31 GIORNATE CARDIOLOGICHE TORINESI

TURIN
October
24th-26th
2019

Anticoagulation Therapy: is everithing clear?

Chairpersons: A.S. Bongo, A. Dellavalle

DOACs in elderly and fragile patient

Massimo Giammaria
Cardiologia Ospedale Maria Vittoria Torino
Asl Citta' di Torino

OLD AGE

HEALTH

Ageing is a privilege and a goal of society, but it's also a challenge that will have an impact on all aspects of XXI centuty society
(OMS 2005)

FRAILTY

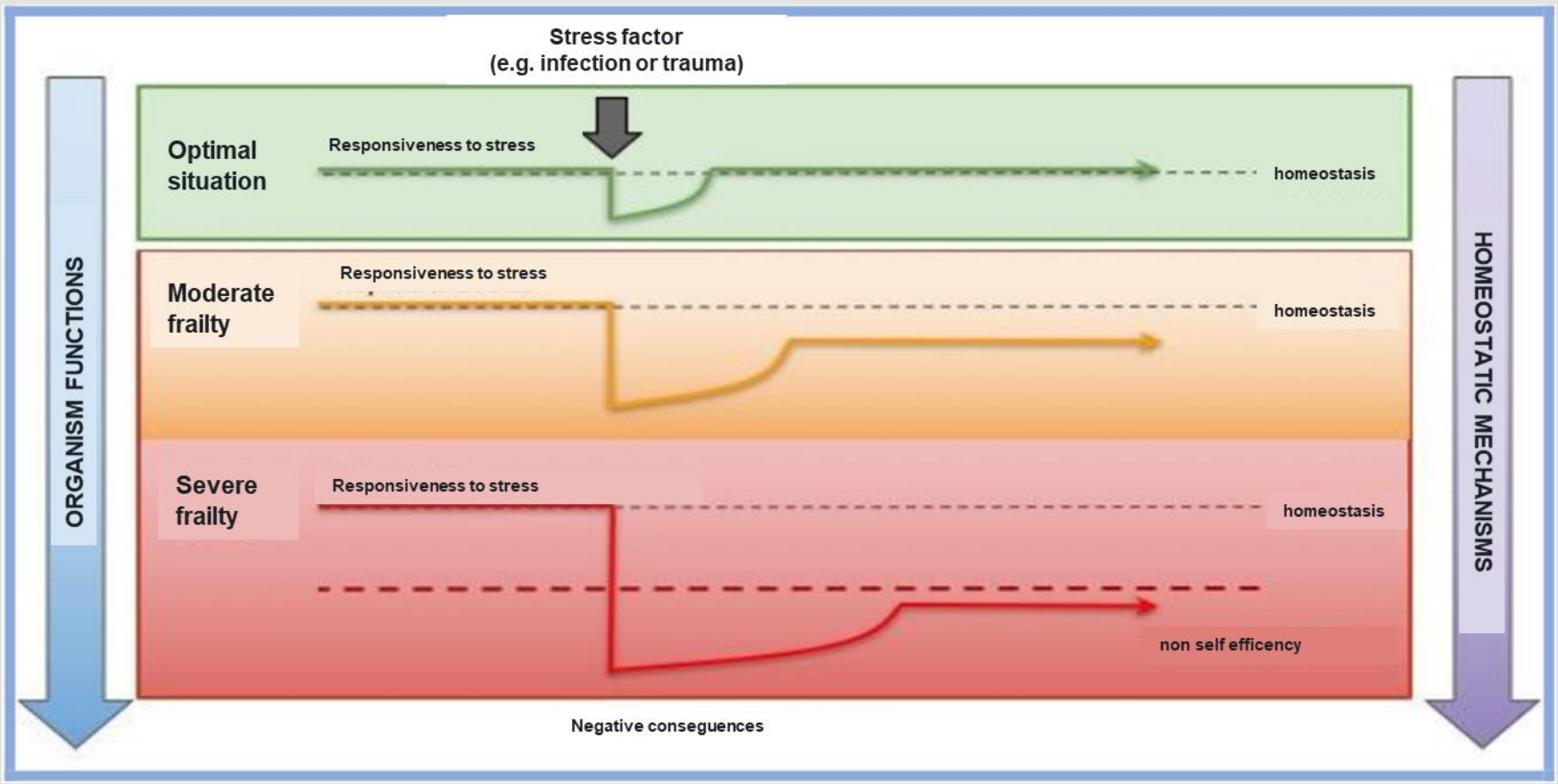
FRAIL?

ELDERLY OVER 75?

HIGH BLEEDING RISK?

- Previous bleeding
- Low body mass
- Anemia
- Liver/Kidney dysfunctions
- GI bleedings
- NSAIDs
- Triple antithrombotic therapy

DRUG-DRUG INTERACTIONS?


Stress factor
(e.g. infection or trauma)
ORGANISM FUNCTIONS
HOMEOSTATIC MECHANISMS
Optimal situation
Responsiveness to stress
homeostasis
Moderate frailty
Responsiveness to stress
homeostasis
Severe frailty
Responsiveness to stress
homeostasis
non self efficency
Negative conseguences

Frailty Indicators and Scale

Frailty indicator	Measure
Weight loss	Self-reported weight loss >4.5 kg or recorded weight loss ⩾5% per annum
Exhaustion	Self-reported exhaustion on CES-D scale (3ñ4 days per week or most of the time)
Low energy expenditure	Energy expenditure <383 Kcal/week (males) or <270 Kcal/week (females)
Slowness	Standardised cut-off times to walk 15 feet, stratified for se and height
Weakness	Grip strength, stratified by sex and BMI

BMI = body mass index; CES-D = Center for Epidemiological Studies Depression.

Cardiovascular Health Study[10,11]
Study of Osteoporotic Fractures[12,13]
Deficit Model[14,15]
FRAIL – International Academy of Nutrition and Aging[16,17]
SHARE-FI[18,19]
Vulnerable Elder Survey-13[20–22]
Tilburg Frailty Index[23,24]
Groningen Frailty Indicator[25,26]

