ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY
XXIX GIORNATE CARDIOLOGICHE TORINESI

EDOXABAN
"ULTIMO NATO MA FRUTTO DI TANTA ESPERIENZA"

Ferdinando Varbella
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STUDIO ENGAGE-AF TIMI 48

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361:** 1139–1151.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *Engl J Med* 2011; **365:** 883–891.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365:** 981–992.

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369:** 2093–2104.


GISE
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10 - 13 October 2017
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Milano - Italy


Beat


38°

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

Giugliano RP et al. N Engl J Med 2013

TIMI Study Group

An Academic Research Organization of Brigham & Women's Hospital and an Affiliate of Harvard Medical School

ABOUT TIMI | WHAT WE DO | CLINICAL TRIALS

Innovative clinical trials that enhance the understanding of cardiovascular disease and improve the care of patients.

Clinical Trials Index

(To access information about each trial, click on the link below.)

Current Trials

- HPS3/TIMI 55 REVEAL — anacetrapib
- DECLARE-TIMI 58
- CAMELLIA-TIMI 61
- PIONEER-HF

Recently Completed Trials

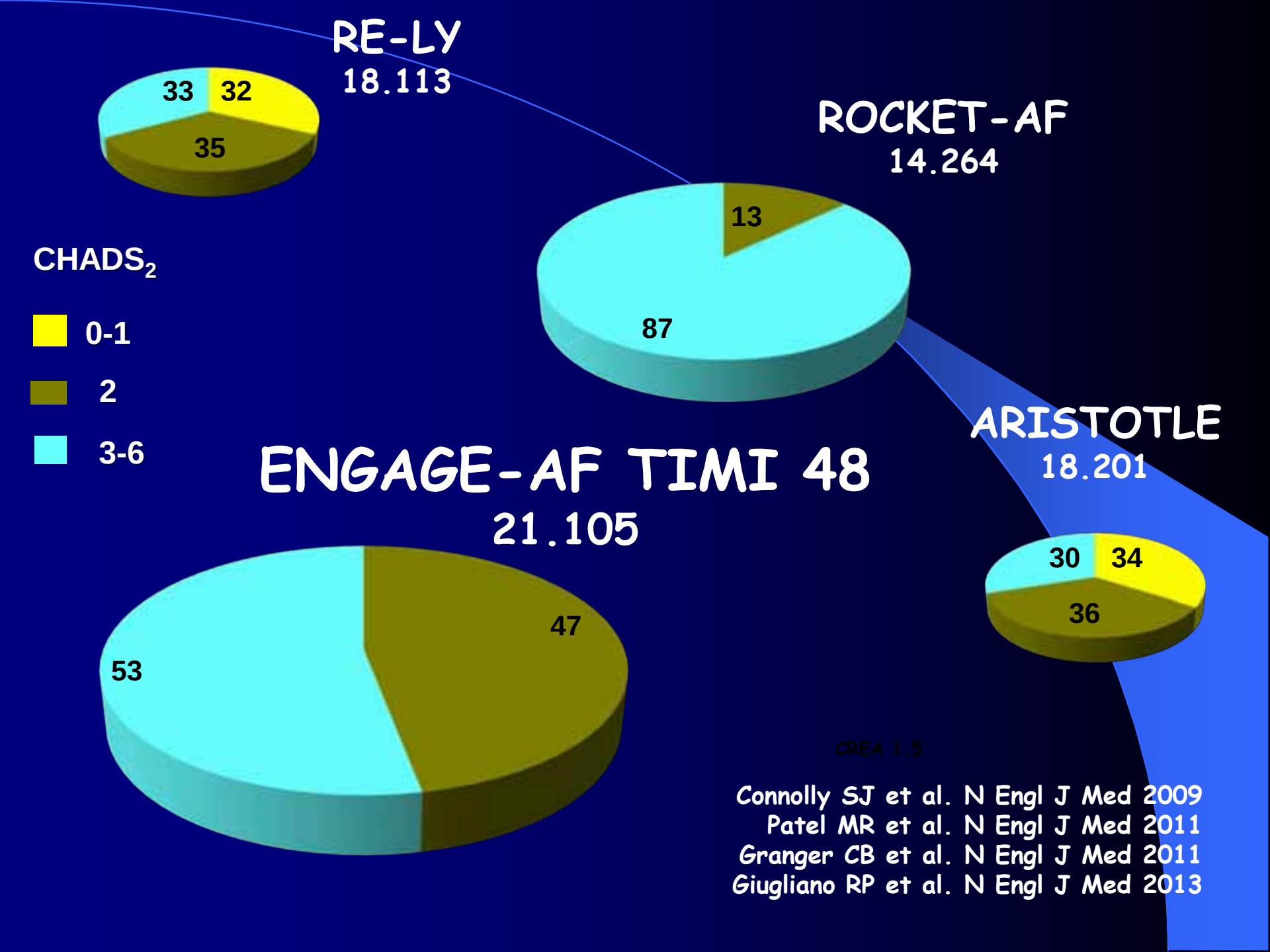
- IMPROVE-IT (TIMI 40)
- ENGAGE AF-TIMI 48
- TRA 2°P-TIMI 50 — vorapaxar
- ATLAS ACS2-TIMI 51 — rivaroxaban2.5
- SOLID-TIMI 52
- SAVOR-TIMI 53
- ELEVATE-TIMI 56
- PEGASUS-TIMI 54 — long ticagrelor
- LAPLACE-TIMI 57
- FOURIER (TIMI 59) / EBBINGHAUS — evolocumab
- LATITUDE-TIMI 60

Other Research Collaborations

- OSLER — evolocumab
- PLATO — ticagrelor ACS
- BWH-TIMI ED

Past Trials

- TIMI 1
- TIMI 2A
- TIMI 2B
- TIMI 3A
- TIMI 3B
- TIMI 3 REG
- TIMI 4
- TIMI 5
- TIMI 6
- TIMI 7
- TIMI 8
- TIMI 9A
- TIMI 9B
- TIMI 9 REG
- TIMI 10A
- TIMI 10B
- ASSENT 1-TIMI 10C
- TIMI 11A
- TIMI 11B
- TIMI 12
- TIMI 14
- TIMI 15A
- TIMI 15B
- OPUS-TIMI 16
- INTIME II-TIMI 17
- TACTICS-TIMI 18 → PCI in UA/NSTE
- ER-TIMI 19
- INTEGRITI-TIMI 20
- A2Z-TIMI 21
- PROVE IT-TIMI 22 — atorvastatin
- ENTIRE-TIMI 23
- FASTER-TIMI 24
- EXTRACT-TIMI 25
- JUMBO-TIMI 26
- PROXIMATE-TIMI 27
- CLARITY-TIMI 28 — plavix STEMI
- ADVANCE MI-TIMI 29
- PROTECT-TIMI 30
- TIMI 31
- ANTHEM-TIMI 32
- DISPERSE2-TIMI 33
- TITAN-TIMI 34
- PROMPT-TIMI 35
- MERLIN-TIMI 36 — ranolazina
- TIMI 37A
- TRITON-TIMI 38 — prasugrel PCI GPI/ NSTEMI
- EARLY ACS-TIMI 39
- SEPIA ACS-TIMI 42
- AVANT GARDE-TIMI 43
- PRINCIPLE-TIMI 44
- ATLAS ACS-TIMI 46 — rivaroxaban2.5
- IC TITAN-TIMI 47
- ICET-TIMI 49



Connolly SJ et al. N Engl J Med 2009
Patel MR et al. N Engl J Med 2011
Granger CB et al. N Engl J Med 2011
Giugliano RP et al. N Engl J Med 2013

