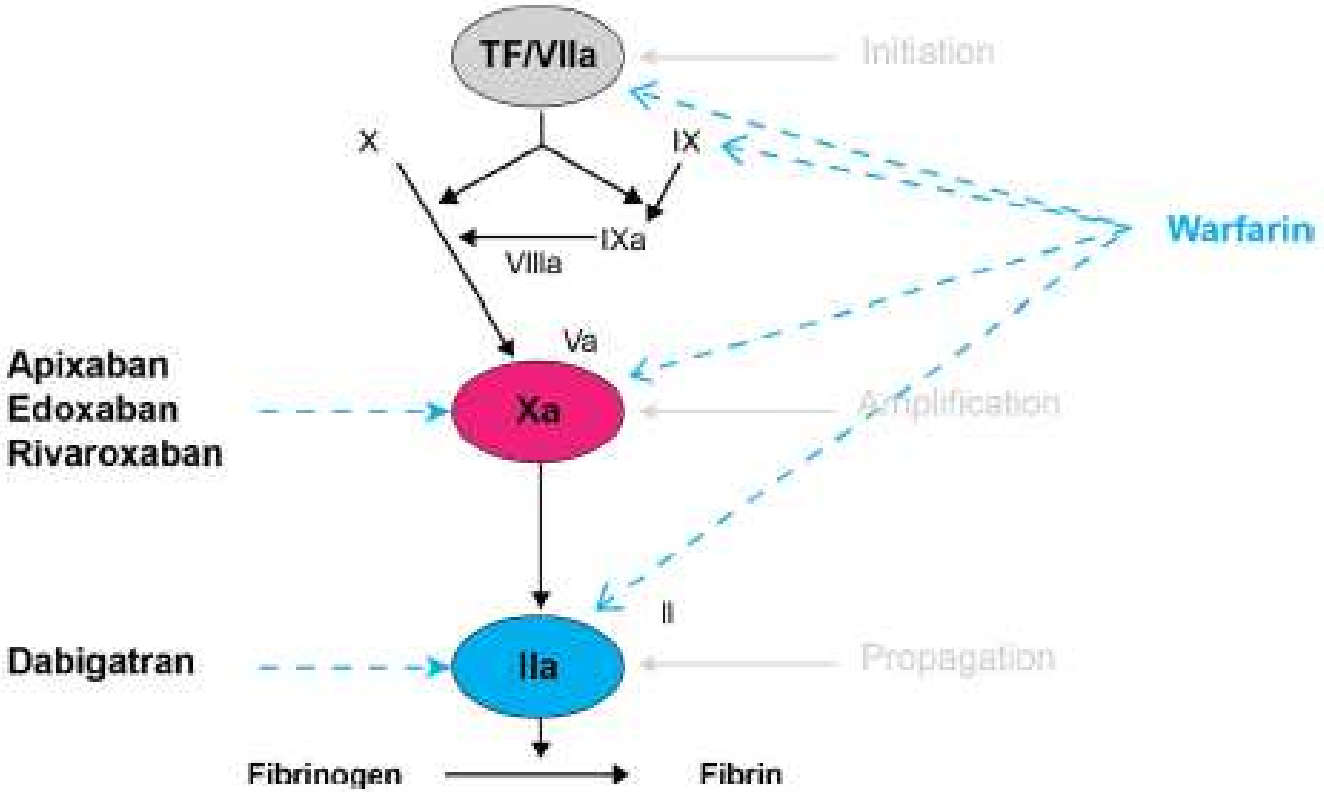
# **Gestione della terapia con DOAC** in presenza di eventi emorragici e in previsione di manovre invasive/interventi chirurgici

Dott.ssa Maria, Rosa Lombardi

*UO Medicina Interna ad Indirizzo Angiologico e Coagulativo-Centro Emostasi*

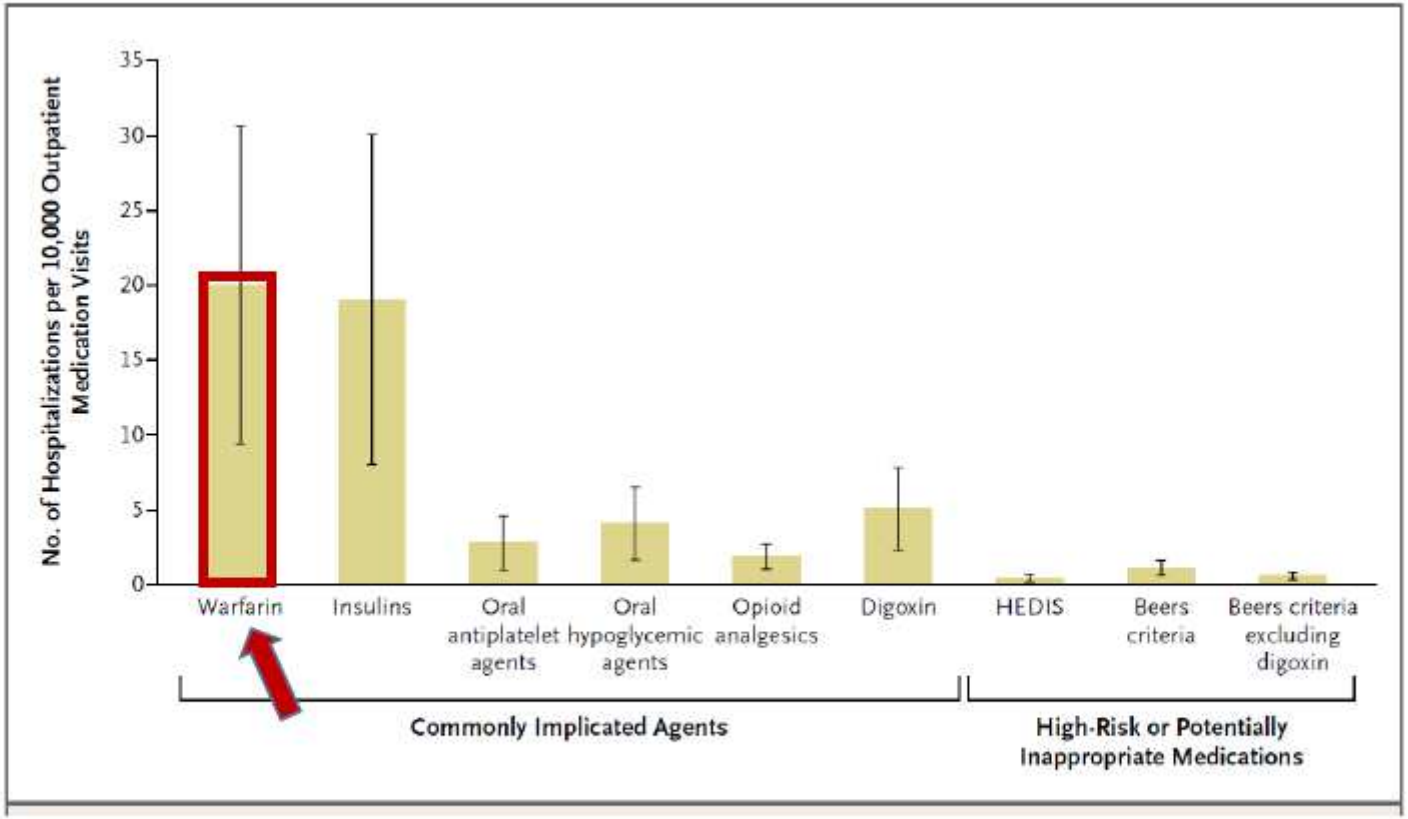
# I NUOVI ANTICOAGULANTI ORALI-INIBITORI DIRETTI




J Thromb Thombolysis 2016 41:206-232

# EMERGENCY HOSPITALIZATIONS FOR ADVERSE DRUG EVENTS IN OLDER AMERICANS

*99,628 emergency hospitalizations for adverse drug events per year; 4 medications were implicated alone or in combinat*




*Improved management of antithrombotics and antidiabetic drugs has the potential to reduce hospitalizations for adverse drug events in older adults.*

*Budnitz D.S et al . New Engl. J. Med 2011*

# NAO : VANTAGGI e …..

**Table 2. Potential Advantages and Disadvantages of DOACs Over Vitamin K Antagonist**

| | Implications |
|---|---|
| Advantages | |
| Decreased risk of intracranial bleeding | Safer anticoagulant therapy |
| Predictable anticoagulant effect | Convenience of fixed dosing without routine laboratory monitoring |
| Quick onset of action | Obviates need for heparin/low molecular weight heparin bridging |
| Quick offset of action | Simplifies periprocedural management and reduces need for reversal agents |
| Fewer drug and food interactions | Predictable anticoagulant effect |
| Disadvantages | |
| Higher acquisition cost | Limits uptake in some countries and patient groups |
| Reversal agents for oral factor Xa inhibitors not yet licensed | Limits uptake because of perceived concern about uncontrollable bleeding<br>Complicates management of patients who require urgent intervention |
| Limited access to standardized assays for drug level measurement | Complicates identification of bleeding patients who require reversal and timing of urgent surgery or intervention |
| Dependence on renal clearance | Contraindicates use of DOACs in patients with severe renal failure |
| Fecal excretion of active anticoagulant | May predispose at-risk patients to gastrointestinal bleeding |