Chronic Disorders by age-group

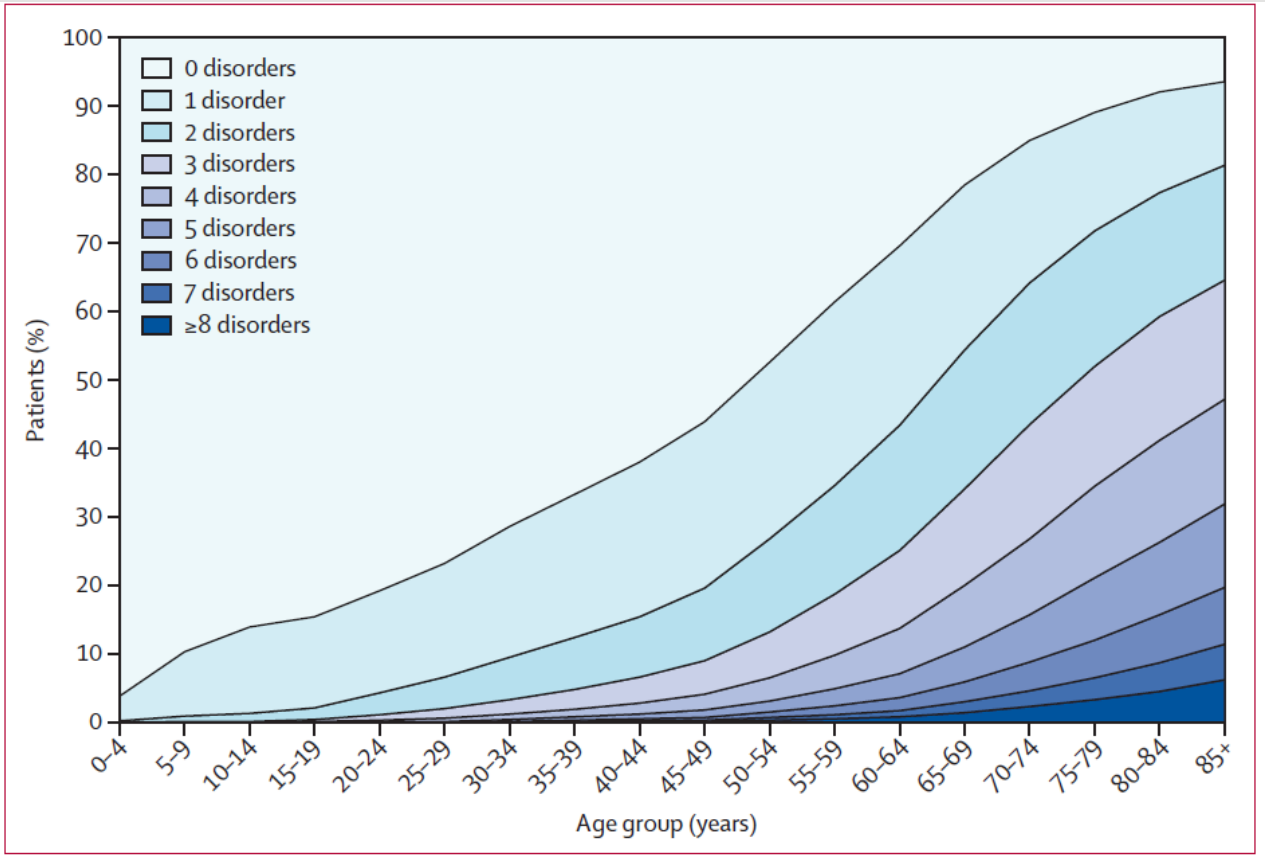
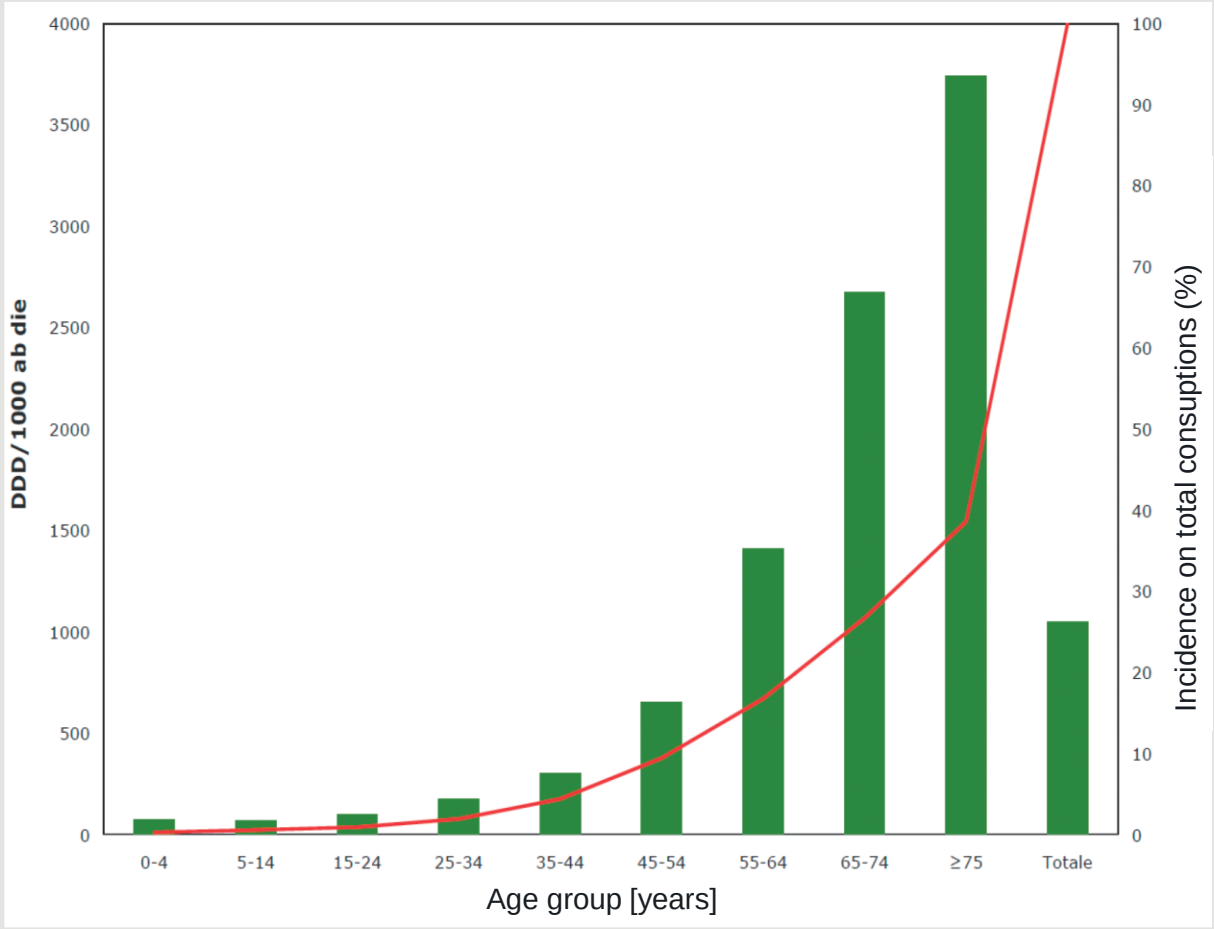


Figure 1: Number of chronic disorders by age-group

Barnett K, Lancet 2014

Drugs consumption by age-group



modificato da OSMED 2014

RCTs trials

	Dabigatran 150 mg	Dabigatran 110 mg	Apixaban 5/2.5 mg	Rivaroxaban 20/15 mg	Edoxaban 60/30 mg
Dosing frequency	BID		BID	OD	OD
RCTs: major bleeding vs warfarin[1–4]	Not significant	↓ 20%	↓ 31%	Not significant	↓ 20%
RCTs: stroke/SE vs warfarin[1–4]	↓ 35%	Not significant	↓ 21%	Not significant	Not significant
RCTs: ischaemic stroke vs warfarin[3–6]	↓ 24%	Not significant	Not significant	Not significant	Not significant
RCTs: haemorrhagic stroke vs warfarin[1–5]	↓ 74%	↓ 69%	↓ 49%	↓ 41%	↓ 46%
Superior safety profile reinforced by comparative real-world data[7,8]	✓		✓	✗	✗
Specific reversal agent available	✓		✗	✗	✗

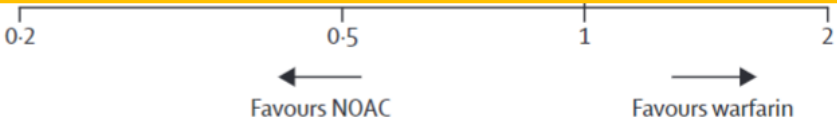
No head-to-head RCT comparison. Head-to-head data available from observational studies

SE, systemic embolism

1. Connolly et al. N Engl J Med 2014; **2.** Granger et al. N Engl J Med 2011; **3.** Patel et al. N Engl J Med 2011; **4.** Giugliano et al. N Engl J Med 2013; **5.** Pradaxa®: EU SPC, 2016; **6.** Lopes et al. Lancet 2012; **7.** Larsen et al. BMJ 2016; **8.** Lin et al. ESC 2015

