And in the end, it's not the years in your life that count. It's the life in your years. (Abraham Lincoln)

TAO o NAO

S. Basili

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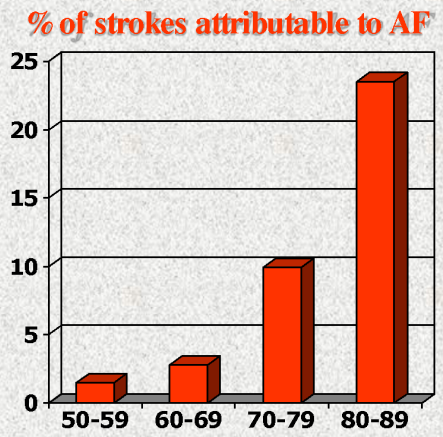
Anticoagulant therapy is used to treat and/or **prevent** both arterial and venous thrombosis.

Atrial Fibrillation

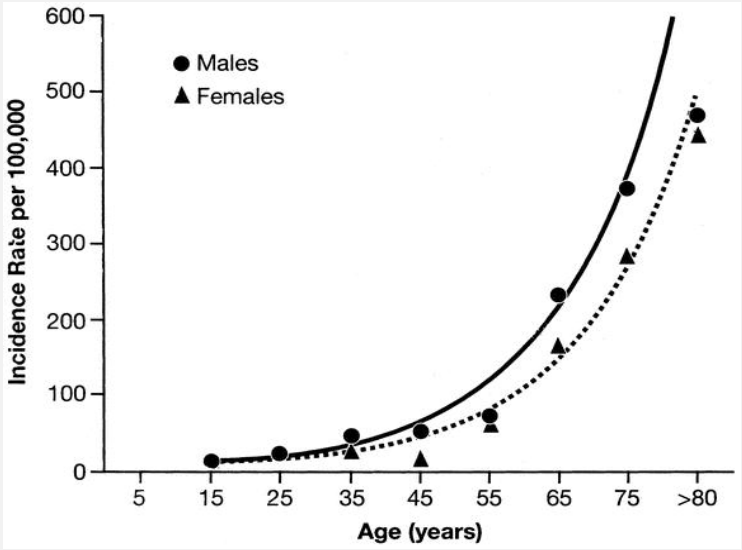
Outcomes: Stroke

- Leading cause of stroke from embolism
- AF increases stroke risk
  - ~17X w/ Rheumatic Heart Dz
  - ~ 5X in non-valvular AF
  - Risk of stroke ~5%/yr
- Proportion of strokes attributable to AF increases with ⇑ Age



[Kannel 1998]

Annual Incidence of VTE



Arch Intern Med 1991;151:933

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AF

Anticoagulant therapy : **ATRIAL FIBRILLATION**

Chest. 2010; 137: 263-72.

CHA_2DS_2VASc Score

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

Any high-risk factor (score=2) or > 1 moderate-risk factor: Anticoagulant Therapy

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VTE

Venous ThromboEmbolic Disease (VTE)

Incidenza annuale (corretta per sesso ed età):

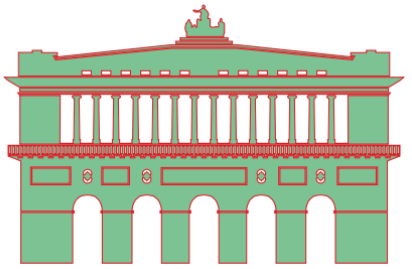
117 (in Italia 70) casi per 100.000 pazienti per anno

Trombosi Venosa Profonda (DVT) ~ **5,000,000/anno (in Italia 50,000 pazienti).** Più del 50% si complica con embolia polmonare.

L'embolia polmonare rappresenta il 6 % di TUTTE le MORTI in ospedale.

TERZA PIU' COMUNE CAUSA DI MORTE CARDIOVASCOLARE

Un appropriato trattamento anticoagulante, iniziato tempestivamente, riduce la mortalità al 2-8%



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(European Journal of Haematology, 2012; 89: 281-7)

VTE is the silent killer

- VTE is under recognized and goes undiagnosed
- When diagnosis is based on clinical signs and symptoms:
  - <50% of all cases of fatal PE are detected prior to death
  - 80% of cases of DVT are clinically silent
- No tests to predict who will have a VTE

TERZA PIU' COMUNE CAUSA DI MORTE CARDIOVASCOLARE

PREVENTION IS KEY!!

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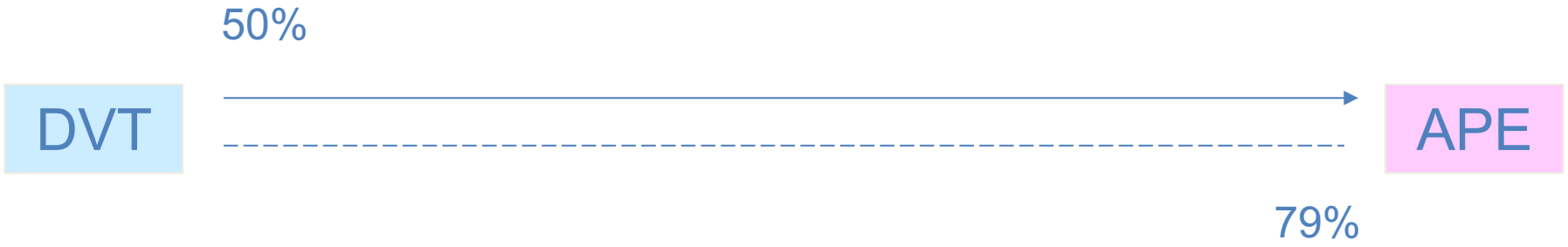
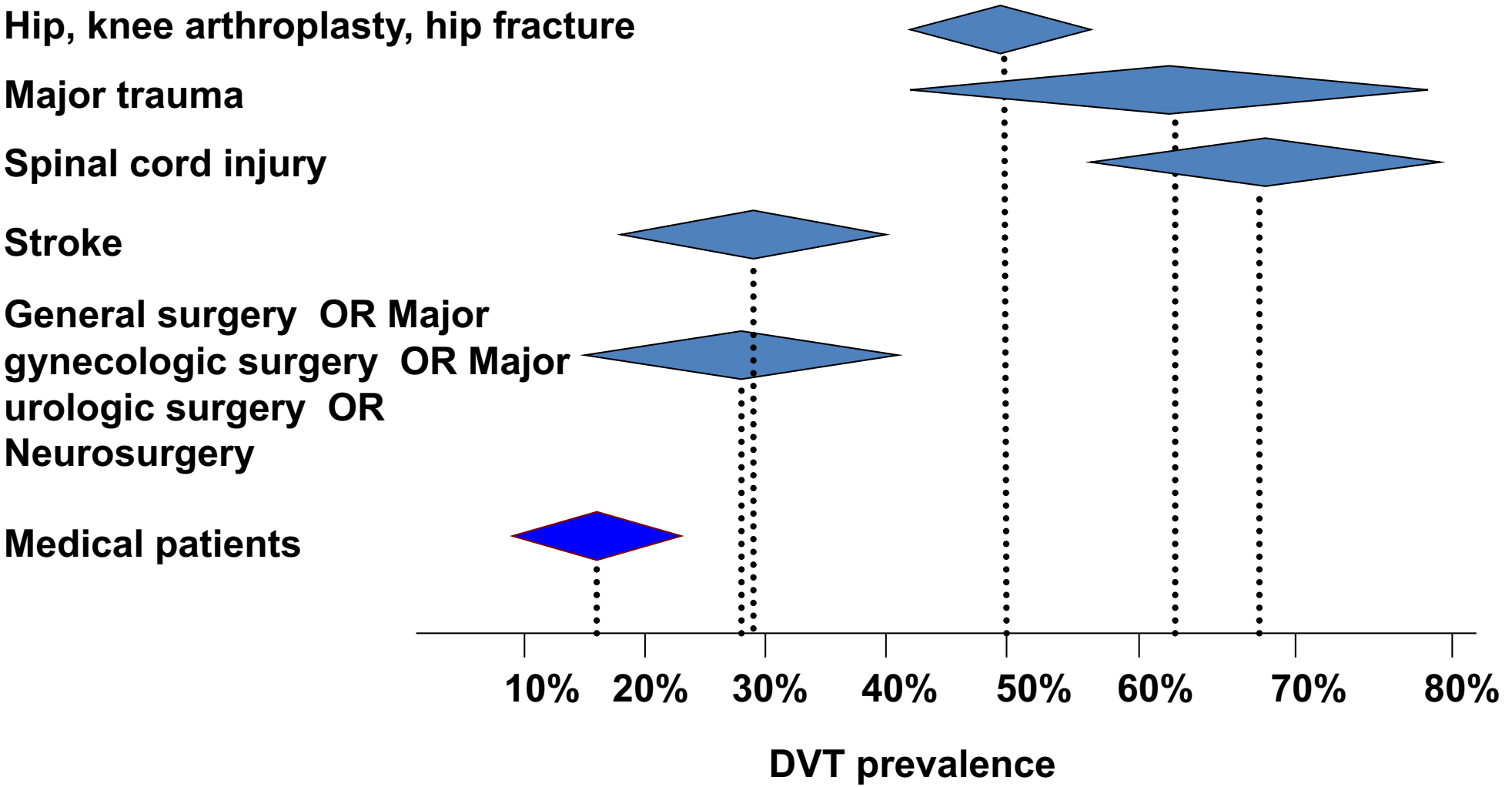
ACUTE PULMONARY EMBOLISM PATHOPHISIOLOGY



- APE occurs in 50% of patients with proximal DVT.

- 79% of the patients with APE have evidence of DVT in their legs. If DVT is not detected, it is very possible that the whole thrombus has embolized.

Prevalence of DVT in Hospitalized Patients



Geerts – Chest June, 2008

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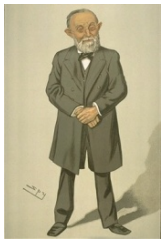
Tromboembolia venosa

Triade di Virchow



1821-1902

Rudolf Virchow's Triad

Ipercoagulabilità

Ereditaria *Acquisita*

Stasi

Acquisita

Lesione vascolare

Acquisita

Trombosi venosa

Virchow R. In Gesammelte Abhandlugen zur Wissenschaftlichen Medizin, 1856; Frankfurt: Staatsdruckerei
Rosendaal FR. Lancet 1999; 353:1167–1173

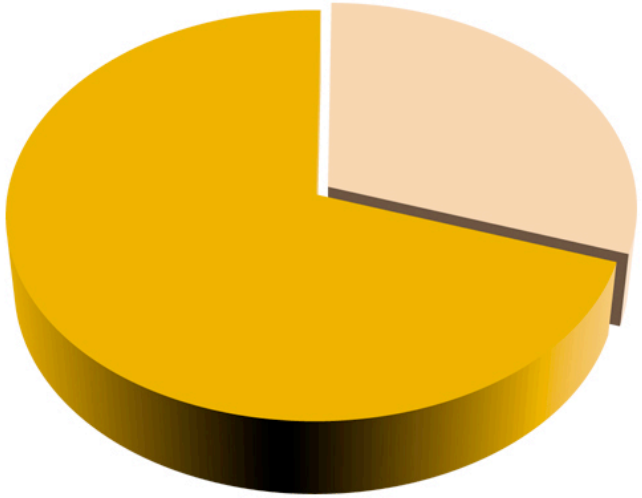
Risk Factors

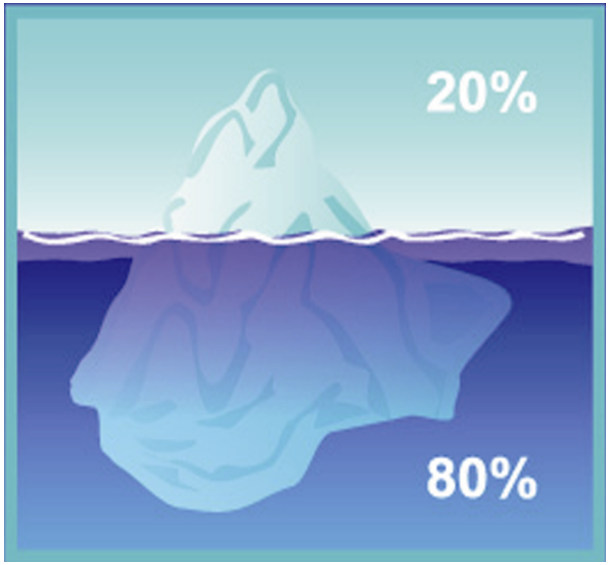
- CHF
- Malignancy
- Obesity
- Estrogen/OCP
- Pregnancy (esp post partum)
- Lower ext injury
- Coagulopathy
- Venous Stasis
- Prior DVT
- Age > 70
- Prolonged Bed Rest
- Surgery requiring > 30 minutes general anesthesia
- Orthopedic Surgery

Diagnosi

Il TEV spesso non viene diagnosticato se non quando è troppo tardi

Oltre il 70% delle EP fatali viene scoperto post mortem





Circa l'80% delle TVP è clinicamente silente[2,3]

1. Stein PD, et al. Chest 1995; 108(4): 978–81
2. Lethen H, et al. Am J Cardiol 1997; 80(8): 1066–9
3. Sandler DA, et al. J R Soc Med 1989; 82(4): 203–5

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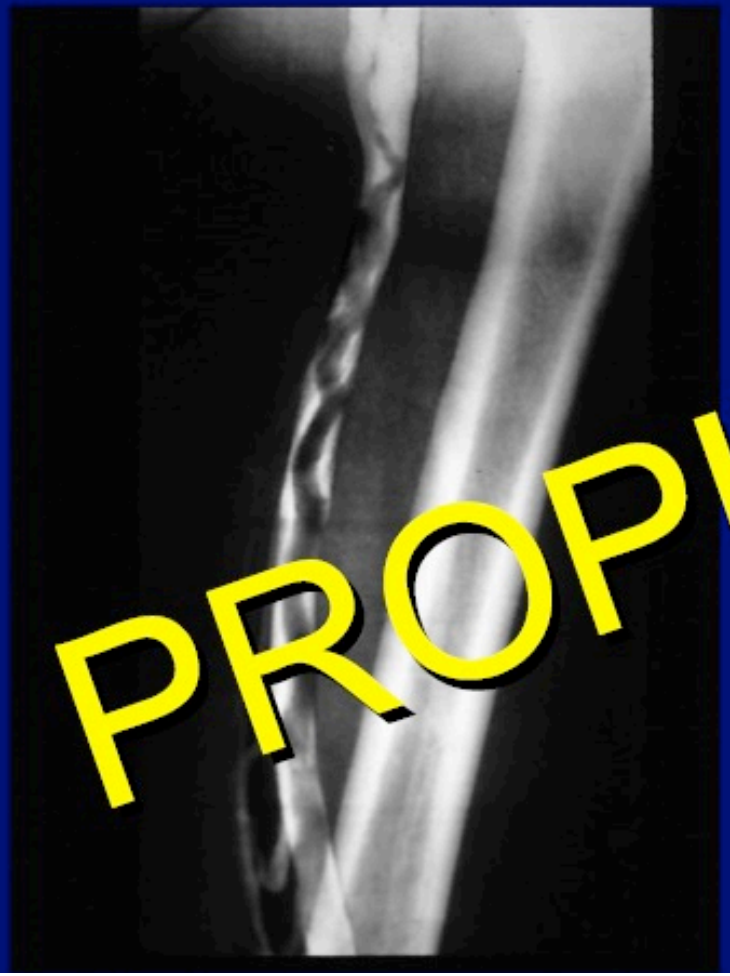
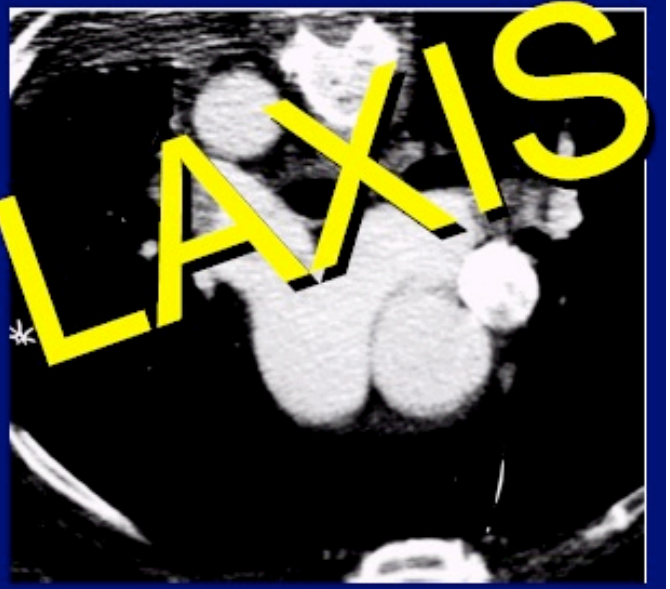
Deep vein thrombosis