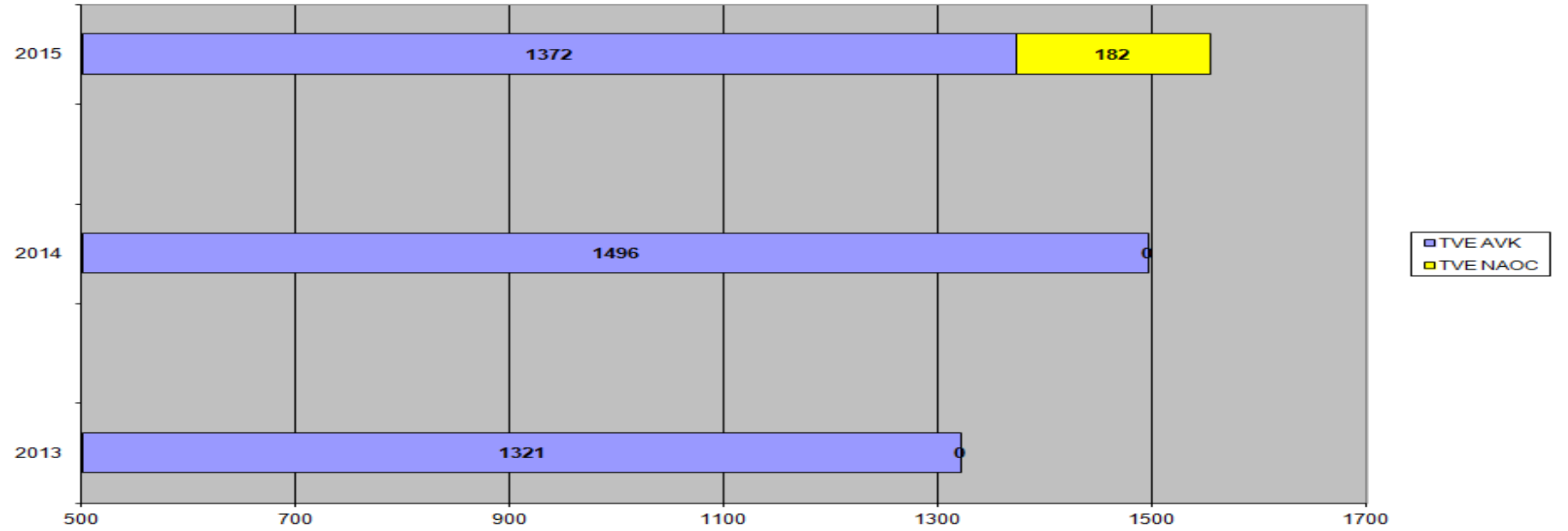
DOAC indicates direct oral anticoagulants.

## Evolving Treatments for Arterial and Venous Thrombosis
### Role of the Direct Oral Anticoagulants

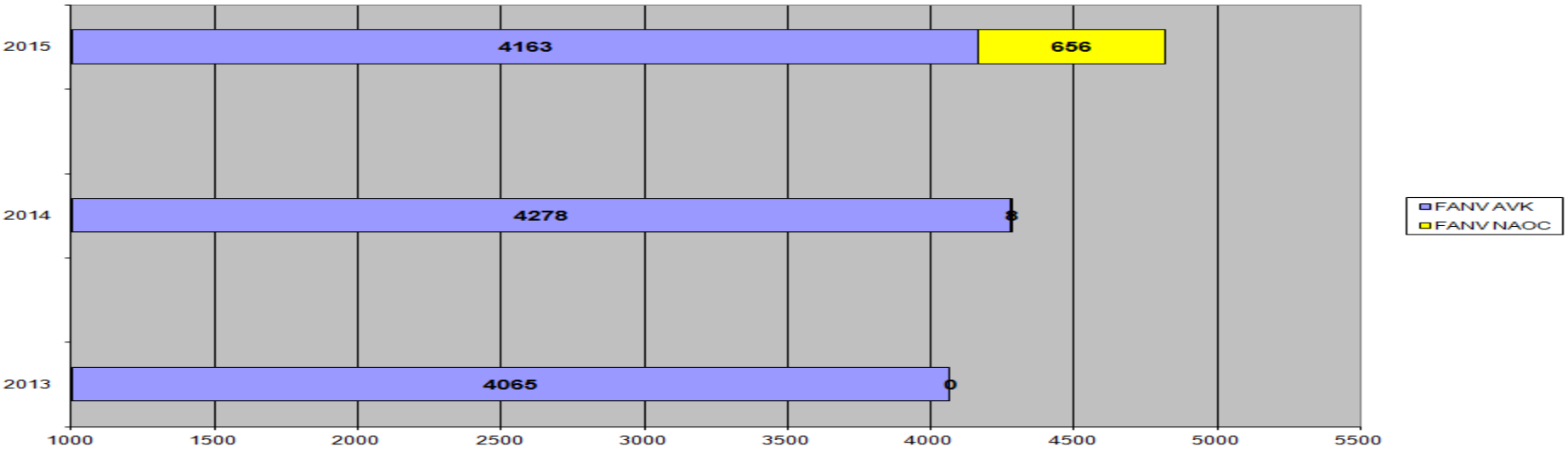
Noel C. Chan, John W. Eikelboom, Jeffrey I. Weitz

(*Circ Res*. 2016;118:1409-1424. DOI: 10.1161/CIRCRESAHA.116.306925.)

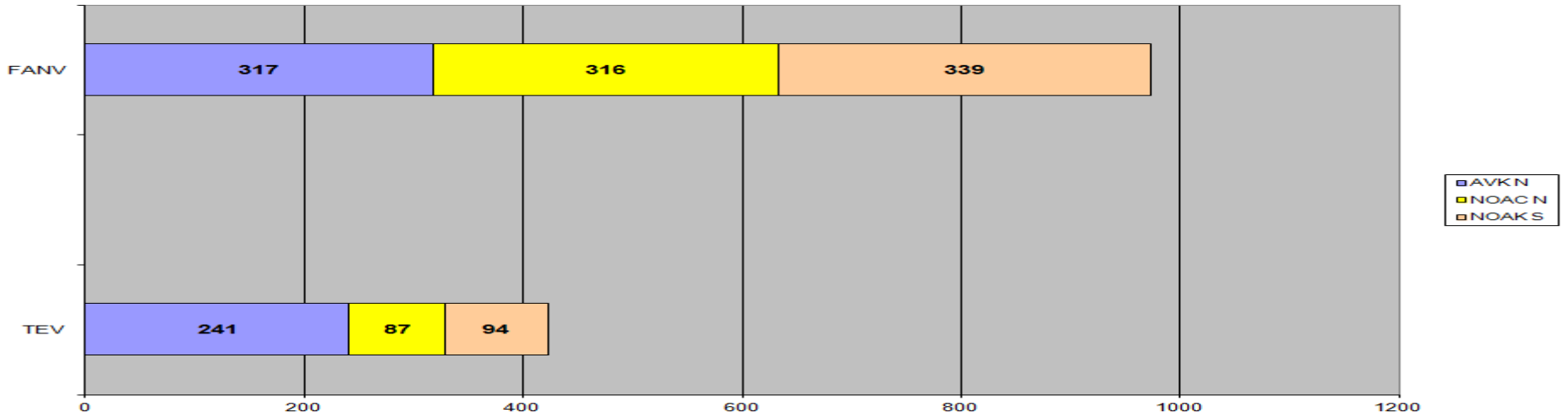
## TRATTAMENTO ANTITROMBOTICO PAZIENTI CON TEV



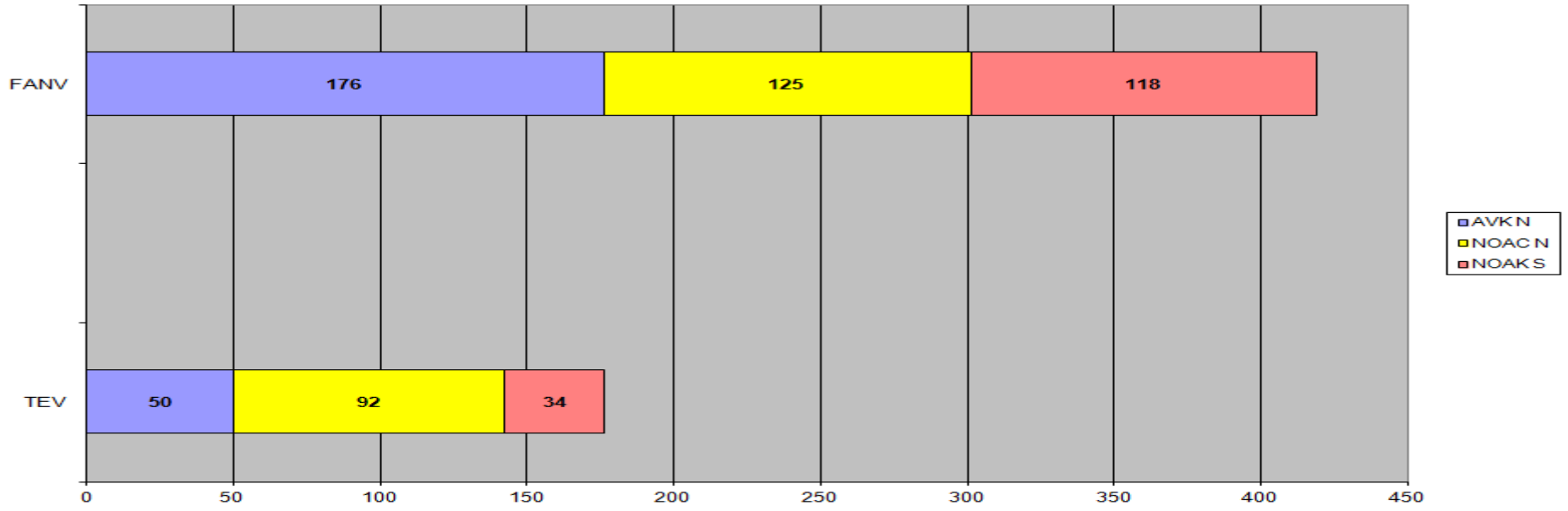

## TRATTAMENTO ANTITROMBOTICO PAZIENTI CON FANV



## INIZIO TRATTAMENTO ANTITROMBOTICO ANNO 2015




## INIZIO TRATTAMENTO ANTOTROMBOTICO ANNO 2016




Dr Manotti Cesare

Journal of the American Geriatrics Society

# New Oral Anticoagulants in Elderly Adults: Evidence From a Meta-analysis of Randomized Trials

Partha Sardar, MD; Saurav Chatterjee, MD; Shobhana Chaudhari, MD; Gregory Y. H. Lip, MD

Disclosures

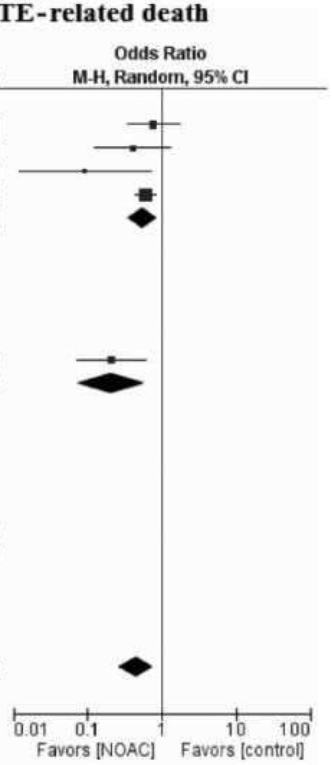
J Am Geriatr Soc. 2014;62(5):857-864.

