SESSIONE CONGIUNTA AME FADOI

Trattamento e follow up dei parametri extraglicemici dopo la dimissione

Terapia anti-trombotica/anti-coagulante

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SOCIETA' SCIENTIFICA DI MEDICINA INTERNA
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FEDERAZIONE DELLE ASSOCIAZIONI DEI DIRIGENTI OSPEDALIERI INTERNISTI

Associazione
Medici
Endocrinologi

ITALIAN CHAPTER

2nd AME Diabetes Update

Diabete mellito e danno macrovascolare: gestione clinica

Bologna, 10 - 11 febbraio 2017

Novotel Bologna Fiera

Programma preliminare

2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for Antiplatelet, Statin, and Antihypertensive Agents		
COR	**LOE**	**Recommendations**
Antiplatelet Agents		
I	A	Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD (121-124).
IIa	C-EO	In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.
IIb	B-R	In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain (67, 68, 121, 124).
IIb	B-R	The effectiveness of dual-antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established (125, 126).
IIb	C-LD	Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization (127-130).
IIb	B-R	The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain (131-134).

Studio CAPRIE

Clopidogrel ↓ 10% eventi vascolari maggiori rispetto ad ASA (p=0.03)

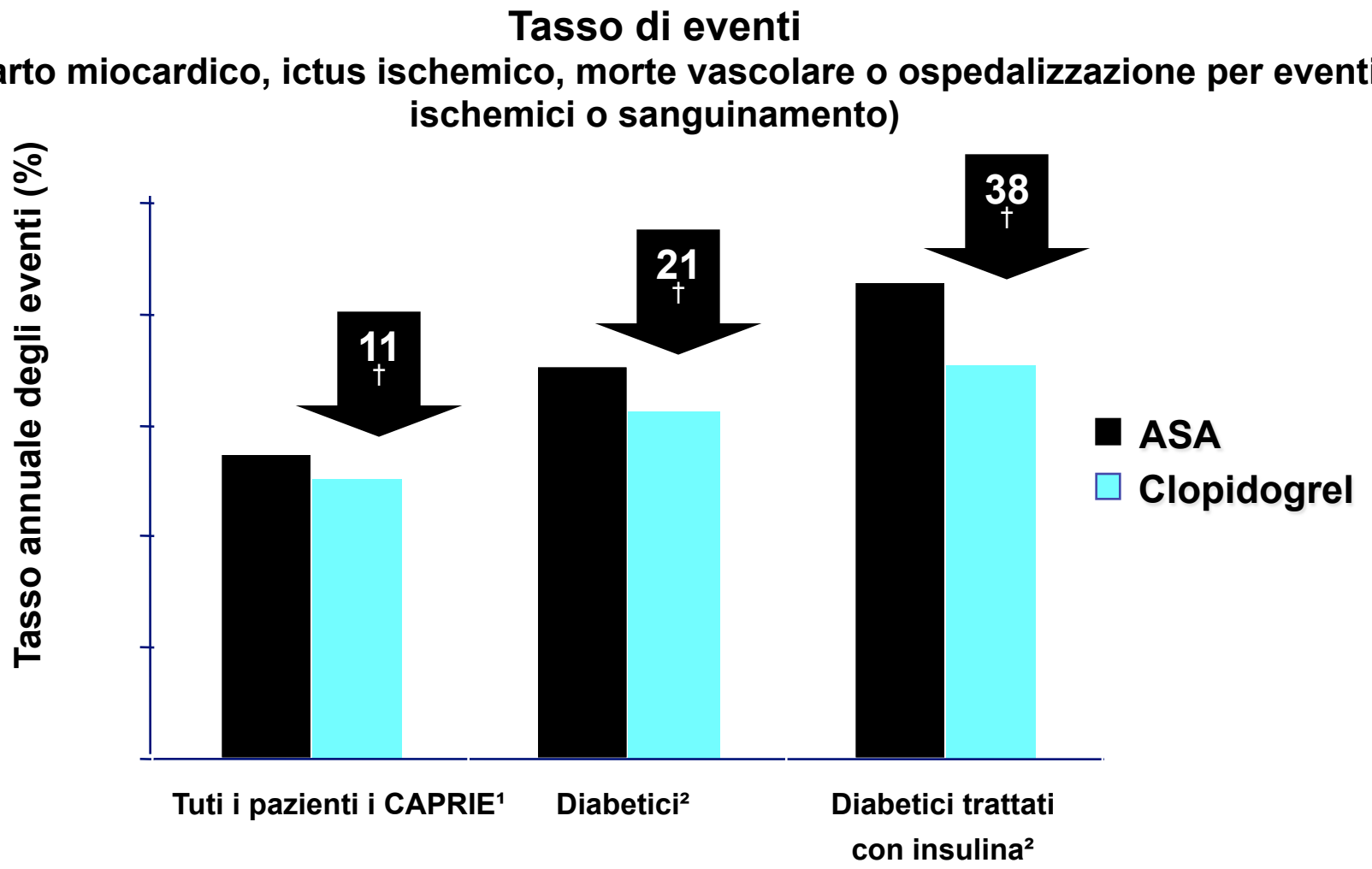
follow-up 1-3 anni in pazienti con angina cronica stabilizzata

aspirina 5.04%

clopidogrel 4.2%

RRR 19.2%;p=0.0008

CAPRIE: maggiore beneficio di clopidogrel nei pazienti diabetici



1. Bhatt DL *et al*. *Am Heart J* 2000; 140: 67–73. **2.** Jarvis B, Simpson K. *Drugs* 2000; 60: 347–77.

American College of Chest Phisicians 9th 2012

Prima e dopo PTA doppia antiaggregazione con aspirina (75-100 mg/die) e clopidogrel (75 mg/die) per 1 mese ed a seguire singola antiaggregazione a lungo termine. Se è presente uno stent 3 mesi di doppia antiaggregazione

Dopo by-pass doppia antiaggregazione con aspirina (75-100 mg/die) e clopidogrel (75 mg/die) per 1 anno piuttosto che singola antiaggregazione ed anticoagulante.

