
**FRIDAY 27**

***LUNCHEON II | Sala PIEMONTE***

**Dabigatran: indications, patient and dose selection, clinical use**

*Chairmen: G. Pistis (Alessandria) - R. Riccardi (Pinerolo, To)*

# Use Safety: which dose for which patients?

Università di Torino

**M. BO - SCDU GERIATRIA e MMO**
**CITTA' DELLA SALUTE E DELLA SCIENZA**
**TORINO**

## CONFLITTO DI INTERESSI:

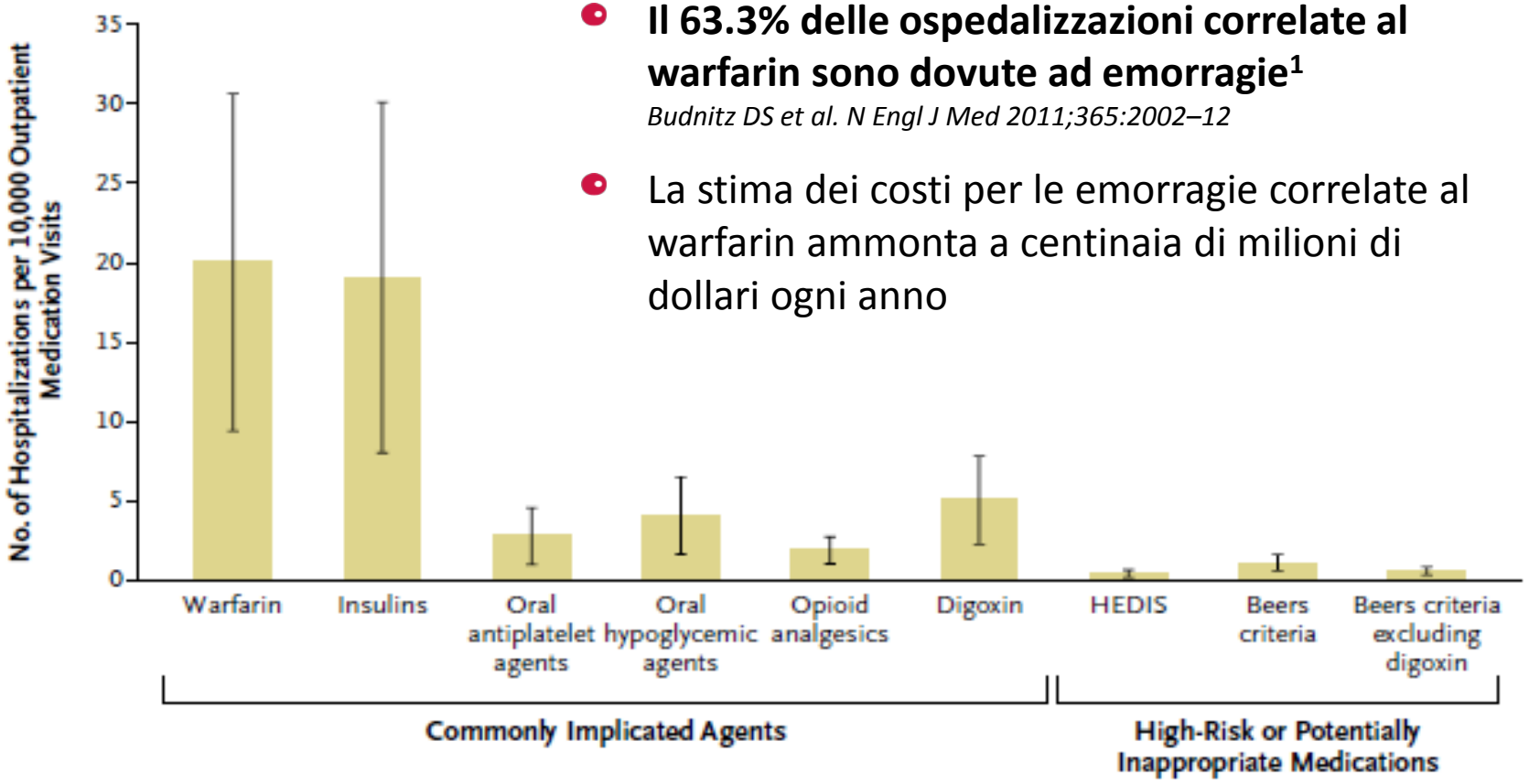
Onorari per relazioni scientifiche dalle seguenti aziende:
-Pfizer-BMS
-Astra Zeneca
-Boehringer Ingelheim
-Menarini
-Guidotti
-Sigma Tau
-MSD

Le diapositive di questa presentazione sono state preparate personalmente e la mia relazione non è influenzata da interessi economici

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2011;365:2002-12.

SPECIAL ARTICLE

# Emergency Hospitalizations for Adverse Drug Events in Older Americans




- **Il 63.3% delle ospedalizzazioni correlate al warfarin sono dovute ad emorragie[1]**
  *Budnitz DS et al. N Engl J Med 2011;365:2002–12*
- La stima dei costi per le emorragie correlate al warfarin ammonta a centinaia di milioni di dollari ogni anno

**Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.**

## Complicanze emorragiche da AVK - Emorragie intracraniche

**0.3%-1.0%** incidenza annuale di emorragie intracraniche in pazienti con FA trattati con AVK in studi clinici

**≈20%** di tutte le emorragie intracraniche primarie sono associate a trattamento anticoagulante orale

*Flaherty ML, Semin Neurol 2010; 30(5): 565-572*

**50%-90%** delle emorragie intracraniche si verificano con AVK in range INR tra 2 e 3

*Bechtel et al. International Journal of Emergency Medicine 2011, 4:40*

**46%-68%** mortalità associata ad emorragie intracraniche in pazienti trattati con anticoagulanti orali

*Hart RG et al. Stroke. 1995; 26: 1471-1477*

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2009;361.

# Dabigatran versus Warfarin in Patients with Atrial Fibrillation

**Table 3. Safety Outcomes, According to Treatment Group.***

| Event | Dabigatran, 110 mg | | Dabigatran, 150 mg | | Warfarin | | Dabigatran, 110 mg, vs. Warfarin | | Dabigatran, 150 mg, vs. Warfarin | | Dabigatran, 150 mg vs. 110 mg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Relative Risk (95% CI) | P Value | Relative Risk (95% CI) | P Value | Relative Risk (95% CI) | P Value |
| | *no. of patients* | % /yr | *no. of patients* | % /yr | *no. of patients* | % /yr | | | | | | |
| Major bleeding | 322 | **2.71%** | 375 | **3.11%** | 397 | **3.36%** | 0.80 (0.69–0.93) | 0.003 | 0.93 (0.81–1.07) | 0.31 | 1.16 (1.00–1.34) | 0.052 |
| Life threatening | 145 | 1.22 | 175 | 1.45 | 212 | 1.80 | 0.68 (0.55–0.83) | <0.001 | 0.81 (0.66–0.99) | 0.04 | 1.19 (0.96–1.49) | 0.11 |
| Non–life threatening | 198 | 1.66 | 226 | 1.88 | 208 | 1.76 | 0.94 (0.78–1.15) | 0.56 | 1.07 (0.89–1.29) | 0.47 | 1.14 (0.95–1.39) | 0.17 |
| Gastrointestinal† | 133 | 1.12 | 182 | **1.51%** | 120 | **1.02%** | 1.10 (0.86–1.41) | 0.43 | 1.50 (1.19–1.89) | <0.001 | 1.36 (1.09–1.70) | 0.007 |
| Minor bleeding | 1566 | 13.16 | 1787 | 14.84 | 1931 | 16.37 | 0.79 (0.74–0.84) | <0.001 | 0.91 (0.85–0.97) | 0.005 | 1.16 (1.08–1.24) | <0.001 |
| Major or minor bleeding | 1740 | 14.62 | 1977 | 16.42 | 2142 | 18.15 | 0.78 (0.74–0.83) | <0.001 | 0.91 (0.86–0.97) | 0.002 | 1.16 (1.09–1.23) | <0.001 |
| Intracranial bleeding | 27 | **0.23%** | 36 | **0. 30%** | 87 | **0.74%** | 0.31 (0.20–0.47) | <0.001 | 0.40 (0.27–0.60) | <0.001 | 1.32 (0.80–2.17) | 0.28 |
| Extracranial bleeding | 299 | | 342 | | 315 | | 0.94 (0.80–1.10) | 0.45 | 1.07 (0.92–1.25) | 0.38 | 1.14 (0.97–1.33) | 0.11 |
| Net clinical benefit outcome‡ | 844 | 7.09 | 832 | 6.91 | 901 | 7.64 | 0.92 (0.84–1.02) | 0.10 | 0.91 (0.82–1.00) | 0.04 | 0.98 (0.89–1.08) | 0.66 |

