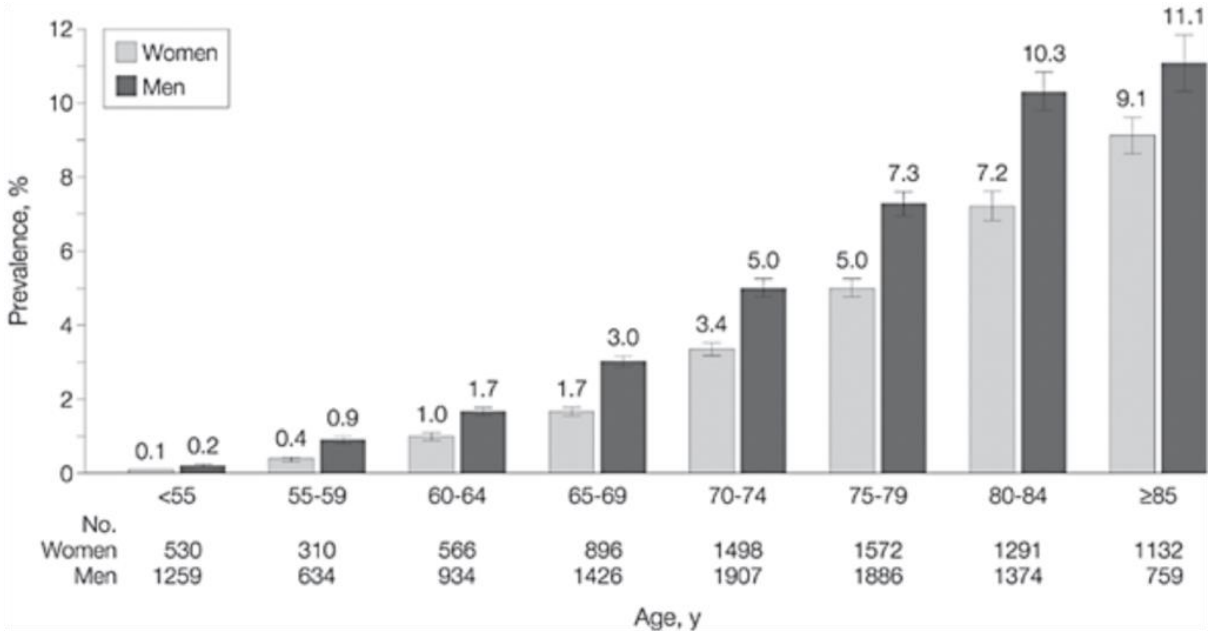
I NAO negli anziani, nei pazienti obesi e sottopeso

Dr. Giovanni Vitale

Cardiologia, Ospedale di Imola

- **Western countries populations** are getting older
- Age is an independent risk factor for the development of AF, and is related to an increase in **both ischemic and hemorrhagic risk**

Increasing risk of AF with age



Increasing risk of VTE with age

Decreased renal function

Increased comordibidities

Decreased hepatic function

Polymedications

Frailty

Sindrome multifattoriale con ridotta capacità di adattamento ad eventi stressanti

Drug-drug interaction

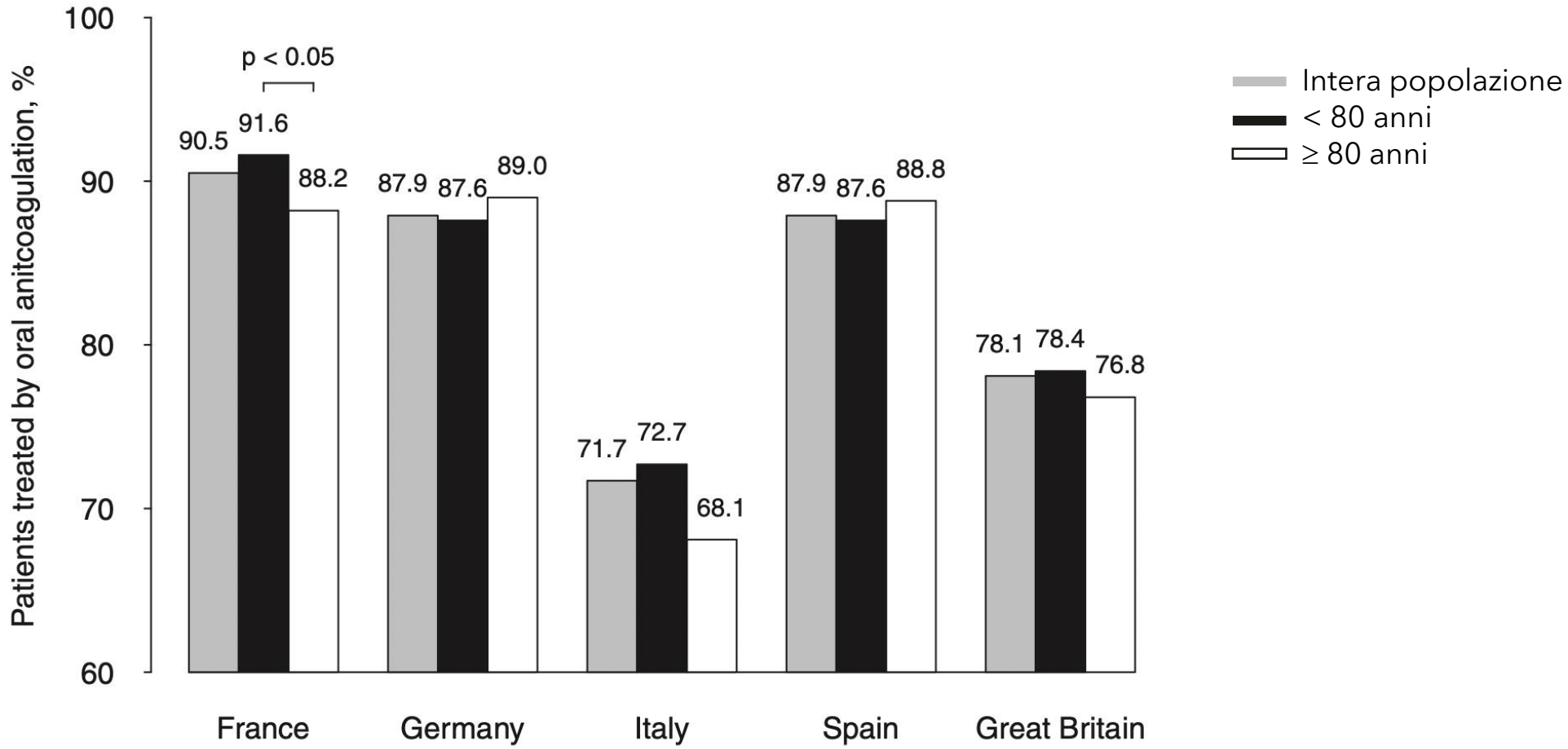
Risk of falls

Increased bleeding risk

In clinical trials, elderly patients are **underrepresented**!!!

Oral anticoagulant use in octogenarian European patients with atrial fibrillation: A subanalysis of PREFER in AF

Olivier Hanon [a,b,*,1], Jean-Sébastien Vidal [a,b,1], Jean-Yves Le Heuzey [c,1], Paulus Kirchhof [d,e,f,1], Raffaele De Caterina [g,h,1], Josef Schmitt [i,1], Petra Laeis [i,1], Pier Mannuccio Mannucci [j,k,1], Maura Marcucci [k,l,1]



Hanon O et al, Int J Cardiol. 2017;232:98-104.

Identification of risk factors for inappropriate and suboptimal initiation of direct oral anticoagulants

Molly Howard[1] · Andrew Lipshutz[2] · Breanne Roess[3] · Emily Hawes[4] · Zachariah Deyo[5] · Jena Ivey Burkhart[5] · Stephan Moll[6] · Betsy Bryant Shilliday[7]

Table 3 Patients prescribed the appropriate DOAC dose and having obtained laboratory measurements within the month prior to DOAC initiation

	Appropriate dose	Hemoglobin, creatinine, ALT, and total bilirubin obtained	Hemoglobin	Creatinine	ALT	Total bilirubin
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**143 (85.6)**	**58 (34.7)**	**119 (71.3)**	**129 (77.2)**	**80 (47.9)**	**60 (35.9)**
Age (n)						
<65 (48)	46 (95.8)	22 (45.8)	34 (70.8)	39 (81.3)	**29 (60.4)**	**23 (47.9)**
65–74 (38)	35 (92.1)	15 (39.5)	29 (76.3)	29 (76.3)	19 (50.0)	15 (39.5)
≥75 (81)	**62 (76.5)**	**21 (25.9)**	56 (69.1)	61 (75.3)	**32 (39.5)**	**22 (27.2)**
DOAC (n)						
Dabigatran (19)	16 (84.2)	5 (26.3)	12 (63.2)	15 (78.9)	8 (42.1)	5 (26.3)
Rivaroxaban (105)	91 (86.7)	41 (39.0)	80 (76.2)	81 (77.1)	53 (50.5)	42 (40.0)
Apixaban (43)	36 (83.7)	12 (27.9)	27 (62.8)	33 (76.7)	19 (44.2)	13 (30.2)

Howard M et al, J Thromb Thrombolysis. 2017;43(2):149-156.