Le Linee Guida della Società Europea di Chirurgia Vascolare riportano che nei primi 6 mesi dopo una rivascolarizzazione chirurgica l'utilizzo di anticoagulanti orali aumenti la pervietà primaria del graft, sebbene la raccomandazione non sia di grado elevato

Per prevenire un evento vascolare maggiore
Prevenzione primaria NNT 1429
Prevenzione secondaria NNT 67

Age (years)	10-year CVD risk	Family history of CRC		No family history of CRC	
		HBR	no HBR	HBR	no HBR
<50	<5%	No ASA	No ASA	No ASA	No ASA
<50	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	10–20%	Clinical judgment	Initiate ASA	No ASA	Initiate ASA
60–69	10–20%	Clinical judgment	Initiate ASA	No ASA	Clinical judgment
≥70	≥20%	No ASA	Clinical judgment	No ASA	Clinical judgment

Figure 3. Risk stratification approach for aspirin use in primary prevention of cardiovascular disease for a patient with diabetes mellitus, on the background assumption of optimal management of other cardiovascular disease risk factors.

High bleeding risk (HBR) is defined as a history of bleeding without reversible causes and concurrent use of other medications that increase bleeding risk. Clinical judgment includes a balanced assessment of risk and benefits of aspirin therapy and factors patients' preference and willingness to comply with aspirin for the subsequent 10 years. CRC indicates colorectal cancer; and CVD, cardiovascular disease.

RESISTENZA ALL'ASPIRINA nei pazienti con diabete mellito

Incapacità dell'aspirina di inattivare completamente le COX-1 delle piastrine

-Rara
-Fenomeno inesistente

Spesso legata all'interazione con altri farmaci (NSAIDs)

Ridotto assorbimento legato alle formulazioni «protette»

Parma Marathon 16 ottobre 2016

Il Campa è “tornato”

	annual stroke incidence %
50 – 59 anni	1.3
80 anni	5.1
80 – 89 anni	23.5

- Mortalità ad un anno 30%
- 15 – 30 % sopravvissuti ad uno stroke rimane disabile

Rischio trombotico uguale nella AF persistente e parossistica

- AF aumenta il rischio di stroke di 3 – 4 volte
- Gli stroke cardio-embolici sono più disabilitanti e determinano una > mortalità rispetto agli stroke non cardioembolici

Goldstein LB et al. Stroke 2006;37:1583-1633

Goldstein LB et al. JAMA 2001;285:2864-70

ALTRE LOCALIZZAZIONI EMBOLICHE

- **INFARTO SPLENICO**
- **TROMBOEMBOLISMO RENALE 0.01%/anno**
- **ISCHEMIA MESENTERICA 0.14%/anno**
- **ISCHEMIA ARTI 0.4%/anno**