CARATTERISTICHE DI EDOXABAN

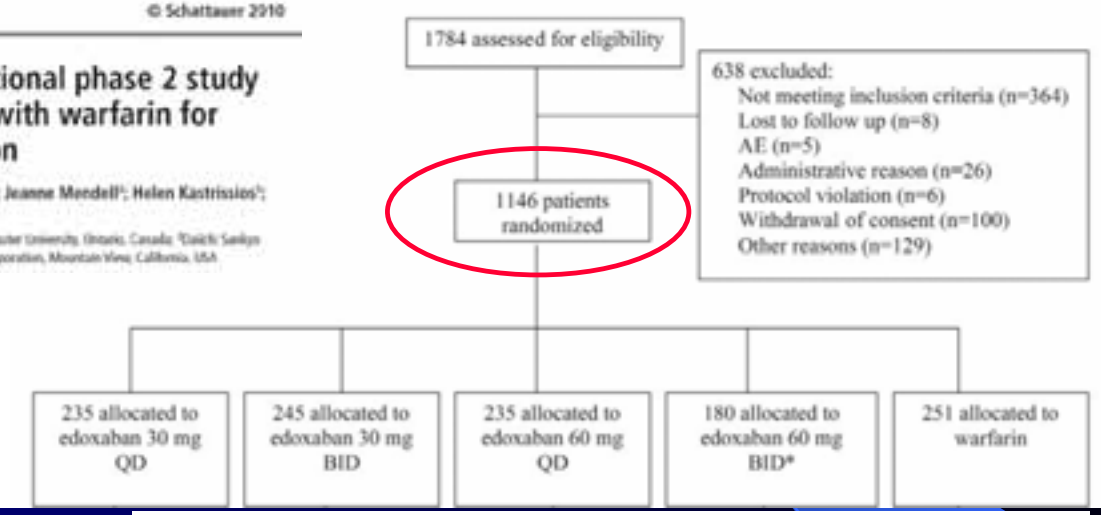
- inibitore diretto fattore Xa
- picco plasmatico 1-2 ore più rapido (2-3 ore gli altri)
- biodisponibilità 62 % non influenzata dal cibo
- eliminazione 50% urine e 50% feci

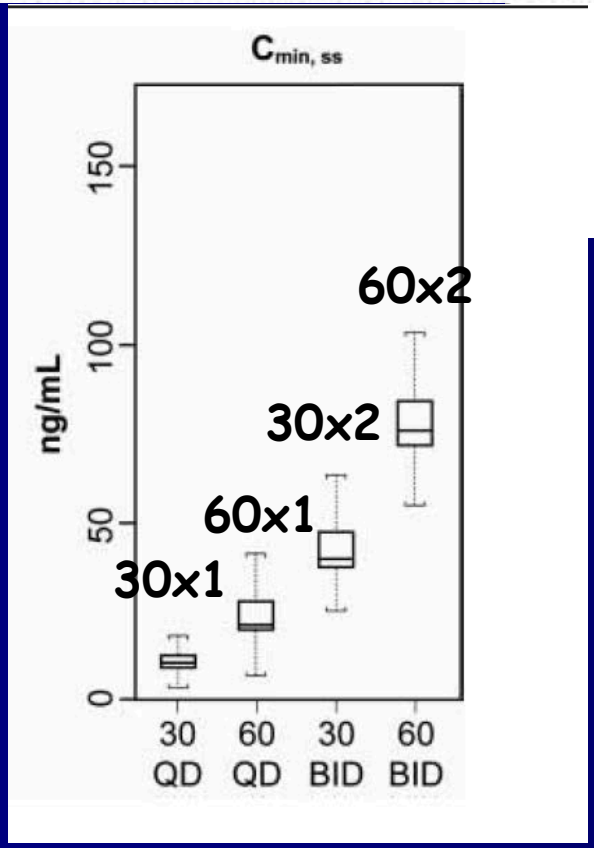
LA MONOSOMMISTRAZIONE DERIVA DA UNO STUDIO FASE 2

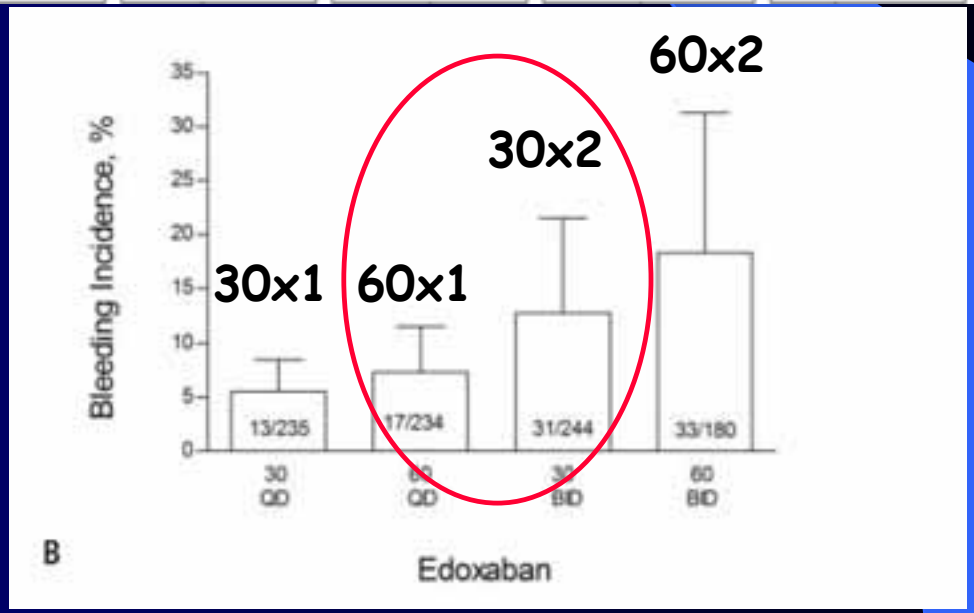
New Technologies, Diagnostic Tools and Drugs © Schattauer 2010

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

Jeffrey I. Weitz[1]; Stuart J. Connolly[2]; Indravadan Patel[3]; Daniel Salazar[4]; Shishank Rohatagi[4]; Jeanne Mendell[5]; Helen Kastrissios[5]; Jianqing Jin[5]; Satoshi Kunitada[3]







Weitz JI, Connolly SJ, Patel I et al. Thromb Haemost 2010

STUDY DRUGS

A total of 21,105 patients underwent randomization, of whom 21,026 (99.6%) received the study drug. A total of 5330 patients (25.3%) received a reduced dose of edoxaban or matching placebo at three treatment groups. The median duration of treatment exposure was 907 days, excluding interruptions; the median follow-up was 1022 days (2.8 years).

the warfarin group, the median time in the therapeutic range was 68.4% of the treatment period (interquartile range, 56.5 to 77.4), and the

