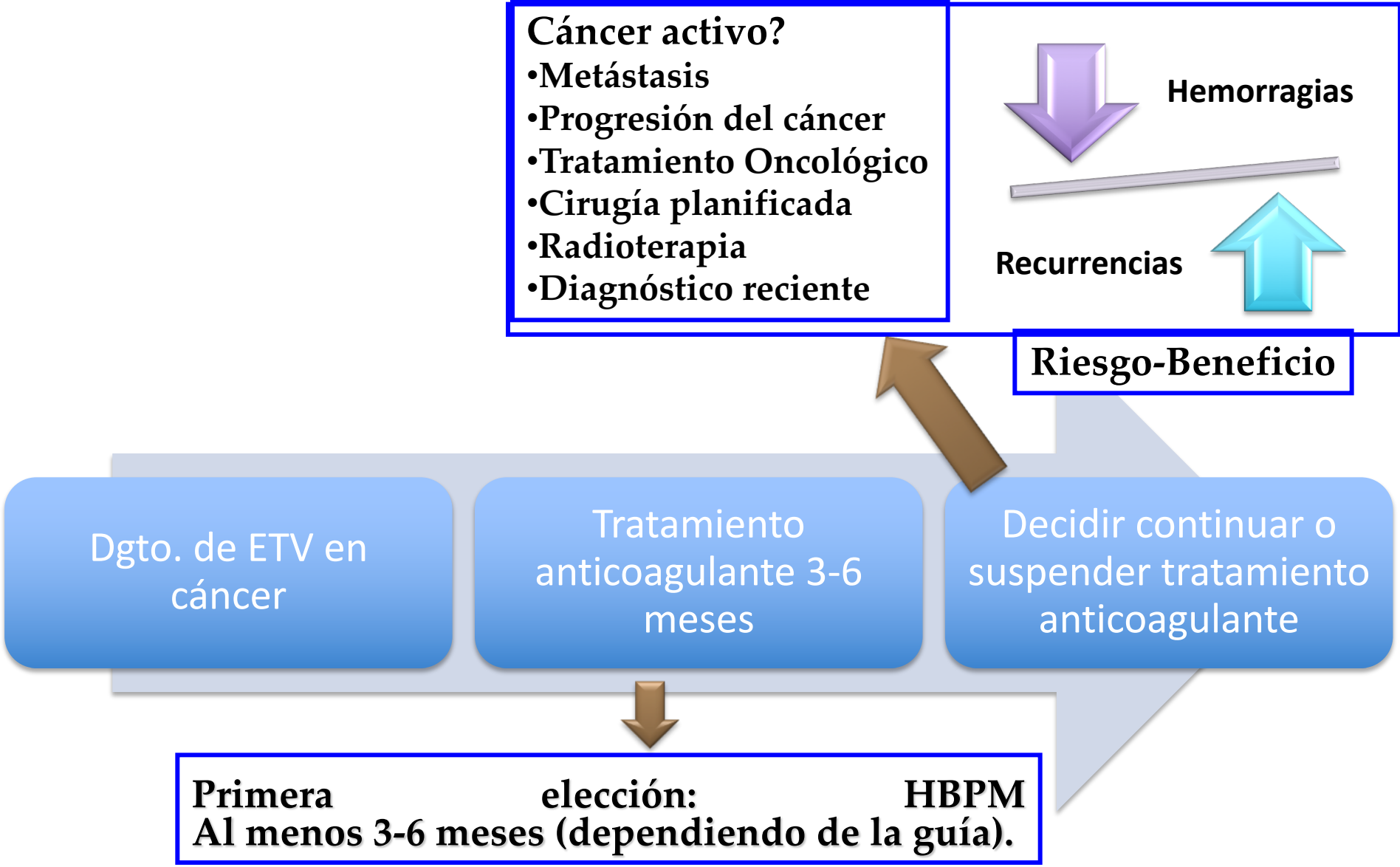
En cáncer asociado a la ETV: HBPM al menos 3 meses.