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

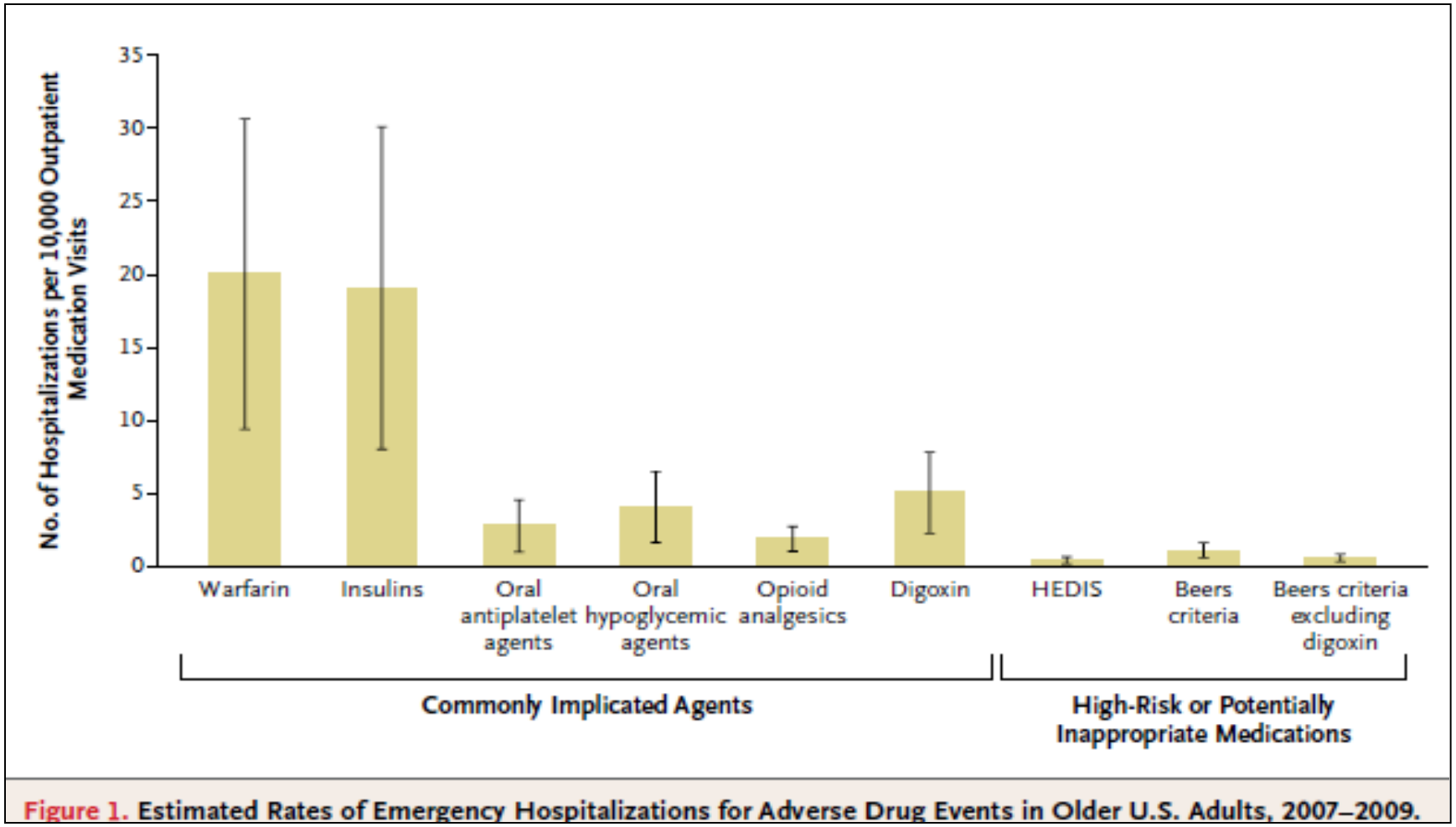


Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.

Rischio tromboembolico per età

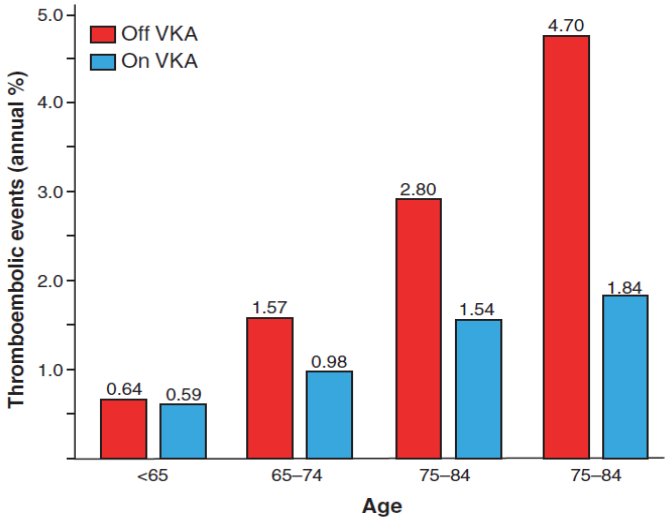


Fig. 2 *Rates (annual rate/100) of thromboembolic events per age (adapted from Singer et al. [7]).*

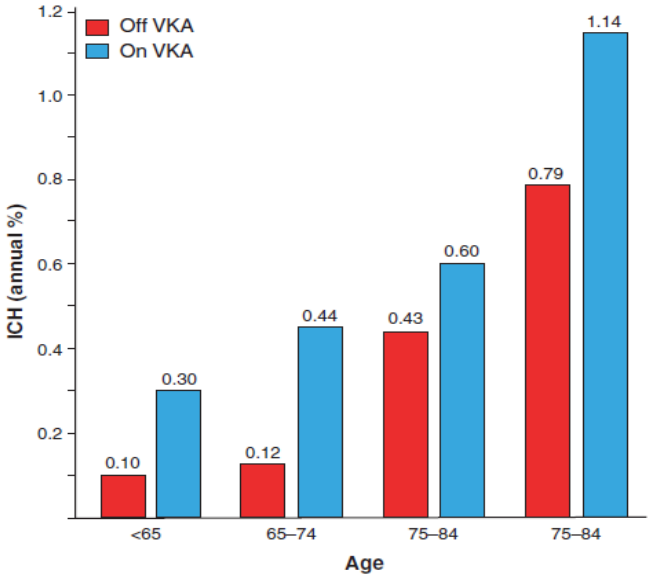


Fig. 3 *Rates (annual rate/100) of intracranial haemorrhages per age (adapted from Singer et al. [7]).*

Sinnaeve Journal of Internal Medicine 2012

CHA2DS2-VASc score Linee guida ESC2016

Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n = 7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Table 12 Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores

Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60%[a] in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatoy drugs[a,d]
Excess alcohol (≥8 drinks/week)[a,b]
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Age[a] (>65 years)[a] (≥75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[b]
Malignancy[b]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin[a]
Growth differentiation factor-15[a]
Serum creatinine/estimated CrCl[a]

Tabella 22. Raccomandazioni per la terapia antitrombotica per la riduzione del rischio tromboembolico nei pazienti con fibrillazione atriale.

	Terapia antitrombotica raccomandata	Classe[a]	Livello[b]
FA con CHA_2DS_2-VASc score 0	Nessuna	I	B
FA con CHA_2DS_2-VASc score 1[c]	Warfarin (INR 2.0-3.0) o dabigatran, rivaroxaban, apixaban	IIb	B
FA con CHA_2DS_2-VASc score ≥2	Warfarin (INR 2.0-3.0) o dabigatran, rivaroxaban, apixaban	I	A

[a]classe di raccomandazione.
[b]livello di evidenza.
[c]all'interno della categoria CHA_2DS_2-VASc score 1 esistono pazienti a basso rischio per i quali non è raccomandata alcuna terapia (sesso femminile di età <65 anni) oppure è raccomandata aspirina (malattia vascolare). La presenza di disfunzione renale (clearance della creatinina <60 ml/min) identifica pazienti ad alto rischio per i quali è invece indicata la terapia anticoagulante orale.

Net Clinical Benefit with Warfarin in the Elderly, According to Age

Age	Events prevented per 100 person-years
≥ 85 yrs	2.34 (1.29 – 3.30)
75 – 84 yrs	1.00 (0.44 – 1.40)
65 – 74 yrs	0.11 (-0.37 – 0.40)
< 65 yrs	-0.25 (-0.65 – 0.08)

Singer DE, et al. *Ann Intern Med*. 2009;151:297-305.

