17th WORLD CONGRESS of ARRHYTHMIAS
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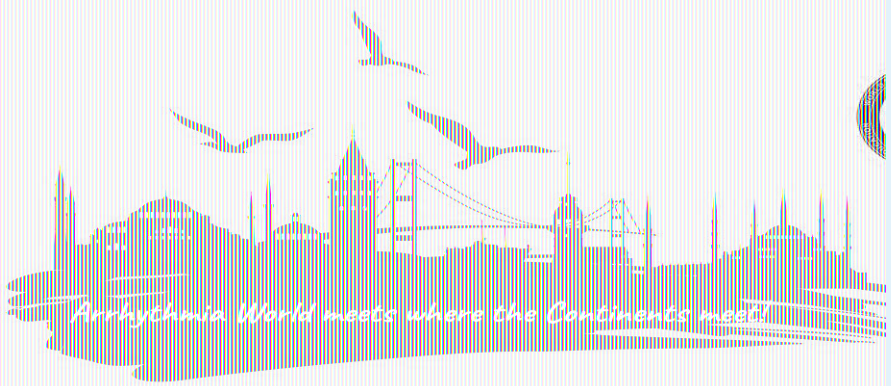
Elite World Convention Center



Extremes of body weight, too low or too high

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Instituto do Coração HC InCor FMUSP - BRAZIL

I have no conflicts of interest for this presentation

TOO HIGH

BMI > 40

Obesity (BMI ≥ 30 kg/m_2): from 30.5 to 42.4%
Severe obesity (BMI ≥ 40 kg/m_2): from 4.7 to 9.2%,

TOO LOW

BMI < 18 or <50kg

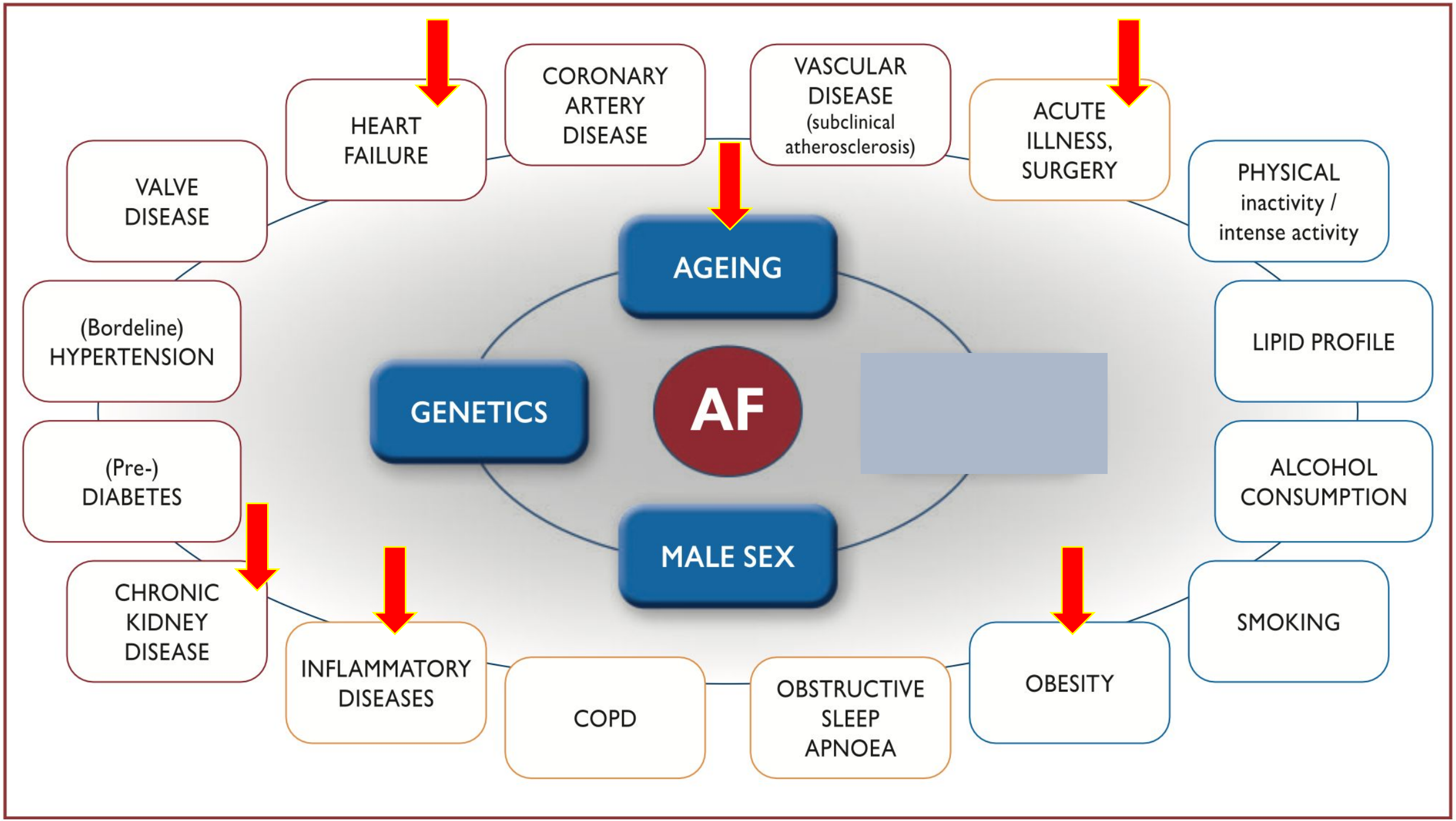
HEART FAILURE
CORONARY ARTERY DISEASE
VASCULAR DISEASE (subclinical atherosclerosis)
ACUTE ILLNESS, SURGERY
VALVE DISEASE
PHYSICAL inactivity / intense activity
AGEING
(Bordeline) HYPERTENSION
LIPID PROFILE
GENETICS
AF
(Pre-) DIABETES
ALCOHOL CONSUMPTION
MALE SEX
CHRONIC KIDNEY DISEASE
SMOKING
INFLAMMATORY DISEASES
OBESITY
COPD
OBSTRUCTIVE SLEEP APNOEA

