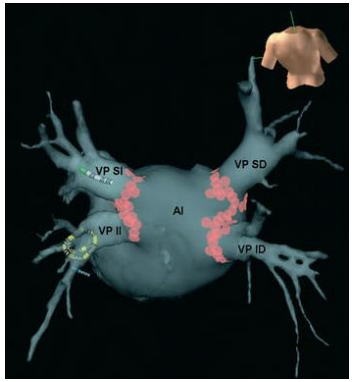
50 Congreso Sociedad Andaluza de Cardiología
"Congreso Andaluz de las Enfermedades Cardiovasculares"
14 – 16 mayo 2015
Hotel Abades Nevada Palace - Granada

# Novedades en anticoagulación oral en FANV

Dr. Pérez Cabeza

- NO VOY A HABLAR DE:

BAYER
X-VERT



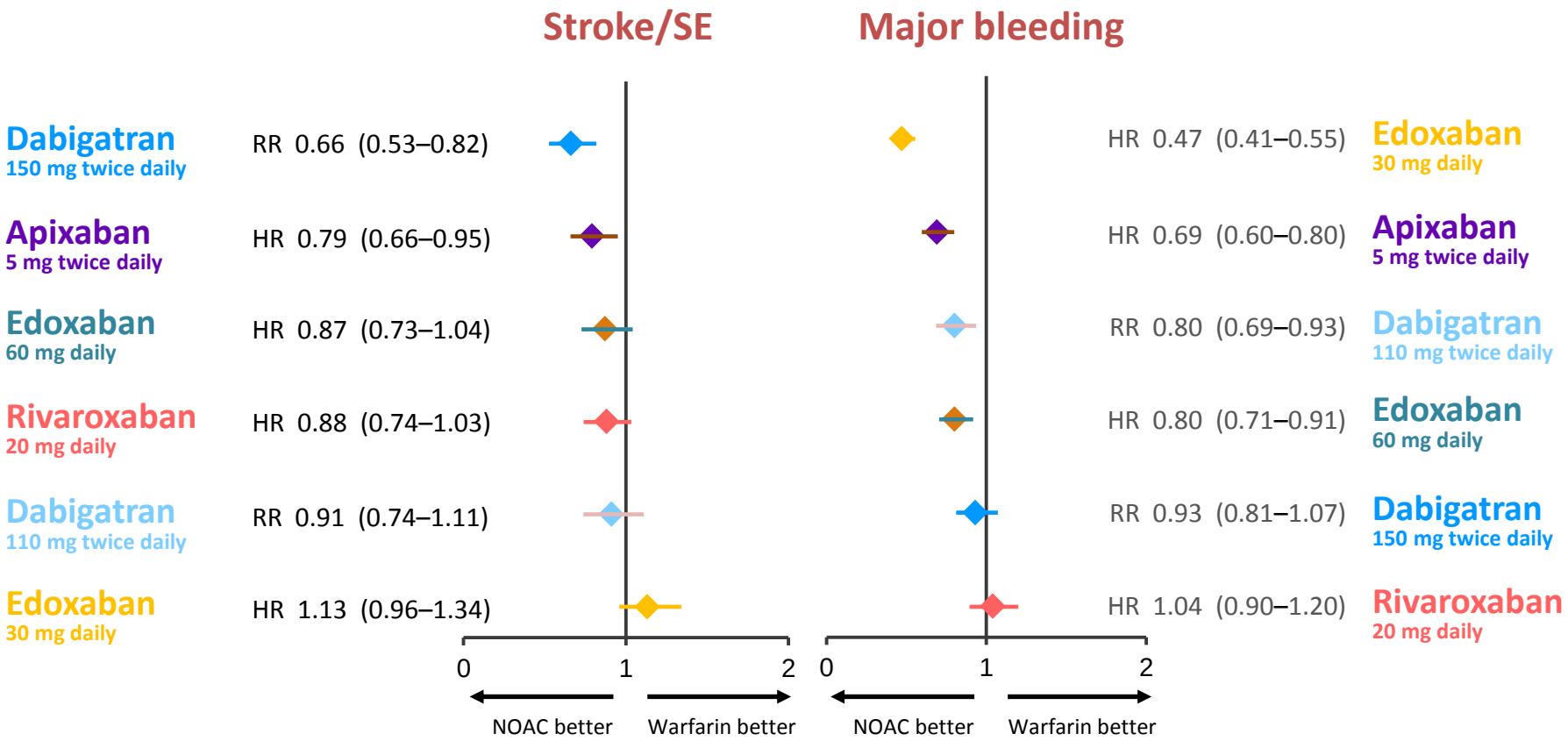

Mini-Sentinel

INFORME MEDICARE

Dresden NOAC registry

ADHERENCIA

CUMPLIMIENTO TERAPÉUTICO
+
PERSISTENCIA

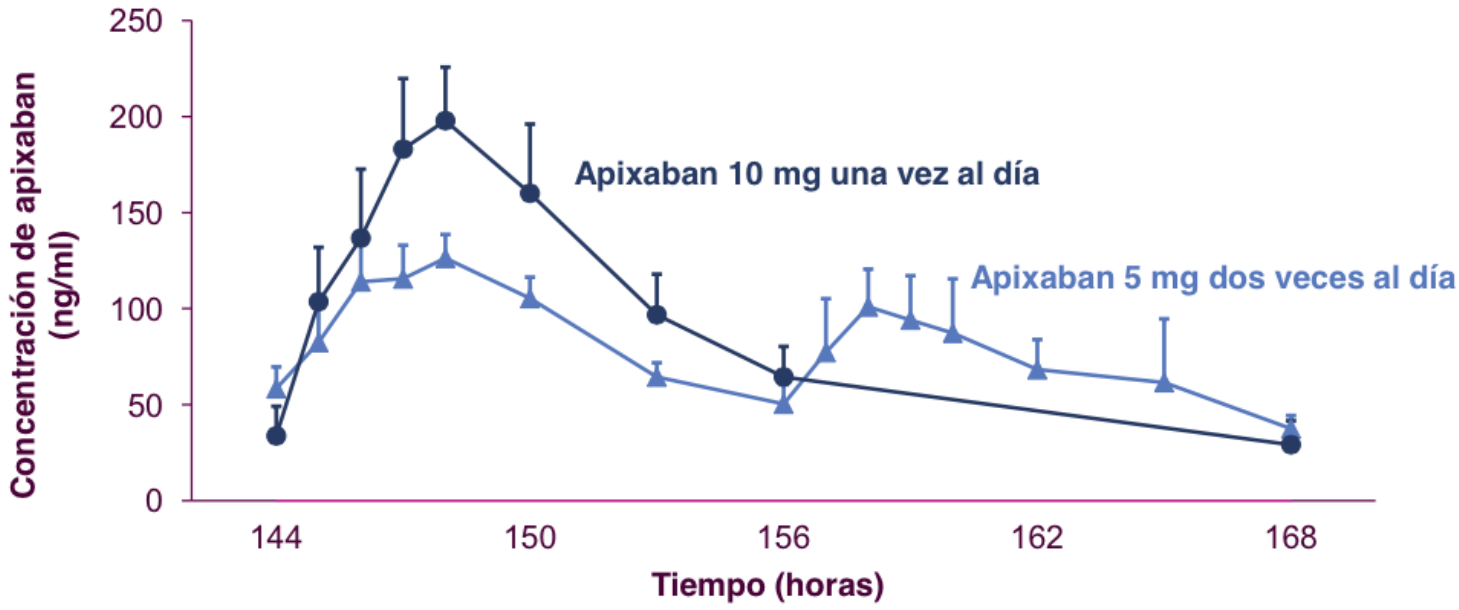


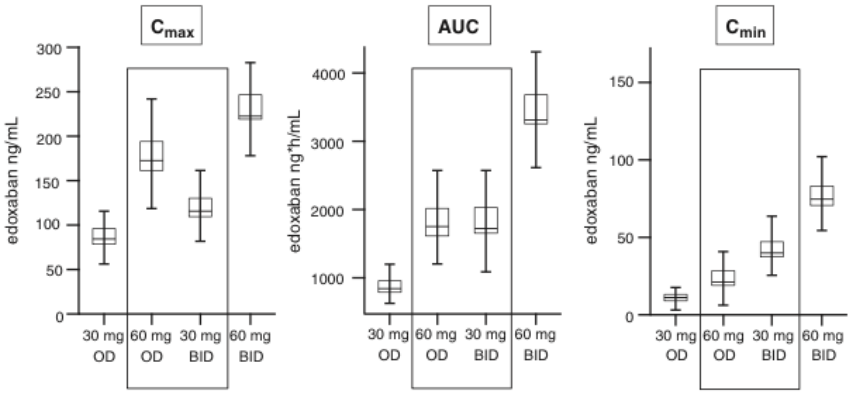

SE, systemic embolism; RR, risk ratio

Schulman *Thromb Haemost* 2014;111:575-82

¿Son comparables los NACOS en eficacia y seguridad?