BAFTA: Bleeding Complications with Warfarin vs Aspirin in AF Patients > 75 Years

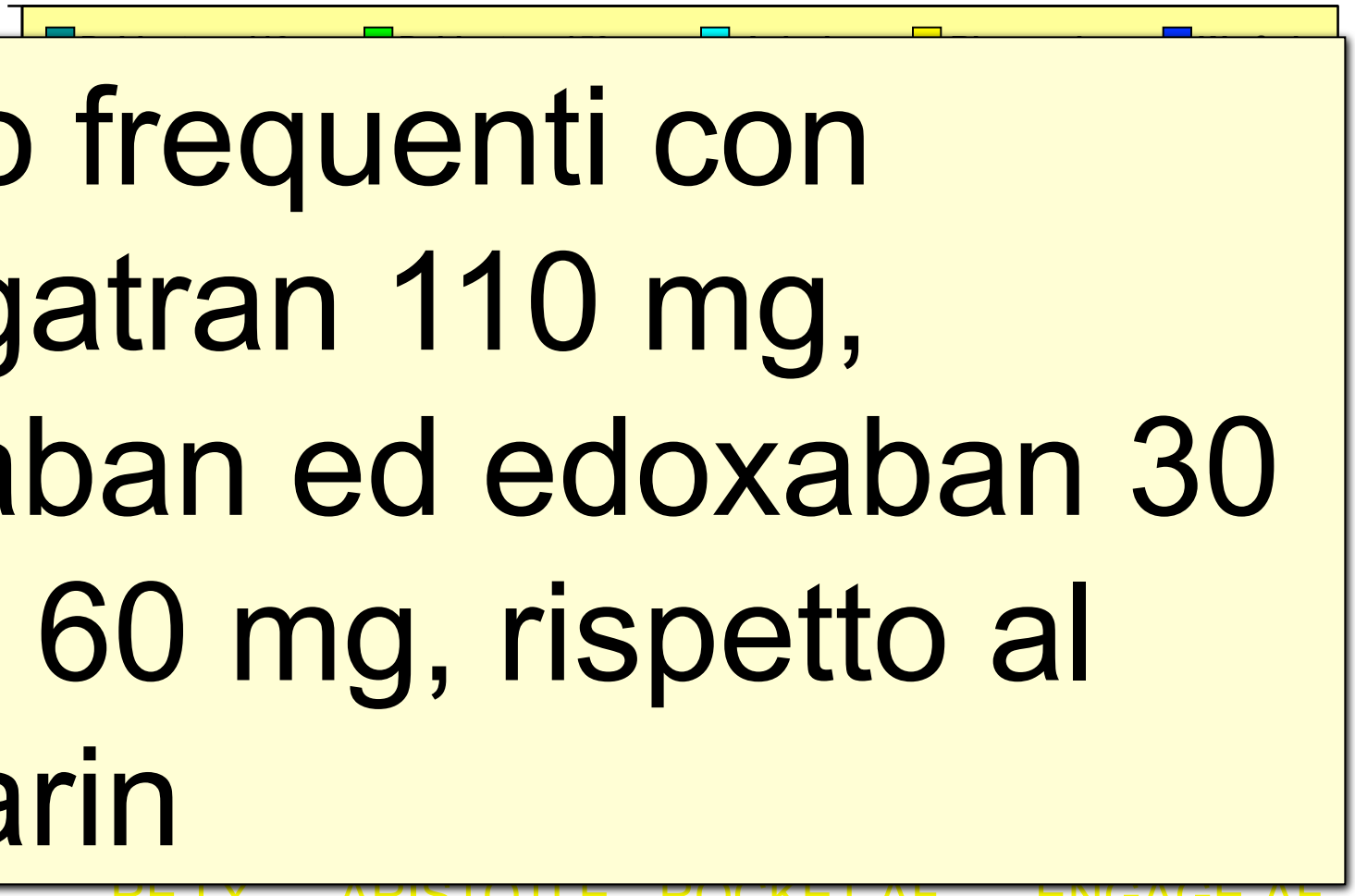
End Point	Warfarin	Aspirin	Hazard Ratio (95% CI)
Major extracranial hemorrhage	1.4	1.6	0.87 (0.43 – 1.73)
All major hemorrhages	1.9	2.0	0.96 (0.53 – 1.75)

Mant J, et al. *Lancet*. 2007;370:493-503.

RE-LY, ROCKET AF, ARISTOTLE, ENGAGE-AF
Risultati Principali (rispetto al warfarin)

