3° Convegno di Anticoagulazione.it
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Terapia anticoagulante nell'anziano con TEV: dati attuali e prospettiva di uno studio clinico mirato

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Venous thromboembolism in centenarians: Findings from the RIETE registry

Beatriz Lacruz [a], Gregorio Tiberio [a], Manuel Jesús Núñez [b], Luciano López-Jiménez [c], Antoni Riera-Mestre [d], Eros Tiraferri [e], Peter Verhamme [f], Lucia Mazzolai [g], José González [h], Manuel Monreal [i,*], for the RIETE Investigators [1]

Eur J Intern Med 2016

47 (0.08%) were aged ≥100 years.

Most patients (95%) were treated initially with LMWH; 30% switched to VKA and 62% kept receiving long-term LMWH

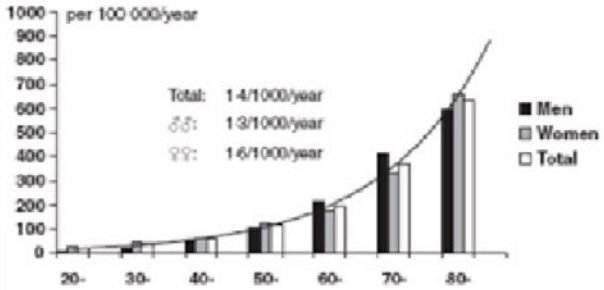
During anticoagulant therapy (mean duration, 139 days), mortality was high (15/47; 32%)

5 (11%) had minor bleeding, but no major bleeding was reported.

Conclusions: the risk of VTE recurrences during the course of anticoagulation outweighed the risk of bleeding.

Paradox : Age

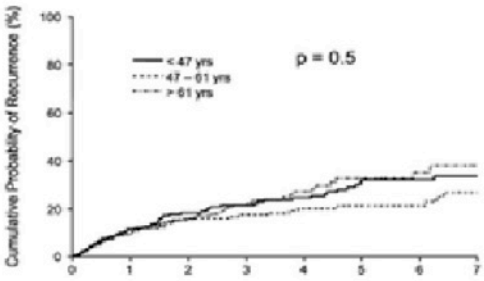
First VT



Naess et al, 2007.

Naess, J Thromb Haemost 2007;

Recurrent VT



Eischer, Medicine (Baltimore) 2009

Journal of Thrombosis and Haemostasis, 6: 577–582 DOI: 10.1111/j.1538-7836.2008.02889.x

ORIGINAL ARTICLE

Unprovoked recurrent venous thrombosis: prediction by D-dimer and clinical risk factors

T. BAGLIN,* C. R. PALMER,† R. LUDDINGTON* and C. BAGLIN*

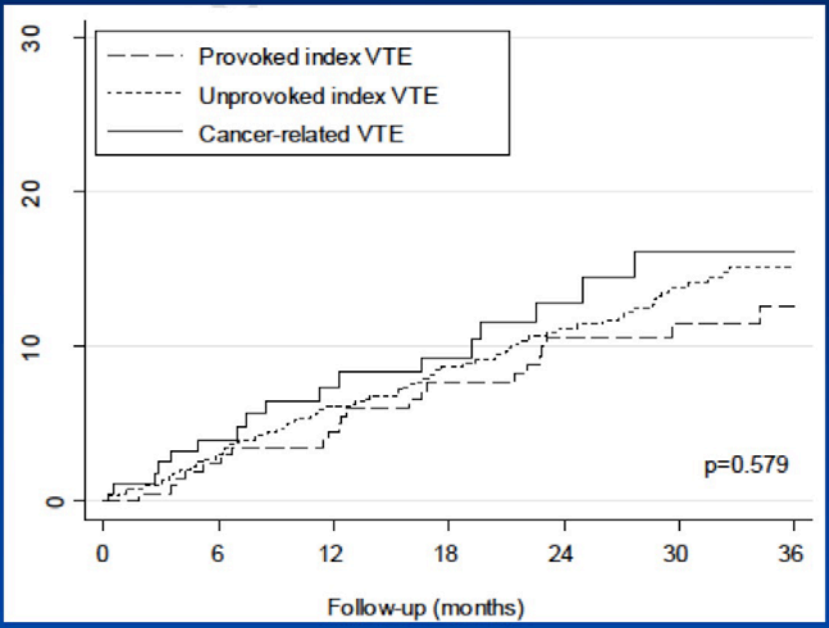
2008

Cox proportional hazards modelling of the likelihood of unprovoked recurrent thrombosis. The assumption of proportional hazards was satisfactory by graphical methods