Qual è la definizione di paziente anziano???

Elderly patients

≥ 75 years

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Study	Design	Mean/Median Age	Comparison	Elderly patients (% of the RCT)	Follow-up
ARISTOTLE	Double-blinded RCT	70	Apixaban 5 mg BID *vs.* VKA, Target INR 2.0-3.0	5678 (31.2%)	1.8 years
RE-LY	Open-label RCT	71	Dabigatran 110 mg/150 mg BID *vs.* VKA, Target INR 2.0-3.0	7238 (40.0%)	2 years
ENGAGE-AF	Double-blinded RCT	72	Edoxaban 60 mg/30 mg OD *vs.* VKA, Target INR 2.0-3.0	8432 (40.1%)	2.8 years
ROCKET-AF	Double-blinded RCT	73	Rivaroxaban 20 mg OD *vs.* VKA, Target INR 2.0-3.0	6150 (43.4%)	1.9 years

JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

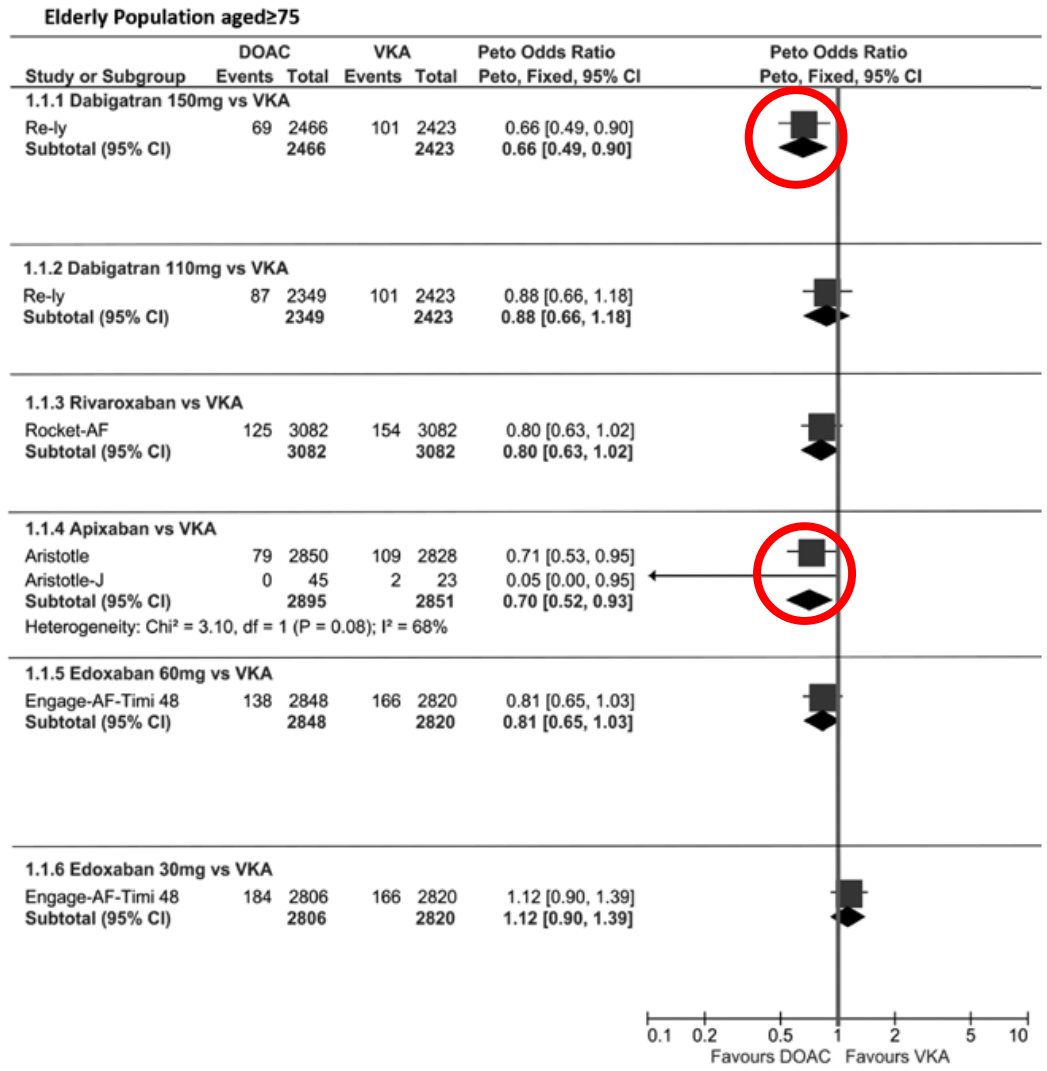
Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

>25.000 pazienti elderly (≥75 aa)

Robert P. Giugliano, M.D., Christia wald, M.D., Sabina A. Murphy, M.P.H., Steph berin, M.D., Albert L. Waldo, M.D., Michael D Veitz, 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*

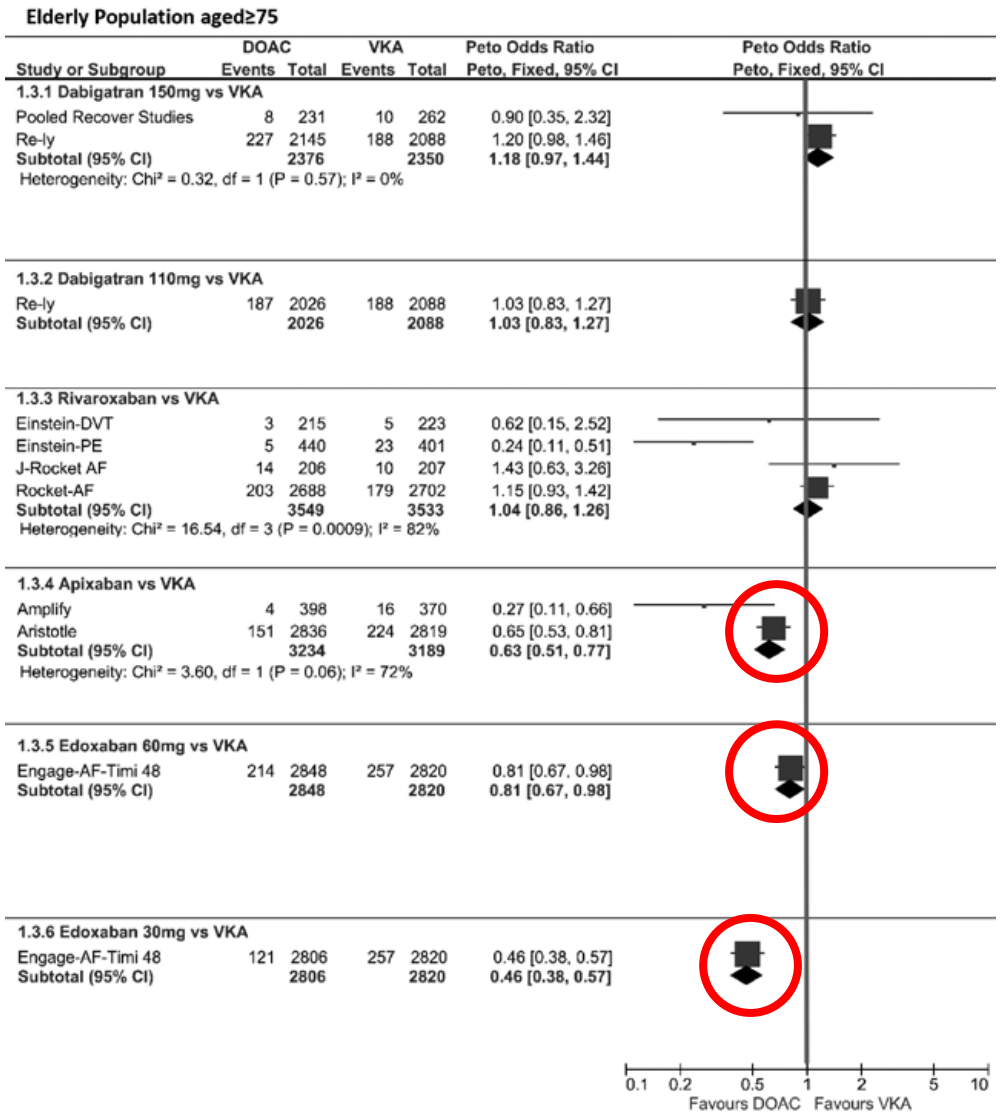
Risk of stroke or systemic embolism



DOAC at least as effective as VKA

(significant reduction in the risk of stroke/SE for dabigatran 150 mg and apixaban)

Risk of major bleeding



Significant reduction in the risk of major bleeding for apixaban, edoxaban (60 and 30 mg)