1

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3

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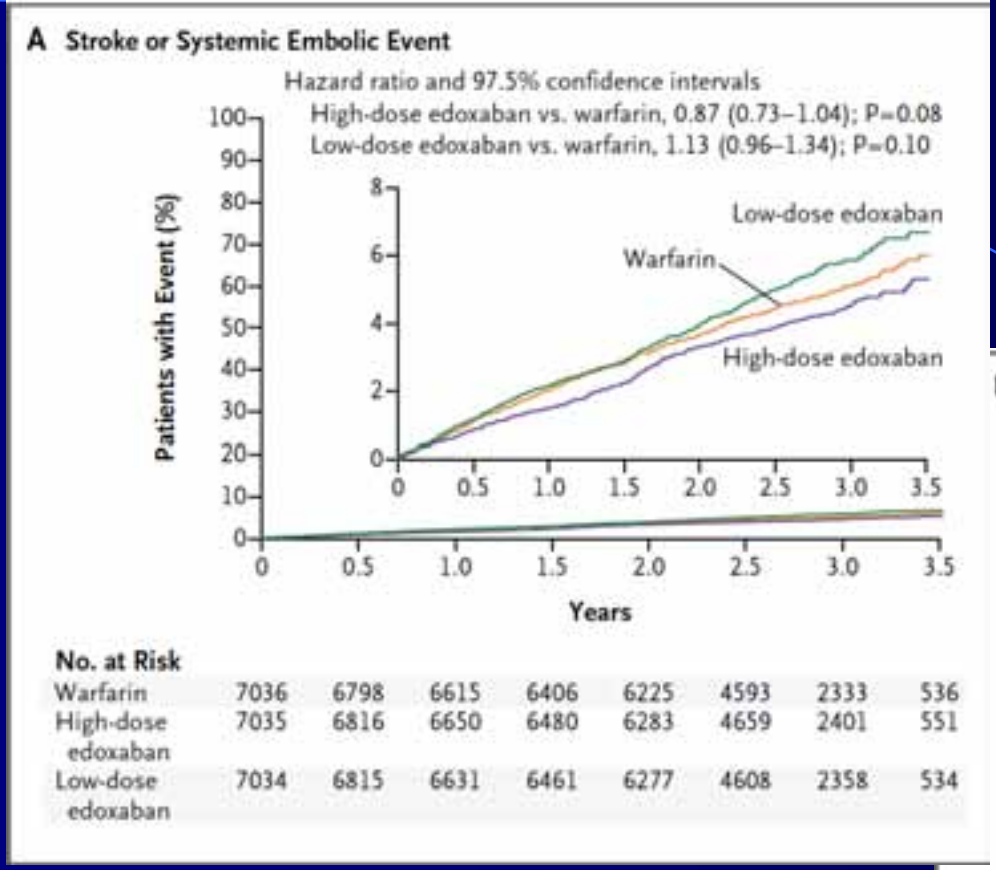
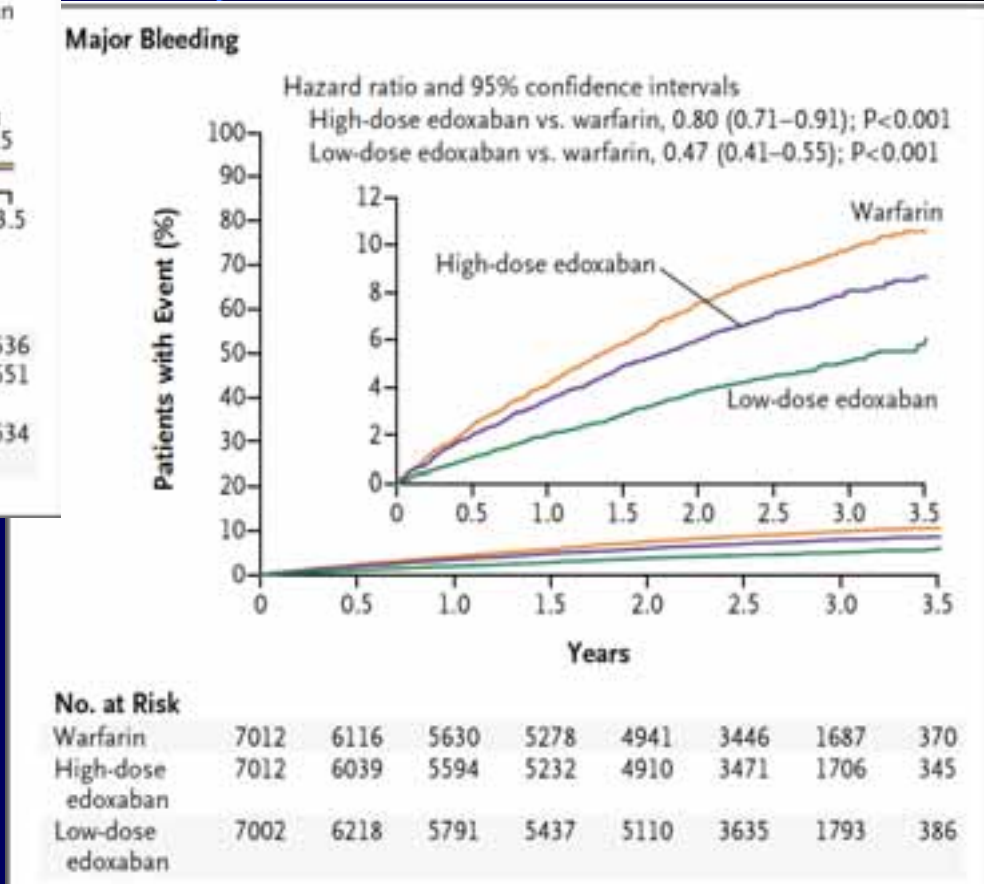
Giugliano RP et al. N Engl J Med 2013

SAFETY





EFFICACY

FDA ed EMA registrata solo HDER

Giugliano RP et al. N Engl J Med 2013

RIASSUMENDO

HDER 60/30 vs VKA

1. Non inferiore per SSEE
2. trend verso superiorità iTT
3. riduzione stroke emorragico
4. riduzione mortalità cardiovascolare
5. riduzione sanguinamenti maggiori, pericolosi o minori rilevanti

Table 2 Main efficacy and safety outcomes with edoxaban 60/30 mg vs warfarin in ENGAGE AF-TIMI 48

	HR (95% CI)	*P* value
Stroke/SEE		
mITT	0.79 (0.63–0.99)	<0.001[b]
ITT	0.87 (0.73–1.04)[a]	0.08[b]
Stroke	0.88 (0.75–1.03)	0.11
Hemorrhagic	0.54 (0.38–0.77)	<0.001
Ischemic	1.00 (0.83–1.19)	0.97
Death		
All-cause	0.92 (0.83–1.01)	0.08
CV	0.86 (0.77–0.97)	0.013
Myocardial infarction	0.94 (0.74–1.19)	0.60
Bleeding		
Major	0.80 (0.71–0.91)	<0.001
Life-threatening	0.51 (0.38–0.70)	<0.001
Major or CRNM	0.86 (0.80–0.92)	<0.001

De Caterina R et al. Adv Ther 2017

VANTAGGI

- monosomministrazione
- interazioni = la più bassa interazione (pGP & CitP450)
- non richiede riduzione di dose per amiodarone, verapamil
- sicurezza con associazione antipiastrinici

INTERAZIONI FARMACOLOGICHE
amiodarone verapamil chinidina non richiedono riduzione

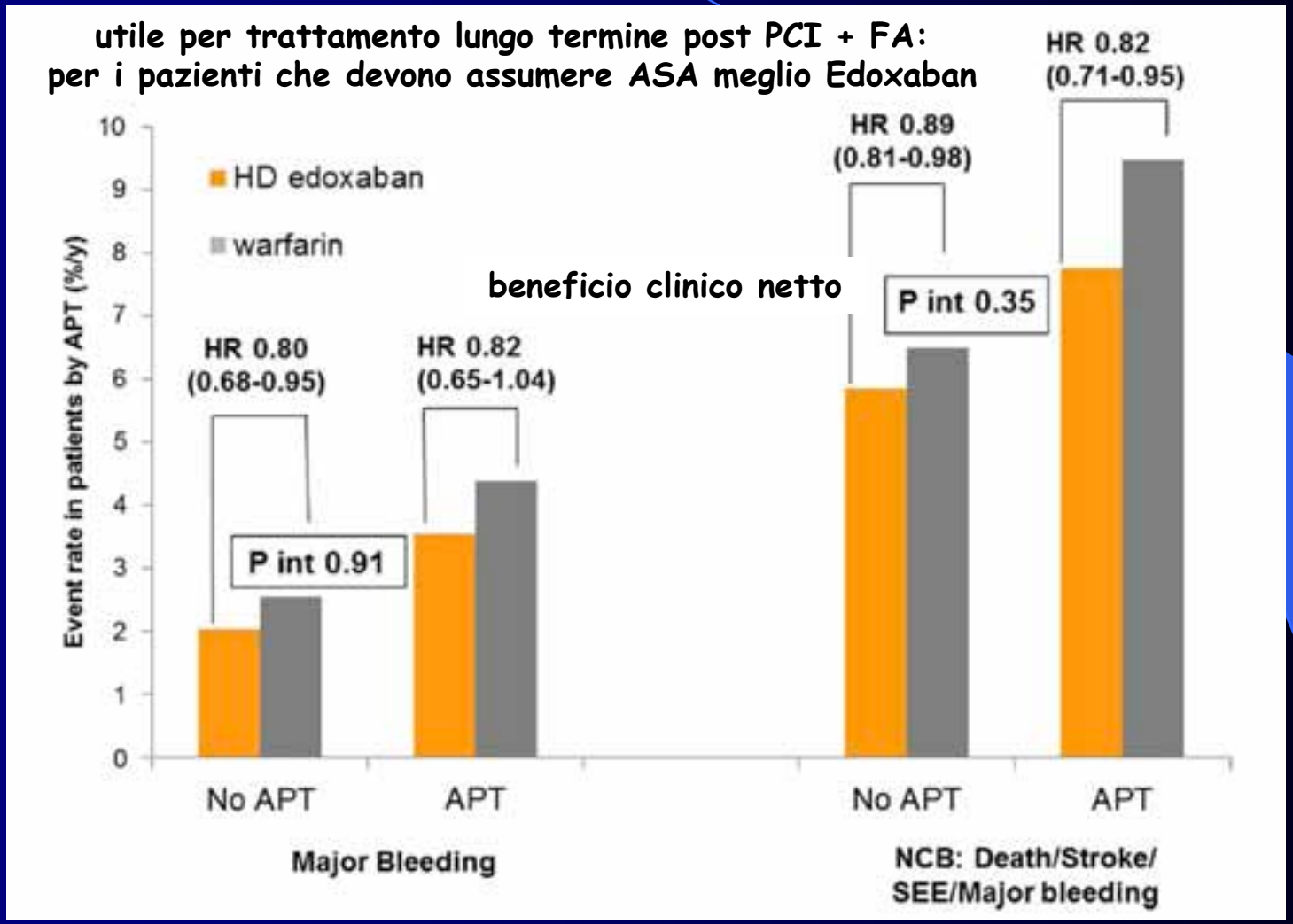
Inhibitors	via	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Antiarrhythmics drugs					
Dronedarone	P-gp competition and CYP3A4 inhibition	Contraindicated/ not recommended	Moderate effect but no PK or PD data: caution and try to avoid	No PK or PD data: caution	Reduce from 60 mg to 30 mg
Fungostatics					
Itraconazole, ketoconazole, posaconazole, voriconazole	Potent P-gp and BCRP competition; CYP3A4 inhibition	Contraindicated/ not recommended	Contraindicated/ not recommended	Contraindicated/ not recommended	Reduce from 60 mg to 30 mg
ciclosporina		NO	NO	NO	ridurre 30 mg
Inducers					
Carbamazepine, phenobarbital, phenytoin, St John's wort	P-gp/BCRP and CYP3A4/ CYP2 J inducers	Contraindication for simultaneous use	Contraindication for simultaneous use	Contraindication for simultaneous use	Co-administration is possible