Table 11 Dose selection criteria for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
Lower dose	110 mg b.i.d.			30 mg o.d.
Reduced dose		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d./15 mg o.d.
Dose-reduction criteria	Dabigatran 110 mg b.i.d. in patients with: • Age ≥80 years • Concomitant use of verapamil, or • Increased bleeding risk	CrCl 15 - 49 mL/min	At least 2 of 3 criteria: • Age ≥80 years, • Body weight ≤60 kg, or • Serum creatinine ≥1.5 mg/dL (133 µmol/L)	If any of the following: • CrCl 30 - 50 mL/min, • Body weight ≤60 kg, • Concomitant use of verapamil, quinidine, or dronedarone

b.i.d. = bis in die (twice a day); CrCl = creatinine clearance; o.d. = *omni die* (once daily).

Hindricks G, Eur Heart J. 2021 Feb 1;42(5):373-498. PMID: 3286(

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RE-LY
2% with <50 kg
21% higher geometric mean concentration
17% of patients weighed > 117 kg
20% lower geometric mean concentration

ARISTOTLE study
11% with ≤60 kg
No difference efficacy or safety
4% with > 120kg

Hindricks G, Eur Heart J. 2021 Feb 1;42(5):373-498. PMID: 3286(

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ROCKET AF
14% of patients had a BMI ≥35 kg/m2

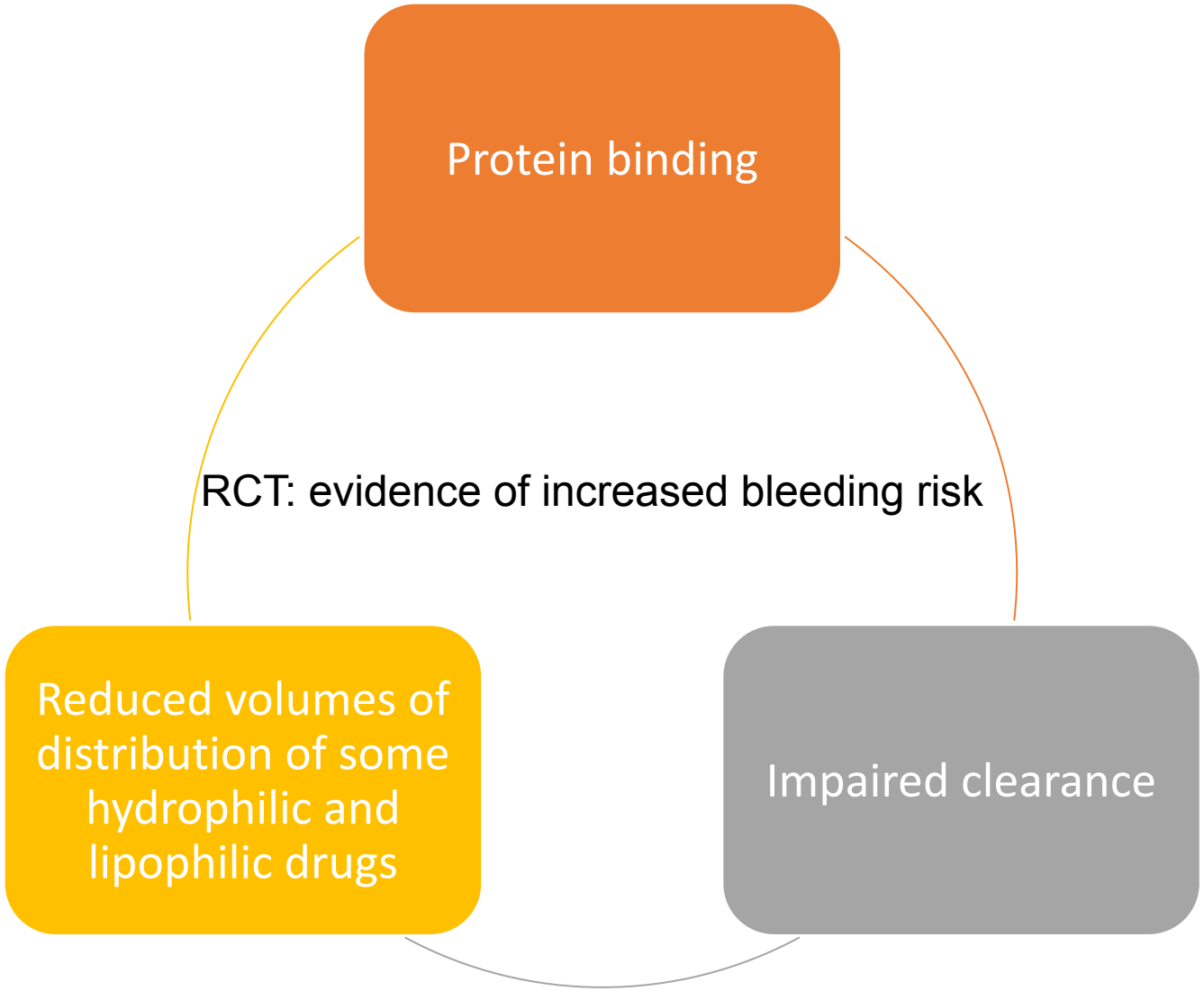
ENGAGE
10% < 60kg
0.8% BMI < 18.5
15% BMI > 35

