I Sessione; come trattare i pazienti complessi con trombosi venose

Varese
10-11 Marzo 2016

Trombosi Venose Cerebrali

Francesco Dentali
Dipartimento di Medicina Clinica
Università dell' Insubria, Varese

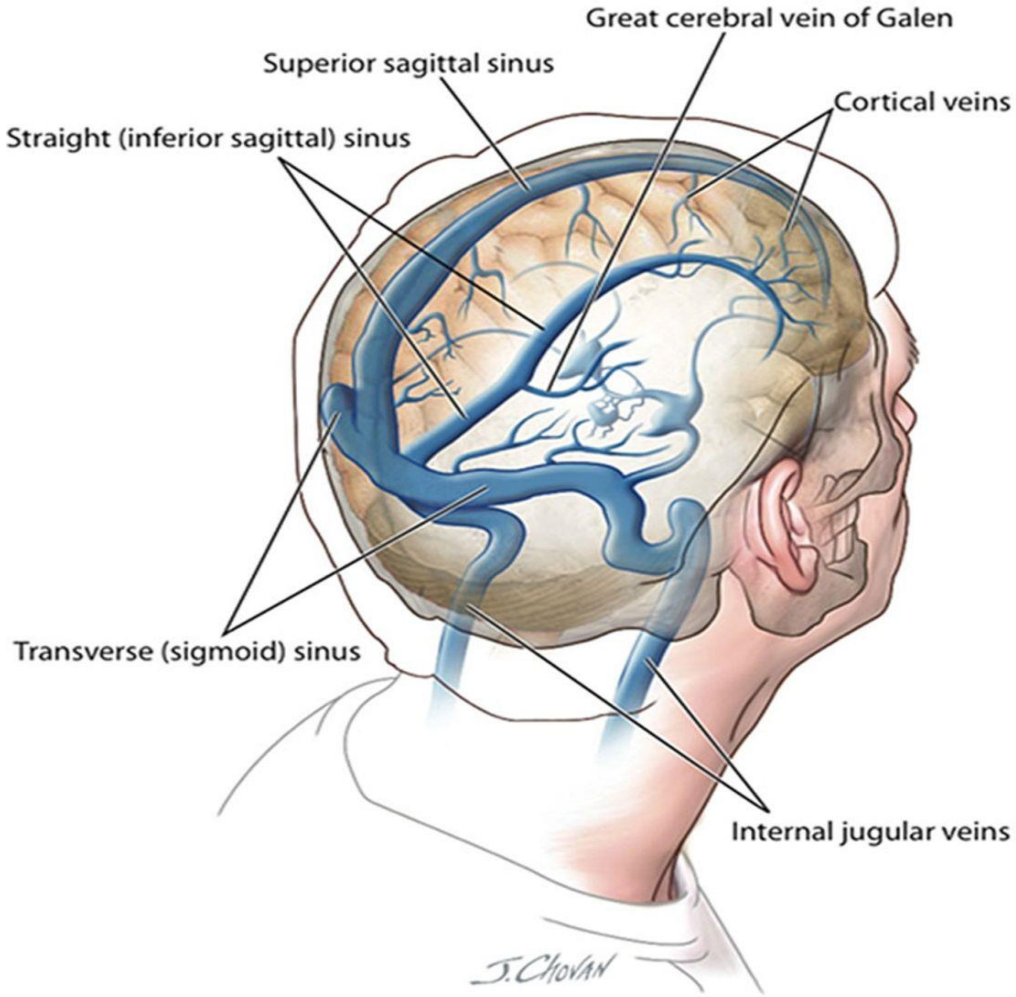
Conflitti di Interesse

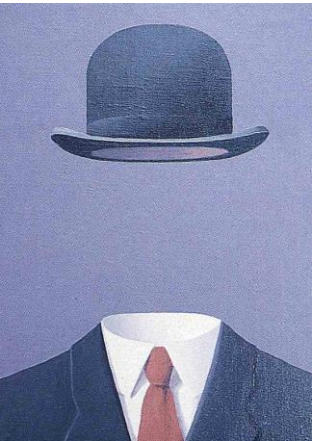
Letture
Protocolli di Ricerca
Advisory Boards

- Bayer
- BMS/Pfizer
- Boheringer
- Daiichi
- Sanofi
- Alfa Wasserman

Di cosa parliamo?