Pulmonary embolism



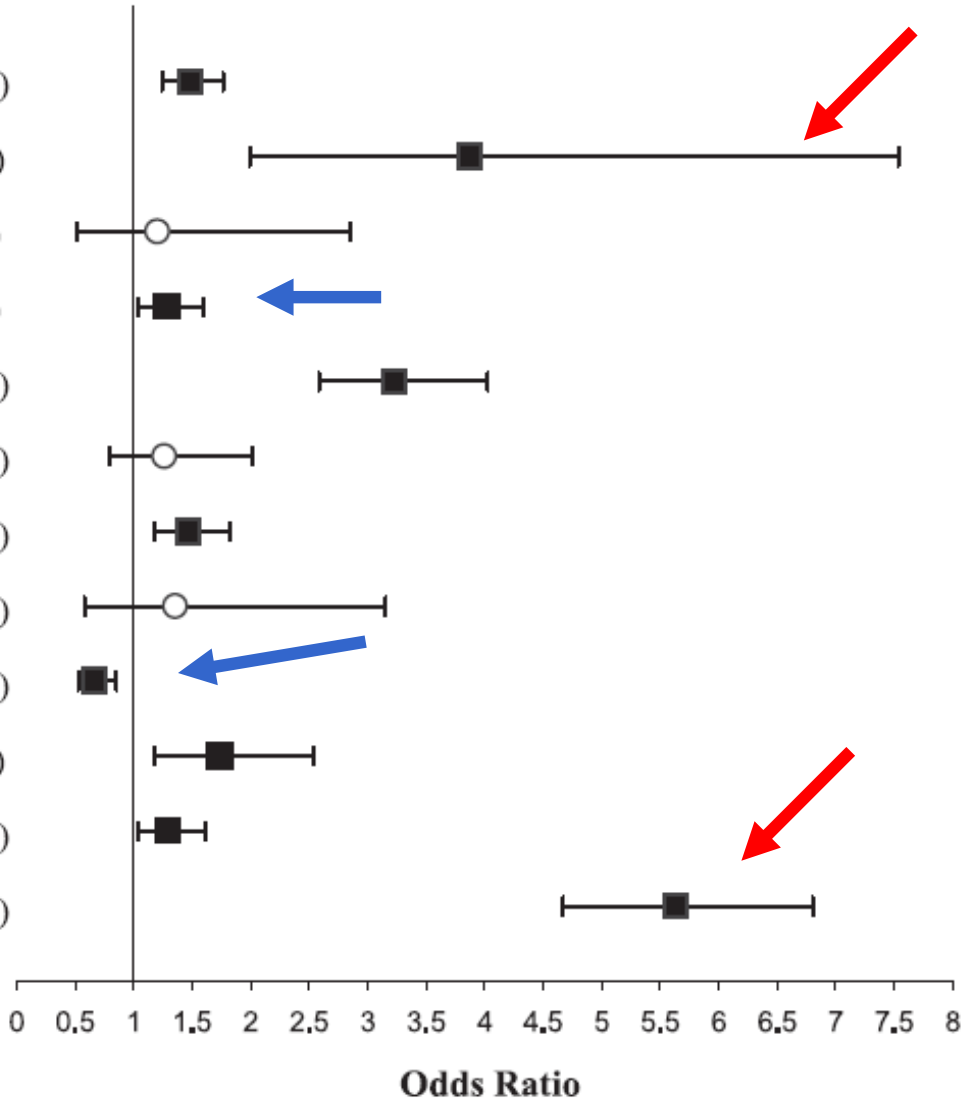
PROPHYLAXIS

GEMINI STUDY - 27 Internal Medicine Departments (all in Italy) (4,846 patients)

58.7% of those for whom prophylaxis was recommended

Thromb Haemost. 2009 May;101(5):893-901

Effect	Odds Ratio	(95% CI)
Age class	1.48	(1.24 – 1.76)
Previous VTE	3.87	(1.99 – 7.54)
Recent surgery	1.2	(0.51 – 2.9)
Obesity	1.28	(1.04 – 1.6)
CHF	3.22	(2.58 – 4.03)
Acute MI	1.26	(0.79 – 2.01)
COPD	1.46	(1.12 – 1.82)
IBD	1.35	(0.58 – 3.15)
Cancer	0.67	(0.52 – 0.85)
Hemi-paraparesis/Hemi-paraplegia	1.73	(1.19 – 2.53)
Fever	1.29	(1.04 – 1.60)
Bed rest	5.64	(4.67 – 6.81)



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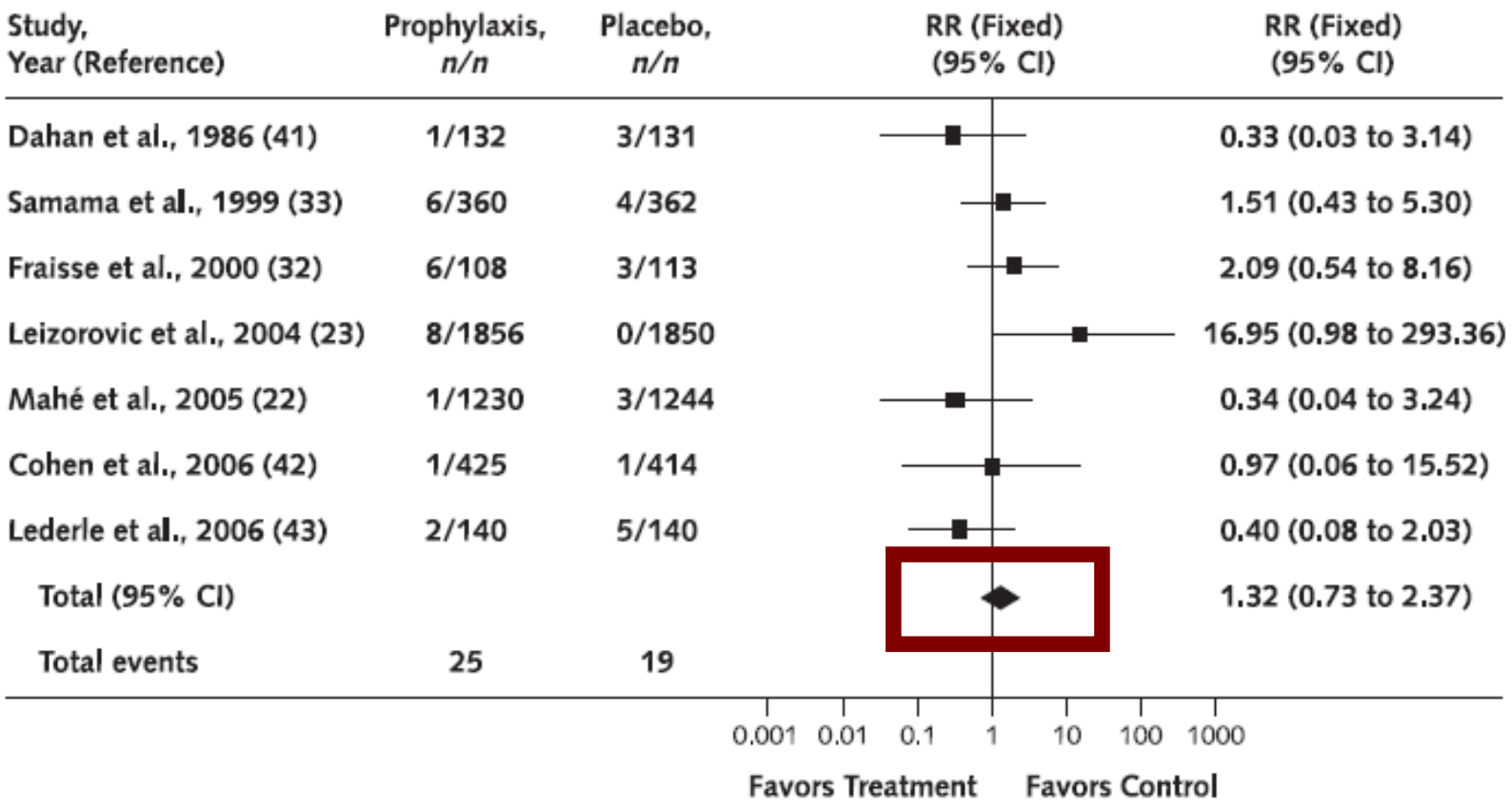
Meta-analysis: Anticoagulant Prophylaxis to Prevent Symptomatic Venous Thromboembolism in Hospitalized Medical Patients (*Ann Intern Med.* 2007;146:278-288)

Major bleeding during anticoagulant prophylaxis. **9 studies (*n* = 19,958)**

M

P

A



In 25 of 4301 (0.58%) patients who received prophylaxis and in 19 of 4304 (0.44%) patients who received no prophylaxis (relative risk, 1.32 [CI, 0.73 to 2.37], ns)

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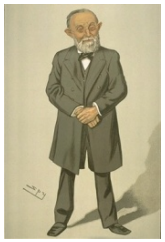
Tromboembolia venosa

Triade di Virchow



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Rosendaal FR. Lancet 1999; 353:1167–1173

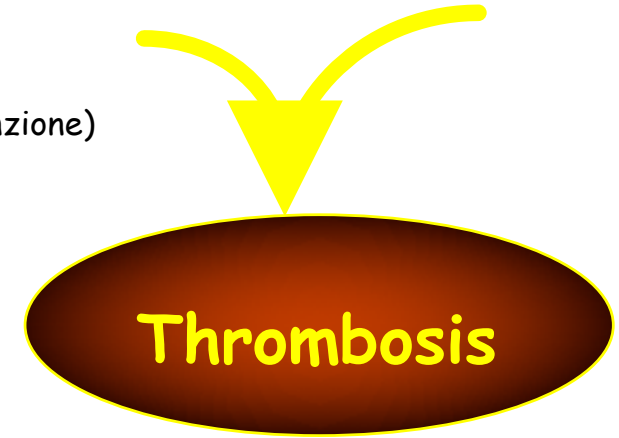
Inherited Prothrombotic Mutation(s)

1. **FACTOR V LEIDEN/ Cambridge/ Hong Kong** (aumento di funzione)
2. **PROTHROMBIN 20210A** (aumento di funzione)
3. **PROTEIN C DEFICIENCY** (perdita di funzione)
4. **PROTEIN S DEFICIENCY** (perdita di funzione)
5. **ANTITHROMBIN DEFICIENCY** (perdita di funzione)

Acquired Prothrombotic Stimulus

- **ANTIPHOSPHOLIPID ANTIBODIES/LAC**
- **Elevated levels of FVIII**

(Combined)



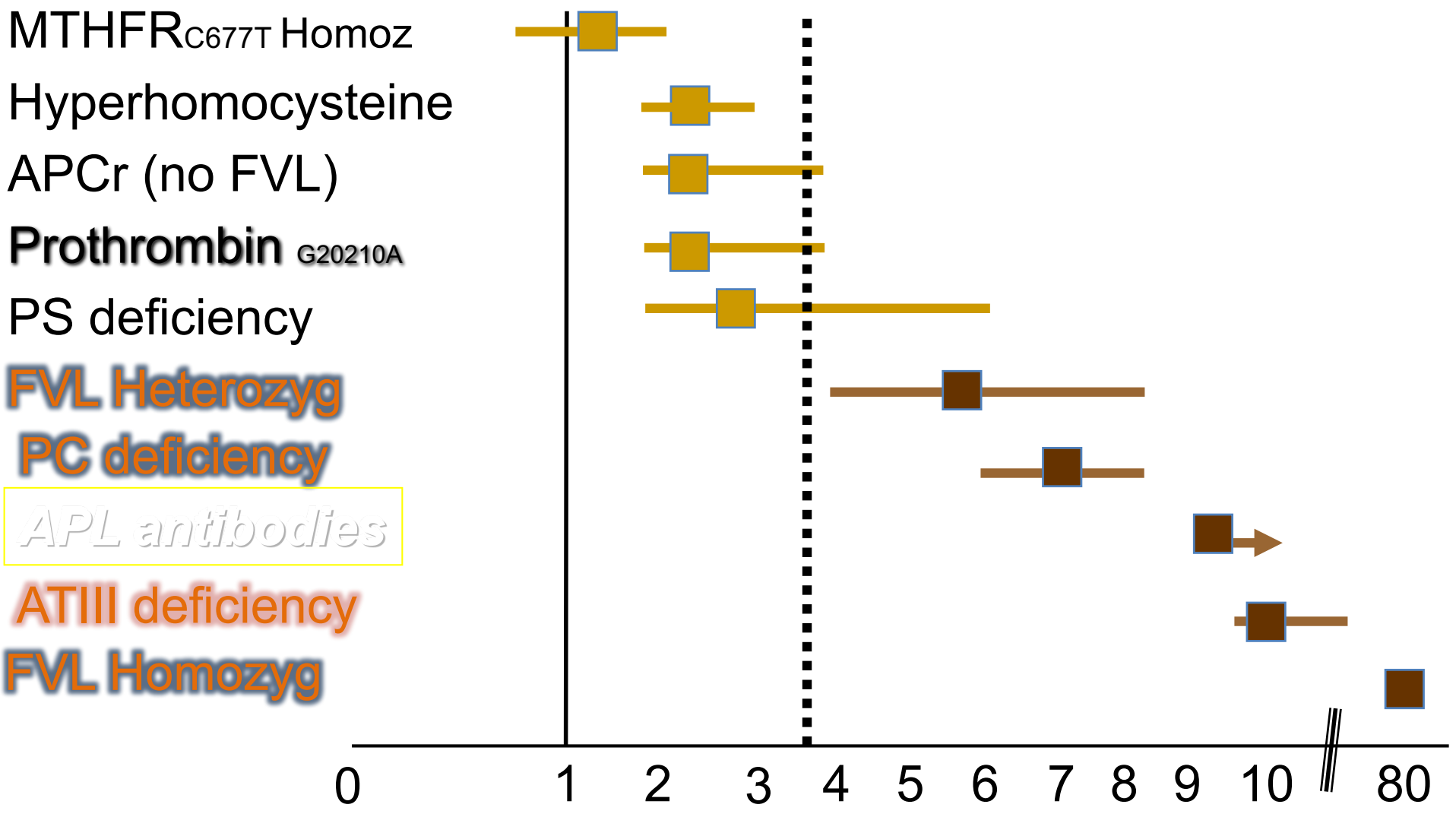
(*International Consensus Statement. Int J Angiol 2005; American Society of Haematology, 2005*)

Prevalenza delle alterazioni trombofiliche.