# RE-LY® sanguinamenti intracranici ed extracranici in relazione all'età

| | Incidenza annuale (%) | | | D110 BID vs. warfarin | | D150 BID vs. warfarin | |
|---|---|---|---|---|---|---|---|
| | D110 BID | D150 BID | Warfarin | RR (95% CI) | P value* | RR (95% CI) | P value* |
| **Sanguinamento intracranico** | | | | | | | |
| <75 anni | 0.14 | 0.26 | 0.61 | 0.22 (0.11–0.45) | | 0.43 (0.25–0.74) | |
| ≥75 anni | 0.37 | 0.41 | 1.00 | 0.37 (0.21–0.64) | 0.28 | 0.42 (0.25–0.70) | 0.91 |
| **Sanguinamento extracranico** | | | | | | | |
| <75 anni | 1.76 | 1.91 | 2.44 | 0.72 (0.57–0.90) | | 0.78 (0.63–0.98) | |
| ≥75 anni | 4.10 | 4.68 | 3.44 | 1.20 (0.97–1.48) | 0.001 | 1.39 (1.13–1.70) | <0.001 |

**Si osserva un beneficio del Dabigatran in termini di sanguinamenti intracranici a tutte le età, mentre il beneficio nei confronti dei sanguinamenti extracranici è limitato ai pazienti di età <75 anni.**

*Eikelboom JW et al. Circulation 2011;123:2362–72*

# Intracranial Hemorrhage in Atrial Fibrillation Patients During Anticoagulation With Warfarin or Dabigatran

## The RE-LY Trial

(*Stroke*. 2012;43:1511-1517.)

***Background and Purpos*** associated with differe
***Methods***—Analysis of 18 therapY (RE-LY) trial mg or 110 mg, both t
***Results***—During a mean intracerebral (49% m intracranial hemorrhag and dabigatran 110 m hemorrhages occurred warfarin (n=32; *P*<( dabigatran (11 patient warfarin). Independen aspirin use (relative ris attack (relative risk, 1

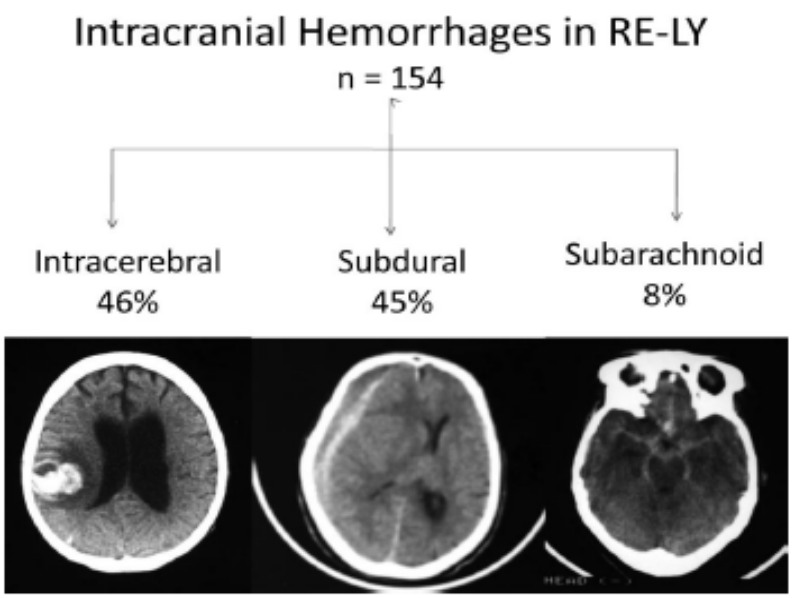



**Figure.** Sites of intracranial bleeding.

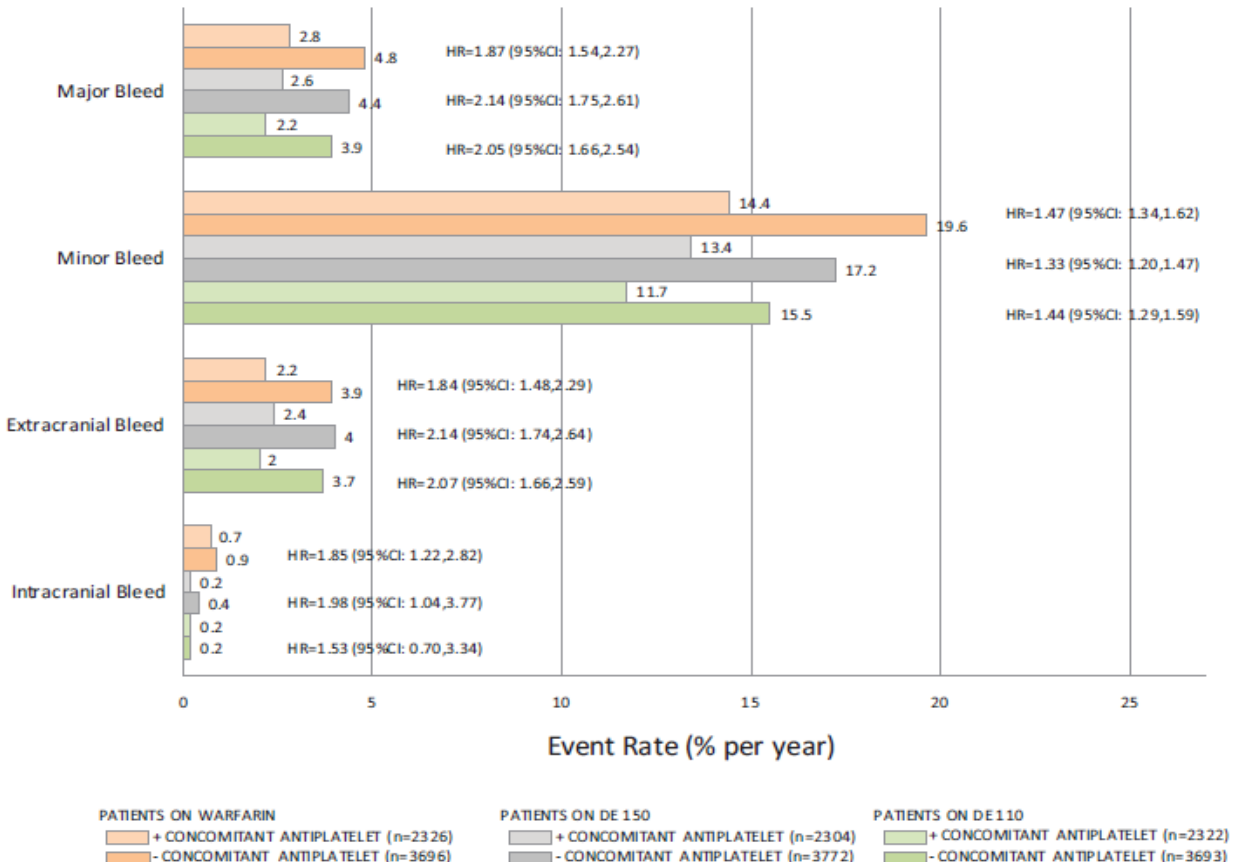
complication of anticoagulation. Outcomes in versus dabigatran have not been defined. ized Evaluation of Long-term anticoagulant al normalized ratio, 2–3) or dabigatran (150

rhages occurred in 153 participants: 46% barachnoid (31% mortality). The rates of se assigned to warfarin, dabigatran 150 mg, versus warfarin). Fewer fatal intracranial mg (n=13 and n=11, respectively) versus rhages occurred among those assigned to s; *P*<0.05 for both dabigatran doses versus nt to warfarin (relative risk, 2.9; *P*<0.001), 001), and previous stroke/transient ischemic

***Conclusioni-*** Lo spettro clinico di emorragie intracraniche era simile nei pazienti che ricevevano Dabigatran e Warfarin. **L'incidenza assoluta** di tutti gli **eventi emorragici** fatali e traumatici era **minore con il Dabigatran** rispetto al Warfarin. L'assunzione concomitante di aspirina era il più importante fattore di rischio indipendente modificabile per l'emorragia intracranica

(*Circulation*. 2013;127: 634-640.)