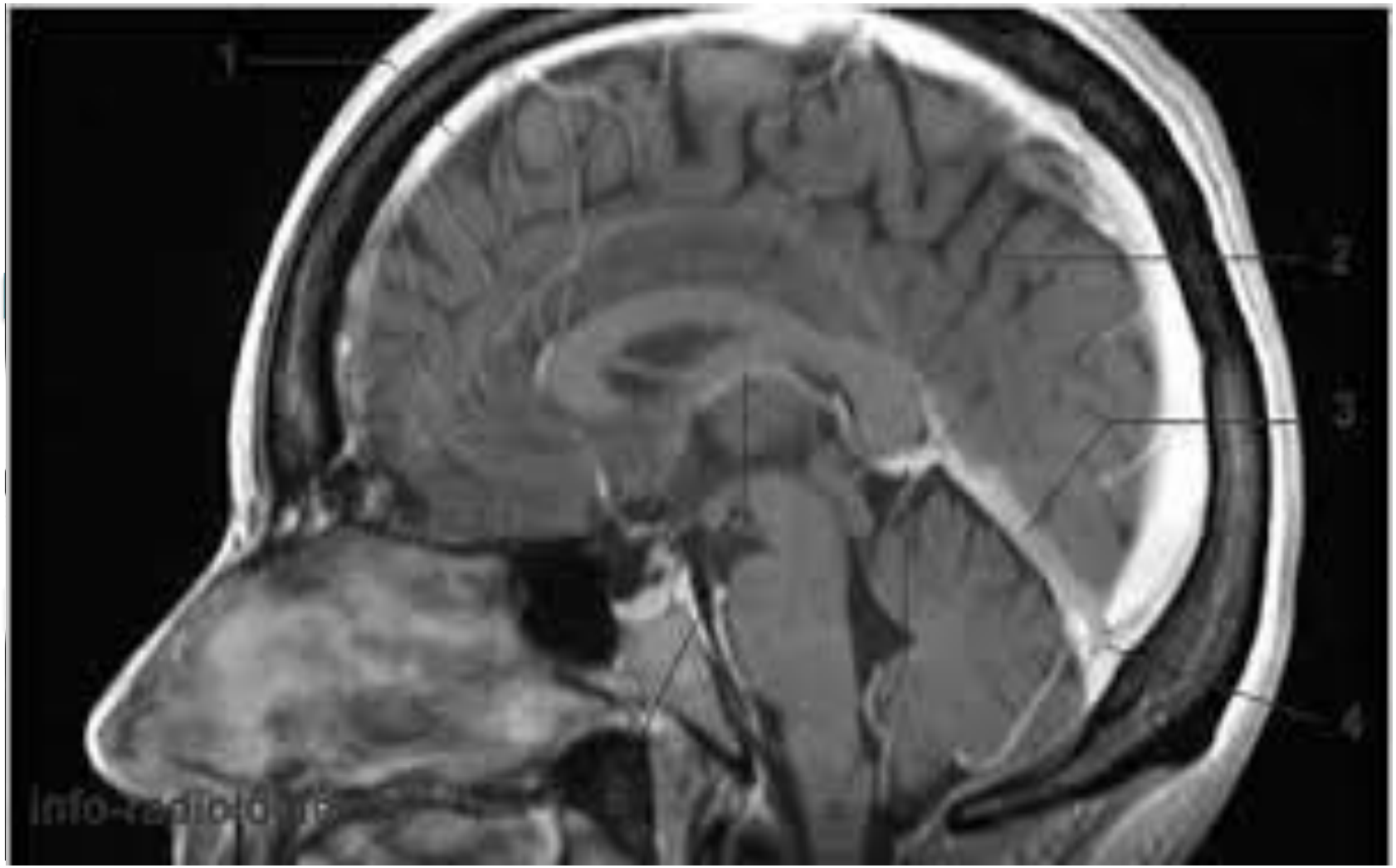
The anatomy and terminology of the cerebral and sinus veins.





Moll and Waldron; Circulation. 2014

Incidenza



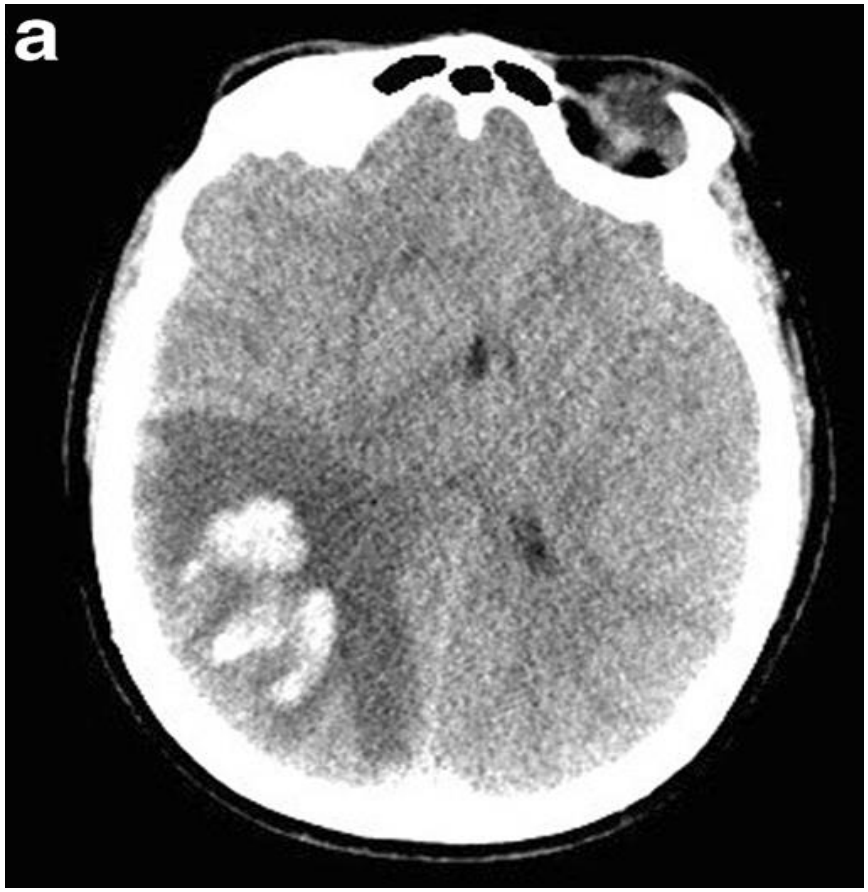
Coutinho et al; Stroke 2012

ORIGINAL ARTICLE

Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study

F. DENTALI[*], D. POLI[†], U. SCODITTI[‡], M. N. D. DI MINNO[§], V. D. STEFANO[¶], S. SIRAGUSA[**], M. KOSTAL[††], G. PALARETI[‡‡], M. T. SARTORI[§§], E. GRANDONE[¶¶], M. C. VEDOVATI[***], W. AGENO[*] and FOR THE CEVETIS (CEREBRAL VEIN THROMBOSIS INTERNATIONAL STUDY) INVESTIGATORS[1]

Total number, *n*	706
Male gender, *n* (%)	186 (26.3)
Mean age, years (± SD)	40.0 (16.3)
Principal sites of thrombosis, *n* (%)	Superior sagittal sinus 267 (37.8)
	Left lateral sinus 281 (39.8)
	Right lateral sinus 225 (31.9)
Concomitant intracranial hemorrhage, *n* (%)	197 (27.9)
Risk factors at first CVT, *n* (%)	Infections 59 (8.3)
	Trauma 18 (2.5)
	OC or HRT 278 (39.4)
	Pregnancy/puerperium 55 (7.8)
	Cancer or MPD 52 (7.4)
	Thrombophilic abnormalities (one at least) 290 (41.1)
	Severe thrombophilic abnormalities 83 (11.7)
	Unprovoked 312 (44.2)
Personal history of VTE, *n* (%)	54 (7.6)
Family history of VTE, *n* (%)	109 (15.4)