## Concentración plasmática media después de dosis orales múltiples de apixaban



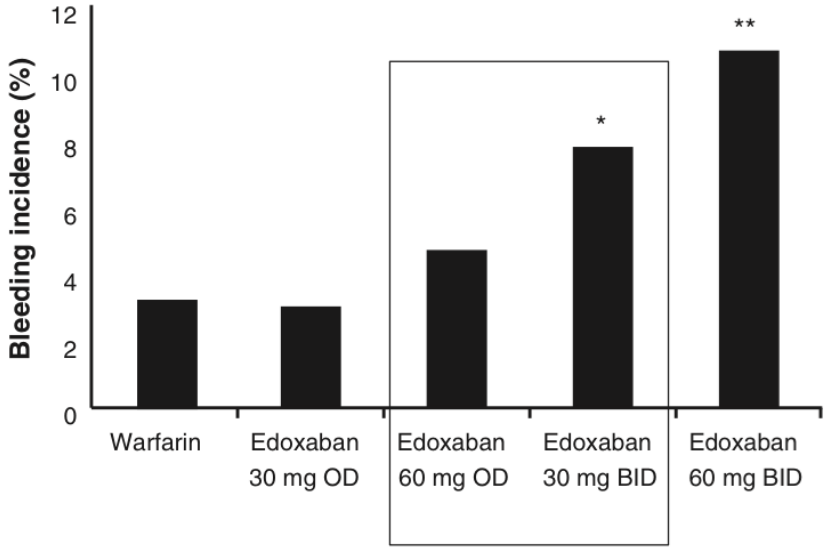




**Fig. 1.** Edoxaban Phase II dose finding study in atrial fibrillation: major and clinically relevant non-major bleeding events. Figure shows the bleeding incidence in patients with atrial fibrillation treated with edoxaban at different doses and dosing regimens. $^{*}p < 0.05$, $^{**}p < 0.01$, vs warfarin. OD = once daily; BID = twice daily. Modified from Weitz et al. [51].

[51] Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral Factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost 2010;104:633–41.

## Outcomes of Discontinuing Rivaroxaban Compared With Warfarin in Patients With Nonvalvular Atrial Fibrillation

Analysis From the ROCKET AF Trial

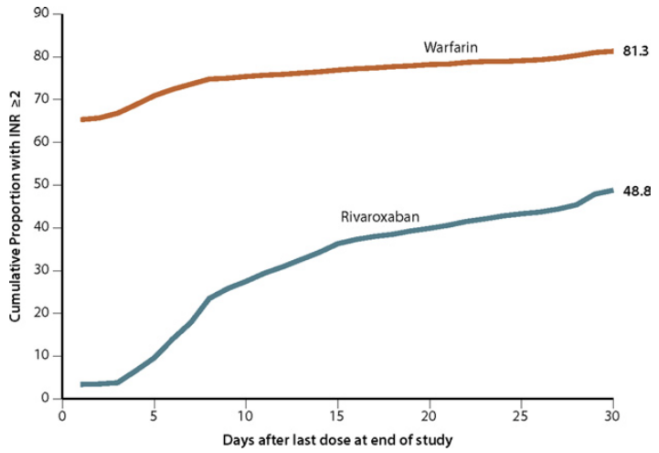



**Figure 2** Time to Therapeutic International Normalized Ratio

Cumulative proportion of patients with international normalized ratio (INR) of 2 or more after the end of the study for those treated with warfarin and rivaroxaban during the ROCKET AF study.

| | Eventos por 100 pac/año (total de eventos) | | Rivaroxaban: Warfarina HR (IC 95%) | p |
|---|---|---|---|---|
| | Rivaroxaban | Warfarina | | |
| ACV o embolia periférica | 6,42 (22) | 1,73 (6) | 3,72 (1,51-9,16) | 0,0044 |
| ACV, embolia periférica, IAM o muerte vascular | 9,05 (31) | 4,03 (14) | 2,24 (1,19-4,22) | 0,012 |
| Sangrado mayor | 7,29 (25) | 2,01 (7) | 3,62 (1,56-8,36) | 0,0026 |

JACC Vol. 61, No. 6, 2013
February 12, 2013:651–8

# Dabigatran dosed according to European Society of Cardiology Guidelines

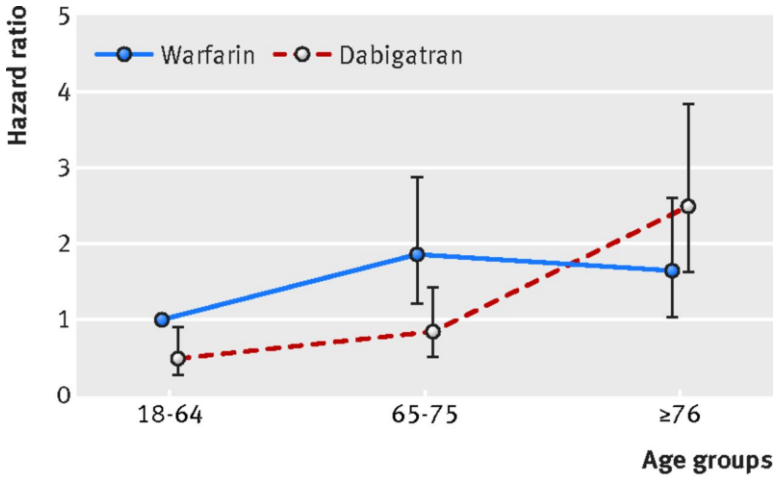
| Source | Comparison vs. VKA | Stroke/SE RR (95% CI) | Major Bleed RR (95% CI) | Mortality RR (95% CI) |
|---|---|---|---|---|
| ESC | Dabigatran | 0.74 (0.60-0.91) | 0.85 (0.73-0.98) | 0.86 (0.75-0.98) |
| RE-LY | Dabigatran 110 mg bid | 0.90 (0.74-1.10) | 0.80 (0.70-0.93) | 0.91 (0.80-1.03) |
| | Dabigatran 150 mg bid | 0.65 (0.52-0.81) | 0.93 (0.81-1.07) | 0.88 (0.77-1.00) |

Connolly SJ, et al. NEJM 2009; Lip GYY, et al. Presented at ESC 2013

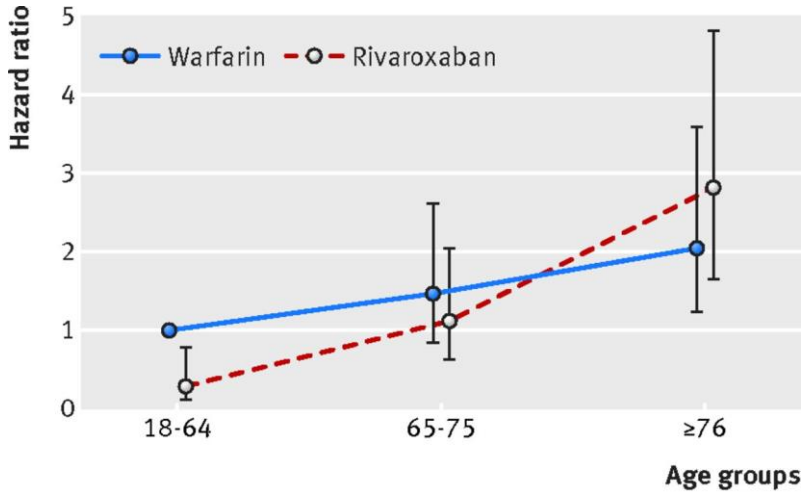
Sangrado extracraneal


# Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

Abraham NS et al. BMJ 2015;350:h1857



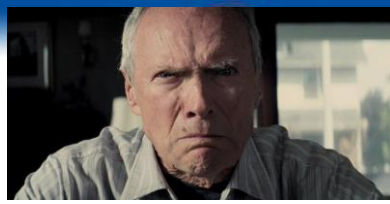

| | 18-64 | 65-75 | ≥76 |
|---|---|---|---|
| Warfarin | 3046 | 2635 | 2068 |
| Dabigatran | 3039 | 2647 | 2063 |




| | 18-64 | 65-75 | ≥76 |
|---|---|---|---|
| Warfarin | 1649 | 1908 | 1609 |
| Rivaroxaban | 1608 | 1976 | 1582 |