Safety and Efficacy vs Warfarin

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29 292	724/29 221	0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29 292	263/29 221	0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29 292	432/29 221	0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29 292	2245/29 221	0·90 (0·85–0·95)	0·0003
Safety				
Intracranial haemorrhage	204/29 287	425/29 211	0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29 287	591/29 211	1·25 (1·01–1·55)	0·043



Ruff C T et al. Lancet 2014 383 955 962

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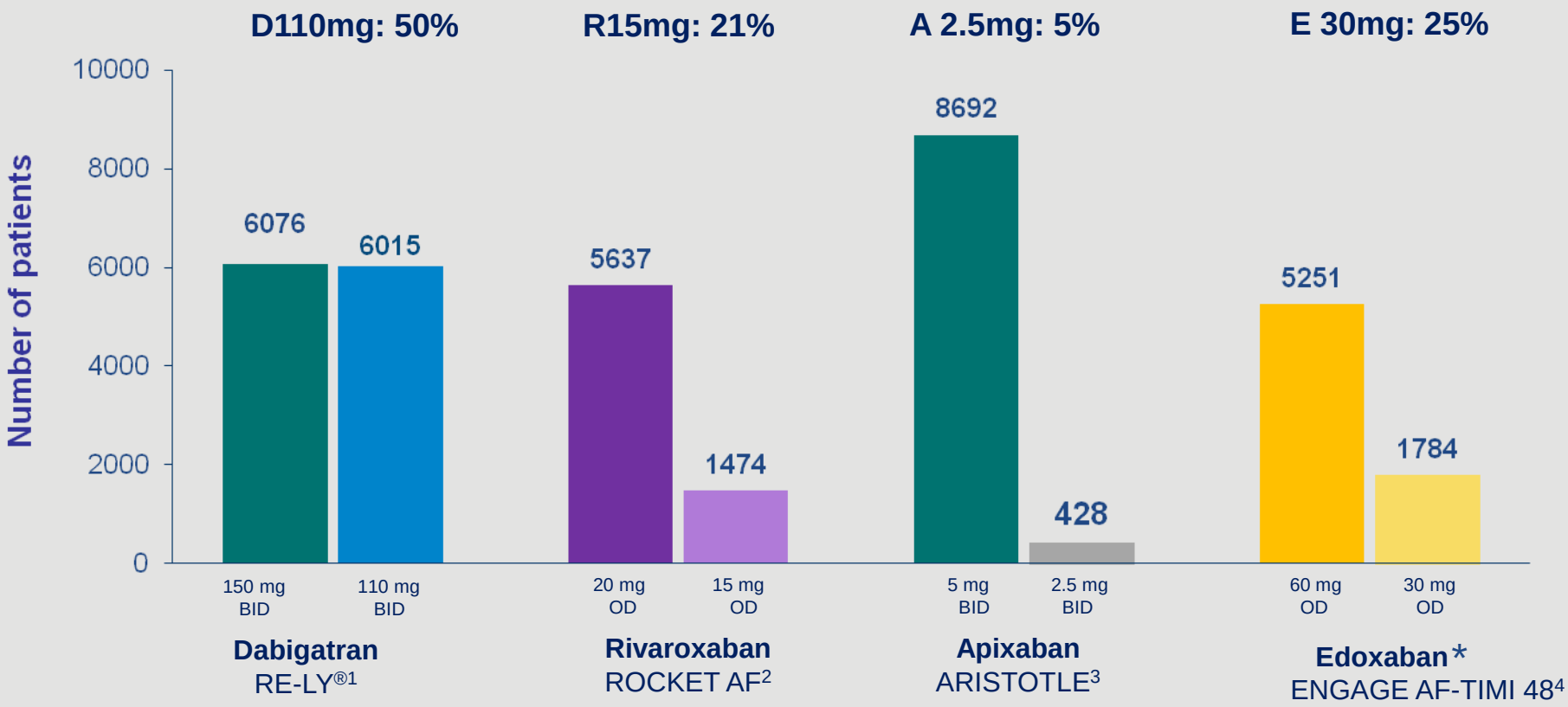
DRUG-DRUG INTERACTIONS?

NOAC «low dose» in RCTs vs. warfarin



*Approved doses in EU

1. Connolly et al. N Engl J Med 2009; **2.** Fox et al. Eur Heart J 2011; **3**. Granger et al. N Engl J Med 2011; **4.** Giugliano et al. N Engl J Med 2013

Dabigatran 110 MG is the only NOAC low dose tested in the unselected populations in RCTs

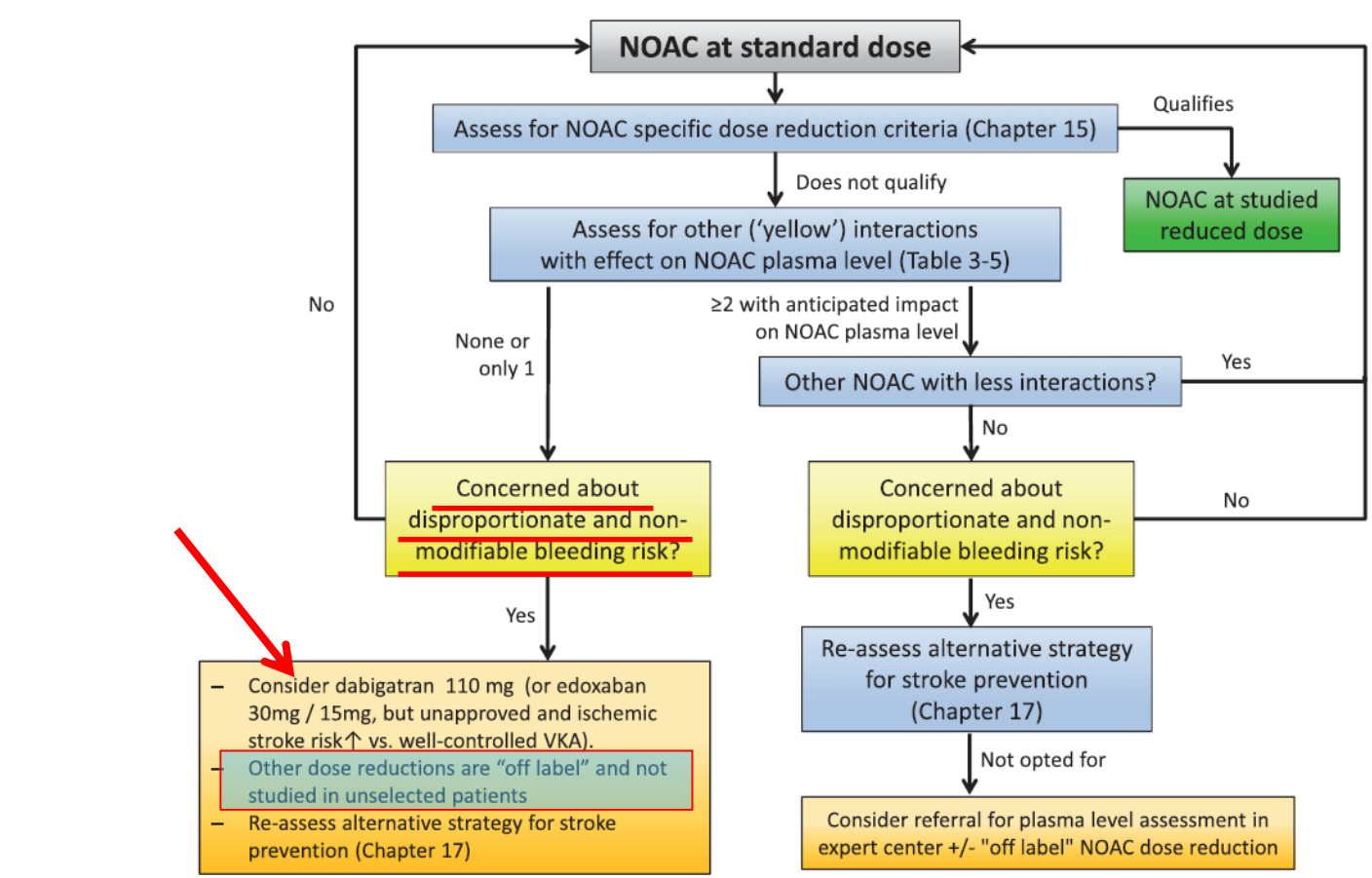
Low dose		Reduced dose		
RE-LY[1]		ROCKET AF[2]	ARISTOTLE[3]	ENGAGE AF-TIMI 48[4]
Dabigatran 150 mg bid	Dabigatran 110 mg bid	Rivaroxaban 20 mg/die	Apixaban 5 mg bid	Edoxaban 60 mg/die
⇩	⇩	⇩	⇩	⇩
No dose adjustment	No dose adjustment	15 mg/die se ClCr 30-49 ml/min	2.5 mg bid se ≥2 tra: età ≥80 anni, peso ≤60 kg, creatinina ≥1.5 mg/dl oppure se ClCr 15-29 ml/min	30 mg/die se ≥1 tra: ClCr 30-50 ml/min, peso ≤60 kg, concomitant inhibitor P-glicoprotein