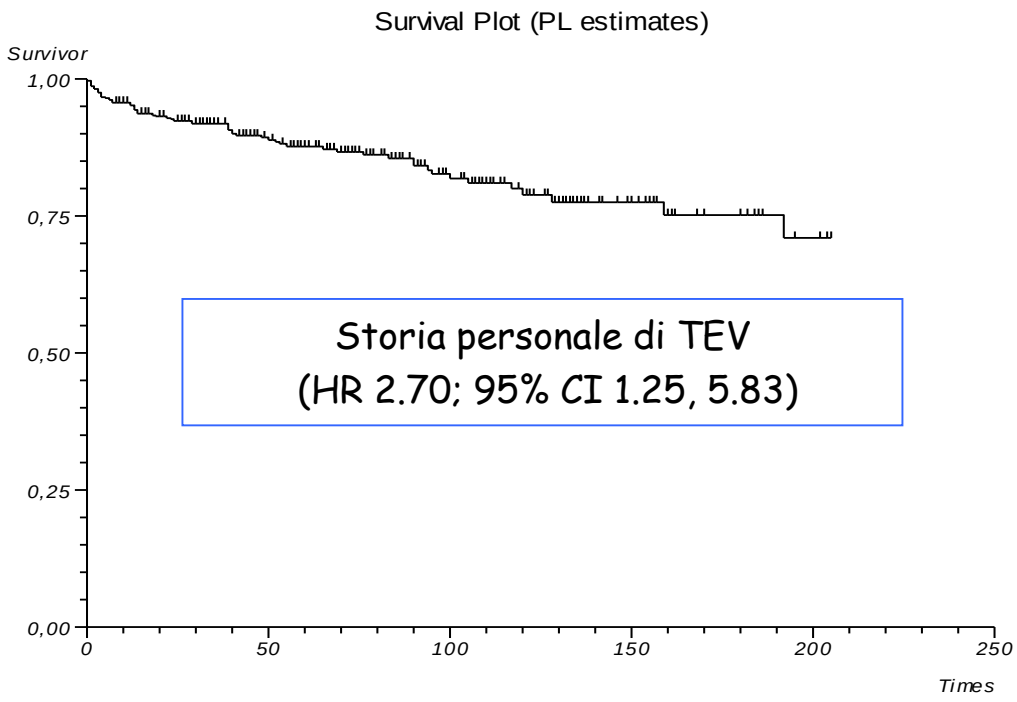
Recidiva

19 studi; 1488 pazienti

Il 2.8% (range 0-11.7%) ha una recidiva di CVT diagnosticata obbiettivamente

Il 3.7% (range 0-8.6%) ha un altro evento tromboembolico venoso durante il follow up

706 pazienti



Storia personale di TEV
(HR 2.70; 95% CI 1.25, 5.83)

Dentali et al; Blood 2006
Dentali er al; JTH 2012

RCT

Terapia Medica ultimi 5 anni

- …
- …
- …

RCT

Terapia Chirurgica ultimi 5 anni

- …
- …
- …

Anticoagulation for Cerebral Vein Sinus Thrombosis

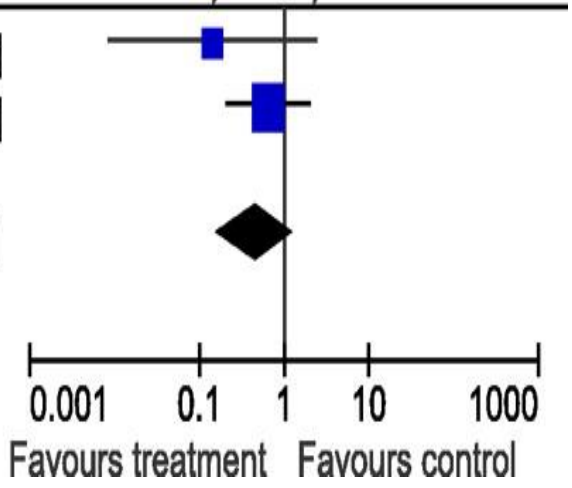
THE COCHRANE COLLABORATION®

Death or Dependency

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Einhaupl 1991	0	10	3	10	36.5%	0.14 [0.01, 2.45]
CVST Group 1999	4	30	6	29	63.5%	0.64 [0.20, 2.05]
Total (95% CI)		40		39	100.0%	0.46 [0.16, 1.31]
Total events	4		9			

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%

Test for overall effect: Z = 1.45 (P = 0.15)