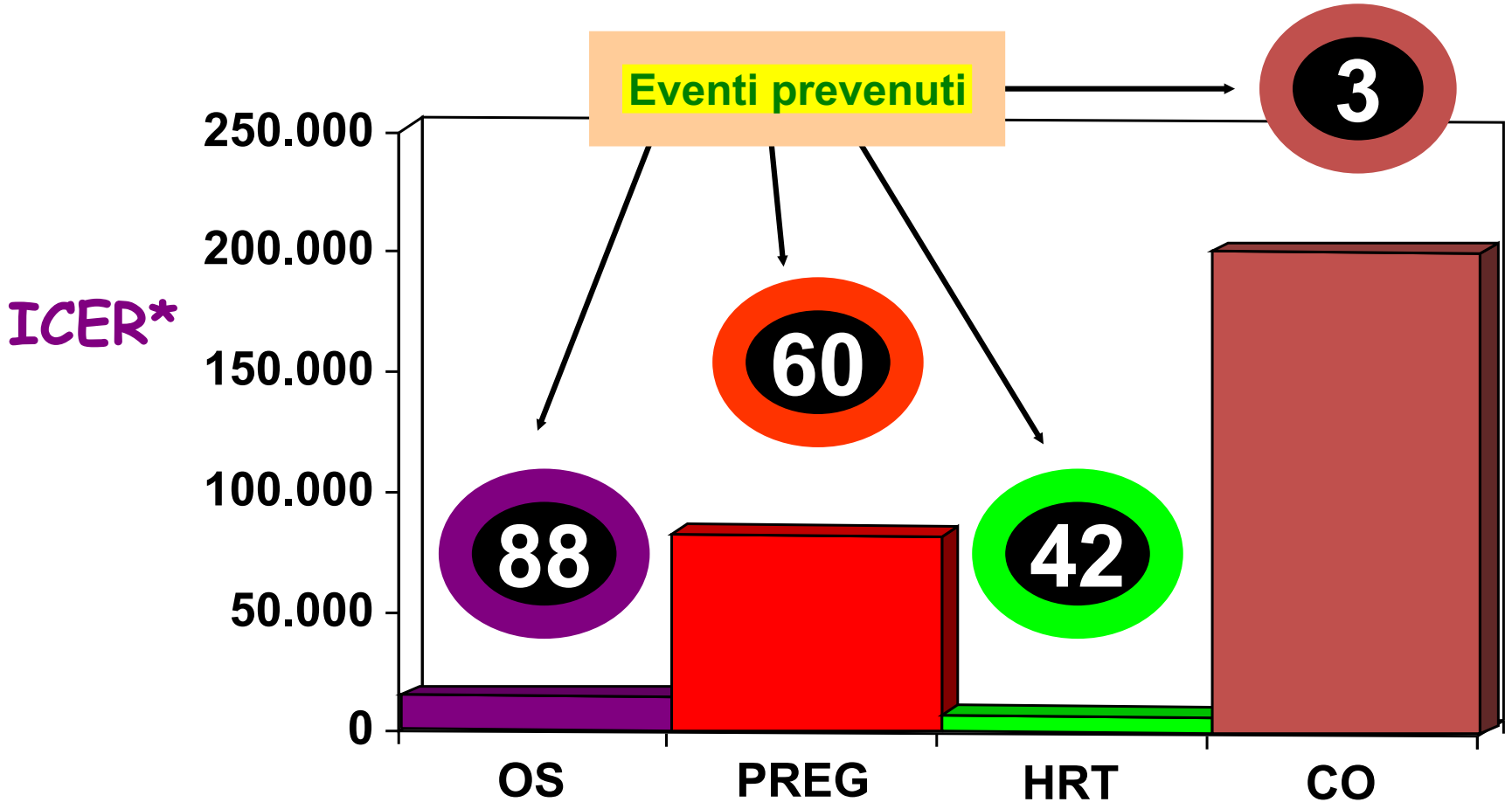
	popolazione generale	TEV
ATIII	0.02%	1%
PC	0.2-0.4%	3%
PS	0.02% (?)	1-2%
FV Leiden	4-7 %	15-20%
PT 20210A	1-3%	6%
Fattore VIII	10%	25%
Hcy	5%	10%
LAC/ACA	?	5%

Estimated Prevalence of Thrombophilic Disorders (OR for VTE) -Review

*(American Journal of Obstetrics and Ginecology **2004**; 191: 412-24)*



RAPPORTO COSTO-BENEFICIO NELLO **SCREENING UNIVERSALE**. (N=10.000)



* Incremental Cost-Effectiveness Ratios (ICER) = Δcosts/Δbenefits; i.e. costs (screening -no screening)/clinical complications prevented (screening - no screening).

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APS: impact on real life

*There are two major 'new' diseases of the late twentieth century – AIDS and Hughes Syndrome.(**APS**).."*

…… accounts for approximately:

1 in 5 Deep Vein Thrombosis ('DVTs')

1 in 5 young strokes (under 45)

1 in 5 recurrent miscarriages

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Antiphospholipid syndrome (APS)

ACQUIRED AUTOIMMUNE THROMBOPHILIA in which

vascular thrombosis and/or recurrent pregnancy losses

occur in patients having laboratory evidence for antibodies against phospholipids or phospholipid-binding protein cofactors in their blood.

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SAPPORO 1998 + ISTH 2006 - Ann Rheum Dis. 2007 Mar 2

AT LEAST ONE OF THE CLINICAL CRITERIA:

1. Vascular Thrombosis

2. Pregnancy Morbidity

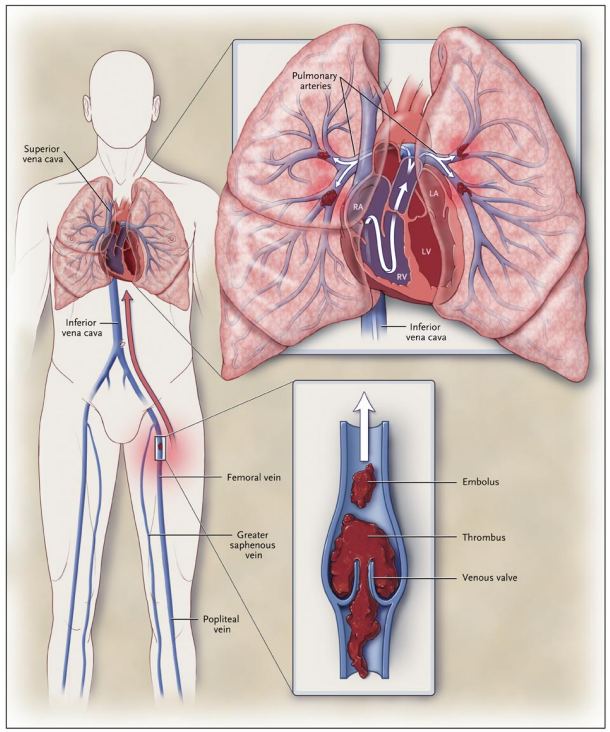
a) death of normal fetus at > 10 wks
b) premature birth at < 34 wks due to preeclampsia
c) >3 consecutive abortions at <10wks
d) placental insufficiency at < 34 wks

AND AT LEAST ONE OF THE LABORATORY CRITERIA:

1. Lupus anticoagulant (LA) on >two occasions at least 12 weeks apart.

2. Anticardiolipin (aCL) antibody of IgG and/or IgM present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart.

3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart.



- Both Pulmonary embolism and DVT are treated the same
- An adequate level of anticoagulation is essential
- There are no randomized studies investigating the timing of anti-coagulation therapy initiation in patients with suspected DVT/EP.

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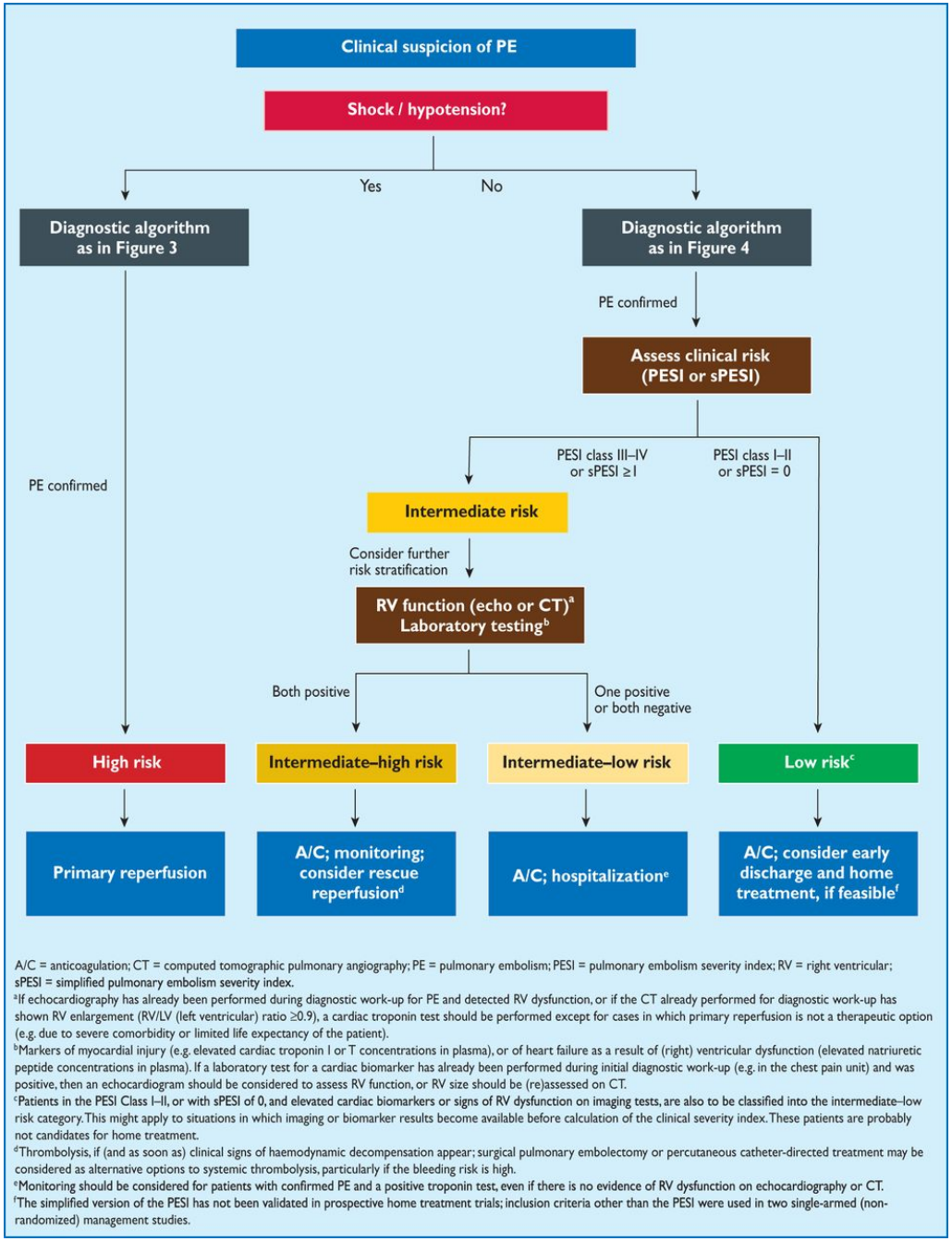
JAMA Intern Med. doi:10.1001/jamainternmed.2015.1687 Published online May 18, 2015.

European Heart Journal

Risk-adjusted management strategies in acute PE



A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; sPESI = simplified pulmonary embolism severity index.

[a]If echocardiography has already been performed during diagnostic work-up for PE and detected RV dysfunction, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/LV (left ventricular) ratio ≥0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g. due to severe comorbidity or limited life expectancy of the patient).

[b]Markers of myocardial injury (e.g. elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g. in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT.

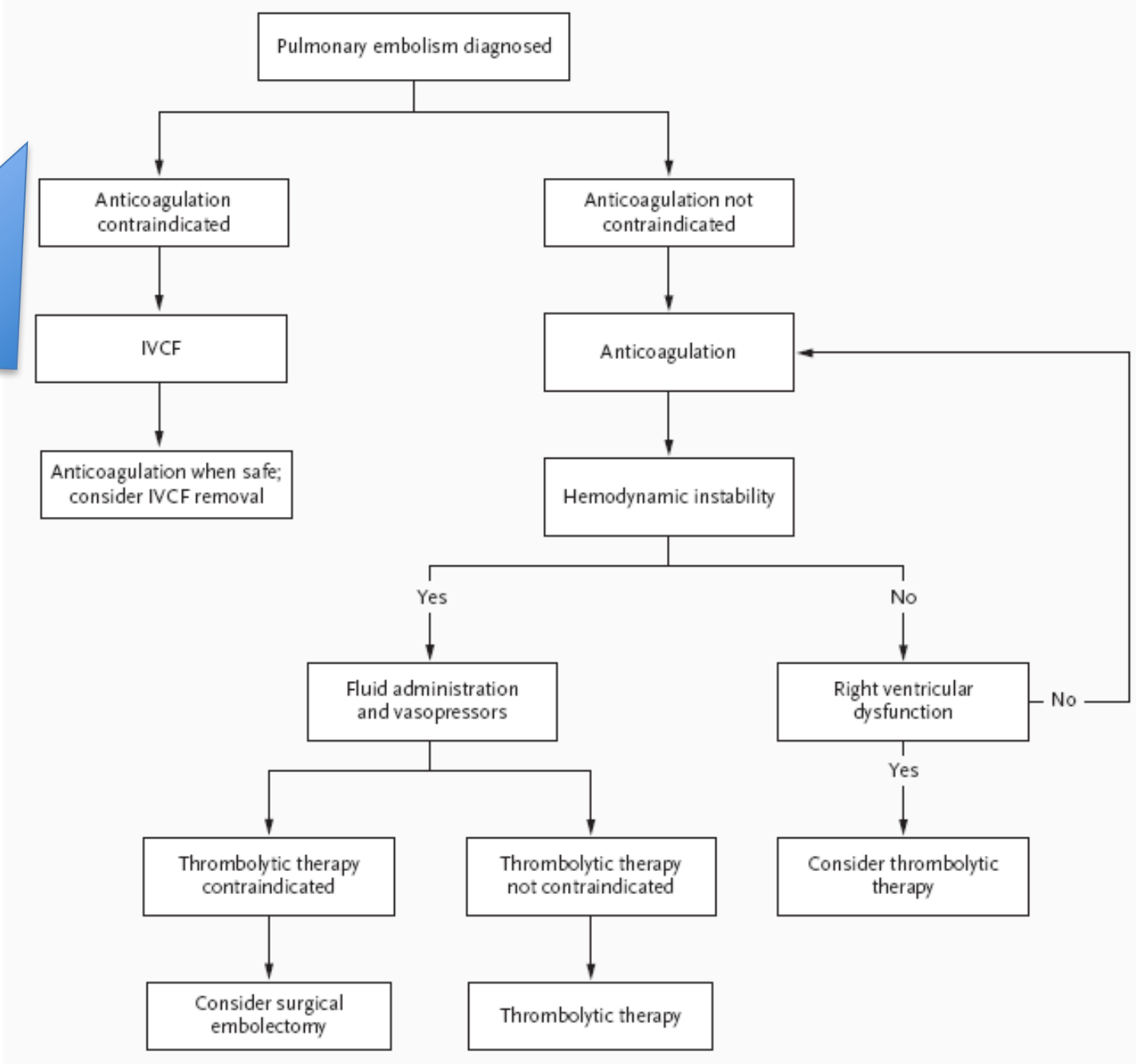
[c]Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate–low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably not candidates for home treatment.

[d]Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

[e]Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.

[f]The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-armed (non-randomized) management studies.

Flow chart trattamento embolia polmonare



The NEW ENGLAND JOURNAL of MEDICINE

2008;358:1037-52.

Venous filters

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

Venous filters are usually placed in the infrarenal portion of the inferior *vena cava* (IVC).

Early complications— 10% of patients.
Late complications - recurrent DVT in approximately 20% of patients and post-thrombotic syndrome in up to 40%.

Occlusion of the IVC affects approximately 22% of patients at 5 years and 33% at 9 years, regardless of the use and duration of anticoagulation.

American College of Chest Physicians 2012

2014 ESC Guidelines

~~IVC filters~~

- **Non-permanent are classified as temporary or retrievable devices.**
- **Temporary filters must be removed within *few days*, while retrievable filters can be left in place for longer periods.**
- **When non-permanent filters are used, it is recommended that they be removed as soon as it is safe to use anticoagulants.**
- ***Despite this, they are often left in situ for longer periods, with a late complication rate of at least 10%.***

When should clinicians start anticoagulants?

- **In patients with a *high pretest probability of VTE and a low risk for bleeding*, it is reasonable to initiate a short-acting anticoagulant while awaiting the results of the diagnostic work-up, particularly if there is a delay in testing.**

- **In patients with *an intermediate clinical suspicion* of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).**

- **In patients with *a low clinical suspicion of acute VTE*, it is suggested not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).**

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5 May 2015 Annals of Internal Medicine -

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1 pre test

Indici predittivi della probabilità di EP
Canadian (Wells) Prediction Score

Valutazione Clinica

Items	Clinical decision rule points	
Wells rule	**Original version[95]**	**Simplified version[107]**
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

2014 ESC Guidelines

Thromb Haemost. **2008**; 99(1):229-34

2pre test

Indici predittivi della probabilità di EP
Revised Geneva Score

Valutazione Clinica

Revised Geneva score	Original version[93]	Simplified version[108]
Previous PE or DVT	3	1
Heart rate 75–94 b.p.m. ≥95 b.p.m.	 3 5	 1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

Arch Intern Med. **2008**;168(19):2131-6.

