SISET

Workshop SISET

Società Italiana per lo Studio dell'Emostasi e della Trombosi

POST-ISTH:
Novità dal meeting di Toronto 2015

Epidemiologia e Diagnosi del TEV

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What is known about VTE epidemiology

- Prevalence of VTE in the general population (=baseline risk)
- Incidence of VTE in at-risk populations
  - The concept of risk factor
- Risk-factors for recurrent VTE
  - The concept of predictive factors

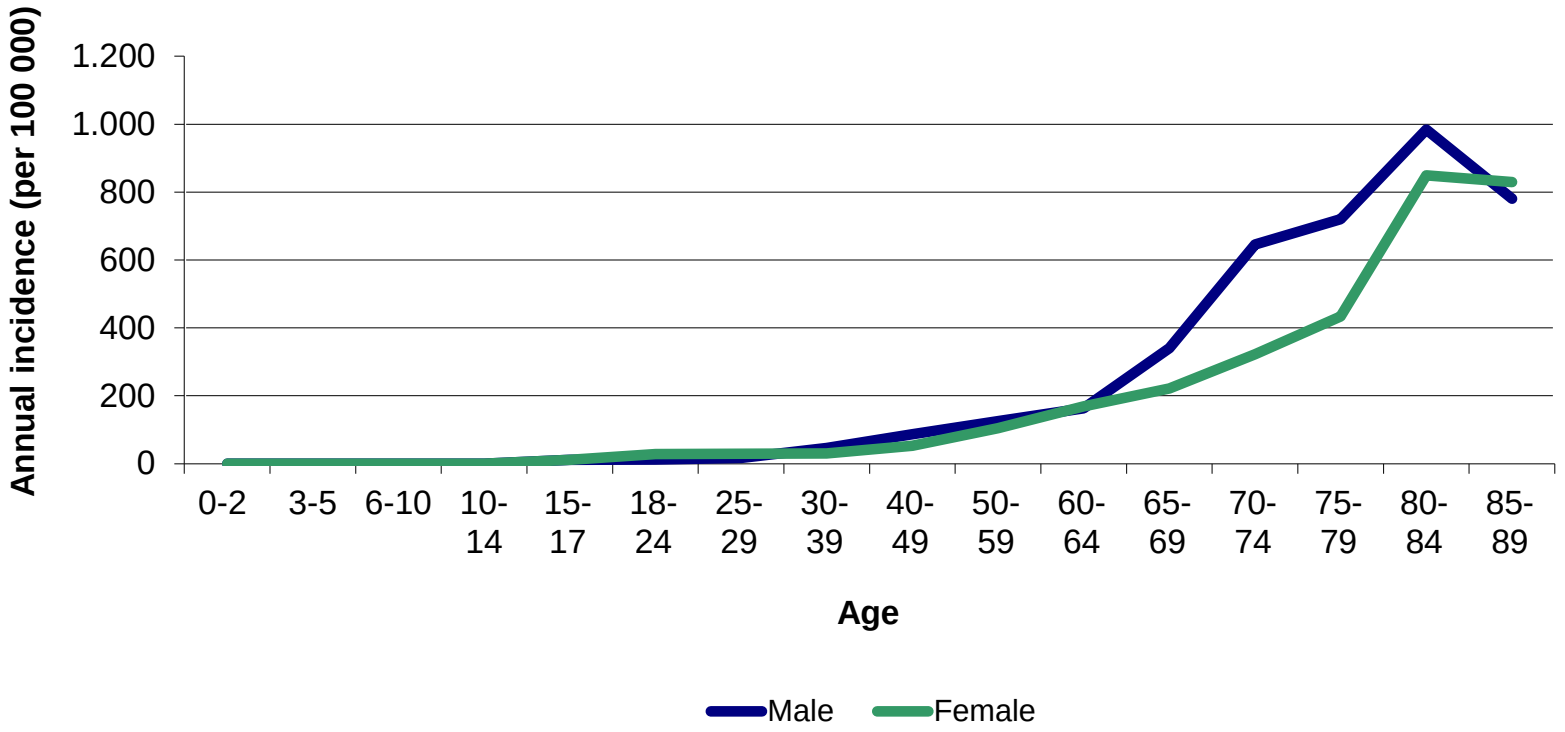
Diagnostic criteria for VTE influence incidence estimates