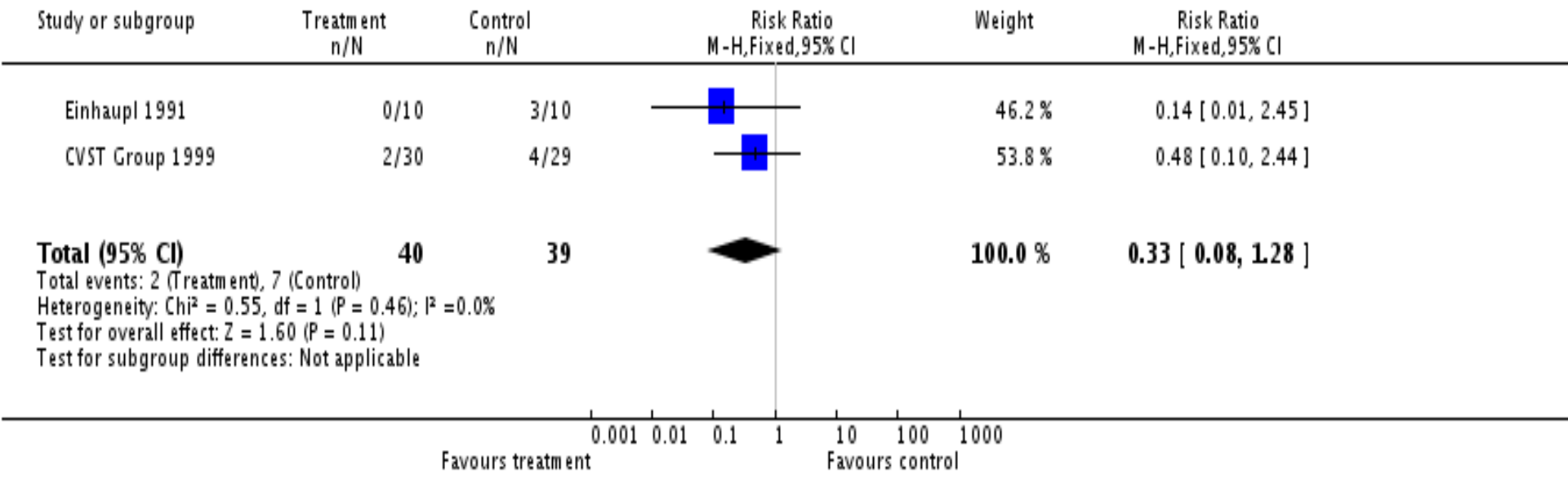


Anticoagulation for Cerebral Vein Sinus Thrombosis

THE COCHRANE COLLABORATION®

Death

Review: Anticoagulation for cerebral venous sinus thrombosis
Comparison: 1 Overall benefit or harm of (LMW) heparin
Outcome: 1 Death



Trattamento Fase Acuta

ISCVT

UFH	64%
LMWH	34.9%
Antiplatelets	5.9%
Thrombolysis	2.1%

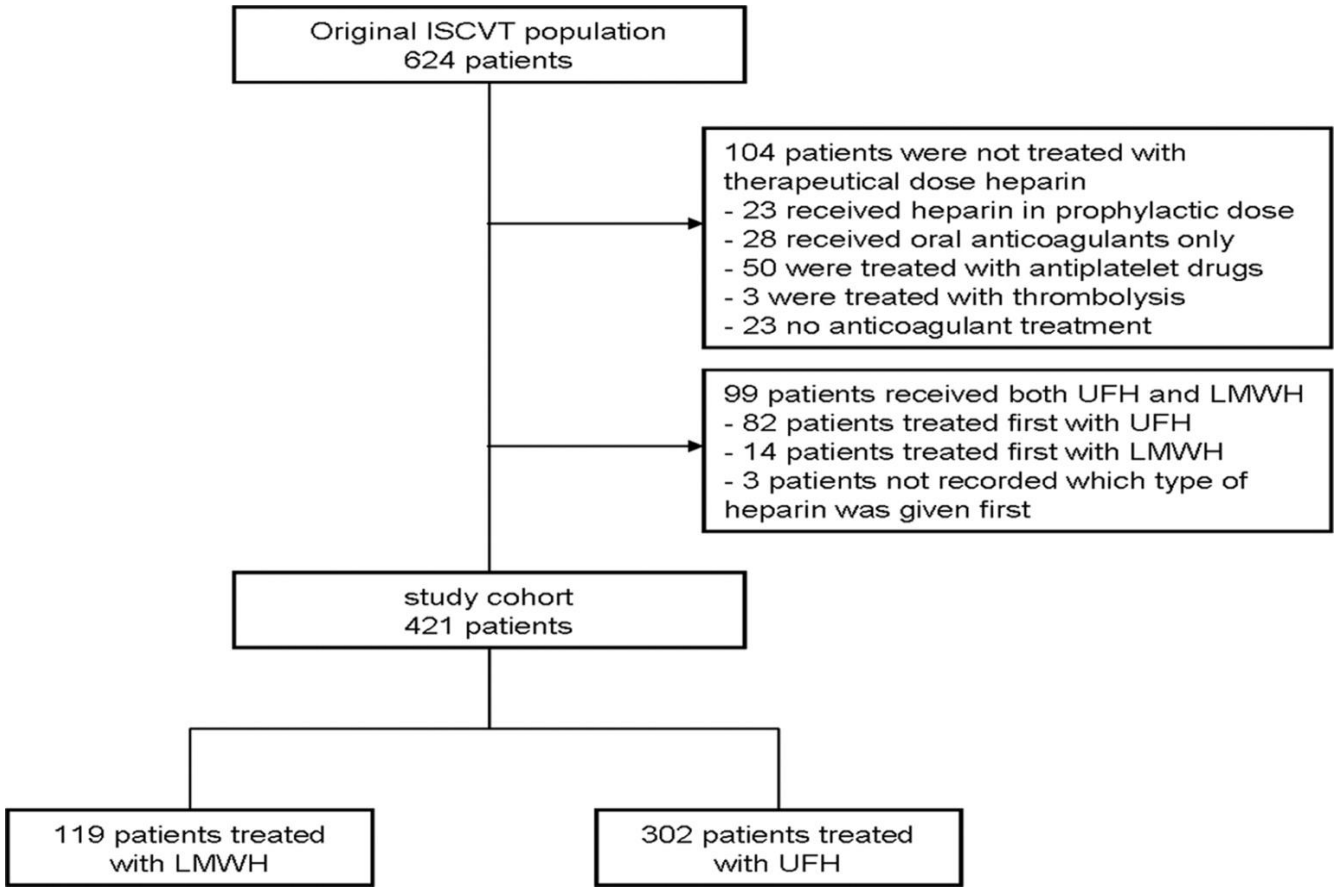
CEVETIS

UFH	21.9%
LMWH	62.7%
Antiplatelets	0%
Thrombolysis	1.5%

Dentali et al; JTH 2012
Ferro et al; Stroke 2004

Unfractionated or Low–Molecular Weight Heparin for the Treatment of Cerebral Venous Thrombosis

Jonathan M. Coutinho, MD; José M. Ferro, MD, PhD; Patrícia Canhão, MD, PhD; Fernando Barinagarrementeria, MD; Marie-Germaine Bousser, MD, PhD; Jan Stam, MD, PhD; for the ISCVT Investigators