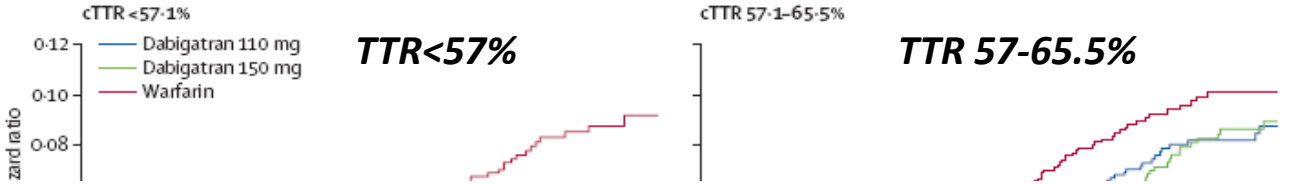
## Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial




***Conclusioni*- L'assunzione concomitante di farmaci antipiastrinici aumenta il rischio di sanguinamenti maggiori senza modificare il vantaggio del Dabigatran** rispetto al Warfarin. La scelta della dose di 110 o 150 mg richiede un'attenta valutazione del bilancio rischio-beneficio

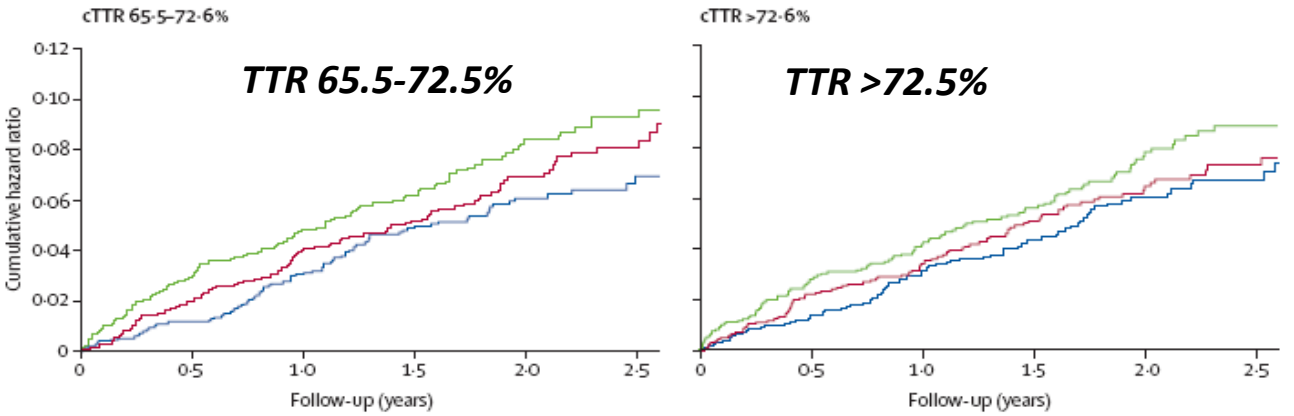
# Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lancet 2010; 376: 975–83




**Interpretation** The benefits of 150 mg dabigatran at reducing stroke, 110 mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. For all vascular events, non-haemorrhagic events, and mortality, advantages of dabigatran were greater at sites with poor INR control than at those with good INR control. Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabigatran 150 mg | 1509 | 1448 | 1399 | 1135 | 680 | 276 | 1526 | 1467 | 1416 | 1160 | 774 | 377 |
| Warfarin | 1504 | 1430 | 1371 | 1065 | 614 | 231 | 1514 | 1460 | 1403 | 1140 | 729 | 333 |




| Number at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabigatran 110 mg | 1474 | 1445 | 1392 | 1108 | 736 | 364 | 1482 | 1438 | 1385 | 1087 | 706 | 336 |
| Dabigatran 150 mg | 1484 | 1415 | 1372 | 1105 | 715 | 343 | 1514 | 1455 | 1399 | 1109 | 716 | 350 |
| Warfarin | 1487 | 1445 | 1398 | 1121 | 725 | 344 | 1509 | 1452 | 1411 | 1129 | 714 | 354 |

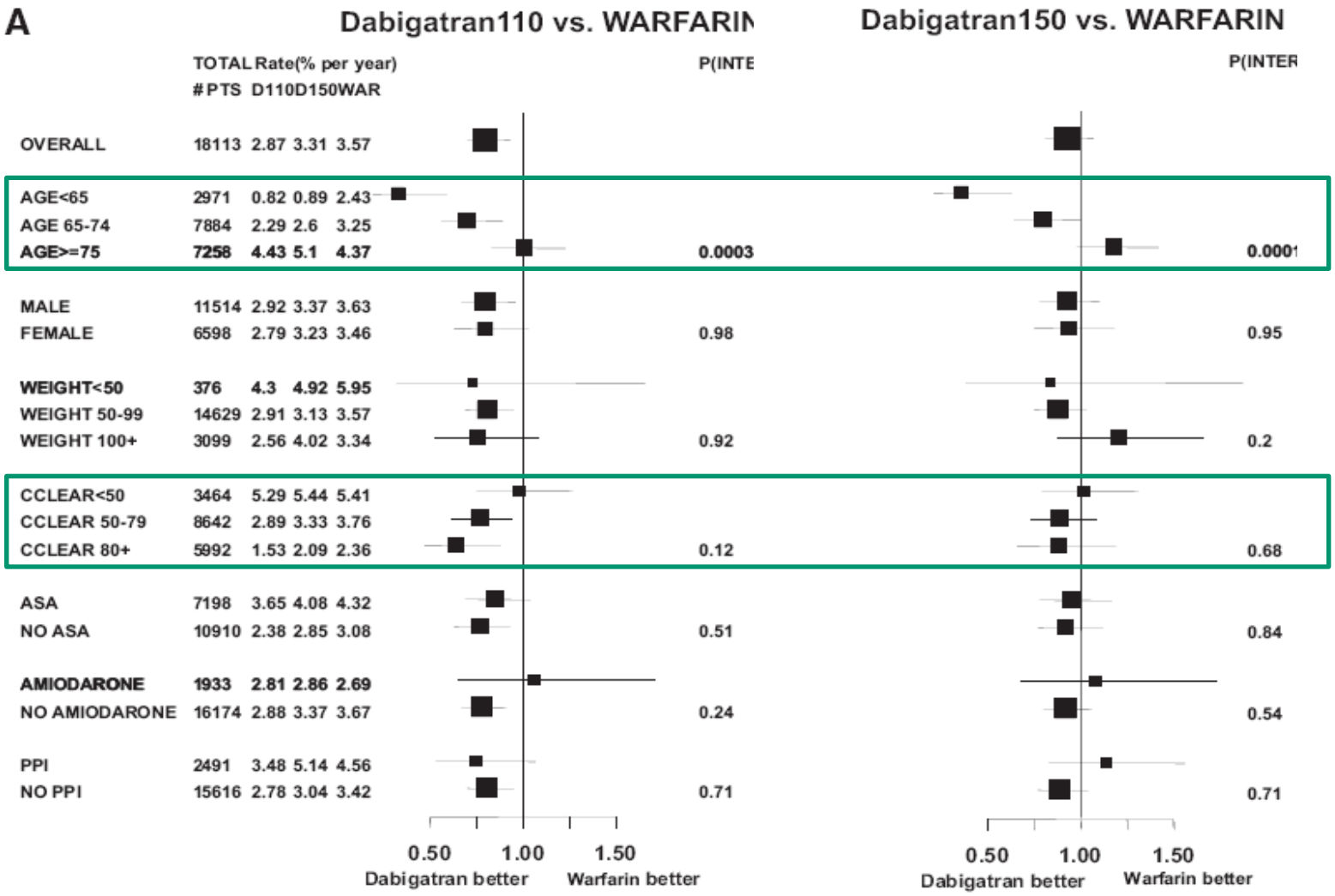
***Time to major bleeding event in each quartile of center's mean time in therapeutic range***

**Health Services and Outcomes Research**

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

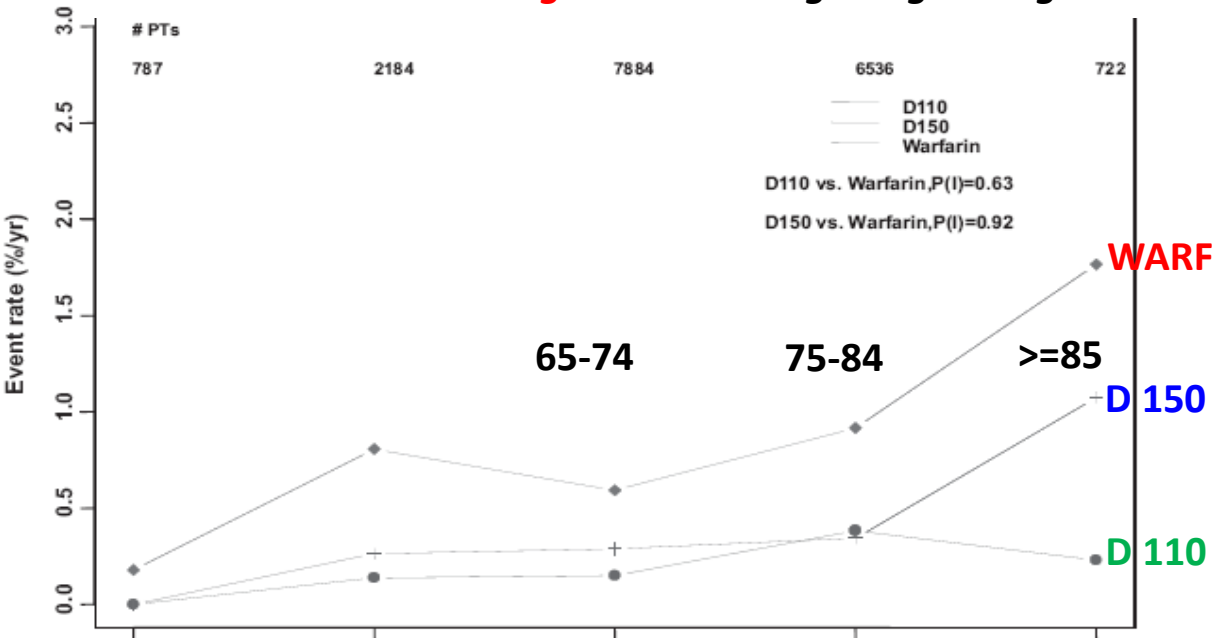
# Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

