

IV° Convegno Anticoagulazione.it
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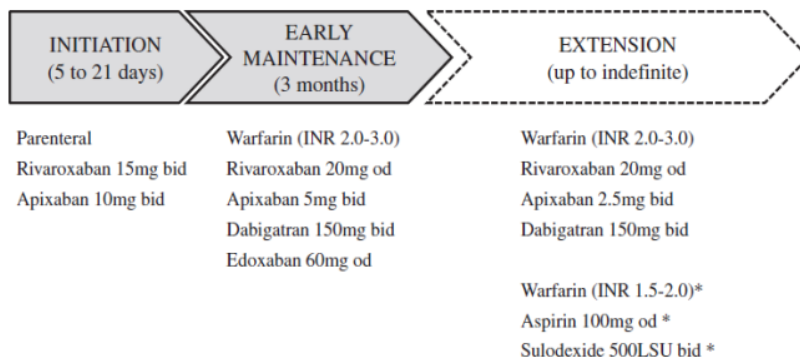
La profilassi secondaria del TEV nell'anziano e lo studio Giasone

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Fondazione «Arianna Anticoagulazione», Bologna



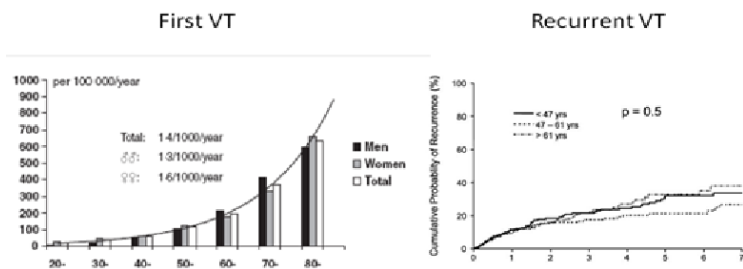
PHASES OF TREATMENT FOR VENOUS THROMBOEMBOLISM



From Blondon & Bounameaux, Circulation 2015

Quale il rischio di recidiva negli anziani?

Paradox : Age



Naess et al, 2007.

Naess, J Thromb Haemost 2007;

Eischer, Medicine (Baltimore) 2009

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

ORIGINAL ARTICLE

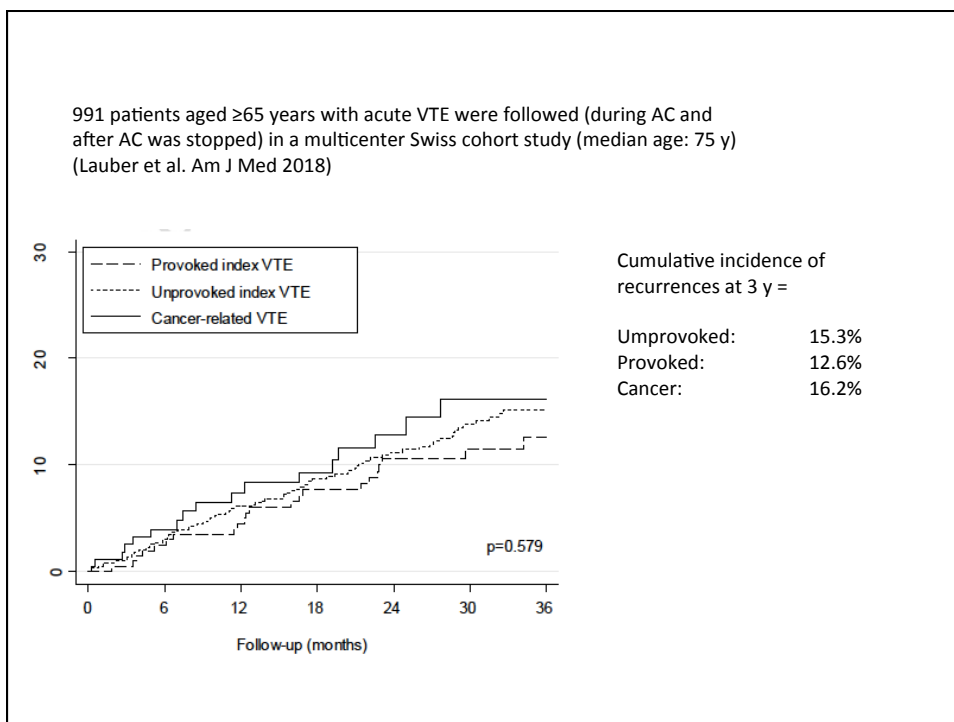
Unprovoked recurrent venous thrombosis: prediction by D-dimer and clinical risk factors 2008