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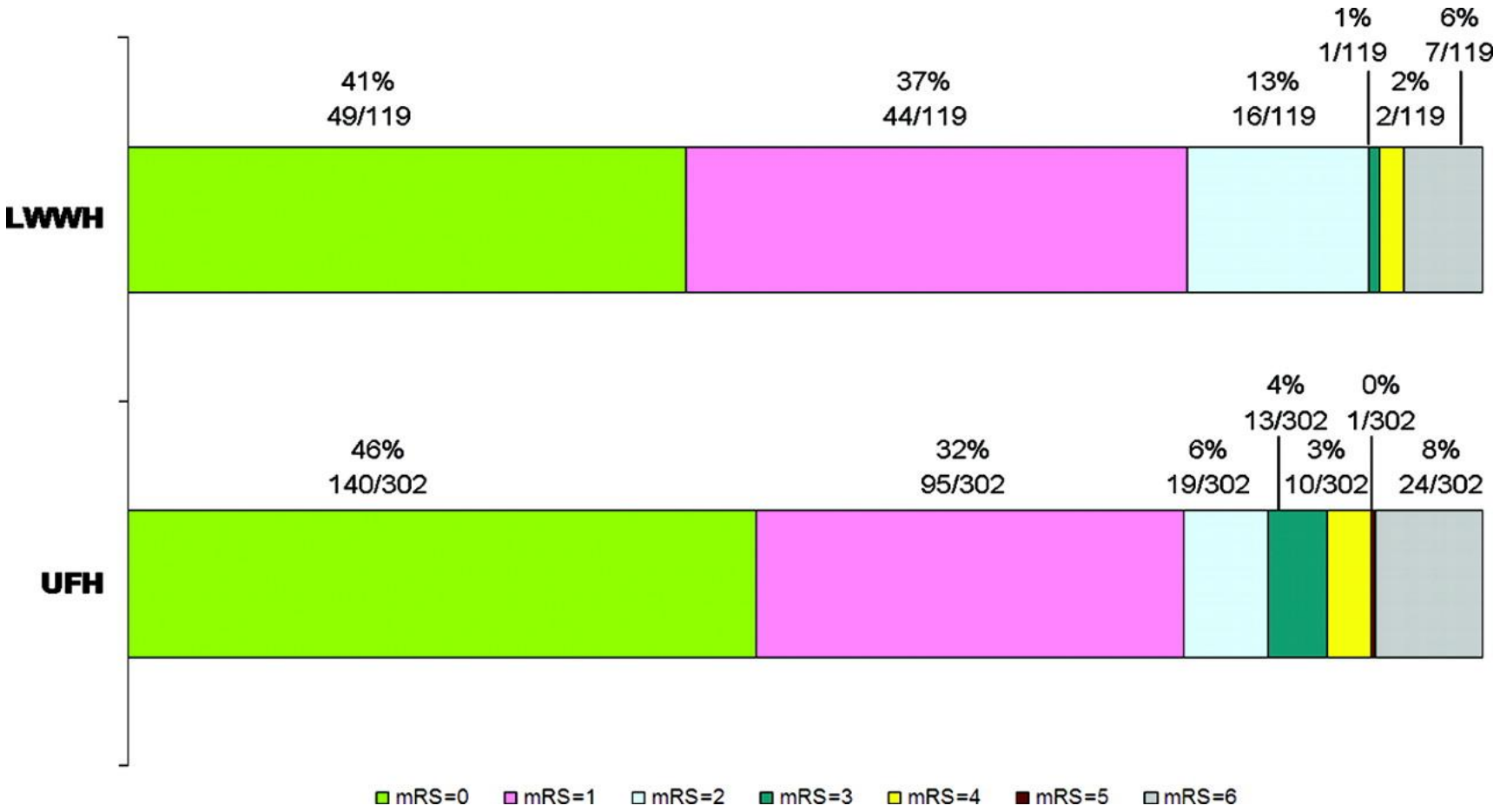

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	LMWH n=119	UFH n=302	Univariate Analysis		Multivariate Analysis†	
			Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Primary end point						
Independency (mRS 0–2)	92%	84%	2.1 (1.0–4.2)	0.04	2.4 (1.0–5.7)	0.04
Secondary end points						
Complete recovery (mRS 0 or 1)	78%	78%	1.0 (0.61–1.7)	0.94	0.94 (0.55–1.9)	0.94
Mortality	6%	8%	0.72 (0.30–1.7)	0.47	0.81 (0.29–2.3)	0.70
New intracranial hemorrhage*	10%	16%	0.61 (0.22–1.7)	0.35	0.29 (0.07–1.3)	0.10

*The percentages of patients who underwent repeated CT or MRI are given.

†*P* value for Hosmer–Lemeshow test was >0.20 and <0.85 for each of the multivariate analyses.