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

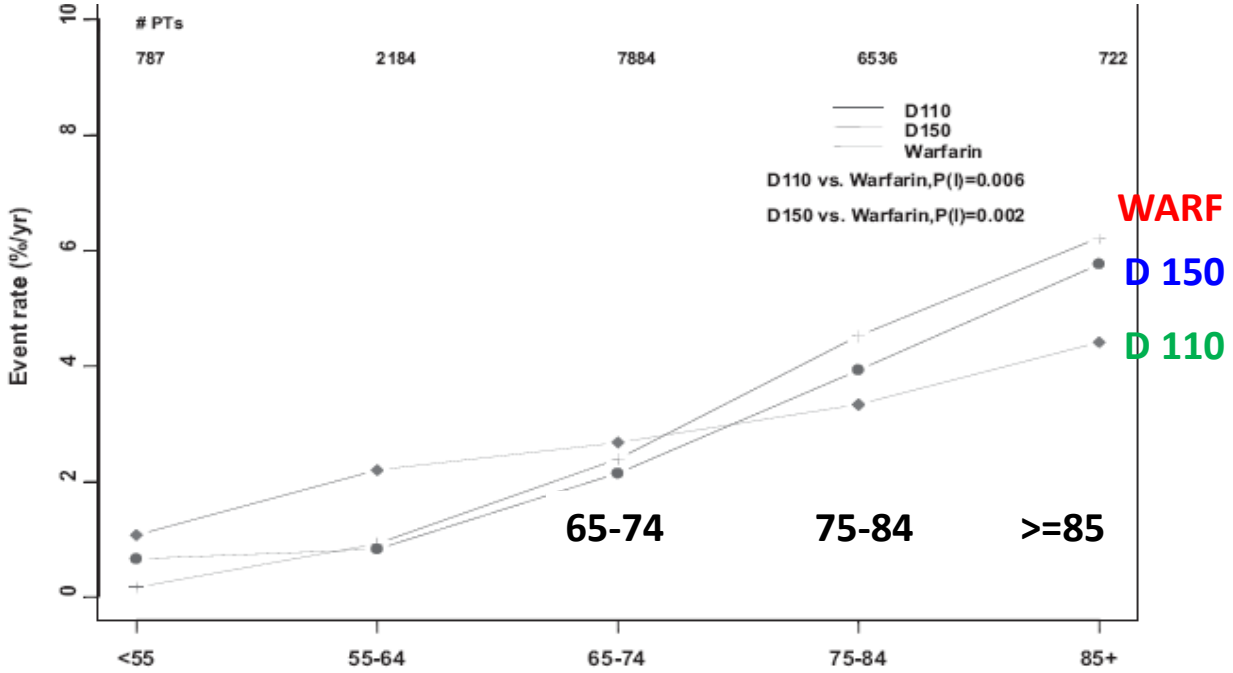



**OVERALL MAJOR BLEEDING**

**A** ***RELY: intracranial bleeding rate according to age categories***




**B** ***RELY: extracranial major bleeding rate according to age categories***



**Health Services and Outcomes Research**

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

# 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

Entrambe le dosi di Dabigatran forniscono sostanziali benefici in termini di sicurezza rispetto al warfarin, con un minor rischio di emorragie maggiori (intra e extra craniche) nei pazienti al di sotto di 75 anni…
Nei pazienti ultrasettantacinquenni entrambe le dosi di Dabigatran si associano ad una minor incidenza di sanguinamenti intracranici e ad un'incidenza simile o maggiore di sanguinamenti extracranici …

# Very elderly subgroup analysis: baseline characteristics

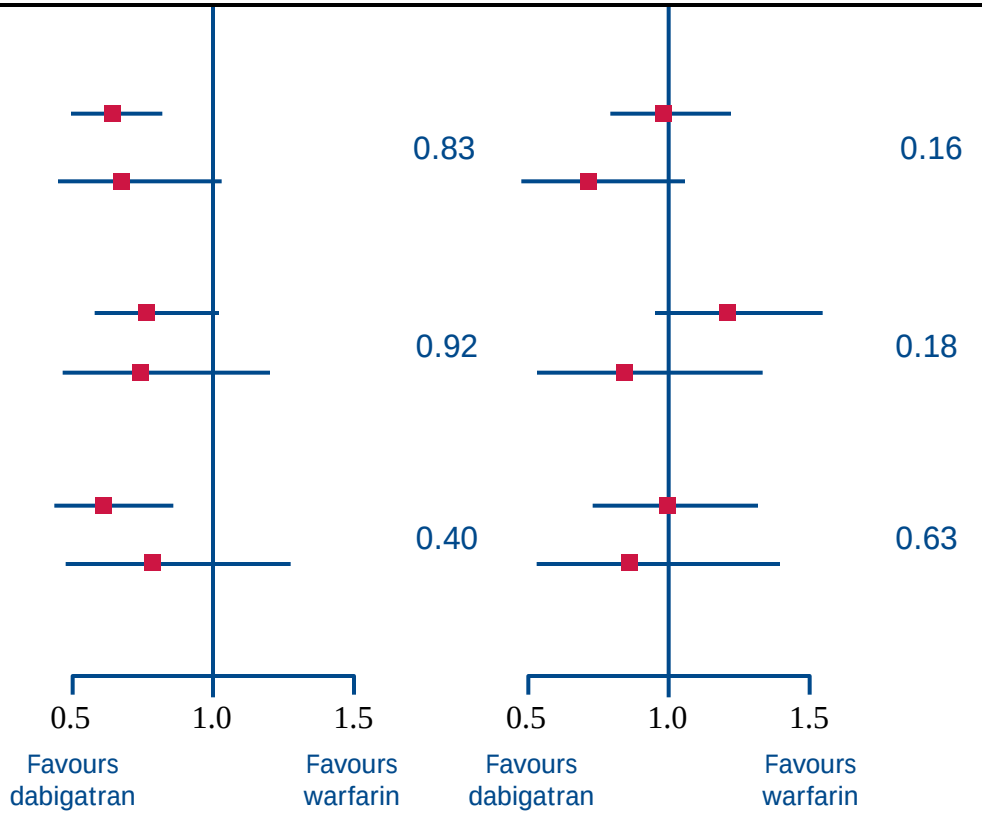
**RE-LY® included very elderly patients: 3027 ≥80 yrs, 722 ≥85 yrs, and 79 ≥90 yrs**

| Baseline characteristic | <80 years (n=15 086) | ≥80 years (n=3027) | P value |
|---|---|---|---|
| Body weight, kg, mean | 84.2 | 75.3 | <0.001 |
| eGFR, mL/min, mean | 77.1 | 52.6 | <0.001 |
| eGFR 30–50 mL/min, % | 14 | 50 | |
| Co-medications, % | | | |
| Anti-platelet (ASA or clopidogrel) | 41 | 43 | 0.24 |
| NSAID | 6 | 7 | 0.21 |
| Amiodarone | 11 | 8 | <0.001 |
| Verapamil or diltiazem | 12 | 15 | <0.001 |
| PPI | 12 | 19 | <0.001 |
| $CHADS_2$ score, mean | 2.1 | 2.6 | <0.001 |
| Stroke risk factors, % | | | |
| CHF | 33 | 27 | <0.001 |
| Hypertension | 80 | 76 | <0.001 |
| Diabetes | 24 | 18 | <0.001 |
| Prior stroke/TIA | 20 | 20 | 0.44 |
| Coronary artery disease | 28 | 29 | 0.20 |
| Peripheral arterial disease | 4 | 5 | <0.001 |