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

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 |

The risk of recurrence decreased by a factor of 0.8 for each 10-year increase in age.



Accepted Manuscript

2016



Predictors and causes of long-term mortality in elderly patients with acute venous thromboembolism: a prospective cohort study


Nicolas Faller, MD-PhD, Andreas Limacher, PhD, MAS, MSc, Marie Méan, MD, Marc Righini, MD, Markus Aschwanden, MD, Jürg Hans Beer, MD, Beat Frauchiger, MD, Josef Osterwalder, MD, MPH, Nils Kucher, MD, Bernhard Lämmle, MD, Jacques Comuz, MD, MPH, Anne Angelillo-Scherer, MD, Christian M. Matter, MD, Marc Husmann, MD, Martin Banyai, MD, Daniel Staub, MD, Lucia Mazzolai, MD, PhD, Olivier Hugli, MD, Nicolas Rodondi, MD, MAS, Drahomir Augesky, MD, MSc

- 991 patients aged ≥ 65 y with acute VTE were followed in a multicenter Swiss cohort study.

Conclusions

- Elderly patients with acute VTE have a substantial longterm overall mortality (21%)
- Cancer (34%), pulmonary embolism (18%), infection (17%), and bleeding (6%) were the most common causes of death.

Quale il rischio emorragico con il
trattamento prolungato?


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 No VKA | 154 (15.2%) | 15 (9.7%) | / |
| => 75 y VKA | 162 (16.1%) | 3 (1.8%) | 8 (4.9) (1 fatal) |

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

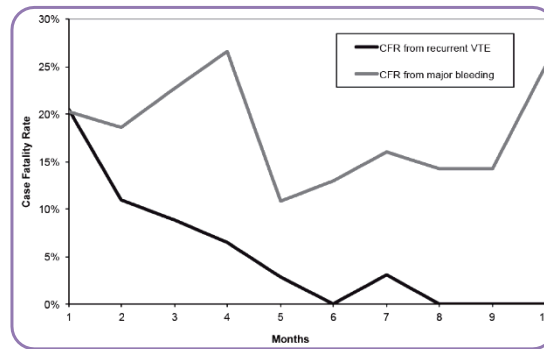
| Risk Factors ^a |
|--|
| Age >65 y ¹⁸⁴⁻¹⁹³ |
| Age >75 y ^{184-188,190,192,194-202} |
| Previous bleeding ^{185,191-193,198,201-204} |
| Cancer ^{187,191,195,198,205} |
| Metastatic cancer ^{181,204} |
| Renal failure ^{185,191-193,196,199,201,206} |
| Liver failure ^{186,189,195,196} |
| Thrombocytopenia ^{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 factors) = 0.8%/y MB
 Moderate (one factor) = 1.6%/y
 High (two or more factors) = ≥6.5%/y “

