Il D-dimero e la valutazione del rischio di recidiva del TEV

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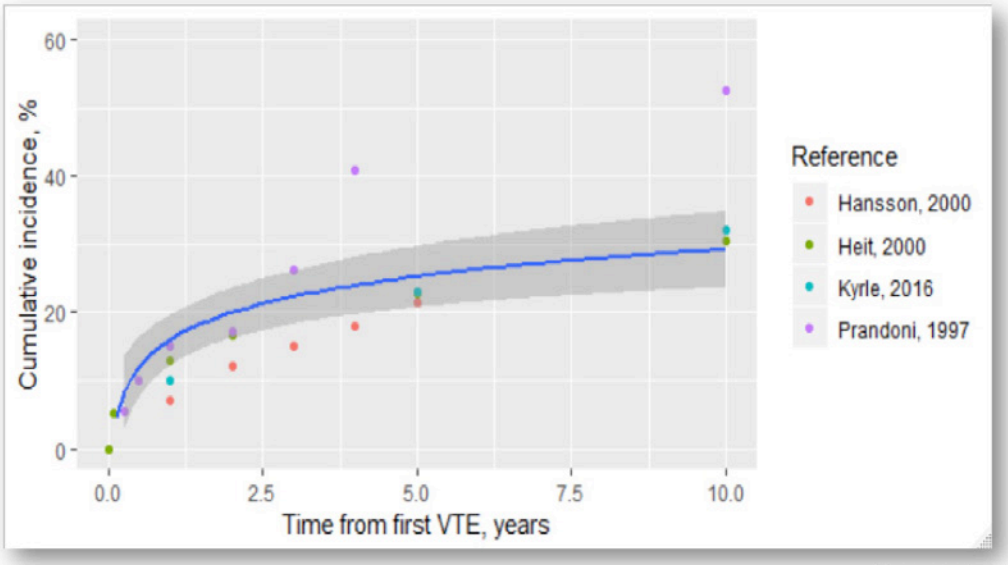
Annual rate of VTE recurrence after unprovoked VTE:
15% in the first year, <2% thereafter



Hansson et al., Arch Intern Med, 2000
J. A. Heit, et al., Arch Intern Med, 2000
P. Prandoni, et al., Haematologica, 2007

REVIEW ARTICLE

Risk of Recurrence After a First Episode of Symptomatic Venous Thromboembolism Provoked by a Transient Risk Factor

A Systematic Review

Alfonso Iorio, MD; Clive Kearon, MD; Esmeralda Filippucci, MD; Maura Marcucci, MD; Ana Macura, MD; Vittorio Pengo, MD; Sergio Siragusa, MD; Gualtiero Palareti, MD

- At 24 months, the rate of recurrence was
  - 3.3% per patient-year for all patients with a transient risk factor,
  - 0.7% per patient-year in the subgroup with a surgical factor
  - 4.2% per patient-year in the subgroup with a nonsurgical factor
- In the same studies, the rate of recurrence after unprovoked VTE was 7.4% per patient-year.

Iorio et al., Arch Intern Med, 2010

Preventing VTE recurrence after proximal unprovoked VTE

1. Treat all who have acceptable bleeding risk (i.e., suspend if high bleeding risk)
2. Treat all who have high recurrence risk (i.e., suspend if low recurrence risk)

What the guidelines say

First approach: suspend if high bleeding risk (ACCP 2016)

- In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a
  - *low or moderate bleeding risk*: we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)
  - *high bleeding risk*: we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)

Kearon et al., Chest, 2016

When a patient has a *high* bleeding risk?