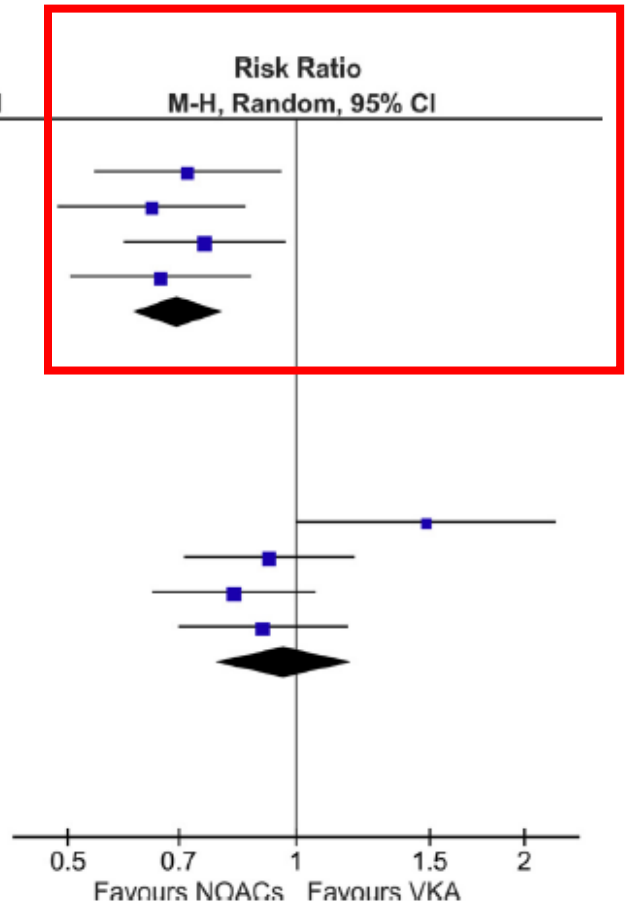
Sharma M et al, Circulation. 2015;132(3):194-204

Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: A systematic review with meta-analysis and trial sequential analysis

Daniel Caldeira[a,b,c,*], Afonso Nunes-Ferreira[c], Raquel Rodrigues[a,b], Eunice Vicente[a,b], Fausto J. Pinto[c], Joaquim J. Ferreira[a,b]

Stroke and systemic embolism

Study or Subgroup	NOACs Events	Total	VKA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
≥75 years						
ARISTOTLE	79	2850	109	2828	22.7%	0.72 [0.54, 0.96]
ENGAGE AF	75	2838	115	2805	22.5%	0.64 [0.48, 0.86]
RE-LY	152	4815	101	2423	30.3%	0.76 [0.59, 0.97]
ROCKET AF	82	3073	124	3077	24.5%	0.66 [0.50, 0.87]
Subtotal (95% CI)		**13576**		**11133**	**100.0%**	**0.70 [0.61, 0.80]**
Total events	388		449			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 3 (P = 0.83); I² = 0%						
Test for overall effect: Z = 5.18 (P < 0.00001)						
<75 years						
ARISTOTLE	61	6270	41	6253	17.2%	1.48 [1.00, 2.20]
ENGAGE AF	107	4174	117	4207	27.2%	0.92 [0.71, 1.19]
RE-LY	164	7276	98	3599	28.3%	0.83 [0.65, 1.06]
ROCKET AF	107	4000	119	4021	27.3%	0.90 [0.70, 1.17]
Subtotal (95% CI)		**21720**		**18080**	**100.0%**	**0.97 [0.79, 1.18]**
Total events	439		375			
Heterogeneity: Tau² = 0.02; Chi² = 6.28, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 0.34 (P = 0.73)						



30% di rischio in meno di eventi cardioembolici rispetto a VKA

Maggiore efficacia negli anziani rispetto ai pazienti «più giovani»

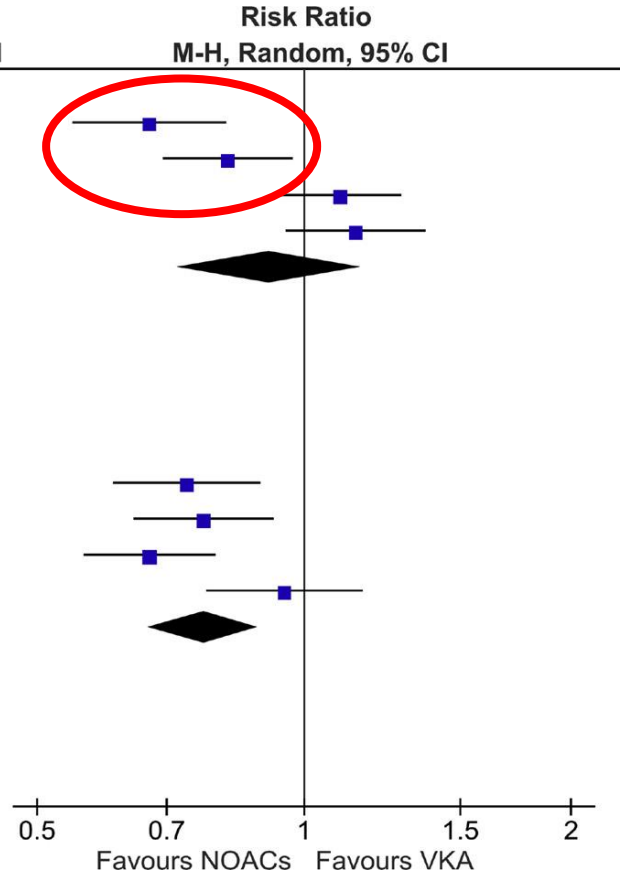
Caldeira C et al, Arch Gerontol Geriatr. 2019;81:209-214.

Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: A systematic review with meta-analysis and trial sequential analysis

Daniel Caldeira[a,b,c,*], Afonso Nunes-Ferreira[c], Raquel Rodrigues[a,b], Eunice Vicente[a,b], Fausto J. Pinto[c], Joaquim J. Ferreira[a,b]

Major bleeding

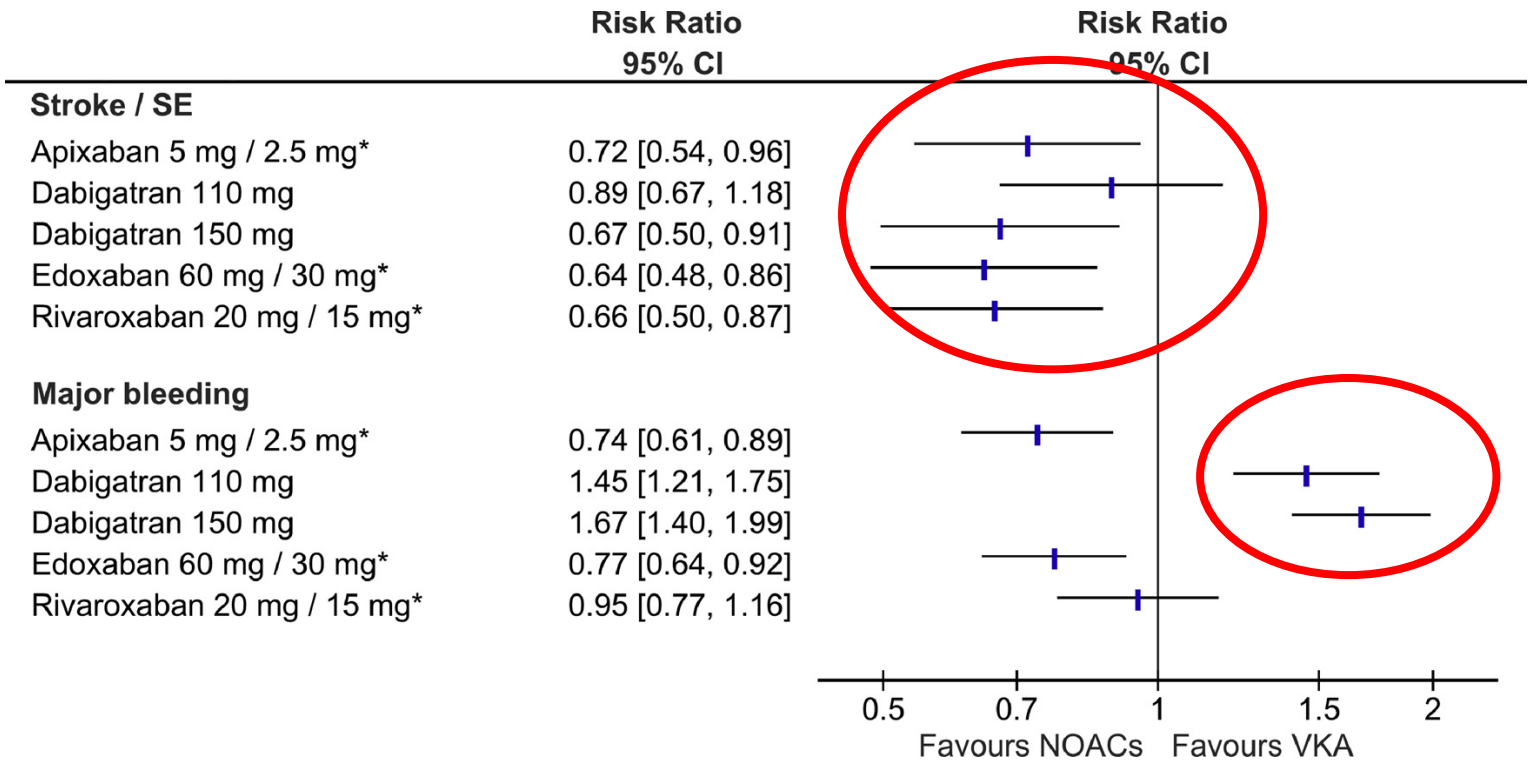
Study or Subgroup	NOACs Events	Total	VKA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
≥75 years						
ARISTOTLE	151	2850	224	2828	24.1%	0.67 [0.55, 0.82]
ENGAGE AF	224	2838	270	2805	25.3%	0.82 [0.69, 0.97]
RE-LY	450	4815	206	2423	25.8%	1.10 [0.94, 1.29]
ROCKET AF	233	3073	204	3077	24.8%	1.14 [0.95, 1.37]
Subtotal (95% CI)		**13576**		**11133**	**100.0%**	**0.91 [0.72, 1.16]**
Total events	1058		904			
Heterogeneity: Tau² = 0.05; Chi² = 21.92, df = 3 (P < 0.0001); I² = 86%						
Test for overall effect: Z = 0.74 (P = 0.46)						
<75 years						
ARISTOTLE	176	6270	238	6253	24.4%	0.74 [0.61, 0.89]
ENGAGE AF	194	4174	254	4207	25.6%	0.77 [0.64, 0.92]
RE-LY	291	7276	215	3599	26.9%	0.67 [0.56, 0.79]
ROCKET AF	172	4000	182	4021	23.1%	0.95 [0.77, 1.16]
Subtotal (95% CI)		**21720**		**18080**	**100.0%**	**0.77 [0.67, 0.89]**
Total events	833		889			
Heterogeneity: Tau² = 0.01; Chi² = 6.80, df = 3 (P = 0.08); I² = 56%						
Test for overall effect: Z = 3.64 (P = 0.0003)						



