NOACs vs vitamin K antagonists in patients with extreme body weights

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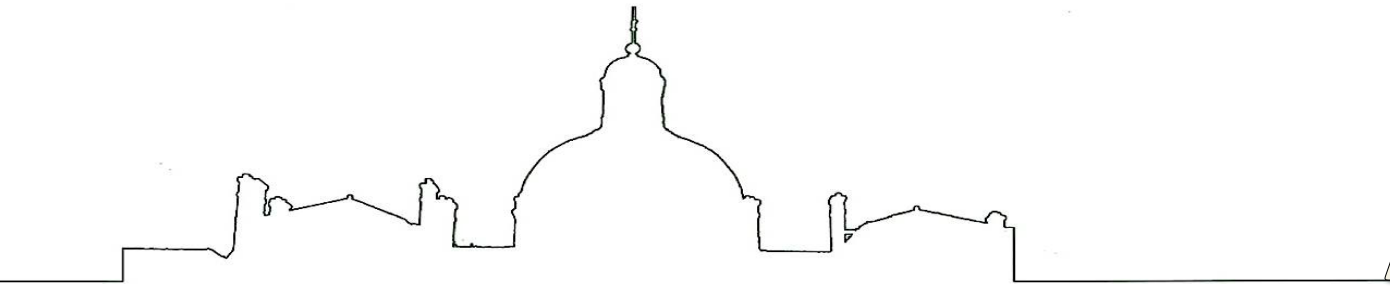
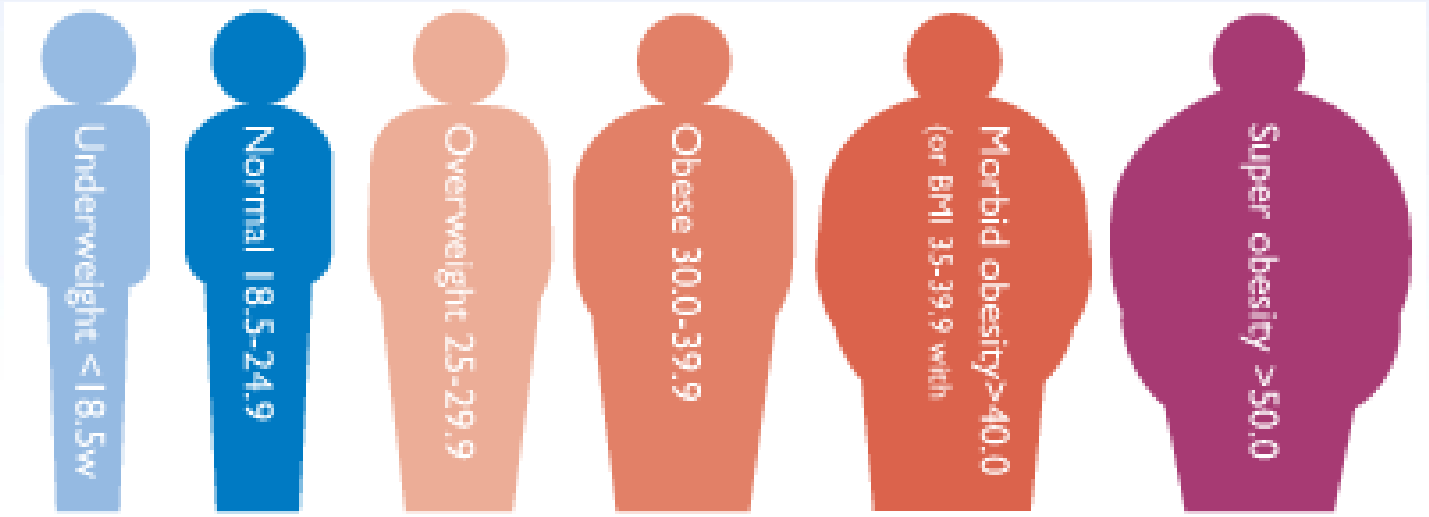


Declaration of conflict of interest

- Speakers fees: BMS/Pfizer, Bayer, Servier, Astra-Zeneca.
- Consultant fees: BMS/Pfizer, Bayer.
- Proctoring: Medtronic.
- Research Grants: BMD/Pfizer, Medtronic.