ev 75 mg

De Caterina R et al. Adv Ther 2017

associazione con Singolo AntiPiastrinico (sAPT)

>30% dei pazienti alla randomizzazione assumeva ASA
25% dei pazienti proseguiva APT dopo 3 mesi



Xu H, Ruff CT, Giugliano RP et al. J Am Heart Assoc 2016

VANTAGGI ANZIANI, IRC E BASSE DOSI

- pazienti *fragili anziani* a rischio di cadute

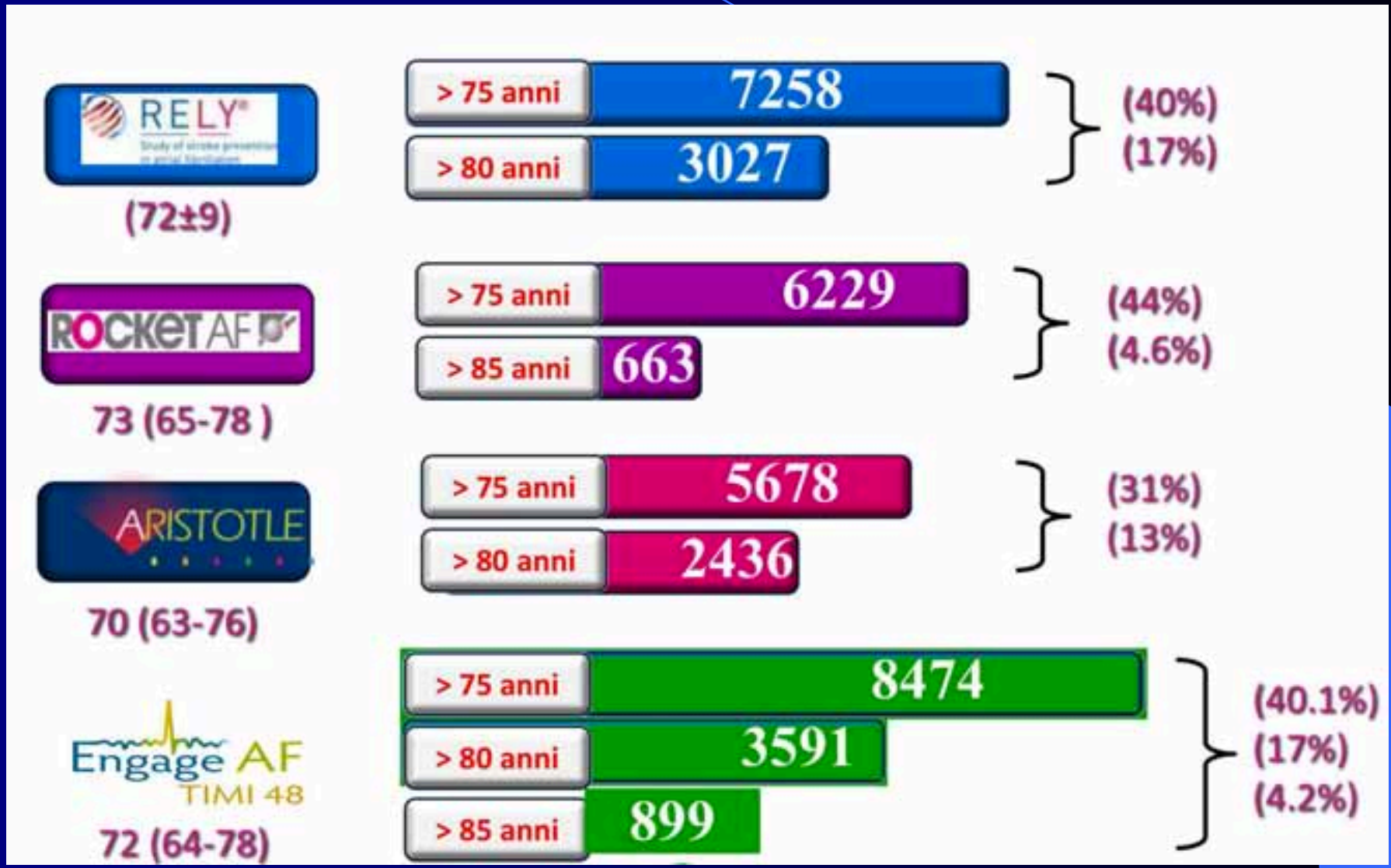
lo studio che include il maggior numero di anziani:

- pazienti con *Insufficienza renale*
  ENGAGE-AF-TIMI 48 ha il 19.3 % di pazienti con GFR 30-50 ml/min