Una riduzione non significativa (9%) di sanguinamenti maggiori rispetto a VKA

Caldeira C et al, Arch Gerontol Geriatr. 2019;81:209-214.

Efficacy and safety of the **different approved regimens** for AF in elderly patients



All NOACs, except dabigatran 110 mg, **reduce significantly the risk of stroke or SE**

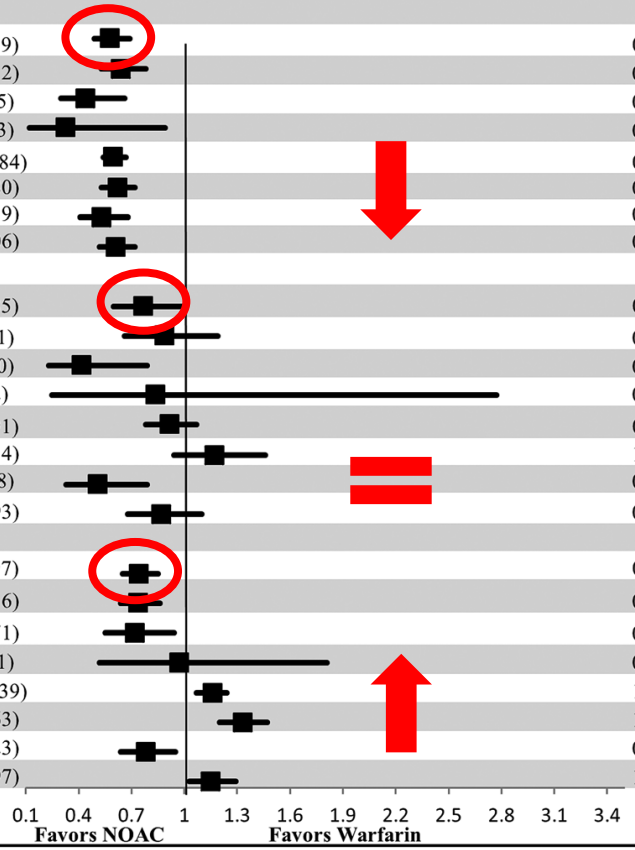
Dabigatran increases significantly the risk of major bleeding in a **dose-dependent manner**

Caldeira C et al, Arch Gerontol Geriatr. 2019;81:209-214.

Dati dal "mondo reale"

Studio **osservazionale retrospettivo** che ha arruolato oltre 80.000 pazienti con ≥ 80 aa (analisi di sottogruppo dello studio ARISTOPHANES)

	NOAC	Warfarin	Hazard Ratio (95% CI)	P-value
	No. of events (incidence per 100 person-years)			
Apixaban vs. Warfarin				
Stroke/SE	197 (1.80)	382 (2.89)	0.58 (0.49 – 0.69)	<0.001
Ischemic	161 (1.47)	280 (2.12)	0.64 (0.53 – 0.78)	<0.001
Hemorrhagic	32 (0.29)	86 (0.65)	0.44 (0.30 – 0.66)	<0.001
SE	5 (0.05)	17 (0.13)	0.33 (0.12 – 0.89)	0.029
Major Bleeding	540 (4.96)	1,024 (7.84)	0.60 (0.54 – 0.67)	<0.001
GI Bleeding	274 (2.50)	502 (3.80)	0.62 (0.53 – 0.72)	<0.001
ICH	82 (0.75)	185 (1.39)	0.53 (0.41 – 0.68)	<0.001
Other Bleeding	218 (1.99)	404 (3.06)	0.61 (0.52 – 0.72)	<0.001
Dabigatran vs. Warfarin				
Stroke/SE	103 (2.18)	137 (2.85)	0.77 (0.60 – 0.99)	0.045
Ischemic	84 (1.78)	97 (2.01)	0.89 (0.66 – 1.19)	0.421
Hemorrhagic	14 (0.29)	34 (0.70)	0.42 (0.23 – 0.79)	0.007
SE	5 (0.11)	6 (0.12)	0.84 (0.25 – 2.77)	0.769
Major Bleeding	295 (6.30)	329 (6.91)	0.92 (0.78 – 1.07)	0.281
GI Bleeding	172 (3.66)	151 (3.14)	1.17 (0.94 – 1.46)	0.160
ICH	31 (0.65)	62 (1.28)	0.51 (0.33 – 0.79)	0.003
Other Bleeding	119 (2.52)	141 (2.93)	0.87 (0.68 – 1.10)	0.244
Rivaroxaban vs. Warfarin				
Stroke/SE	396 (2.20)	541 (2.97)	0.74 (0.65 – 0.85)	<0.001
Ischemic	288 (1.60)	394 (2.16)	0.74 (0.64 – 0.86)	<0.001
Hemorrhagic	92 (0.51)	130 (0.71)	0.72 (0.55 – 0.94)	0.016
SE	19 (0.11)	20 (0.11)	0.97 (0.52 – 1.81)	0.918
Major Bleeding	1,512 (8.50)	1,331 (7.39)	1.16 (1.07 – 1.24)	<0.001
GI Bleeding	857 (4.78)	659 (3.63)	1.33 (1.20 – 1.47)	<0.001
ICH	173 (0.96)	225 (1.23)	0.78 (0.64 – 0.95)	0.015
Other Bleeding	612 (3.40)	540 (2.97)	1.15 (1.03 – 1.29)	0.017



Less stroke/SE
but…

… **different risk of major bleeding**

Deitelzweig S et al, J Am Geriatr Soc. 2019;67(8):1662-1671

ORIGINAL RESEARCH ARTICLE

Circulation

Oral Anticoagulation in Very Elderly Patients With Atrial Fibrillation

A Nationwide Cohort Study

- Pts ≥ 90 years with AF taking **antiplatelet agents** showed **no significant difference in ischemic stroke** compared with those taking no antithrombotic therapy
- Compared with nonwarfarin treatment, warfarin was associated with a **lower risk of ischemic stroke**, with no difference in intracranial hemorrhage risk → **positive net clinical benefit**
- Compared with warfarin, DOAC were associated with **a lower risk of intracranial hemorrhage**, with no difference in risk of ischemic stroke

DOACs is the favorable choice in very elderly patients

Chao T et al, Circulation. 2018;138(1):37-47.

Drug adherence

Polymedications

Declining cognition

Vision/hearing impairment

Limited social resources

La modalità di somministrazione di un farmaco condiziona davvero l'**aderenza alla terapia**?

Contents lists available at ScienceDirect

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Correspondence

Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke

Mark J. Alberts [a], W. Frank Peacock [b], Larry E. Fields [c], Thomas J. Bunz [d], Elaine Nguyen [d,e], Dejan Milentijevic [c], Jeff R. Schein [c], Craig I. Coleman [d,e,*]

Table 2
Association between suboptimal adherence (PDC<80%) and ischemic stroke risk among users of direct oral anticoagulants of differing dosing frequencies.