## Conclusion

In elderly adults enrolled in randomized trials, bleeding with NOACs was not different from that with conventional anticoagulants. NOACs might be more effective than conventional agents in this population. An individualized approach matching the particular NOAC to the participant profile, taking into consideration the risk of bleeding and other comorbidities, should be taken rather than a generalized "one drug fits all" approach in elderly adults.

**Patients aged 75 years: Venous thromboembolism (VTE) or VTE-related death**

| Study or Subgroup | NOAC Events | NOAC Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.1 Rivaroxaban** | | | | | | |
| EINSTEIN PE, 2012 | 11 | 441 | 13 | 402 | 22.7% | 0.77 [0.34, 1.73] |
| EINSTEIN, 2010 | 4 | 215 | 10 | 225 | 14.5% | 0.41 [0.13, 1.32] |
| EINSTEIN-Extension, 2010 | 1 | 89 | 11 | 99 | 5.9% | 0.09 [0.01, 0.72] |
| MAGELLAN, 2013 | 60 | 1,084 | 102 | 1,149 | 40.7% | 0.60 [0.43, 0.84] |
| **Subtotal (95% CI)** | | **1,829** | | **1,875** | **83.8%** | **0.55 [0.35, 0.87]** |
| Total events | 76 | | 136 | | | |
| Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 3.98$, df = 3 (P = 0.26); $I^2 = 25\%$ | | | | | | |
| Test for overall effect: Z = 2.54 (P = 0.01) | | | | | | |
| **1.2 Apixaban** | | | | | | |
| AMPLIFY-EXT, 2013 | 5 | 220 | 11 | 109 | 16.2% | 0.21 [0.07, 0.61] |
| **Subtotal (95% CI)** | | **220** | | **109** | **16.2%** | **0.21 [0.07, 0.61]** |
| Total events | 5 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.85 (P = 0.004) | | | | | | |
| **1.3 Dabigatran** | | | | | | |
| RE-MEDY, 2013 | 0 | 140 | 0 | 119 | | Not estimable |
| **Subtotal (95% CI)** | | **140** | | **119** | | **Not estimable** |
| Total events | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **2,189** | | **2,103** | **100.0%** | **0.45 [0.27, 0.77]** |
| Total events | 81 | | 147 | | | |
| Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 7.23$, df = 4 (P = 0.12); $I^2 = 45\%$ | | | | | | |
| Test for overall effect: Z = 2.91 (P = 0.004) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.70$, df = 1 (P = 0.10), $I^2 = 63.0\%$ | | | | | | |




Medscape

European Heart Journal Advance Access published February 4, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw069

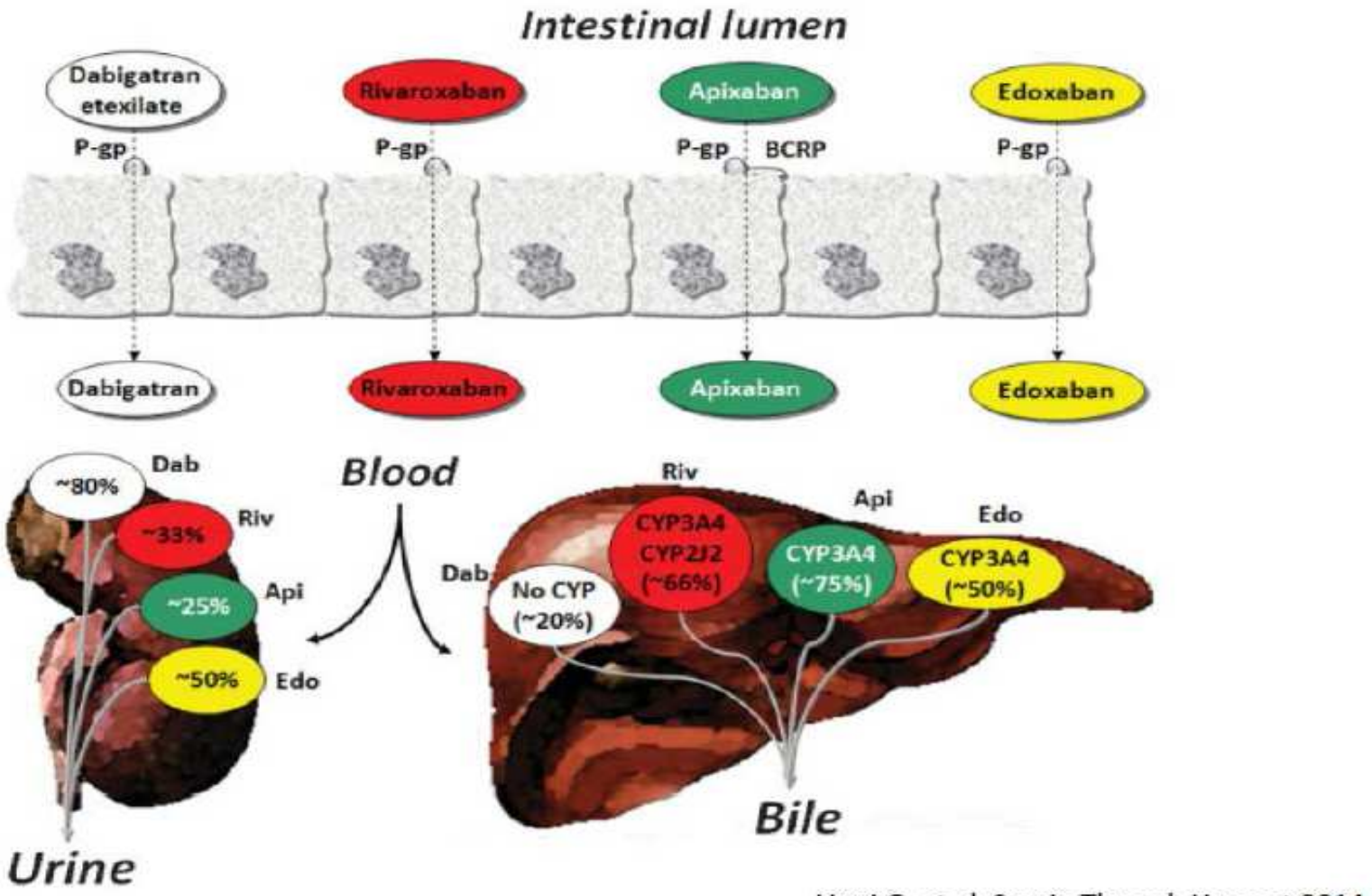
REVIEW

# Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

## Non-vitamin K oral anticoagulants and age

| | |
|---|---|
| First choice | In patients older than 75 years, we suggest apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 μmol/L)] |
| Second choice | Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily |

# ASSORBIMENTO E METABOLISMO DEI NAO




Lippi G. et al. Semin Thromb Hemost 2014

# Considerazioni su interferenze farmacologiche

- **E’ importante tener conto che esistono interazioni farmacologiche anche con i NAO**

- **Quando si prescrivono i NAO, effettuare una accurata anamnesi farmacologica rilevando tutti i farmaci potenzialmente interferenti**

- **L’impatto può essere meno rilevante rispetto al Warfarin poiché i NAO hanno una emivita relativamente breve; tuttavia in caso di terapie a lungo termine interferenti (antibiotici o chemioterapici) potrebbero esserci dei problemi**

- **Alcuni farmaci (es. fenobarbitale, rifampicina) riducono l'effetto: la riduzione è accettabile? (non è previsto un aumento del dosaggio dei NAO)**

- **Quali misure adottare ? Misurare il livello dei NAO? Basarsi solo su valutazioni cliniche?**

# MECCANISMI CHE REGOLANO LE INTERAZIONI FARMACOLOGICHE: CINQUE COLORI DIVERSI

Cinque livelli di allarme:

**Rosso** – controindicato/non raccomandato l'uso

**Arancione** – adattare la dose del NAO

dabigatran: 150 mg vs 110 mg BID

rivaroxaban: 20 mg vs 15 mg QD

apixaban: 5 mg vs 2.5 mg BID

**Yellow** – considerare la riduzione del dosaggio se sono presenti due interazioni gialle concomitanti.

**Brown** - possibile controindicazione

**Blue**- solo per edoxaban, non clinicamente rilevante anche se riduce la concentrazione plasmatica del farmaco

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

# INTERAZIONI FARMACOLOGICHE

| | via | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| **Other cardiovascular drugs** | | | | | |
| Atorvastatin | P-gp competition and CYP3A4 inhibition | +18%[251] | No data yet | No effect | No effect[252] |
| **Antibiotics** | | | | | |
| Clarithromycin; Erythromycin | moderate P-gp competition and CYP3A4 inhibition | +15-20% | No data yet | +90%[64] (reduce NOAC dose by 50%) | +30-54%[42, 247] |
| Rifampicin*** | P-gp/ BCRP and CYP3A4/CYP2J 2 inducers | **minus 66%[253]** | **minus 54%[238]** | avoid if possible: minus 35%, but with compensatory increase of active metabolites[243] | **Up to minus 50%** |
| **Antiviral drugs** | | | | | |
| HIV protease inhibitors (e.g. ritonavir) | P-gp and BCRP competition or inducer; CYP3A4 inhibition | No data yet | Strong increase[SmPC] | No data yet | Up to +153%[247] |

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

# Continua….

| | via | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| **Fungostatics** | | | | | |
| Fluconazole | Moderate CYP3A4 inhibition | No data yet | No data yet | No data yet | +42% (if systemically administered)[247] |
| Itraconazole; Ketoconazole; Posaconazole; Voriconazole; | potent P-gp and BCRP competition; CYP3A4 inhibition | +140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min) | +100%[60] | +87-95%[64] (reduce NOAC dose by 50%) | Up to +160%[247] |
| **Immunosuppressive** | | | | | |
| Cyclosporin; Tacrolimus | P-gp competition | Not recommended | No data yet | +73% | Extent of increase unknown |
| **Antiphlogistics** | | | | | |
| Naproxen | P-gp competition | No data yet | +55%[254] | No effect (but pharmacodynamically increased bleeding time) | No data yet. |
| **Antacids** | | | | | |
| H2B; PPI; Al-Mg-hydroxide | GI absorption | Minus 12-30%[45, 53, 58] | No effect[55] | No effect | No effect[241, 242] |
| **Others** | | | | | |
| Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort*** | P-gp/ BCRP and CYP3A4/CYP2J 2 inducers | minus 66%[253] | minus 54%[SmPC] | minus 35% | Up to minus 50% |

| Other factors: | | | | | |
|---|---|---|---|---|---|
| Age ≥ 80 years | Increased plasma level | | # | % | |
| Age ≥75 years | Increased plasma level | | | % | |
| Weight ≤ 60 kg | Increased plasma level | | # | | |
| Renal function | Increased plasma level | See Table 8 | | | |
| Other increased bleeding risk | | Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3 | | | |

- **La co-somministrazione di antiaggreganti aumenta il rischio di sanguinamento: attenta valutazione della reale necessità della terapia combinata**

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

European Heart Journal Advance Access published February 4, 2016

European Heart Journal
doi:10.1093/eurheartj/ehv643

REVIEW

*Prevention*

# Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Hans-Christoph Diener[1*], James Aisenberg[2], Jack Ansell[3], Dan Atar[4], Günter Breithardt[5], John Eikelboom[6], Michael D. Ezekowitz[7,8,9], Christopher B. Granger[10], Jonathan L. Halperin[11], Stefan H. Hohnloser[12], Elaine M. Hylek[13], Paulus Kirchhof[14,15], Deirdre A. Lane[16], Freek W.A. Verheugt[17], Roland Veltkamp[18], and Gregory Y.H. Lip[19,20]

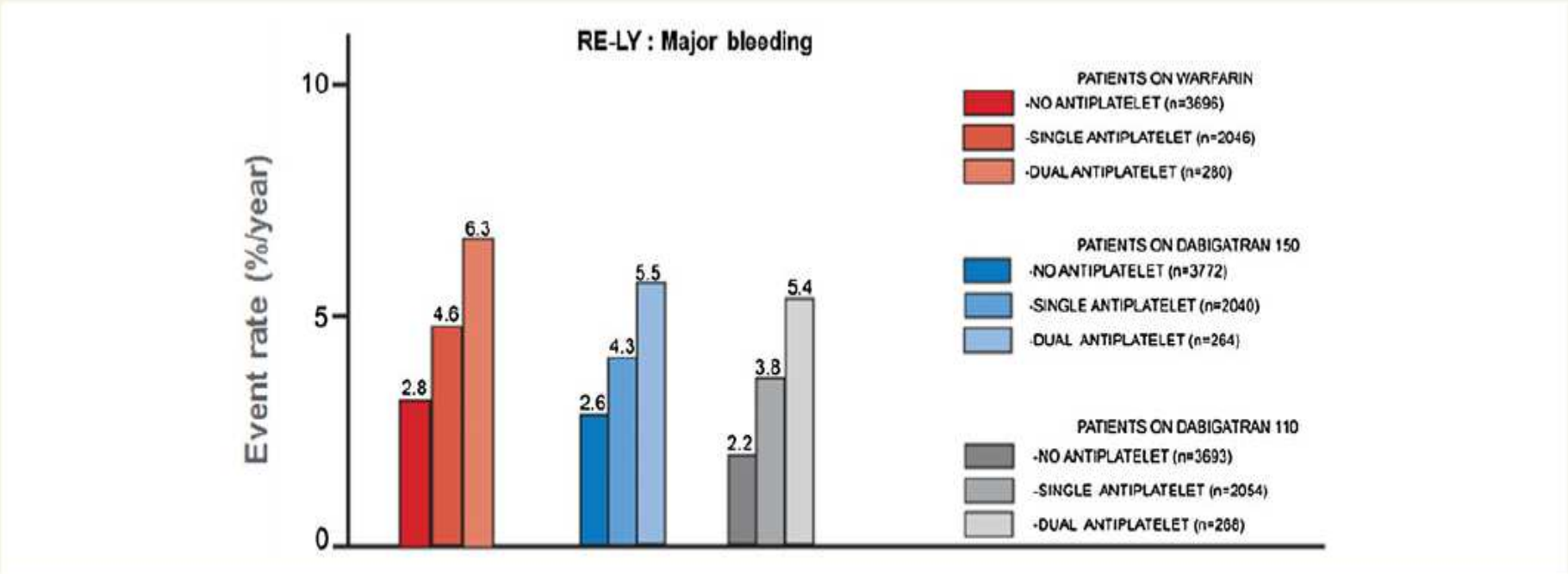
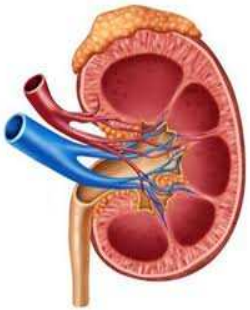



**Figure 1** *Post hoc* analysis from the RE-LY trial: Dabigatran (low dose: grey bars; high dose: blue bars) and warfarin (red bars) have been analysed with regard to the occurrence of major-bleeding complications, stratified according to single OAC administration (light colour), combination therapy with one antiplatelet agent (middle-intensity colour), and together with dual antiplatelet therapy (high-intensity colour). Adapted from Dans *et al.*[10]



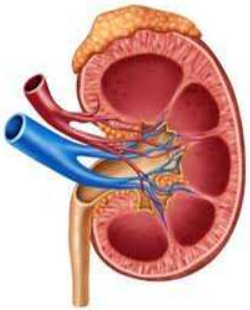
# NAO E INSUFFICIENZA RENALE

**Table 7** Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| CrCl >80 mL/min | 12–17 h[61] | 12 h | 10–14 h[51,65] | 5–9 h (young)<br>11–13 h (elderly) |
| CrCl 50–80 mL/min<br>CKD Stages I and II | ~17 h[122]<br>(+50%) | ~14.6 h[123]<br>(+16%) | ~8.6 h[124]<br>(+32%)[SmPC] | ~8.7 h[125]<br>(+44%)[126] |
| CrCl 30–50 mL/min<br>CKD Stage III | ~19 h[122]<br>(+320%) | ~17.6 h<br>(+29%) | ~9.4 h[124]<br>(+74%)[SmPC] | ~9.0 h<br>(+52%)[126] |
| CrCl 15–30 mL/min<br>CKD Stage IV | ~28 h[122]<br>(+530%) | ~17.3 h<br>(+44%) | ~16.9 h[124]<br>(72%)[SmPC] | ~9.5 h<br>(+64%)[126] |
| CrCl ≤ 15 mL/min<br>CKD Stage V; off-dialysis | No data | –<br>(+36%) | –<br>(+93%)[SmPC] | –<br>(+70%)[127] |

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309



# NAO E INSUFFICIENZA RENALE

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

**Table 8 Approved European labels for NOACs and their dosing in CKD**

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Fraction renally excreted of absorbed dose | 80% | 27%[52–55] | 50%[36] | 35% |
| Bioavailability | 3–7% | 50% | 62%[51] | 66% without food<br>Almost 100% with food |
| Fraction renally excreted of administered dose | 4% | 12–29%[52–55] | 37%[36] | 33% |
| Approved for CrCl ≥ … | ≥30 mL/min | ≥15 mL/min | ≥15 mL/min | ≥15 mL/min |
| Dosing recommendation | CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID) | Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a] | CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b] | CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD) |
| Dosing if CKD | When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5]<br>Note: 75 mg BID approved in US only[c]:<br>if CrCl 15–30 mL/min<br>if CrCl 30–49 mL/min and other orange factor: *Table 6* (e.g. verapamil) | CrCl 15–29 mL/min: 2.5 mg BID<br>If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID | 30 mg OD when CrCl 15–49 mL/min | 15 mg OD when CrCl 15–49 mL/min |
| Not recommended if | CrCl < 30 mL/min | CrCl < 15 mL/min | CrCl < 15 mL/min | CrCl < 15 mL/min |