EN ETV ASOCIADA A CÁNCER

EL PACIENTE SE IRÁ DEL HOSPITAL CON HBPM



J. Clin. Oncol. 2015; 33 (6) (2014) 654–656.
Chest. 2016 Feb;149(2):315-52. doi: 10.1016/j.chest.2015.11.026.



J. Clin. Oncol. 2015; 33 (6) (2014) 654–656.
Chest. 2016 Feb;149(2):315-52. doi: 10.1016/j.chest.2015.11.026.

Actualmente hay pocos datos que soporten la utilización de HBPM más allá de 6 meses

Clini
A service of

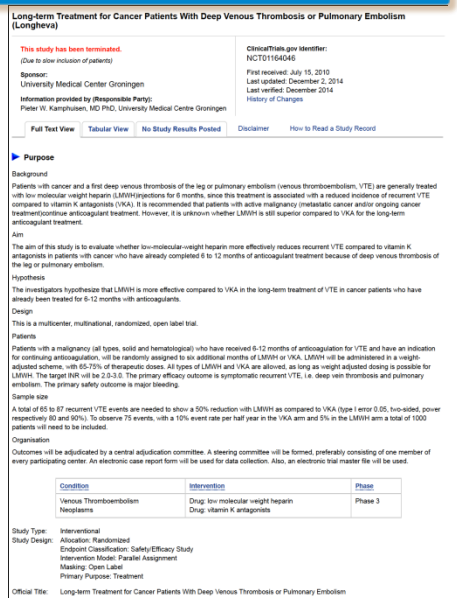
for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Long-term Treatment … ep Venous Thrombosis or Pulmonary Embolism (Longheva)

Condition		Phase
Venous Thromboembolism Neoplasms	Drug … arin	Phase 3

Interventional
Allocation: Randomized
Endpoint Classification: Safety/Efficacy
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

N=1000 PATIENTS


Long-term Treatment for Cancer Patients With Deep Venous Thrombosis or Pulmonary Embolism (Longheva)

This study has been terminated.
(Due to slow inclusion of patients)

Sponsor:
University Medical Center Groningen

Information provided by (Responsible Party):
Pieter W. Kamphuisen, MD PhD, University Medical Centre Groningen

ClinicalTrials.gov Identifier:
NCT01164046

First received: July 15, 2010
Last updated: December 2, 2014
Last verified: December 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

Background

Patients with cancer and a first deep venous thrombosis of the leg or pulmonary embolism (venous thromboembolism, VTE) are generally treated with low molecular weight heparin (LMWH)injections for 6 months, since this treatment is associated with a reduced incidence of recurrent VTE compared to vitamin K antagonists (VKA). It is recommended that patients with active malignancy (metastatic cancer and/or ongoing cancer treatment)continue anticoagulant treatment. However, it is unknown whether LMWH is still superior compared to VKA for the long-term anticoagulant treatment.

Aim

The aim of this study is to evaluate whether low-molecular-weight heparin more effectively reduces recurrent VTE compared to vitamin K antagonists in patients with cancer who have already completed 6 to 12 months of anticoagulant treatment because of deep venous thrombosis of the leg or pulmonary embolism.

Hypothesis

The investigators hypothesize that LMWH is more effective compared to VKA in the long-term treatment of VTE in cancer patients who have already been treated for 6-12 months with anticoagulants.

Design

This is a multicenter, multinational, randomized, open label trial.

Patients

Patients with a malignancy (all types, solid and hematological) who have received 6-12 months of anticoagulation for VTE and have an indication for continuing anticoagulation, will be randomly assigned to six additional months of LMWH or VKA. LMWH will be administered in a weight-adjusted scheme, with 65-75% of therapeutic doses. All types of LMWH and VKA are allowed, as long as weight adjusted dosing is possible for LMWH. The target INR will be 2.0-3.0. The primary efficacy outcome is symptomatic recurrent VTE, i.e. deep vein thrombosis and pulmonary embolism. The primary safety outcome is major bleeding.

Sample size

A total of 65 to 87 recurrent VTE events are needed to show a 50% reduction with LMWH as compared to VKA (type I error 0.05, two-sided, power respectively 80 and 90%). To observe 75 events, with a 10% event rate per half year in the VKA arm and 5% in the LMWH arm a total of 1000 patients will need to be included.