Patients younger than age of 65 have fewer gastrointestinal bleeding events when treated with novel anticoagulants compared with warfarin

However, the risk of gastrointestinal bleeding increases over the age of 65 and is particularly concerning for people aged over 75 years

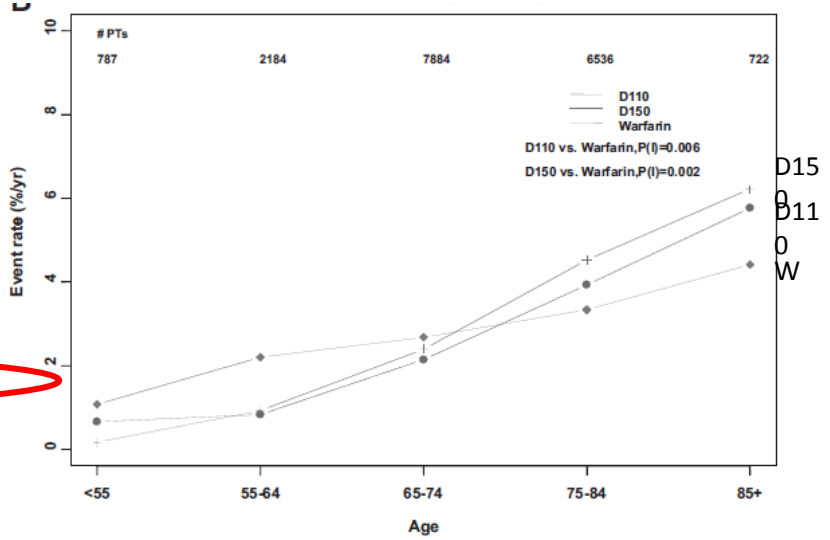


# Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

## An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

Sangrados extracraneales

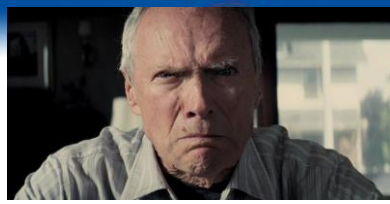

Risk of major bleeding with dabigatran versus warfarin




D15
0
D11
0
W

*Conclusions*—In patients with atrial fibrillation at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

(*Circulation*. 2011;123:2363-2372.)



# Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial

| | No. of patients | Apixaban *number of events (%/year)* | Warfarin | Hazard ratio (95% C I) | Interaction *P* value |
|---|---|---|---|---|---|
| Major bleeding (*n*=18 140) | | | | | 0.63* |
| Age <65 | 5455 | 56(1.17) | 72(1.51) | 0.78 (0.55, 1.11) | |
| Age 65 – <75 | 7030 | 120(1.99) | 166(2.82) | 0.71 (0.56, 0.89) | |
| Age ≥75 | 5655 | 151(3.33) | 224(5.19) | 0.64 (0.52, 0.79) | |
| All bleeding (*n*=18 140) | | | | | 0.94* |
| Age <65 | 5455 | 570(13.6) | 746(19.1) | 0.73 (0.65, 0.81) | |
| Age 65 – <75 | 7030 | 926(17.9) | 1196(25.9) | 0.70 (0.65, 0.77) | |
| Age ≥75 | 5655 | 860(23.5) | 1118(33.7) | 0.71 (0.65, 0.78) | |
| Intracranial bleeding (*n*=18 140) | | | | | 0.20* |
| Age <65 | 5455 | 15(0.31) | 17(0.35) | 0.87 (0.43, 1.74) | |
| Age 65 – <75 | 7030 | 17(0.28) | 48(0.81) | 0.35 (0.20, 0.60) | |
| Age ≥75 | 5655 | 20(0.43) | 57(1.29) | 0.34 (0.20, 0.57) | |
| Net clinical events (*n*=18 201) | | | | | 0.18* |
| Age <65 | 5471 | 228(4.51) | 218(4.29) | 1.05 (0.87, 1.26) | |
| Age 65 – <75 | 7052 | 340(5.27) | 426(6.71) | 0.79 (0.68, 0.91) | |
| Age ≥75 | 5678 | 441(8.91) | 524(10.9) | 0.82 (0.72, 0.93) | |

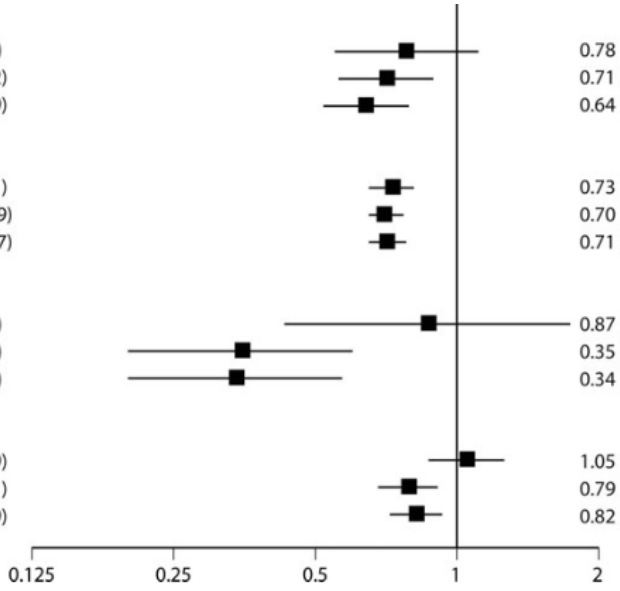
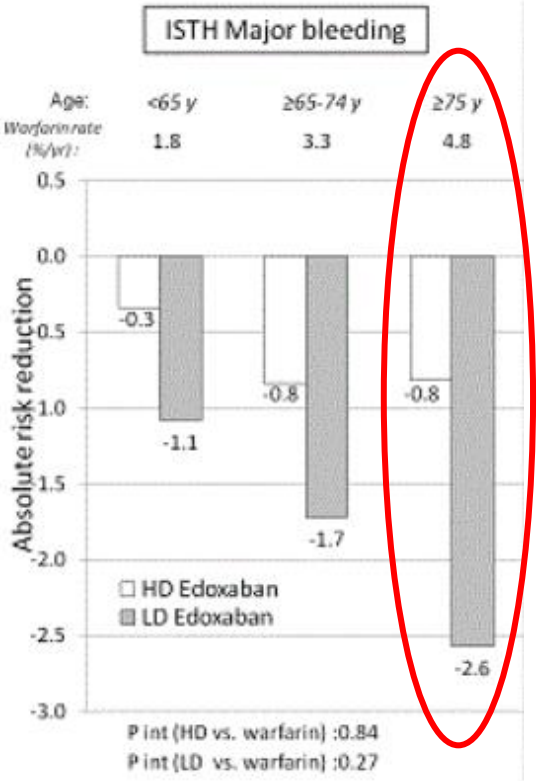



**Figure 2** The effect of apixaban vs. warfarin on major study outcomes according to age. *Interaction *P*-values are based on continuous age.