- No consensus
- According to the ACCP 2016 guidelines, high-risk patients should have an **eightfold** risk of major bleeding to justify withholding therapy

Average risk of anticoagulant-related bleeding in patients with venous thromboembolism

Treatment period	VKA (case-fatality rate %)	DOAC (case-fatality rate %)
Initial treatment in the first 5–10 days	1.2% (0–40%)	-
Treatment in the first 3 months	2.1% (9.3%)	-
Extended treatment	2.7% patient-years (9.1%) 1.0 % (8.1%)#	0.1–0.9% in 6–12 months following an initial treatment period of 6–12 months (0–4%)

2.7 x 8 = **21.6% patient-years**

1.0 x 8 = **8.8% patient-years**

Adapted from:
Klok et al., Eur Respir J, 2015
Linkins et al., Ann Intern Med, 2003
 # Palareti et al., Intern Emerg Med, 2017

What is an high bleeding risk?

- No consensus
- According to the ACCP 2016 guidelines, high-risk patients should have an **eightfold** risk of major bleeding to justify withholding therapy (corresponding to 8-15% per-year)
- In three validation studies, in the highest-risk categories the absolute risk of major bleeding was ***2 to 5% per-year*** for the ACCP, HAS-BLED and VTE-BLEED score respectively [1-3]

1 Palareti et al., J Thromb Haemost, 2018
2 Brown et al., J Am Heart Assoc, 2018
3 Klok et al., Br J Haematol, 2018

What is an high bleeding risk?

- No consensus
- A...

Is the "suspend if high bleeding risk" paradigm valid?
Probably not
Could be useful only for very complex cases (e.g., thrombocytopenia, GI active disease)

...tegories the
...eeding was 2-5% per-year for the
..., HAS-BLED and VTE-BLEED score respectively [1-3]

1 Palareti et al., J Thromb Haemost, 2018
2 Brown et al., J Am Heart Assoc, 2018
3 Klok et al., Br J Haematol, 2018

What the guidelines say

Second approach: suspend if low recurrence risk (ESC 2018)

– Decision to discontinue or not anticoagulation should be individually tailored, balancing risk of recurrence against bleeding risk, taking into account patients' preferences and compliance.

Mazzolai et al., Eur Heart J, 2017

What the guidelines say

Second approach: suspend if low recurrence risk (ESC

Without an established clinical gestalt or guidance, It is likely that most patients receive indefinite therapy in the DOAC era

Mazzolai et al., Eur Heart J, 2017

Fatality rate after recurrent VTE

	Studies included	Patients	Fatal recurrent VTE	Recurrent VTE	Pooled case-fatality rate % (95% CI)	I^2 %	Pooled rate of recurrent fatal VTE per 100 patient-years (95% CI)	Pooled rate of recurrent VTE per 100 patient-years (95% CI)
VTE at baseline in studies with low or moderate risk of bias								
Unprovoked VTE	18	6758	58	1079	2.6 (0.86–5.0)	66.60	0.17 (0.047–0.33)	6.3 (5.42–7.3)
Unprovoked DVT	13	3675	45	669	2.7 (0.50–6.1)	63.52	0.18 (0.025–0.43)	6.2 (4.6–8.0)
Unprovoked PE	9	1783	8	243	1.6 (0–5.7)	48.43	0.060 (0–0.28)	5.6 (4.2–7.1)
Other subgroups								
Overall VTE	24	8914	64	1545	2.0 (0.69–3.8)	65.21	0.13 (0.036–0.25)	6.2 (5.4–7.2)
Overall DVT	17	4544	49	887	2.3 (0.52–4.8)	60.39	0.14 (0.022–0.33)	6.3 (5.0–7.6)
Overall PE	13	2730	9	426	0.12 (0–1.8)	34.90	0.011 (0–0.11)	4.9 (4.2–5.7)
Enrolment before 2000	11	4245	55	883	4.0 (1.3–7.8)	76.46	0.27 (0.038–0.59)	6.8 (5.4–8.4)
Enrolment after January 1, 2000	12	4508	9	642	0.71 (0.063–1.8)	0	0.039 (0.0028–0.1)	5.9 (0.47–7.2)
Cohort	16	6020	51	1161	1.7 (0.19–4.2)	74.62	0.11 (0.009–0.29)	6.4 (5.3–7.6)
RCT	9	2894	13	384	2.5 (0.69–5.0)	26.83	0.14 (0.021–0.33)	6.0 (4.6–7.6)
Follow-up ⩽2.5 years	12	5183	16	574	1.8 (0.46–3.8)	34.85	0.11 (0.018–0.27)	6.7 (5.2–8.3)
Follow-up >2.5 years	12	3731	48	971	2.2 (0.22–5.4)	76.57	0.13 (0.076–0.35)	5.8 (4.8–7.0)