Organisation

Outcomes will be adjudicated by a central adjudication committee. A steering committee will be formed, preferably consisting of one member of every participating center. An electronic case report form will be used for data collection. Also, an electronic trial master file will be used.

Condition	Intervention	Phase
Venous Thromboembolism Neoplasms	Drug: low molecular weight heparin Drug: vitamin K antagonists	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Long-term Treatment for Cancer Patients With Deep Venous Thrombosis or Pulmonary Embolism

ESTE ESTUDIO SE TERMINÓ (POR BAJO RECLUTAMIENTO DE PACIENTES)

TRATAMIENTO ANTICOAGULANTE MÁS ALLÁ DE 6 MESES EN CANCER ASOCIADA A TROMBOSIS

Journal of Thrombosis and Haemostasis, 13: 1–8 DOI: 10.1111/jth.12923

ORIGINAL ARTICLE

Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study

C. W. FRANCIS,* C. M. KESSLER,† S. Z. GOLDHABER,‡ M. J. KOVACS,§ M. MONREAL,¶ M. V. HUISMAN,** D. BERGQVIST,†† A. G. TURPIE,‡‡ T. L. ORTEL,§§ A. C. SPYROPOULOS,* I. PABINGER¶¶ and A. K. KAKKAR***

J Thromb Haemost 2015; DOI: 10.1111/jth.12923.

OBJETIVO: SEGURIDAD de Dalteparina desde el mes 7-12 en ETV asociada a cáncer

TRATAMIENTO ANTICOAGULANTE MÁS ALLÁ DE 6 MESES EN CANCER ASOCIADA A TROMBOSIS

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J Thromb Haemost 2015; DOI: 10.1111/jth.12923.

Table 3 Incidence of adjudicated new or recurrent venous thromboembolism (deep vein thrombosis/pulmonary embolism)

Total (N = 334)

Time period	Incidence n/N[a]	(%)	95% confidence interval[b]
1–6 months	29/334	8.7	5.9, 12.2
7–12 months	8/194	4.1	1.8, 8.0

Table 2 Incidence of major bleeding*

Total (N = 334)

Time period	Incidence n/subject months at risk[b]	%	95% confidence interval[a]
1–6 months	26/1571	1.7	1.1, 2.4
7–12 months	8/1086	0.7	0.3, 1.4

- Dalteparina tiene un perfil de seguridad
- Las hemorragias mayores fueron menos frecuentes en el segundo periodo de estudio (7 – 12 months)

Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study

Luis Jara-Palomares [a,*], Aurora Solier-Lopez [a], Teresa Elias-Hernandez [a], Maribel Asensio-Cruz [a], Isabel Blasco-Esquivias [b], Lucia Marin-Barrera [a], Maria Rodriguez de la Borbolla-Artacho [c], Juan Manuel Praena-Fernandez [d], Emilio Montero-Romero [e], Silvia Navarro-Herrero [f], Maria Pilar Serrano-Gotarredona [f], José María Sánchez-Díaz [g], Carlos Palacios [e], Remedios Otero [a]