	Hazards ratio	Lower 95% CI	Upper 95% CI	*P* value
Adjusted				
Positive D-dimer	2.00	1.01	3.94	0.046
Age at diagnosis	0.77	0.64	0.92	0.003
Male sex	2.88	1.38	6.01	0.005
First event unprovoked	1.92	0.97	3.78	0.06

*Age at diagnosis is per decade (i.e. hazard ratio relates to each 10-year increase in age).

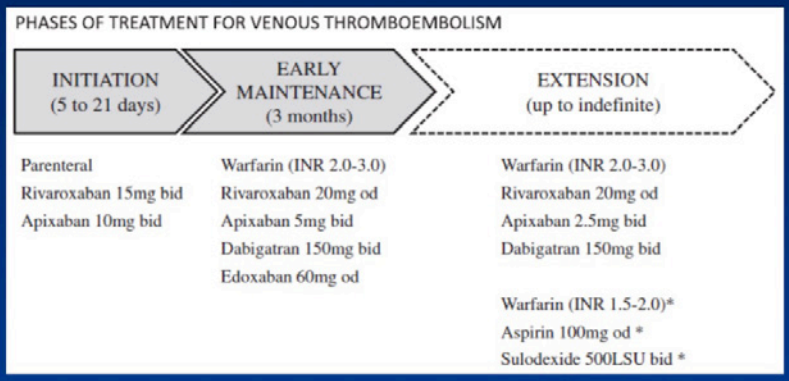
991 patients aged ≥65 years with acute VTE were followed (during AC and after AC was stopped) in a multicenter Swiss cohort study (median age: 75 y) (Lauber et al. Am J Med in print)



Cumulative incidence of recurrences at 3 y =

Umprovoked: 15.3%
Provoked: 12.6%
Cancer: 16.2%

From Blondon & Bounameaux, Circulation 2015



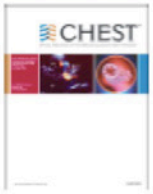
Initial Long Term Extended

From Kearon et al., Chest 2016

Accepted Manuscript

Antithrombotic Therapy for VTE Disease: CHEST Guideline

Clive Kearon, MD, PhD, Elie A. Akl, MD, MPH, PhD, Joseph Ornelas, PhD, Allen Blaivas, DO, FCCP, David Jimenez, MD, PhD, FCCP, Henri Bounameaux, MD, Menno Huisman, MD, PhD, Christopher S. King, MD, FCCP, Timothy Morris, MD, FCCP, Namita Sood, MD, FCCP, Scott M. Stevens, MD, Janine R.E. Vintch, MD, FCCP, Philip Wells, MD, Scott C. Woller, MD, Col. Lisa Moores, MD, FCCP



2016

In patients with a first unprovoked proximal DVT or PE and who have a:

(i) low or moderate bleeding risk, we suggest extended AC therapy (no scheduled stop date) (Grade 2B)

(ii) high bleeding risk, we recommend 3 months of AC therapy over extended therapy (Grade 1B)

All patients who receive extended AC therapy should be reassessed at periodic intervals (e.g. annually).