- **Antithrombotic Therapy for Venous Thromboembolic Diseases.**

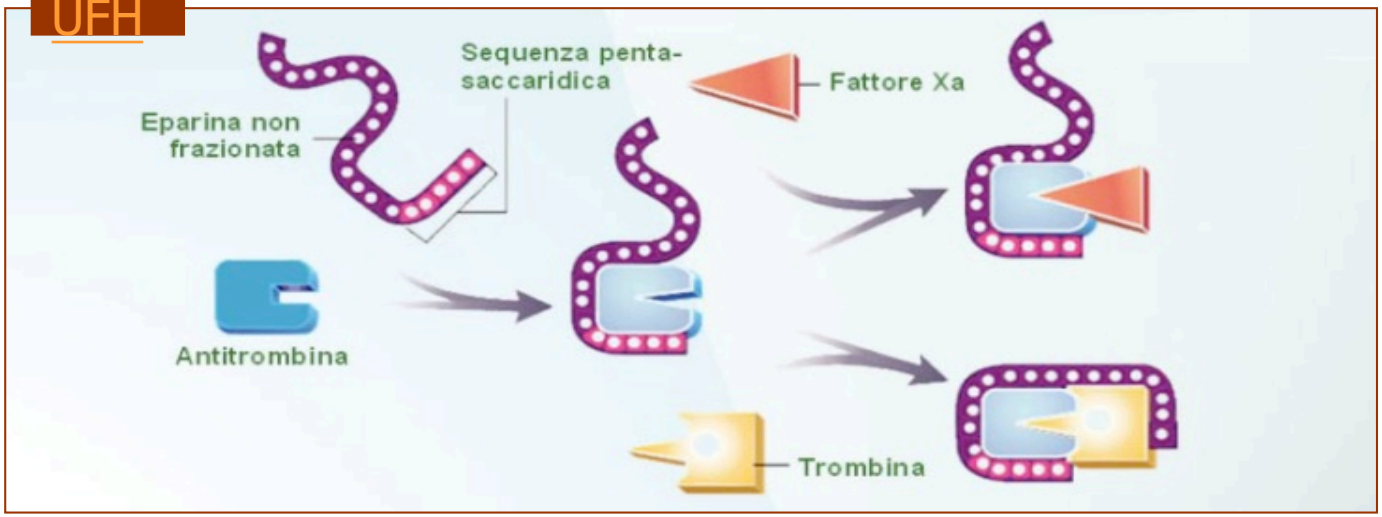
Antithrombotic Therapy and Prevention of Thrombosis: ACCP Evidence-Based Clinical Practice Guidelines, 9th ed (Chest 2012)

- **2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism.**

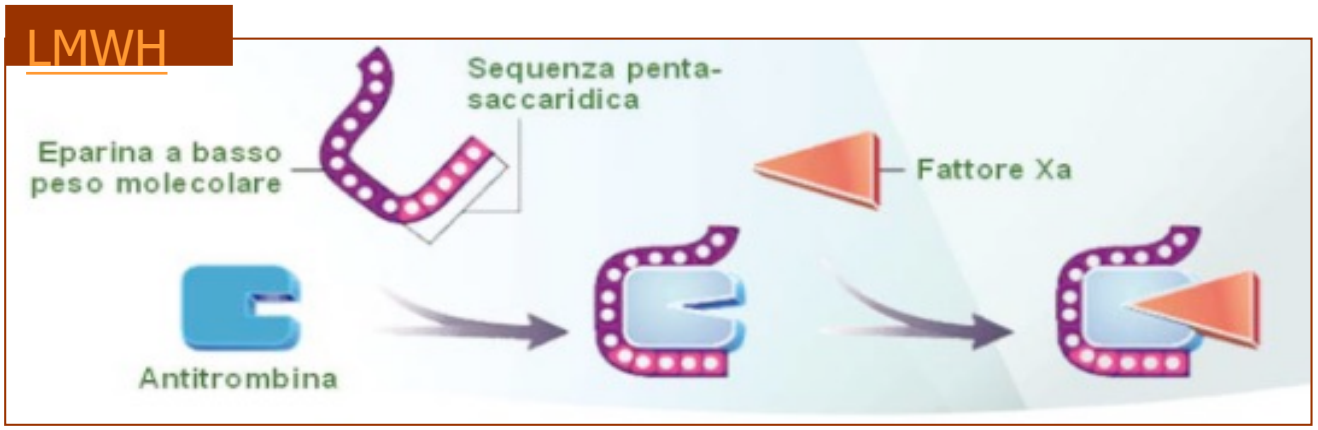
The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)
Endorsed by the European Respiratory Society (ERS)
(European Heart Journal 2014)

Come agiscono le eparine?

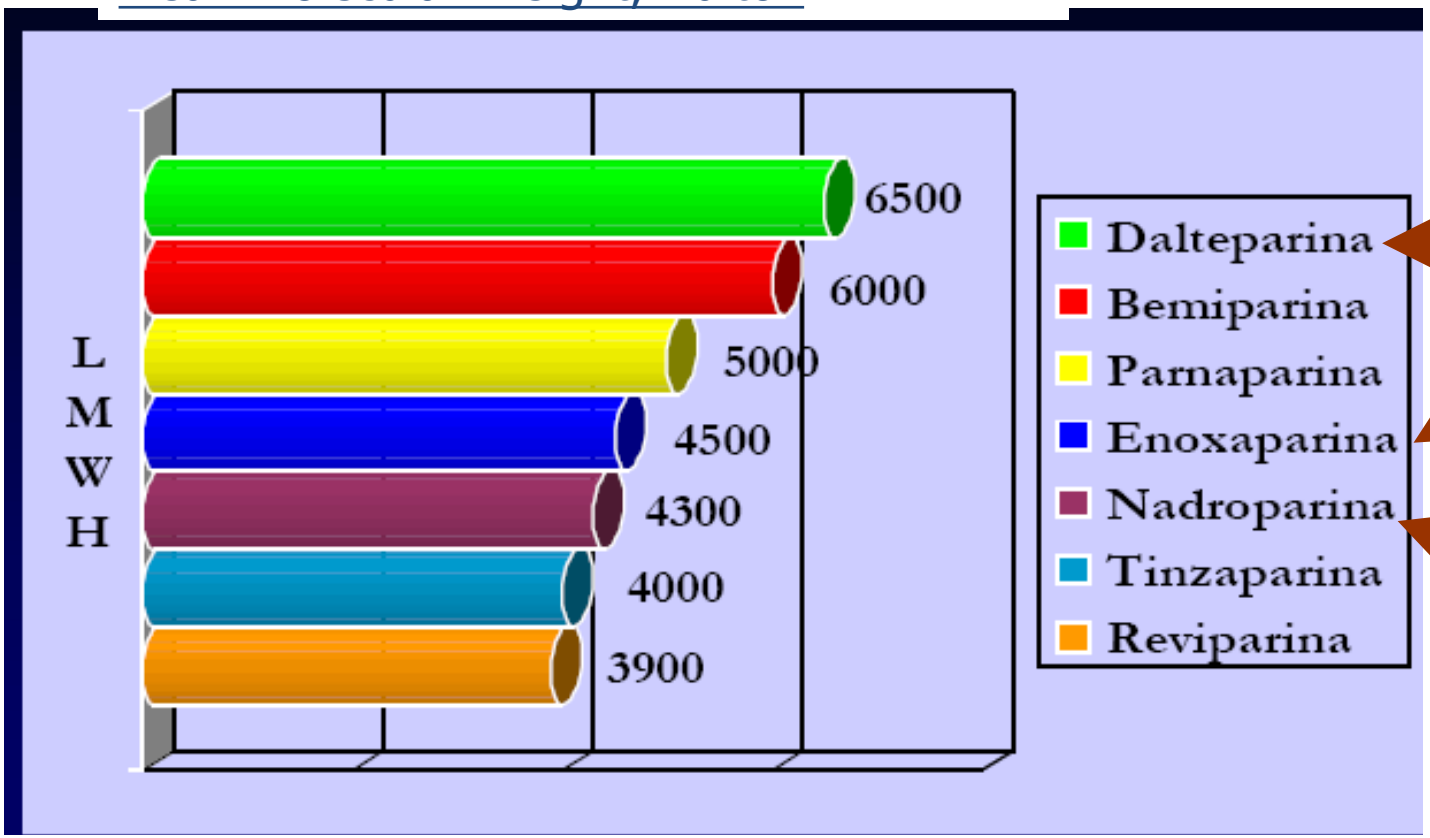
UFH



LMWH



Are All Low Molecular Weight Heparins Equivalent? 1



Method of Preparation

Nitrous acid depolymerization

Benzylation followed by alkaline hydrolysis

Nitrous acid depolymerization

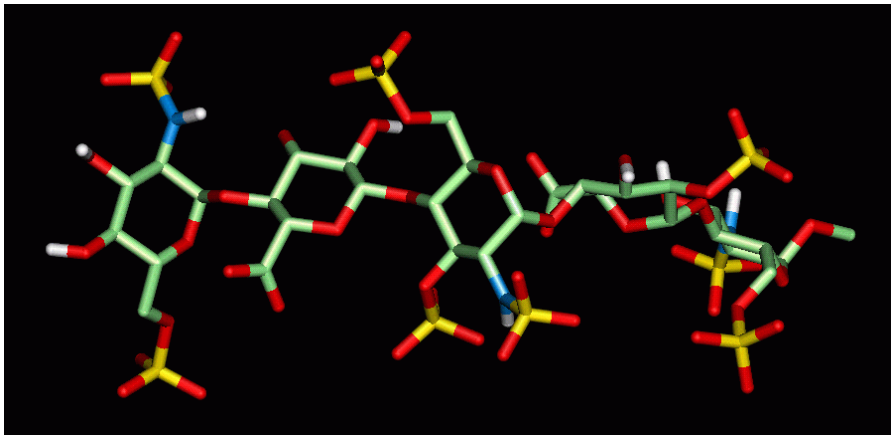
Clinical and Applied Thrombosis/Hemostasis / Vol. 14, No. 4, October 2008

Are All Low Molecular Weight Heparins Equivalent? 2

POTENZA anti-Xa e anti-IIa

	UHF	Tinzaparine	Dalteparine	Enoxaparine	Nadroparine
Anti Xa:IIa	1:1	1.9:1	2.7:1	3.8:1	3.6:1
Inizio azione	20-30 min	4-6 h	4 h	3 h	3 h
Emivita	30-90 min	2-4 h	2-5 h	3-6 h	2-3.5 h
Via eliminazione	SRE + rene	Rene	Rene	Rene	Rene
Dose Terapia Embolia Polmonare	80 U/kg + 18 U/kg/h	175U/kg die	100 U/kg x 2	100 U/kg x 2	90 U/kg x 2

Fondaparinux :synthetic selective inhibitors of factor Xa



- **Five saccharide units**
- **Synthetic**
- **Highly selective for ATIII**
- **Factor Xa inhibition**
- **No binding with plasma proteins**
- **No effect on platelet function**
- **No thrombocytopenia**

5.0, 7.5, or 10.0 mg in patients weighing less than 50, 50 to 100, or more than 100 kg, subcutaneously once daily.

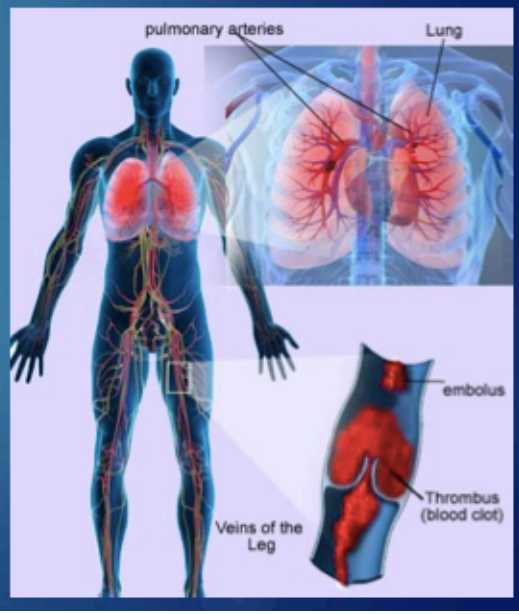
The Matisse Investigators
N Engl J Med 2003; 349:1695-1702

	Limitations	Consequences
UFH	▸ Parenteral ▸ Unpredictable due to unspecific binding ▸ Risk of HIT	▸ Inconvenient for long term use ▸ Monitoring of aPTT required
LMWH	▸ Parenteral ▸ Risk of HIT	▸ Inconvenient and expensive for long term use ▸ Monitoring of platelets
Fondaparinux	▸ Parenteral	▸ Inconvenient and expensive for long term use

Lassen MR. Vasc Health Risk Manag. 2008;4(6):1373-86.

Treatment of Acute Venous Thromboembolism

Antithrombotic therapy



ANTICOAGULATION

In patients with acute PE, anticoagulation is recommended, with the objective of preventing both early death and recurrent symptomatic or fatal VTE.
Acute-phase treatment consists of administering parenteral anticoagulation [UF), LMWH or fondaparinux] over the first 5–10 days.

Low-molecular-weight heparins and pentasaccharide (fondaparinux) approved for the treatment of pulmonary embolism

	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg[a]	Every 12 hours Once daily[a]
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg[b] or 200 IU/kg[b]	Every 12 hours[b] Once daily[b]
Nadroparin[c]	86 IU/kg or 171 IU/kg	Every 12 hours Once daily
Fondaparinux	5 mg (body weight <50 kg); 7.5 mg (body weight 50–100 kg); 10 mg (body weight >100 kg)	Once daily

All regimens administered subcutaneously.
IU = international units; LMWH = low-molecular-weight heparin.
[a]Once-daily injection of enoxaparin at the dosage of 1.5 mg/kg is approved for inpatient (hospital) treatment of PE in the United States and in some, but not all, European countries.

2014 ESC Guidelines

Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

- ***LMWH or fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and heparin-induced thrombocytopenia (HIT).***

- On the other hand, UFH is recommended for patients in whom primary reperfusion is considered, as well as for those with serious renal impairment (creatinine clearance <30 mL/min), or severe obesity.