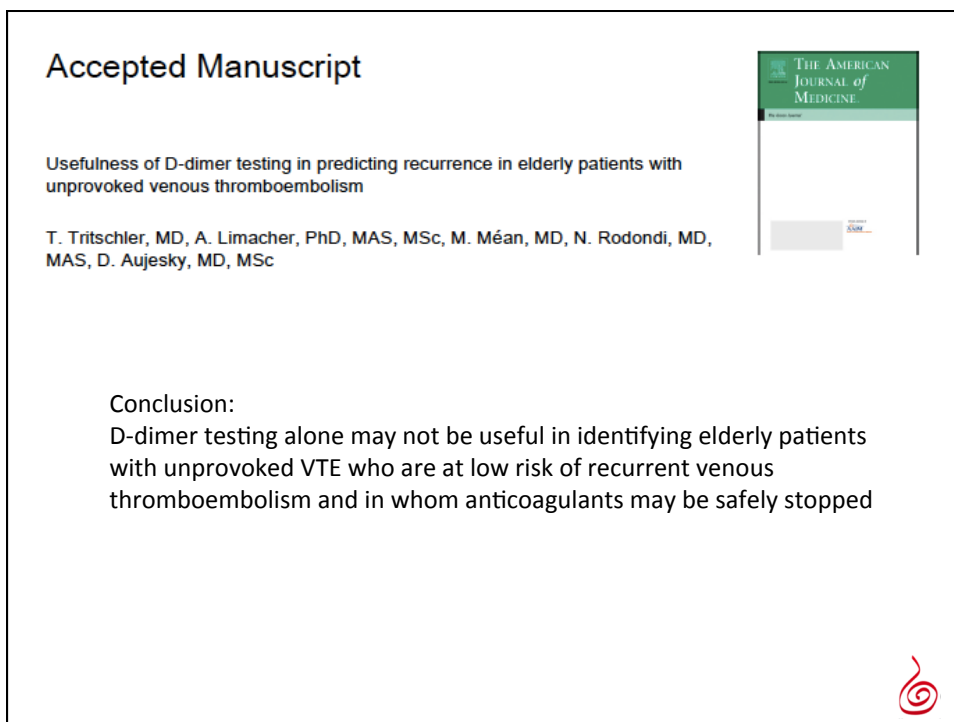
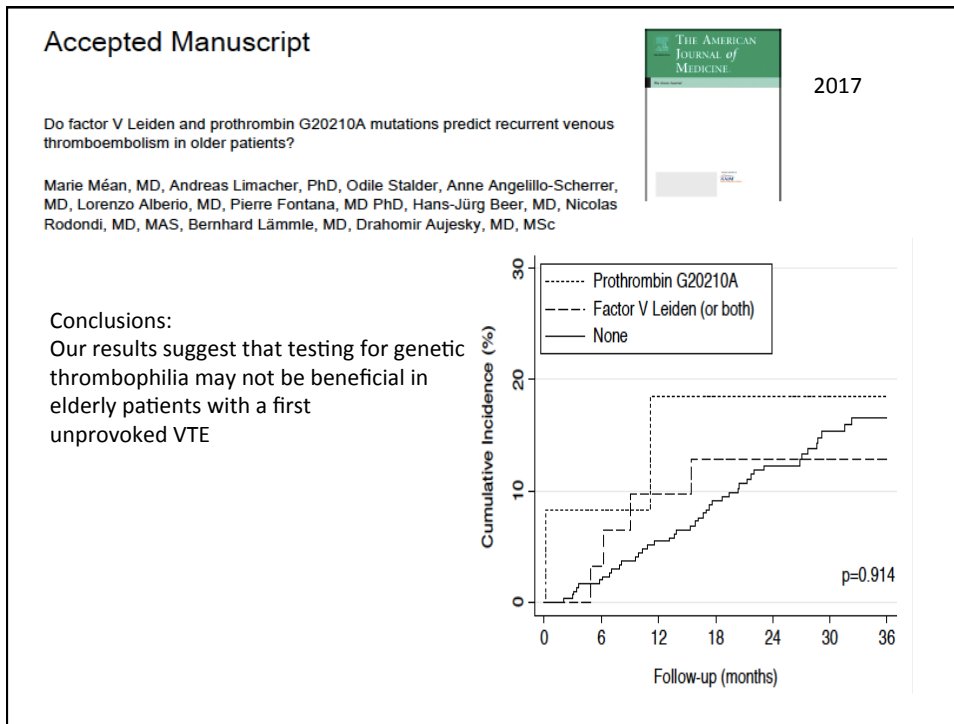
Dynamics of case-fatality rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism