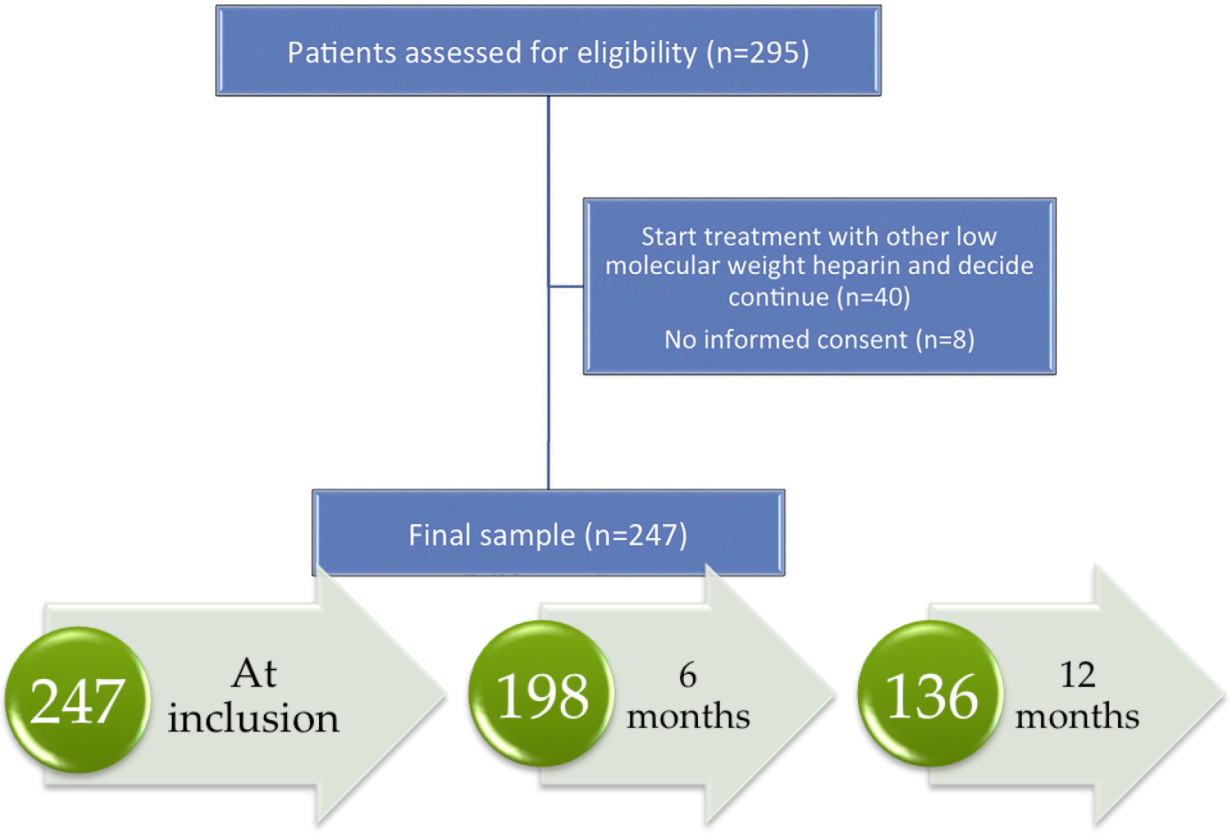
Thrombosis Research 157 (2017) 90–96

Thrombosis Research 157 (2017) 90–96

OBJETIVO:
Seguridad de Tinzaparina en el periodo 7-12 meses en cancer asociada a trombosis