- **These recommendations are based on the short half-life of UFH, the ease of monitoring its anticoagulant effects, and its rapid reversal by protamine.**

2014 ESC Guidelines

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2014 ESC Guidelines

- **VKAs (warfarin, acenocoumarol) should be initiated as soon as possible, and preferably on the same day as the parenteral anticoagulant.**

- **Warfarin can be started at a dose of 10 mg in younger (e.g. <60 years of age), otherwise healthy outpatients, and at a dose of 5 mg in older patients and in those who are hospitalized.**

- **The daily dose is adjusted according to the INR over the next 5–7 days, aiming for an INR level of 2.0–3.0.**

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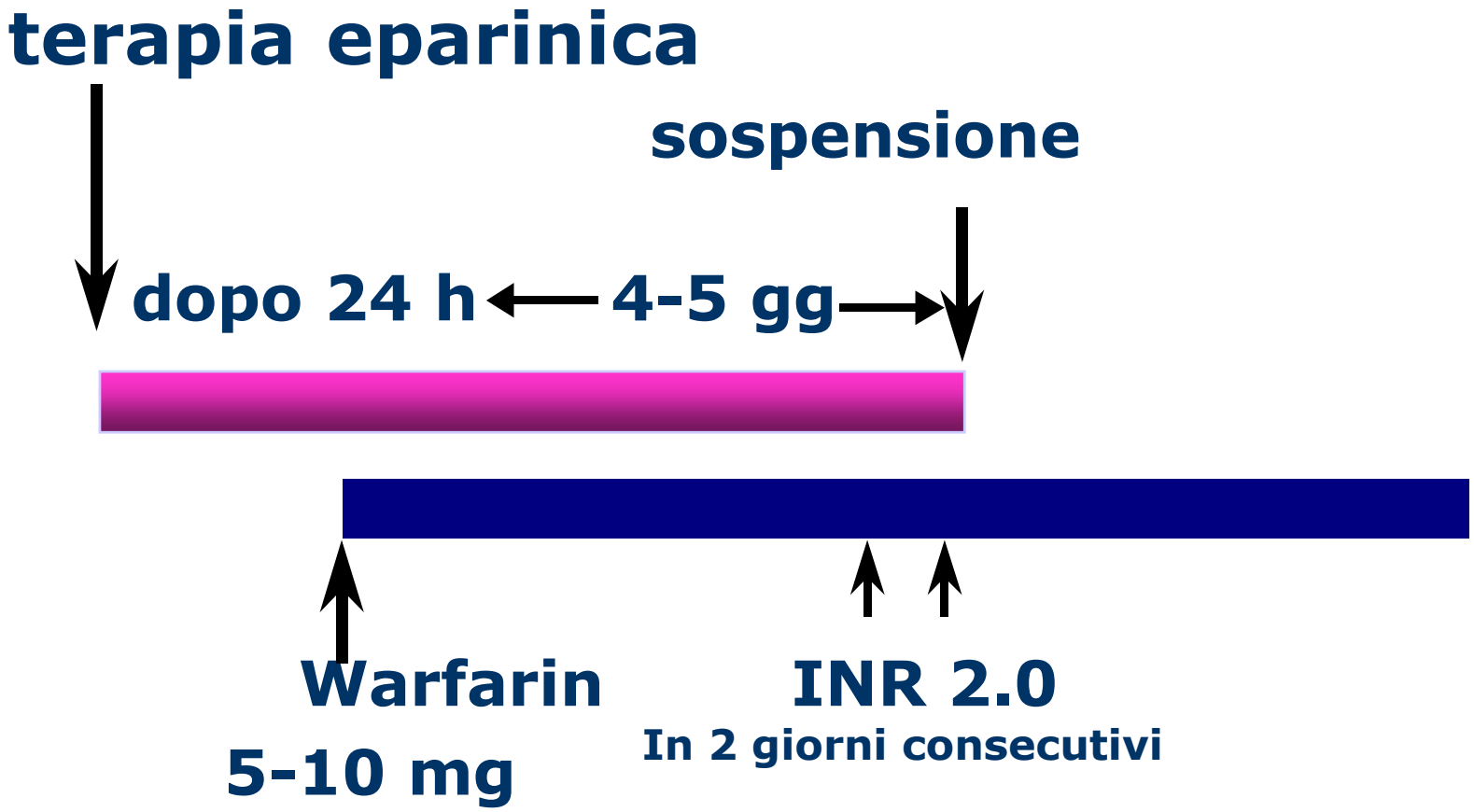

terapia anticoagulante orale

Duration of anticoagulation

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1. **patients with PE should receive at least 3 months of anticoagulant treatment**

2. **after withdrawal of anticoagulant treatment, the risk of recurrence if anticoagulants are stopped after 6 or 12 months can be expected to be similar to that after 3 months**

3. **indefinite treatment reduces the risk for recurrent VTE by about 90%, but this benefit is partially offset by a 1% or higher annual risk of major bleeding**

Ann Intern Med 2007;**147**(11):766-774
N Engl J Med 1995;**332**(25):1661-1665
N Engl J Med 1997;**336**(6):393-398.

Duration of Anticoagulation?

3 months: . Shorter treatment periods are associated with a higher rate of recurrence and are not recommended.

Transient risk *(e.g., surgery, immobilization, estrogen use, trauma)*

STOP

***Idiopathic or medical risk*: 6 or 12 months** (considered for indefinite anticoagulation therapy).
- aPL; FVL+prothrombin 20210 mut; deficiency of ATIII, pC, pS.

Long Time

Recurrent disease or continued risk factors (active cancer; 2 or > episodes of documented DVT)

Indefinite

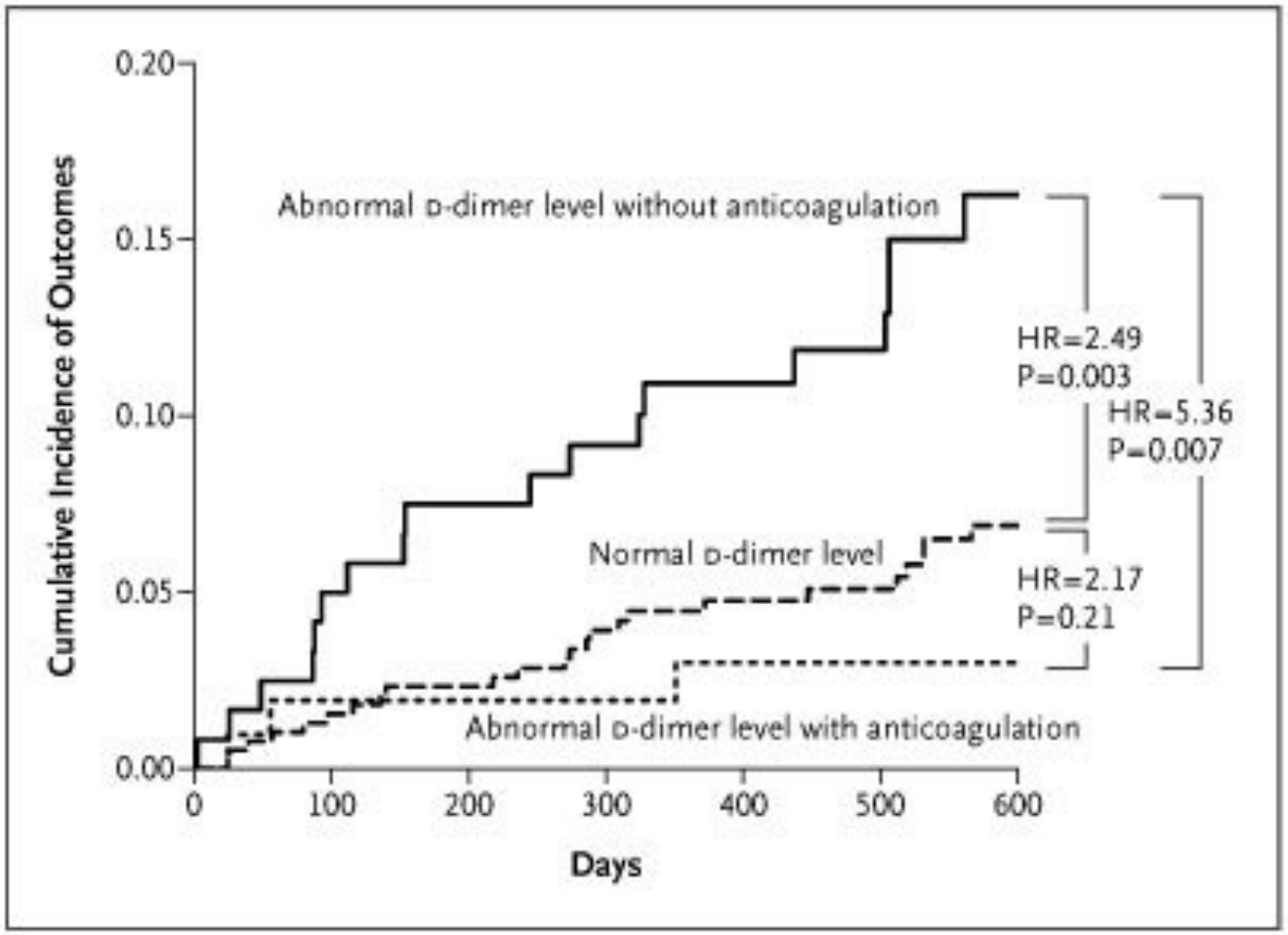
American College of Chest Physicians 2012

The *optimal duration of oral anticoagulation* in patients with **idiopathic** venous thromboembolism is *uncertain*.

Testing of D-dimer (HS) levels may play a role in the assessment of the need for prolonged anticoagulation.

Optimal duration of OAT

PROLONG Study



Cumulative Incidence of and Hazard Ratios (HRs) for Main Outcomes

Palareti G et al. N Engl J Med 2006;355:1780-1789

The NEW ENGLAND JOURNAL of MEDICINE

DULCIS (D-dimer and ULtrasonography in Combination Italian Study)

Table 2. Age- and sex-specific cutoff levels for the different D-dimer assays adopted in the study

Commercial D-dimer assay (manufacturer) ng/mL	Males ≤70 y	Males >70 y	Females ≤70 y	Females >70 y	Cutoff values currently recommended by manufacturers for VTE exclusion
VIDAS D-dimer Exclusion (bio-Merrieux)	490	1050	600	1300	500
Innovance D-DIMER (Siemens)	500	950	550	1150	500
HemosIL D-dimer HS (Instrumentation Laboratory)	170	345	215	430	230
HemosIL D-dimer (Instrumentation Laboratory)	205	300	225	330	230
STA Liatest D-dimer (Diagnostica Stago)	340	700	450	1050	500

For comparison, the cutoff values recommended by manufacturers for VTE exclusion are also shown.

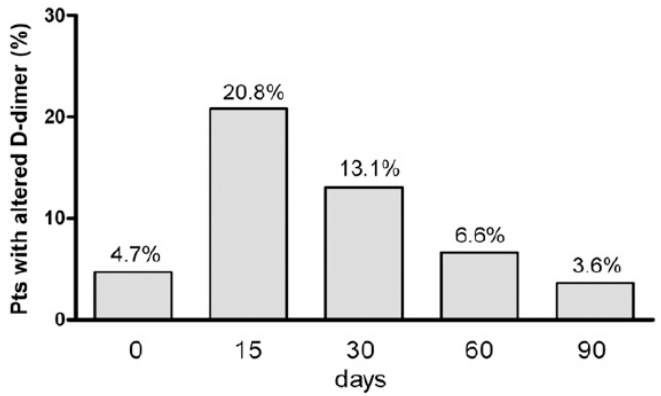
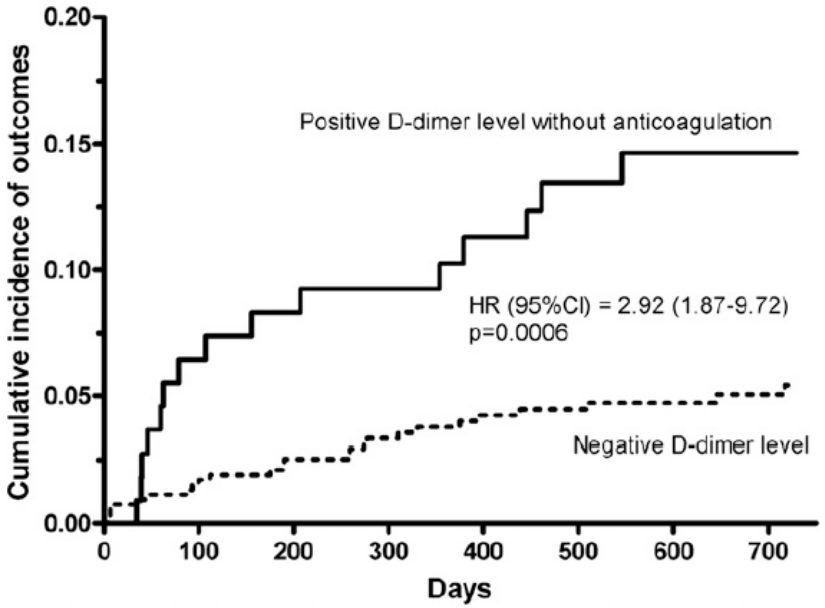


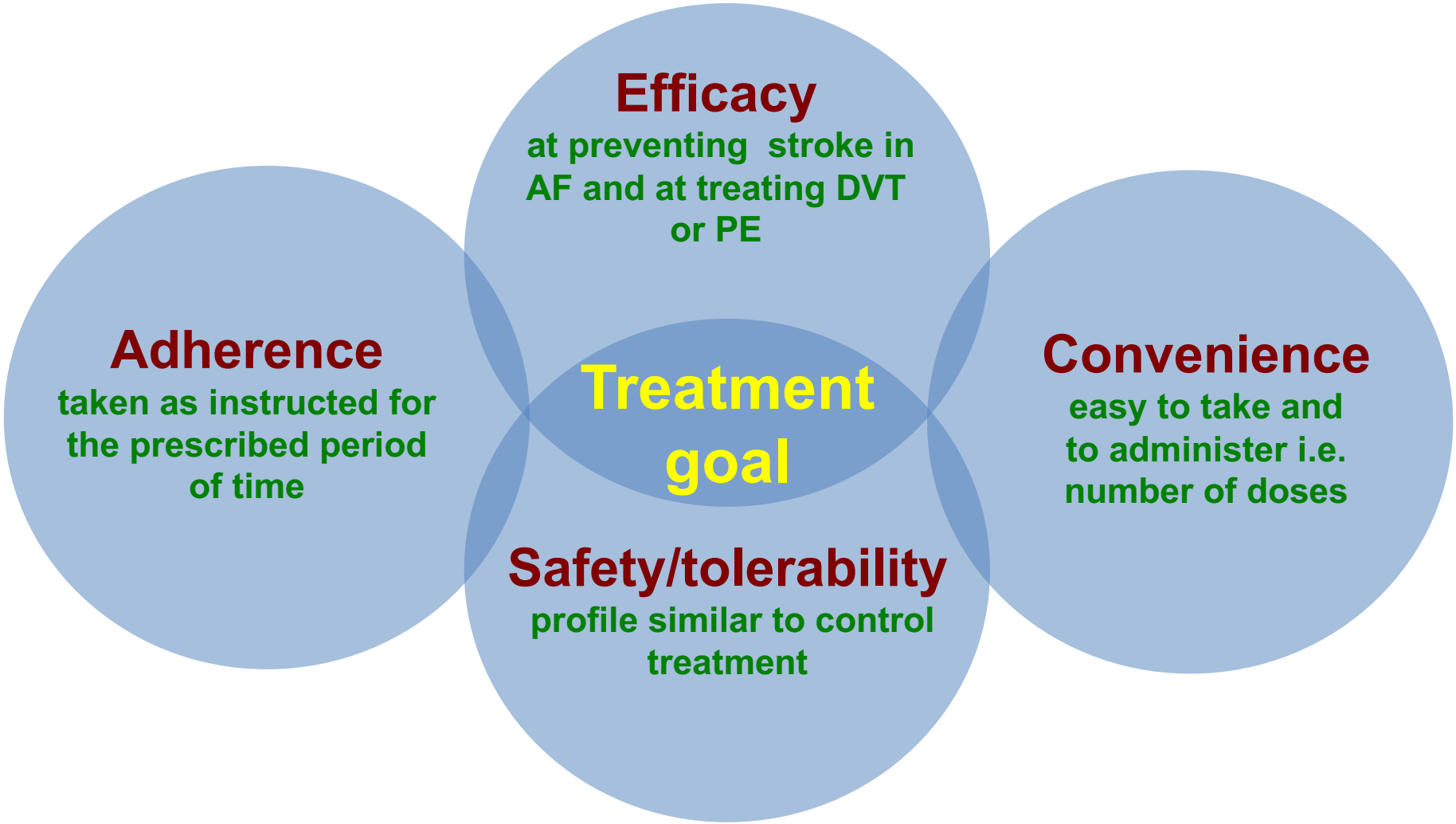
Figure 2. Prevalence of first-time-ever D-dimer result above the predefined cutoff levels in the investigated study population at the serial measurement days after VKA withdrawal. The percentages are calculated vs the total number of patients included.



Blood. 2014;124: 196-203

TAO
o
NOACs

An effective antithrombotic treatment could combine in any single patient …..



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TAO

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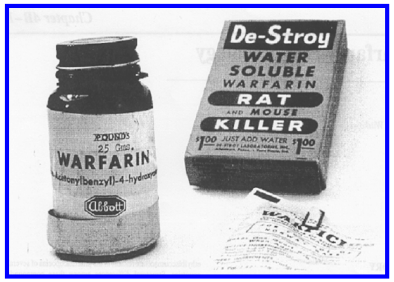
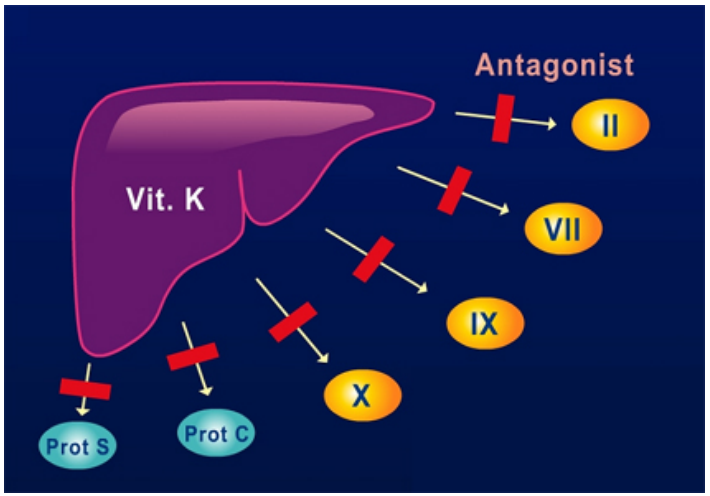
Vitamin K antagonists

Sweet clover
Melilotus alba

1941	First clinical use (short term)
1944	Use of dicumarol in long-term prophylaxis after MI
1948	Synthesis of warfarin as a rat poison
1954	Warfarin introduced in clinical practice





They have been the 'gold standard' in oral anticoagulation for more than 50 years.