*Coppens M et al. Circulation 2012;126:A15537*

# Very elderly subgroup analysis: efficacy outcomes

| | D150 | D110 | VKA | D150 vs VKA | P value* | D110 vs VKA | P value* |
|---|---|---|---|---|---|---|---|
| **Stroke or non-CNS systemic embolism** | | | | | | | |
| <80 yrs | 0.97 | 1.48 | 1.52 | | 0.83 | | 0.16 |
| ≥80 yrs | 1.83 | 1.87 | 2.70 | | | | |
| **Ischaemic or unspecified stroke** | | | | | | | |
| <80 yrs | 0.82 | 1.29 | 1.07 | | 0.92 | | 0.18 |
| ≥80 yrs | 1.43 | 1.60 | 1.92 | | | | |
| **Disabling or fatal stroke** | | | | | | | |
| <80 yrs | 0.52 | 0.84 | 0.86 | | 0.40 | | 0.63 |
| ≥80 yrs | 1.38 | 1.50 | 1.77 | | | | |

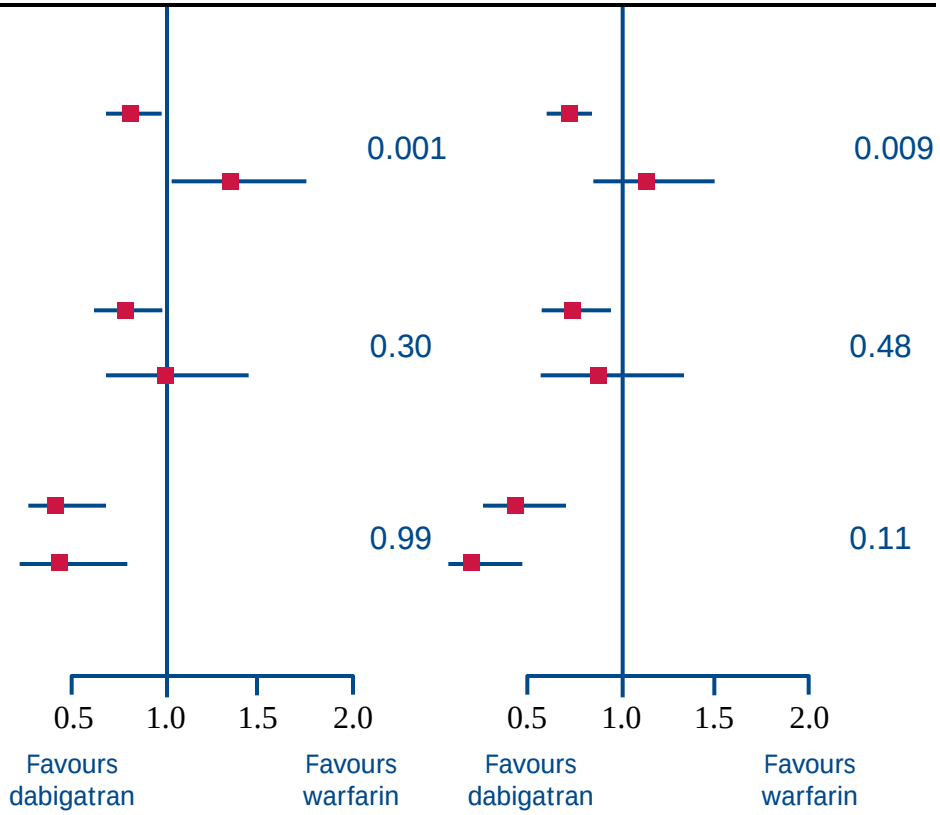



**Effect of dabigatran vs warfarin consistent between age groups**

*Coppens M et al. Circulation 2012;126:A15537*

# Very elderly subgroup analysis: safety outcomes

| | D150 | D110 | VKA | D150 vs VKA | P value* | D110 vs VKA | P value* |
|---|---|---|---|---|---|---|---|
| **Major bleeding** | | | | | | | |
| <80 yrs | 2.73 | 2.43 | 3.35 | | 0.001 | | 0.009 |
| ≥80 yrs | 6.23 | 5.24 | 4.68 | | | | |
| **Life-threatening bleeding** | | | | | | | |
| <80 yrs | 1.18 | 1.02 | 1.74 | | 0.30 | | 0.48 |
| ≥80 yrs | 3.01 | 2.40 | 2.39 | | | | |
| **Intracranial haemorrhage** | | | | | | | |
| <80 yrs | 0.24 | 0.23 | 0.66 | | 0.99 | | 0.11 |
| ≥80 yrs | 0.74 | 0.32 | 1.30 | | | | |




**Significant AGE-interaction for major and minor bleeding**

**Reduced risk of ICH for dabigatran vs warfarin regardless of age**

*Coppens M et al. Circulation 2012;126:A15537*

**Dabigatran Etexilato 110 mg BID nei pazienti con:**

- **Insufficienza renale moderata (eGFR 30-50 ml/min)**
- **età ≥ 80 anni**
- **uso contemporaneo di verapamil**
- **paziente con più elevato rischio di sanguinamento (HASBLED>=3)**

http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf

REVIEW ARTICLE

ONLINE FIRST

# Dabigatran Association With Higher Risk of Acute Coronary Events

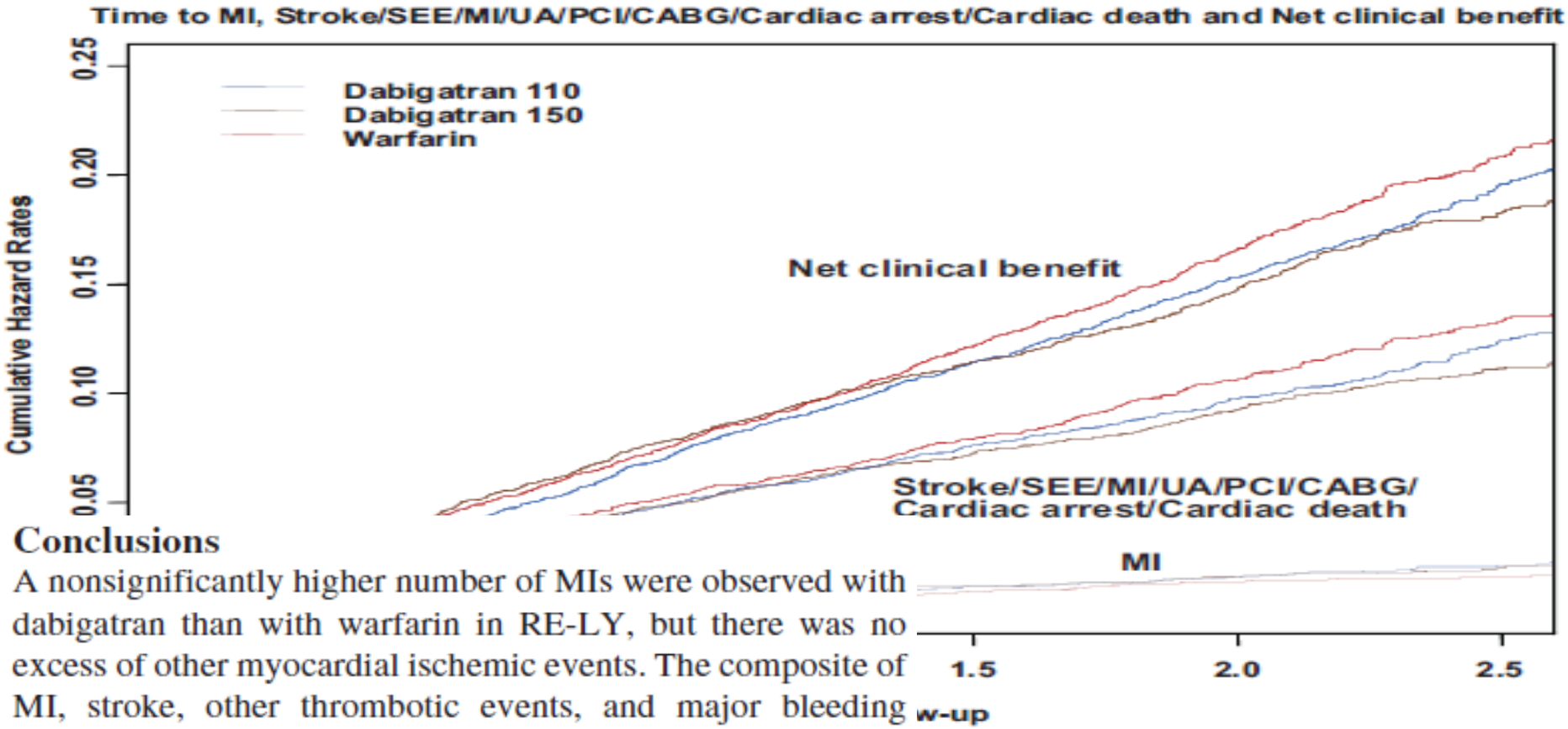
*Meta-analysis of Noninferiority Randomized Controlled Trials*

The overall benefit and risk balance of dabigatran use appears to be favorable in patients with AF because of reduction in ischemic stroke. However, the cardiac risk of dabigatran should be investigated further, especially if it is used in populations at high risk of MI or ACS.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

(*Circulation*. 2012;125:669-676.)

# Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial




## Conclusions

A nonsignificantly higher number of MIs were observed with dabigatran than with warfarin in RE-LY, but there was no excess of other myocardial ischemic events. The composite of MI, stroke, other thrombotic events, and major bleeding occurred less frequently with each dose of dabigatran than with warfarin and for the higher dose of dabigatran was nominally statistically significant.

The NEW ENGLAND JOURNAL of MEDICINE

# Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

**Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.***

| Analysis | Dabigatran | | | Warfarin | | |
|---|---|---|---|---|---|---|
| | No. of Patients | No. of Events | Incidence *no. of events/ 100,000 days at risk* | No. of Patients | No. of Events | Incidence *no. of events/ 100,000 days at risk* |
| **Gastrointestinal hemorrhage** | | | | | | |
| Analysis with required diagnosis of atrial fibrillation | 3,541 | 160 | 3.5 | | | |
| Sensitivity analysis without required diagnosis of atrial fibrillation | 9,940 | 338 | 3.1 | | | |
| **Intracranial hemorrhage** | | | | | | |
| Analysis with required diagnosis of atrial fibrillation | 3,594 | 109 | 2.4 | | | |
| Sensitivity analysis without required diagnosis of atrial fibrillation | 0,020 | 204 | 1.9 | | | |

Although some have noted the lack of an available reversal agent for the anticoagulant effects of dabigatran as an important limitation of its use, data from RE-LY are reassuring with respect to bleeding. We believe that dabigatran provides an important health benefit when used as directed. Further analysis of the Mini-Sentinel and other claims databases is ongoing, as is routine postmarketing surveillance through FAERS.

# Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

## A Prospective Nationwide Cohort Study

(J Am Coll Cardiol 2013;61:2264–73)

From the Danish Registry of Medical Product Statistics, 4978 Dabigatran users vs 8936 Warfarin users (Cox proportional hazards models stratified on propensity-matched groups)

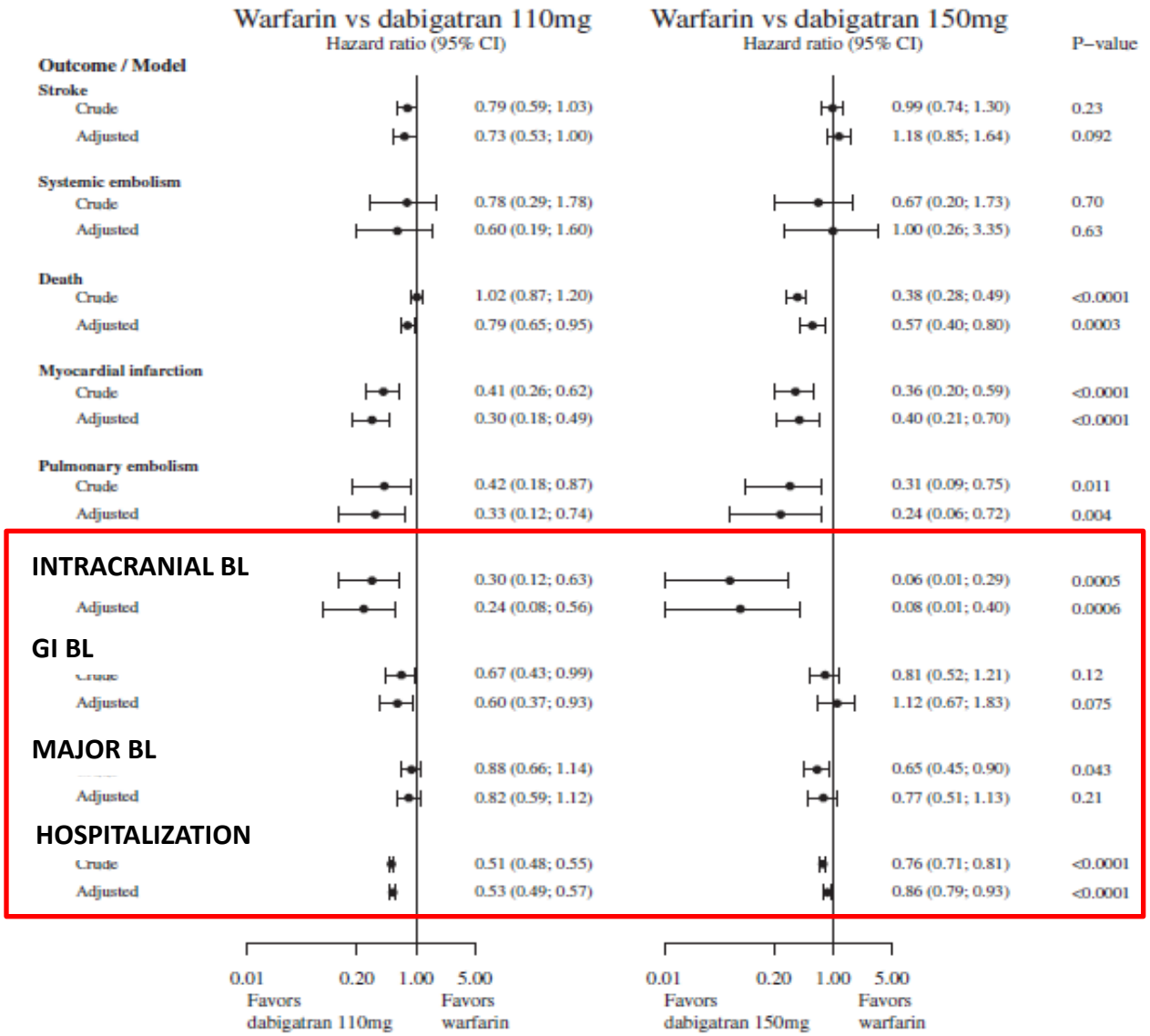


**Table 3** Subgroup Analysis on Dabigatran Users With More Than 1-Year Follow-Up

| Outcome | Warfarin vs. Dabigatran 110 mg b.i.d. HR | 95% CI | Warfarin vs. Dabigatran 150 mg b.i.d. HR | 95% CI | p Value* |
|---|---|---|---|---|---|
| Stroke | | | | | |
| Crude | 0.95 | (0.62–1.41) | 1.58 | (1.06–2.30) | 0.05 |
| Adjusted | 0.84 | (0.53–1.31) | 1.53 | (0.96–2.43) | 0.15 |
| Death | | | | | |
| Crude | 0.93 | (0.72–1.18) | 0.39 | (0.25–0.59) | <0.0001 |
| Adjusted | 0.82 | (0.62–1.06) | 0.58 | (0.35–0.92) | 0.03 |
| Myocardial infarction | | | | | |
| Crude | 0.60 | (0.33–1.02) | 0.62 | (0.30–1.14) | 0.10 |
| Adjusted | 0.50 | (0.26–0.89) | 0.74 | (0.34–1.48) | 0.06 |
| Major bleeding | | | | | |
| Crude | 0.77 | (0.51–1.14) | 0.63 | (0.36–1.02) | 0.12 |
| Adjusted | 0.74 | (0.47–1.14) | 0.66 | (0.36–1.14) | 0.15 |

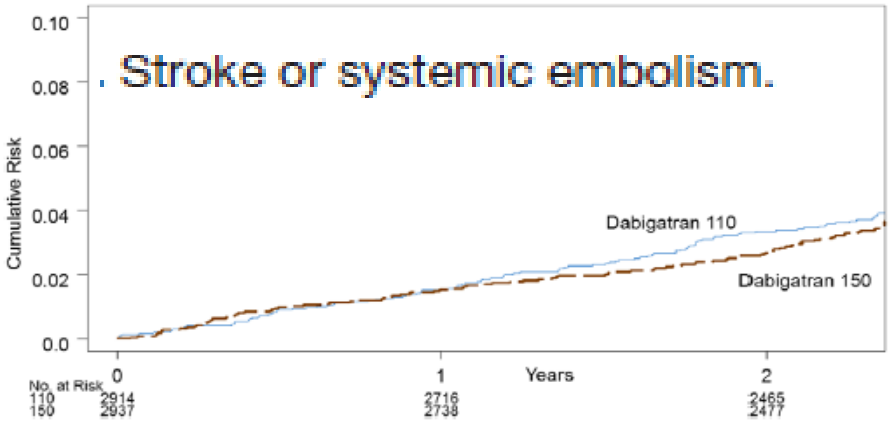
**Conclusioni.** …in questo «mondo clinico reale» **mortalità, TEP ed IMA erano minori con entrambe le dosi di Dabigatran**…l'incidenza di sanguinamenti maggiori era simile nei due gruppi mentre i **sanguinamenti intracranici erano meno frequenti con entrambe le dosi di Dabigatran**…le preoccupazioni ventilate circa maggior rischio di sanguinamenti o infarti nei pazienti trattati con Dabigatran non erano evidenti in questa analisi nel mondo clinico reale