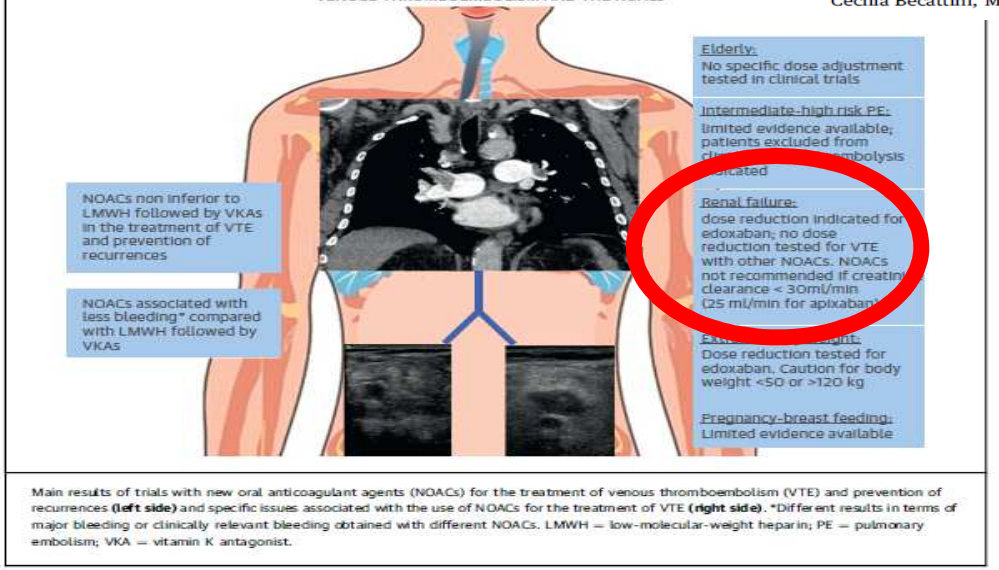
**Red:** contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

STATE-OF-THE-ART REVIEW

## Treatment of Venous Thromboembolism With New Anticoagulant Agents

Cecilia Becattini, MD, PhD, Giancarlo Agnelli, MD

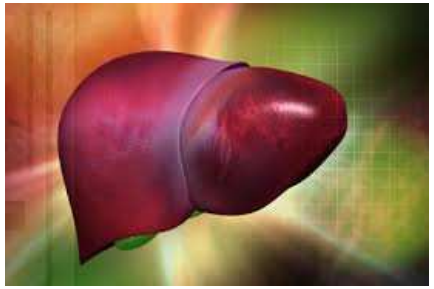
**FIGURE 1 VTE and the NOACs**




Main results of trials with new oral anticoagulant agents (NOACs) for the treatment of venous thromboembolism (VTE) and prevention of recurrences **(left side)** and specific issues associated with the use of NOACs for the treatment of VTE **(right side)**. *Different results in terms of major bleeding or clinically relevant bleeding obtained with different NOACs. LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PUBLISHED BY ELSEVIER



# NAO E INSUFFICIENZA EPATICA

**Edoxaban**

**Tabella 4.** Raccomandazioni posologiche dei nuovi anticoagulanti orali.

| | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| Patologia renale | | | |
| Minima (ClCr >50 ml/min) | 150 mg bid | 20 mg/die | 5 mg bid |
| Moderata (ClCr 30-49 ml/min) | 110 mg bid | 15 mg/die | 5 mg bid |
| Grave (ClCr <30 ml/min) | Non raccomandato | 15 mg/die | 2.5 mg bid |
| Patologia epatica | | | |
| Minima | 150 mg bid | 20 mg/die | 5 mg bid |
| Moderata | 150 mg bid | Non raccomandato | 5 mg bid |
| Grave | Non raccomandato | Non raccomandato | Non raccomandato |
| Disfunzione epatica | Non raccomandato | Non raccomandato | Non raccomandato |
| Variabili demografiche | | | |
| Etnia, asiatici | 150 mg bid | 15 mg/die | 5 mg bid |
| Età >75-80 anni | 110 mg bid | 20 mg/die | 2.5 mg bid[a] |
| Peso <50 kg | 150 mg bid | 20 mg/die | 2.5 mg bid[a] |
| Interazioni tra farmaci | | | |
| Inibitori P-gp | 110 mg bid | 15 mg/die | 2.5 mg bid |
| Inibitori CYP3A4 | 150 mg bid | 15 mg/die | 2.5 mg bid |
| Induttori P-gp/CYP3A4 | Non raccomandato | Non raccomandato | Non raccomandato |

ClCr, clearance della creatinina; CYP, citocromo P450; P-gp, P-glicoproteina.
Per edoxaban non sono ancora disponibili le raccomandazioni posologiche.
[a]con uno solo dei criteri non occorre ridurre il dosaggio.
Modificata da Gong e Kim[14].

# Cosa fare prima di un intervento chirurgico d'elezione?

J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

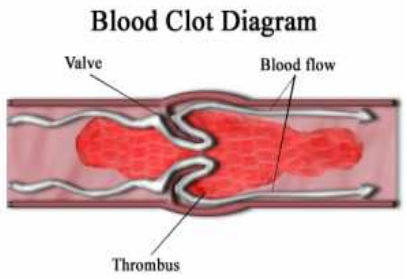
# Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment

Allison E. Burnett[1] · Charles E. Mahan[2] · Sara R. Vazquez[3] · Lynn B. Oertel[4] · David A. Garcia[5] · Jack Ansell[6]

**Table 10** Patient-specific risk factors for bleeding

| General risk factors | Medical patient risk factors |
|---|---|
| Active or metastatic cancer | Age—increasing |
| Age (e.g. >65 years) | Active cancer |
| Anemia | Anemia and other blood dyscrasias |
| Comorbidity and reduced functional capacity | Current liver disease |
| Concomitant medications such as NSAIDs, antiplatelets or other anticoagulants administered possibly in a transition period | Central venous catheter placement |
| Diabetes | History of bleeding |
| Alcohol abuse | Hospital stay of ≥3 days |
| Frequent falls | ICU/CCU stay |
| Hepatic or renal dysfunction | Male gender |
| History of bleeding complications | Previous or active gastroduodenal ulcer |
| Previous stroke | Thromboembolic stroke |
| Recent surgery | Recent re-hospitalization |
| Thrombocytopenia | Renal failure |
| | Rheumatic disease |

*NSAIDs* Nonsteroidal anti-inflammatory drugs, *ICU* intensive care unit, *CCU* cardiac care unit




J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

CrossMark

# Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment

Allison E. Burnett[1] · Charles E. Mahan[2] · Sara R. Vazquez[3] · Lynn B. Oertel[4] · David A. Garcia[5] · Jack Ansell[6]

| High risk for thromboembolism: | Intermediate risk for thromboembolism: | Low risk for thromboembolism: |
|---|---|---|
| • Known hypercoagulable state as documented by a thromboembolic event and one of the following:<br>Protein C deficiency<br>Protein S deficiency<br>Antithrombin III deficiency<br>Homozygous factor V Leiden mutation<br>Antiphospholipid-antibody syndrome<br>• Hypercoagulable state suggested by recurrent (two or more) arterial or idiopathic venous thromboembolic events (not including primary atherosclerotic events, such as stroke or myocardial infarction due to intrinsic cerebrovascular or coronary disease)<br>• Venous or arterial thromboembolism within the preceding 1-3 months<br>• Rheumatic atrial fibrillation<br>• Acute intracardiac thrombus visualized by echocardiogram<br>• Atrial fibrillation plus mechanical heart valve in any position<br>• Older mechanical valve model (single-disk or ball-in-cage) in mitral position<br>• Recently placed mechanical valve (<3 mo)<br>• Atrial fibrillation with history of cardioembolism | • Cerebrovascular disease with multiple (2 or more) strokes or transient ischemic attacks without risk factors for cardiac embolism<br>• Newer mechanical valve model (eg, St. Jude) in mitral position<br>• Older mechanical valve model in aortic position<br>• Atrial fibrillation without a history of cardiac embolism but with multiple risks for cardiac embolism (eg, ejection fraction <40%, diabetes, hypertension, nonrheumatic valvular heart disease, transmural myocardial infarction within preceding month)<br>• Venous thromboembolism >3-6 months ago* | • One remote venous thromboembolism (>6 mo ago)*<br>• Intrinsic cerebrovascular disease (eg, carotid atherosclerosis) without recurrent strokes or transient ischemic attacks<br>• Atrial fibrillation without multiple risks for cardiac embolism<br>• Newer model prosthetic valve in aortic position |

# Intervento e rischio emorragico correlato

## Interventions not necessarily requiring discontinuation of anticoagulant

Perform procedures at ‘through’ levels of NOAC. Consider scheduling intervention

18-24 h after last intake and then restart 6 h later (i.e. skipping 1 dose with BID NOAC)

**Dental interventions**

- Extraction of 1 to 3 teeth
- Paradontal surgery
- Incision of abscess
- Implant positioning

**Ophthalmology**

- Cataract or glaucoma intervention

**Endoscopy without surgery**

**Superficial surgery** (e.g. abscess incision, small dermatological excision)

# Intervento e rischio emorragico correlato

## Low risk

- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation

## High risk

- Complex left-sided ablation: pulmonary vein isolation, VT ablation
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy

# Tempistica di interruzione della terapia

In base alla :

- Funzione renale del paziente
- Tipologia d'intervento

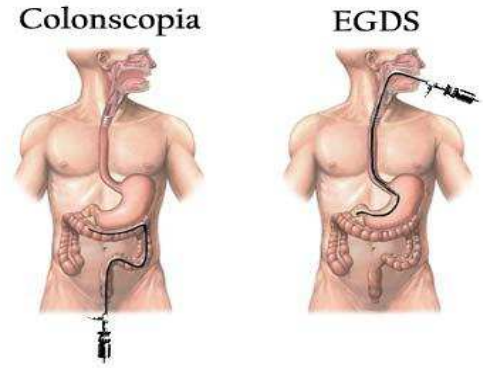
**Table 10** Last intake of drug before elective surgical intervention

| | Dabigatran | | Apixaban–edoxaban–rivaroxaban | |
|---|---|---|---|---|
| | No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake) | | | |
| | Low risk | High risk | Low risk | High risk |
| CrCl ≥ 80 mL/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| CrCl 50–80 mL/min | **≥36 h** | **≥72 h** | ≥24 h | ≥48 h |
| CrCl 30–50 mL/min[a] | **≥48 h** | **≥96 h** | ≥24 h | ≥48 h |
| CrCl 15–30 mL/min[a] | Not indicated | Not indicated | **≥36 h** | **≥48 h** |
| CrCl < 15 mL/min | No official indication for use | | | |
| There is no need for bridging with LMWH/UFH | | | | |

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines

Veitch AM, *et al*. *Gut* 2016;**65**:374–389.