van der Wall, et al., European Respiratory Review, 2018

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NNT to avoid 1 death: 590 patients

van der Wall, et al., European Respiratory Review, 2018

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NNT to avoid 1 death: 2564 patients

van der Wall, et al., European Respiratory Review, 2018

Why we do need D-dimer (or a more formal CPG) to assess patients with unprovoked VTE?

- Identification of patients at high bleeding risk is still difficult
- The consequences of recurrence are manageable in most cases
- A “treat-them-all” approach could be challenged (at least in some patients)

Presentation topics

- Why we do need CPG to assess patients with unprovoked VTE
- Which type of DVT/PE may be assessed with a CPG?

Crude incidences of recurrent VTE according to individual risk factors (Einstein CHOICE)

Risk factor	Recurrent VTE, n (%)	
	Rivaroxaban 10 and 20 mg	Placebo/aspirin
Provoked by minor persistent risk factors, n (%)		
Inflammatory bowel disease	0/26 (0.0)	0/14 (0.0)
Lower extremity paralysis or paresis	0/12 (0.0)	0/4 (0.0)
Congestive heart failure	2/23 (8.7)	0/10 (0.0)
Body mass index >30 kg/m^2	13/907 (1.4)	25/536 (4.7)
Creatinine clearance <50 mL/min	2/122 (1.6)	8/104 (7.7)
Family history of VTE	2/31 (6.5)	0/13 (0.0)
Hereditary thrombophilia	3/173 (1.7)	8/102 (7.8)
Acquired thrombophilia	1/20 (5.0)	0/5 (0.0)
Provoked by minor transient risk factors, n (%)		
Immobilization	1/99 (1.0)	5/68 (7.4)
Travel >8 h	0/11 (0.0)	0/9 (0.0)
Use of estrogen therapy	0/75 (0.0)	1/64 (1.6)
Pregnancy or puerperium	0/17 (0.0)	0/2 (0.0)
Leg injury with impaired mobility	0/76 (0.0)	2/40 (5.0)