- The *validity* of estimates depends on data source
  - Population studies
    - Physical examination (Tecumseh)
    - Structured questionnaire & venous reflux at Doppler US (VITA Project)
  - Hospital-based
    - ICD discharge diagnosis (based on US, CT, MRI…)

Age-adjusted incidence rates of venous thromboembolism
(per 100.000 pt/yr)

	Worchester	Olmsted	Bretagne	Nord-Trøndelag
VTE	128	96	183	143
Male	118	107	152	128
Female	135	88	203	158

Age and VTE incidence (rate)



Heit et al, Thromb Haemostas, 2001
Silverstein et al, Arch Int Med, 1998

Venous Thromboembolism – Epidemiology

Puurunen et al: Epidemiology of venous thromboembolism in the Framingham heart study.

- In the population-based Framingham cohort with a median follow-up of 9.8 years (n=9747) the VTE incidence was 268 per 100 000 (95% CI, 238-301)
- 29.0% were unprovoked, 40.1% provoked, 30.9% cancer-related

Venous Thromboembolism – Epidemiology

Arshad et al: Time trends in incidence rates of venous thrombo embolism in a large cohort recruited from the general population.

- In the population-based Tromsø study (n = 26 855), the incidence of VTE was 150 per 100 000 in 1996/7 and 190 per 100 000 in 2012
- The incidence of PE rose from 40 per 100 000 in 1996/7 to 100 per 100 000 in 2012
- Improvement of diagnostic tool could explain this increase

Venous Thromboembolism – Epidemiology

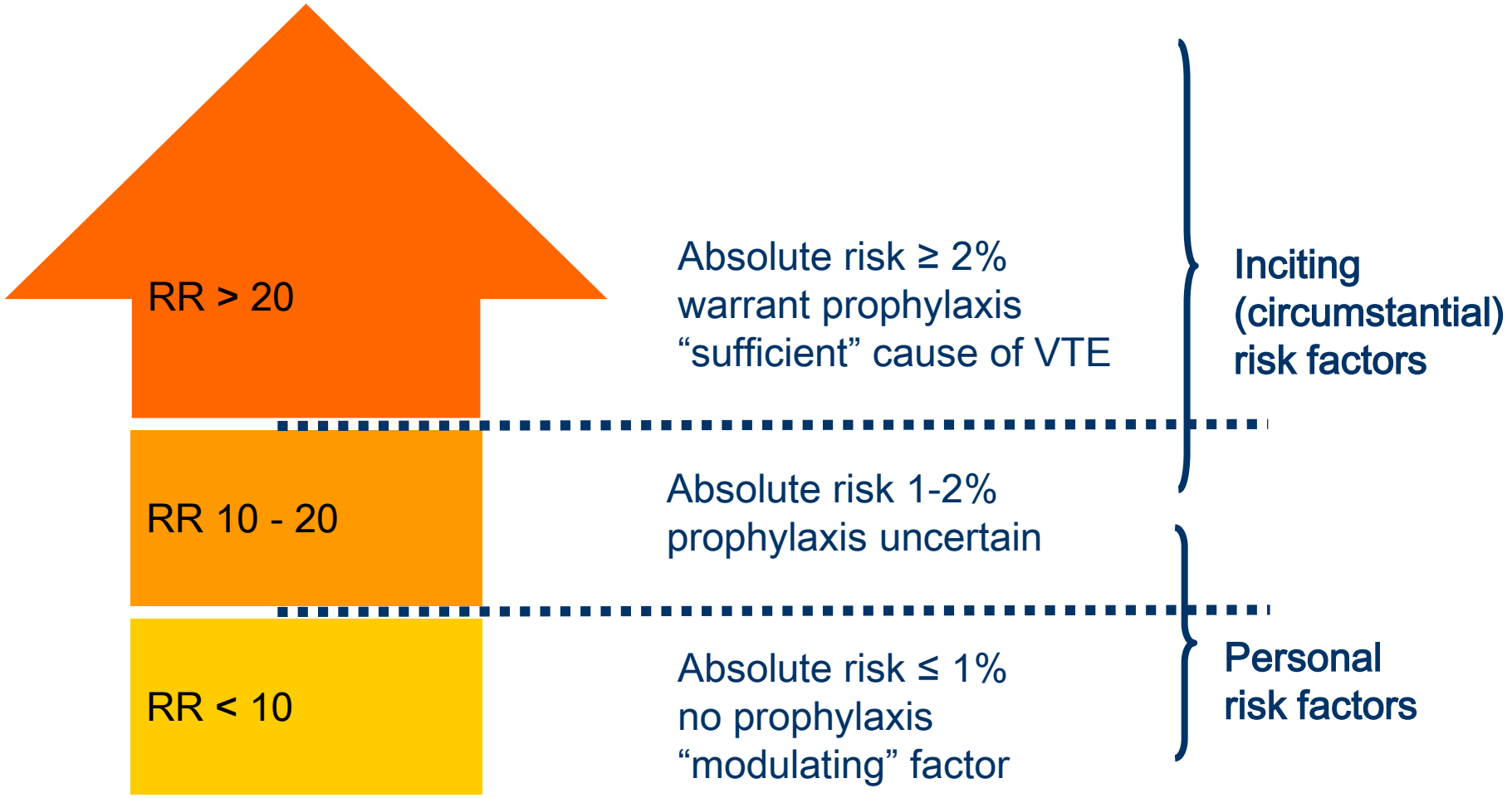
Dentali et al: Time trends and case fatality rate of pulmonary embolism during 11 years of observation in northwestern Italy.