	Proportion with a PDC < 80%	Number of ischemic strokes[a] (rate/100-PYs)	Adjusted[b] HR (95% CI) for ischemic stroke when PDC < 80%[#]
All DOAC users (N = 36,868)	29.7%	794 (2.3)	1.50 (1.30–1.73)
Once-daily users (N = 18,434)	27.2%	404 (2.4)	1.47 (1.20–1.80)
Twice-daily users (N = 18,434)	32.1%[∫]	390 (2.3)	1.50 (1.23–1.83)[¶]

PDC (proportion of day covered)< 80%: aderenza subottimale

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

ESC European Society of Cardiology

11.13 The elderly and frail with atrial fibrillation

The prevalence of AF increases progressively with age[67,1200–1206], and age is an independent risk factor for adverse outcomes in AF.[372,1200,1207,1208] Older people are less likely to receive OAC[1209–1216] despite sufficient evidence supporting the use of OAC in this population. Frailty, comorbidities, and increased risk of falls[1217–1219] do not outweigh the benefits of OAC given the small absolute risk of bleeding in anticoagulated elderly patients.[339,390,391,1220–1223] Evidence from RCTs,[441,1224] meta-analyses[423,1225] and large registries[339,433,1209,1226] support the use of OAC in this age group. Antiplatelets are neither more effective nor safer than warfarin and may even be harmful,[433] whereas NOACs appear to have a better overall risk–benefit profile compared with warfarin.[423,433,441,1035,1225,1227–1236] Prescribing a reduced dose of OAC is less effective in preventing AF adverse outcomes.[1107,1211,1237,1238]

→ **Trattare il paziente**, quando indicato

→ Scegliere la **terapia adeguata!**

→ Scegliere la **dose giusta!**

Take home messages

- L'età si associa ad un **aumento del rischio di FA**, e contemporaneamente del **rischio ischemico ed emorragico**

- I pazienti anziani beneficiano di una terapia anticoagulante orale, quando indicata

- Rispetto al VKA, i NAO hanno:

➢ un'**efficacia almeno sovrapponibile**

➢ un **rischio minore di sanguinamento intracranico** (il dabigatran ha però un maggior rischio di sanguinamento gastro-intestinale)

➢ una **migliore aderenza terapeutica**

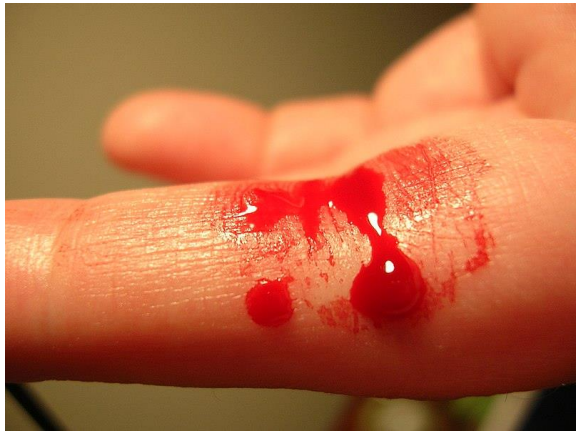
- **Minimizzare i fattori di rischio di sanguinamento!!!**

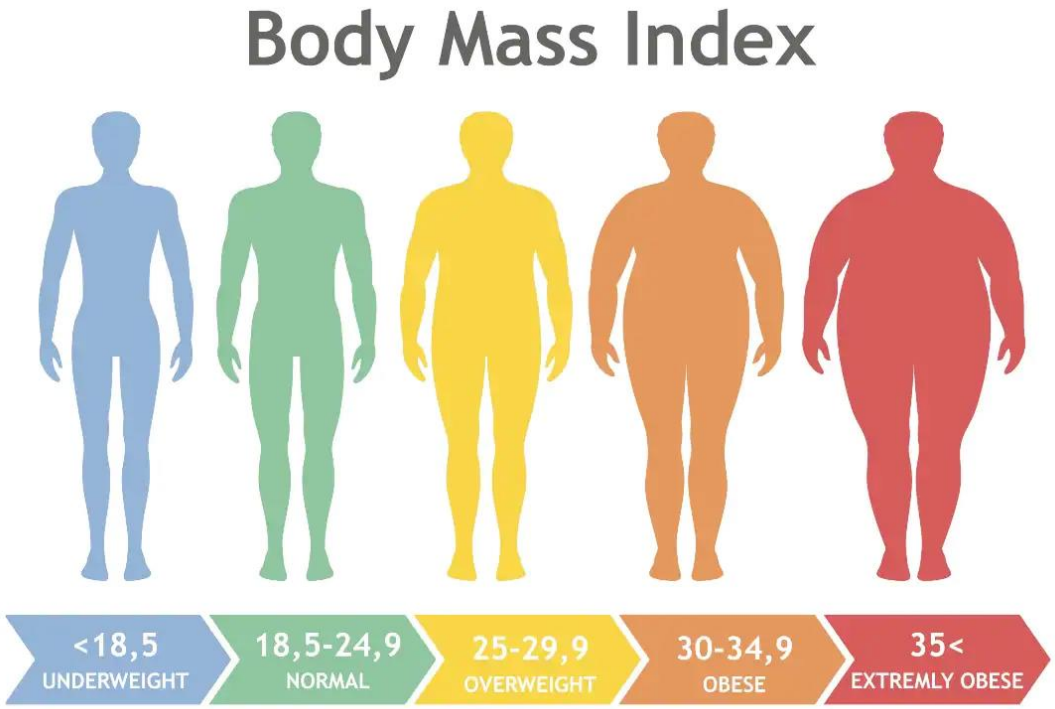
Obesity

Obesity is a relevant risk factor for the development of AF:
- Increasing the **risk of AF** by almost **50%** (linearly with increasing BMI)
- Increasing the risk of **recurrent AF after ablation** (13% risk increase)
- Independent predictor of **progression from paroxysmal to sustained AF**

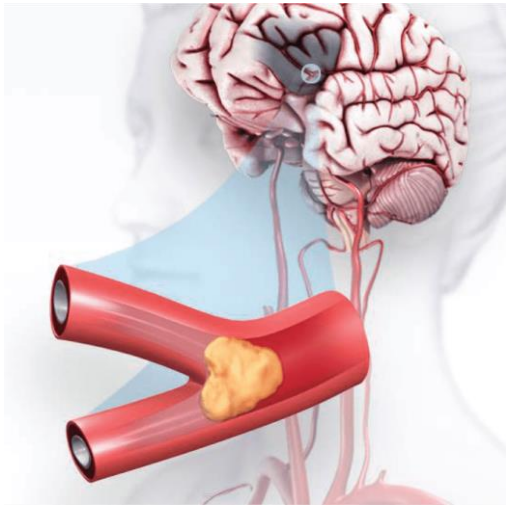
Weight loss is crucial for the **prevention** and **treatment** of patients with AF

Sovradosaggio





Sottodosaggio



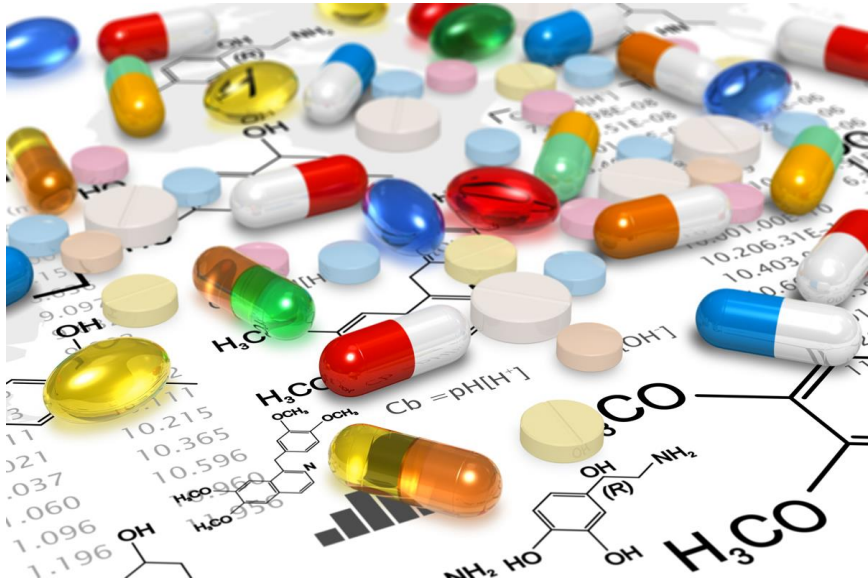
Una dose fissa va bene per tutti?

Pharmacokinetic data

- Different weight-dependend change in plasmatic levels, volume distribution and half live, **clinically not significant**

- For dabigatran and rivaroxaban**: renal function has greater effect** on plasmatic concentration and DOAC exposure, compared to weight

Dati di farmacocinetica rassicuranti!!!