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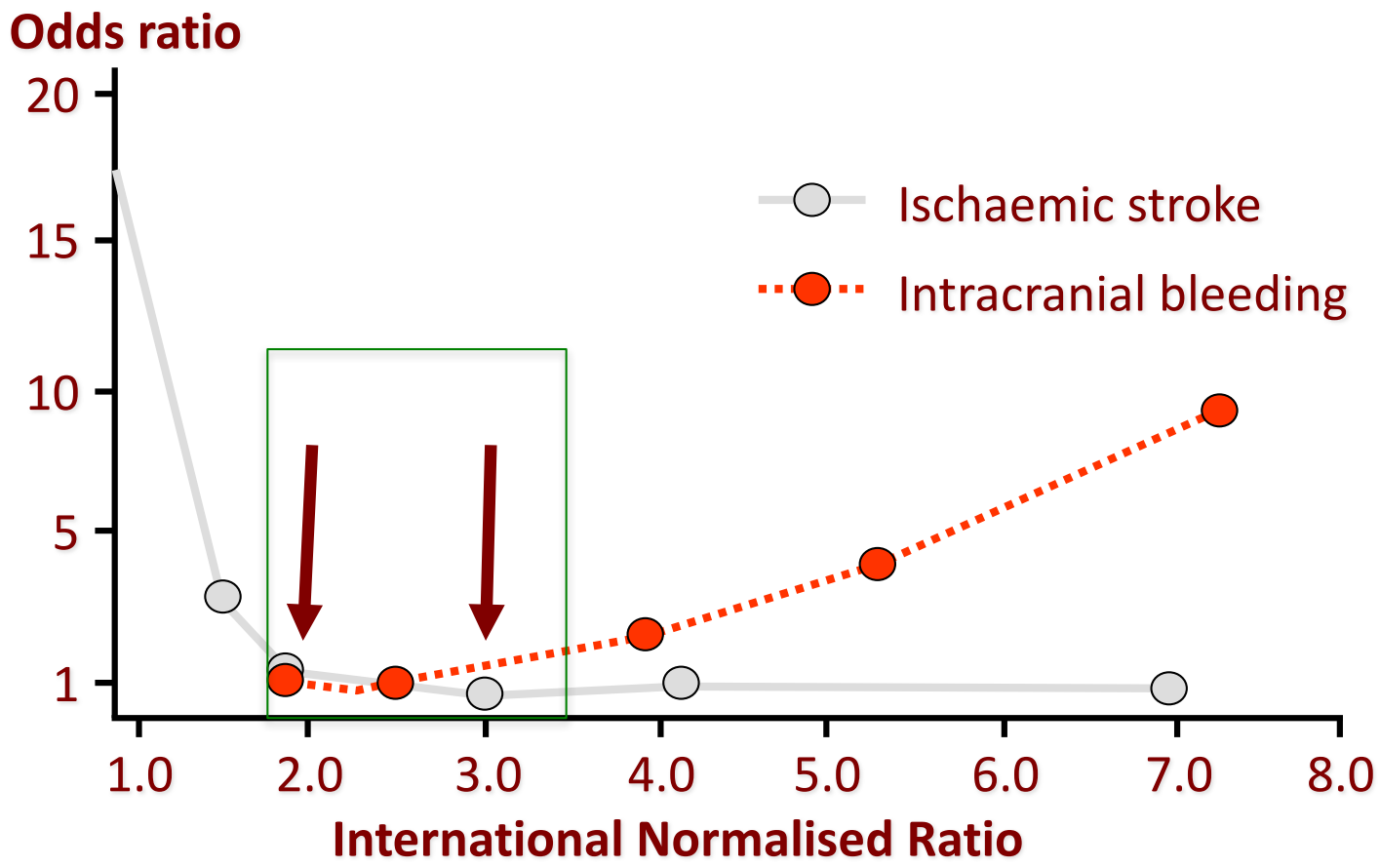
ASA vs Warfarin in Elderly with AF

- BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged (≥75 years)

	Warfarin (INR 2-3)	ASA 75 mg/d	*p*
Fatal/disabling stroke, ICH, systemic embolism	1.8%/yr	3.8%/yr	0.003
Ischemic stroke	0.8%/yr	2.5%/yr	0.0004
Hemorrhagic stroke	0.5%/yr	0.4%/yr	0.83

Lancet 2007;370:493

Adjusted odds ratios for ischaemic stroke and intracranial bleeding
Randomised trials of VKAs therapy for patients with AF



ACC/AHA/ESC Guidelines. Circulation 2001;104:2118-30

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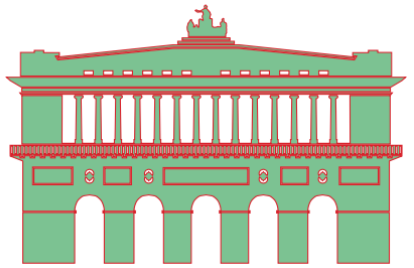
What's wrong with VKAs?

- Unpredictable
- Slow onset of action
- Narrow therapeutic window

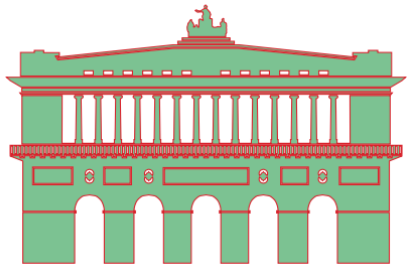
- Regular monitoring and dose adjustments
- Risk of adverse events (bleeding)



INR Lower than Expected

- Compliance
- Compliance
- Compliance
- Miscommunication about dosing or change in dosing (doctor or patient)

  "Tell me what doses you've taken since the last INR"
- Nutrition change – increase vitamin K
- New medication – ginseng, green tea



INR Higher than Expected

- Miscommunication about dosing or change in dosing (doctor or patient)

  "Tell me what doses you've taken since the last INR"
- New medication – antibiotics, high dose acetaminophen, amiodarone, NSAIDs, statins, omeprazole, OTC, herbals
- Substantial alcohol excess
- Stopped medication – phenytoin
- Intercurrent illness
- Nutrition change – decrease vitamin K intake

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Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment

The study included 4093 patients ≥ 80 years of age who were naïve to VKA for thromboprophylaxis of atrial fibrillation or after venous thromboembolism.

In the whole population, time in the therapeutic range was 62% (IQR: 49% to 75%).

Total, n (rate per 100 patient-y)	179 (1.87)
Mean age (range), y	85 (80–94)
Time elapsed from start of VKA treatment, mo	14.2 (1–109)
Median INR (range)	2.5 (1.0–13.8)
Bleeds with INR of 2.0–3.0, n (%)	147 (82.1)
Patients <85 y, n (rate per 100 patient-y)	115 (1.71)
Patients ≥85 y, n (rate per 100 patient-y)	64 (2.22)*

Circulation. 2011;124:824-829

The rate of bleeding complications was low, suggesting that age in itself should not be considered a contraindication to treatment. Adequate management of VKA therapy through careful monitoring of patients in specifically trained centers allows very old and frail patients to benefit from VKA thromboprophylaxis.

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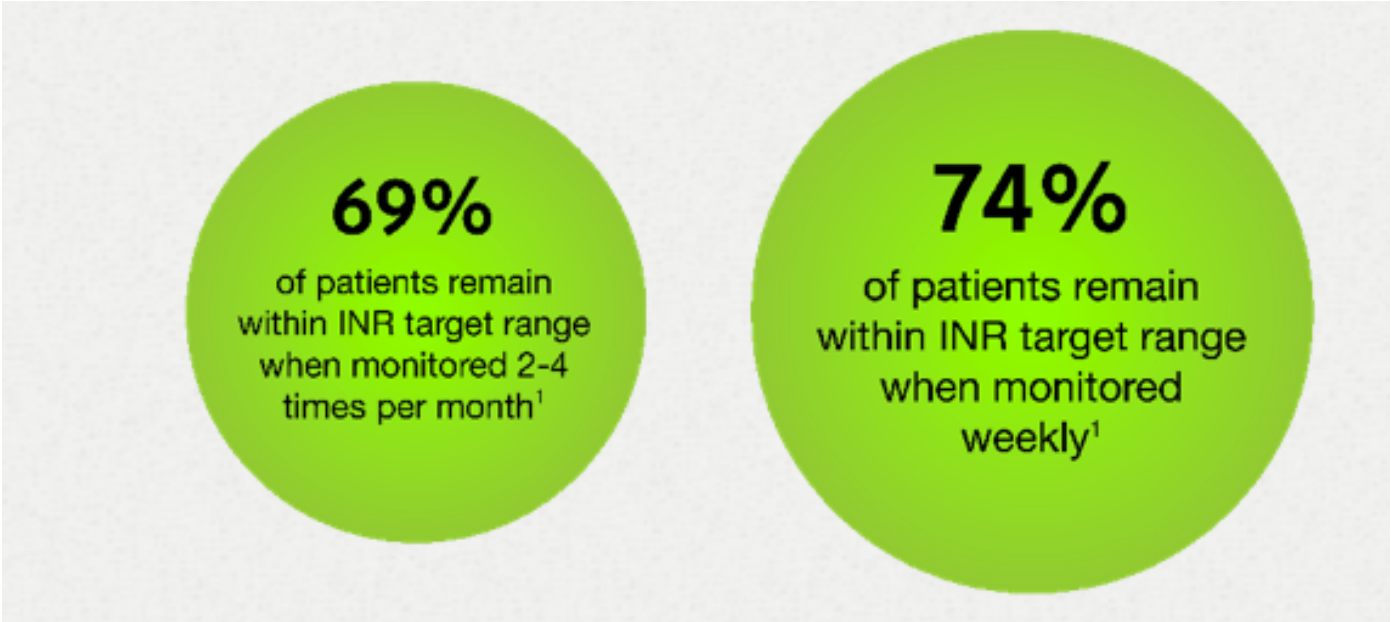
STABLE results.

- Home international normalized ratio (INR) monitoring.
- 29,457 patients with multiple indications for warfarin
- Time in therapeutic INR range (TTR) - a surrogate for the quality of anticoagulation) during the first 4–12 weeks of therapy



Older individuals had a higher TTR than younger patients.
Weekly testers experienced significantly fewer critical values (INR <1.5 or >5.0) than did variable testers.

Am J Manag Care. 2014; 20: 202-9.

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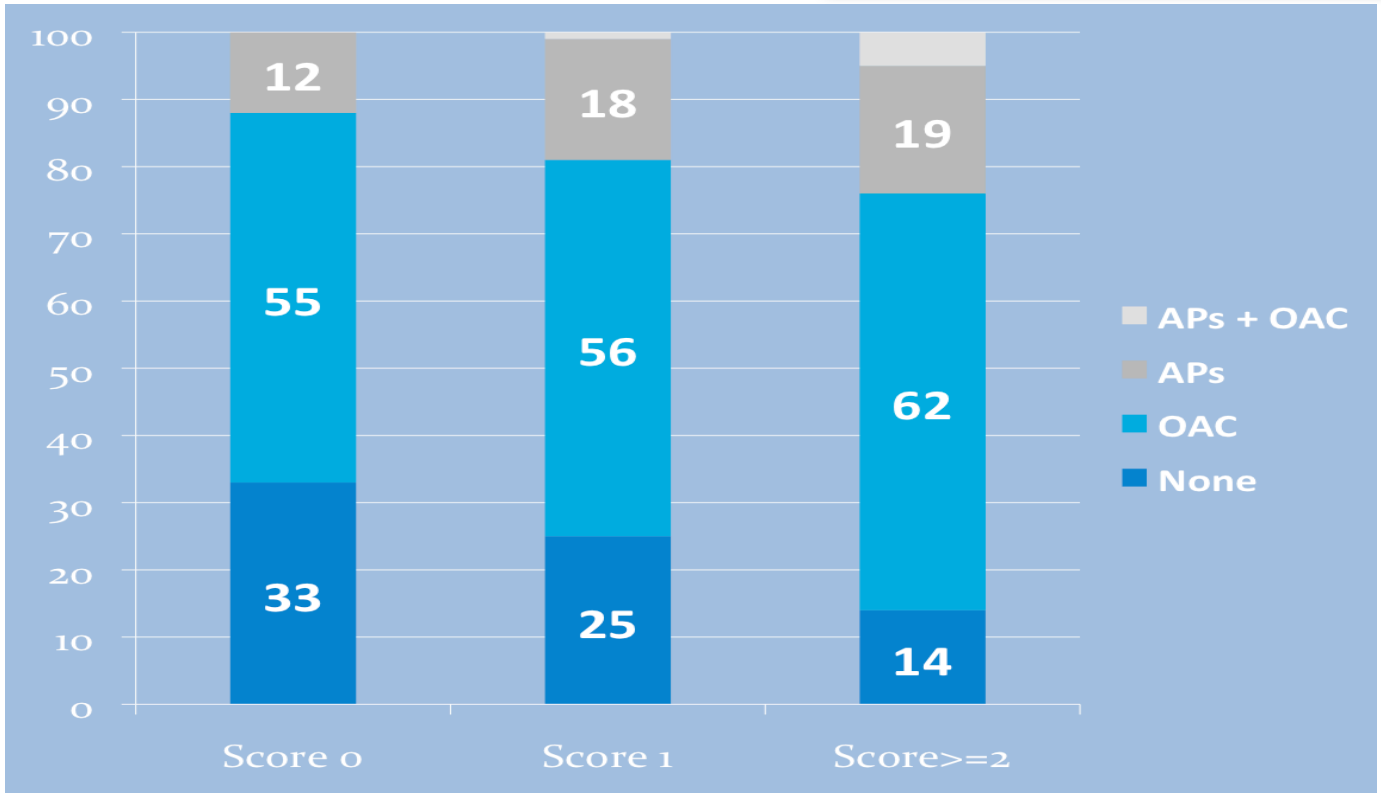
Antithrombotic treatment: Guidelines' adherence (CHA_2DS_2-VASc)

AGE (mean±SD): 73±10 yrs.



Atrial fibrillation **R**egistry for **A**nkle-Brachial Index **P**revalence **A**ssessment: **C**ollaborative **I**talian **S**tudy

2027 patients

Intern Emerg Med. 2014 Dec;9(8):861-70.