bid, 2 volte al giorno; ClCr, clearance della creatinina.

ONLY FOR DABIGATRAN NO DOSE REDUCTIONS ARE REQUIRED

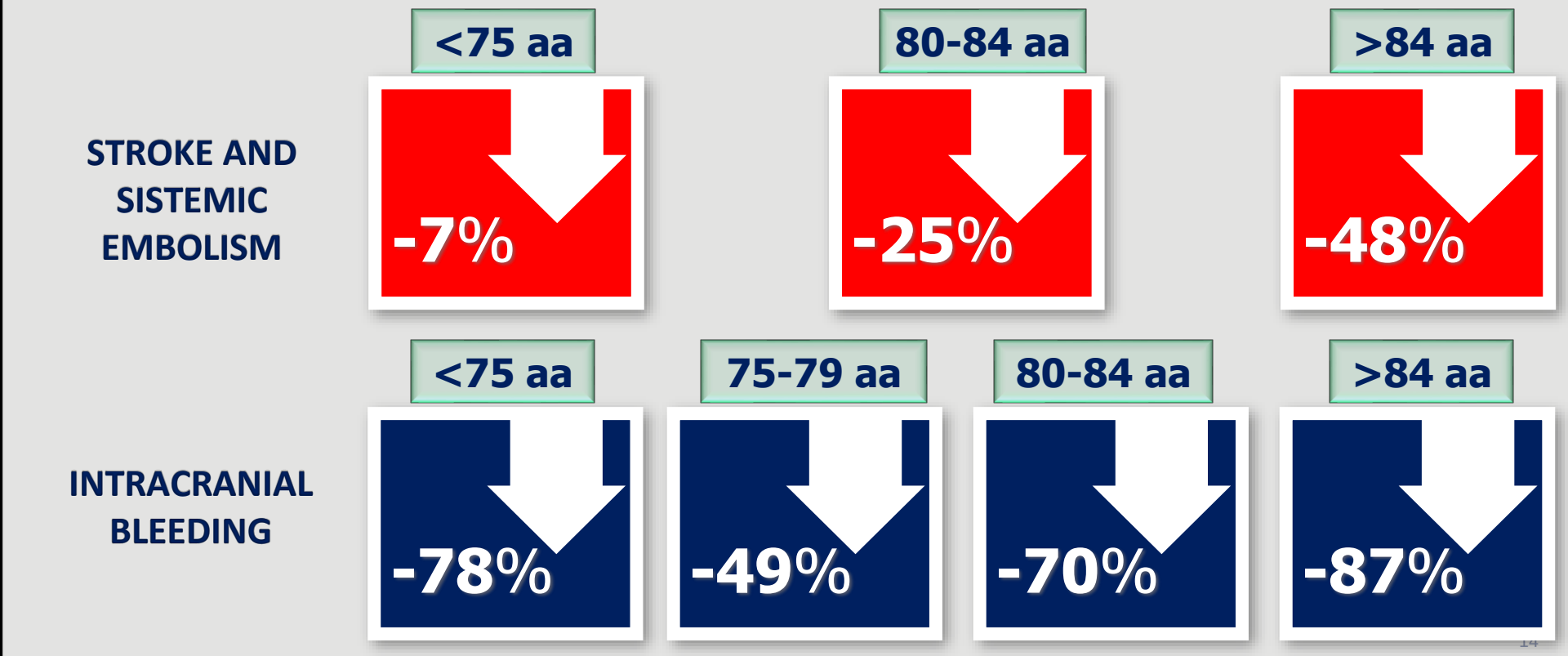
1- Connolly SJ et al. N Engl J Med 2009;361:1139-51; 2- Patel MR et al. N Engl J Med 2011;365:883-91 ; 3- Granger CB et al. N Engl J Med 2011;365:981-92 ; 4-Giugliano RP et al. N Engl J Med 2013;369:2093-10

EHRA 2018 Practical Guide on the use of NOAC in patients with Atrial Fibrillarion



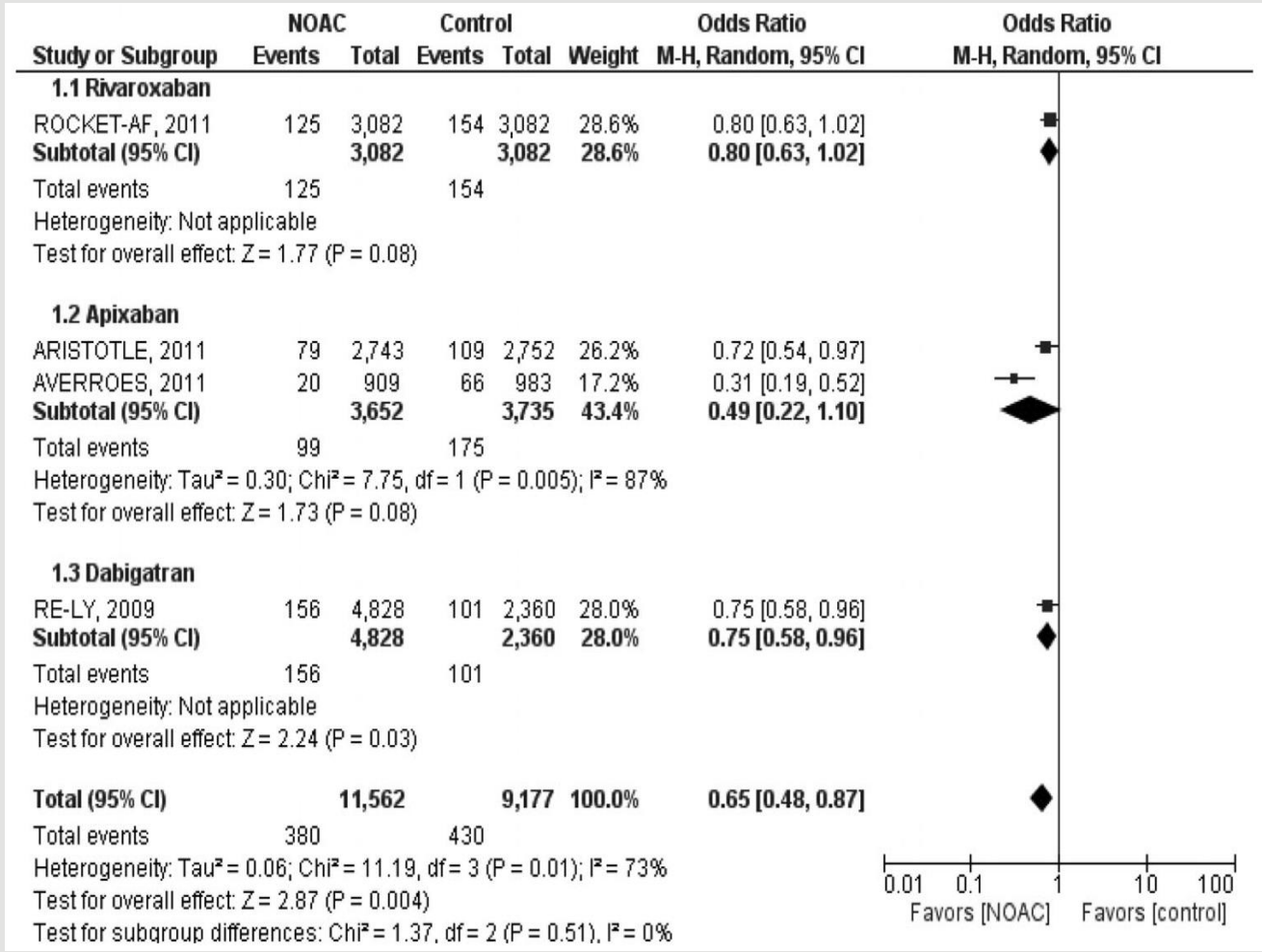
The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