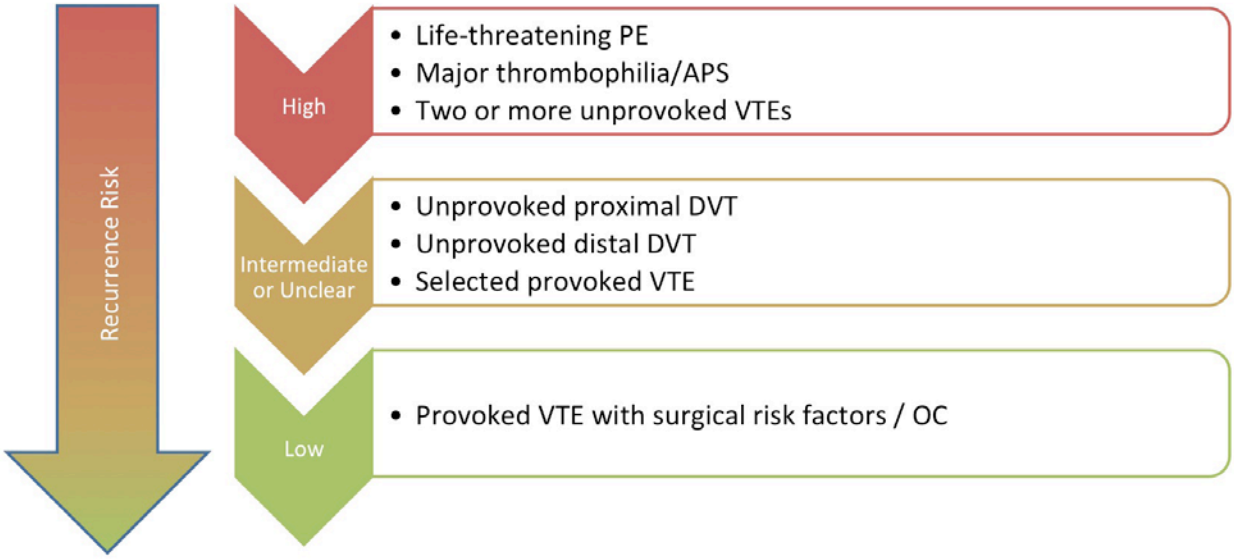
Prins et al., Blood Adv, 2018

Recurrence risk according to VTE type

VTE type	First year	Annual rate after first year
First episode of unprovoked VTE	10 percent	5 percent
Second episode of unprovoked VTE	15 percent	7.5 percent
First VTE provoked by surgery	1 percent	0.5 percent
First VTE provoked by non-surgical factor (e.g., OC, long-haul flights)	5 percent	2.5 percent

Iorio et al., Arch Intern Med, 2010
Kearon et al., Chest, 2016

The clinical usefulness of a CPG is anchored on the estimated recurrence risk



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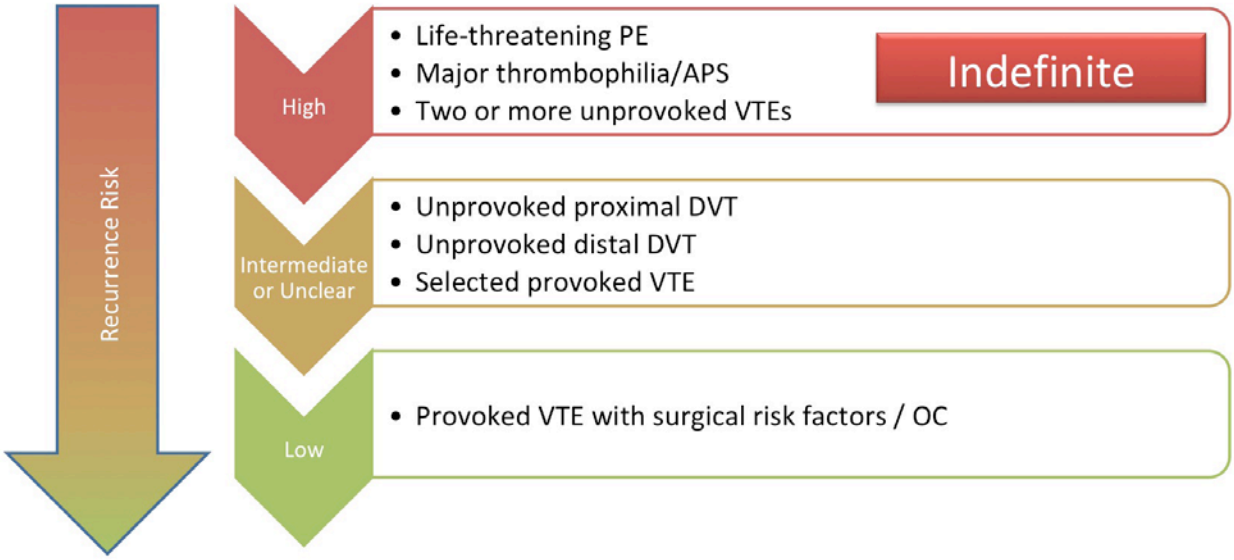