J Am Coll Cardiol. 2013 Dec 10;62(23):2255-6

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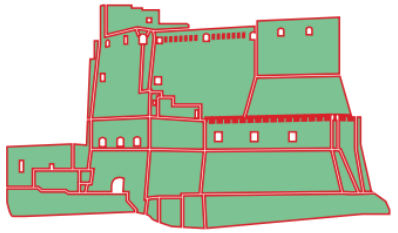
Anticoagulation in the Elderly: *The Important Concerns*

1. Frequently indicated
2. And under-utilized
3. Elderly more sensitive to warfarin
4. Narrow therapeutic index drug
5. Multiple comorbidities
6. Polypharmacy
7. Nutritional



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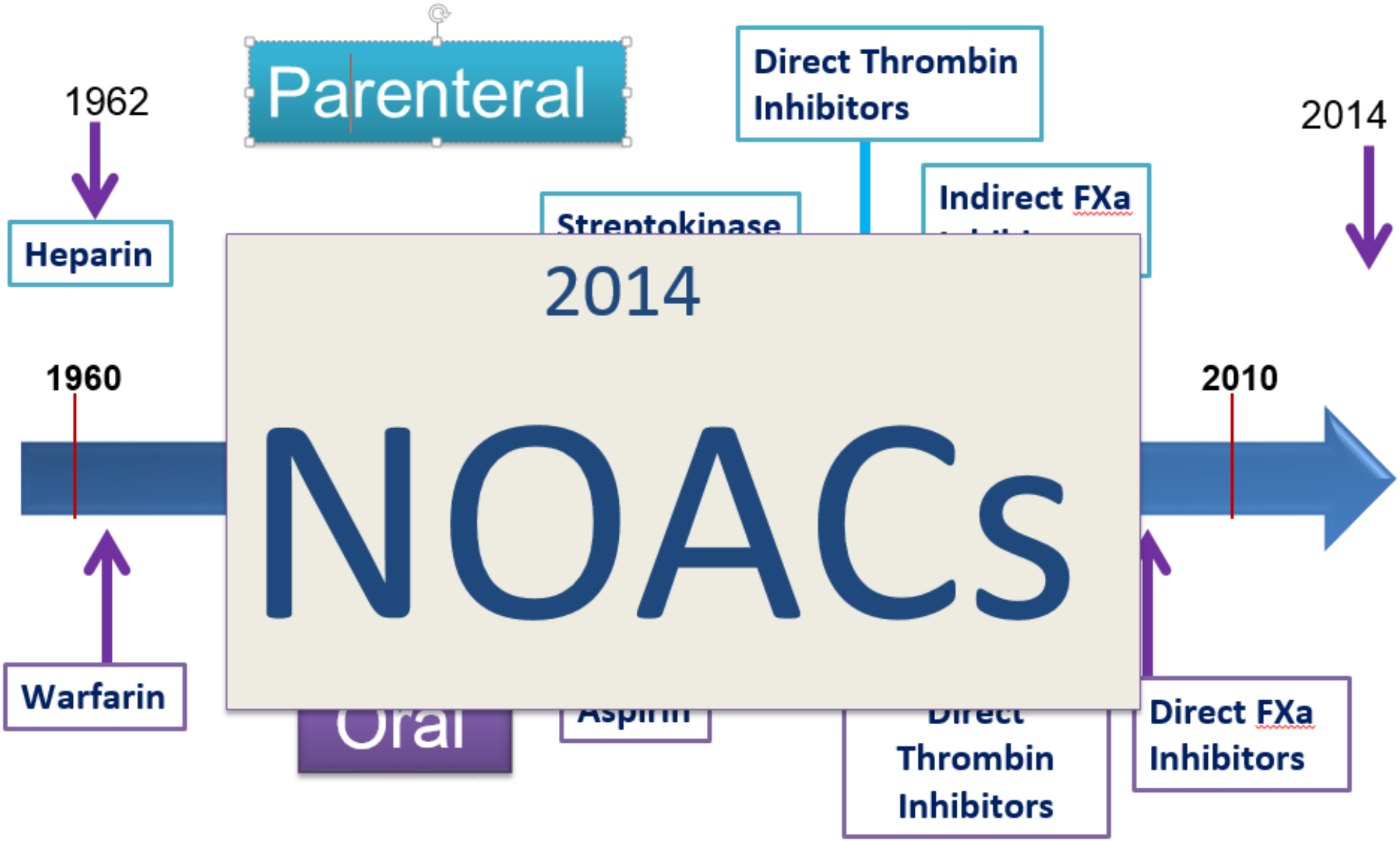
Evolution of antithrombotics



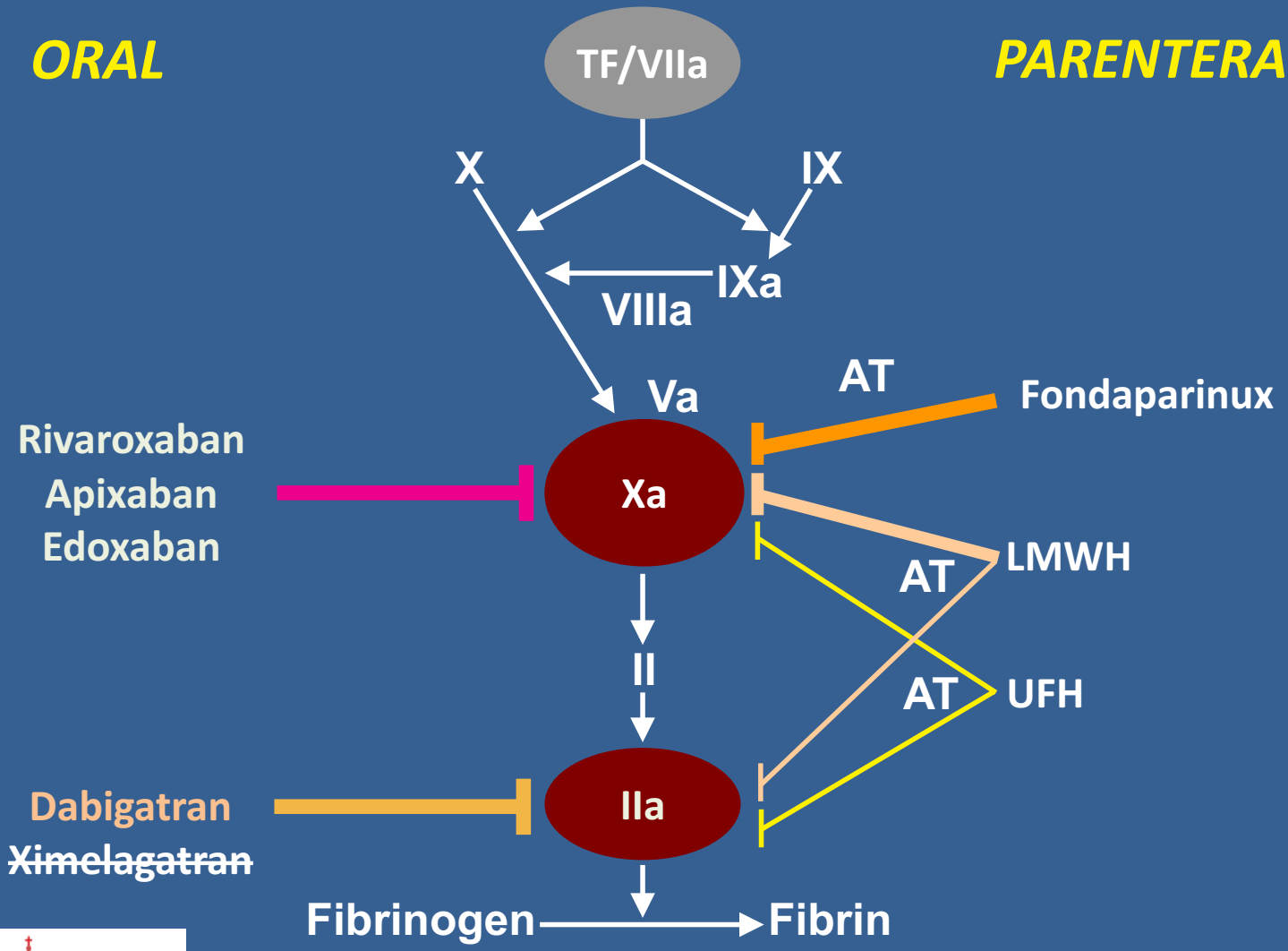
Adapted from: Weitz J, Hirsh J. Chest. 2001;119:95S; Alban. *Eur J Clin Invest* 2005; Link. *Circulation* 1959; Maraganore *et al. Biochemistry*

Advantages of non-VKA oral anticoagulant (NOAC) compared with WKA

Advantages	Clinical Implication
Rapid Onset of Action	NO NEED FOR BRIDGING
Predictable Anticoagulation Effect	NO NEED FOR ROUTINE COAGULATION MONITORING
Specific Coagulation Enzyme Target	LOW RISK OF OFF-TARGET ADVERSE EFFECTS
Low potential for drug interactions	FEW DRUG RESTRICTIONS

improved efficacy/safety ratio

Targets dei Nuovi Anticoagulanti Orali



Adapted from 1. Weitz JI *et al. J Thromb Haemost* 2005;3:1843–1853; 2. Weitz JI *et al. Chest* 2008;133:234–256

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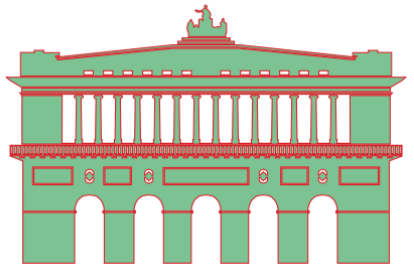
Effectiveness

- Non-inferior for prevention of stroke/embolism in AF
- Non-inferior for treatment of DVT/PE
- Probable reduced hemorrhagic stroke rate
- Reduced rate of fatal bleeding events
- Increased incidence of GI bleeds



Elderly patients included in the NOA AF trials and in a "real-life" registry

Study	Patients > 75 y (%)
RE-LY (dabigatran)	39.9
Rocket (rivaroxaban)	43.3
Aristotle (apixaban)	31.2
Engage (edoxaban)	40.1
START-Register (VKA)	72.0

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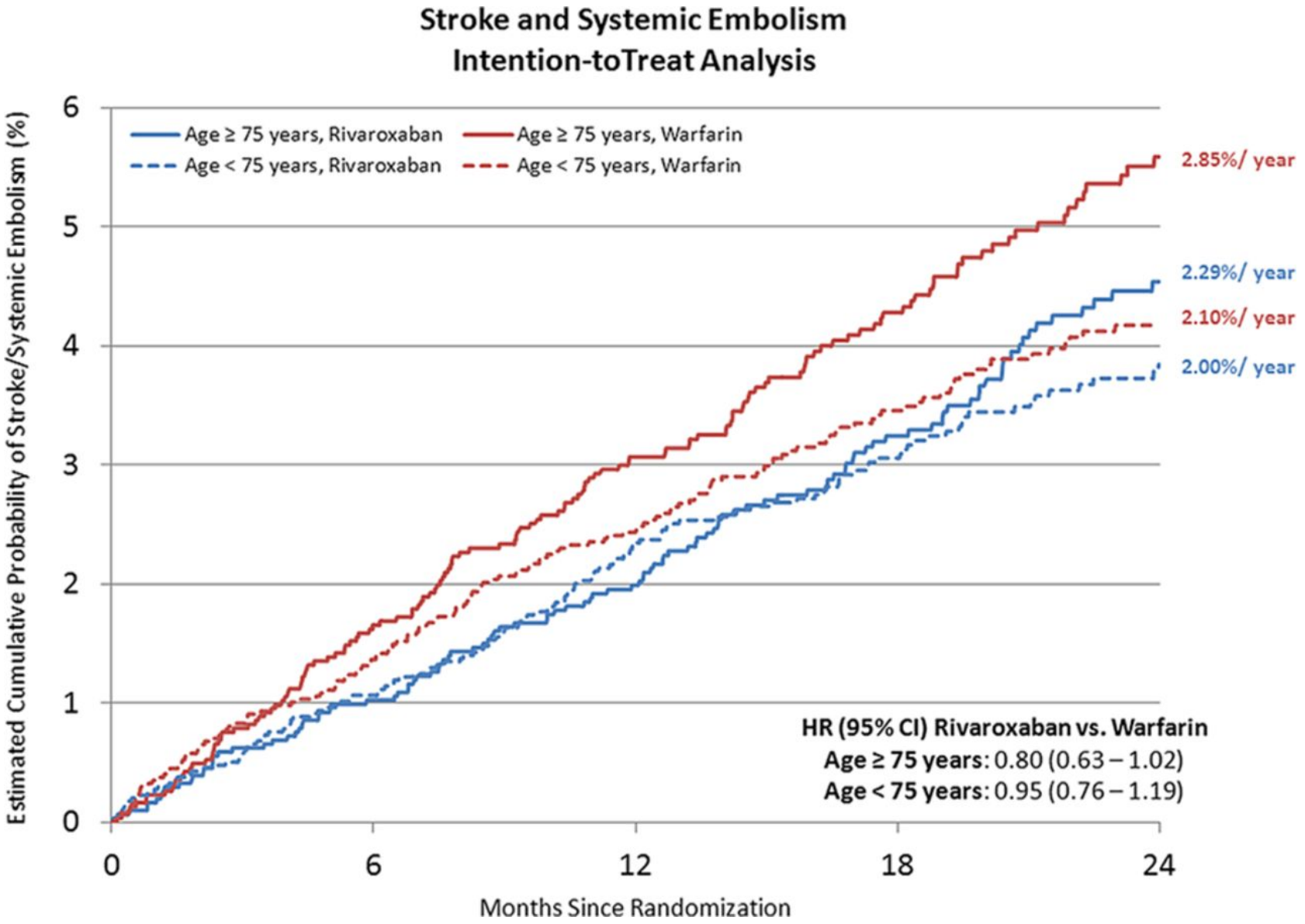
ROCKET AF



Jonathan L. Halperin et al. Circulation. 2014;130:138-146

American Heart Association.

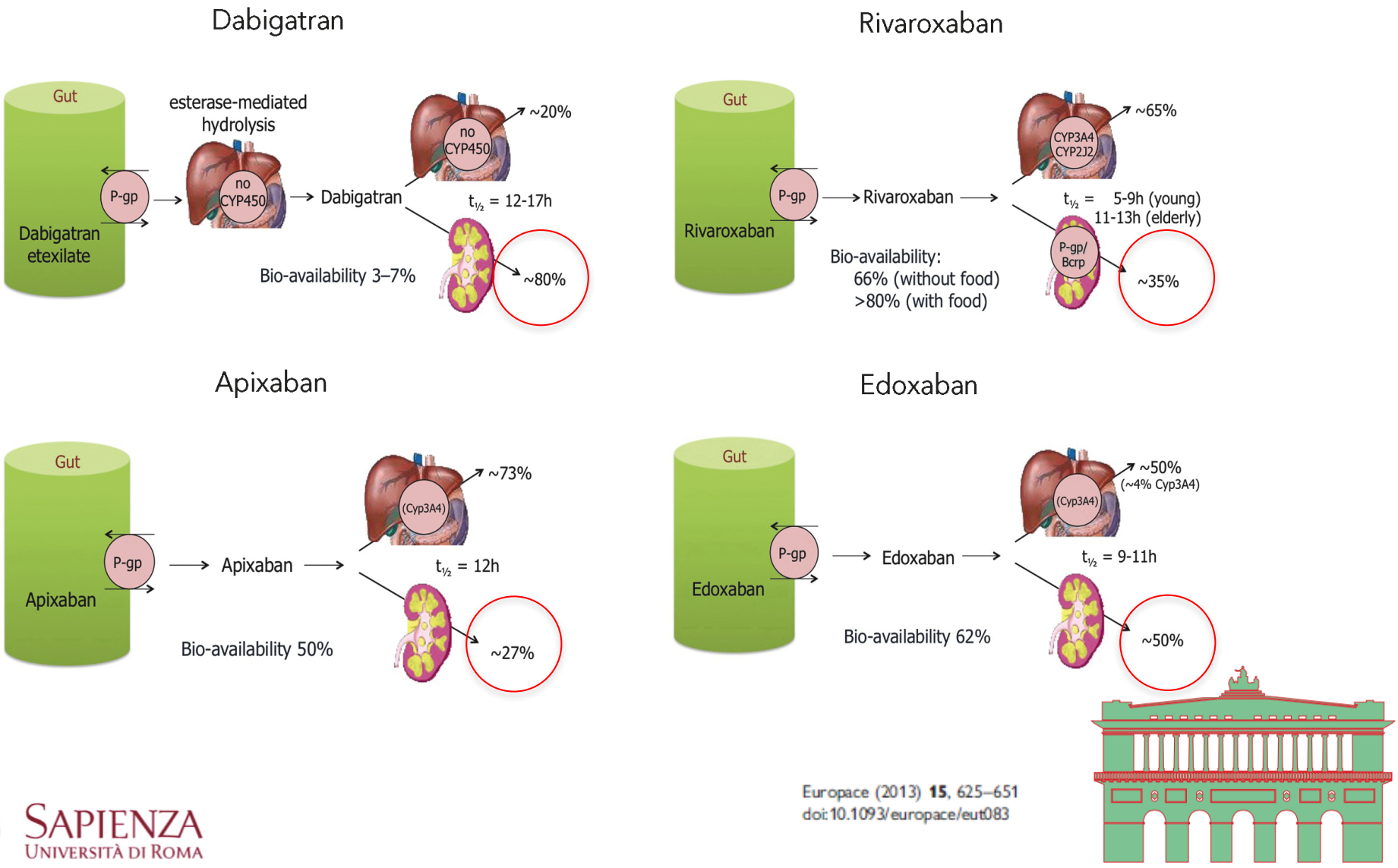
Differenti caratteristiche farmacologiche dei NOAC