The effects of dabigatran 110 mg vs warfarin on stroke prevention and intracranial bleeding are consistent across all age groups



Lauw MN, Heart 2017

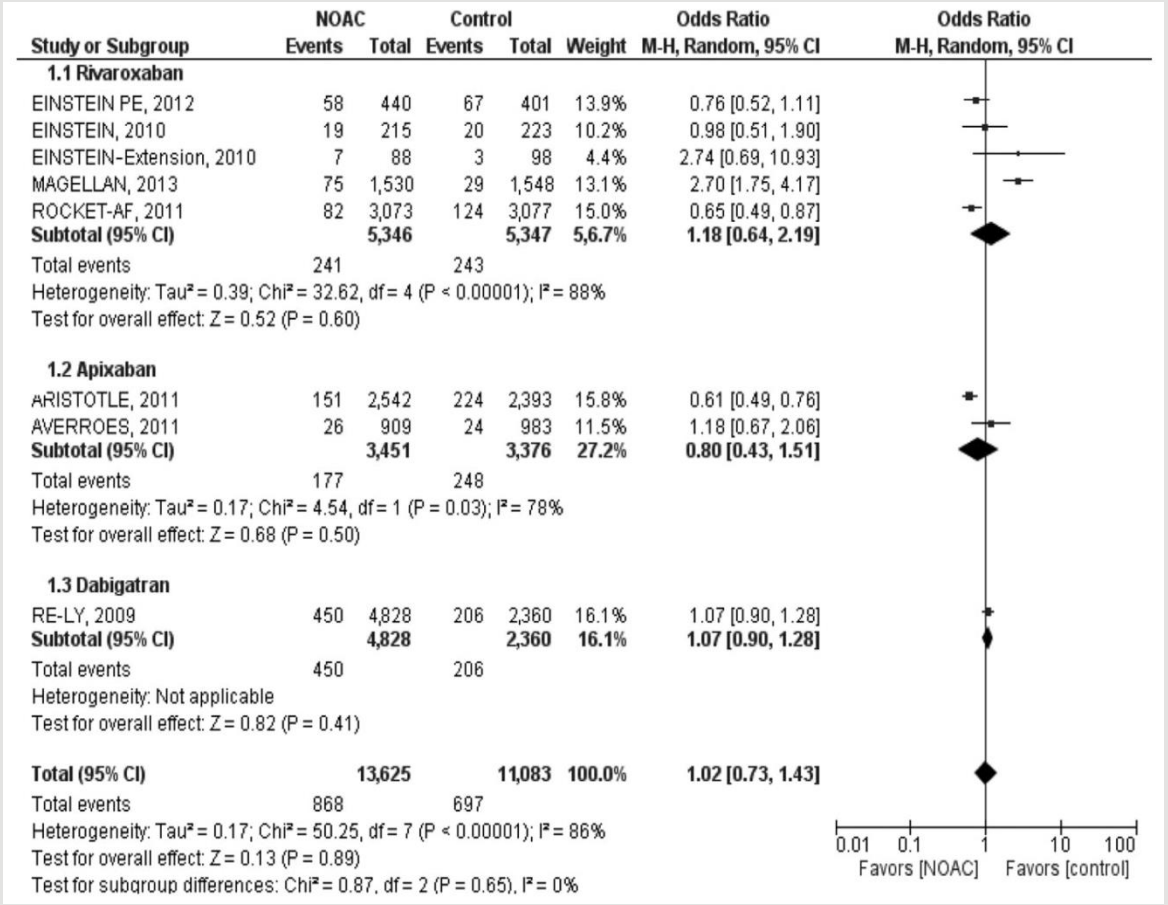
Patients ≥ 75 years *Stroke or SE*



Sardar et al; JAGS 2014

Patients ≥ 75 years

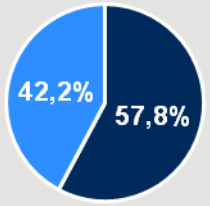
Major or Clinically Relevant Bleeding



Sardar et al; JAGS 2014

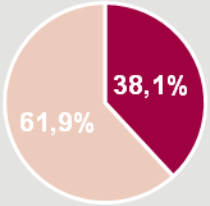
NOAC LOW DOSES TO «PROTECT» FROM BLEEDING RISKS

dabigatran



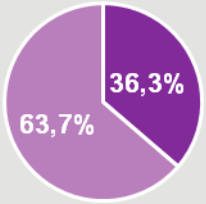
- Dabigatran 110 mg
- Dabigatran 150 mg

apixaban



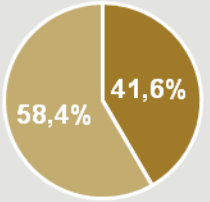
- Apixaban 2.5 mg
- Apixaban 5 mg

rivaroxaban



- Rivaroxaban 15 mg
- Rivaroxaban 20 mg

edoxaban

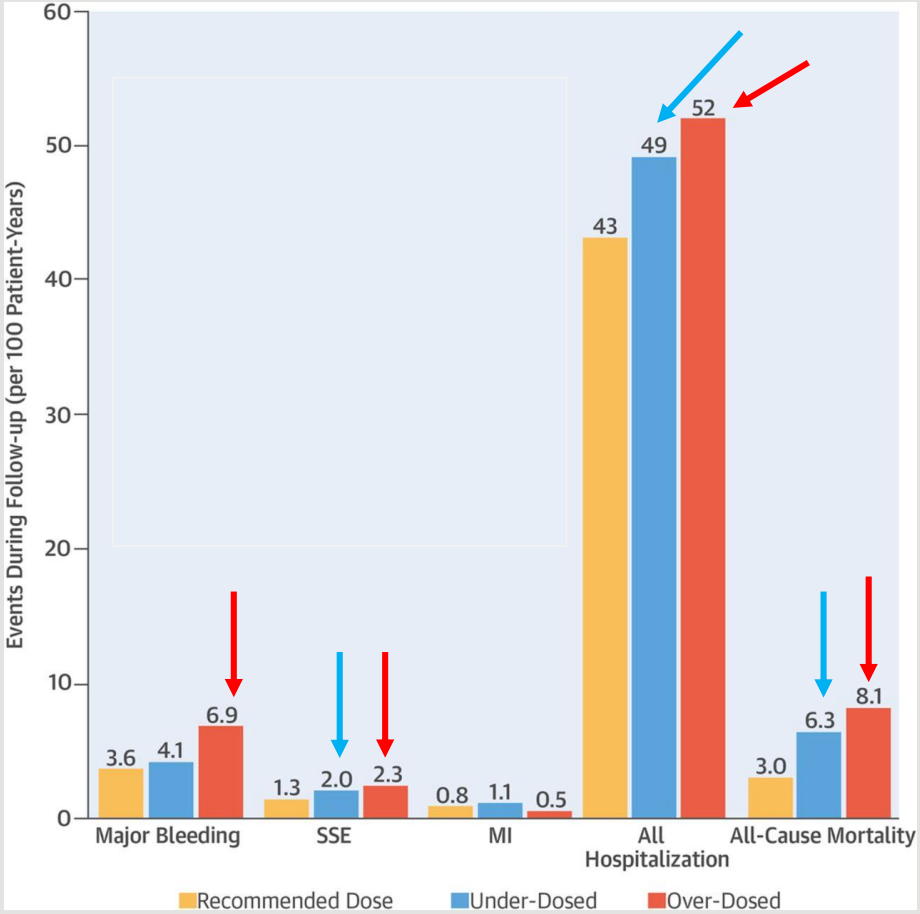


- Edoxaban 30 mg
- Edoxaban 60 mg

In Italian market, over 37% of patients are treated with a reduced dose of NOAC

Fonte: Dati IMS 2017

Off-label NOAC dosage and outcomes from ORBIT-AF II registry



Steinberg BA et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol. 2016 Dec 20;68(24):2597-2604. doi: 10.1016/j.jacc.2016.09.966