- Crude incidence of PE from hospital-admission records: 55.4 and 40.6 per 100 000
- Increasing incidence during the 11-years period, with reduced case-fatality rate from 15.6-17.6% in females and males to 10.2-10.1%

.. but are there subgroups at increased risk?

- The *absolute* VTE risk may be modulated by
  - Personal (usually permanent) risk factors
  - Environmental (usually modifiable) risk factors

Relative risk of VTE and causality



Venous Thromboembolism – Risk factors

Rinde et al: Impact of incident myocardial infarction on future risk of venous thromboembolism.

- In the population-based Tromsø study (n = 29 506), occurrence of a first event of myocardial infarction was associated with a 51% increased risk of VTE (HR 1.51; 95% CI, 1.08–2.10) and 70% increased risk of pulmonary embolism (PE) (HR 1.70, 95% CI 1.05–2.75)
- The highest risk estimates were observed during the first sixth months after MI (HR 8.49; 95% CI, 4.00–18.77).

Venous Thromboembolism – Risk factors

Braekkan et al: Regular physical activity and future risk of myocardial infarction and venous thrombosis

- In the population-based Tromsø study (n = 29 506), increasing hours of physical activity were associated with reduced risk of MI, and subjects who reported ≥ 3 h/week had 35% lower risk than those who reported no activity
- There was no gradient across increasing categories of physical activity and risk of VTE (p for trend 0.7)

Venous Thromboembolism – Risk factors

Braekkan et al: Weight change and VTE risk

- In the population-based Tromsø study (n = 7 189), an increase in body weight in the last quintile (> 5.1 kg) was associated with a 3-fold increase of subsequent VTE risk, independent from body weight

Venous Thromboembolism – Lab risk factors

Author	Factor	Effect size	Comment
Winckers	Thrombin-generation	RR=5.6 Q4 vs Q1	MEGA study; first episode
Morange	TSPAN15; SLC44A2	OR=1.31 and 1.21, respectively	Meta-analysis
Elbers	Glucorticoid receptor, GR-9β	OR=1.29 hetero, 2.4 homoz	MEGA study; first episode
Sticchi	Apolipo(a) Kringle-IV type2	38% vs 18% of repeat number <10	516 unprovoked VTE and 1117 controls
Bucciarelli	RBC distribution width	RWD >90 pctl: OR=2.5	730 cases, 352 controls

D-Dimer in prediction models

- Vienna Prediction model:
  - D-Dimer level (quantitative)
  - Proximal/Distal DVT or PE
  - Male sex

- DASH Model
  - D-Dimer (+ve/-ve)
  - Age <50
  - Male sex
  - Use of OC

Eichinger et al. Circulation, 2010.
Tosetto et al. J Thromb Haemost, 2012.