Trombolisi
Revisione sistematica

15 STUDI SELEZIONATI (156 Pazienti)

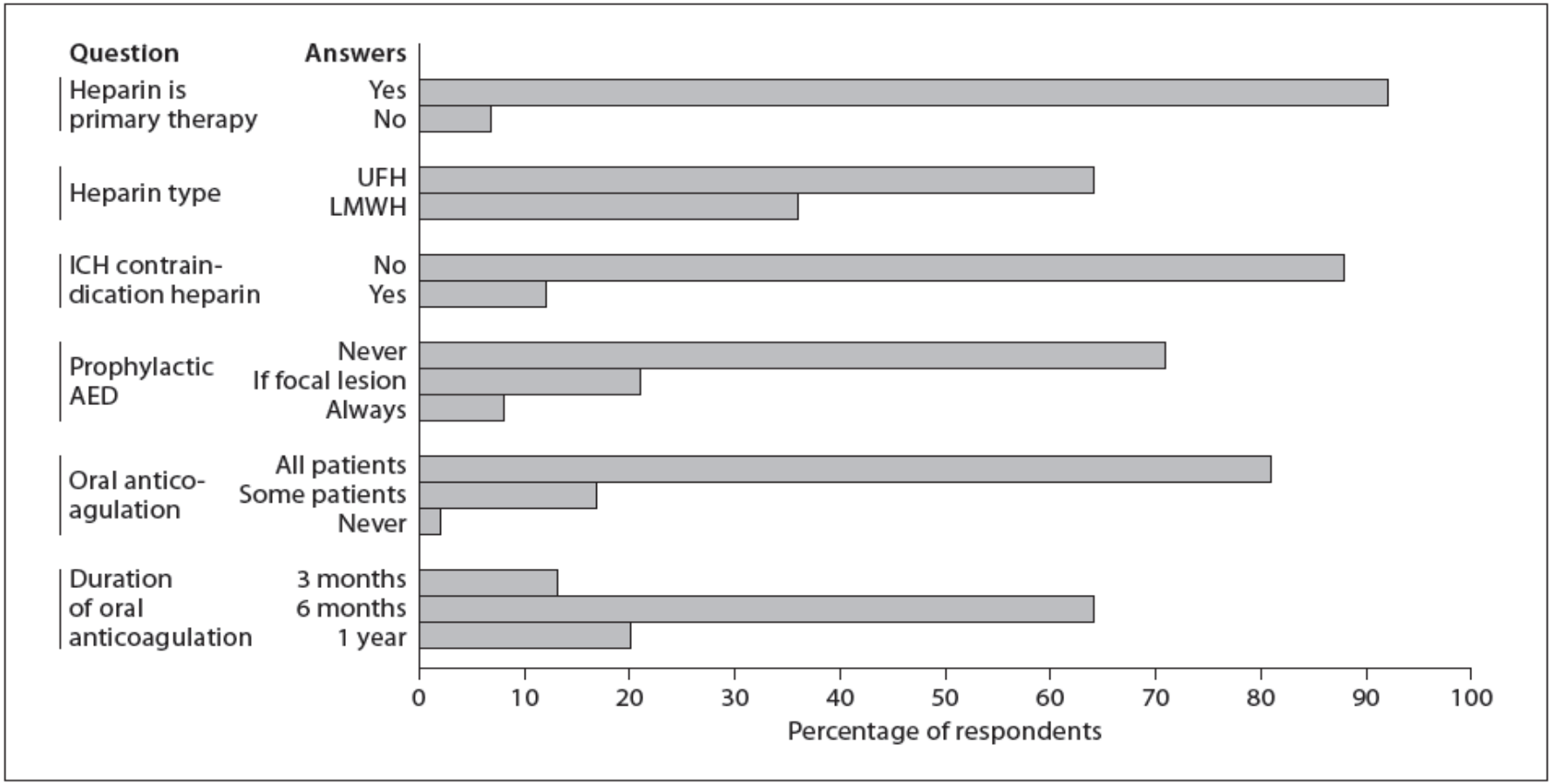
Mortalità	9.2% (95% CI 4.3 – 15.7%)
Emorragia Maggiore	9.8% (95% CI 5.3 – 15.6%)
Emorragia Intracranica	7.6% (95% CI 3.5 – 13.1%)

Dentali et al; Thromb Haem 2010

Cerebrovasc Dis 2011;32:298–300
DOI: 10.1159/000330646

Treatment Variations in Cerebral Venous Thrombosis: An International Survey

J.M. Coutinho[a], R. Seelig[a], M.-G. Bousser[b], P. Canhão[c], J.M. Ferro[c], J. Stam[a]



	With E-ICH (n=245)	Without E-ICH (n=379)	*P*
Demographic characteristics			
Age (median; range)	40 (16–82)	34.5 (16–96)	0.001
Women	189 (76%)	275 (73%)	0.219
Site of venous thrombosis			
Superior sagittal	156 (64%)	231 (61%)	0.546
Left lateral	122 (50%)	156 (41%)	0.039
Right lateral	81 (33%)	176 (47%)	0.001
Deep venous system	28 (11%)	40 (11%)	0.758
Therapeutic heparin	178 (73%)	287 (76%)	0.359
Any treatment heparin	202 (82%)	317 (84%)	0.644
SC heparin/LMWH at preventive dosage	36 (15%)	35 (9%)	0.068
Antiplatelet drugs	52 (21%)	25 (7%)	0.188

ESO EUROPEAN STROKE ORGANISATION
The European Stroke Organisation Conference 2015
17-19 April, 2015
Glasgow, UK

EUROPEAN STROKE ORGANIZATION GUIDELINE ON CEREBRAL VENOUS THROMBOSIS

José M Ferro[1,2], Marie-Germaine Bousser[3], Patrícia Canhão[1,2], Jonathan M Coutinho[4], Isabelle Crassard[3], Francesco Dentali[5], Matteo di Minno[6], Alberto Maino[7], Ida Martinelli[7], Florian Masuhr[8], Diana Aguiar de Sousa[1], Jan Stam[4]

Recommendation: we recommend treating adult patients with acute cerebral venous thrombosis with heparin in therapeutic dosage. This recommendation also applies to patients with an intracerebral hemorrhage at baseline. No recommendation can be given on the treatment of children with CVT.

Quality of evidence: moderate

Strength of recommendation: strong

Recommendation: we suggest treating patients with acute cerebral venous thrombosis with low-molecular weight heparin instead of unfractionated heparin. This recommendation does not apply to patients with a contraindication for LMWH (e.g. renal insufficiency) or situations where fast reversal of the anticoagulant effect is required (e.g. patients who have to undergo neurosurgical intervention).

Quality of evidence: low

Strength of recommendation: weak

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Recommendation: we cannot provide a recommendation on thrombolysis for cerebral venous thrombosis.

Quality of evidence: very low

Strength of recommendation: uncertain

Recommendation. We suggest using oral anticoagulants (vitamin K antagonists) for a variable period (3-12 months) after CVT to prevent recurrent CVT and other venous thromboembolic events

Quality of evidence: very low

Strength of recommendation: weak

Prospettive Future?