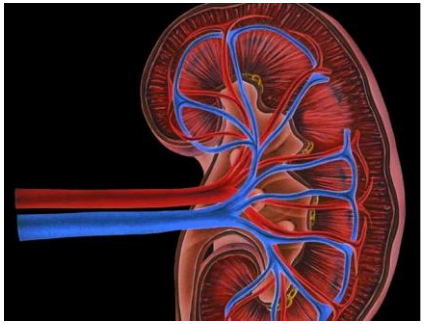
European Heart Journal
doi:10.1093/eurheartj/ehu046

# Abstract 16612

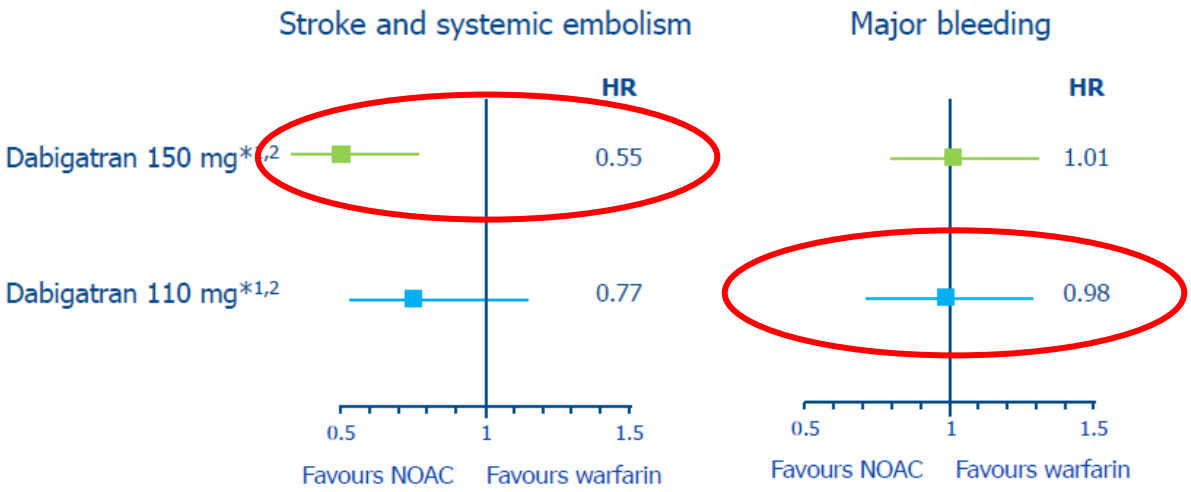



Circulation.
2014;130:A16612

# RE-LY –IRC MODERADA (CrCl 30-50 ml/min)



## Efficacy and safety profile of dabigatran demonstrated in patients with moderate renal impairment

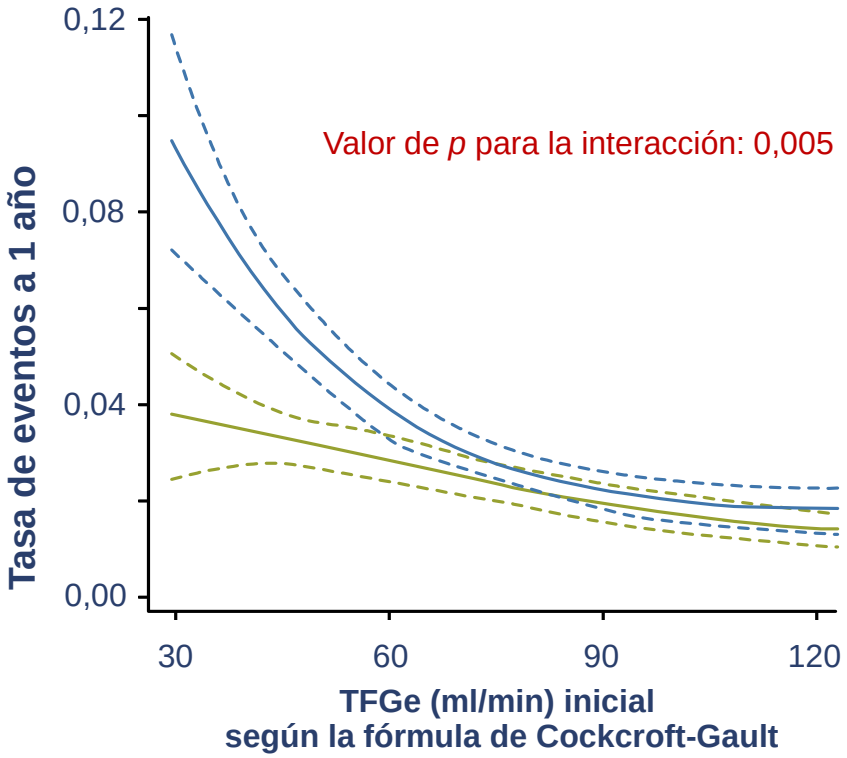


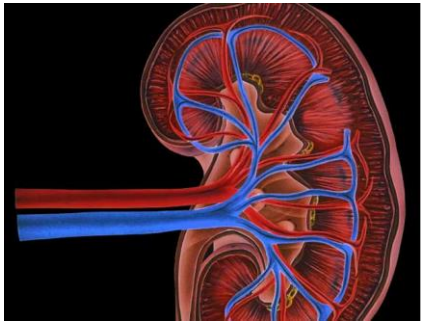

*Includes patients with CrCl <50 mL/min; error bars = 95% CI; GFR=glomerular filtration rate

1. Connolly S et al. N Engl J Med 2009; 361:1139–51; **2.** Eikelboom J et al. Circulation 2011;123:2363–72;
**3.** Böhm M et al. Presented at ESC 2014

# ARISTOTLE: ANALISIS SEGUN TASA DE FILTRADO GLOMERULAR

## Sangrado mayor



| | Apixaban | Warfarina | Hazard ratio (IC del 95%) |
|---|---|---|---|
| | % anual (n.º de eventos) | | |
| Sangrado mayor | | | |
| TFGe > 80 ml/min[1] | 1,46% (96) | 1,84% (119) | |
| TFGe > 50 a 80 ml/min[2] | 2,45% (157) | 3,21% (199) | |
| TFGe ≤ 50 ml/min[3] | 3,21% (73) | 6,44% (142) | |

Traducido de Hohnloser *et al. Eur Heart J* 2012; e-published August 29; doi:10.1093/eurheartj/ehs274.

# The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

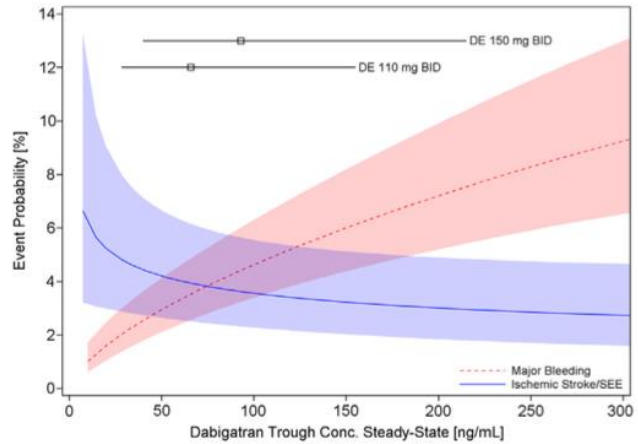



**Figure 2** **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles.
Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).

**Table 2** **Dose-Normalized Plasma Concentrations (ng/ml/mg) of Dabigatran According to Demographic Characteristics in the RE-LY Trial**

| Characteristic | Measure | Subgroup 1 | Subgroup 2 | Subgroup 3 | Subgroup 4 |
|---|---|---|---|---|---|
| Sex | | Male (n = 5,524) | Female (n = 2,925) | | |
| | gMean | 0.727 | 0.942 | — | — |
| | gCV, % | 78.2 | 69.3 | — | — |
| | Median | 0.736 | 0.967 | — | — |
| | P10 | 0.324 | 0.419 | — | — |
| | P90 | 1.7 | 2.21 | — | — |
| Age, yrs | | <65 (n = 1,466) | 65 to <75 (n = 3,787) | ≥75 (n = 3,196) | |
| | gMean | 0.586 | 0.749 | 0.982 | — |
| | gCV, % | 86 | 75.2 | 76 | — |
| | Median | 0.595 | 0.761 | 0.994 | — |
| | P10 | 0.241 | 0.341 | 0.45 | — |
| | P90 | 1.43 | 1.69 | 2.22 | — |
| Weight, kg | | <50 (n = 163) | 50 to <100 (n = 6,852) | ≥100 (n = 1,433) | |
| | gMean | 0.998 | 0.824 | 0.652 | — |
| | gCV, % | 83.8 | 80.6 | 77.1 | — |
| | Median | 1.01 | 0.84 | 0.66 | — |
| | P10 | 0.41 | 0.365 | 0.281 | — |
| | P90 | 2.63 | 1.94 | 1.56 | — |
| CrCl, ml/min | | <30 (n = 18) | 30 to <50 (n = 1,512) | 50 to <80 (n = 3,937) | ≥80 (n = 2,690) |
| | gMean | 1.87 | 1.29 | 0.828 | 0.564 |
| | gCV, % | 51.9 | 78 | 71.7 | 70.2 |
| | Median | 2.11 | 1.33 | 0.857 | 0.582 |
| | P10 | 0.905 | 0.601 | 0.395 | 0.262 |
| | P90 | 3.16 | 2.83 | 1.77 | 1.2 |