Hindricks G, Eur Heart J. 2021 Feb 1;42(5):373-498. PMID: 3286(

BMI of <18.5 kg/m2

Changes in pharmacokinetic

COMORBIDITIES

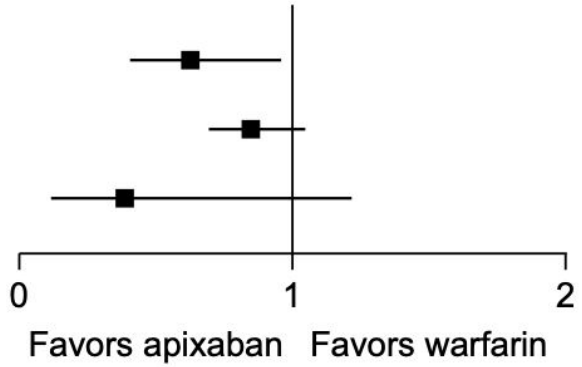


Overweith population: the volume of distribution can vary significantly, depending in particular on the degree of lipophilicity of each specific drug.

Nonlinear increase in drug clearance (hepatic and renal) with increasing weight has been proposed.

A

Body weight category	Apixaban, n (N)	Warfarin, n (N)	Relative Risk (95% CI)	$P_{interaction}$
⩽ 60 kg	34 (1018)	52 (967)	0.63 (0.41–0.96)	0.64
61–120 kg	173 (7590)	201 (7582)	0.85 (0.70–1.05)	
> 120 kg	4 (480)	11 (502)	0.39 (0.12–1.22)	



B

Body weight category	Apixaban, n (N)	Warfarin, n (N)	Relative Risk (95% CI)	$P_{interaction}$
⩽ 60 kg	36 (1018)	62 (967)	0.55 (0.36–0.82)	0.015
61–120 kg	277 (7590)	379 (7582)	0.71 (0.61–0.83)	
> 120 kg	13 (480)	19 (502)	0.74 (0.37–1.50)	

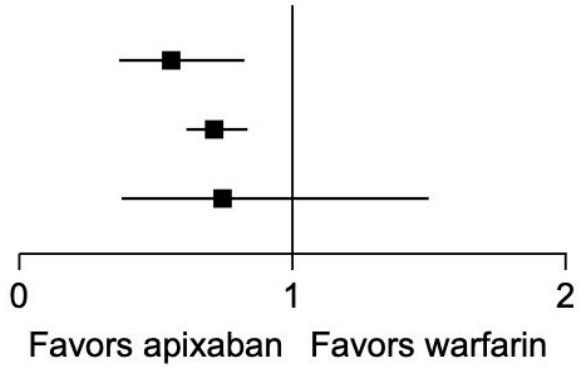


Fig. 4 Body weight categories vs relative risk of **A** stroke or SE and **B** ISTH MB in patients with NVAF in the ARISTOTLE trial [70]. *ISTH* International Society on Thrombosis and Haemostasis, *MB* major bleeding, *NVAF* nonvalvular atrial fibrillation, *SE* systemic embolism

Jamieson MJ et al. American Journal of Cardiovascular Drugs (2022) 22:615–631

Table 3 Outcomes from a multivariable model according to body mass index categories (adjusted analysis)

Body mass index (kg/m^2)	Normal (18.5 to <25) *N.* of events (%)	Overweight (25 to <30) HR[a] (95% CI)	Moderately obese (30 to <35) HR[a] (95% CI)	Severely obese (35 to <40) HR[a] (95% CI)	Very severely obese (≥40) HR[a] (95% CI)	*P* for trend
Stroke/SEE	273 (2.3)	0.91 (0.78–1.07)	0.82 (0.68–1.00)	0.68 (0.52–0.89)	0.54 (0.35–0.83)	<0.001
Ischaemic Stroke/SEE	229 (2.0)	0.91 (0.77–1.09)	0.80 (0.65–0.98)	0.70 (0.52–0.94)	0.48 (0.30–0.77)	<0.001
Mortality	629 (5.2)	0.79 (0.71–0.87)	0.77 (0.68–0.88)	0.75 (0.63–0.9)	0.78 (0.62–0.98)	0.037
Major bleeding	283 (2.9)	1.03 (0.88–1.20)	1.12 (0.94–1.34)	1.18 (0.94–1.48)	1.28 (0.96–1.70)	0.045
Net outcome[b]	987 (8.7)	0.91 (0.83–0.98)	0.92 (0.83–1.01)	0.87 (0.77–1.00)	0.95 (0.80–1.12)	0.44
Major or clinically relevant non-major bleeding	1014 (11.8)	1.05 (0.97–1.14)	1.10 (1.00–1.20)	1.17 (1.04–1.32)	1.27 (1.10–1.47)	<0.001
Any bleeding	1234 (15.0%)	1.04 (0.97–1.12)	1.06 (0.97–1.15)	1.15 (1.04–1.28)	1.23 (1.08–1.40)	<0.001

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SEE, systemic embolic event.

