SOCIETÀ ITALIANA DI FLEBOLINFOLOGIA CONGRESSO DEL TRENTENNALE FERRARA 20 – 22 OTTOBRE 2016

NAO e TEP: Indicazioni, Vantaggi ed Eventi Avversi

La Recidiva di TVP: Aspetti Clinici

G. G. Arpaia

Direttore SC di Medicina Interna

ASST di Vimercate, Ospedale di Carate Brianza

QUALCHE DEFINIZIONE!

«as venous thrombosis of a site that was either previously uninvolved or had interval documentation of incident DVT or PE resolution» (Heit Blood 2011)

Definition of terms

The definitions of recurrence and progression are as follows:

1 VTE recurrence: PE and/or DVT occurring after a successful acute treatment; 'successful' means a clear clinical improvement of patient symptoms and signs; 'acute' means the first 2 weeks of treatment.

2 Early VTE recurrence: VTE occurring within the first 3 months.

3 Late recurrence: VTE occurring after the initial 3 months.

4 VTE progression: new PE and/or DVT occurring or worsening during the acute treatment.

Ageno JTH 2013

MA…LA DIAGNOSI DI RECIDIVA DI TVP…PUÒ ESSERE CLINICA?

Journal of Thrombosis and Haemostasis, **11**: 1597–1602 DOI: 10.1111/jth.12301

RECOMMENDATIONS AND GUIDELINES

The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH

W. AGENO,* A. SQUIZZATO,* P. S. WELLS,† H. R. BÜLLER‡ and G. JOHNSON§

**Department of Clinical and Experimental Medicine, Research Center on Thromboembolic Disorders and Antithrombotic Therapies, University of Insubria, Varese, Italy; †Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; ‡Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands; and §Hematology/Oncology Section, VA Medical Center, Minneapolis, MN, USA*

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MA…LA DIAGNOSI DI RECIDIVA DI TVP…PUÒ ESSERE CLINICA?

Scope and methodology

This document is intended to give clinical guidance for the diagnosis of symptomatic recurrent pulmonary embolism (PE) and/or deep vein thrombosis (DVT). We define recurrent PE and DVT as those events occurring after an initial course of adequate antithrombotic treatment for a first venous thromboembolic event (VTE) [1,2]. The issue of a correct diagnosis of recurrence is clinically relevant because many patients with a previous VTE will complain of signs or symptoms suggesting the possibility of a recurrent event. Indeed, in patients with a previous DVT, symptoms and signs of post-thrombotic syndrome are often confusing for the clinician (and patient) and are interpreted as possible recurrent DVT. Moreover, only 20–30% of all suspected recurrences of both DVT and PE have been confirmed by central adjudication committees in randomized controlled trials [3]. However, even if only a minority of patients will be objectively diagnosed with a recurrent VTE [1], this remains a major clinical problem occurring in approximately 11% of patients after 1 year from the first unprovoked event and in approximately 40% of patients after 10 years [4].

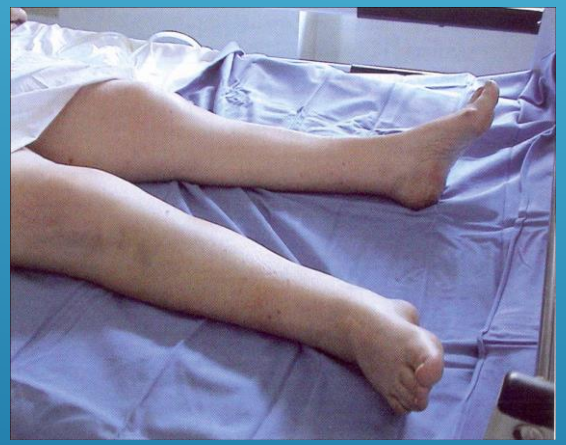
NO!

MA…LA DIAGNOSI DI RECIDIVA DI TVP…PUÒ ESSERE CLINICA?

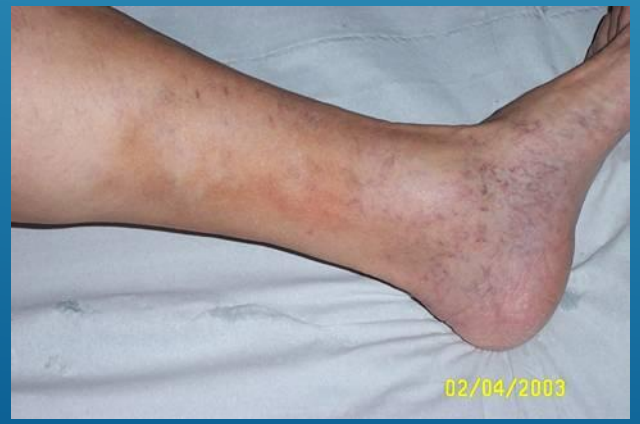
Quali armi vengono suggerite?