Definition


Underweight <18.5w
Normal 18.5-24.9
Overweight 25-29.9
Obese 30.0-39.9
Morbid obesity>40.0
(or BMI 35-39.9 with
Super obesity >50.0

Definition

Classification	*BMI (kg/m^2)*
Underweight	**< 18.5[1]** – Moderate thinness: 16-16.99 – Severe thinness: <16
Normal weight	**18.5-24.99[1]**
Overweight (pre-obesity)	**25-29.99[1]**
Obese	**≥30[1]**
Class 1	30-34.99[1]
Class 2 (moderate obesity)	35-39.99[1]
Class 3 (severe or morbid obesity)	≥40[1]
Class 4 (super-obesity)	≥50
Class 5 (super-super or extreme)	≥60

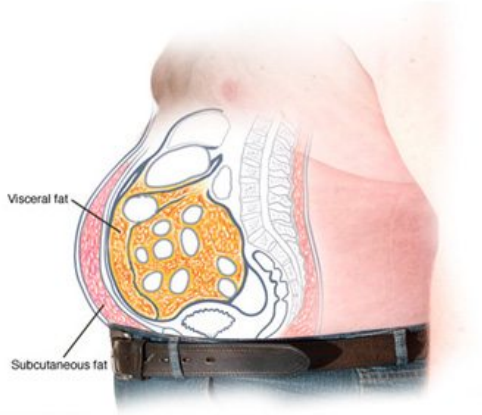
Obesity affects 33.9% of US adults and between 10% (Italy) and 23% (UK) of EU adults. http://apps.who.int/bmi/index.jsp.

Definition

Classification	BW (kg or lbs)
Underweight	<60 or ≤56[190] or ≤50kg; ≤12 lbs[190]
Normal weight	>60 or >50 up to 70 or 76 or 85kg; 125-168lbs[190]
Overweight (pre-obesity)	≥76 up to 92or 100 kg; 169-20 lbs[190]
Obese	**>100 or >92kg;** **>20%increase of the IBW;** **≥203lbs[190]**
Class 1	
Class 2 (moderate obesity)	>100% of the IBW
Class 3 (severe or morbid obesity)	≥150 or ≥123kg[190]; ≥ 271lbs[190]
Class 4 (super-obesity)	--
Class 5 (super-super or extreme)	--