Venous Thromboembolism – Predictors

Heit et al: Predictors of VTE recurrence

- In the population-based Olmsted study, patients with previous VTE (n = 1 262) had an overall recurrence rate at 5 years of 24.5%
- Male sex (HR=1.3), baseline active cancer (HR=2.6), and heparin-resistance at time of first VTE treatment (HR=1.6) were associated with VTE recurrence

Venous Thromboembolism – Predictors

Timp et al: Long-haul travel and VTE recurrence

- In the population-based MEGA study, the risk of recurrent VTE was not increased by long-haul travels, either flights (OR=0.9) or others (OR=0.8)
- Preventive measures were equally distributed among cases and controls, not explaining this finding

Venous Thromboembolism – Predictors

Fuchs et al: DNA in plasma indicates disease extenbt and predicts mortality in VTE patients

- In a prospective cohort of 863 patients aged >65 years, plasma DNA in the top quartile was associated with mortality at 12 months (HR=2.40)

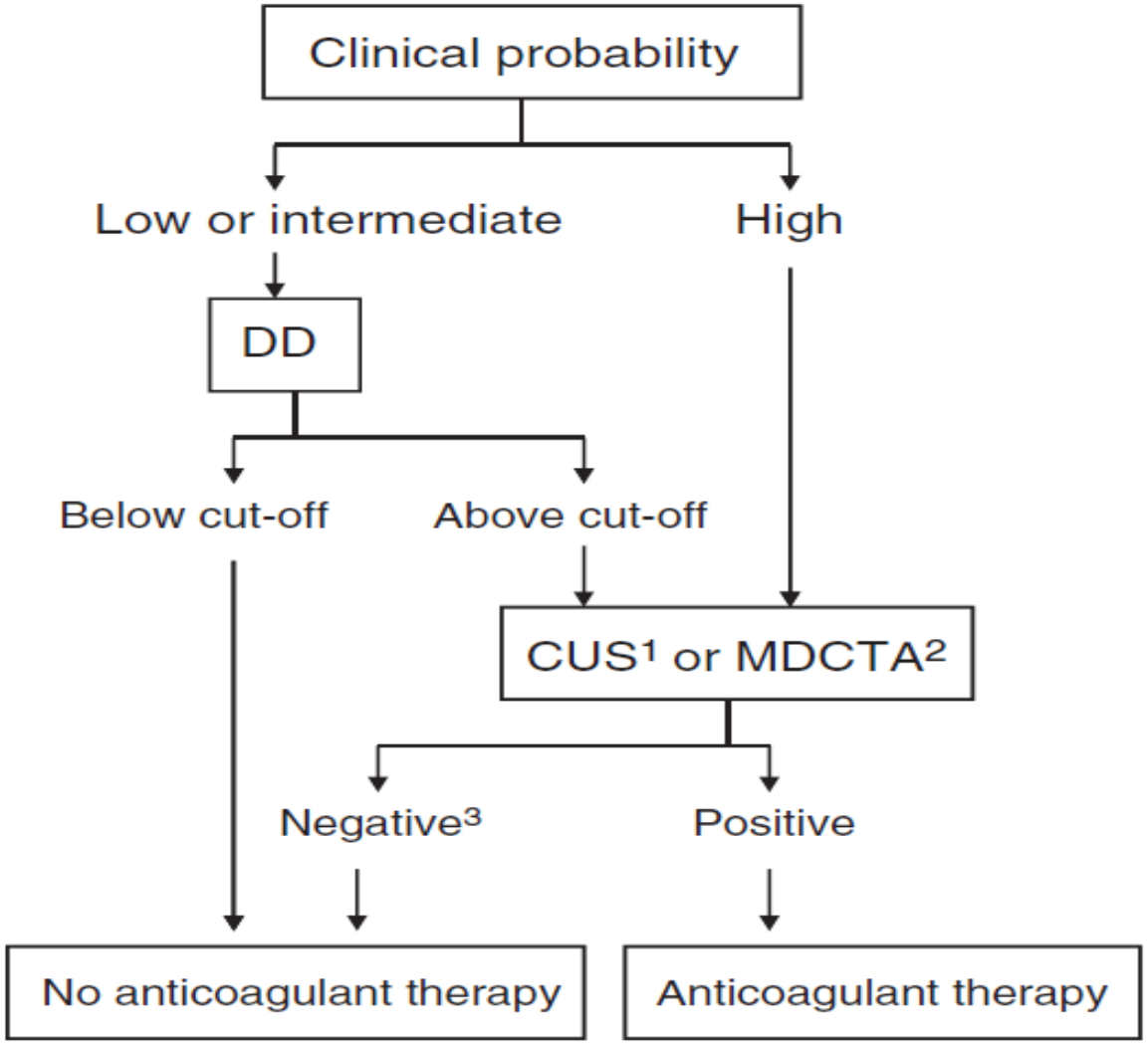
Venous Thromboembolism – Predictors

Huang et al: Risk-assessment model of recurrence within 3 months after a first episode of acute venous thromboembolism: Worcester venous thromboembolism study

- In a population-based surveillance study among residents of central Massachusetts, 2989 study patients, 141 developed recurrent VTE within 3 months of the index event (while possibly still on treatment)
- Hypercoagulable state, presence of inferior vena cava filter, varicose vein stripping, major trauma, anticoagulant at admission, and presence of active cancer were all associated with risk of recurrence

What is known about VTE diagnosis

- Diagnosis of VTE is relevant, but objective methods are still burdensome (CT, echography)
- Pre-test probability useful to reduce number of needed tests



[1] CUS (compression ultrasonography) in case of suspected DVT.
[2] Multi-detector CT angiogram (MDCTA) in case of suspected PE.

Bounameaux, J Int Med 2010

Venous Thromboembolism – Diagnosis

Ageno et al: A prospective algorithm incorporating limited and whole-leg assessment of the deep venous system in symptomatic outpatients (the Palladio study)