- *Bassi dosaggi* testati su 1784 (30 mg) pazienti.
  Oltre 5000 con 30 mg

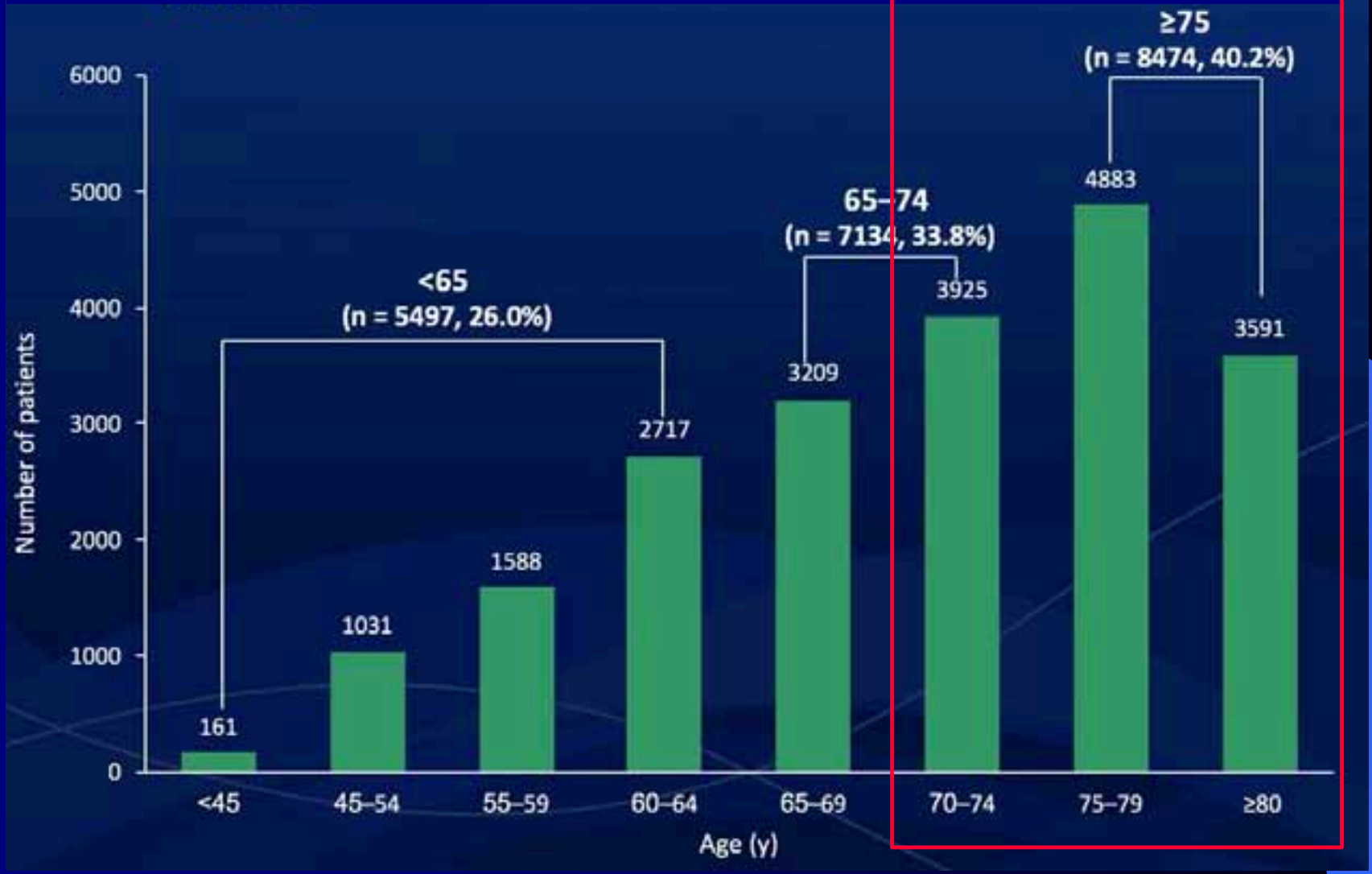
PAZIENTI ANZIANI

RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE-AF-TIMI 48

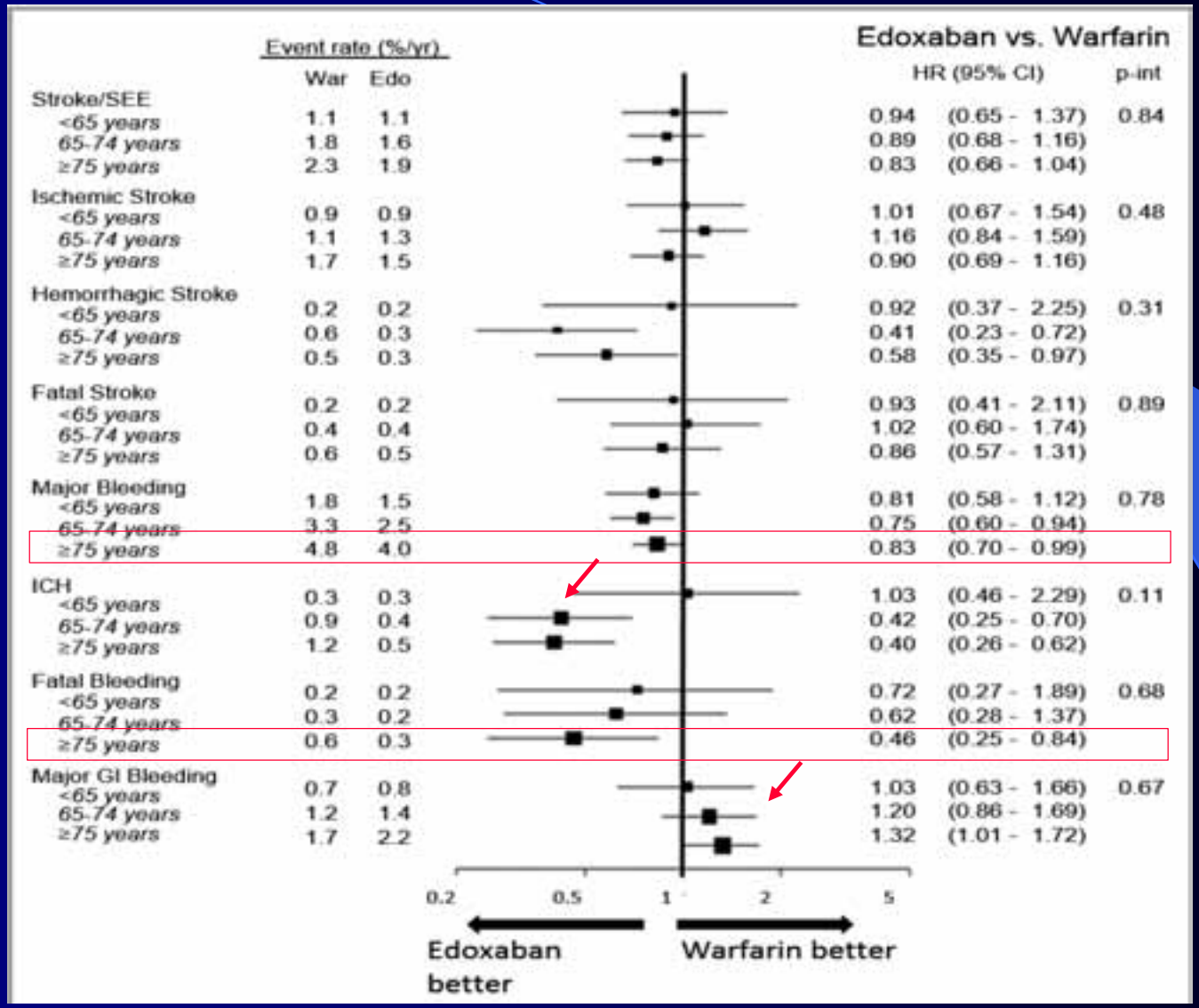


PAZIENTI ANZIANI

la maggior parte dei pazienti nello studio ENGAGE-AF-TIMI 48 è anziana



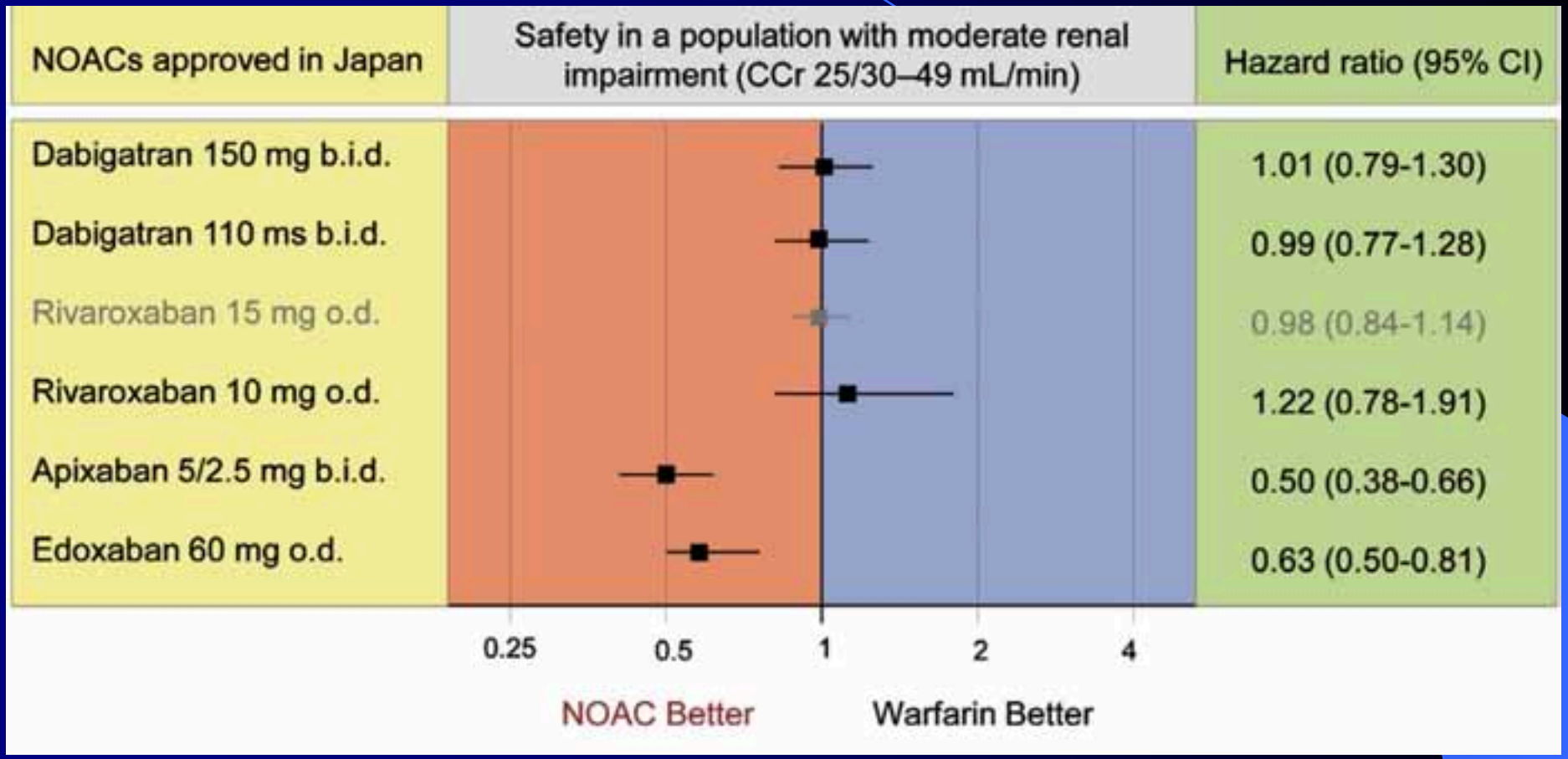
PAZIENTI ANZIANI



Kato ET, Giugliano RP, Ruff CT et al. J Am Heart Assoc 2016

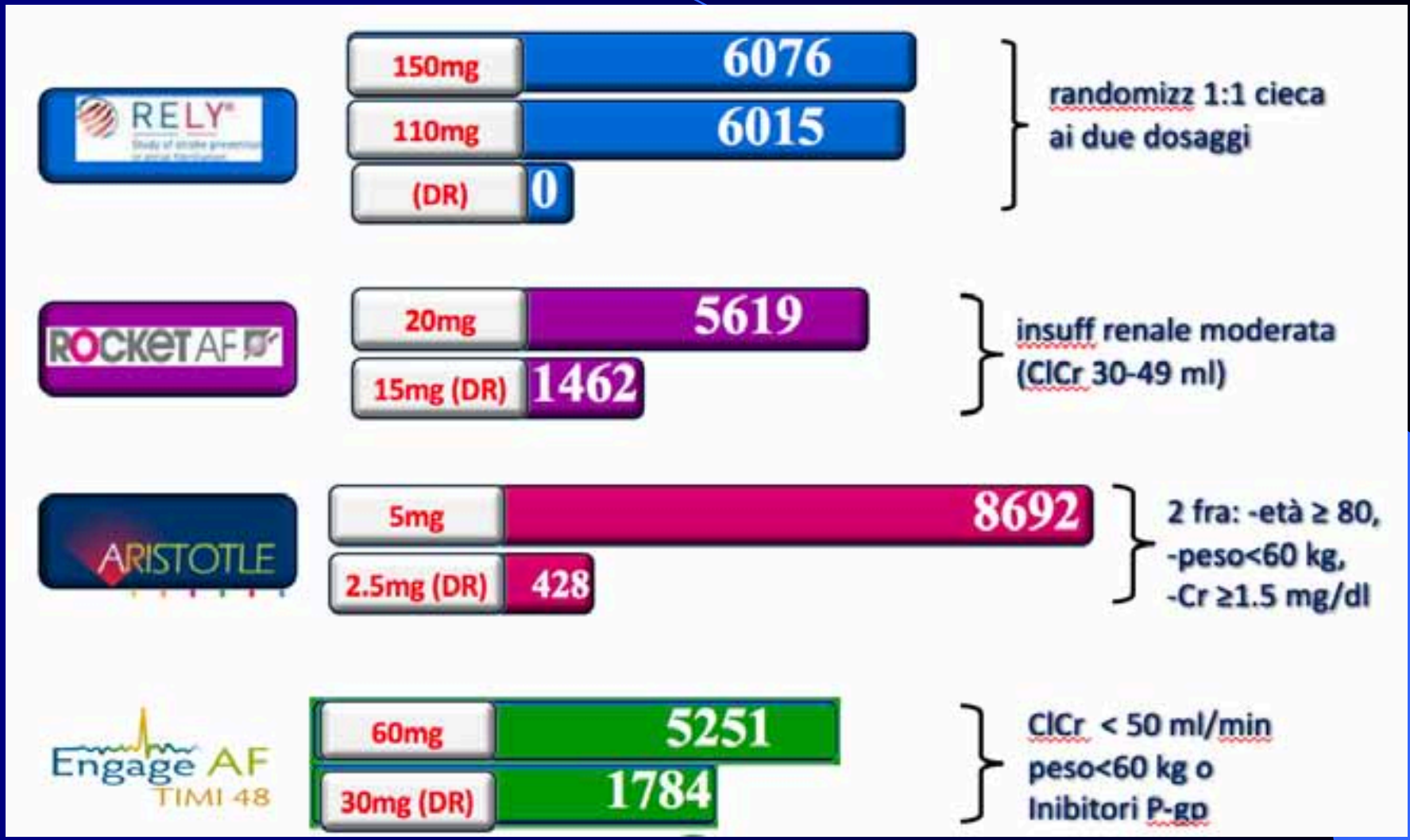