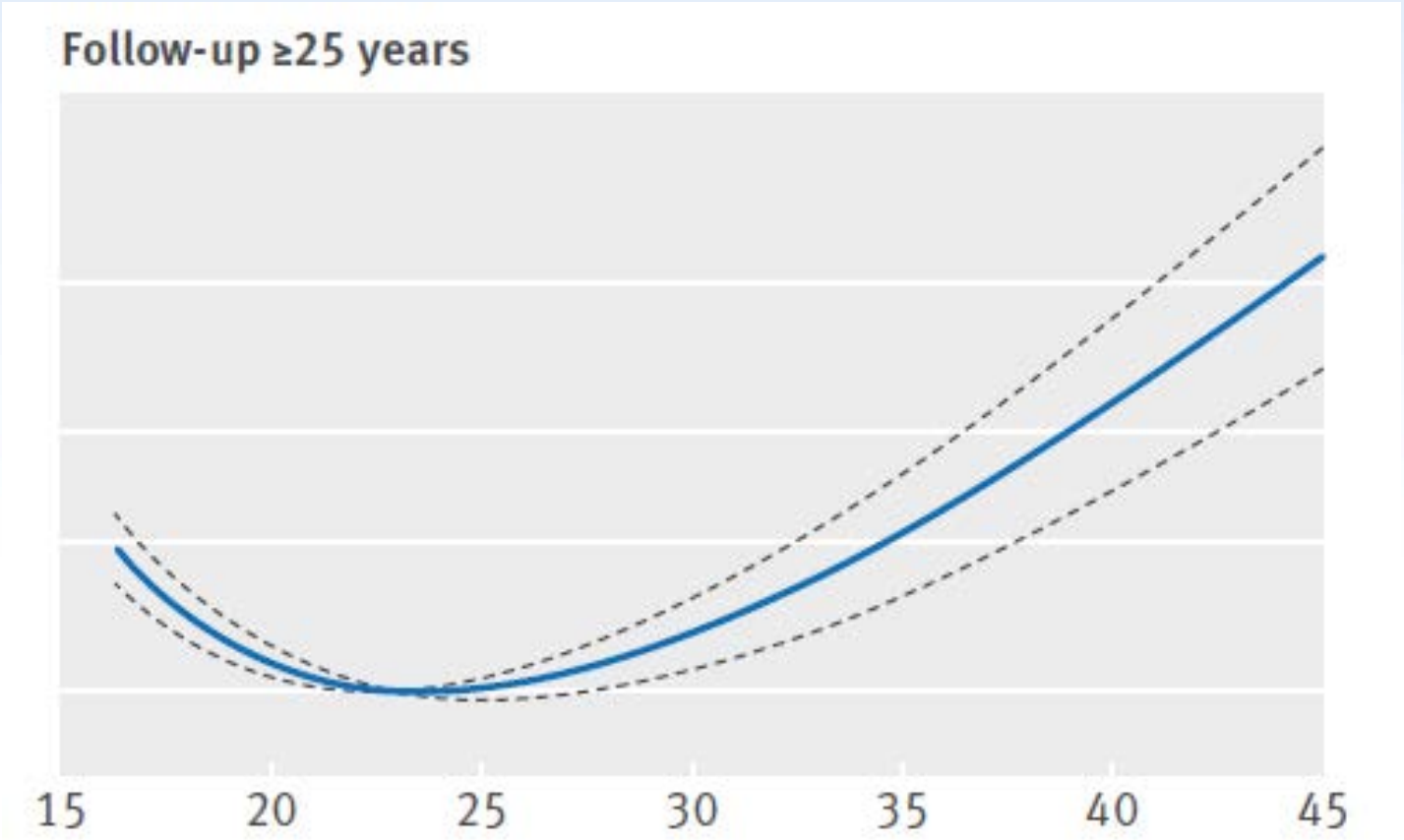
The drawbacks of using BMI

- BMI a good marker of CV risk if not necessarily the best measure of adiposity.
- Ethnic differences and gradual global increase in BMI values cast doubts over the “normal range” definition.
- BMI does not differentiate between metabolically-healthy and metabolically-abnormal obesity (increased visceral fat and insulin resistance).