[a]Adjusted hazard ratio with normal BMI as the referent. The model is adjusted for treatment group, $CHADS_2$ score at screening, verapamil or quinidine use at screening, paroxysmal vs. non-paroxysmal AF, sex, region, age, previous use of vitamin K antagonist for ≥60 days, baseline use of aspirin, thienopyridine agents, amiodarone, digoxin or digitalis preparations, smoking status, history of hypertension, stroke or TIA, CHF, diabetes, and creatinine at baseline.

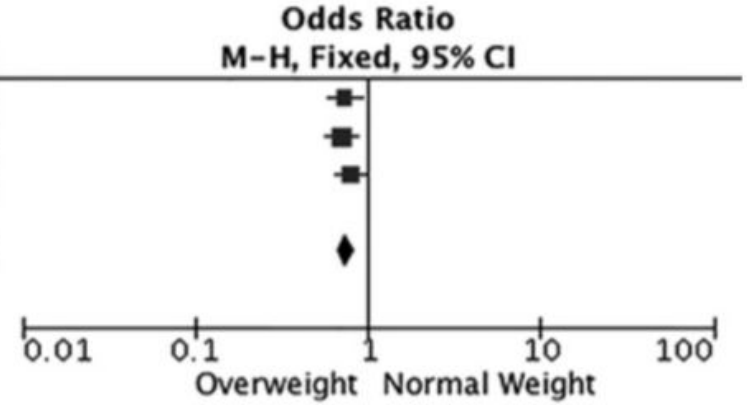
[b]Net outcome: composite of stroke, systemic embolic event, major bleeding, or death.

Boriani G et al. European Heart Journal (2019) 40, 1541–1549

A Stroke/SEE

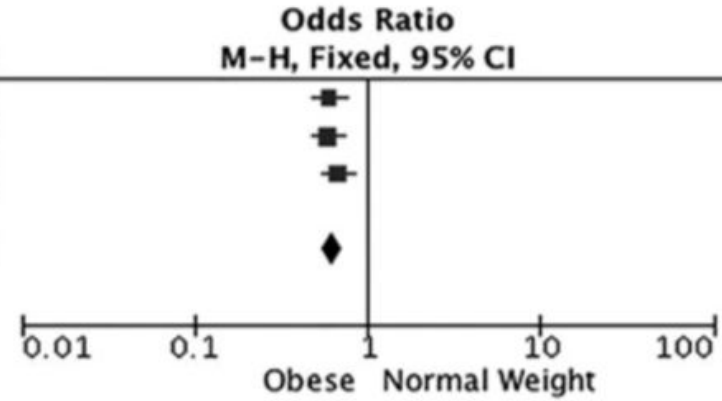
Study or Subgroup	Overweight Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	174	6702	142	4052	29.4%	0.73 [0.59, 0.92]
RE-LY	196	7111	182	4697	36.4%	0.70 [0.57, 0.86]
ROCKET AF	225	5523	167	3314	34.2%	0.80 [0.65, 0.98]
Total (95% CI)		**19336**		**12063**	**100.0%**	**0.75 [0.66, 0.84]**
Total events	595		491			

Heterogeneity: $Chi^2 = 0.79$, $df = 2$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 4.73$ ($P < 0.00001$)



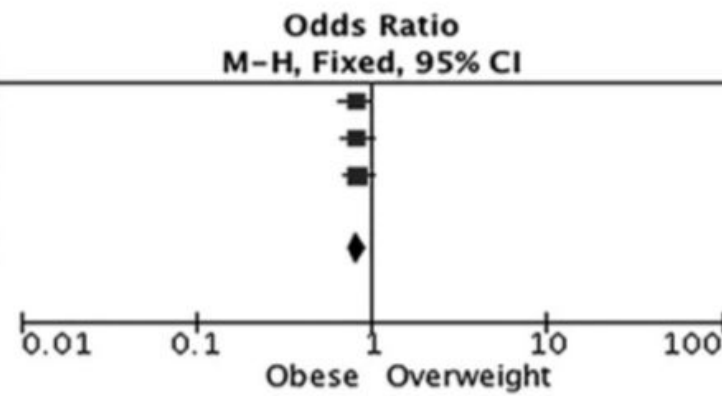
Study or Subgroup	Obese Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	142	4052	30.7%	0.60 [0.47, 0.75]
RE-LY	145	6279	182	4697	35.2%	0.59 [0.47, 0.73]
ROCKET AF	179	5194	167	3314	34.1%	0.67 [0.54, 0.83]
Total (95% CI)		**18632**		**12063**	**100.0%**	**0.62 [0.54, 0.70]**
Total events	476		491			