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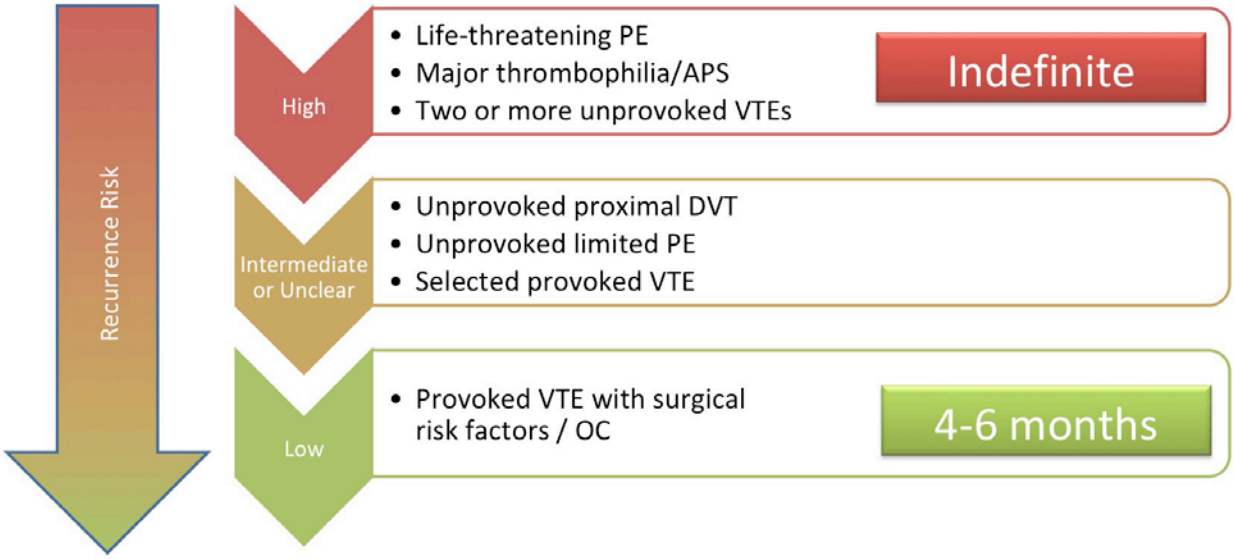

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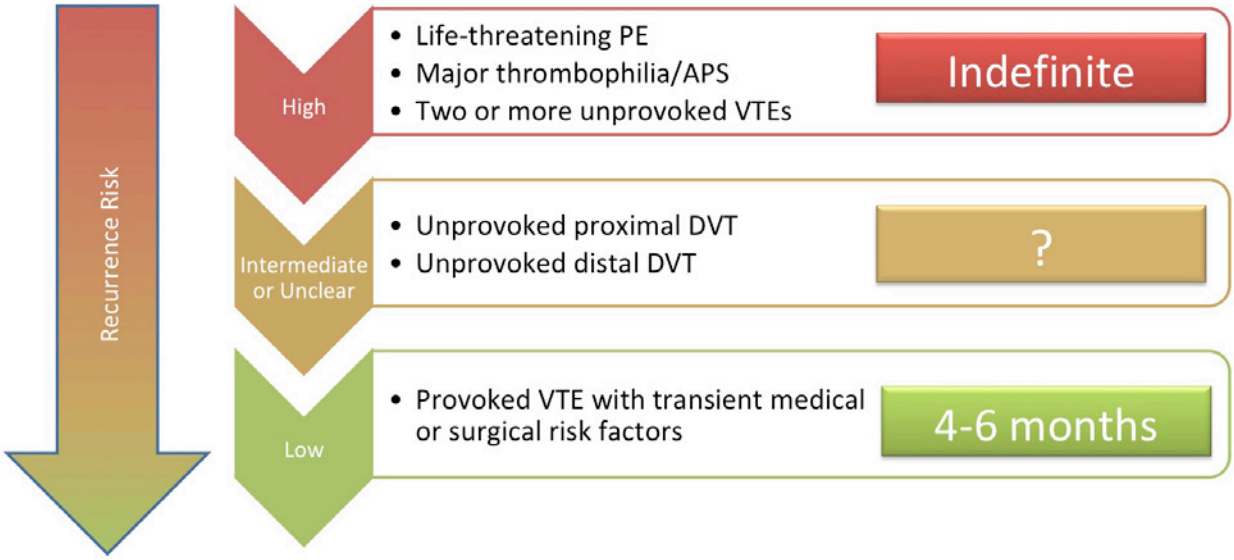