Clinical data

- Weight or BMI was **not an exclusion factor** in the randomized NOAC-trials in AF
- However, pivotal randomized controlled trials had **minimal representation** of patients with **BMI ≥40 kg/m2** or **weight ≥120 kg**

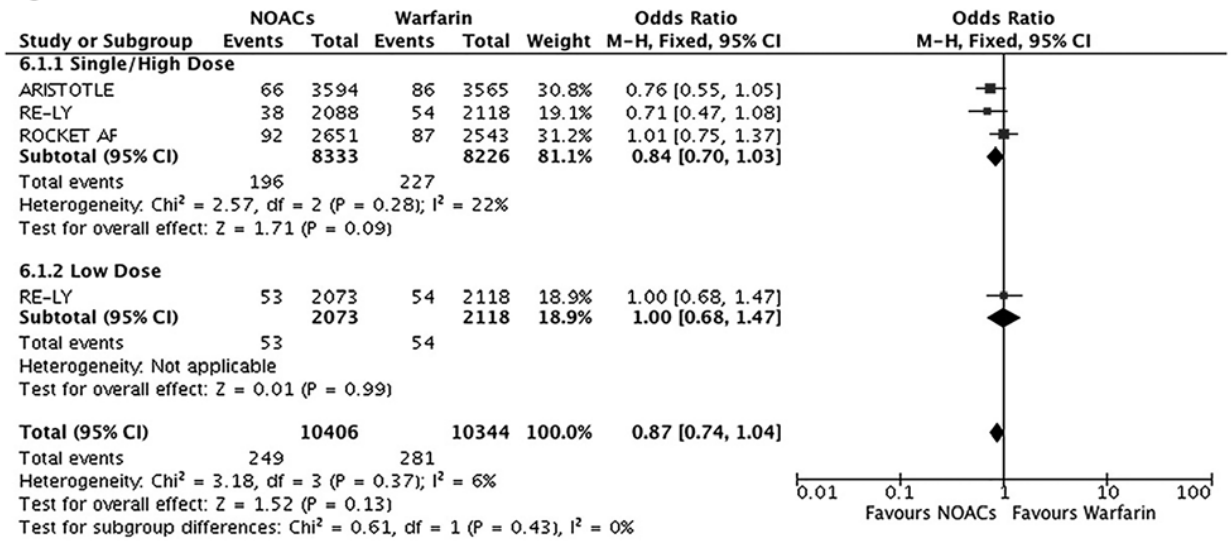
Patients with obesity in different trials		
	BMI ≥ 30 kg/m2	**BMI ≥ 40 kg/m2**
ARISTOTLE	7159	1003 (5,5%)
ENGAGE AF-TIMI 48	8457	1149 (5,4%)
ROCKET-AF	5206	620 (4,3%)
RE-LY	6279	Not reported (3099 ≥ 100 kg)

Is There an Obesity Paradox for Outcomes in Atrial Fibrillation?

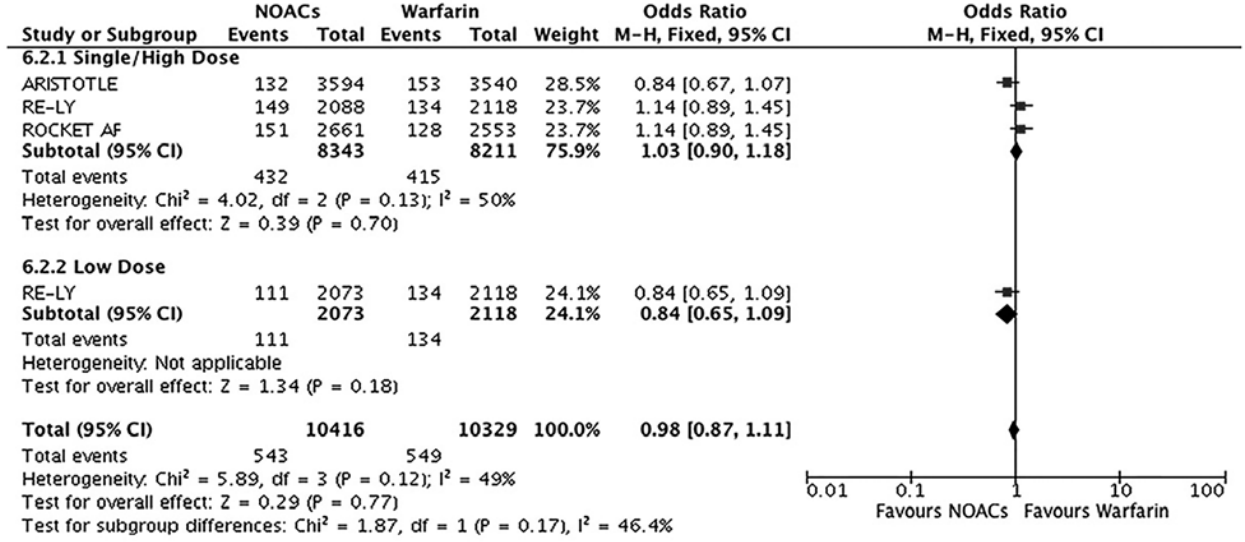
A Systematic Review and Meta-Analysis of Non–Vitamin K Antagonist Oral Anticoagulant Trials

Marco Proietti, MD; Elisa Guiducci, MD; Paola Cheli, MD; Gregory Y.H. Lip, MD

C Obese



F Obese



No difference in stroke/SE

No difference in major bleeding

- Compared with normal weight, overweight and obese pts had a lower risk of stroke/SEE
- Compared with overweight, obese pts had a significantly lower risk of stroke/SEE

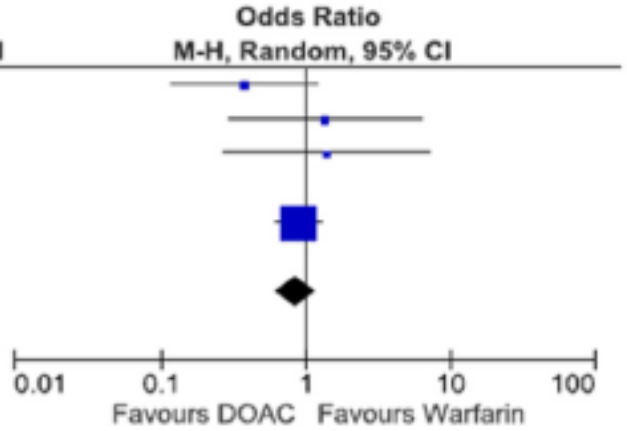
Proietti M et al, Stroke. 2017;48(4):857-866.

Meta-Analysis Comparing Direct Oral Anticoagulants Versus Warfarin in Morbidly Obese Patients With Atrial Fibrillation

Stroke or systemic embolism

Study or Subgroup	DOAC Events	DOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Random, 95% CI
Hohnloser 2019	4	480	11	502	8.7%	0.38 [0.12, 1.19]
Kido 2019	4	64	3	64	4.9%	1.36 [0.29, 6.32]
Kushnir 2019	5	277	2	152	4.2%	1.38 [0.26, 7.19]
Perales, 2019	0	37	0	30		Not estimable
Peterson 2019	52	3563	59	3563	82.1%	0.88 [0.60, 1.28]
Total (95% CI)		**4421**		**4311**	**100.0%**	**0.85 [0.60, 1.19]**
Total events	65		75			

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

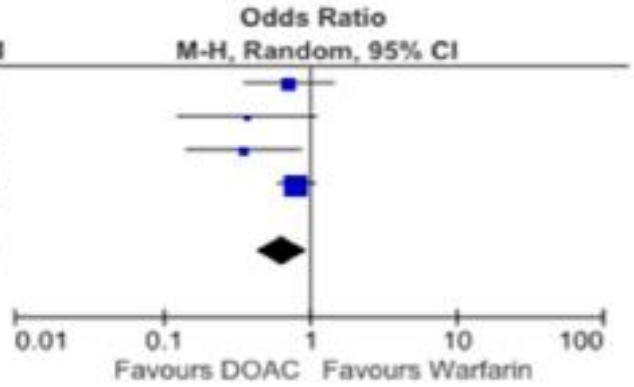


No significant difference in the event rate of stroke/SE

Major bleeding

Study or Subgroup	DOAC Events	DOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Random, 95% CI
Hohnloser 2019	13	480	19	502	21.5%	0.71 [0.35, 1.45]
Kido 2019	5	64	12	64	10.7%	0.37 [0.12, 1.11]
Kushnir 2019	8	277	12	152	14.7%	0.35 [0.14, 0.87]
Peterson 2019	77	3563	96	3563	53.0%	0.80 [0.59, 1.08]
Total (95% CI)		**4384**		**4281**	**100.0%**	**0.63 [0.43, 0.94]**
Total events	103		139			

Heterogeneity: Tau² = 0.05; Chi² = 4.26, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 2.29 (P = 0.02)



Significant lower major bleeding

Kido K et al, Am J Cardiol. 2020;126:23-28.

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

Because of limited data in extreme obesity, the use of VKA in patients with a BMI ≥40 kg/m^2 or weight >120 kg should be considered (in line with recommendations from the International Society on Thrombosis and Haemostasis).[427]

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CONTEMPORARY REVIEW

Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges

betrixaban within this patient population. Within the obese population (patients >120 kg and/or >40 kg/m^2), it is recommended that use of dabigatran, edoxaban, and betrixaban be avoided and that rivaroxaban and apixaban may be used with caution.

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Based on the pharmacokinetic properties and the available evidence the use of all NOACs appears to be safe and effective up to a BMI of 40 kg/m^2 (barring other clinically relevant factors). At BMI ≥40 kg/m^2 data are less robust.[381,385,388–390]

At a BMI ≥50 kg/m^2 plasma level measurements with any of the NOACs (including the inherent associated limitations, see 'NOAC plasma level measurements: technical approach, indications, pitfalls' section) or conversion to VKA therapy may be reasonable (*Figure 23*). Whether trough or peak plasma levels are preferable is a topic of further research; due to better reproducibility and correlation with clinical outcomes we generally advise for trough level measurement with peak level assessment only in selected cases.