Ramón Lecumberri¹; Ana Alfonso¹; David Jiménez²; Carmen Fernández Capitán³; Paolo Prandoni⁴; Philip S. Wells⁵; Gemma Vidal⁶; Giovanni Barillari⁷; Manuel Monreal⁸; and the RIETE investigators*



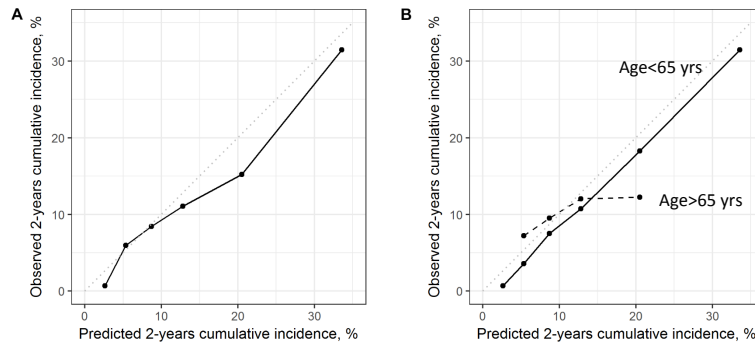
The case-fatality rate of recurrent VTE decreases over time during anticoagulation, while that of major bleeding remains stable

Possiamo identificare e trattare solo gli anziani a più alto rischio di recidiva?