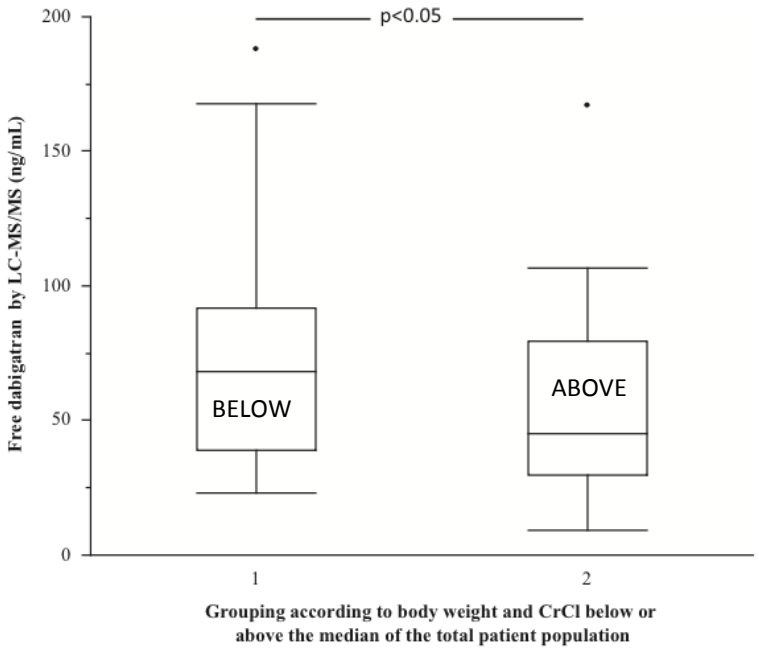
# El problema de la monitorización

- Situaciones clínicas:

A) Cirugía urgente
B) Ictus isquémico (dosis infraterapéutica, ineficacia, olvido?).
C) Tratamiento con fibrinolisis

- Dosificación en situaciones especiales

# On the monitoring of dabigatran treatment in "real life" patients with atrial fibrillation




Skeppholm et al. Thrombosis Research 134 (2014) 783-789

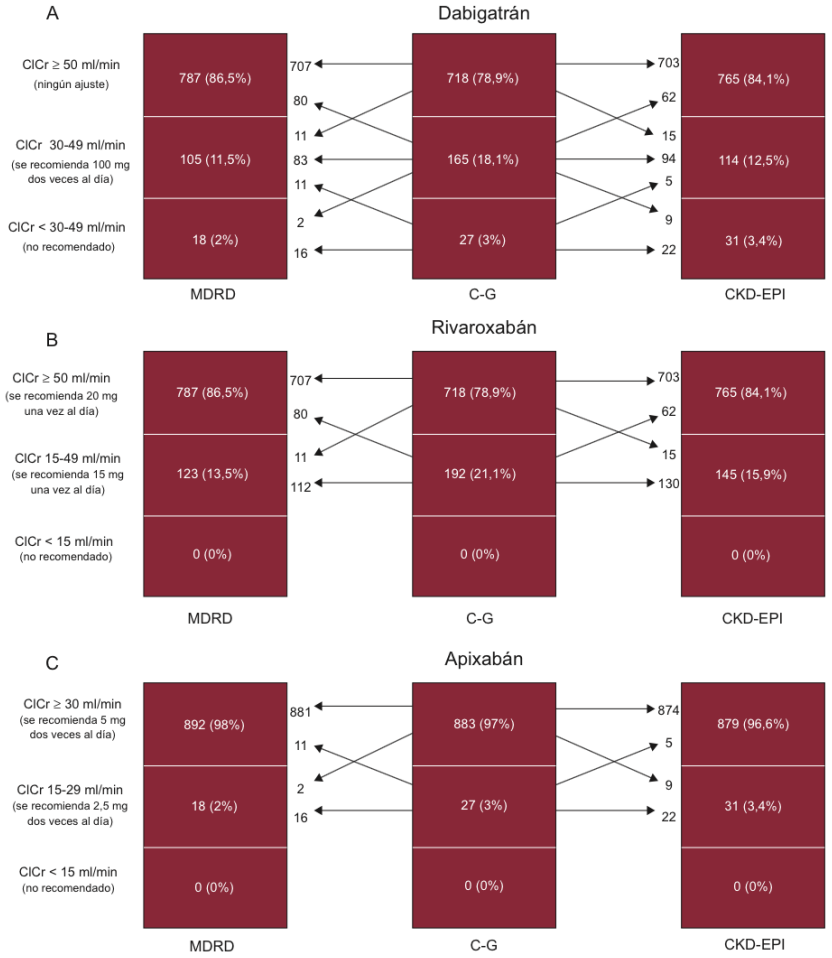



**Figura 2.** Discrepancias en la posología de los nuevos anticoagulantes orales en función de las ecuaciones utilizadas para calcular el filtrado glomerular estimado. C-G: Cockcroft-Gault; CKD-EPI: *Chronic Kidney Disease Epidemiology Collaboration;* ClCr: aclaramiento de creatinina; MDRD: *Modification of Diet in Renal Disease.*

Comparación de las ecuaciones de filtrado glomerular estimado para determinar la posología de los nuevos anticoagulantes orales para pacientes con fibrilación auricular

Sergio Manzano-Fernández[a], José M. Andreu-Cayuelas[a], Francisco Marín[a], Esteban Orenes-Piñero[a], Pilar Gallego[b], Mariano Valdés[a], Vicente Vicente[c], Gregory Y.H. Lip[d,*] y Vanessa Roldán[c]

Rev Esp Cardiol. 2014

-Discrepancia en las posología según la ecuación de FG empleada.

-Especialmente en ancianos con IRC.

-Mayor discrepancia para dabigatrán y rivaroxabán, con posología más alta con MDRD y CKD-EPI.

| | 1ª ELECCION |
|---|---|
| ALTO RIESGO TROMBOEMBOLICO<br>BAJO RIESGO HEMORRAGICO | D150 |
| ALTO RIESGO TROMBOEMBOLICO<br>ALTO RIESGO HEMORRAGICO | APIXABAN |
| RIESGO TROMBOEMBOLICO MODERADO | APIXABAN<br>D110<br>EDOXABAN |
| INSUFICIENCIA RENAL CRONICA<br>BAJO RIESGO HEMORRAGICO | APIXABAN<br>RIVAROXABAN 15<br>¿D150? |
| INSUFICIENCIA RENAL CRONICA<br>+/-<br>ALTO RIESGO HEMORRAGICO<br>+/-<br>ANCIANO | APIXABAN<br>EDOXABAN 30 o 15 |
| CONVENIENCIA/ADHERENCIA | EDOXABAN<br>RIVAROXABAN |
| ANTECEDENTE O ALTO RIESGO<br>SANGRADO GASTROINTESTINAL | APIXABAN<br>EDOXABAN 30/15<br>D110 |
| ANCIANOS | APIXABAN<br>EDOXABAN |

¿HAY QUE TENER MIEDO A LOS SANGRADOS CON ANTICOAGULANTES ORALES DIRECTOS?

**Table 3** Characteristics of Major Extracranial Hemorrhage

| | Overall (n = 18,140) | Apixaban (n = 9088) | Warfarin (n = 9052) | Apixaban vs. Warfarin HR (95% CI) | p Value* |
|---|---|---|---|---|---|
| Led to hospitalization | 1.23 (374) | 1.05 (162) | 1.41 (212) | 0.75 (0.61–0.92) | 0.0052 |
| Fall in hemoglobin ≥2 g/dl | 1.25 (381) | 1.06 (164) | 1.44 (217) | 0.74 (0.60–0.91) | 0.0035 |
| Led to transfusion | 1.06 (325) | 0.89 (137) | 1.25 (188) | 0.71 (0.57–0.89) | 0.0025 |
| Required medical or surgical consultation | 1.74 (527) | 1.54 (236) | 1.94 (291) | 0.79 (0.67–0.94) | 0.0080 |
| Required medical or surgical intervention to stop | 0.77 (236) | 0.65 (100) | 0.90 (136) | 0.72 (0.56–0.93) | 0.012 |
| Associated with hemodynamic compromise | 0.32 (97) | 0.26 (40) | 0.38 (57) | 0.69 (0.46–1.029) | 0.069 |
| Caused changed in antithrombotic therapy | 1.31 (398) | 1.14 (176) | 1.47 (222) | 0.78 (0.64–0.95) | 0.012 |

Values are rate (per 100 patient-years of follow-up) (number of events). *p values compare apixaban to warfarin rates of bleeding.

## Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

(J Am Coll Cardiol 2014;63:2141–7)

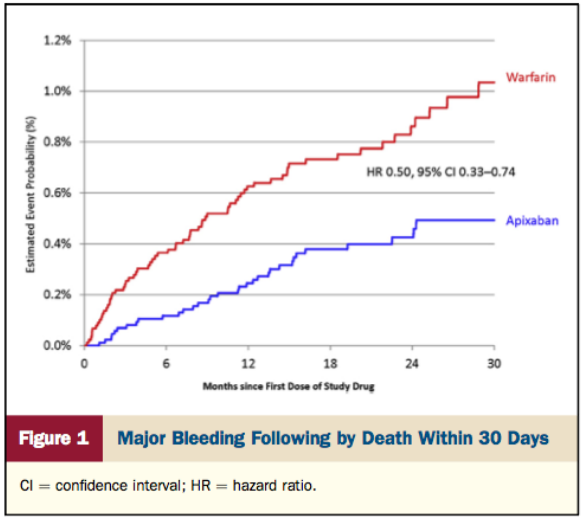
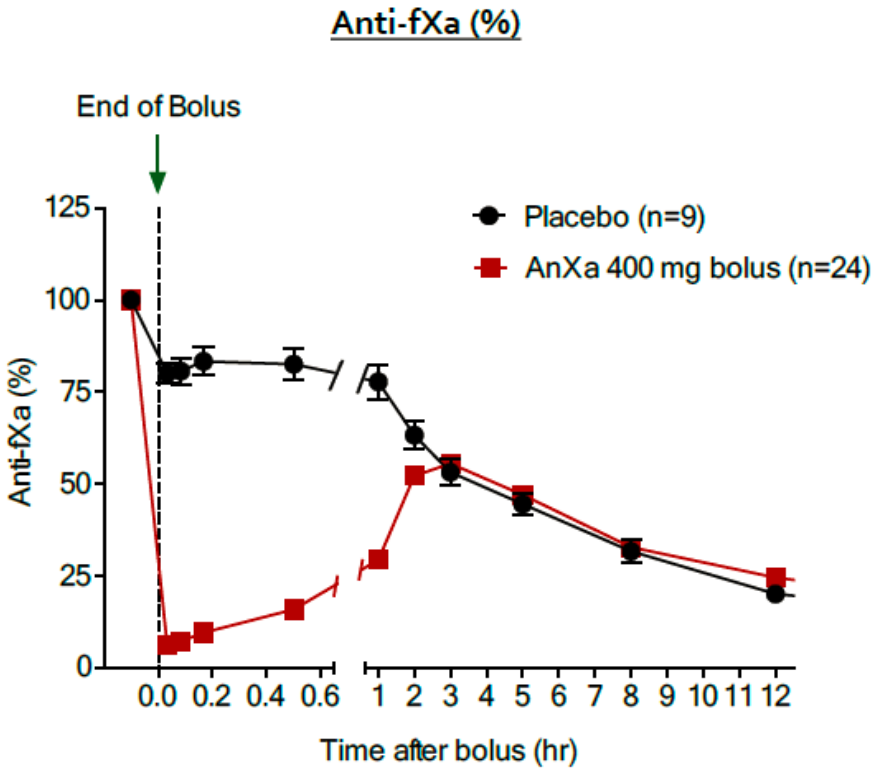



**Figure 1** Major Bleeding Following by Death Within 30 Days

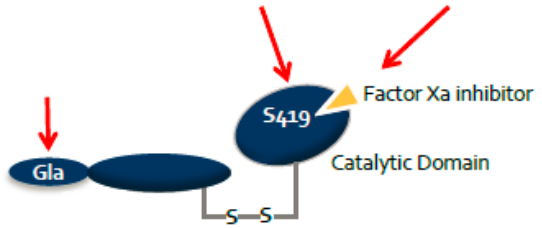
CI = confidence interval; HR = hazard ratio.

# ANNEXA™-A (Apixaban, Part I) Primary Endpoint: Anti-fXa

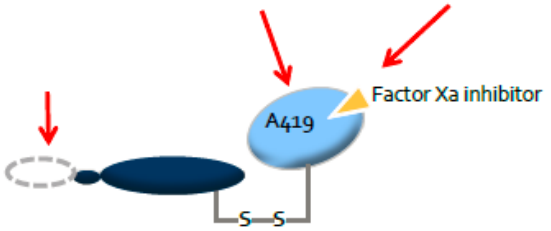
PORTOLA PHARMACEUTICALS




**Versión recombinante de Factor Xa humano**

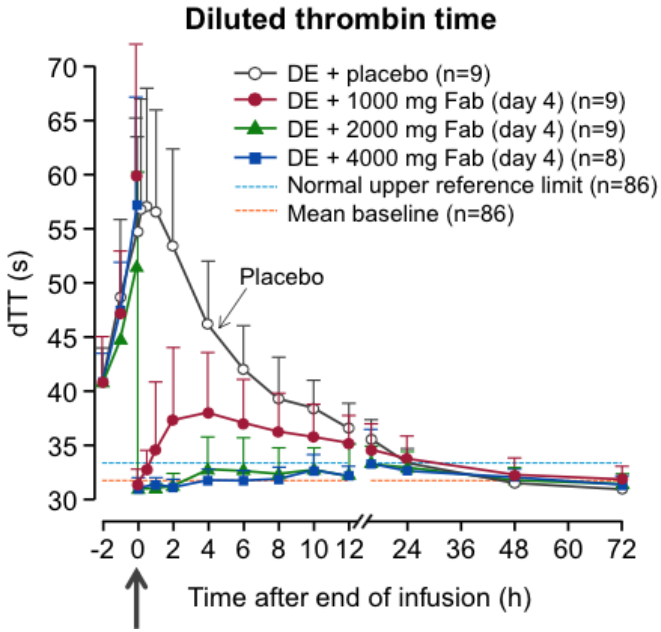


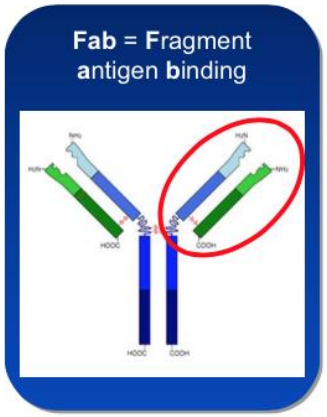

Factor Xa

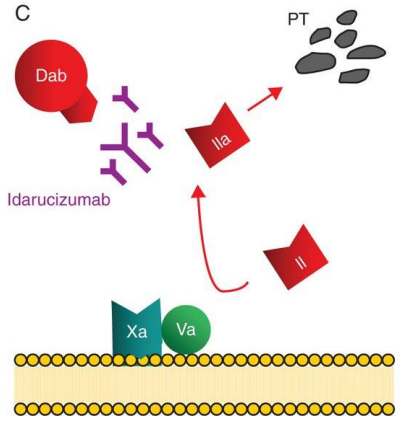



Andexanet

# *Idarucizumab*




- Fab was well tolerated and showed a positive safety profile, both alone and in combination with dabigatran

## Concentrados de complejo protrombínico

**Tabla 1** Concentrados del complejo protrombínico

| | Beriplex | Octaplex | Protromplex |
|---|---|---|---|
| FII (UI/ml) | 20-48 | 11-38 | 30 |
| FVII (UI/ml) | 10-25 | 9-24 | 25 |
| FIX (UI/ml) | 20-31 | 25 | 30 |
| FX (UI/ml) | 22-60 | 18-30 | 30 |
| PC (UI/ml) | 15-45 | 7-31 | > 20 |
| AT (UI/ml) | 0,2-1,5 | ND | 0,75-1,15 |
| Heparina (UI/ml) | 0,4-2,0 | 5-12,5 | > 15 |
| Inactivación por eliminación | Pasteurización, nanofiltración | Solvente/detergente, nanofiltración | Calor a presión, nanofiltración |
| Trasvasador | Mix 2 Vial | *Set* de transferencia estándar | *Set* de transferencia estándar |
| Velocidad de infusión | 8,4 ml/min (210 UI/min) | 3 ml/min (75 UI/min) | 1 ml/min |
| Conservación | < 25 °C | < 25 °C | +2 a +8 °C |
| Validez | 3 años | 2 años | 3 años |

## Concentrado de complejo protrombínico activado

| FEIBA |
|---|
| Factor II de la coagulación, humano |
| Factor IX de la coagulación, humano |
| Factor X de la coagulación, humano |
| Factor VII activado |
| Antígeno del factor VIII coagulante |

## PLASMA FRESCO CONGELADO

-Contiene cantidades normales de todos los factores de la coagulación.
-Se administra en grandes volúmenes.
-Precisa descongelación previa.
-Precisa compatibilidad ABO.
-No es útil para revertir el efecto anticoagulante de los NACO.