Multicentre, open, single-arm study in adult patients with active cancer

January 2009 to September 2015



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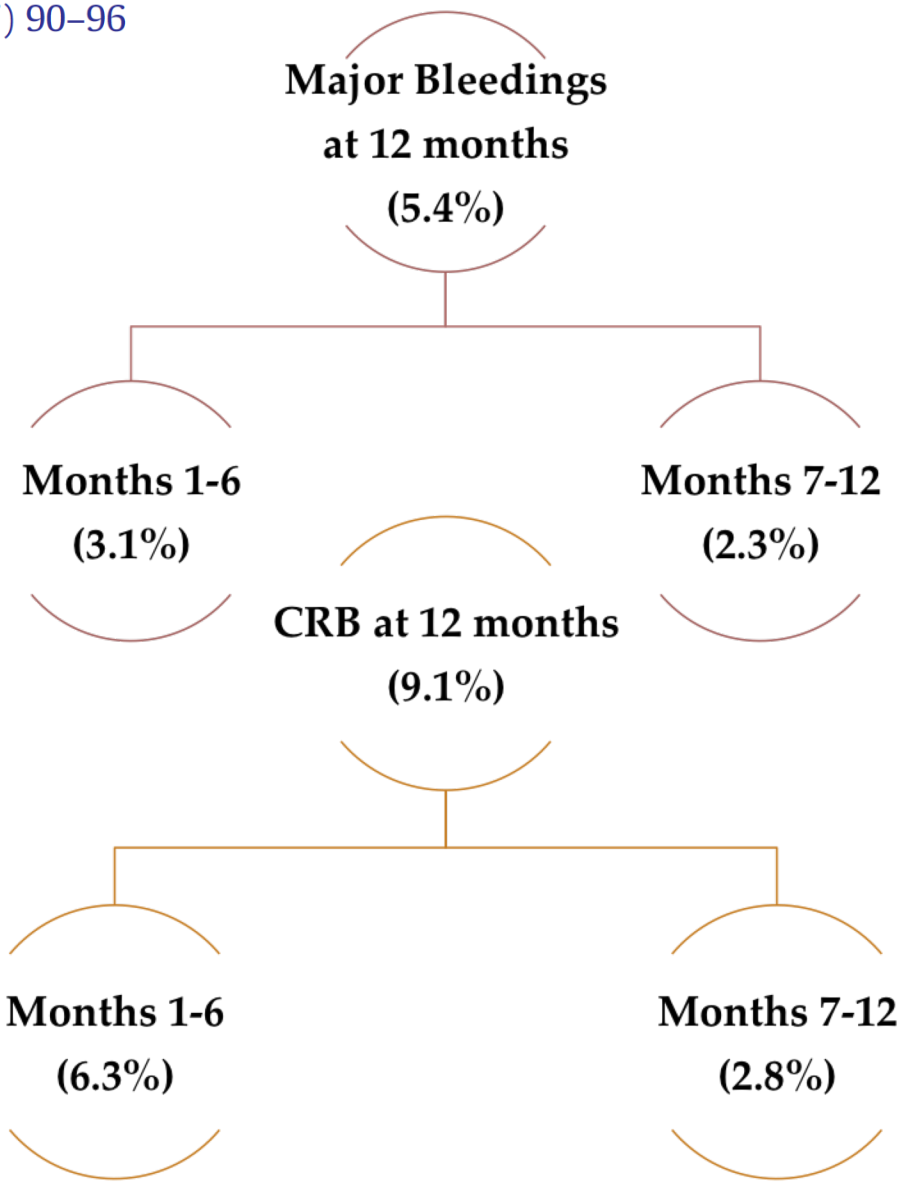
Thrombosis Research 157 (2017) 90–96

CRB: Clinically Relevant Bleeding
MB: Major Bleeding
NM-CRB: Non Major Clinically Relevant Bleeding



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Thrombosis Research 157 (2017) 90–96

- El tratamiento con tinzaparina tiene un perfil de seguridad en pacientes con cáncer y ETV, más allá de los 6 meses

- En los pacientes oncológicos con ETV, Tinzaparina y Dalteparina son seguras más allá de los 6 primeros meses.

TEP incidental

Luis Jara-Palomares
Neumología. Unidad Médico Quirúrgica de Enfermedades Respiratorias.
Instituto de Biomedicina de Sevilla (IBiS)
Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES)
Hospital Universitario Virgen del Rocío, Sevilla.

INTRODUCCION

TEP Incidental: Defecto de repleción de arteria pulmonar NO SOSPECHADO, identificado en un TAC de tórax de rutina por otro motivo.

TEP incidental:

- Cáncer.
- Estudio coronario
- Infecciones pulmonares
- Politrauma.

En EE. UU., ETV incidentales: 375.000-425.000/año

- Coste: $7 billones - $10 billones.

No hay ensayos clínicos en marcha

Tema de debate

Di Nisio M, Lee AY, Carrier M, et al. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost 2015; 13: 880–883.

Grosse SD, Nelson RE, Nyarko KA, et al. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res 2016; 137: 3–10.

En cancer

- Estudio para ver TEP incidental en cáncer en AngioTAC (4 coronas)
  (Sebastian AJ. Clin Radiol 2006)
  - N=385
  - Incidencia: 2.6% (IC95% 1.2–4.7).

- Análisis conjunto de 8 estudios (n=8491) utilizando Angio-TAC modernos
  - Incidencia: 3.6% (IC95% 2.6–4.6)

- TAC antiguos vs. modernos:
  - TAC antiguos: 1.8% (3 estudios, 3253 pacientes; IC95% 0.64–2.9)
  - TAC modernos: 3.3% (3 estudios, 3465 pacientes; IC95% 1.60–5.0)

- Los pacientes con metástasis tienen más riesgo de TEP incidental que aquellos con enfermedad limitada.