ESC
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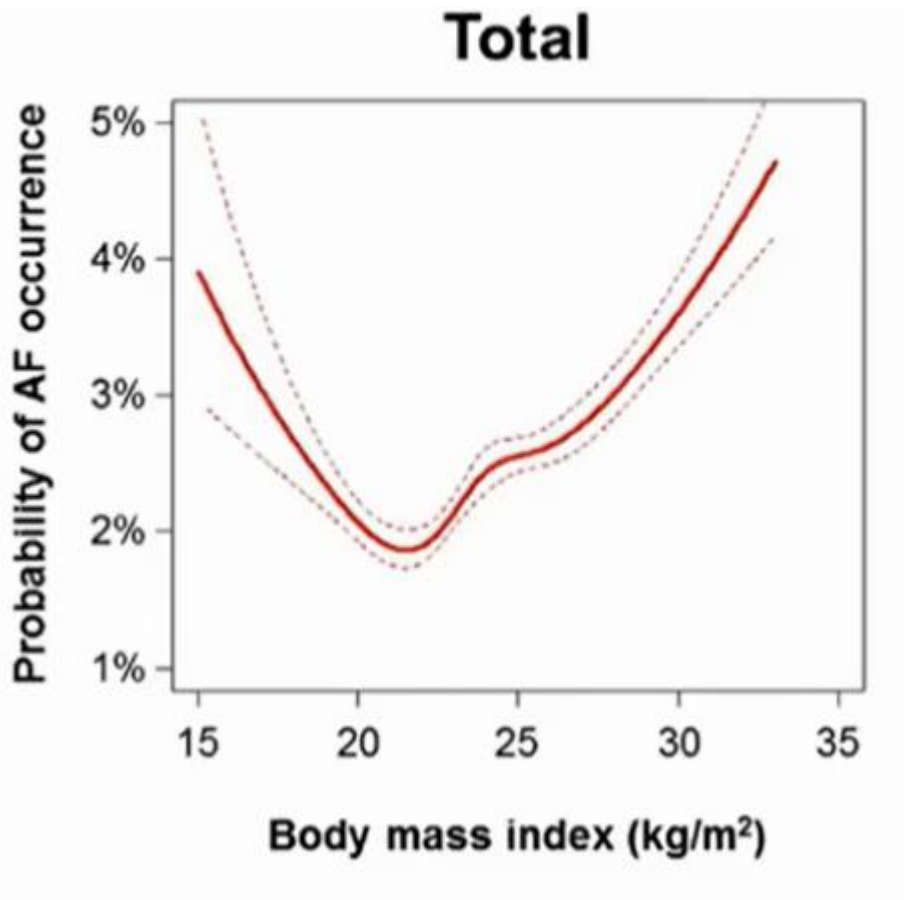
I NAO nei pazienti sottopeso

I NAO nei pazienti sottopeso



- There is no universal definition (poor consistency across the studies)
- **Underweight**: BMI <18.5 kg/m2
- **Low body weight**: ≤ 60 kg

- Low body weight **may increase exposure to any NOAC** → increased risk of bleeding

- Patients with low body weight frequently have **other co-morbidities** (including old age, frailty, cancer, and CKD) → **increased risk of stroke and bleeding**

- **Renal function may be overestimated** in underweight patients due to their reduced muscle mass (especially with the MDRD formula)

- **Body weight ≤ 60 kg** is **a criterion for dose reduction** of apixaban and edoxaban

Increased risk of major bleeding in underweight patients with atrial fibrillation who were prescribed non-vitamin K antagonist oral anticoagulants

Chan Soon Park, MD, Eue-Keun Choi, MD, PhD, Hyue Mee Kim, MD, So-Ryoung Lee, MD, Myung-Jin Cha, MD, Seil Oh, MD, PhD, FHRS

Underweight: BMI <18,5 kg/m2

Normal weight: BMI: 18,5-24,9 kg/m2

Overweight to obese: BMI >25 kg/m2

Table 2 Risk of major bleeding, thromboembolic events, and all-cause death in atrial fibrillation patients by body mass index.

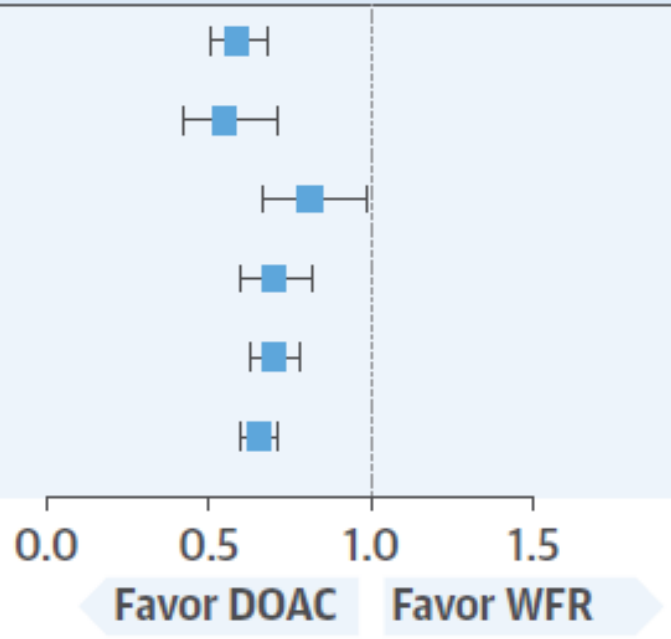
			Univariate analysis		Multivariate analysis†	
Variable	No. of events	Incidence*	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Major bleeding						
Underweight group	6/62	10.40	4.432 (1.734–11.328)	.002	4.135 (1.442–11.854)	.008
Normal weight group	16/753	2.43	1.00 (reference)		1.00 (reference)	
Overweight-to-obese group	7/538	1.56	0.627 (0.258–1.524)	.303	0.773 (0.305–1.959)	.587
Thromboembolism						
Underweight group	1/62	1.73	1.256 (0.159–9.923)	.829	1.133 (0.131–9.800)	.910
Normal weight group	9/753	1.37	1.00 (reference)		1.00 (reference)	
Overweight-to-obese group	1/538	0.22	0.164 (0.023–1.292)	.086	0.166 (0.021–1.341)	.092
All-cause death						
Underweight group	6/62	10.40	12.024 (3.877–37.288)	<.001	10.524 (2.949–37.561)	<.001
Normal weight group	6/753	0.91	1.00 (reference)		1.00 (reference)	
Overweight-to-obese group	3/538	0.67	0.702 (0.176–2.809)	.617	0.924 (0.218–3.928)	.915

Compared to normal weight and overweight/obese pts, underweight pts have **similar risk of stroke/SE**, but **more major bleeding and higher mortality**

Park CS et al, Heart Rhythm. 2017;14(4):501-507.

Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight → ≤ 60 kg

Pooled Direct Oral Anticoagulant Versus Warfarin	p Value
Ischemic Stroke	<0.001
Intracranial Hemorrhage	<0.001
Hospitalization for GI Bleeding	0.045
Hospitalization for Major Bleeding	<0.001
All-Cause Death	<0.001
Composite Outcome	<0.001



Compared with VKA, DOACs were associated with **lower risks of ischemic stroke and major bleeding**

These results were consistent in patients with weight ≤ 50 kg

Lee SR et al. JACC. 2019;73(8):919-931.