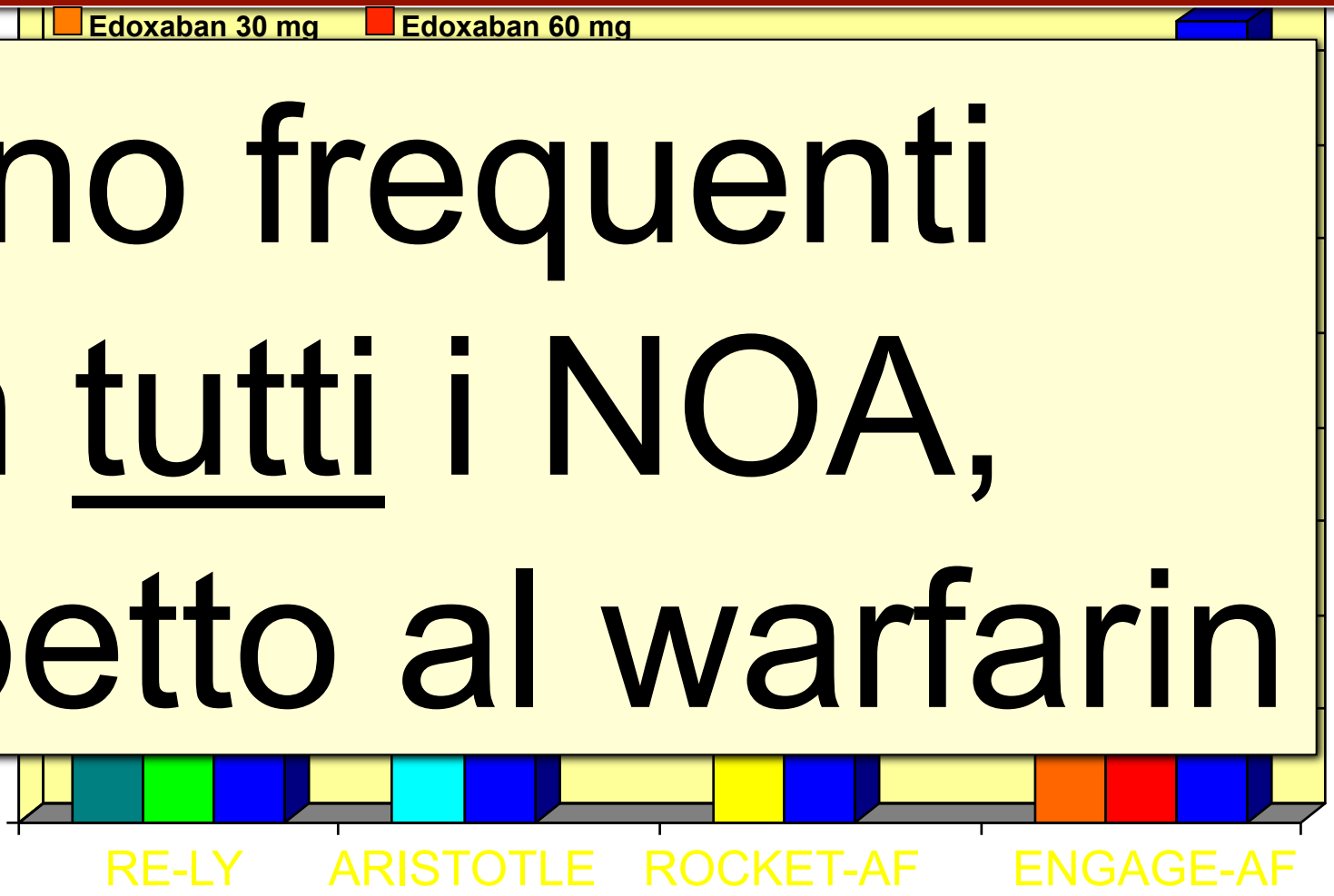
Effetto su major end-points	Dabigatran 150 mg	Dabigatran 110 mg	Rivaroxaban	Apixaban	Edoxaban 60 mg	Edoxaban 30 mg
End-point primario: Non-inferiorità	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata
End-point primario: Superiorità	Dimostrata (Intention-to-treat)		(Dimostrata) (In-treatment population)	Dimostrata (Intention-to-treat)	(Dimostrata) (In-treatment population)	
Riduzione ictus emorragico	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata
Riduzione ictus ischemico	Dimostrata					
Riduzione mortalità totale	(Dimostrata) HR 0.88 [0.77-1.00; p=0.051]			Dimostrata HR 0.89 [0.90-0.998]; p=0.047		Dimostrata HR 0.87 [0.79-0.96; P=0.006]
Riduzione emorragie maggiori		Dimostrata		Dimostrata	Dimostrata	Dimostrata
Riduzione emorragie intra-craniche	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata

Emorragie Maggiori



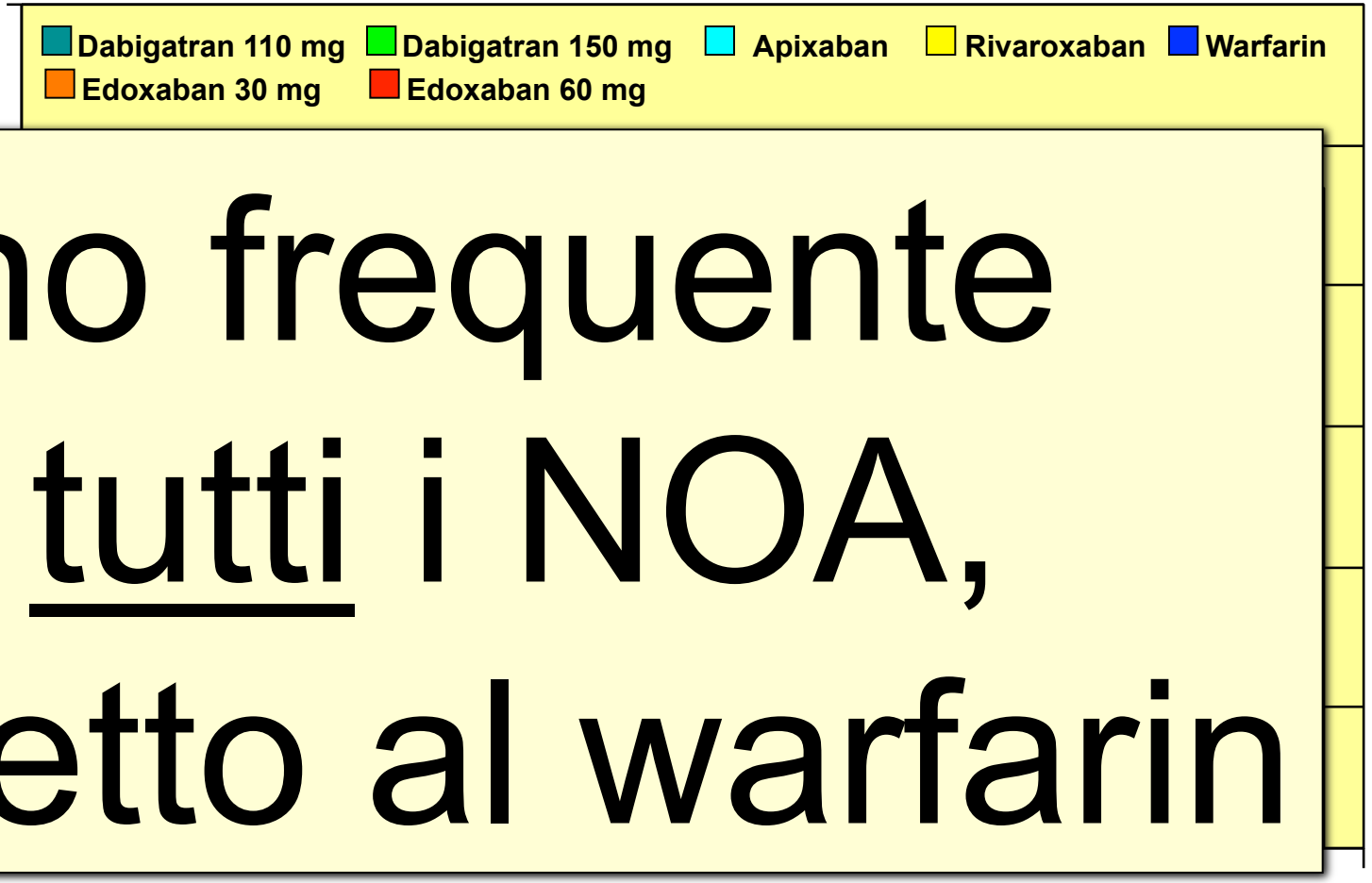
Meno frequenti con dabigatran 110 mg, apixaban ed edoxaban 30 mg e 60 mg, rispetto al warfarin