GFR < 50 PROFILO DI SICUREZZA

matanalisi RE-LY, ROCKET-AF, J-ROCKET-AF, ARISTOTLE, ENGAGE-AF-TIMI 48



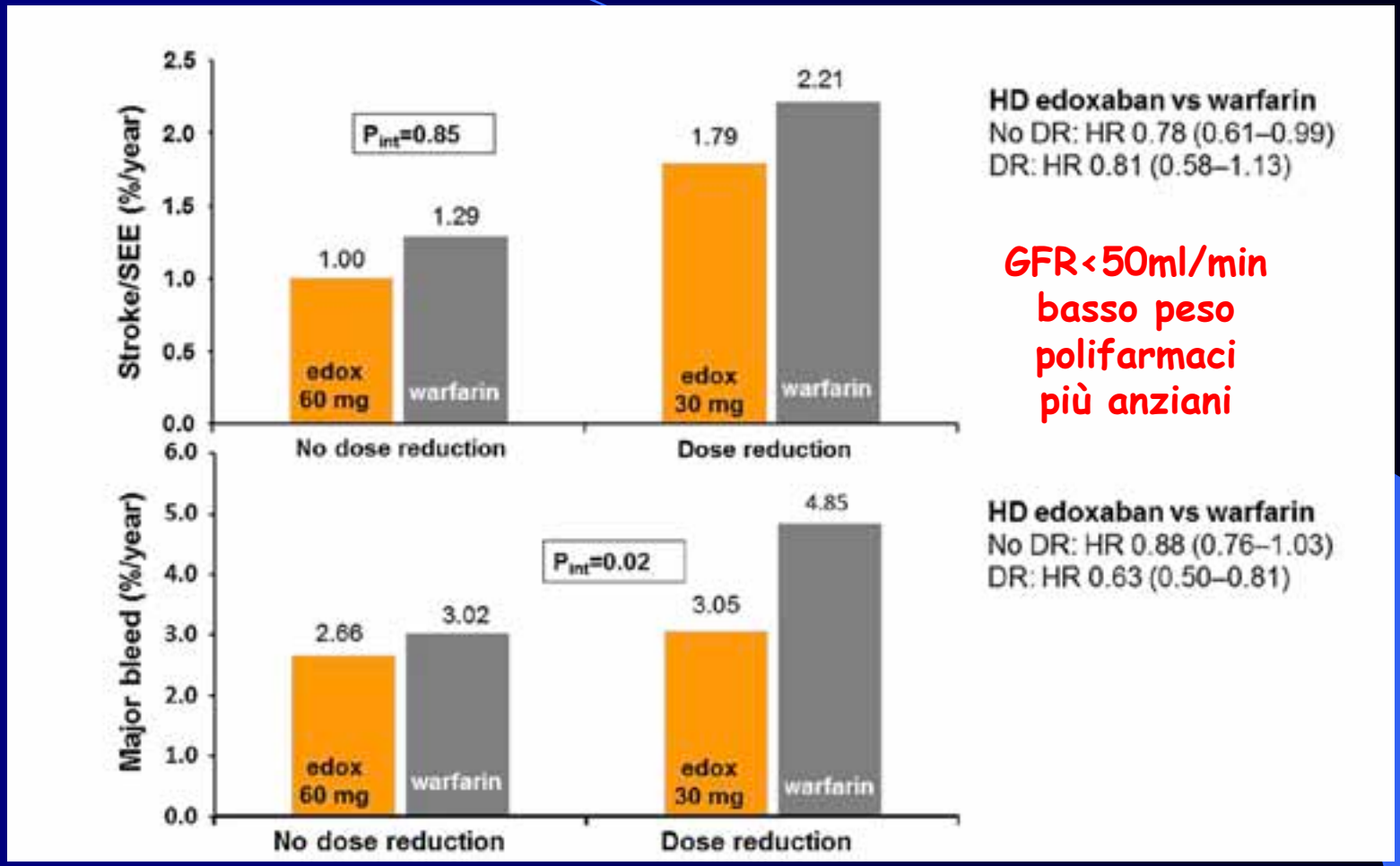
Takanori Ikeda Circ J 2015

EFFICACIA E SICUREZZA DELLE BASSE DOSI



\+ Includendo LDER vi sono oltre 5000 con 30 mg

EFFICACIA E SICUREZZA DELLE BASSE DOSI



i pazienti in cui è necessaria bassa dose sono più a rischio ma la bassa dose di Edoxaban è più efficace e sicura di Warfarin

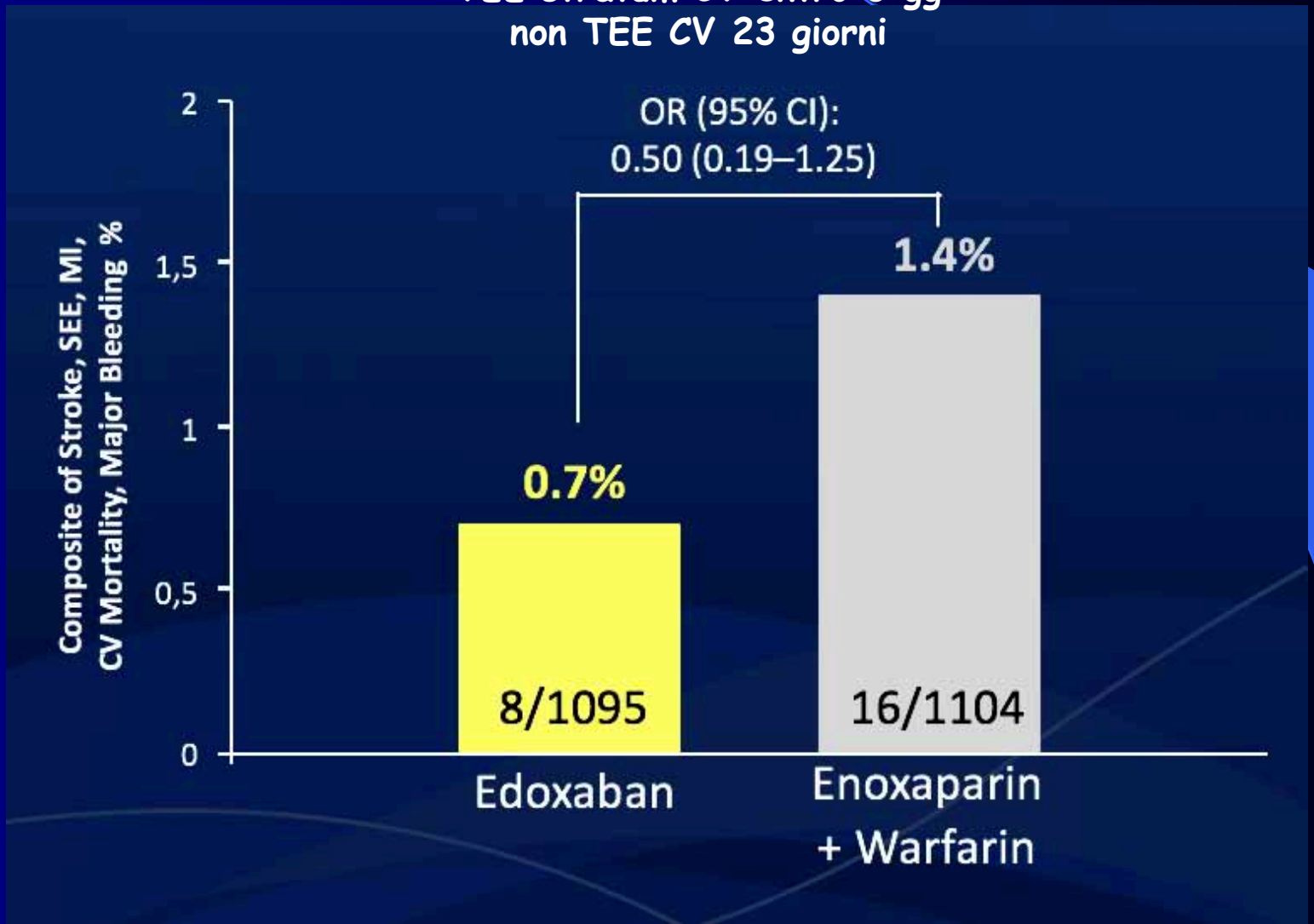
De Caterina R et al. Adv Ther 2017