TABLE 11] Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories[a]

Risk Factors[b]
Age >65 y[184-193]
Age >75 y[84-188,190,192,194-202]
Previous bleeding[185,191-193,198,201-204]
Cancer[187,191,195,198,205]
Metastatic cancer[181,204]
Renal failure[185,191-193,196,199,201,206]
Liver failure[186,189,195,196]
Thrombocytopenia[195,204]
Previous stroke[185,192,195,207]
Diabetes[185,186,196,200,202]
Anaemia[185,189,195,198,202]
Antiplatelet therapy[186,195,196,202,208]
Poor anticoagulant control[189,196,203]
Comorbidity and reduced functional capacity[191,196,204]
Recent surgery[189,209,c]
Frequent falls[195]
Alcohol abuse[191,192,195,202]
Nonsteroidal anti-inflammatory drug[210]

Kearon et al.
ACCP
Chest 2016

Low risk (no bleeding factors) = 0.8%/y major bleeding
Moderate (one bleeding factor) = 1.6%/y " "
High (two or more factors) = ≥6.5%/y " "

Prevalence of elderly VTE patients (=> 75 y) in recent studies for secondary prevention

Studies	Elderly/total	%
DULCIS (2014) (management)	316/1010	31.3
START-Registry	663/2263	29.3
AMPLIFY Extension (2013) (trial)	329/2482	13.2
EINSTEIN CHOICE (2017) (trial)	394/3365	11.7

dulcis

Blood 2014

CLINICAL TRIALS AND OBSERVATIONS

D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study

Gualtiero Palareti,[1] Benilde Cosmi,[1] Cristina Legnani,[1] Emilia Antonucci,[2] Valeria De Micheli,[3] Angelo Ghirarduzzi,[4] Daniela Poli,[2] Sophie Testa,[5] Alberto Tosetto,[6] Vittorio Pengo,[7] and Paolo Prandoni,[8] on behalf of the DULCIS (D-dimer and ULtrasonography in Combination Italian Study) Investigators

Patients (total 1010)	Number	Recurrences	Major Bleed (total 14)
=> 75 y	316 (31.3%)	18 (5.7%)	8 (2.5%); 8/14 (57.1)
=> 75 y No VKA	154 (15.2%)	15 (9.7%)	/
=> 75 y VKA	162 (16.1%)	3 (1.8%)	8 (4.9) (1 fatal)

Apixaban versus placebo for extended treatment in the elderly

Apixaban for Extended Treatment of Venous Thromboembolism

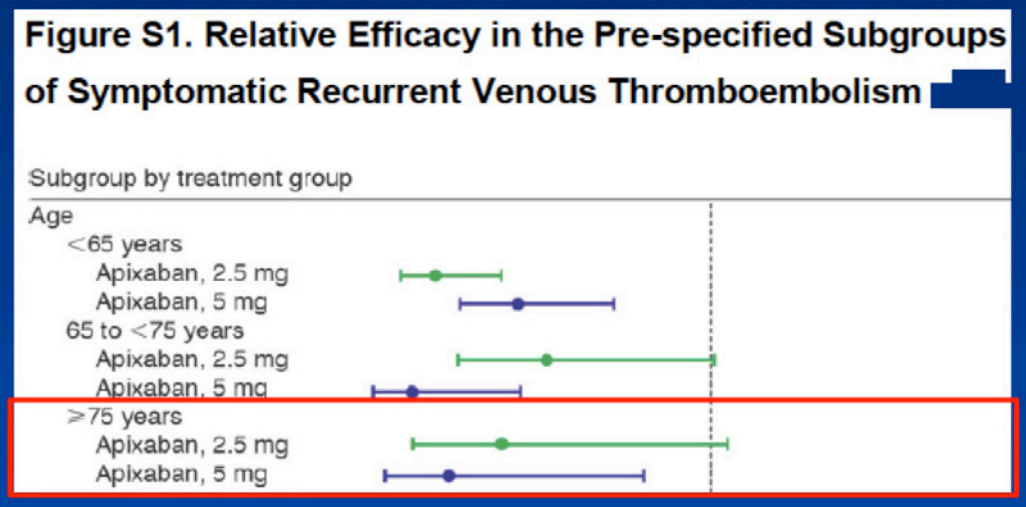
Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

NEJM 2013

Mean age = 56.6 y
=> 75 y = 329/2482 (13.2%)

EFFICACY

Figure S1. Relative Efficacy in the Pre-specified Subgroups of Symptomatic Recurrent Venous Thromboembolism



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NEJM 2013

Mean age = 56.6 y
=> 75 y = 329/2482 (13.2%)

SAFETY (MB+CRNMB)