1. Clinical Prediction Rules (Wells per TVP)
2. D-Dimero
3. CUS (con misurazione del trombo residuo e se possibile comparativa con esame –di buona qualità- eseguito alla cessazione della terapia anticoagulante)

QUINDI…BEN POCO SPAZIO PER LA CLINICA MA:



- Adeguata stratificazione del rischio
- Controllo della aderenza alla terapia
- Esecuzione di accurati test strumentali alla cessazione della terapia anticoagulante
- Adeguata informazione del Paziente ed accesso facilitato anche solo in caso di sospetta recidiva



QUALI I PAZIENTI A MAGGIOR RISCHIO DI RECIDIVA?

Table 1: Risk factors for recurrence after a first VTE event.

Thrombosis related	Patient related
	Men
Unprovoked event	Active cancer
Nonsurgical transient versus surgical risk factor associated with the first event	Antiphospholipid syndrome
	Inherited thrombophilic alterations
Proximal (especially if iliofemoral) versus distal DVT	Pregnancy and puerperium
	Hormonal therapies
Pulmonary embolism	Obesity
Persistence of residual vein thrombosis	Presence of inferior vena cava filter
	Polycythemia vera and essential thrombocythemia, especially in the presence of JAK2 V617F mutation

Palareti Scientifica 2012

QUALI I PAZIENTI A MAGGIOR RISCHIO DI RECIDIVA?

Il D-Dimero

post-anticoagulazione

Provoked and unprovoked DVT: maggior rischio di recidiva se elevato

Unprovoked DVT: maggior rischio se elevato

Unprovoked DVT: maggior rischio se elevato indipendentemente dalla presenza o meno di residuo trombotico

Unprovoked DVT: predittivo di recidiva se si incrementa nel tempo

Durante anticoagulazione: predittivo di recidiva nella donna se elevato

Palareti Scientifica 2012

QUINDI «UNPROVOKED» PEGGIO DI «PROVOKED»

VTE PROVOKED BY A TRANSIENT RISK FACTOR*

Major transient risk factor during the 3 months before diagnosis of VTE

A risk factor is considered 'major' if it has been shown to be associated with:

(1) half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 3 months before the VTE†; or

(2) a greater than10-fold increase in the risk of having a first VTE.

Examples:

- Surgery with general anesthesia for greater than 30 min.
- Confined to bed in hospital (only 'bathroom privileges') for at least 3 days with an acute illness.
- Cesarean section.

Minor (yet important) transient risk factor during the 2 months before diagnosis of VTE

A risk factor is considered 'minor' if it has been shown to be associated with:

(1) half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 2 months before the VTE†; or

(2) a 3 to 10-fold increase in the risk of having a first VTE.

Examples:

- Surgery with general anesthesia for less than 30 min.
- Admission to hospital for less than 3 days with an acute illness.
- Estrogen therapy.
- Pregnancy or puerperium.
- Confined to bed out of hospital for at least 3 days with an acute illness.
- Leg injury associated with reduced mobility for at least 3 days.

VTE PROVOKED BY A PERSISTENT RISK FACTOR

Active cancer

Cancer is considered active if any of the following apply:

(1) has not received potentially curative treatment; or

(2) there is evidence that treatment has not been curative (e.g. recurrent or progressive disease)‡; or

(3) treatment is ongoing.

On-going non-malignant condition associated with at least a 2-fold risk of recurrent VTE after stopping anticoagulant therapy

Example:

Inflammatory bowel disease.

UNPROVOKED VTE

No provoking risk factor (transient or persistent)

We suggest that, in this context, patients are considered to have unprovoked VTE if they do not meet the criteria for VTE that was provoked by a transient or a persistent risk factor that are outlined above§

Kearon JTH 2016

GLI «SCORE» PER LA VALUTAZIONE DEL RISCHIO DI RECIDIVA DI TEV

HERDOO2: 2008

Vienna: 2010

DASH: 2012

Predicting VTE recurrence – MEN continue and HERDOO2

- Prospective cohort study (N=646, 11 centers, 3 counties, 2001-2006)
- Patients with first unprovoked VTE s/p anticoagulation x 5-7 mo
- Mean age 53 (18-95), 49% were female, mean f/u: 3.1 year
- High risk women with ≥ 2 of
  - **H**yperpigmentation
  - **E**dema or **R**edness
  - Vidas **D**-dimer >250 µg/L (on anticoagulation)
  - **O**besity (BMI>30)
  - **O**lder age (>65)
- Annual risk of recurrent VTE
  - Man- 13.7% (95% CI 10.8-17%)
  - High risk (≥2 risk factors) women- 14.1% (10.9-17.3%)
  - Low risk (0-1 risk factors) women- 1.6% (0.3-4.6%)
- Conclusion: Women with low risk can safely discontinue anticoagulation, but Validation is needed

Rodger MA et al. CMAJ 2008;179(5):417-426.