**Low Risk Procedure**
Diagnostic procedures +/- biopsy
Biliary or pancreatic stenting
Device-assisted enteroscopy without polypectomy

**Warfarin**

**Continue Warfarin**
Check INR during the week before endoscopy
If INR within therapeutic range continue usual daily dose
If INR above therapeutic range but <5 reduce daily dose until INR returns to therapeutic range

**DOAC**
Dabigatran
Rivaroxaban
Apixaban
Edoxaban

**Omit DOAC on morning of procedure**

# Quando riprendere i NAO dopo intervento?

| | |
|---|---|
| Procedures with immediate and complete haemostasis; atraumatic spinal/epidural anethesia or clean lumbar puncture. | Resume 6–8 h after surgery |
| Procedures associated with immobilization | Initiate reduced o intermediate dose of LMWH 6–8 h after surgery if haemostasis achieved. |
| Procedures with post-operative risk of bleeding | Restart NOACs 48–72h after surgery upon complete haemostasis<br><br>Thromboprophylaxis (e.g. with LMWH) can be initiated 6-8 h after surgery |

# In caso di chirurgia d’urgenza?

- Interrompere NAO, il tempo gioca a nostro favore

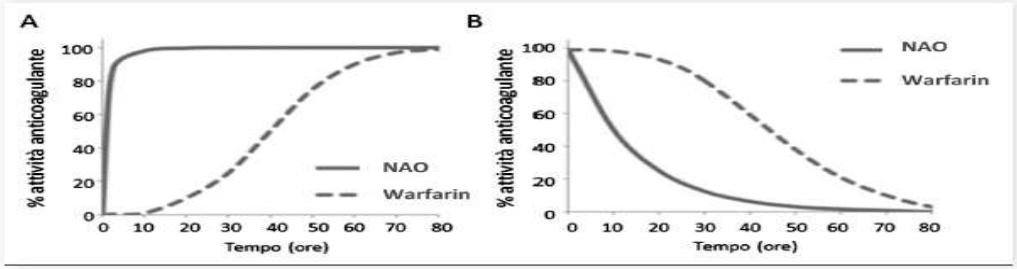



**Figura 7.** Effetto tempo-dipendente di warfarin e dei nuovi anticoagulanti orali (NAO) sulla coagulazione. Grazie al loro differente meccanismo d’azione, i NAO agiscono più rapidamente di warfarin (*A*) e il loro effetto svanisce altrettanto più rapidamente dopo l’interruzione della terapia (*B*). Modificata da Desai et al.[34].

- Provare a rinviare l'intervento chirurgico per almeno 12 ore e, idealmente, 24 ore dopo l'ultima dose.
- Chirurgia d'urgenza associata a tassi molto più elevati di sanguinamento rispetto alle procedure elettive, ma inferiori rispetto ai pazienti trattati con AVK.
- Test di laboratorio : quali e quando?
- Disponibilità di antidoti

# QUALI TEST ?

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| aPTT | ✓ | X | X | X |
| TT, dTT | ✓ | X | X | X |
| ECT | ✓ | X | X | X |
| Anti-FXa assays | X | ✓ | ✓ | ✓ |
| PT | X | ✓ | X | X |
| INR | X | X | X | X |

✓ = quantitative; ✓ = qualitative; **X** = not applicable

Time of last NOAC dose should always be considered when interpreting test results.

aPTT = activated partial thromboplastin time; dTT = diluted thrombin time; ECT = ecarin clotting time; FXa = activated Factor X; PT = prothrombin time; TT = thrombin time

Heidbuchel H, et al. *Europace*. 2015;17:1467-1507.

# QUANDO ?

J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

## Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment

Allison E. Burnett[1] · Charles E. Mahan[2] · Sara R. Vazquez[3] · Lynn B. Oertel[4] · David A. Garcia[5] · Jack Ansell[6]



Table 7 Potential indications for DOAC measurement [38–40]

| Detection of clinically relevant levels | Detection of expected on-therapy levels | Detection of excessive levels |
|---|---|---|
| Urgent or emergent invasive procedure | Assessing adherence | Hemorrhage |
| Neuraxial anesthesia | Breakthrough thrombosis | Diminished/changing renal function |
| Major trauma | | Hepatic impairment |
| Potential thrombolysis in acute thromboembolism | | Accidental or intended overdose |
| Hemorrhage | | Drug interactions |
| | | Advanced age |

**RACCOMANDAZIONE**

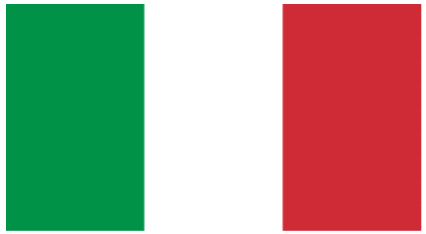
In situazioni cliniche di urgenza/emergenza nei pazienti in trattamento certo o presunto con un NAO (dabigratan, rivaroxaban, apixaban) il GdL raccomanda l'esecuzione di specifici test per conoscere la presenza dell'effetto anticoagulante e misurarne l'entità.
Le principali condizioni di urgenza/emergenza in cui è raccomandabile l'esecuzione di tali test sono:

- emorragia in atto
- eventi trombotici acuti
- valutazione degli effetti dei trattamenti somministrati per la neutralizzazione dell'attività anticoagulante dei farmaci
- valutazione preliminare ad interventi chirurgici in urgenza/emergenza
- valutazione preliminare a manovre invasive (diagnostiche o terapeutiche) in urgenza/emergenza

In queste situazioni il GdL raccomanda di utilizzare test specifici per la misurazione dell'effetto anticoagulante dei NAO:

- per i pazienti in trattamento con **dabigatran**:
  ⇒ Tempo di Trombina diluito o dosaggio cromogenico dell'attività anti-IIa
- per i pazienti in trattamento con **rivaroxaban** e **apixaban**
  ⇒ Dosaggio cromogenico dell'attività anti Xa

**Il GdL raccomanda che tali test siano eseguibili in urgenza.**



# DEFINIZIONE DELL'EMORRAGIE

**Moderate to severe bleeding:** riduzione dell'Hb di almeno 2 gr% e/o trasfusione di almeno 2 Unità di sangue o emorragia sintomatica in una sede critica (intraoculare, intraspinale, intracranica, retroperitoneale, pericardica, intramuscolare con sindrome compartimentale).

**Life-threatening bleeding** (sottoclasse di emorragia maggiore): emorragia fatale, emorragia cerebrale sintomatica, emorragia con una riduzione dell'Hb di almeno 5 gr% o che richieda trasfusione di almeno 4 Unità di sangue o l'uso di agenti inotropi o che necessiti di intervento chirurgico.

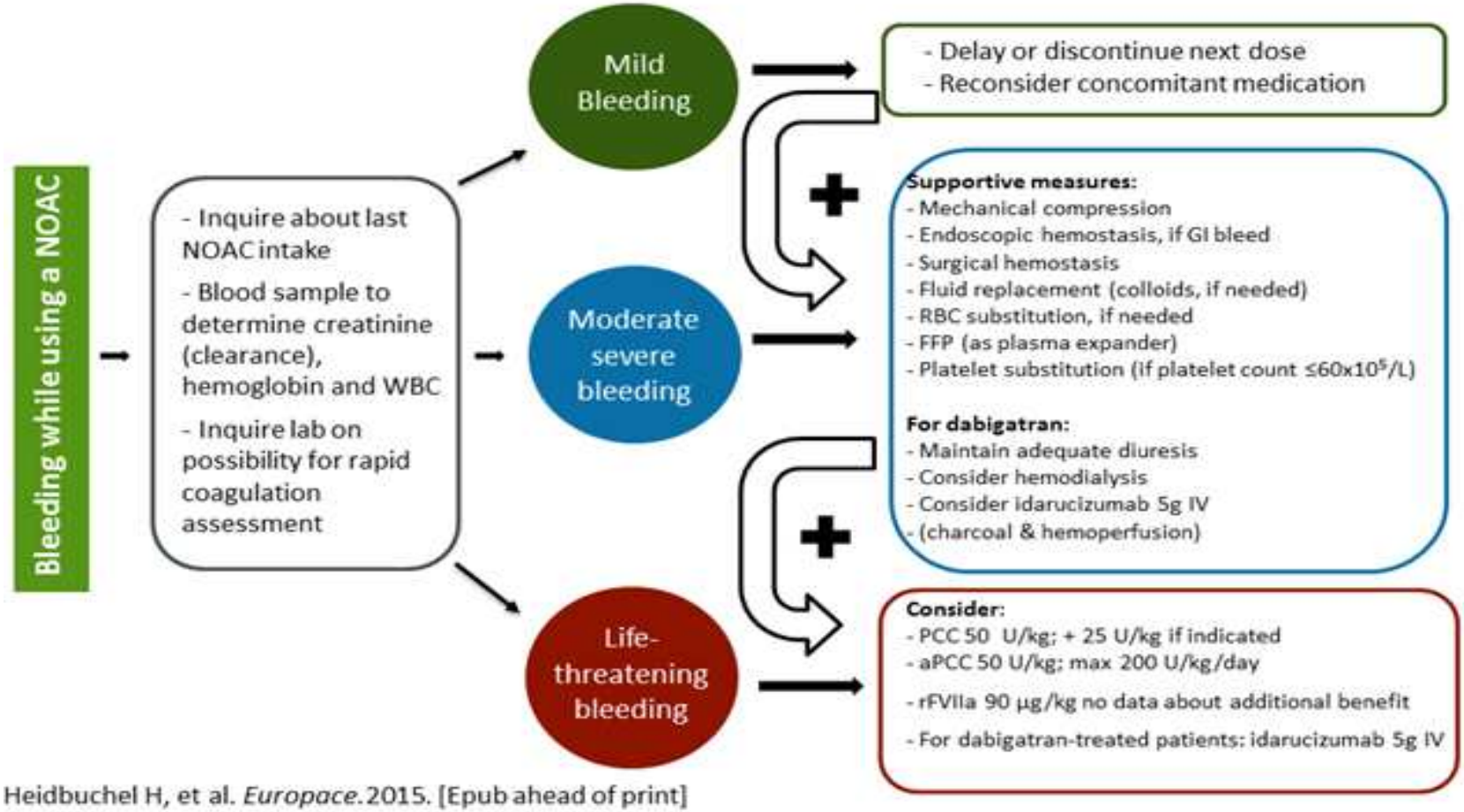
**Minor bleeding**: tutte le altre emorragie *ISHT, Schulman J Haem Thromb 2005*