CARDIOVERSIONE ENSURE-AF

Goette A, Merino JL et al. Lancet 2016

BENEFICIO CLINICO NETTO ENSURE-AF EFFICACY

primo trial ad arruolare GFR 15-30 ml/min
maggior numero 2200 pazienti
TTR in Warfarin 70.8
TEE stratum CV entro 3 gg
non TEE CV 23 giorni



FIBRILLAZIONE ATRIALE VALVOLARE O NON VALVOLARE

EDOXABAN E AF "VALVOLARE" SOTTOSTUDIO ENGAGE-TIMI48

2824 (13%) moderata o severa VHD vs 18222 (87%) no VHD

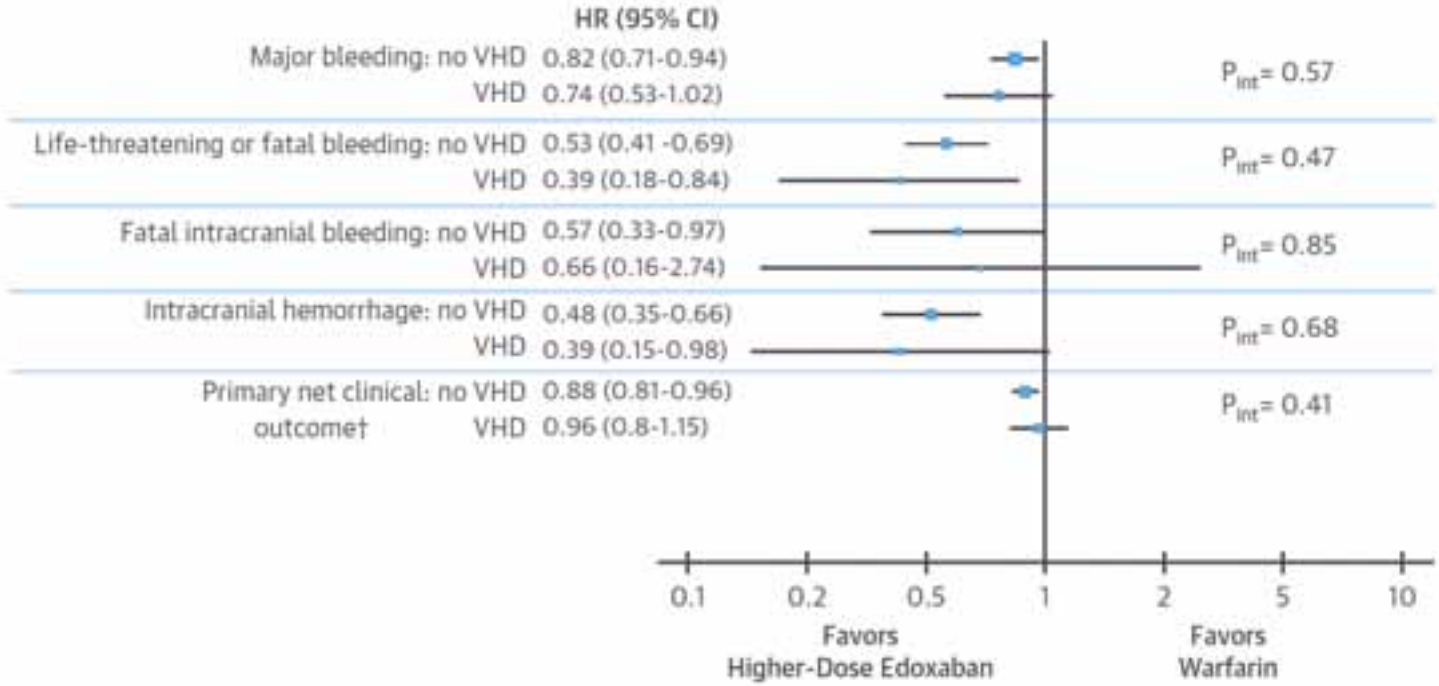
TABLE 1 Types and Frequency of VHD Patients in ENGAGE AF-TIMI 48