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

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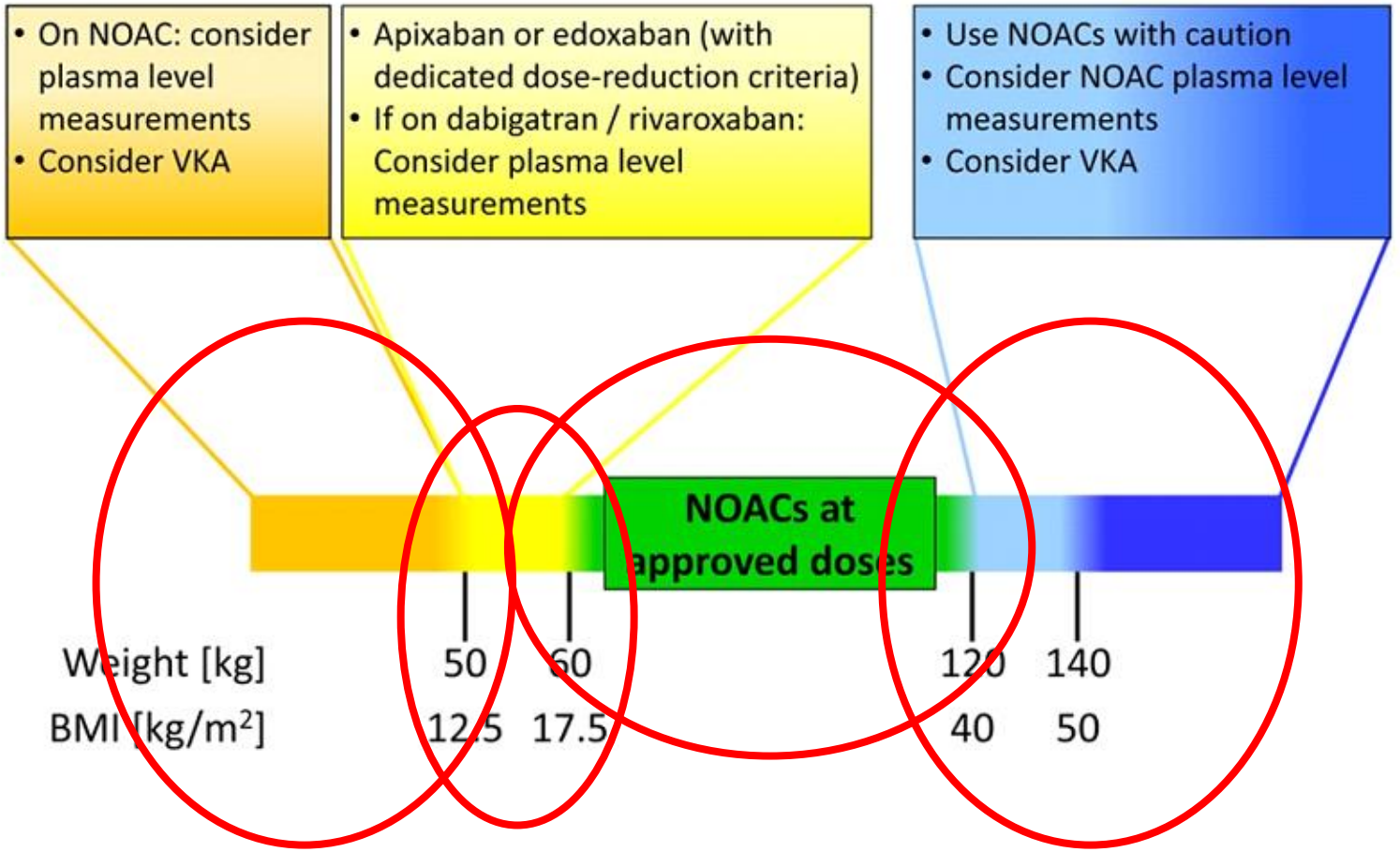

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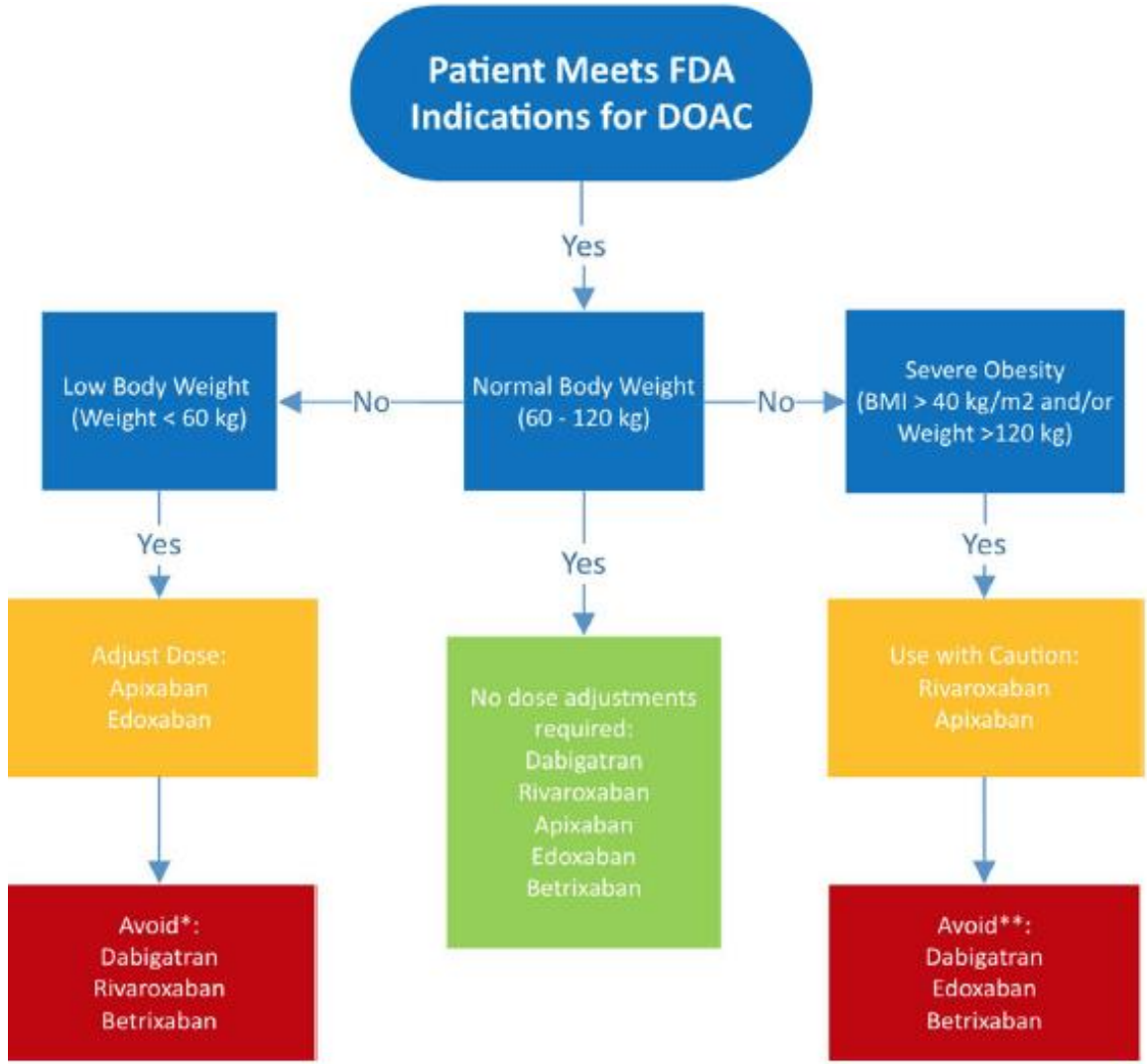

Livelli plasmatici attesi al picco e a valle				
	DABIGATRAN	APIXABAN	EDOXABAN	RIVAROXABAN
Livelli di picco	52-383	69-321	101-228	178-343
Livelli di valle	2-215	34-230	12-43	12-137

No studies have investigated if measurement of drug levels and dose adjustment based on laboratory coagulation parameters improve the overall benefit of NOACs

Routine monitoring of plasma levels and subsequent dose adaptation is generally discouraged

Take home messages

- I NAO sembrano efficaci e sicuri nei pazienti con obesità, tuttavia **le evidenze sono poco robuste**, e lo sono ancora meno per i pazienti sottopeso

- Nei pazienti con **BMI ≥ 40 kg/m2 e/o peso ≥ 120 kg preferire i VKA** (eventualmente usare con cautela apixaban e rivaroxaban)

- Per l'apixaban e l'edoxaban **il peso < 60 kg è un criterio per la riduzione della posologia**

- Il dosaggio dei livelli plasmatici **non va richiesto di routine**

Caso 1

Mario, 85 anni (80 kg, 170 cm)

- FRCV: ipertensione arteriosa sistemica, DM 2

- Pat ass: TIA nel 2013, IRC di grado moderato, asportazione endoscopica di polipo
- del colon sanguinante nel 2015

- Per cardiopalmo esegue ECG Holter: parossismo di fibrillazione atriale di 2 ore

- LAB: Hb: 13 g/dl; PLT: 215000; creatinina: 1,4 mg/dl (VFG sec Cockroft Gault: 44 ml/min), AST ed ALT nn
- Terapia in corso: Cardioaspirin 100 mg, atorvastatina 20 mg, ramipril 2.5 mg x 2, metformina 500 mg x 2

Quale terapia iniziare?

A) Prosegue Cardioaspirina
B) Anticoagulazione con Coumadin
C) Antocoagulazione con NAO

Quale NAO scegliere?

A) Rivaroxaban 20 mg
B) Dabigatran 150 mg x 2
C) Apixaban 2,5 mg x 2
D) Apixaban 5 mg x 2
E) Edoxaban 30 mg

Caso 2

Silvia, 65 anni (130 kg, 165 cm, BMI: 48 kg/m2)

- FRCV: ipertensione arteriosa sistemica, ex fumo, dislipidemia
- Pat ass: quadrantectomia destra per carcinoma mammario
- Fibrillazione atriale parossistica in Coumadin
- LAB: Hb: 12 g/dl; MCV: 89 fl; PLT: 215000; creatinina: 1,1 mg/dl (VFG sec Cockroft Gault: 105 ml/min)
- Terapia in corso: Coumadin, rosuvastatina 10 mg, nebivololo 5 mg
- Ricoverata per ictus ischemico (INR a range) → valutazione cardiologica

Quale terapia ?

A) Dabigatran 150 mg x 2
B) Prosegue Coumadin
C) Apixaban 5 mg x 2, senza dosaggio dei livelli plasmatici
D) Apixaban 5 mg x 2,con dosaggio dei livelli plasmatici