Subgroup by treatment group	Apixaban Events	Apixaban Patients	Placebo Events	Placebo Patients
Age				
<65 years				
Apixaban, 2.5 mg	11	565	13	546
Apixaban, 5 mg	21	549		
65 to <75 years				
Apixaban, 2.5 mg	9	164	8	171
Apixaban, 5 mg	9	154		
≥75 years				
Apixaban, 2.5 mg	7	111	1	109
Apixaban, 5 mg	5	108		

Rivaroxaban or aspirin for extended treatment in the elderly

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

NEJM 2017

mean age = 57.9 y
=> 75 y = 394/3365 (11.7%)

EFFICACY

Subgroups	HR (95% CI)	Rivaroxaban 20 mg	Aspirin 100 mg
Age			
<65 years		10/691 (1.4%)	30/684 (4.4%)
65–75 years		6/301 (2.0%)	14/301 (4.7%)
>75 years		1/115 (0.9%)	6/146 (4.1%)

Subgroups	HR (95% CI)	Rivaroxaban 10 mg	Aspirin 100 mg
Age			
<65 years		6/678 (0.9%)	30/684 (4.4%)
65–75 years		3/316 (0.9%)	14/301 (4.7%)
>75 years		4/133 (3.0%)	6/146 (4.1%)

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

NEJM 2017

mean age = 57.9 y
=> 75 y = 394/3365 (11.7%)

SAFETY (M+CRNMB)

Subgroups	HR (95% CI)	Rivaroxaban 20 mg	Aspirin 100 mg
Age			
<65 years		26/691 (3.8%)	9/684 (1.3%)
65–75 years		5/301 (1.7%)	6/301 (2.0%)
>75 years		5/115 (4.3%)	8/146 (5.5%)

Subgroups	HR (95% CI)	Rivaroxaban 10 mg	Aspirin 100 mg
Age			
<65 years		16/678 (2.4%)	9/684 (1.3%)
65–75 years		9/316 (2.8%)	6/301 (2.0%)
>75 years		2/133 (1.5%)	8/146 (5.5%)

Comments
Extended treatment for VTE in elderly population

a) the recent extension studies with DOACs proved less satisfactory, both for efficacy and safety in elderly patients

b) Aspirin was poorly effective against recurrences, with a high rate of bleeding

Recent data on elderly VTE patients from the Italian START-Registry

	Patients ≤75 (n. 1600; 70.7%)	Patients >75 (n. 663; 29.3%)	
Total bleeds	29 (1.8%)	19 (2.9%)	NS
(MB+CRNMB) [rate]	[1.4]	[1.9]	NS
Incidence of bleeds			
During the first 90 d.	3.5%	1.8%	NS
After 90 d.	0.9%	1.9%	P= 0.03

Elderly pts are always at high risk of bleeding during anticoagulants

INITIATION (5 to 21 days) → EARLY MAINTENANCE (3 months)

- ≥ 75 y: Stop ACs
- < 75 y: Individual risk
  - Low → Stop ACs
  - Moderate (?) Personal pref. → Sulodex., ASA, DOACs (?)
  - High → DOACs at low bleeding risk

Contraind. to AC= Sulodex., ~~ASA~~

Sulodexide for the Prevention of Recurrent Venous Thromboembolism

The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Andreozzi et al. Circulation 2015

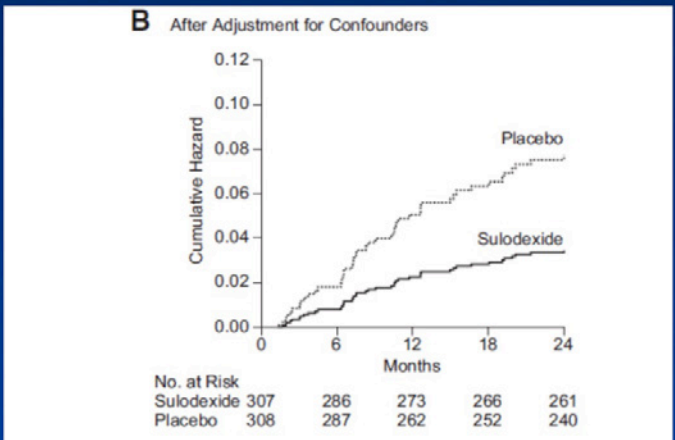

Figure 2. Risk of recurrence of venous thromboembolism in patients randomly assigned to sulodexide or placebo. **A**, Cumulative risk of recurrent venous thromboembolism. **B**, Results of an analysis of risk after adjustment for age, sex, index event (pulmonary embolism, or deep vein thrombosis), duration of anticoagulant therapy, and time from completion of anticoagulation therapy to randomization.