Emorragie intracraniche



Meno frequenti con <u>tutti</u> i NOA, rispetto al warfarin

Ictus emorragico



Meno frequente con tutti i NOA, rispetto al warfarin

Emorragie Gastrointestinali

Meno frequenti con edoxaban 30 mg rispetto al warfarin.

Più frequenti con dabigatran 150 mg, rivaroxaban ed edoxaban 60 mg, rispetto al warfarin.

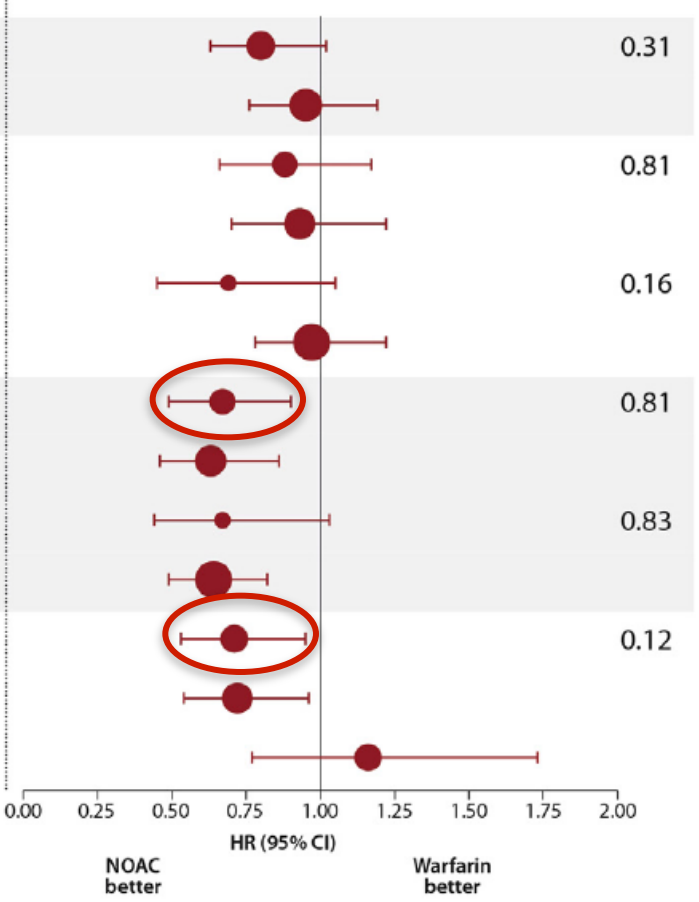
RE-LY ARISTOTLE ROCKET-AF ENGAGE-AF

Are patients over 75 year represented in NOACs trials?

Patients ≥ 75 years in RE-LY trial	7258	
Patients ≥ 75 years in ROCKET trial	6164	
Patients ≥ 75 years in ARISTOTLE trial	5678	
Patients ≥ 75 years in ENGAGE AF trial	8474	
Patients ≥ 75 years treated with DAB in RE-LY	4828	40%
Patients ≥ 75 years treated with RIV in ROCKET	3082	44%
Patients ≥ 75 years treated with API in ARISTOTLE	2850	31%
Patients ≥ 75 years treated with EDO in ENGAGE AF	5654	27%

Stroke or systemic embolism in phase III RCTs comparing NOACs with VKA in Elderly patients