Clinical impact of extreme BMI

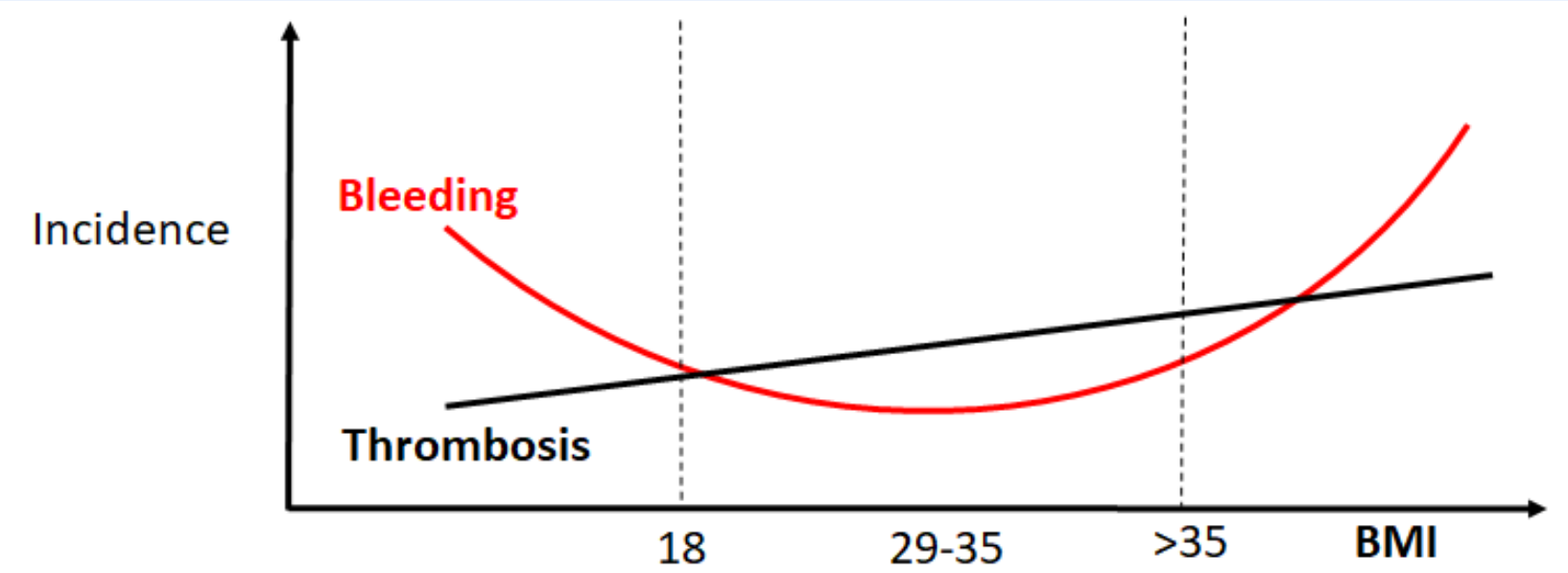
Weight and mortality



Mortality rates are increased up to 12-fold in morbidly-obese subjects (nadir 23-24)

Aune D. BMJ 2016;**353**:i2156.

Cardio-Vascular events according to BMI



- U-shaped relation between BMI and spontaneous bleeding
- Enhanced risk of ICH and extracranial bleeds among underweight
- Greater risk of deep ICH and extracranial bleeding among obese individuals
- Blood pressure should be carefully controlled in individuals on antithrombotic therapy

Aune D. BMJ 2016;**353**:i2156.
Hansel B. Eur J Prev Cardiol 2015;**22**(2):215-22.