Heterogeneity: $Chi^2 = 0.89$, $df = 2$ ($P = 0.64$); $I^2 = 0\%$
Test for overall effect: $Z = 7.31$ ($P < 0.00001$)



Study or Subgroup	Obese Events	Total	Overweight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	174	6702	31.1%	0.81 [0.65, 1.01]
RE-LY	145	6279	196	7111	31.7%	0.83 [0.67, 1.04]
ROCKET AF	179	5194	225	5523	37.2%	0.84 [0.69, 1.03]
Total (95% CI)		**18632**		**19336**	**100.0%**	**0.83 [0.73, 0.94]**
Total events	476		595			

Heterogeneity: $Chi^2 = 0.05$, $df = 2$ ($P = 0.98$); $I^2 = 0\%$
Test for overall effect: $Z = 2.98$ ($P = 0.003$)

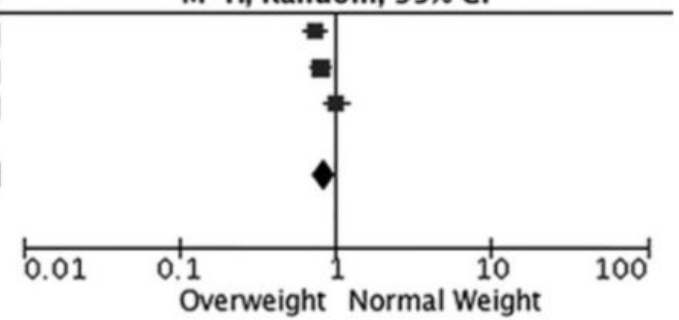


Proietti M. Stroke. 2017;48:857–866

B Major Bleeding

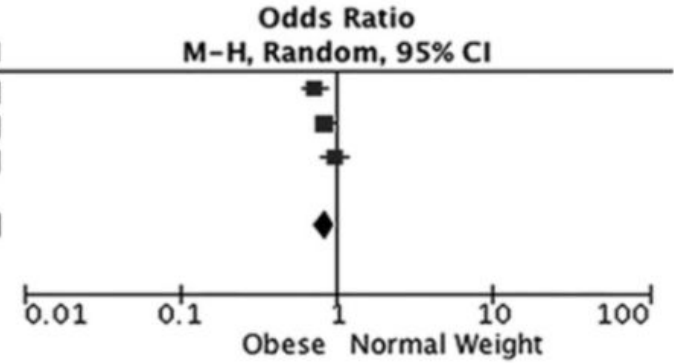
Study or Subgroup	Overweight Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	271	6687	219	4035	32.1%	0.74 [0.61, 0.88]
RE-LY	424	7111	344	4697	36.3%	0.80 [0.69, 0.93]
ROCKET AF	312	5555	183	3327	31.5%	1.02 [0.85, 1.23]
Total (95% CI)		**19353**		**12059**	**100.0%**	**0.84 [0.70, 1.01]**
Total events	1007		746			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 1.87 (P = 0.06)



Study or Subgroup	Obese Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	285	7134	219	4035	32.2%	0.73 [0.61, 0.87]
RE-LY	394	6279	344	4697	37.3%	0.85 [0.73, 0.98]
ROCKET AF	279	5214	183	3327	30.5%	0.97 [0.80, 1.18]
Total (95% CI)		**18627**		**12059**	**100.0%**	**0.84 [0.72, 0.98]**
Total events	958		746			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.77$, df = 2 (P = 0.09); $I^2 = 58\%$
Test for overall effect: Z = 2.21 (P = 0.03)



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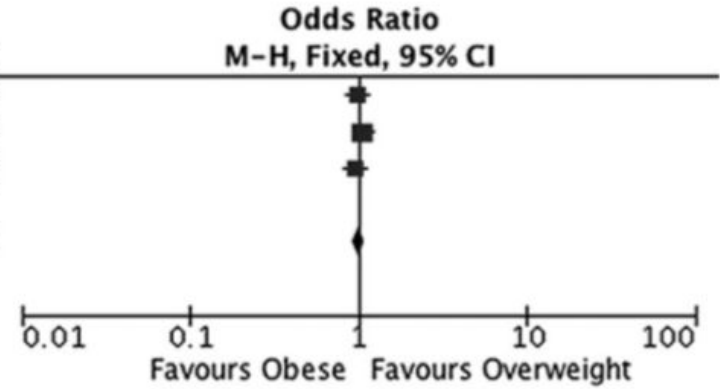
ROCKET AF	279	5214	312	5555	30.8%	0.95 [0.80, 1.12]
Total (95% CI)		**18627**		**19353**	**100.0%**	**1.00 [0.92, 1.10]**
Total events	958		1007			

Heterogeneity: $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)