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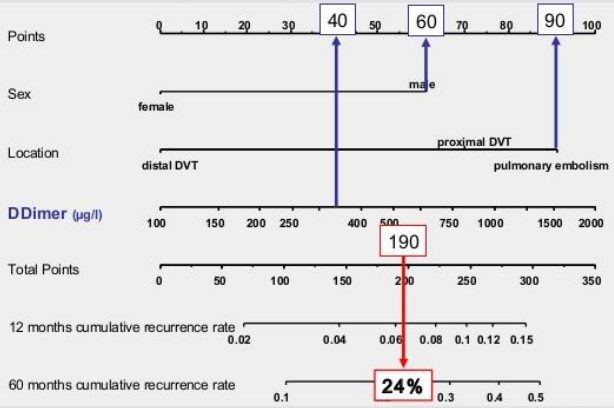
AUREC

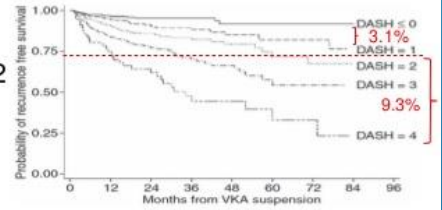
Nomogram to predict recurrence



Eichinger, Circulation 2010

Predicting VTE recurrence – DASH score

- Retrospective pooled analysis (N=1818)
- Patients with first unprovoked VTE treated for at least 3 months of anticoagulation
- Risk factors ($D_2A_1H_1S_{-2}$)
  - **D**-dimer (elevated after stopping anticoagulation) +2
  - **A**ge (≤ 50yo) +1
  - **S**ex (male) +1
  - **H**ormonal therapy (VTE not associated with H) -2



- Conclusion: In patients with DASH score ≤ 1, can stop anticoagulation after 3 mo of treatment

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BMJ Open

Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE

Joie Ensor,[1] Richard D Riley,[1] David Moore,[2] Kym I E Snell,[2] Susan Bayliss,[2] David Fitzmaurice[3]

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[1]Research Institute of Primary Care and Health Sciences, Keele University, Staffordshire, UK
[2]Public Health, Epidemiology and Biostatistics, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[3]Primary Care Clinical Sciences, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

Correspondence to:
Joie Ensor;
j.ensor@keele.ac.uk

ABSTRACT

Objectives: To review studies developing or validating a prognostic model for individual venous thromboembolism (VTE) recurrence risk following cessation of therapy for a first unprovoked VTE. Prediction of recurrence risk is crucial to informing patient prognosis and treatment decisions. The review aims to determine whether reliable prognostic models exist and, if not, what further research is needed within the field.

Design: Bibliographic databases (including MEDLINE, EMBASE and the Cochrane Library) were searched using index terms relating to the clinical field and prognosis. Screening of titles, abstracts and subsequently full texts was conducted by 2 reviewers independently using predefined criteria. Quality assessment and critical appraisal of included full texts was based on an early version of the PROBAST (Prediction study Risk Of Bias Assessment Tool) for risk of bias and applicability in prognostic model studies.

Setting: Studies in any setting were included.

Primary and secondary outcome measures: The primary outcome for the review was the predictive accuracy of identified prognostic models in relation to VTE recurrence risk.

Results: 3 unique prognostic models were identified including the HERDOO2 score, Vienna prediction model and DASH score. Quality assessment highlighted the Vienna and DASH models were developed with generally strong methodology, but the HERDOO2 model had many methodological concerns. Further, all models were considered at least at moderate risk of bias, primarily due to the need for further external validation before use in practice.

Conclusions: Although the Vienna model shows the most promise (based on strong development methodology, applicability and having some external validation), none of the models can be considered ready for use until further, external and robust validation is performed in new data. Any new models should consider the inclusion of predictors found to be consistently important in existing models (sex, site of index event, D-dimer), and take heed of several methodological issues identified through this review.

PROSPERO registration number: CRD42013003494.