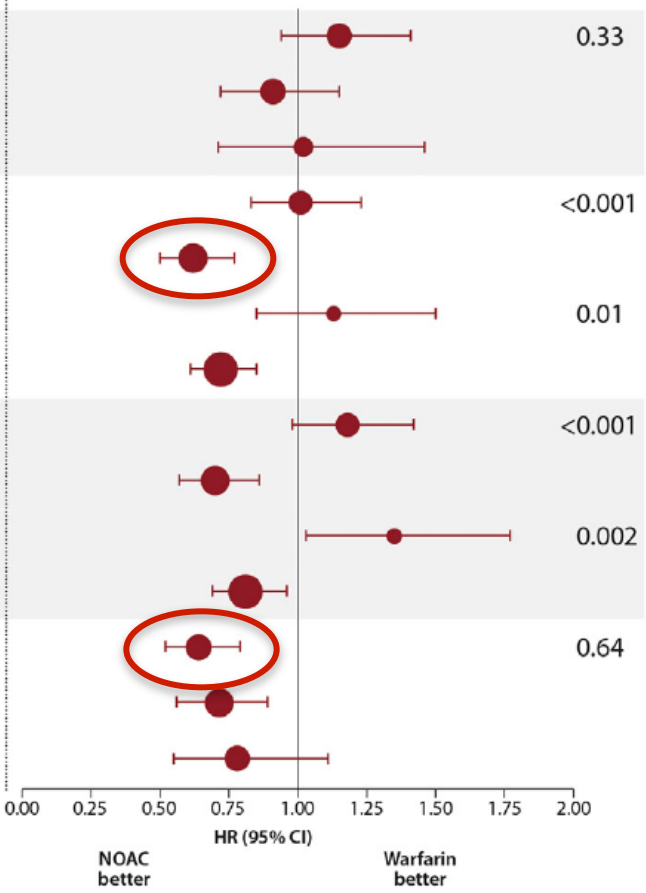
Drug	Age	NOAC n/N	NOAC %/yr	Warfarin n/N	Warfarin %/yr	Int-P
Rivaroxaban 20 mg QD *	≥75	125/3082	2.29	154/3082	2.85	0.31
	<75	144/3999	2.00	152/4008	2.10	
Dabigatran 110 mg BID	≥75	87/2354	1.89	101/2430	2.14	0.81
	<75	96/3661	1.32	101/3592	1.43	
	≥80	35/974	1.87	52/994	2.70	0.16
	<80	148/5041	1.48	150/5028	1.52	
Dabigatran 150 mg BID	≥75	69/2474	1.43	101/2430	2.14	0.81
	<75	65/3602	0.90	101/3592	1.43	
	≥80	37/1059	1.83	52/994	2.70	0.83
	<80	97/5017	0.97	150/5028	1.52	
Apixaban 5 mg BID †	≥75	79/2850	1.56	109/2828	2.19	0.12
	≥65-74	82/3539	1.25	112/3513	1.73	
	<65	51/2731	1.00	44/2740	0.86	



Barco S et al. Best Prac & Res Clin Haematol 2013;26:215-24

Major bleeding in phase III RCTs comparing NOACs with VKA in Elderly patients

Drug	Age	NOAC n/N	NOAC %/yr	Warfarin n/N	Warfarin %/yr	Int-P
Rivaroxaban 20 mg QD *	>75	203/2688	5.16	179/2702	4.47	0.33
	≥65-75	133/2777	3.04	148/2781	3.34	
	<65	59/1646	2.21	59/1642	2.16	
Dabigatran 110 mg BID	≥75	204/2354	4.43	206/2430	4.37	<0.001
	<75	138/3661	1.89	215/3592	3.04	
	≥80	98/974	5.24	90/994	4.68	0.01
	<80	244/5041	2.43	331/5028	3.35	
Dabigatran 150 mg BID	≥75	246/2474	5.10	206/2430	4.37	<0.001
	<75	153/3602	2.12	215/3592	3.04	
	≥80	126/1059	6.23	90/994	4.68	0.002
	<80	273/5017	2.73	331/5028	3.35	
Apixaban 5 mg BID †	≥75	151/2836	3.33	224/2819	5.19	0.64
	≥65-74	120/3529	1.99	166/3501	2.82	
	<65	56/2723	1.17	72/2732	1.51	

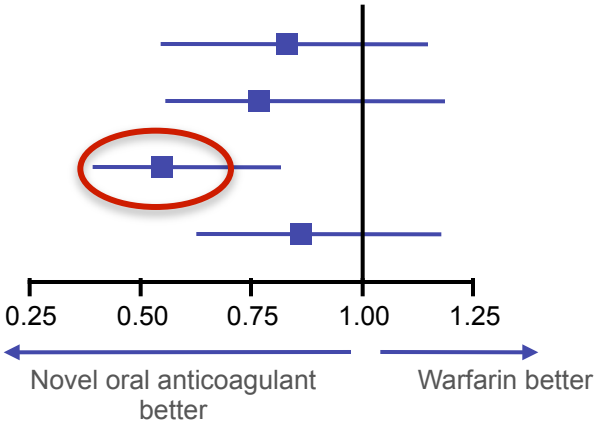


Barco S et al. Best Prac & Res Clin Haematol 2013;26:215-24

Stroke/SE and major bleeding event rates for subgroups of pts with CKD* from trials comparing NOACs and VKA

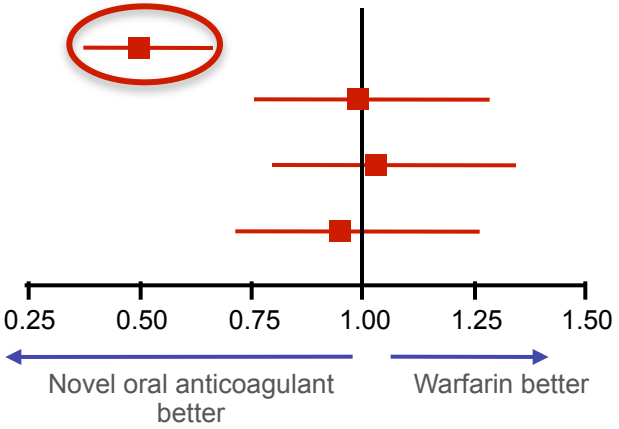
Stroke/SE

estimated creatinine clearances:		Hazard Ratio (95% CI)
25-50 mL/min	Apixaban 2.5/5.0 mg bid	0.79 (0.55 – 1.14)
30-49 mL/min	Dabigatran 110 mg bid	0.77 (0.51 – 1.18)
	Dabigatran 150 mg bid	0.55 (0.40 – 0.81)
30-49 mL/min	Rivaroxaban 15 mg qd	0.86 (0.63 – 1.17)



Major bleeding

estimated creatinine clearances:		
25-50 mL/min	Apixaban 2.5/5.0 mg bid	0.50 (0.38 – 0.66)
30-49 mL/min	Dabigatran 110 mg bid	0.99 (0.76 – 1.28)
	Dabigatran 150 mg bid	1.03 (0.80 – 1.34)
30-49 mL/min	Rivaroxaban 15 mg qd	0.95 (0.72 – 1.26)