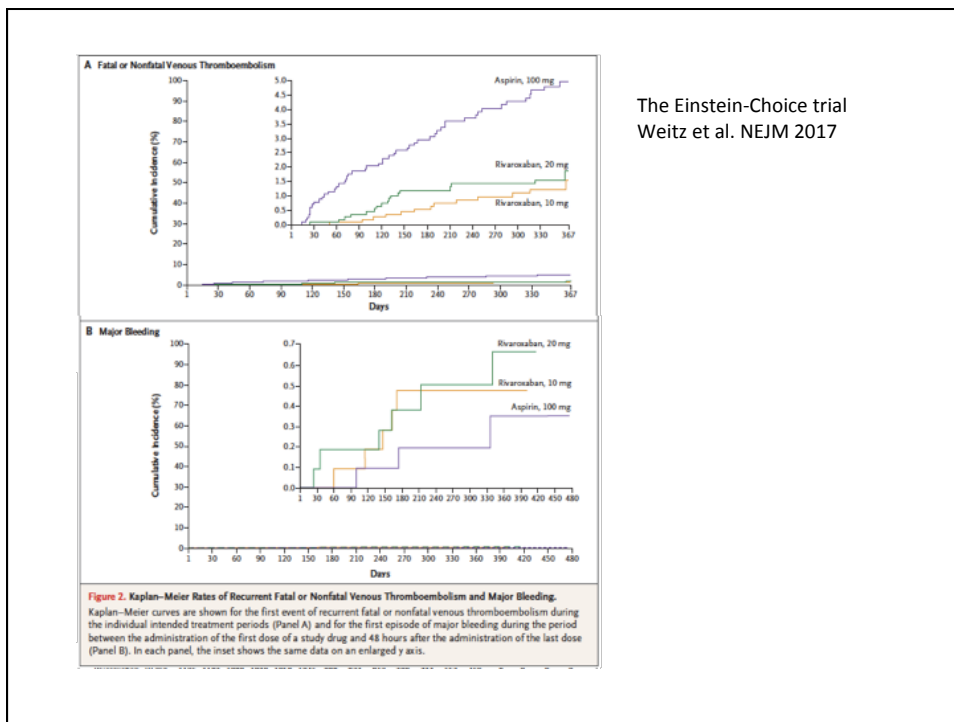
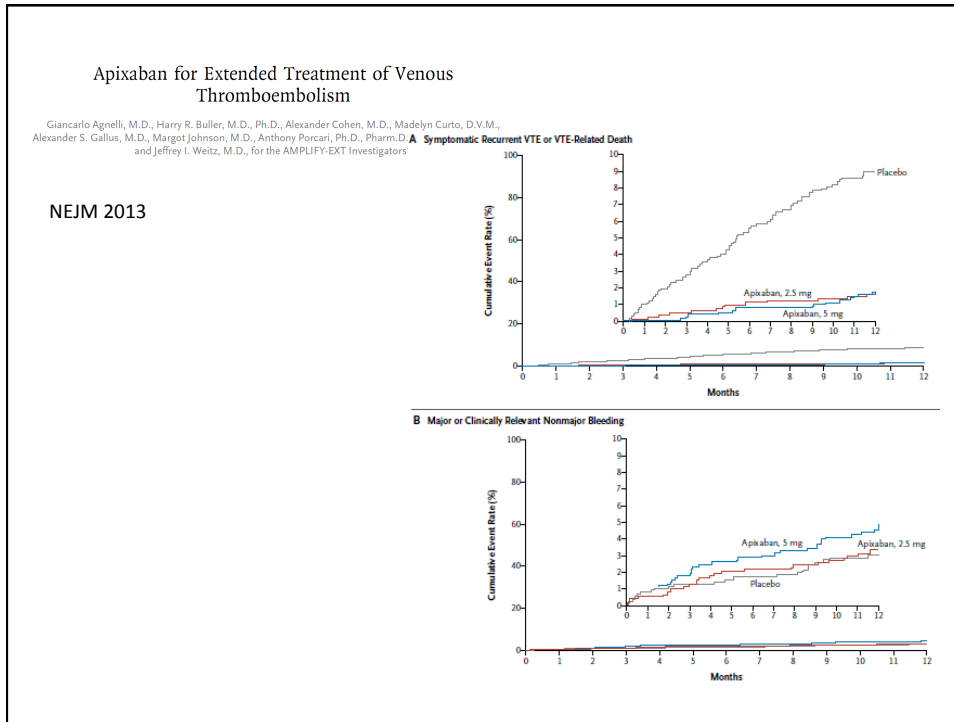
DASH Model validation

Predictions are accurate, but limited predictive value for patients >65 years



Tosetto et al. *J Thromb Haemost*, 2017.

Sono i DOAC a basso dosaggio la soluzione definitiva?



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

| Studies | Elderly/total | % |
|----------------------------------|---------------|------|
| DULCIS (2014) (management) | 316/1010 | 31.3 |
| START2-Register | 663/2263 | 29.3 |
| AMPLIFY Extension (2013) (trial) | 329/2482 | 13.2 |
| EINSTEIN CHOICE (2017) (trial) | 394/3365 | 11.7 |

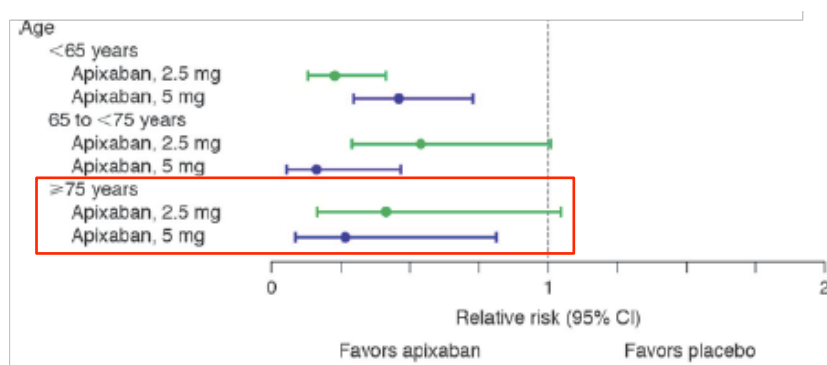
Apixaban for Extended Treatment of Venous Thromboembolism