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
TARGET	Thrombin	Factor Xa	Factor Xa	Factor Xa
Bioavailability	3-7%	50%	62%	66% (w/o food) ~100% with food
Prodrug	**yes**	no	no	no
Clearance: non-renal/renal of adsorbed dose if normal renal function	20%/**80%**	73%/**27%**	50%/**50%**	65%/**35%**
Liver metabolism: CYP3A4	no	yes (elimination; minor CYP3A4)	minimal (<4% of elimination)	yes (elimination)
Absorption with food	no effect	no effect	6-22% more	+39%
Intake with food?	no	no	no official recommendation yet	mandatory
Absorption with H2B/PPI	plasma level -12 to -30%	no effect	no effect	no effect
Asian ethnicity	plasma level +25%	no effect	no effect	no effect
GI tolerability	dyspepsia 5-10%	no problem	no problem	no problem
Elimination half-life	12-17h	12h	9-11h	5-9h (young)/11-13h (elderly)

SAPIENZA UNIVERSITÀ DI ROMA * not approved yet

Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

Impatto dei NoAC sull'emuntorio renale



Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

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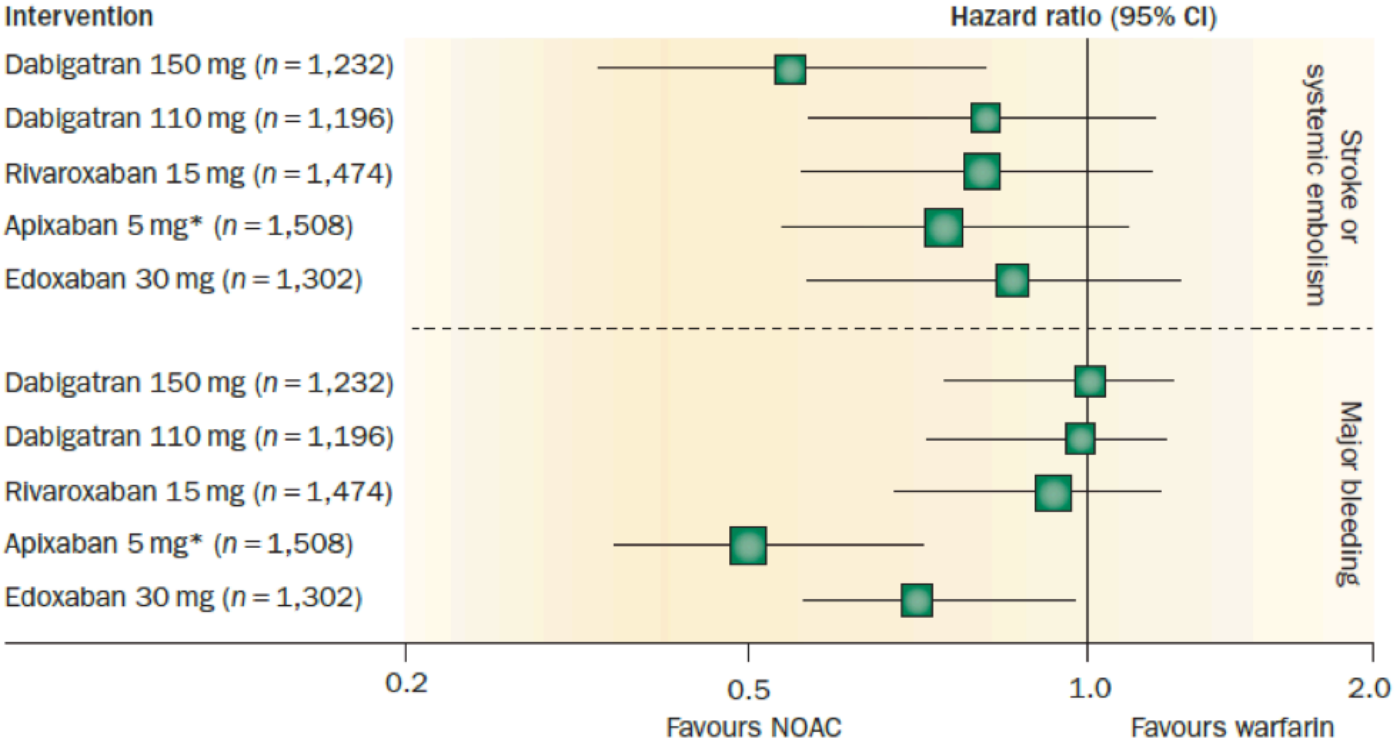
Efficacy and Safety of NOACs for SPAF in Patients with Moderately Severe CKD



Qamar A, Bhatt DL. Nat Rev Nephrol 2015; 11: 200-202

I NOAC e le differenti interazioni farmacologiche (1)

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/ wk CYP3A4	+12–180%		+ 53% (slow release)	
Diltiazem	P-gp/ wk CYP3A4	no effect	+40%		
Quinidine	P-gp	+50%		+80%	+50%
Amiodarone	P-gp	+12–60%		no effect	
Dronedarone	P-gp/CYP3A4	+70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	+140–150%	+100%		up to +160%

Red – contraindicated; **Orange** – reduce dose; **Yellow** – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

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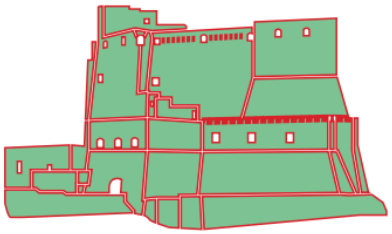
I NOAC e le differenti interazioni farmacologiche (2)

	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	+42%
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	+50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	+15–20%	no data	no data	+30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4	no data	strong increase	no data	up to +153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	up to -50%
Antacids	GI absorption	-12-30%	no data	no effect	no effect

Red – contraindicated;
orange – reduce dose;
yellow – consider dose reduction if another yellow factor present;
hatching – no data available; recommendation made from pharmacokinetic considerations

NOAC e indicazioni approvate

		Rivaroxaban	Dabigatran	Apixaban
Prevenzione TEV in ortopedia	EU	✓	✓	✓
	FDA	✓		✓
Prevenzione dell'ictus e dell'ES in pz con FANV	EU	✓	✓	✓
	FDA	✓	✓	✓
Trattamento di TVP ed EP	EU	✓	✓	✓
	FDA	✓	✓	✓
Prevenzione eventi CV in pz con SCA	EU	✓		
	FDA			



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	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Atrial fibrillation	150 mg BID; 110 mg BID (EU and Canada) in patients aged >80 y, CrCl=30–50 mL/min, or high risk for bleeding; 75 mg BID (US) when CrCl=15–30 mL/min	20 mg OD; 15 mg OD when CrCl=30–50 mL/min (EU and Canada) and 15–50 mL/min (US)	5 mg BID; 2.5 mg BID in patients with 2 of the following: age >80 y, weight <60 kg, or creatinine >1.5 mg/dL (133 μmol/L)	60 mg OD; 30 mg OD when CrCl=15–50 mL/min; edoxaban should not be used when CrCl >95 mL/min (US)
Venous thromboembolism treatment	150 mg BID (after at least 5 days of heparin)	15 mg BID for 21 days, then 20 mg OD	10 mg BID for 7 days, then 5 mg BID	60 mg OD (after 5–10 days of heparin); 30 mg OD if CrCl=15–50 mL/min, weight ≤60 kg or if taking potent P-gp inhibitors
Thromboprophylaxis after hip or knee arthroplasy	220 mg OD (EU and Canada); 150 mg OD in patients aged ≥75 y, CrCl=30–50 mL/min, concomitant verapamil, amiodarone, or quinidine	10 mg OD	2.5 mg BID	Not licensed in EU or North America

BID indicates twice daily; EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily; P-gp, P-glycoprotein; and US, United States.

Arterioscler Thromb Vasc Biol. 2015;35:1056-1065.

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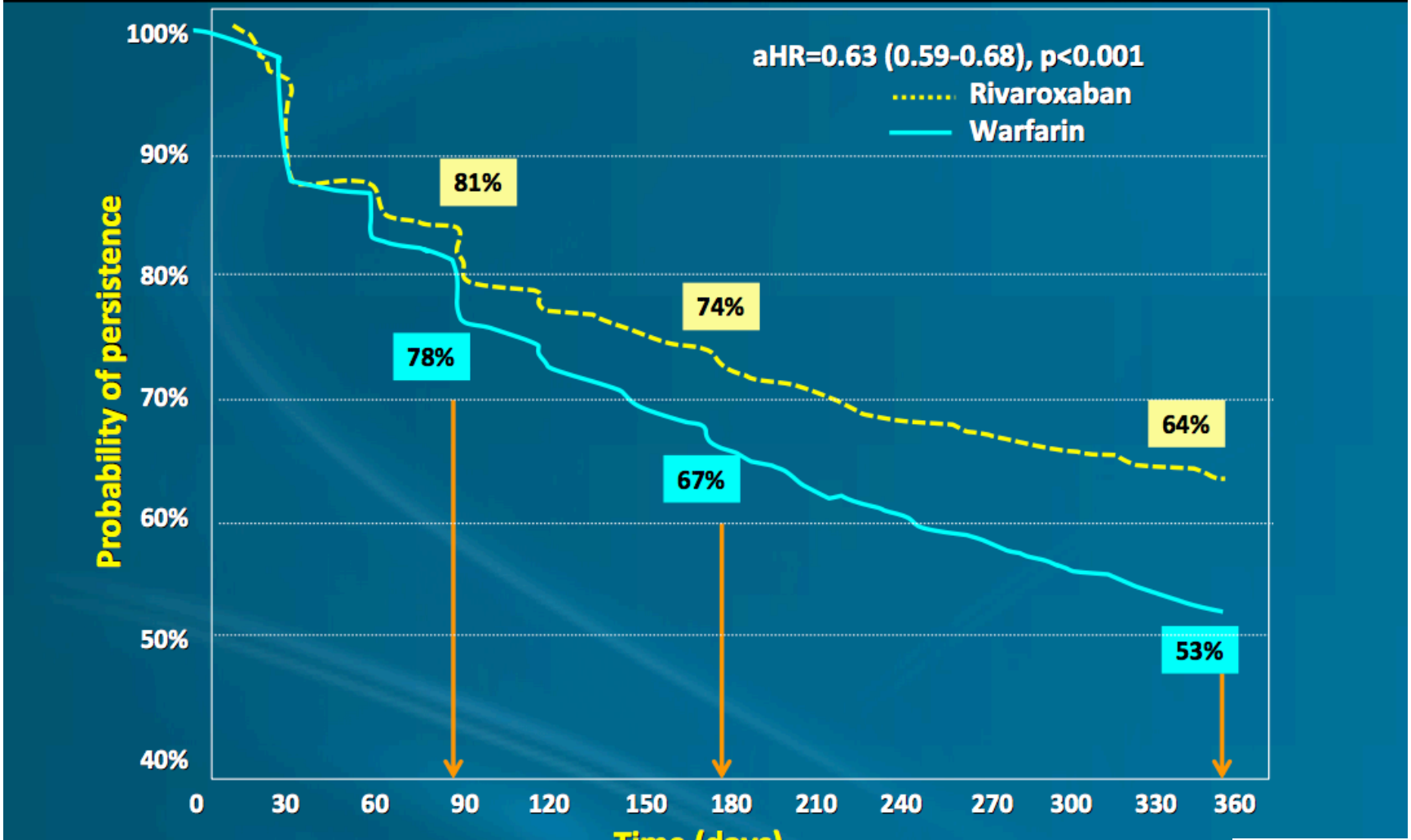
Kaplan–Meier Curve for Persistence on Therapy



Curr Med Res Opin. 2015 Jul 27:1-31.

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Conclusions

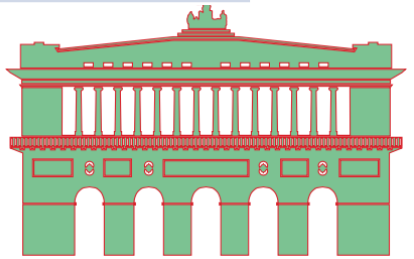
- Managing older patients with AF presents many challenges.
- In AF patients with comorbidities, doctors may overestimate the risks of anticoagulation and fail to treat AF patients who would benefit from NOACs.
- The lower dose of each NOAC may be the best option for many AF patients with comorbidities.
- NOACs appear safe and effective compared with warfarin for both renally impaired and older patients.
- Medication persistence appears to be improved by use of once-daily NOACs.

I NOAC e le differenti tempistiche di interruzione pre intervento chirurgico

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Rivaroxaban	
	No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)					
	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	**≥24h**	**≥48h**	**≥24h**	**≥48h**	**≥24h**	**≥48h**
CrCl 50–80 ml/min	**≥36h**	**≥72h**	**≥24h**	**≥48h**	**≥24h**	**≥48h**
CrCl 30–50 ml/min §	**≥48h**	**≥96h**	**≥24h**	**≥48h**	**≥24h**	**≥48h**
CrCl 15–30 ml/min §	**not indicated**	**not indicated**	**≥36h**	**≥48h**	**≥36h**	**≥48h**
CrCl <15 ml/min	**no official indication for use**					

Low risk: surgery with low risk of bleeding.
High risk: surgery with high risk of bleeding § many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).



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www.escardio.org/EHRA

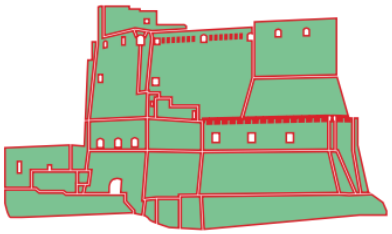
The Laboratory and the New Oral Anticoagulants

Armando Tripodi

"Laboratories are involved in the management of anticoagulants in 2 ways.

The first, ***monitoring****, implies laboratory testing to assess the drug's effect and* **to adjust the dosage to maintain anticoagulation within** *the therapeutic interval.*

The second way, ***measurement****, implies laboratory evaluations of drug effect to determine* **whether patients are under- or over-anticoagulated**, *information that can be useful for decision-making in special circumstances"*



Clinical Chemistry 59:2353–362 (2013)

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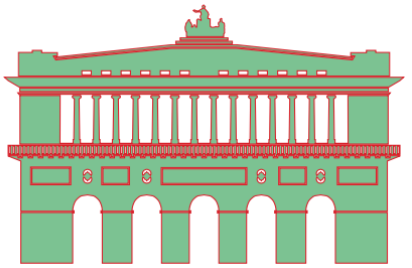
How to deal with dosing errors

Missed dose:	BID: take missed dose up to 6 h after scheduled intake. If not possible skip dose and take next scheduled dose. QD: take missed dose up to 12 h after scheduled intake. If not possible skip dose and take next scheduled dose.
Double dose:	BID: skip next planned dose and restart BID after 24 h. QD: continue normal regimen.
Uncertainty about intake:	BID: continue normal regimen. QD: take another dose then continue normal regimen.
Overdose:	Hospitalization advised.

Underlying bleeding tendency:
Prothrombin time (PT)
Partial thromboplastin time (APTT)
Blood cell counts and ***others that will depend on which drug is used for treatment***

Assessment of creatinine clearance *is indicated not only before starting treatment but also at regular intervals during treatment, as kidney function may deteriorate rapidly, especially in the elderly.*

Blood. 2013;121(20):4032-4035
Thromb Haemost 2011; 106: 868–876



Laboratory Measurement of the Anticoagulant Activity of the Non–Vitamin K Oral Anticoagulants

(J Am Coll Cardiol 2014;64:1128–39)

TABLE 1 Laboratory Monitoring of NOACs

NOAC	Preferred Method	In an Emergency
Dabigatran	1. Ecarin clotting time 2. Dilute thrombin time	APTT (preferably with specific calibrated reagents)
Rivaroxaban	Anti-factor Xa	PT (preferably with specific calibrated reagents)
Apixaban	Anti-factor Xa	Dilute PT
Edoxaban	Anti-factor Xa	Few firm data

Opinion pooled from references 3, 10, and 11.

APTT = activated partial thromboplastin time; NOAC = non-vitamin K oral anticoagulant; PT = prothrombin time.

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Specific antidotes to NOACs

	Idarucizumab	PER977	Andexanet alpha
Structure	Humanized Fab fragment	Synthetic small molecule	Human rXa variant
Target	Dabigatran	Universal	FXa inhibitors
Binding	Non-competit. High affinity	?	Competitive
Clinical studies	Rapid complete reversal	?	Rapid, near complete reversal