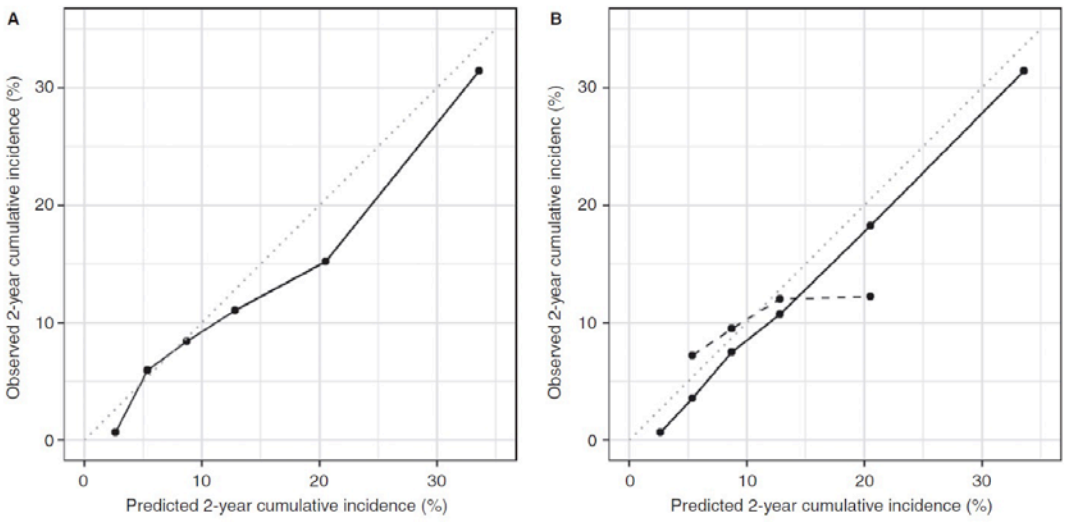
Presentation topics

- Why we do need CPG to assess patients with unprovoked VTE
- Which type of DVT/PE may be assessed with a CPG?
  - First episode of unprovoked VTE, or VTE with selected risk factors
  - Not a life-threatening episode

Presentation topics

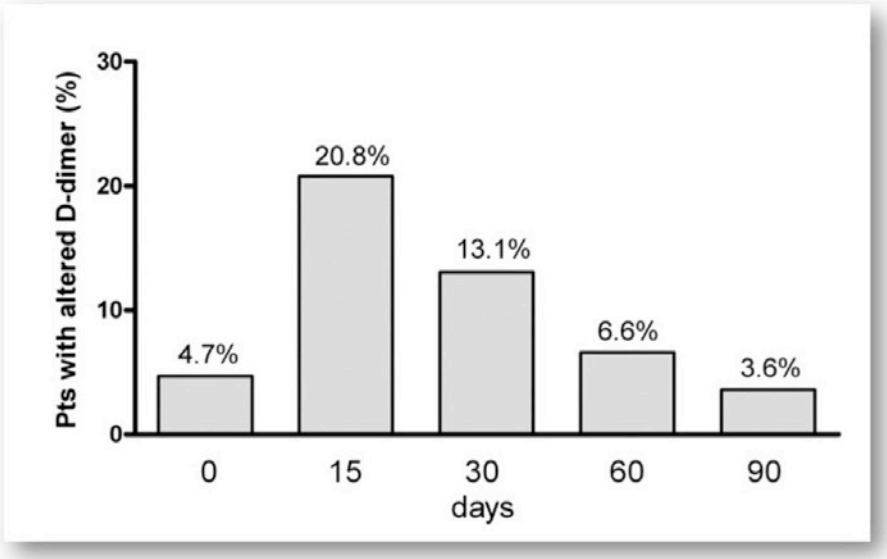
- Why we do need CPG to assess patients with unprovoked VTE
- Which type of DVT/PE may be assessed with a CPG?
- Which type of patient may benefit more?