Off Label use of DOACs

	nOAC Maintenance, n (%)	No nOAC, n (%)	p
Specialty			
Neurologist	9 (56)	19 (59)	NS
Hematologist	7 (44)	13 (41)	
Duration of practice, y			
Resident/fellow	0 (0)	1 (3)	0.008
<3	0 (0)	7 (21)	
3–5	0 (0)	2 (6)	
6–10	3 (20)	9 (27)	
>10	12 (80)	14 (42)	

Field et al; IJS 2016

Novel Factor Xa Inhibitor for the Treatment of Cerebral Venous and Sinus Thrombosis

First Experience in 7 Patients

Christina Geisbüsch, MD; Daniel Richter, MD; Christian Herweh, MD; Peter A. Ringleb, MD; Simon Nagel, MD

Background and Purpose—Thrombosis of cerebral veins and sinus (cerebral venous thrombosis) is a rare stroke pathogenesis. Pharmaceutical treatment is restricted to heparin and oral anticoagulation with vitamin K antagonists (VKAs).

Methods—Between January 2012 and December 2013, we recorded data from our patients with cerebral venous thrombosis. The modified Rankin scale was used to assess clinical severity; excellent outcome was defined as modified Rankin scale 0 to 1. Recanalization was assessed on follow-up MR angiography. Patients were then divided into 2 treatment groups: phenprocoumon (VKA) and a novel factor Xa inhibitor. Clinical and radiological baseline data, outcome, recanalization status, and complications were retrospectively compared.

Results—Sixteen patients were included, and 7 were treated with rivaroxaban. Overall outcome was excellent in 93.8%, and all patients showed at least partial recanalization. No statistical significant differences were found between the groups, except the use of heparin before start of oral anticoagulation (P=0.03). One patient in the VKA and 2 patients in the factor Xa inhibitor group had minor bleeding (P=0.55) within the median (range) follow-up of 8 months (5–26).

Conclusions—Factor Xa inhibitor showed a similar clinical benefit as VKA in the treatment of cerebral venous thrombosis. Further systematic prospective evaluation is warranted. **(*Stroke*. 2014;45:2469-2471.)**

Key Words: cerebral veins ■ rivaroxaban ■ thrombosis

Oral direct thrombin inhibitor as an alternative in the management of cerebral venous thrombosis: a series of 15 patients

Marcelo D. Mendonça[1,2]*, Raquel Barbosa[1], Vera Cruz-e-Silva[3], Sofia Calado[1,2], and Miguel Viana-Baptista[1,2]

Background **Cerebral vein thrombosis is a rare cause of stroke with significant risk of death and long-term dependency. Anticoagulation has been associated with better long-term prognosis, and vitamin K antagonists are usually prescribed in this setting.**

Aim **The aim of this study was to present a series of 15 cerebral vein thrombosis patients treated with dabigatran.**

Methods **Retrospective study of clinical, imaging, and follow-up characterization of all patients admitted with cerebral vein thrombosis and treated with dabigatran in a tertiary neurology department between June 2011 and December 2013 was conducted. Complications and adverse effects were recorded. Modified Rankin Scale was used to assess clinical severity; excellent outcome was defined as modified Rankin Scale at six-months of 0 to 1. Recanalization was assessed with an angiographic method (computer tomography, magnetic resonance imaging, or digital subtraction angiography).**

Results **Eighteen patients were admitted for cerebral vein thrombosis. Dabigatran was started in 11 patients, and warfarin was started in 7. Four patients on warfarin were switched to dabigatran because of adverse effects at 0·5, 1, 3·5, and 4 months. A total of 15 patients were treated with dabigatran with median follow-up time of 19 months. Excellent outcome was observed in 87% of patients and recanalization in 80%.**

Conclusions **We report the largest series of cerebral vein thrombosis patients treated with dabigatran. Clinical outcome was excellent in most patients and not different from other studies. Dabigatran could possibly be considered an alternative to warfarin; nevertheless, further prospective assessment with randomized controlled studies is warranted.**

Key words: anticoagulation, cerebral vein, dabigatran, recanalization, stroke, thrombosis