Table 3: Summary of animal and human data for reversal of dabigatran, rivaroxaban, and apixaban using factor concentrates.

| | Dabigatran | | Rivaroxaban | | Apixaban | |
|---|---|---|---|---|---|---|
| | Animal | Human | Animal | Human | Animal | Human |
| 3-factor PCC | | Case report +/− | | | | |
| 4-factor PCC | Rats +/−<br>Rabbits +<br>Mice −<br>Mice ICH + | In vitro +<br>In vivo −<br>Case report − | Rats +<br>Rabbits +/− | In vitro +/−<br>In vivo + | | In vitro +<br>In vivo + |
| aPCC | Rats +/−<br>Mice − | In vitro + | Rat +<br>Primate + | In vitro + | | In vitro + |
| rfVIIa | Rats +/−<br>Mice +/−<br>Mice ICH − | In vitro +<br>Case report +/− | Rat +<br>Rabbits +/−<br>Primate +/− | In vitro +/− | | In vitro + |

+: effective; −: ineffective; +/−: mixed results between studies or between coagulation testing and bleeding outcomes; PCC: prothrombin complex concentrate; aPCC: activated prothrombin complex concentrate; rfVIIa: recombinant factor VIIa.

# Dresden NOAC registry

**Table 3. Severity and management strategies of rivaroxaban-related bleeding complications in the as-treated population**

| 1082 bleeding events in 762 patients | Conservative (no treatment/ compression/tamponade/transfusion) | Surgery or intervention | RBC | Vitamin K | FFP | PCC | rFVII |
|---|---|---|---|---|---|---|---|
| Minor 637/1082 (58.9%) | 637/637 (100.0) | 0 | 0 | 0 | 0 | 0 | 0 |
| NMCR 379/1082 (35.0%) | 328/379 (86.5) | 51/379 (13.5) | 0 | 0 | 0 | 0 | 0 |
| Major 66/1082 (6.1%) | 41/66 (62.1) | 25/66 (37.9) | 40/66 (60.6) | 1/66 (1.5) | 6/66 (9.1) | 6/66 (9.1) | 0 |
| Total | 1006/1082 (93.0) | 76/1082 (7.0) | 40/1082 (3.7) | 1/1082 (0.1) | 6/1082 (0.6) | 6/1082 (0.6) | 0 |

rFVII, recombinant factor VII; vitamin K, vitamin K supplementation.

Rivaroxaban: Tasa de mortalidad tras sangrado mayor a los 30 días: 5.1%

AVK: Tasa de mortalidad tras sangrado mayor en registros previos: 13-18%

Treatment of major rivaroxaban bleeding is simple and rarely requires pro-coagulants; outcome at 90 days is better than that reported for vitamin K antagonists.

# Coming soon…


University Medical Center Groningen
Vascular Medicine

# The first patient trial of a NOAC-specific antidote

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

Clinical practice study to evaluate reversal of the anticoagulant effects of dabigatran with idarucizumab in

- **Bleeding patients** – overt bleeding judged by the physician to require a reversal agent
- **Surgical patients** – require an emergency surgery or procedure for a condition other than bleeding

**Started in April 2014**

**Currently recruiting in >35 countries worldwide**

**The antidote is still under investigation and has not yet been approved for clinical use**



umcg

NCT02104947: Available at http://www.clinicaltrials.gov/ct2/show/NCT02104947; Accessed August 2014

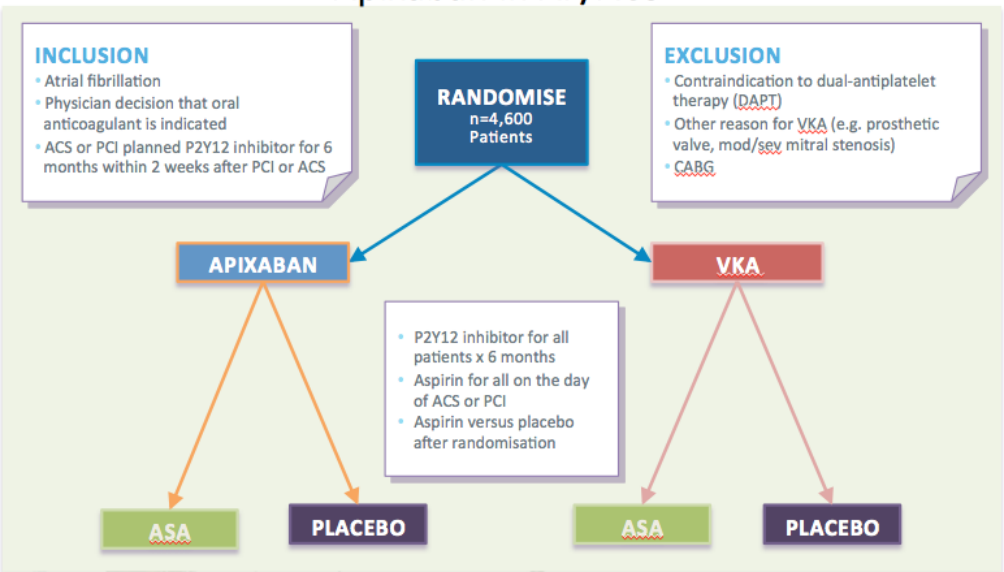
# RE-DUAL PCI™ (*)

Study in NVAF patients undergoing PCI

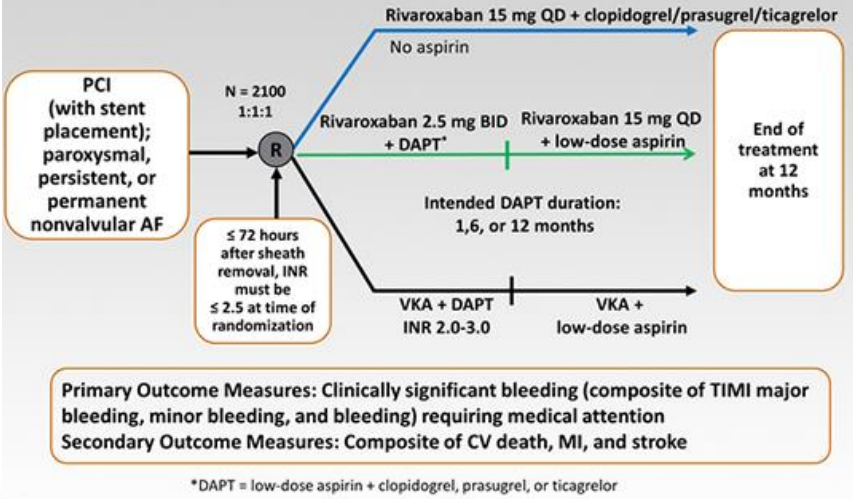
**8.454 PACIENTES** | **15 CENTROS EN ESPAÑA**

Estudio multicéntrico e internacional para evaluar la eficacia y seguridad de Pradaxa® en **8.454 pacientes con FANV** que han sido sometidos a una intervención coronaria percutánea (PCI), con colocación de stent. Se comparará **dabigatrán 150 o 110 mg bid + clopidogrel** frente a **W + ASA + clopidogrel**. Se llevará a cabo en unos 200 pacientes de **15 centros de España**.