* Stage III CKD: estimated creatinine clearances 30-49 mL/min for dabigatran and rivaroxaban; 25-50 mL/min for apixaban.
The width of the 90% CIs are estimated from published figures for dabigatran
bid, twice daily; CI, confidence interval; CKD chronic kidney disease; qd, once daily; NOACs, novel oral anticoagulant; SE, systemic embolism

Head-to-head studies do not exist, and direct comparisons between agents may not be made

Adapted from Hart et al. Canadian Journal of Cardiology 2013;29:S71-S78

Table 14 Dose adjustment for NOACs as evaluated in the PHASE III trials (adapted from Hart *et al.*[316])

	Dabigatran (RE-LY)[318,426]	Rivaroxaban (ROCKET-AF)[320,426]	Apixaban (ARISTOTLE)[319,427]	Edoxaban (ENGAGE AF-TIMI 48)[321]
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 ml/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl <30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 μmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

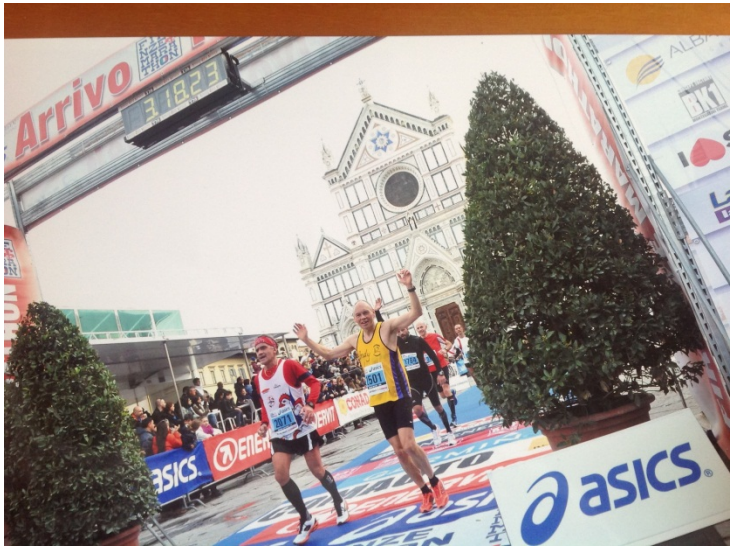
CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration rate; NA = not available.

Venice marathon 2011

3.38.43

Venice marathon 2012

3.28.34



Firenze marathon 2013

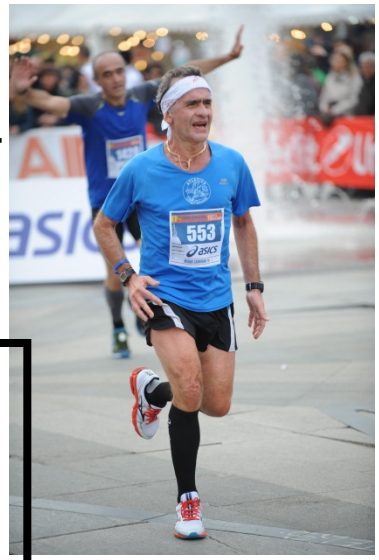
3.18.00

Lago Maggiore marathon 2014

3.24'28"

Turin marathon 2014

3.16.34



2015

Roma marathon 15 marzo 2015

Lago Maggiore marathon 18 ottobre 2015

3.14'28"

Verona marathon 15 novembre 2015

3.29'.51"

Trino marathon 29 novembre 2015

3.26'54"

2016

Parma

Nizza Cannes

Trino

ASPIRINA a basso dosaggio

-**<u>Modesti effetti su COX-2 e PG1</u>**

non aumenta la pressione arteriosa
non peggiora la funzione renale
non interferisce con gli effetti anti-ipertensivi dei diuretici ed ACE-I

-**<u>Inibizione permanente delle COX-1</u>** aumenta il rischio di sanguinamenti gastro-intestinali attraverso

- inibizione aggregazione piastrinica mediata dal TXA_2
- inibizione dose dipendente delle PGI_2 con perdita della citoprotezione della mucosa gastro-intestinale

Interazione con NSAID che esercitano effetto competitivo con l'aspirina sull'acetilazione irreversibile delle piastrine.

<u>NSAID + aspirina in pazienti con precedente IMA</u>

Aumenta il rischio di sanguinamento
Aumenta il rischio di eventi trombotici

Pazienti con diabete mellito sono caratterizzati dall'avere piastrine iperattive

-AUMENTATA ADESIONE
-AUMENTATA ATTIVAZIONE
-AUMENTATA AGGREGAZIONE

Iperglicemia determina un effetto osmotico

-Aumenta lo stress ossidativo
-Induce espressione della P-selectina
-Attiva la protein kinasi C (attivatore delle PLT)

Deficit insulinico determina:
-Aumento della concentrazione di calcio intracellulare

Insulino resistenza provoca:
-Ridotta risposta agli stimoli anti-trombotici quali:
NO
PGI2

Obesità, insufficienza renale, infiammazione sistemica

-Aumentano il calcio citosolico
-Alterano la funzione endoteliale

Minore produzione di NO e PGI2
Aumenta la produzione di TF

Accelerata trombopoiesi determina una più rapida entrata in circolo delle piastrine e quindi minor tempo di esposizione all'effetto dell'aspirina.

-Aumentare il dosaggio dell'aspirina ma aumentano gli eventi avversi
-Somministrazione frazionata 2 volte/die

-US and Food Administration ha approvato una nuova formulazione a rilascio prolungato di 162,5 mg/die
maggiore effetto antiaggregante stabile nelle 24 ore

Non sono disponibili dati clinici

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