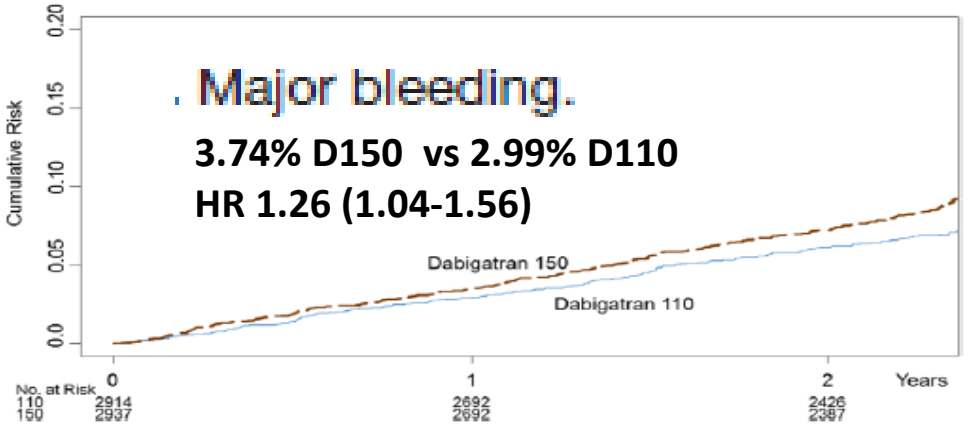
Stroke

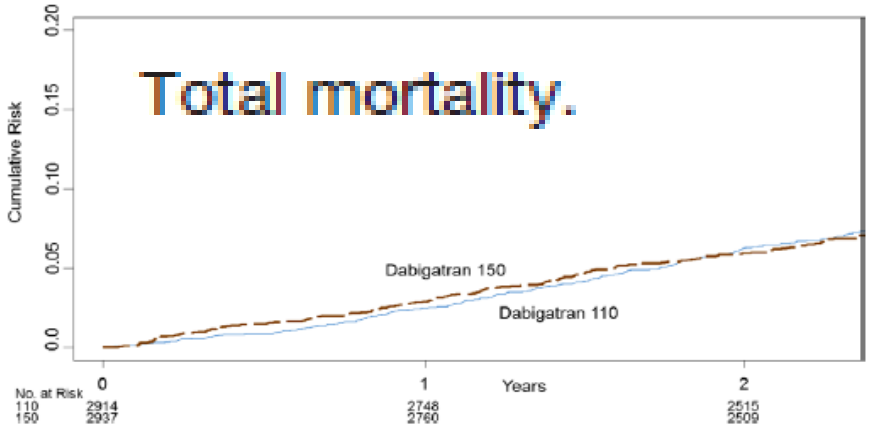
238 Circulation July 16, 2013

# The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study

***Long term Multicenter Extension of Dabigatran treatment in patients with AF (RELY-ABLE), follow-up 2.3 years***




**Conclusioni.** …in questo confronto fra le due dosi di Dabigatran non vi erano differenze significative per quanto riguarda stroke e mortalità, ma si è osservata una maggior incidenza di sanguinamenti maggiori con la dose di Dabigatran più alta

# Editorial

## New Oral Anticoagulants in Atrial Fibrillation Forever?

**Table. Differences in Major Outcomes in RE-LY and RELY-ABLE**

| Study | Dabigatran 150 mg BID | Dabigatran 110 mg BID | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| RE-LY[8] patients (n=18 113), % | | | | |
| Stroke (/y) | 1.0 | 1.4 | 0.70 (0.56–0.89)* | 0.003 |
| Major bleeding (/y) | 3.1 | 2.7 | 1.16 (1.00–1.34)* | 0.05 |
| RELY-ABLE[7] patients (n=5851), % | | | | |
| Stroke (/y) | 1.2 | 1.4 | 0.89 (0.66–1.21) | NA |
| Major bleeding (/y) | 3.8 | 3.0 | 1.26 (1.04–1.53) | NA |

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# European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

**Table 2** Checklist during follow-up contacts of AF patients on anticoagulation

| | Interval | Comments |
|---|---|---|
| 1. Compliance | Each visit | • Instruct patient to bring remaining medication: note and calculate average adherence<br>• Re-educate on importance of strict intake schedule<br>• Inform about compliance aids (special boxes; smartphone applications; . . . ) |
| 2. Thrombo-embolism | Each visit | • Systemic circulation (TIA, stroke, peripheral)<br>• Pulmonary circulation |
| 3. Bleeding | Each visit | • 'Nuisance' bleeding: preventive measures possible? (PPI; haemorrhoidectomy; . . . ). Motivate patient to diligently continue anticoagulation<br>• Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication or dose? |
| 4. Other side effects | Each visit | • Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug. |
| 5. Co-medications | Each visit | • Prescription drugs; over-the-counter drugs (see Section 4)<br>• Careful interval history: also temporary use can be risk! |
| 6. Blood sampling | Yearly<br>6 monthly<br>3 monthly<br>On indication | • Haemoglobin, renal and liver function<br>• Renal function if CrCl 30–60 ml/min, or if on dabigatran and >75 years or fragile<br>• If CrCl 15–30 ml/min<br>• If intercurring condition that may impact renal or hepatic function |

# 3. Drug–drug interactions and pharmacokinetics of new oral anticoagulants

**Table 4** Absorption and metabolism of the different NOACs

| | Dabigatran | Apixaban | Edoxaban[a] | Rivaroxaban |
|---|---|---|---|---|
| Bio-availability | 3–7% | 50% | 62%[17] | 66% without food<br>Almost 100% with food |
| Prodrug | Yes | No | No | No |
| Clearance non-renal/renal of absorbed dose (if normal renal function; see also Section 8) | 20%/80% | 73%/27%[18] | 50%/50%[9] | 65%/35% |
| Liver metabolism: CYP3A4 involved | No | Yes (elimination; minor CYP3A4 contribution)[19] | Minimal (<4% of elimination) | Yes (elimination) |
| Absorption with food | No effect | No effect | 6–22% more[20] | +39% more[21] |
| Intake with food recommended? | No | No | No official recommendation yet | Mandatory |
| Absorption with H2B/PPI | −12–30%[22–24] | No effect | No effect | No effect[21,25] |
| Asian ethnicity | +25%[24] | No effect | No effect[20] | No effect |
| GI tolerability | Dyspepsia 5–10% | No problem | No problem | No problem |
| Elimination half-life | 12–17 h[23] | 12 h | 9–11 h[9] | 5–9 h (young)<br>11–13 h (elderly) |

[a]No EMA approval yet. Needs update after finalization of SmPC.
H2B, H2-blocker; PPI, proton-pump inhibitor; GI, gastro-intestinal.

**Figure 5** Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolisation and excretion. The brackets around (Cyp3A4) in the apixaban graph indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged parent. See also *Table 4* for the size of the interactions based on these schemes.

## 7. Patients with chronic kidney disease

In the context of NOAC treatment, CrCl is best assessed by the Cockroft method, as this was used in most NOAC trials.

**Table 6** Estimated drug half-lives and effect on area under the curve NOAC plasma concentrations in different stages of chronic kidney disease compared to healthy controls

| | Dabigatran | Apixaban | Edoxaban[a] | Rivaroxaban |
|---|---|---|---|---|
| CrCl ≥60 ml/min CKD Stage I and II | ~14 h[48] | No data | ~8.6 h[49] | ~8.5 h[50] (+44%) |
| CrCl 30–60 ml/min CKD Stage III | ~18 h[48] | No data | ~9.4 h[49] | ~9 h (+52%) |
| CrCl 15–30 ml/min CKD Stage IV | ~28 h[48] | No data | ~16.9 h[49] | ~9.5 h (+64%) |
| CrCl ≤15 ml/min CKD Stage V | No data | No data | No data | No data |

## Practical suggestions

Renal function can deteriorate within a few months, and the nature of the kidney disease as well as concomitant conditions that could change the time course of CKD should be considered when deciding on a monitoring scheme.