Category*	n	%
Mitral regurgitation	2,250	10.7
Aortic regurgitation	369	1.7
Aortic stenosis	165	0.8
Valve surgery	325	1.5
Bioprosthetic valves	191	0.9
Valve repair	123	0.6
Valvuloplasty	19	0.9

De Caterina R, Renda G et al JACC 2017

EDOXABAN vs WARFARIN IN AF
VHD vs non VHD

FIGURE 2 Forest Plot for Safety Outcomes in Patients Treated With Edoxaban Versus Those Treated With Warfarin, With or Without VHD

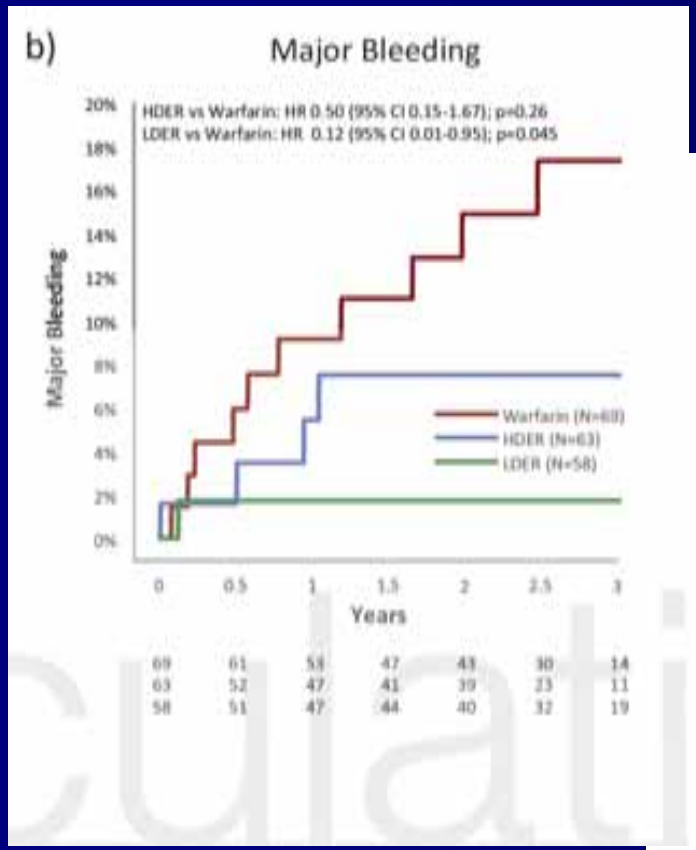


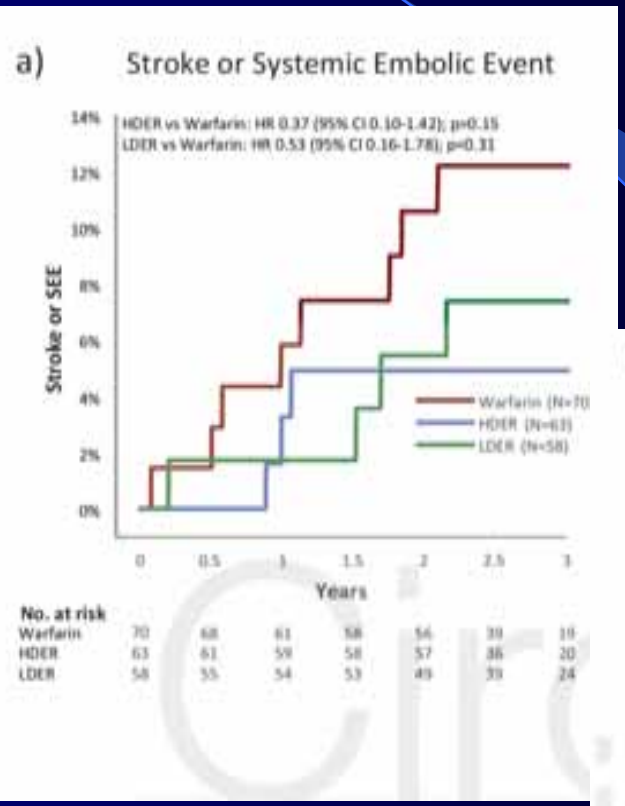
- nessuna differenza di EFFICACY tra Edoxaban e Warfarin in VHD-AF (SSEE, IS-SEE)
- SAFETY: minore incidenza di sanguinamenti

De Caterina R, Renda G et al JACC 2017

191 BIOPROTESI (131 mitraliche, 60 aortiche)
> 30 gg dall'intervento

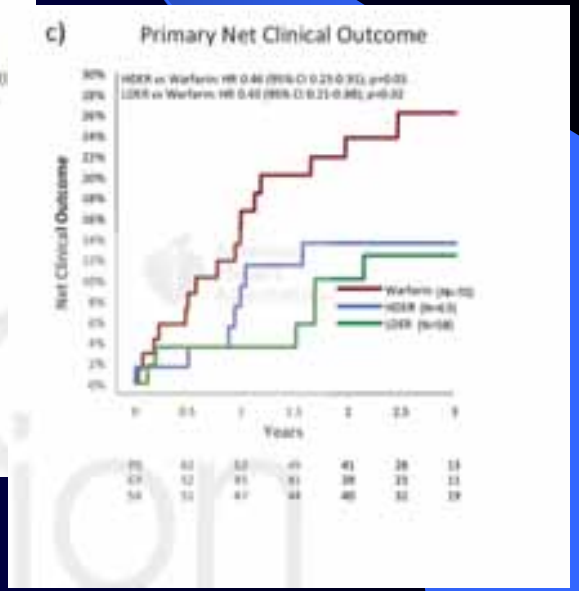
vs n 80 in ARISTOTLE





composito

Stroke+SEE
ISTH major
Morte



età mediana 75
CHADS 3
HAS-BLED 2.7
76 % precedente VKA
21% precedente ictus/TIA
34% con ASA

Carnicelli AP, De Caterina R et al. Circulation 2017

ULTIMA DIAPOSITIVA

A favore di AVK

- TTR >70% nei pazienti già trattati
- Assenza di rischio trombotico/emorragico elevato
- Valvulopatie gravi o protesi valvolari
- Insufficienza renale o epatica grave
- Neoplasie severe
- Pazienti in cui è prevedibile una scarsa aderenza
- Necessità di doppia antiaggregazione (sono in corso studi anche con i NAO a minor dosaggio)
- Trattamento con farmaci che hanno dimostrato interferenze rilevanti con i NAO
- Intolleranza ai NAO
- Preferenza del paziente

Nardi F et al. G Ital Cardiol Nov 2016

A favore di AVK

- ~~TTR >70% nei pazienti già trattati~~
- ~~Assenza di rischio trombotico/emorragico elevato~~
- ~~Valvulopatie gravi~~ o protesi valvolari **MARM-AF** Mechanical And Rheumatic Mitral + biologiche, plastica per 3 mesi
- Insufficienza renale o epatica grave **GFR < 15; CHILD B,C**
- ~~Neoplasie severe~~ **?**
- ~~Pazienti in cui è prevedibile una scarsa aderenza~~
- ~~Necessità di doppia antiaggregazione~~ (sono in corso studi anche con i NAO a minor dosaggio)
- ~~Trattamento con farmaci~~ che hanno dimostrato interferenze rilevanti con i NAO **inibitori proteasi HIV**
- ~~Intolleranza ai NAO~~
- ~~Preferenza del paziente~~

Nardi F et al. G Ital Cardiol Nov 2016

S. Luigi Gonzaga

Orbassano (To)

GRAZIE PER L'ATTENZIONE