Proietti M. Stroke. 2017;48:857–866

Journal of
Clinical Medicine

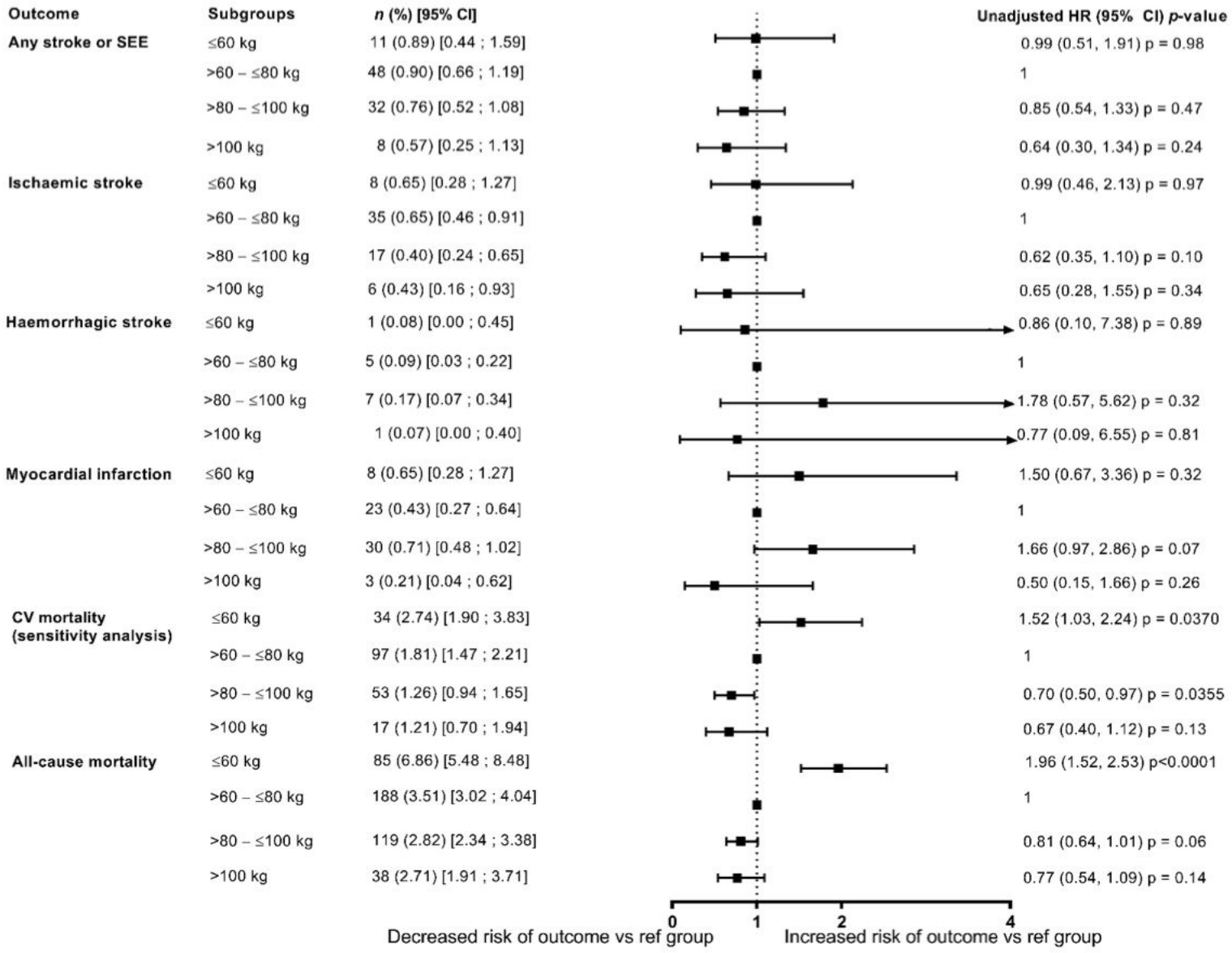
MDPI

Article

Impact of Weight on Clinical Outc Therapy in Atrial Fibrillation Pati ETNA-AF-Europe Registry

Giuseppe Boriani [1,*], Raffaele De Caterina [2,3], Marius Co Paulus Kirchhof [6,7,8]