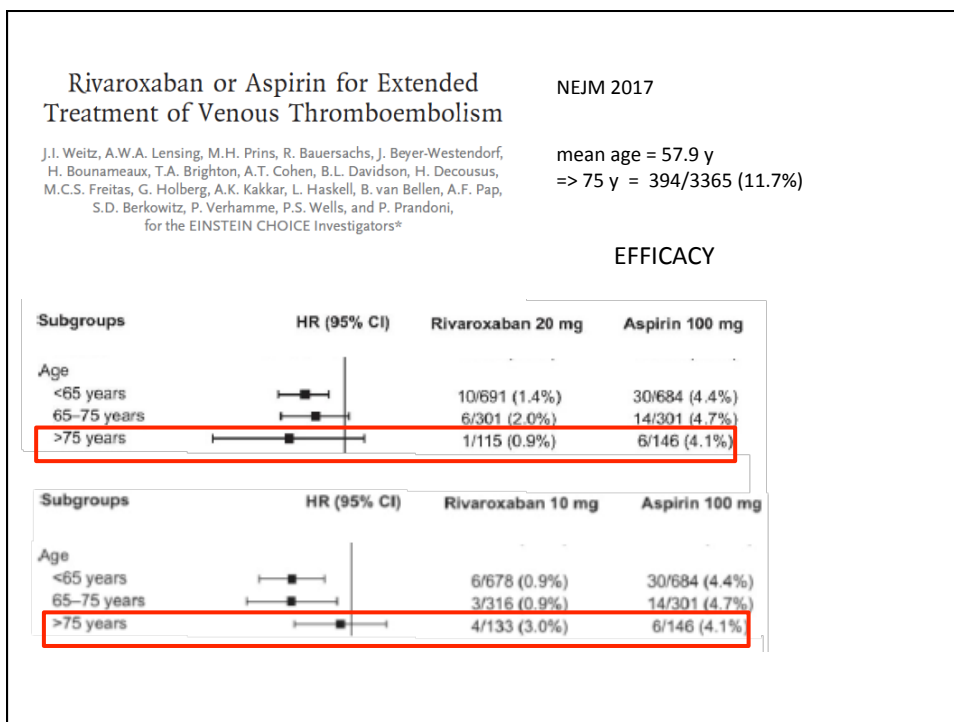
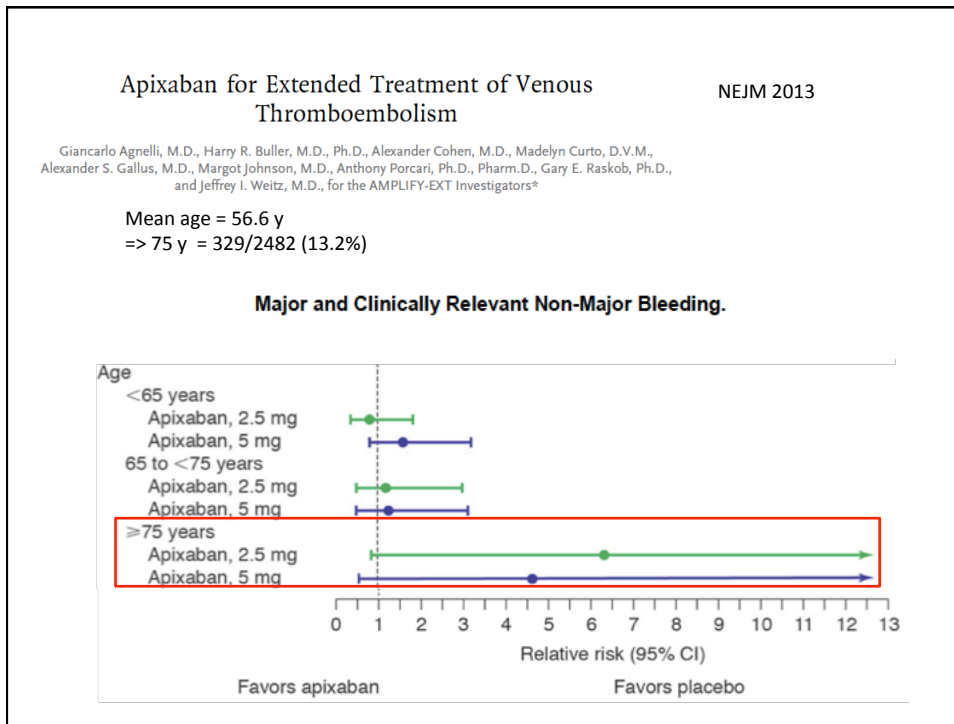
NEJM 2013