Cronin CG. AJR Am J Roentgenol 2007.
Rita LA. Radiology 2007.
Browne AM. J Thorac Oncol 2010.
Tresoldi S. Eur Radiol 2015. Bach AG. Clin Imaging 2015.
Larsen AC. Br J Surg 2014.
Gladish GW. Radiology 2006; 240: 246–255.

RESUMEN DE ESTUDIOS PREVIOS

Estudio	DISEÑO	N patientes	Localización de cáncer	TAC de reevaluación	TAC (coronas)	Grosor TAC	TEP Incidental
Gosselin et al. (1998)	Prospectivo	588	Varios	Si	4-coronas	5-8 mm	10 (1.7%)
Boswell et al. (2004)	Prospectivo	2085	Varios	----	----	2 mm	44 (2.1%)
Storto et al. (2005)	Retrospectivo	410	Varios	Si	4-coronas	5 mm	14 (3.4%)
Sebastian et al. (2006)	Prospectivo	385	Varios	No	4-coronas	5-8 mm	10 (2.6%)
Gladish et al. (2006)	Retrospectivo	403	Varios	Si	4-coronas	3.75 mm	16 (4%)
Cronin et al. (2007)	Retrospectivo	397	Varios	Si	----	8 mm	13 (3.3%)
Larici et al. (2007)	Retrospectivo	787	Varios	Si	16-coronas	2.5 mm	15 (1.9%)
Ritchie et al. (2007)	Prospectivo	343	Varios	Si	4 o 16-coronas	1-3 mm	18 (5.2%)
Hui et al. (2008)	Retrospectivo	765	Varios	Si	16-coronas	2.5 mm	17 (2.2%)
Sun et al. (2010)	Retrospectivo	8014	Lung	No	----	----	180 (2.2%)
Farrel et al. (2010)	Retrospectivo	342	Varios	Si	4 o 16-coronas	1-3 mm	6 (1.8%)
Di Nisio et al. (2010)	Retrospectivo	1921	Tumor sólido	Si	----	----	24 (1.2%)
Browne et al. (2010)	Prospectivo	407	Varios	Si	64-coronas	1-5 mm	18 (4.4%)
Menapace et al. (2011)	Retrospectivo	135	Pancreas	No	----	----	4 (3%)
Shingare et al. (2011)	Retrospectivo	13783	Varios	No	4 o 64-coronas	5-7 mm	395 (2.9%)
Bach et al. (2013)	Prospectivo	3270	Varios	Si	64-coronas	5 mm	123 (3.9%)

SILENTE ES LO MISMO QUE INCIDENTAL?

- **LA MAYORÍA DE LOS PACIENTES PRESENTAN SÍNTOMAS**

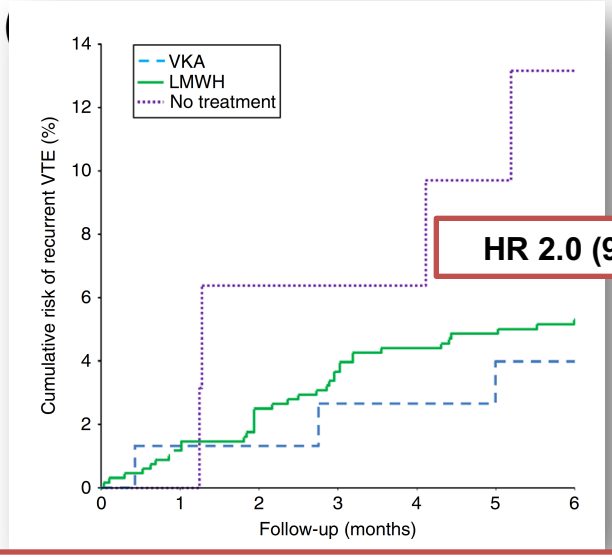
- Estudio casos controles retrospectivo (46 casos/92 controles)
  - (O'Connell CL. J Clin Oncol 2006).
  - **El 75% >1 síntoma.**

- Estudio de cohortes observacional (O'Connell CL. J Clin Oncol 2011)
  - **El TEP incidental 'sintomático' se asoció a peor supervivencia que el TEP incidental 'sintomático'**
  - Esto debe verificarse en otros trabajos