(i) Monitor every year for CKD stage I–II (CrCl ≥ 60 ml/min)
(ii) Monitor every 6 months for CKD stage III (CrCl 30–60 ml/min)
(iii) Monitor every 3 months for CKD stage IV (CrCl ≤30 ml/min)

**Table 7** NOACs in renal dysfunction: Approved European labels and dosing in chronic kidney disease

| | Dabigatran |
|---|---|
| Fraction renally excreted of absorbed dose | 80% |
| Bio-availability | 3–7% |
| Fraction renally excreted of administered dose | 4% |
| Approved for CrCl ≥ ... | ≥30 ml/min |
| Dosing recommendation | CrCl ≥50 ml/min: no adjustment (i.e. 150 mg bid) |
| Dosing if CKD | When CrCl 30–49 ml/min, 150 mg bid is possible (SmPC) but 110 mg bid if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[2]<br>Note: 75 mg bid approved in US only:[b]<br>• if CrCl 15–30 ml/min<br>• if CrCl 30–49 ml/min and other orange factor Table 5 (e.g. verapamil) |
| Not recommended if | CrCl <30 ml/min |

**La funzionalità renale deve essere valutata calcolando la Clearance della Creatinina* prima di iniziare il trattamento per escludere i pazienti con insufficienza renale severa (CrCl <30 mL/min) e per considerare Dabigatran 110 mg BID in pazienti con insufficienza renale moderata (CrCl 30–50 mL/min) (*metodo CG)**

**La funzionalità renale deve essere valutata inoltre**

- **Quando si sospetta una riduzione della funzionalità renale durante il trattamento con Dabigatran (es. ipovolemia, disidratazione, utilizzo concomitante di alcuni farmaci)**
- **Almeno una volta all'anno in pazienti di età ≥75 anni o con insufficienza renale lieve o moderata. Assicurarsi che la funzionalità renale del paziente resti nel range raccomandato e non progredisca verso un'insufficienza renale severa (ClCr <30ml/min) per la quale il trattamento con Dabigatran deve essere interrotto**

# 10. Patients undergoing a planned surgical intervention or ablation

## 10.1 When to stop the new oral anticoagulants?

**Table 9** Last intake of drug before elective surgical intervention

| | Dabigatran | | Apixaban | | Edoxaban[a] | | Rivaroxaban | |
|---|---|---|---|---|---|---|---|---|
| | No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake) | | | | | | | |
| | Low risk | High risk | Low risk | High risk | Low risk | High risk | Low risk | High risk |
| CrCl ≥80 ml/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h | No data | No data | ≥24 h | ≥48 h |
| CrCl 50–80 ml/min | **≥36 h** | **≥72 h** | ≥24 h | ≥48 h | No data | No data | ≥24 h | ≥48 h |
| CrCl 30–50 ml/min[b] | **≥48 h** | **≥96 h** | ≥24 h | ≥48 h | No data | No data | ≥24 h | ≥48 h |
| CrCl 15–30 ml/min[b] | Not indicated | Not indicated | **≥36 h** | **≥48 h** | No data | No data | **≥36 h** | **≥48 h** |
| CrCl <15 ml/min | No official indication for use | | | | | | | |

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.

[a]No EMA approval yet. Needs update after finalisation of SmPC.

[b]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 (15 mg QD).

Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.

CrCl, creatinine clearance.

**Table 5** Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors and recommendations towards NOAC dosing

| | Via | Dabigatran | Apixaban | Edoxaban[a] | Rivaroxaban |
|---|---|---|---|---|---|
| Atorvastatin | P-gp competition and CYP3A4 inhibition | +18%[29] | No data yet | No effect[30] | No effect[27,31] |
| Digoxin | P-gp competition | No effect[32] | No data yet | No effect[30] | No effect[27,33] |
| Verapamil | P-gp competition (and weak CYP3A4 inhibition) | +12–180%[24] (reduce dose and take simultaneously) | No data yet | +53% (SR)[30] (reduce dose by 50%)[a] | Minor effect (use with caution if CrCl 15–50 ml/min) |
| Diltiazem | P-gp competition and weak CYP3A4 inhibition | No effect[24] | +40%[SmPC] | No data yet | Minor effect (use with caution if CrCl 15–50 ml/min) |
| Quinidine | P-gp competition | +50% | No data yet | +80%[30] (reduce dose by 50%)[b] | +50% |
| Amiodarone | P-gp competition | +12–60%[24] | No data yet | No effect[30] | Minor effect (use with caution if CrCl 15–50 ml/min) |
| Dronedarone | P-gp and CYP3A4 inhibitor | +70–100% (US: 2 × 75 mg) | No data yet | +85% (reduce dose by 50%)[a] | No data yet |
| Ketoconazole; itraconazole; voriconazole; posaconazole | P-gp and BCRP competition; CYP3A4 inhibition | +140–150% (US: 2 × 75 mg) | +100%[SmPC] | No data yet | Up to +160%[27] |
| Fluconazole | Moderate CYP3A4 inhibition | No data yet | No data yet | No data yet | +42% (if systemically administered)[27] |
| Cyclosporin; tacrolimus | P-gp competition | No data yet | No data yet | No data yet | +50% |
| Clarithromycin; erythromycin | P-gp competition and CYP3A4 inhibition | +15–20% | No data yet | No data yet | +30–54%[26,27] |
| 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%[27] |
| Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital | P-gp/ BCRP and CYP3A4/CYP2J2 inducers | −66%[24] | −54%[SmPC] | −35% | Up to −50% |
| Antacids (H2B; PPI; Al-Mg-hydroxide) | GI absorption | −12–30%[22–24] | No data yet | No effect | No effect[21,25] |
| **Other factors** | | | | | |
| Age ≥80 years | Increased plasma level | | | No data yet | |
| Age ≥75 years | Increased plasma level | | | No data yet | |
| Weight ≤60 kg | Increased plasma level | | | | |
| Renal function | Increased plasma level | See Table 7 | | | |
| Other increased bleeding risk | | Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3 | | | |

# Safety Dabigatran: conclusioni

- I pazienti anziani con FA traggono elevato beneficio dalla **terapia anticoagulante**. Diversi fattori contribuiscono tuttavia ad uno **scarso uso del warfarin** negli anziani: tra gli altri, il timore di sanguinamenti (intracranici!) e le difficoltà legate alla necessità di un monitoraggio dell'INR, dal quale dipende tra l'altro efficacia e sicurezza della terapia stessa.

- Rispetto al warfarin, **entrambi i dosaggi di dabigatran** sono associati a un **minor rischio di sanguinamenti intracranici** (anche negli anziani), mentre i benefici sui sanguinamenti extracranici sono evidenti solo nei pazienti di età <75 anni

- In termini di sicurezza il **beneficio del Dabigatran** rispetto al Warfarin appare **più evidente** e significativo **nei pazienti con labile controllo dell'INR**

- Il Dabigatran è controindicato in presenza di IRC severa (eGFR<30 ml/min). Nei pazienti di età **<75 anni**, «robusti», **Dabigatran 150 mg BID** è probabilmente preferibile grazie alla maggior riduzione del rischio di ictus; nei pazienti di età **>75-80 anni** e/o in presenza di **insufficienza renale moderata** si può preferire **Dabigatran 110 mg BID** in quanto a fronte di una efficacia simile comporta un minor rischio di sanguinamento intracranico

- Soltanto un uso «sereno» e senza pregiudizi di questi farmaci e l'osservazione dei pazienti trattati potrà, nel tempo, confermare o smentire anche nel mondo clinico reale i risultati incoraggianti evidenziati nei trial randomizzati

# Fatal bleeding associated with medical foolishness

A 78-year-old, 193-kg woman arrived at the emergency department with complaints of generalized weakness and a decreased level of
was hospitalized for
fection, dehydration
was treated with i.v.
ids and 2 units of pa
(PRBCs). At the tim
patient had acute kid
to dehydration, with
24 mL/min, which h
mL/min before disc

Eight days after discharge, the patient was readmitted with increasing weakness. An electrocardiogram showed an acute non-ST-elevation myocardial infarction. Additional acute conditions included dehydration, acute kidney injury (estimated $CL_{cr}$ of 14 mL/min), lower gastrointestinal bleeding, and anemia. Laboratory tests revealed an elevated activated partial thromboplastin time (aPTT) of 71.1 seconds and an INR of 8.3 at that time (21 days after the first hospital admission).

On day 10, the patient developed paroxysmal atrial fibrillation. She was prescribed warfa-
g on hospital days 10,
y 13, her International
(INR) was only 1.3,
an to discontinue war-
e the patient on dabi-
) mg twice daily. Other
medications included
idamole–aspirin.