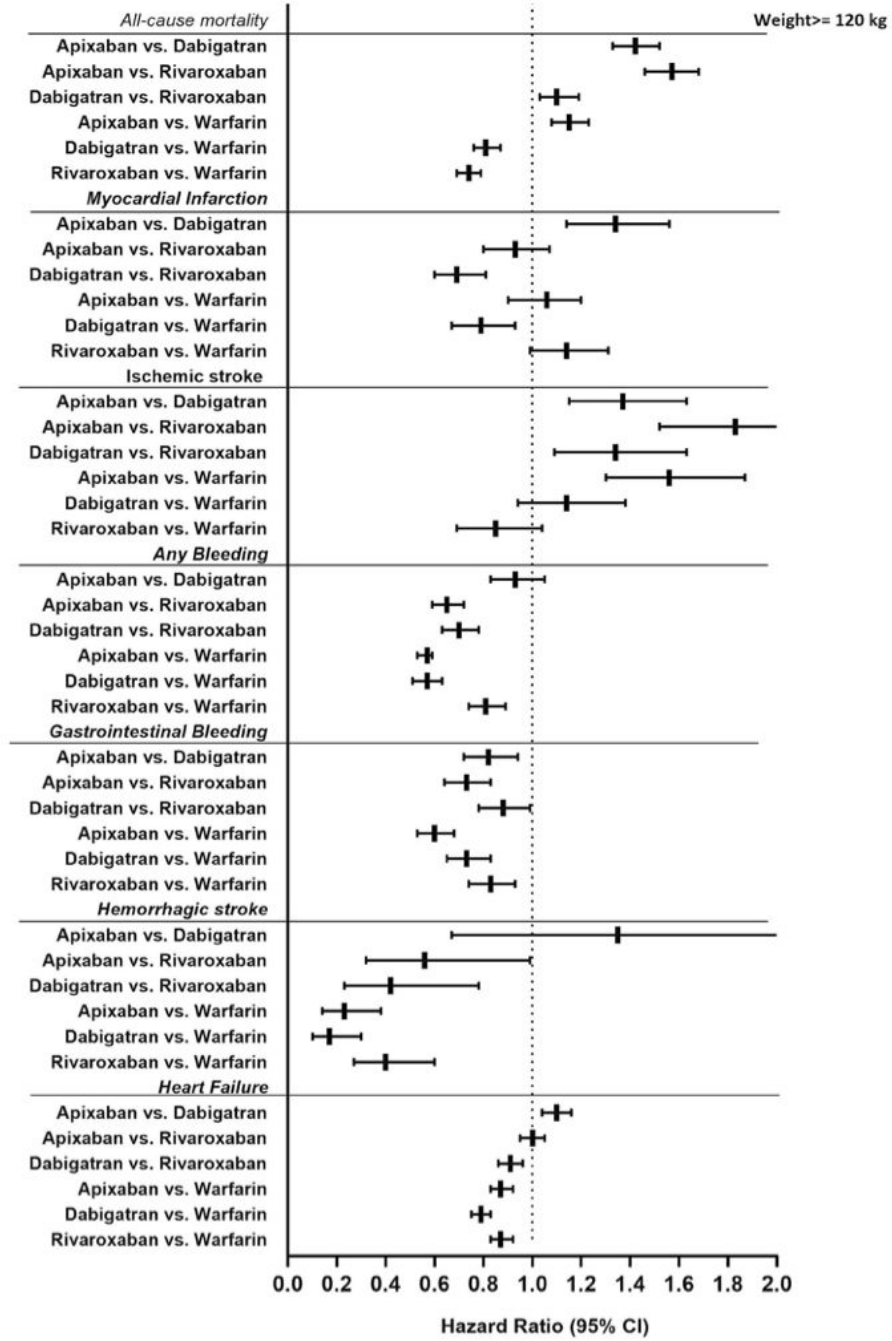
- ✔ Patients at extremes of body weight reported low rates of stroke and bleeding events with edoxaban within the current dosing guidelines.



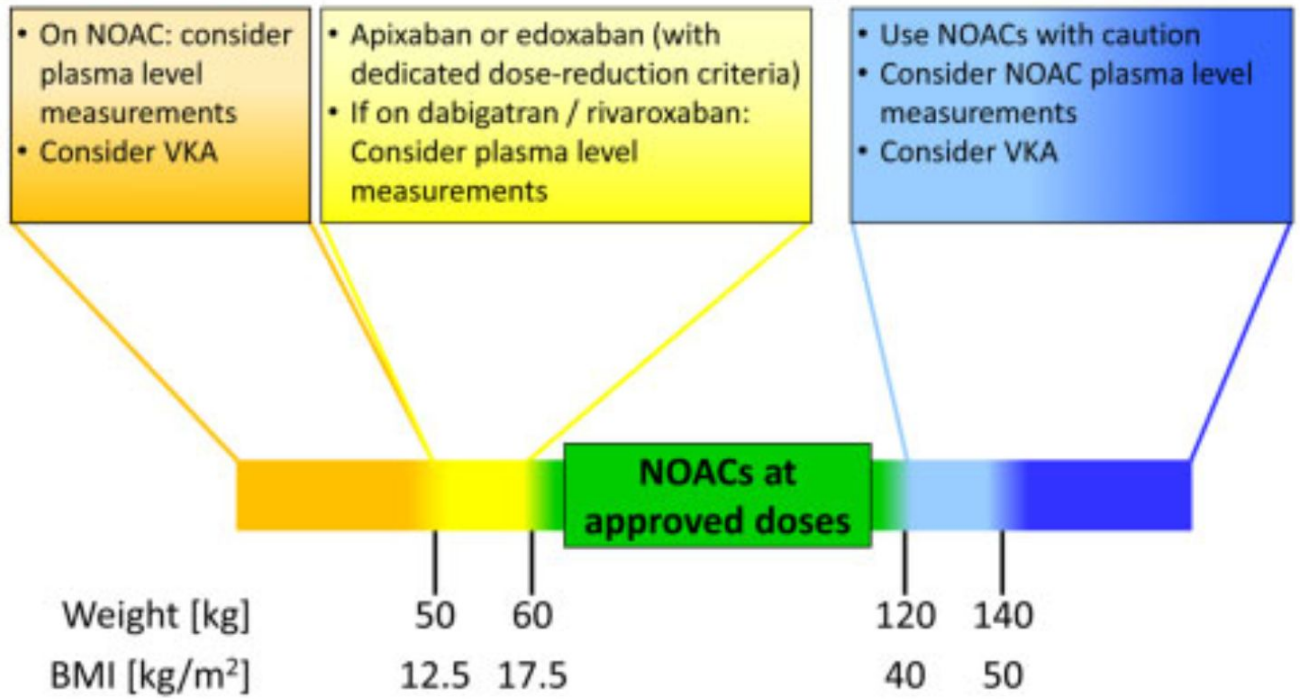
Comparative Effectiveness and Safety of Direct Oral Anticoagulants in Obese Patients with Atrial Fibrillation