Strengths and limitations of this study

- To our knowledge, this is the first systematic review identifying prognostic models for venous thromboembolism recurrence risk in the unprovoked population, using a robust systematic methodology.
- The study is also the first to assess the validity of the existing models in terms of risk of bias and applicability.
- We were unable to perform a quantitative analysis of the identified articles due to a lack of homogeneity in many areas, including the predictors used, model types and study populations.
- All models require further independent external validation, and as such the true performance of the models in the wider unprovoked population must be assessed in new research.

INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular disease after heart attack and stroke; it is a chronic condition with estimated incidence at 1 per 1000 person years.[1–3] VTE often presents as deep vein thrombosis (DVT), with some patients suffering an embolism in the lungs known as a pulmonary embolism. An initial VTE developed in the presence of a known provoking factor may be termed 'provoked', while those developed in the absence of clinical risk factors may be termed 'unprovoked'.[3 4] There are several known predisposing risk factors including surgery, trauma, hormone intake, pregnancy and prolonged immobility.[3 5] Such factors can be considered as acquired risk factors, because they are transient, that is, while they increase the risk of an initial VTE, they are temporary, and when the provoking factor is removed, the patient is at a low risk of recurrence, for example, postsurgery.[3–5]

GLI «SCORE» PER LA VALUTAZIONE DEL RISCHIO DI RECIDIVA DI TEV

Table 2 Study characteristics

Model	HERDOO2	Vienna	DASH
Year of publication	2008	2010	2012
Country	Four countries (unspecified)	Austria	Austria, Canada, Italy, Switzerland, UK, USA
Study setting	12 tertiary care centres, patients enrolled between October 2001 and March 2006	Recruited from 4 thrombosis centres in Vienna between July 1992 and August 2008	Patient-level meta-analysis of previously published studies (11)
Study design	Prospective cohort study	Prospective cohort study	Individual patient data from 7 prospective studies
Clinical outcome	Recurrent VTE	Recurrent VTE	Recurrent VTE
Key prediction time points (months)	12 months	12, 60 months	12, 24, 60 months
Total sample size	646	929	1818
Events	91	176	239

VTE, venous thromboembolism.

Table 3 Study inclusion/exclusion criteria

Model	HERDOO2	Vienna	DASH
Inclusion criteria	First unprovoked VTE Received OAC 5–7 months No recurrent VTE on treatment	First unprovoked VTE Age≥18 Received OAC≥3 months	First unprovoked VTE Including thrombophilic blood abnormalities where there were no other VTE risks
Exclusion criteria	Age<18 Deficiency in antithrombin, protein C or S Presence of lupus anticoagulant Already discontinued OAC Geographically inaccessible to follow-up Not proximal DVT or PE index event	Deficiency in antithrombin, protein C or S Presence of lupus anticoagulant Presence of cancer	Known antiphospholipid antibodies Antithrombin deficiency Not proximal DVT or PE index event

DVT, deep vein thrombosis; OAC, oral anticoagulants; PE, pulmonary embolism; VTE, venous thromboembolism.

GLI «SCORE» PER LA VALUTAZIONE DEL RISCHIO DI RECIDIVA DI TEV

Table 5 Predictors included in final model

Model	HERDOO2	Vienna	DASH
Predictors included			
D-dimer	X	X	X
Age	X	–	X
Sex	–	X	X
BMI	X	–	–
Post-thrombotic signs	X	–	–
Site of index event	–	X	–
Hormone therapy	–	–	X

BMI, body mass index.

In conclusion, currently available models to predict risk of recurrent VTE in an unprovoked population have several limitations. In particular, sufficient external validation has not yet been performed for two of the available models and we recommend further validation studies are required before the models are implemented into practice. Even then the impact of the model on clinical decision-making and, crucially, patient outcomes should be evaluated through a randomised trial, ideally, or health economic modelling exercise.[11 43] Any new models should try to build on the existing work, ensure external validation in multiple populations, transparency in reporting of model development as outlined in the TRIPOD statement,[13] and finally improved statistical analyses to ensure model predictions are more robust.

IN CONCLUSIONE

- Anche la diagnosi di recidiva di TVP, cosi come quella di TVP, non può essere affidata alla sola clinica, anche in mani esperte
- Risulta fondamentale una attenta stratificazione del rischio che deve essere effettuata prima della sospensione della terapia anticoagulante
- Soprattutto in caso di «unprovoked» TVP il monitoraggio post-sospensione TA deve essere attento e probabilmente seriato
- Fondamentale la valutazione ecografica con misurazione dello spessore del trombo residuo, se presente, al termine del trattamento allo scopo di poter successivamente rivalutare il quadro in caso di sospetta recidiva
- Mandatoria l'educazione del Paziente alla corretta aderenza alla terapia anticoagulante e compressiva e la creazione di percorsi privilegiati in caso di variazioni dello stato clinico