(relative risk [RR], 0.90; 95% CI, 0.77–1.06).[65] Compared with VKAs, DOACs were associated with a 39% reduction in the risk of major bleeding (RR, 0.61; 95% CI, 0.45–0.83), a 63% reduction in intracranial bleeding (RR, 0.37; 95% CI, 0.21–0.68), and a 64% reduction in fatal bleeding (RR, 0.36; 95% CI, 0.15–0.84). In addition, clinically relevant nonmajor bleeding was reduced by 27% with the DOACs compared with VKAs (RR, 0.73; 95% CI, 0.58–0.93). Therefore, the DOACs are noninferior to well-managed VKA therapy, but are associated with significantly less bleeding.[65]

NEL TEV

(*Circ Res*. 2016;118:1409-1424. DOI: 10.1161/CIRCRESAHA.116.306925.)

# NOACS: Management of Bleeding




Heidbuchel H, et al. *Europace*. 2015. [Epub ahead of print]

A document has been released on how to manage NOACs in specific clinical situations in patients with atrial fibrillation (36). Although patients with VTE differ from those with atrial fibrillation, and although transfer of evidence from 1 clinical setting to another is not always appropriate, it is conceivable that the same indications can be applied to patients with VTE until specific data become available.

STATE-OF-THE-ART REVIEW

## Treatment of Venous Thromboembolism With New Anticoagulant Agents

Cecilia Becattini, MD, PhD, Giancarlo Agnelli, MD

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PUBLISHED BY ELSEVIER

Regione Emilia-Romagna

# Indicazioni sulla gestione delle emergenze emorragiche in corso di trattamento con farmaci anticoagulanti orali

## RACCOMANDAZIONE

In caso di emorragia maggiore **non a rischio di vita** o di perdita di un organo/funzione in corso di terapia con farmaci anticoagulanti orali il Gruppo di Lavoro raccomanda di adottare le seguenti misure generali di trattamento:

**IN CORSO DI TERAPIA CON QUALUNQUE ANTICOAGULANTE:**

- ⇒ sospendere il trattamento anticoagulante in corso
- ⇒ effettuare in urgenza i test specifici di laboratorio indicati per il farmaco anticoagulante assunto
- ⇒ garantire la terapia di supporto
- ⇒ eseguire, quando possibile, le manovre invasive per l'emostasi meccanica (trattamento endoscopico per effettuare emostasi meccanica in caso di emorragie del tubo gastroenterico e/o delle vie urinarie inferiori, procedure di radiologia interventista con embolizzazione di vasi arteriosi in caso di emorragia maggiore in sedi retroperitoneali e/o di ematomi muscolari).

**IN CORSO DI TERAPIA CON NAO**:

- ⇒ identificare il farmaco, il dosaggio assunto e l'orario dell'ultima assunzione.
- ⇒ calcolare la funzionalità renale (VFG)*:
  - in caso di VFG>50 ml/min il tempo di dimezzamento plasmatico dei NAO consente in genere una completa ripresa della funzione emostatica entro 24 ore dall'ultima assunzione. In questo caso la sola terapia di supporto può essere sufficiente.
  - in caso di VFG <50 ml/min il tempo di dimezzamento plasmatico dei NAO può essere prolungato in maniera clinicamente rilevante, anche se con differenze fra i vari farmaci.
- ⇒ gastrolusi se assunzione <2 ore

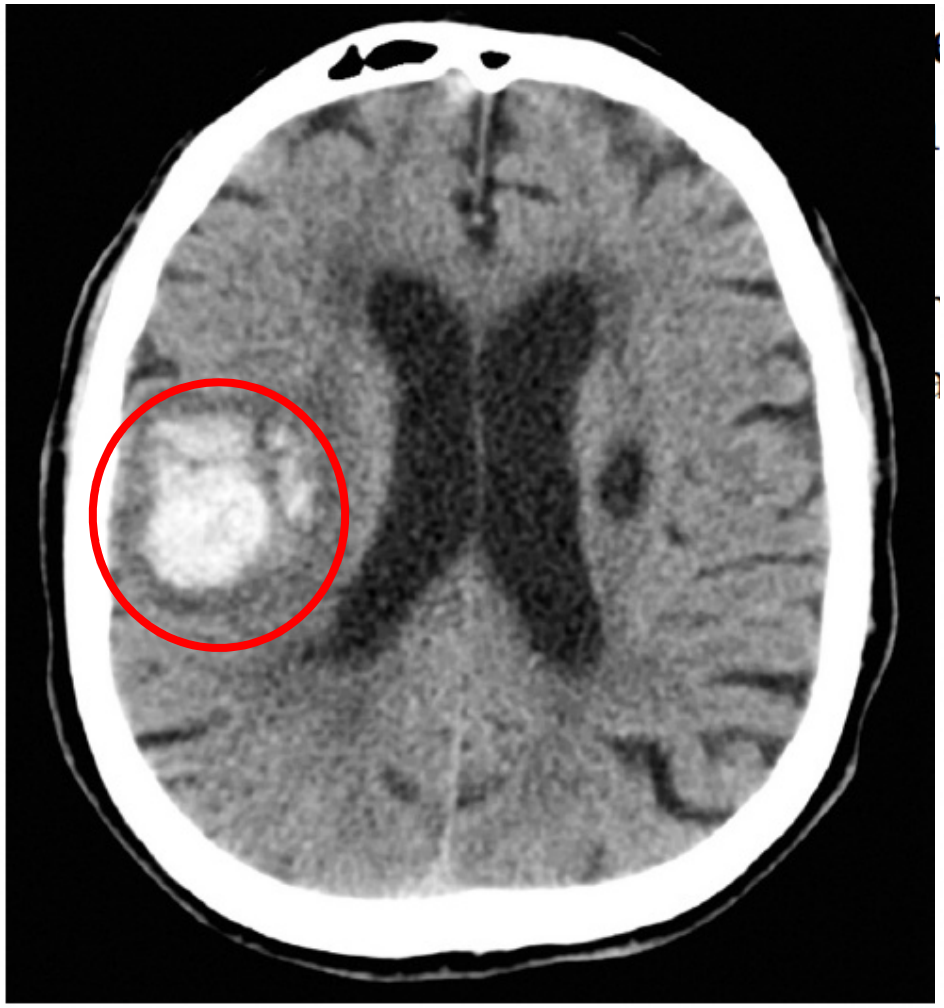
** La formula suggerita per il calcolo del VFG è quella di Cockcroft e Gault*