"Horizontal vs. vertical dose reduction of direct oral anticoagulants in patients with FANV: definition and implications for practice"

	Dabigatran		Rivaroxaban	Apixaban	Edoxaban
Population A (baseline)	150 mg BID →	110 mg BID	20 mg OD ↓	5 mg BID ↓	60 mg OD ↓
Population B (with factors mandating dose reduction[a,b,c])	—	—	*15 mg OD[a]*	*2.5 mg BID[b]*	*30 mg OD[c]*

[a] CrCl 30-49 ml/min; [b] ... e ≥ 1 ... min, body weight ≤60 kg, ... -P in ...

Physician's discretion never inappropriate

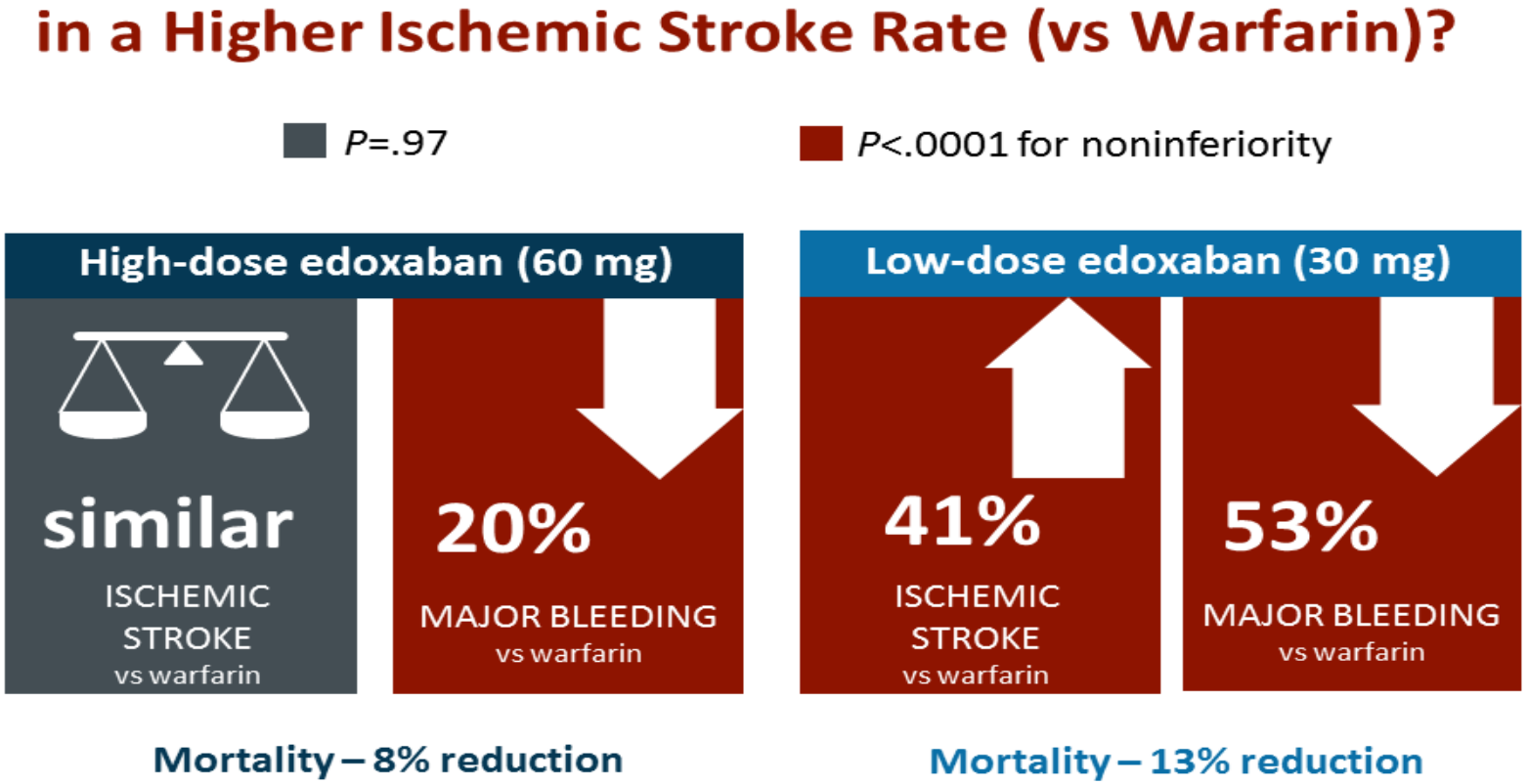
in the absence of the specific criteria **should be regarded as inappropriate**

"horizontal" dose reduction can, and **should, only be performed with dabigatran**.

"horizontal" dose reduction of factor Xa-inhibitors in the absence of the specific criteria **should be regarded as inappropriate.**

Rubboli A, Eur J Intern Med 2019

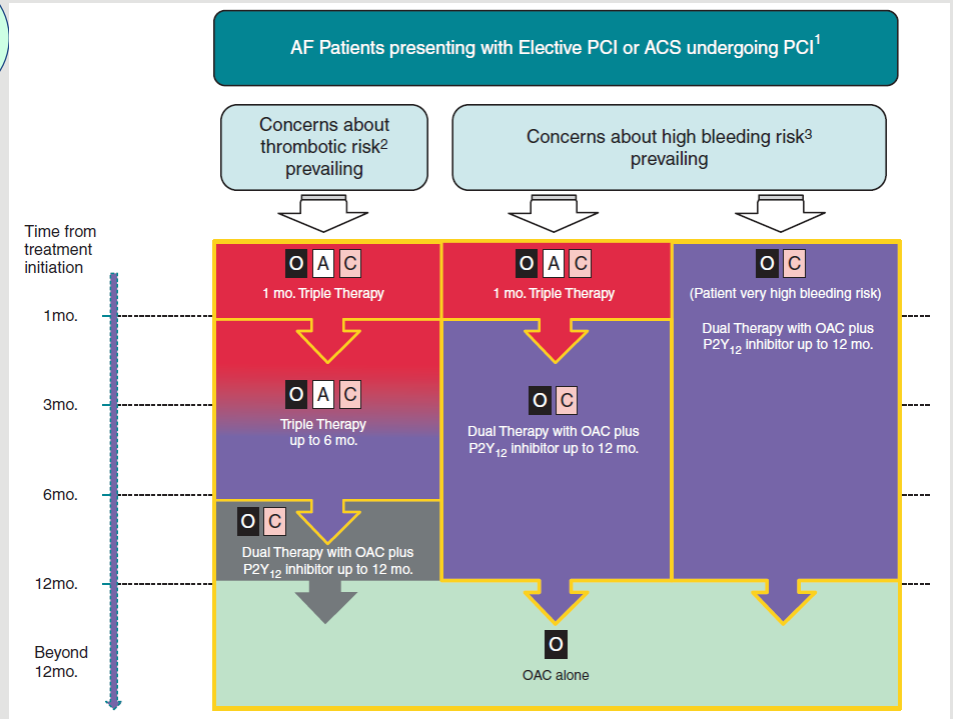
ENGAGE-AF: Does NOAC "Underdosing" Result in a Higher Ischemic Stroke Rate (vs Warfarin)?