Sulodexide for the Prevention of Recurrent Venous Thromboembolism

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Andreozzi et al.
Circulation 2015

Table 2. Number of Outcome Events According to Study Group

Event	Sulodexide (n=307)	Placebo (n=308)	Hazard Ratio (95% CI)	*P* Value
Recurrent VTE				
Total episodes	15	30	0.49 (0.27–0.92)	0.025
Pulmonary embolism	3	6	0.49 (0.12–1.97)	0.32
Deep vein thrombosis	12	24	0.49 (0.25–0.99)	0.045
Bleeding				
Clinically relevant nonmajor bleeding	2	2	0.97 (0.14–6.88)	0.98

Lo studio "Giasone"

- Giasone, fu educato dal centauro Chirone al rispetto degli dei, alle strategie militari, ai principi di giustizia, all'interesse per la medicina.
- Durante un viaggio, dovendo attraversare il guado del fiume Anauro, soccorse un'anziana donna in difficoltà che aveva chiesto inutilmente aiuto ad altri viandanti, e la trasportò sulla riva opposta, nonostante il peso della donna (era la dea Giunone sotto mentite spoglie) aumentasse di minuto in minuto….

Titolo dello studio	**Studio Giasone (The Jason study)** **Prevenzione secondaria con sulodexide nei pazienti anziani dopo una trombosi venosa profonda, con o senza embolia polmonare**
Disegno	Multicentrico, italiano, randomizzato e controllato con placebo
Promotore	Fondazione Arianna Anticoagulazione (Gruppo TRIP)
Supporto	Alfasigma (farmaco+placebo+supporto economico)
Centro Coordinatore	C. Lodigiani (Humanitas, Milano)
Pazienti	≥ 75 a., con 1° TVP ± EP, dopo AC per 3-12 mesi,

Esclusi

- < 75 anni
- Evento "provocato" (3 m. chirurgia o trauma maggiore, o allettamento > 4 giorni, o 3 m. gessi/immobilizzazione
- EP isolata (senza TVP), EP severa (rischio vitale o trombolisi)
- TVP distale isolata o in sedi diverse da arti inferiori
- Necessità di terapia anticoagulante per altri motivi
- Cancro, APLS, grave malattia associata, filtro cavale
- Antiaggreganti diversi da ASA (fino a 140 mg/die)
- Alterazioni trombofiliche maggiori
- Insufficienza cardio-respiratoria (NYHA 3 or 4)
- Impossibilità o volontà di consenso
- Aspettativa di vita < 1 anno

Endpoint

Efficacia:

- Primario: recidiva di TVP prossimale + nuovi episodi di EP + mortalità totale per TEV
- Secondario: Eventi cardiovascolari con ricovero, morte per eventi cardiovascolari

Sicurezza:

- Primario: Incidenza di EM
- Secondario: EM + ENMCR

Obiettivi

- Efficacia: sulodexide (2 cp x 2/die x 12 mesi), e incidenza di recidive di TEV in pazienti anziani, con recente 1° episodio di TVP (con o senza EP), dopo 3-12 mesi di AC.

  Target: recidive: - 30% del placebo
- Sicurezza del sulodexide: non-inferiorità per EM verso placebo

  Target: EM ≈ 1% (lim. sup. confidenza non > 3%)

Attribuzione centrale degli eventi

Endpoint esaminati e attribuiti centralmente da una Commissione di 3 professionisti non partecipanti all'arruolamento e ignari del tipo di trattamento

Previsti circa 50 centri partecipanti

1° paz. previsto entro fine 2018

segreteria@fondazionearianna.org

Grazie