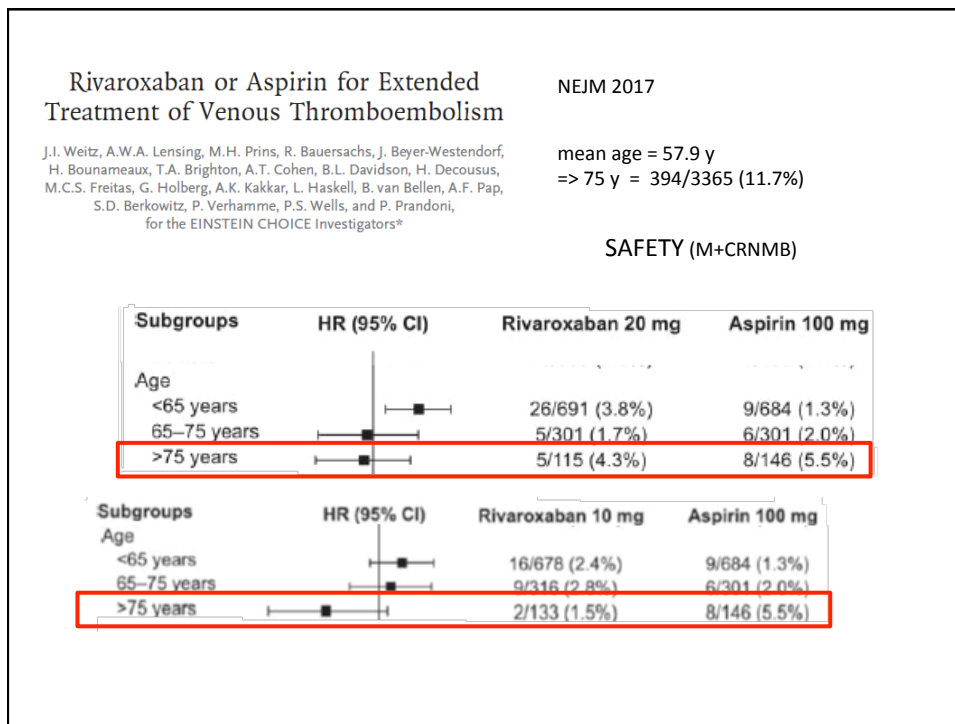
Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

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

EFFICACY







Comments

Extended treatment for VTE in elderly population

- a) the recent extension studies with DOACs proved less satisfactory for efficacy and safety in elderly patients
- b) Aspirin was poorly effective against recurrences, with a high rate of bleeding

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).