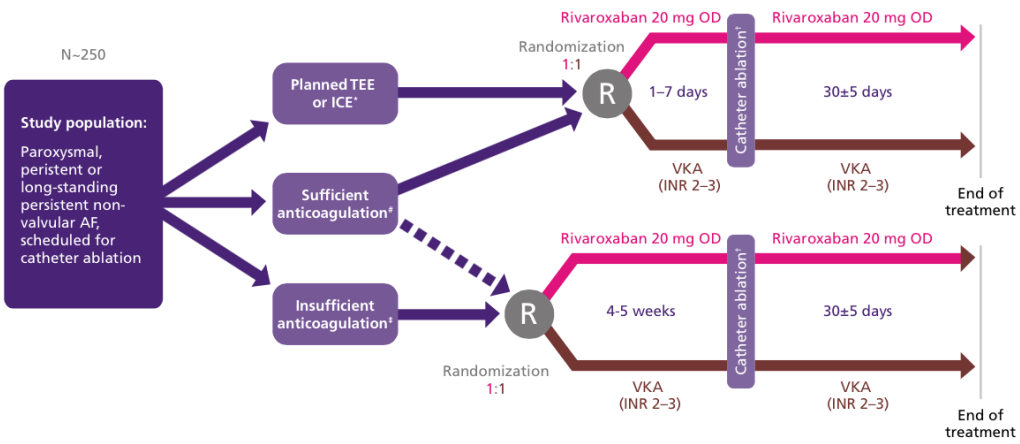
## Apixaban in AF/ACS

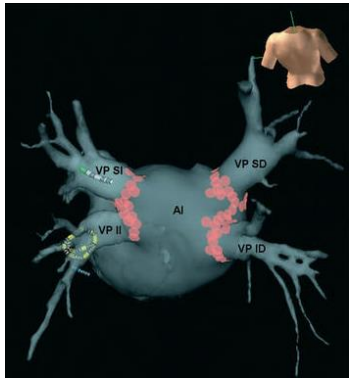



## PIONEER AF-PCI




## VENTURE AF

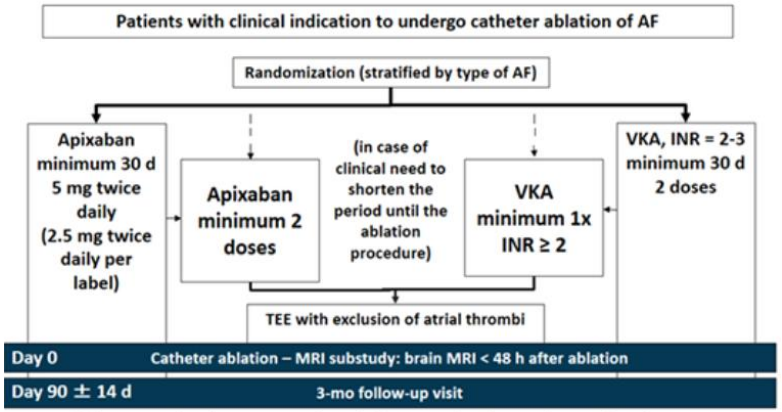



## RE-CIRCUIT®

Study of peri-procedural anticoagulation in AF ablation

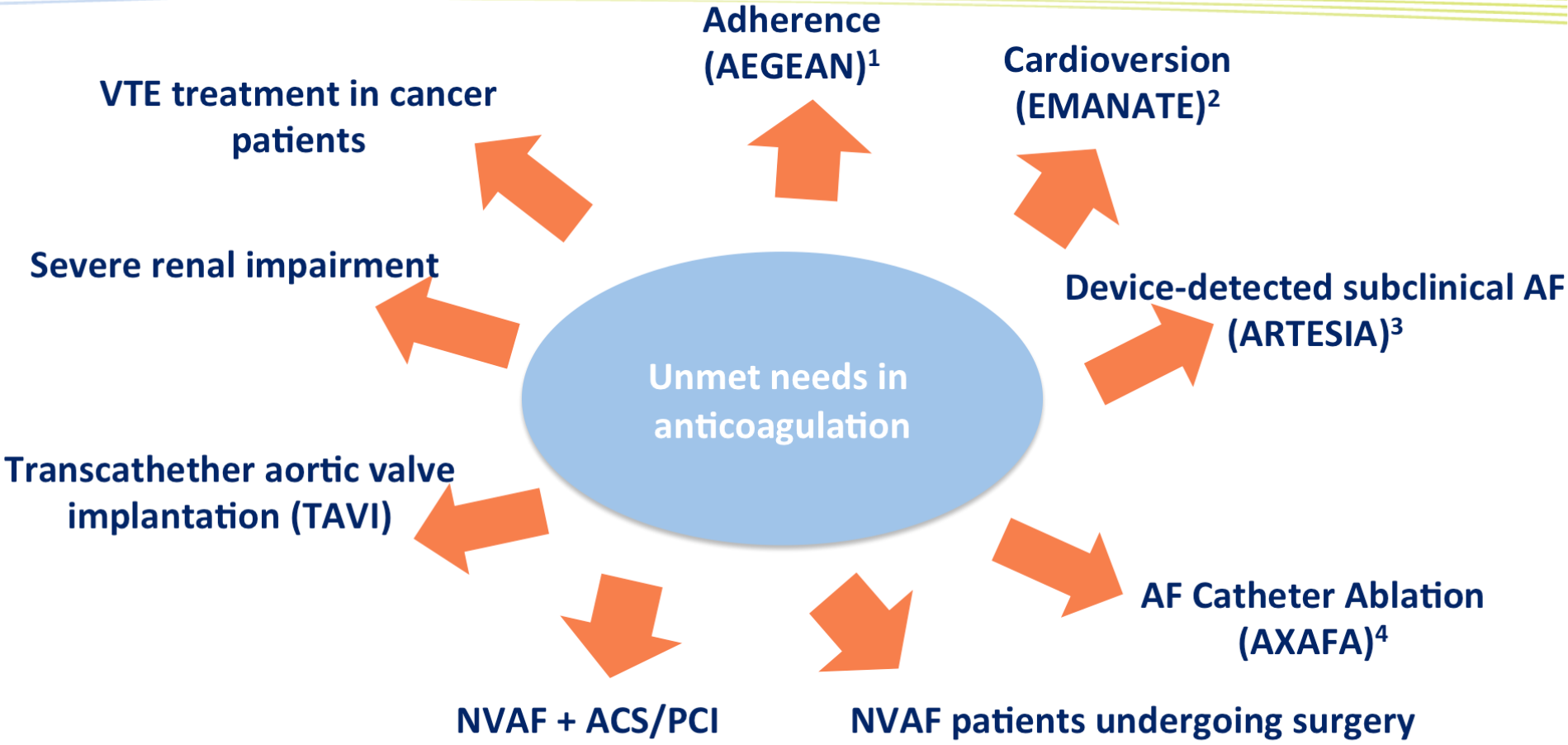
## AXAFA: *Apixaban*




- Primary end point: composite of all-cause death, stroke, and major bleeding events (Bleeding Academic Research Consortium type 2 or higher)

ClinicalTrials.org. NCT02227550.[14]

# Key areas of interest in cardiology and VTE for the BMS/Pfizer alliance




*ACS: acute coronary syndrome ; PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation*

- 1. Assessment of an Education and Guidance Programme for Eliquis Adherence in Non-Valvular Atrial Fibrillation NCT01884350 2. A Phase IV Trial To Assess The Effectiveness Of Apixaban Compared With Usual Care Anticoagulation In Subjects With Non-Valvular Atrial Fibrillation Undergoing Cardioversion NCT02100228; 3. Apixaban for the Reduction of Thrombo-Embolism Due to Sub-Clinical Atrial Fibrillation NCT01938248; 4. Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy (AXAFA) NCT02227550.

# Conclusiones

- No es posible la comparación directa de los Anticoagulantes orales directos (ACOD).
- Como grupo presentan una eficacia al menos similar a la warfarina, con un perfil de seguridad mayor.
- Hay perfiles de pacientes (insuficiencia renal, ancianos…) en los que determinados ACOD han demostrado de forma más rotunda un beneficio clínico neto.
- Existen lagunas de conocimiento que motivan la puesta en marcha de nuevos estudios en la prevención de la enfermedad tromboembólica en FANV.