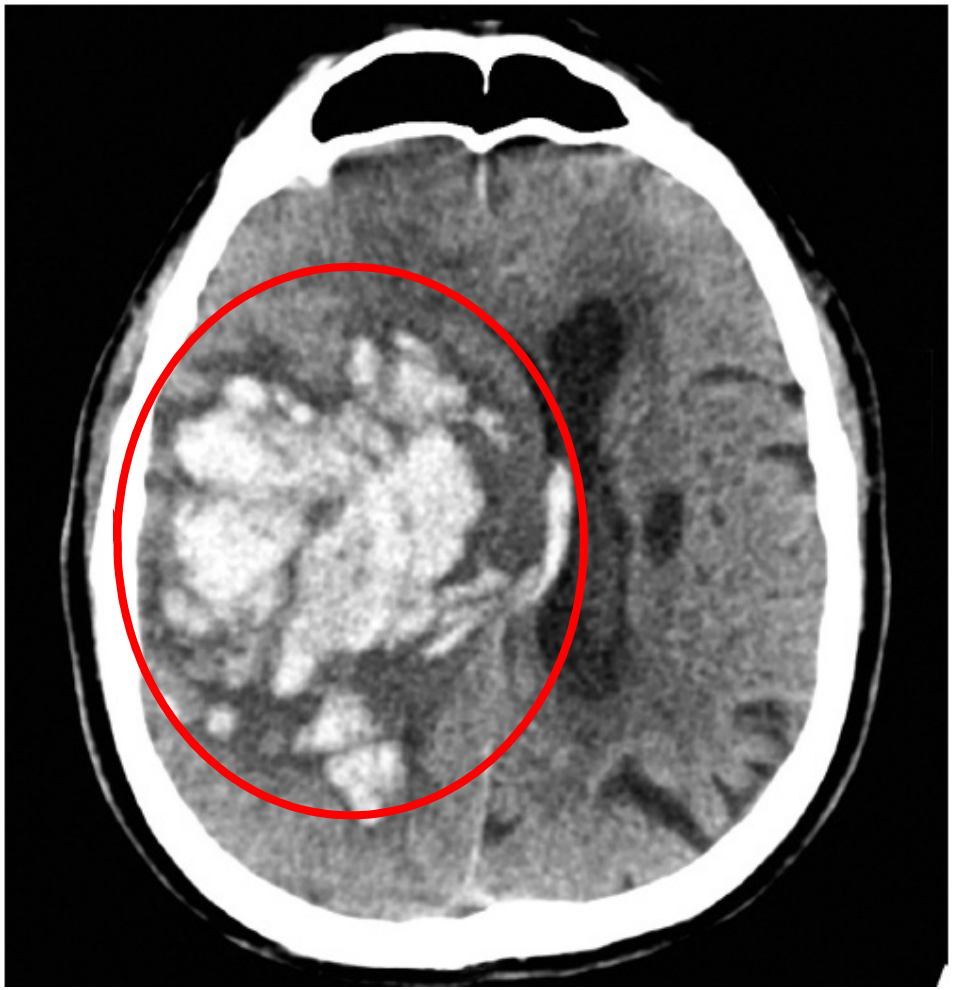

## RACCOMANDAZIONE

In caso di emorragia maggiore a rischio di vita o di perdita di organo/funzione in corso di trattamento con NAO il GdL suggerisce, pur in assenza di evidenze solide, di adottare i seguenti provvedimenti specifici (in aggiunta alle misure generali di trattamento indicate nella Raccomandazione 2):

- somministrare concentrati del complesso protrombinico alle dosi di 25 UI/kg eventualmente ripetibili 1-2 volte dopo attenta valutazione del rischio trombotico;
- somministrare acido tranexamico alle dosi di 15 mg/kg 3 volte al dì per via endovenosa oppure 25 mg/kg 3 volte al dì per os fino al controllo dell'emorragia;
- in caso di emorragia non responsiva ai precedenti trattamenti considerare la possibilità di una somministrazione di concentrati del complesso protrombinico attivati (FEIBA®) alle dosi indicative di 50 UI/kg fino a un massimo di 200 UI/kg al giorno;
- valutare l'opportunità di dialisi in emergenza con filtri a carbone (ultrafiltrazione o dialisi classica) - solo per dabigatran.

Queste misure sono da attuare per concentrazioni di farmaco al di sopra del limite inferiore di riferimento del test di laboratorio, o nel caso in cui il valore del test di laboratorio non sia ottenibile in tempi compatibili con la situazione clinica del paziente.





**16:30: emiparesi sin. e disartria**
**Assunzione Dabigatran??**
**22.00: TC**

**04:00 → GCS=3 → TC**
**Muore alle 10:00**

# Idarucizumab: A Specific Reversal Agent for Anticoagulant Activity of Dabigatran

- Humanized Fab fragment
  - High-affinity binding specific to dabigatran
- Primarily renal excretion
- Short half-life
- No interaction with other drugs
- No intrinsic procoagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion
- Reduces dabigatran-induced bleeding in animal models
- Immediate, complete, and sustained reversal of dabigatran anticoagulation in volunteers


Schiele F, et al. *Blood*. 2013;121:3554-3562.
Glund S, et al. *Throm Haem*. 2015;113:943-951.

**NEWS…** Idarucizumab for Dabigatran Reversal

This article was published on June 22, 2015, at NEJM.org.

N Engl J Med 2015;373:511-20.
DOI: 10.1056/NEJMoa1502000

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

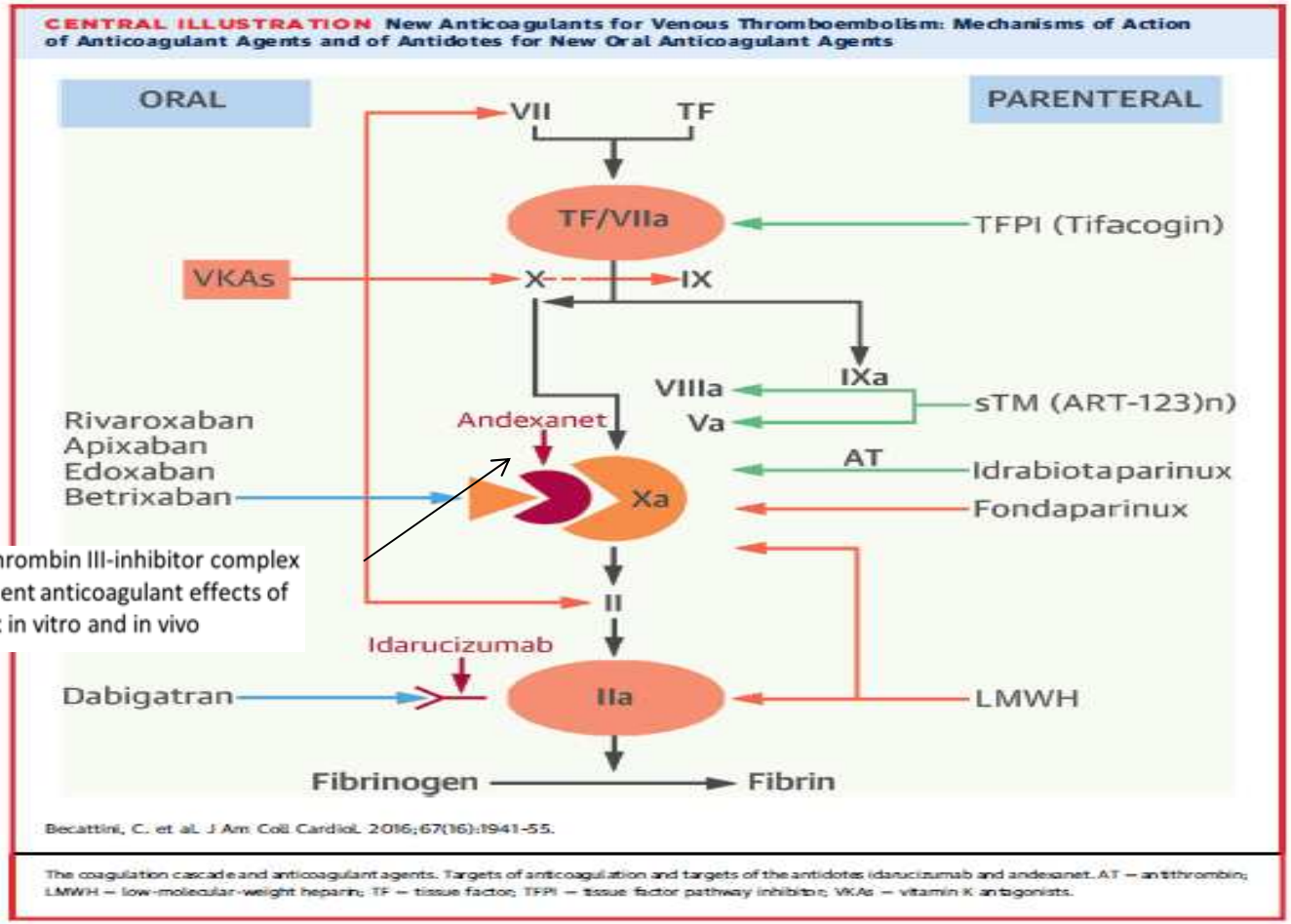
VOL. 67, NO. 16, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.01.072

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Treatment of Venous Thromboembolism With New Anticoagulant Agents

Cecilia Becattini, MD, PhD, Giancarlo Agnelli, MD




Retains high affinity for antithrombin III-inhibitor complex and can reverse ATIII-dependent anticoagulant effects of enoxaparin and fondaparinux in vitro and in vivo

# Ciraparantag


- Small synthetic molecule that binds to unfractionated heparin, LMWH, fondaparinux, dabigatran, and direct Xa inhibitor through hydrogen binding and charge-charge interaction
- Animal study: Seemed to reduce bleeding
- In volunteers: Reversed the effect of edoxaban
- Hypothesized to provide complete reversal of heparin, fondaparinux, dabigatran, rivaroxaban, apixaban, and edoxaban

Gomez-Outes, et al. *Recent Patients on Cardiovascular Drug Discovery.* 2014;9:2-10.

*Journal of Thrombosis and Haemostasis*, **14**: 623–627 DOI: 10.1111/jth.13227


**RECOMMENDATIONS AND GUIDELINES**

# When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

J. H. LEVY,* W. AGENO,† N. C. CHAN,‡ M. CROWTHER,§ P. VERHAMME¶ and J. I. WEITZ,§ FOR THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION

**Duke University School of Medicine, Durham, NC, USA; †University of Insubria, Varese, Italy; ‡Monash University, Clayton, Vic., Australia; §McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada; and ¶University of Leuven, Leuven, Belgium*

**To cite this article:** Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI, for the Subcommittee on Control of Anticoagulation. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016; **14**: 623–7.

**Table 1** Indications for use or non-use of the antidotes

| | |
|---|---|
| Indications for use | • Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage<br>• Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome<br>• Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose<br>• Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance<br>• Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery |
| Potential indication for use | • Need for urgent surgery or intervention in patients with acute renal failure |
| Antidotes should not be used | • Elective surgery<br>• Gastrointestinal bleeds that respond to supportive measures<br>• High drug levels or excessive anticoagulation without associated bleeding<br>• Need for surgery or intervention that can be delayed long enough to permit drug clearance |


GRAZIE