CURRENT GUIDELINES FOR PRACTICE
Oral Anticoagulation for Older Adults

- ≥ 6 months for idiopathic first episode (grade 1A)
- ≥ 12 months for recurrent idiopathic or continuing risk factor (grade 1C)

Sono possibili alternative terapeutiche?
(protezione, con basso rischio emorragico)

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

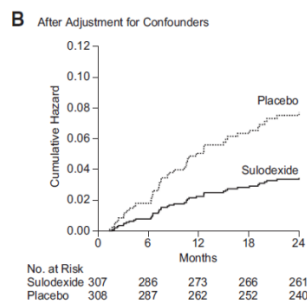


Figure 2. Risk of recurrence of venous thromboembolism in patients randomly assigned to sulodexide or placebo. **A**, Cumulative risk of recurrent venous thromboembolism. **B**, Results of an analysis of risk after adjustment for age, sex, index event (pulmonary embolism, or deep vein thrombosis), duration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

Sulodexide for the Prevention of Recurrent Venous Thromboembolism
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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 |

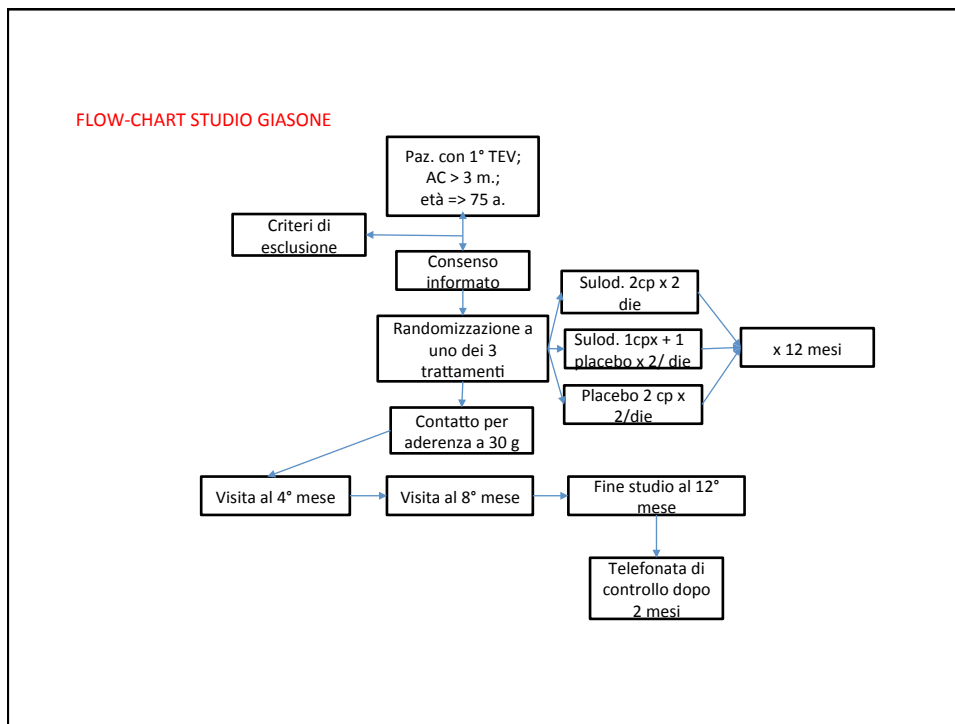
Sulodexide for Secondary Prevention of Recurrent Venous Thromboembolism: A Systematic Review and Meta-Analysis

Qing-Jun Jiang^{1†}, Jun Bai^{1†}, Jie Jin^{1†}, Jian Shi^{2*} and Lefeng Qu^{1*}

Conclusions: Sulodexide could significantly reduce the recurrence of VTE after discontinuation of anticoagulation treatment as compared with placebo.

Lo studio Giasone:
pazienti => 75 a. con 1° TEV
Prevenzione delle recidive
dopo almeno 3 mesi di AC

| | |
|----------------------------|---|
| 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 mesi, |



Obiettivi

- **Efficacia:** sulodexide: incidenza di recidive di TEV in pazienti anziani, con 1° episodio di TEV, dopo > 3 mesi di AC.
Target: - 35% di recidive vs placebo
- **Sicurezza** del sulodexide: non-inferiorità per EM verso placebo
Target: EM ≈ 1% (lim. sup. confidenza non > 3%)

Previsti circa 40 centri

**Marzo 2019: AIFA eComitati Etici
Settembre 2019: 1° paz.**

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Grazie dell'attenzione