Alexandros Briasoulis[1,2], **Amgad Mentias**[1,2], **Alexander Mazur**[1,2], **Paulino Alvarez**[1,2], **Enrique C. Leira**[3], **Mary S. Vaughan Sarrazin**[4,5]

[1]Division of Cardiovascular Diseases, Department of Internal Medicine, University of Iowa Colle of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, USA

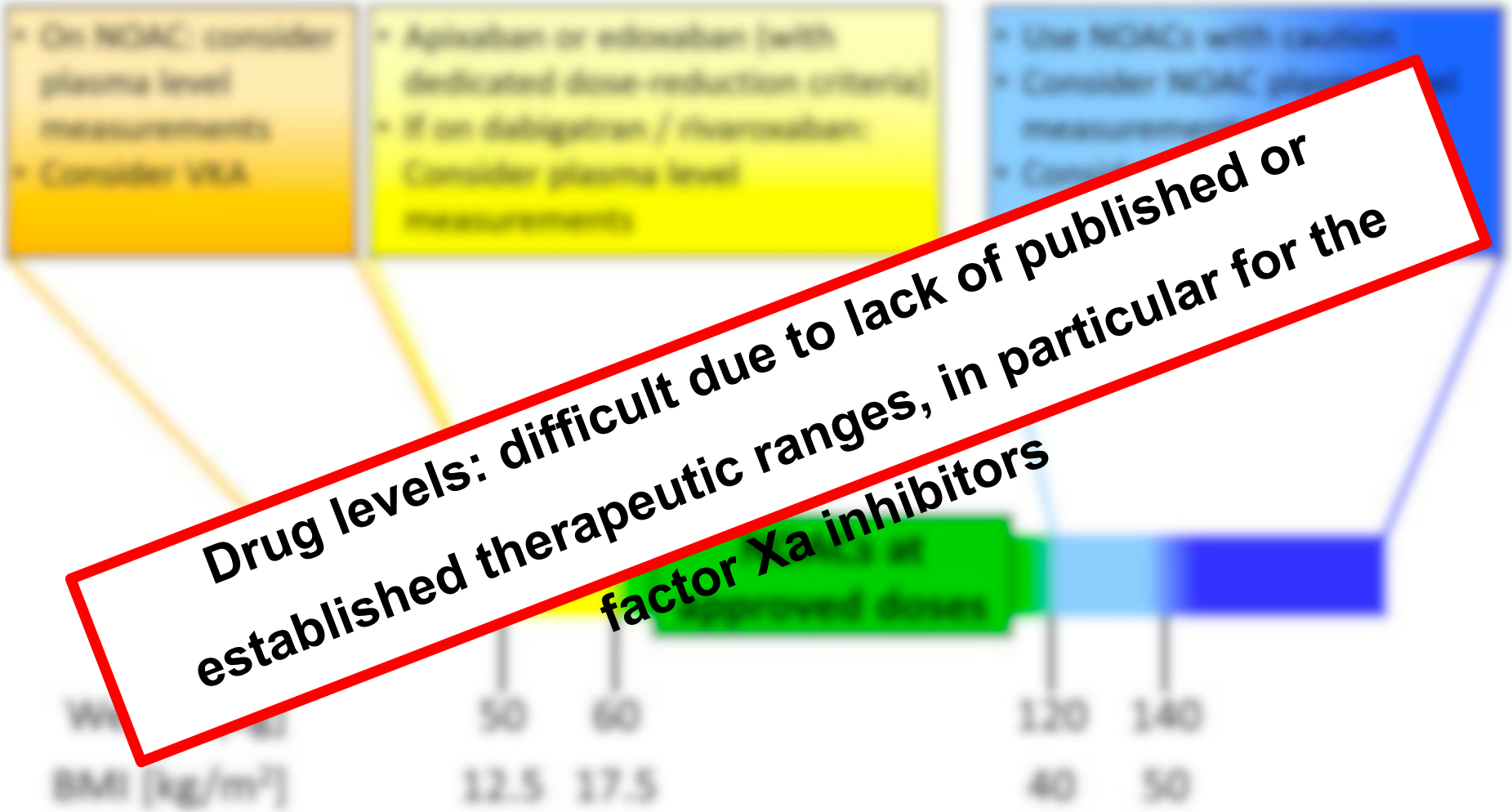


2021 EHRA Practical Guide on the use of NOACs



Steffel J et al. 2021 Europace. 2021;23(10):1612–76.

2021 EHRA Practical Guide on the use of NOACs



Steffel J et al. 2021 Europace. 2021;23(10):1612–76.

CONCLUSION

- ✔ All DOACs present a complex challenge in generating **robust data** regarding efficacy and safety, particularly in individuals with extreme variations in body weight
- ✔ Warfarin is an option? **Plasma** concentration is feasible? New drugs will be safer?
- ✔ Reducing the modifiable factors: drugs interactions, **improve lifestyle**.
- ✔ While this data provides valuable insights, it may not entirely support our clinical decision-making. Shared decision-making remains a viable option. It's worth noting that extreme weight is not conducive to overall health, and efforts in this direction are also warranted.

Thanks - Obrigada

Arritmia_em_foco