D-dimer measurement is not useful for patients >65years



Tosetto et al., J Thromb Haemost, 2017

Serial D-dimer protocol may increase sensitivity



Palareti et al., Blood 2014

Could patients with provoked VTE benefit from D-dimer measurement?

	N	Recurrences	Observation years	Recurrence rate per 100 person-years (95% CI)
Provoked in MEGA[a]	1349	138	8104	1.7 (1.4-2.0)
Low-risk group				
Women, surgery, low D-dimer	121	8	768	1.0 (0.5-2.6)
High-risk group				
Men, no surgery, high D-dimer	73	21	352	6.0 (3.9-9.2)
Men, no surgery, high D-dimer, high factor VIII	25	7	114	6.2 (2.9-12.9)
Unprovoked in MEGA[a]	539	115	3089	3.7 (3.1-4.5)
Low-risk group				
Women, low D-dimer	86	14	539	2.6 (1.5-4.4)
High-risk group				
Men, high D-dimer	153	43	816	5.3 (3.9-7.1)
Men, high D-dimer, high factor VIII	58	19	308	6.2 (3.9-9.7)

[a]Patients with (un)provoked first venous thrombosis in MEGA, excluding patients with missing for surgery or D-dimer.

Timp et al., J Thromb Haemost, 2019

Could patients with provoked VTE benefit from D-dimer measurement?

Recurrence rates in the RIETE Registry

	Increased D-dimer	Normal D-dimer
Major transient risk factors	5.7 (3.2 – 9.6)	2.7 (1.45-4.56)
DD measured ≤ 30 days	3.0 (0.5–10.1)	3.4 (1.1 - 8.2)
DD measured ≤ 30 days	6.8 (3.6–11.9)	2.4 (1.1–4.6)
Minor transient risk factors	7.8 (5.7–10.4)	3.3 (2.4–4.5)
DD measured ≤ 30 days	7.3 (4.93–10.4)	3.2 (2.2–4.7)
DD measured ≤ 30 days	8.9 (5.2–14.5)	3.6 (1.9–6.1)

Avnery et al., J Intern Med, 2020

Presentation topics

- Why we do need CPG to assess patients with unprovoked VTE
- Which type of DVT/PE may be assessed with a CPG?
- Which type of patient may benefit more?
  - Patients at low bleeding risk
  - Willing to suspend anticoagulation & perform at least 1-2 visits after suspension of anticoagulation
  - Age below 65-70 years

Conclusions

- Suspension of VTE therapy after a first unprovoked episode is still a reasonable option in the DOAC era
  - Very high NNT to avoid embolic deaths
  - most recurrences are manageable
- "Suspend only if high bleeding risk" or "Treat-them-all" are not reasonable treatment goals
- An CPG including sensitive D-dimer is a viable alternative to identify "high-risk" patients

Conclusions

- A CPG is best used to "assess" VTE patients and to inform clinicians advices and patients choices (rather than predicting)
- D-dimer based CPGs loose their predictivity with age
  - Aspecific increase of D-dimer with age
  - Haemostatic risk factors less important
  - Circumstantial risk factors (e.g., immobilization, cancer, sepsis) may be more relevant for recurrence
- The use of D-dimer in provoked VTE should be tested