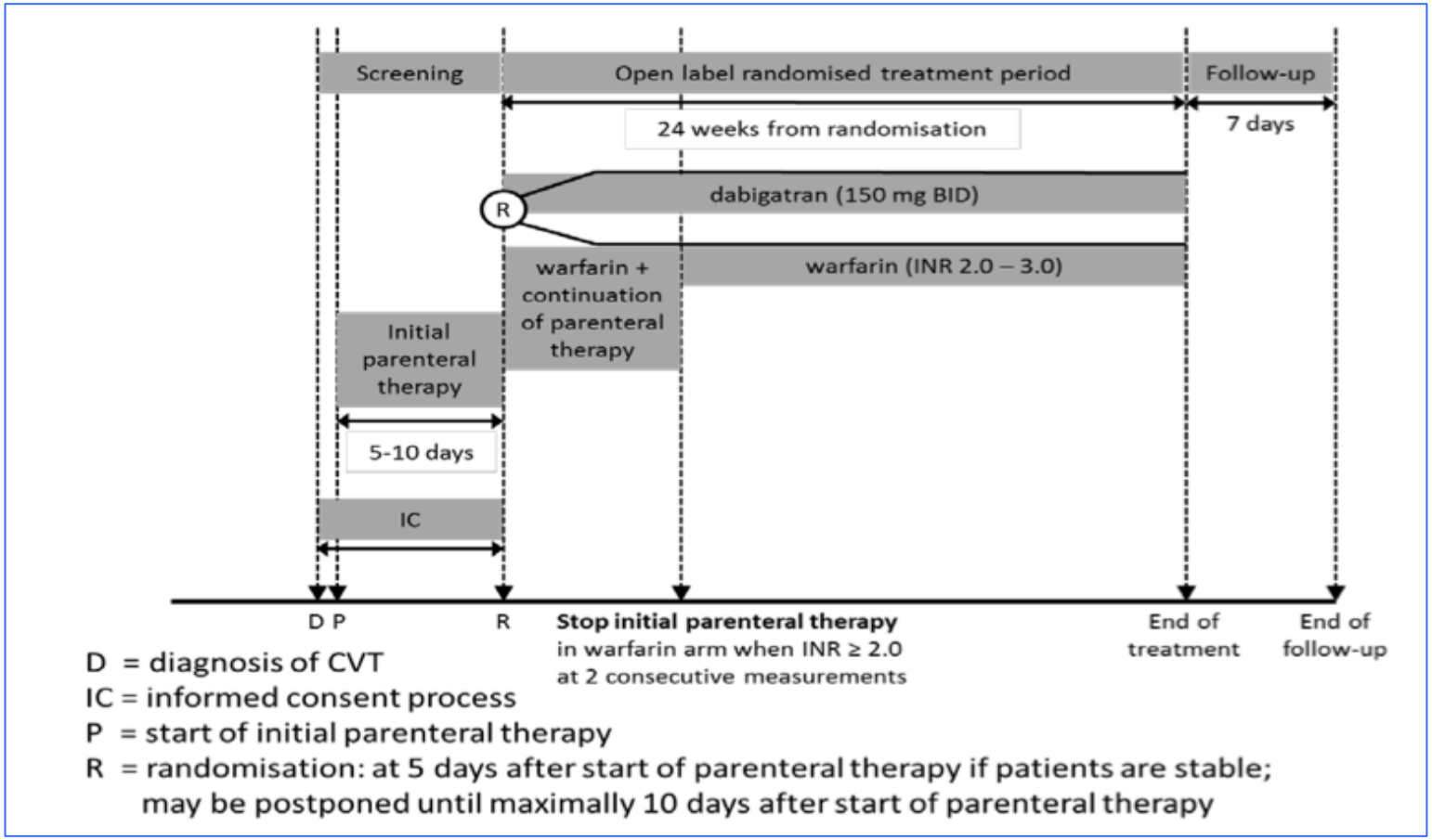
Introduction

Cerebral vein thrombosis (CVT) is a rare cause of stroke with an average rate of death or long-term dependency of 15% (1). Treatment guidelines advocate that both unfractionated heparin (UFH) and weight adjusted low-molecular-weight heparin (LMWH) when used in the acute phase are associated with lower rates of death and dependency (2). Current recommendations suggest oral anticoagulation with a vitamin K antagonist (VKA) during a three- to six-month period after CVT when no major thrombotic risk factors are identified. Nevertheless, there are no controlled data on the benefit and duration of anticoagulant therapy after acute phase (Class IIb, Level of Evidence C) (2).

In this setting, new oral anticoagulants (OACs) could provide an alternative to VKA. Dabigatran etexilate, a direct thrombin inhibitor (DTI), demonstrated to be non-inferior to warfarin both in safety and efficacy measures for treatment and prevention of recurrent thromboembolic events in acute venous thromboembolism (RE-COVER (3) and RE-COVER II (4) trials). The RE-LY trial showed that in the dosage of 150 mg BID, dabigatran seemed to be superior to warfarin in stroke prevention in non-valvular atrial fibrillation (NVAF) with no increase on intracranial bleeding (5). These results led to the EMA (European Medicines Agency) approval of dabigatran for stroke prevention in NVAF in August 2011. It was the first new OAC to be used in Portugal with that indication.

Indirect comparison studies identified a trend for lower haem-

Respect-CVT



Chair: JM Ferro.

Steering Committee: F Dentali, J Coutinho, A Kobayashi, H Diener.

Contact

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Extending oral anticoagulant treatment after Cerebral Vein and Dural Sinus Thrombosis

International Study on Cerebral Vein and Dural Sinus Thrombosis

Case Record Form
In- /exclusion criteria

http://excoa-cvt.com/Homepage.html

Current Number of patients included

Background

Patients suffering a cerebral vein thrombosis (CVT) are likely to be at increased risk of having further venous thromboembolic events (VTEs). Due to the risk of thrombotic recurrence, it is recommended to continue oral anticoagulation after the acute phase of CVT. However, there are no controlled trials assessing the benefit and optimal duration of oral anticoagulation in patients with CVT. Current management of post acute phase of CVT is based on expert consensus and individual patient risks and preferences.

Objective

The purpose of the study is to compare the efficacy and safety of a short (3 months) versus long term (12 months) approach with anticoagulation for the prevention of VTEs after an episode of CVT.

Study Design

Multicentre, multinational prospective study with a cluster randomised allocation design.

Study Population

The study population will consist of consecutive adult subjects with a confirmed cerebral venous thrombosis.

Outcome

The primary outcome will be any symptomatic and confirmed fatal or nonfatal venous thromboembolic event up to the 24 months follow up. Safety endpoints will include bleeding events during both treatment periods, classified as major/minor and according to the site of bleeding and death from any cause.

Researchers

Prof. Dr. J. Stam (neurologist)
Drs. J.M. Coutinho, Drs. S.M. Zuurbier (PhD students)

Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TOACT)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2016 by Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)

Sponsor:
Jan Stam, MD, PhD

Collaborator:
Dutch Heart Foundation

Information provided by (Responsible Party):
Jan Stam, MD, PhD, Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)

ClinicalTrials.gov Identifier:
NCT01204333

First received: September 15, 2010
Last updated: January 18, 2016
Last verified: January 2016
History of Changes

Purpose

Background: Endovascular thrombolysis, with or without mechanical clot removal (ET), may be beneficial for a subgroup of patients with cerebral venous sinus thrombosis (CVT), who have a poor prognosis despite treatment with heparin.

Study population: Patients are eligible if they have a radiologically proven CVT, a high probability of poor outcome (defined by presence of one or more of the following risk factors: mental status disorder, coma, intracranial hemorrhagic lesion or thrombosis of the deep cerebral venous system) and the responsible physician is uncertain if ET or standard anti-coagulant treatment is better.

Conclusioni

- Malattia (relativamente) infrequente
- Poche evidenze di alta qualità
- Nuove evidenze ongoing (DOAC, durata ottimale del trattamento, trombolisi)