'incidental' ≠ 'asintomático'

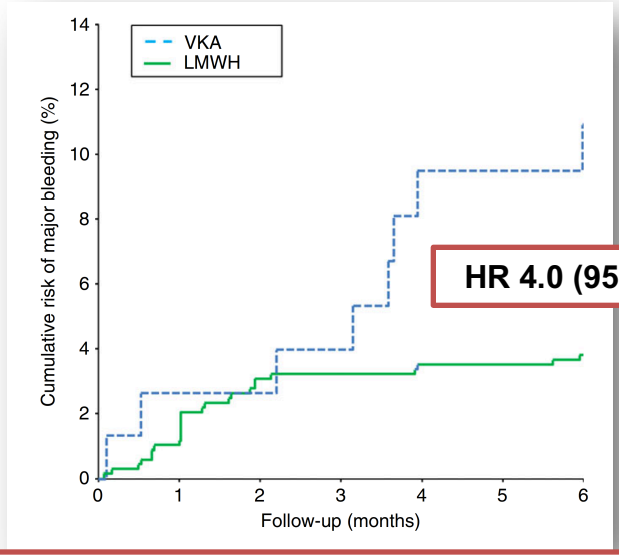
DATOS CLÍNICOS EN TEP INCIDENTAL

- **META-ANÁLISIS DE DATOS DE PACIENTES** (926 pacientes)
  - (van der Hulle T. J Thromb Haemost 2016; 14: 105–113).
  - TEP Incidental no tratados: Riesgo de ETV recurrente a 6 meses (12%) y mortalidad



HR 2.0 (95% CI 0.65–5.9)

adjusted for age, sex, type of cancer, and cancer stage.



HR 4.0 (95% CI 1.5–10)

adjusted for age, sex, type of cancer, and cancer stage

- **TEP Incidental vs. sintomático**: Supervivencia similar
  - (Dentali F. J Thromb Haemost 2011; 9: 1081–1083; den Exter PL. J Clin Oncol 2011; 29: 2405–2409)

TRATAMIENTO DEL TEP INCIDENTAL

- **EL MISMO TRATAMIENTO** para TEP incidental o sintomático
  - ACCP Grado 2B (Kearon C, Chest 2016)
  - ASCO, Consenso informal, recomendación moderada (Lyman GH. J Clin Oncol 2013).

  - **La mayoría de ellos pueden ser tratados de forma ambulatoria**
  - Evaluar situación clínica

- Tratamiento estándar: **Heparina de bajo peso molecular (HBPM) 3-6 meses.**
  - La HBPM se asocia con menos hemorragias y menos ETV recurrente, en comparación con AVK.

- Dado el riesgo similar del TEP sintomático, las guías actuales sugieren **continuar con el tratamiento anticoagulante** si el cáncer no está curado

Management of incidental pulmonary embolism

Frederikus A. Klok and Menno V. Huisman

@ERSpublications
Update in diagnosis and treatment of incidental pulmonary embolism http://ow.ly/qyIb30bRwvE

Cite this article as: Klok FA, Huisman MV. Management of incidental pulmonary embolism. *Eur Respir J* 2017; 49: 1700275 [https://doi.org/10.1183/13993003.00275-2017].

TABLE 1 Overview and practical aspects of management of incidental pulmonary embolism (PE)

Optimal anticoagulant regime	
Cancer-associated incidental PE	LMWH for the first 6 months Alternatively: switch to VKA if subcutaneous therapy is not tolerated
Optimal treatment duration	
Cancer- associated incidental PE	At least 6 months and beyond for the duration of active disease

CONCLUSIONES

- El TEP incidental es un hallazgo frecuente en el TAC de rutina, con una incidencia del 3.6% en pacientes oncológicos

- La incidencia de TEP incidental sub-segmentario se ha incrementado en los años recientes por los avances tecnológicos.

- El curso natural del TEP incidental es comparable al TEP sintomático (en cuanto a ETV recurrente y mortalidad)

- Las guías sugieren el mismo manejo clínico para los pacientes con TEP incidental y TEP sintomático, incluyendo el fármaco, manejo y duración.