Giugliano RP et al. *N Engl J Med*. 2013;369:2093-2104.

2018 Joint European consensus document on the management of antithrombotic therapy in AF patients presenting with acute coronary syndrome and/or undergoing PCI

Aug 2018



Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy; as dual therapy, potent P2Y12 inhibitors (ticagrelor) may be combined with dabigatran; 2: High atherothrombotic risk (For Elective PCI, use SYNTAX score; for ACS, GRACE score >140; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk; 3: Bleeding risk can be estimated using the HAS-BLED score; correct modifiable bleeding risk factors.

'As per prescribing label, **dabigatran 110 mg BID can be considered in elderly patients** and in patients with high bleeding risk both in DAT and TAT regimens'

'With DAT, **dabigatran 150 mg plus P2Y12 is preferred**, unless dose reduction criteria for dabigatran are present.'

'Low dose Dabigatran 110 mg and full dose apixaban 5 mg BID and edoxaban 60 mg OD should be selected to optimize risk-benefit ratio, **if part of a TAT regime.'**

'When rivaroxaban is used as part of DAT, reduced dose 15 mg OD may be considered.'

'when […] used in the absence of factors qualifying patients for dose reduction…safety of reduced-dose apixaban 2.5 mg BID and edoxaban 30 mg OD is likely higher, true efficacy in stroke prevention is unknown and should therefore generally not be used, even when DAPT […] is given in conjunction.'

Lip GYH et al. Europace 2018;doi:10.1093/europace/euy174.

DAT with rivaroxaban or dabigatran and a $P2Y_{12}$ inhibitor is associated with a lower risk of bleeding than TAT with warfarin. 39,40

- None have been sufficiently evaluated with respect to efficacy.

When dabigatran is used as part of DAT, the standard doses of 150 mg bid should be used to reduce the risk of ischaemic events. 39,40

Continued

- As per prescribing label, dabigatran 110 mg bid can be considered in elderly patients, concomitant when PgP inhibitors (e.g. verapamil) are used, and in patients with high bleeding risk
- Both dabigatran 150 mg or 110 mg bid have been shown to be non-inferior (and in the case of 150 mg bid, superior) to warfarin for stroke prevention in AF.

When rivaroxaban is used as part of DAT, reduced dose 15 mg od should be considered. 39

- The efficacy with respect to stroke prevention of this reduced dose in this population has not been sufficiently evaluated.

When apixaban or edoxaban are used as part of TAT or DAT, the standard dose (5 mg bid and 60 mg od, respectively, unless label-guided dose reduction is indicated) should be selected pending results of ongoing trials. Expert consensus

2018 Joint European consensus document on themanagement of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart RhythmAssociation (EHRA) – G.LIP et al.

ESC European Society of Cardiology

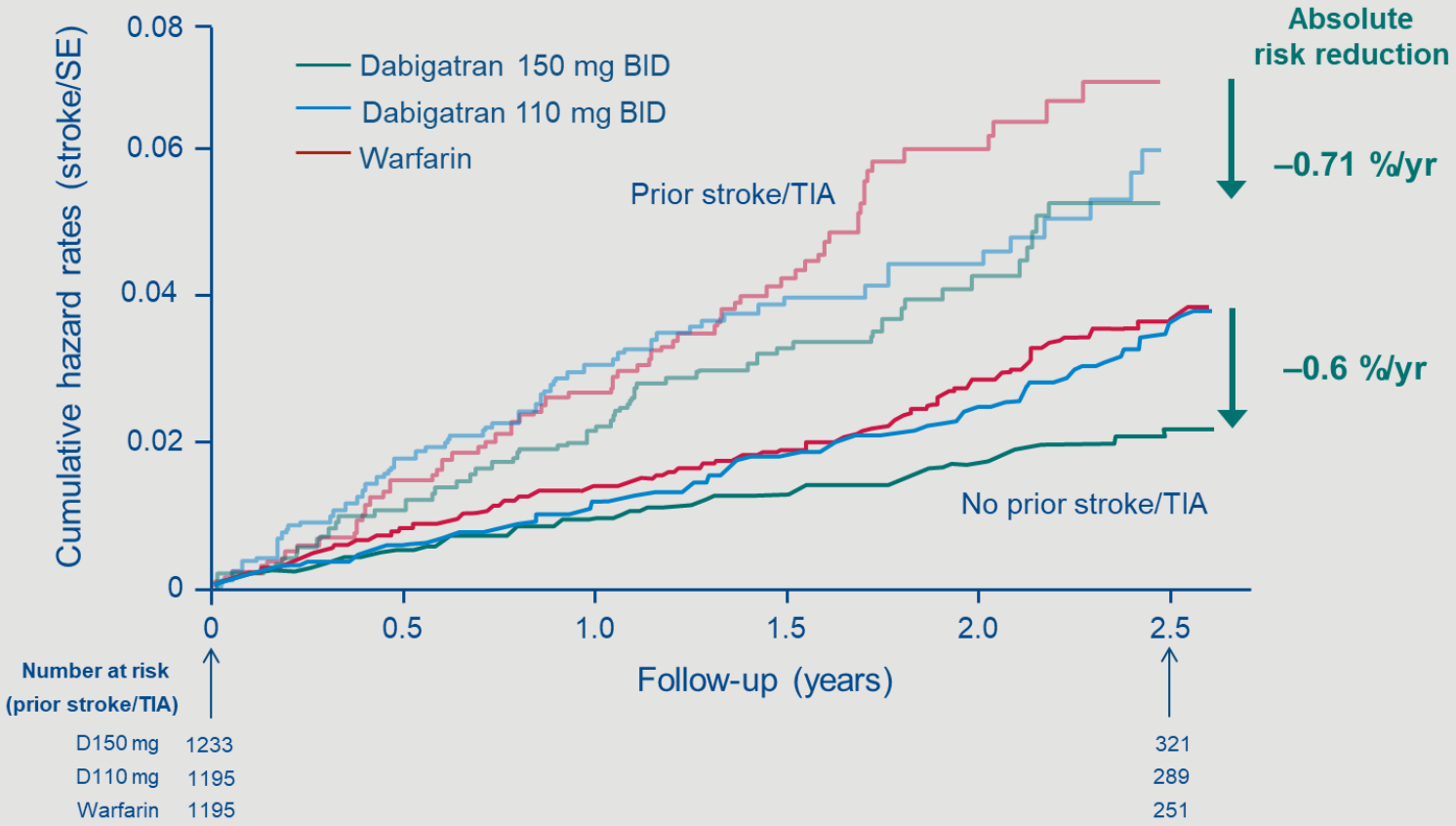
Europace
doi:10.1093/europace/euy174

2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulant in patients with AF – Steffel et al.