- In a prospective study on 1162 patients, VTE was ruled out if low PTP and negative DDimer (n=351); patients with PTP likely or positive DD underwent limited CUS only (n=401, group 2); patients with PTP likely and positive DD underwent extended CUS (n=410, group 3)
- The incidence of VTE in persons not receiving treatment was 1.1% and 2.0% in group 2 and 3 respectively, suggesting that limited CUS may be safe in a subset of patients

Venous Thromboembolism – Diagnosis

van Es et al: The performance of the age-adjusted d-dimer threshold for suspected pulmonary embolism in relevant subgroups: an individual patient data metaanalysis of 7000 patients

- Individual patient data were used from 5 large prospective studies in which the diagnostic management of PE was guided by the Wells rule and D-dimer testing (n=7027)
- In patients > 50 years with a Wells score indicating ‘PE unlikely’, PE could have been excluded in 25% with the age-adjusted Ddimer threshold compared to 18% with the conventional D-dimer threshold

Venous Thromboembolism – Diagnosis

Hendriksen et al: Diagnostic prediction model vs. gestalt in the diagnosis of pulmonary embolism in primary care

- In the prospectively collected AMUSE-2 cohort, the c-statistic was 0.80 (95%CI 0.75–0.86) for the Wells rule and 0.77 (95% CI 0.70–0.83) for gestalt.
- The diagnostic prediction model and gestalt both can safely rule-out PE in primary care. However, GPs tend to overestimate PE probability

Venous Thromboembolism – Diagnosis

Geersing et al: Clinical prediction rules plus D-dimer testing do not enable a safe exclusion of deep vein thrombosis or pulmonary embolism in elderly patients

- In 642 patients living in Dutch nursing homes (348 suspected DVT, 294 suspected PE), VTE was confirmed in 247
- In patients suspected of DVT, 69 were identified as low-risk: DVT was confirmed in 4 patients during follow-up (failure rate 5.8%, 95% CI 2.3–14), suggesting that a clinical prediction rule plus D-dimer testing does not safely rule-out VTE in these elderly patients