The use of NOAC doses inconsistent with drug labelling has been associated with worse outcome; for example, underdosing of apixaban in patients with normal or only mildly reduced renal function has been associated with less effectiveness (i.e. higher stroke rates) and no additional safety benefit in a large 'real-world' AF cohort.[202]

L'uso di dosaggi di NAO non in linea con la scheda tecnica è stato associato a risultati peggiori: per esempio il sottodosaggio di apixaban in pazienti con funzione renale normale o solo lievemente ridotta è stato associato ad una minore efficacia (es. più alti tassi di ictus) e nessun ulteriore vantaggio in termini di sicurezza in una grande coorte di pazienti con FA nel «real world»

Sustained reduction in secondary stroke with both dabigatran 150 mg BD and 110 mg BD

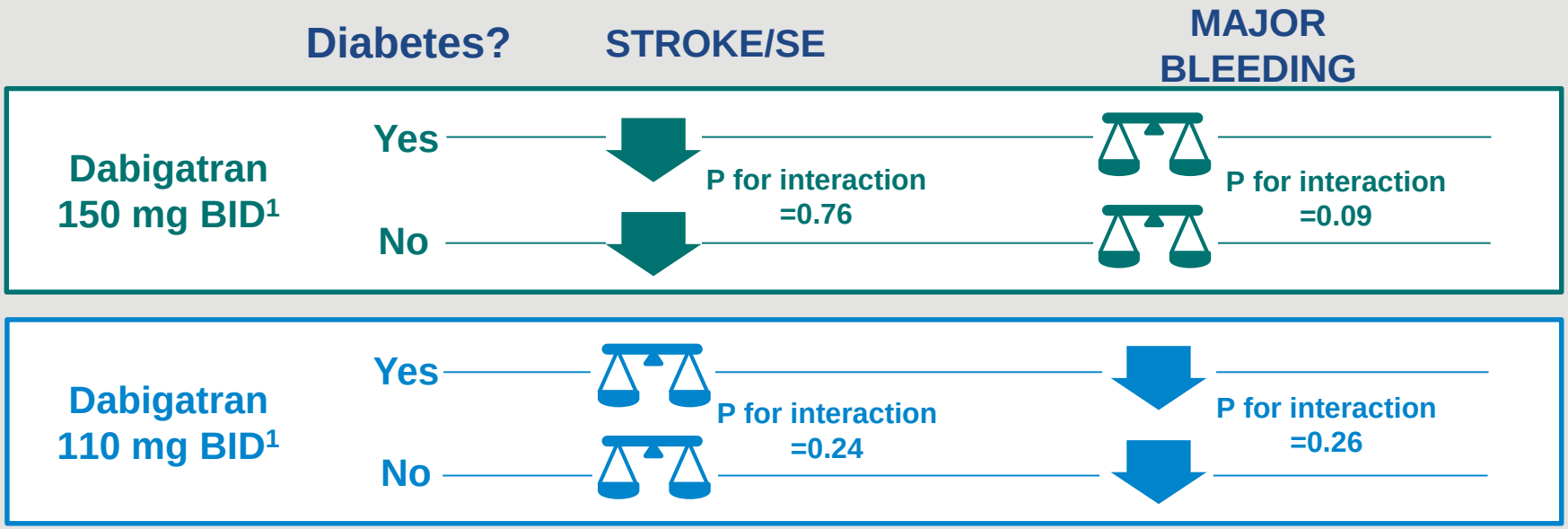


RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

SE, systemic embolism
Adapted from Diener et al. Lancet Neurol 2010 and data on file

Clinical profile of dabigatran consistent in diabetic and overall population, benefit in major bleeding confined to non-diabetic population

Subgroup analyses of patients with or without diabetes*



*Unlabelled arrows indicate lower risk for the respective endpoint independent of diabetes status consistent with the overall study results. 1. Brambatti et al. Int J Cardiol 2015;

In the observation period >18 months, substantial deterioration in renal function (>25% decrease in GFR) was significantly less likely with either dose of dabigatran vs warfarin

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Changes in Renal Function in Patients With Atrial Fibrillation

An Analysis From the RE-LY Trial

Michael Böhm, MD,* Michael D. Ezekowitz, MD, ChB, DPhil,†‡ Stuart J. Connolly, MD,§ John W. Eikelboom, MBBS,§ Stefan H. Hohnloser, MD,‖ Paul A. Reilly, PhD,¶ Helmut Schumacher, PhD,# Martina Brueckmann, MD,#** Stephan H. Schirmer, MD, PhD,* Mario T. Kratz, MD,* Salim Yusuf, MD, DPhil,§ Hans-Christoph Diener, MD,†† Ziad Hijazi, MD,‡‡ Lars Wallentin, MD, PhD‡‡

19%
RRR: **dabigatran 110 mg** BID vs warfarin

21%
RRR: **dabigatran 150 mg** BID vs warfarin

Böhm M et al. J Am Coll Cardiol 2015;65:2481–93

NO Mandatory Dose Adjustment for Patients with Moderate Renal Impairment

Pradaxa® label

- No dose adjustment is necessary in patients with mild renal impairment (CrCl 50–≤ 80 mL/min)
- **For patients with moderate renal impairment (CrCl 30–50 mL/min) the recommended dose of Pradaxa® is 150 mg BID**
  - **However, for patients with high risk of bleeding, a dose reduction of Pradaxa® to 110 mg BID should be considered**
- Treatment with Pradaxa® in patients with severe renal impairment (CrCl <30 mL/min) is contraindicated
- Close clinical surveillance is recommended in patients with renal impairment

Pradaxa®: EU SPC, 2015

OLD AGE

HEALTH

Ageing is a privilege and a goal of society, but it's also a challenge that will have an impact on all aspects of XXI centuty society
(OMS 2005)

FRAILTY

Dabigatran 110 mg is never unappropriate in NVAF patient unlike the other NOAC reduced doses

RE-LY[1]		ROCKET AF[2]	ARISTOTLE[3]	ENGAGE AF-TIMI 48[4]
Dabigatran 150 mg bid	Dabigatran 110 mg bid	Rivaroxaban 20 mg/die	Apixaban 5 mg bid	Edoxaban 60 mg/die
⇩	⇩	⇩	⇩	⇩
No dose adjustment	No dose adjustment	15 mg/die se ClCr 30-49 ml/min	2.5 mg bid se ≥2 tra: età ≥80 anni, peso ≤60 kg, creatinina ≥1.5 mg/dl oppure se ClCr 15-29 ml/min	30 mg/die se ≥1 tra: ClCr 30-50 ml/min, peso ≤60 kg, d concomitant inhibitor P-glicoprotein

bid, 2 volte al giorno; ClCr, clearance della creatinina.

ONLY FOR DABIGATRAN NO DOSE REDUCTIONS ARE REQUIRED

1- Connolly SJ et al. N Engl J Med 2009;361:1139-51; 2- Patel MR et al. N Engl J Med 2011;365:883-91 ; 3- Granger CB et al. N Engl J Med 2011;365:981-92 ; 4-Giugliano RP et al. N Engl J Med 2013;369:2093-10

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1. In the Italian market we observe an high prescriptions of reduced doses of NOAC

2. For High-non modifiable-bleeding risk **Guidelines recommend dabigatran 110 mg;** in absence of reduction criteria according to SMPC, other NOAC reduced doses are considered off-label

3. **Dabigatran 110 mg** is **a safe choice** because it's the only "low dose" with safety (superior) and efficacy (non inferiority) evidences vs warfarin in RCTs and confirmed in clinical real life

4. **Dabigatran 110 mg** is **a simple choice** because it's never unappropriate in NVAF patient unlike the other NOAC reduced doses

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