PK and extreme BMI

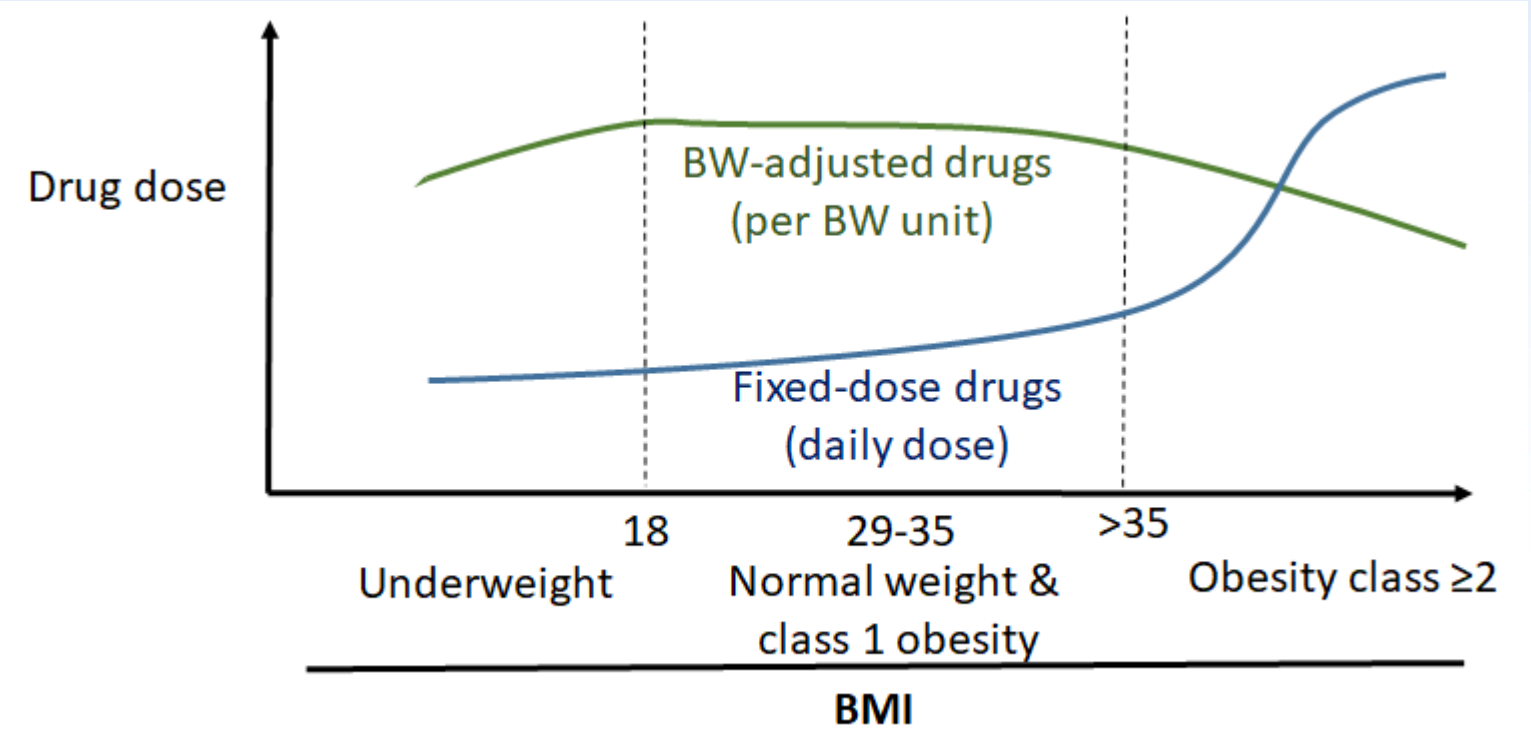
Impact of weight on PK

Organ/apparatus	Type of Change vs. non-obese	Pharmacological effect
Lean mass	↗	↗ Vd for hydrophilic compounds
Fat mass	↗	↗ or normal Vd for lipophilic compounds
Tissue perfusion	↘	↘ concentration of drugs in low-perfused tissues
Blood volume	↗	
Body water	↘	
Acute phase proteins, FFA, α1 acid glycoprotein	↗	↗ or normal protein-drug binding and ↘ free plasma concentration

Impact of weight on PK

Organ/apparatus	Type of Change vs. non-obese	Pharmacological effect
Heart	Excess of epicardial fat, LV hypertrophy, left atrial enlargement. Mostly reversible with weight loss	Variable tissue blood supply
Liver	Early stages: ↗ in hepatic blood flow/Clearance Later stages: non-alcoholic fatty liver or cirrhosis	Early stages: normal or ↗ biotransformation
- **Phase I enzymes (CYP450)**[68]	Reduced 3A4 activity Increased 1A2, 2E1, 2C9 expression or activities	Variable CYP450-dependent biotransformation
- **Phase II enzymes**	Increased glucuronidation and sulfation	↗ biotransformation
Kidney	Early stages: increase in GFR Later stages: chronic kidney disease may develop	Early phases: ↗ renal clearance. Drugs should be adjusted based on the measured rather than calculated CrCl, or CrCl calculated on IBW or LBW

Pharmacology according to BMI



- Fxed-dose ATT drugs might be over- and under-dosed for BMIs <18.75 and ≥35 kg/m^2.
- Relationship between underweight/obesity and BW-adjusted drugs remains unknown.

Clinical consequences

Vitamin-K antagonist (VKA)

- Longer time to achieve target INR and ↗ dose requirement of VKAs in obese
- A positive correlation between BMI and warfarin MD (0.69 mg per 1kg/m^2 BMI increase)
- BMI >30kg/m^2 predicts anticoagulation reversal failure using weight-based PCC.

- This is the opposite in underweight patients

In obese and underweight patients the efficacy/safety profile might be different.
Whether therapeutic INR range should be similar irrespective of BMI is unknown.

Br J Haematol 2011;**155**(2):137-49.
J Thromb Thrombolysis 2013;**36**(1):96-101.

APIXABAN

- In healthy subjects, Cmax and AUC inversely correlate with BW/BMI, showing a 30% ↗ below 50kg and 30% ↘ above 120kg vs. normal weight.
- In ARISTOTLE, safety and efficacy of apixaban vs. warfarin were similar in NVAF patients > and < 60kg
- Obesity was associated with lower mortality (OR 0.63, 95%CI: 0.54-0.74), without differences in stroke/SE (OR 0.79, 95%CI:0.61-1.02) and major bleeding (0.91 95%CI 0.74-1.1).

Consensus statements: In underweight (≤60 kg) patients, apixaban dose should be reduced in association with reduced renal function (creatinine <133 µmol) or age <80 yrs (apixaban)

Eur Heart J 2016;**37**(38):2869-2878.

EDOXABAN

- Edoxaban Cmax is ≈40% ↗ in patients <60kg,[131] causing 50% dose ↘ in HOKUSAI-VTE/ENGAGE AF-TIMI 48.
- In HOKUSAI-VTE, 12% of the patients were underweight and the primary outcome was comparable to the non-underweight population.
- Half dose in the ENGAGE AF trial resulted in ≈30% lower exposure to edoxaban, →significant ↘ of major bleeding vs. full dose but no differences in efficacy.
- No data are available on edoxaban across different degrees of obesity.

Consensus statements: In ≤60 kg patients, edoxaban dose should be reduced

Eur J Clin Pharmacol 2014;**70**(11):1339-51.

RIVAROXABAN

- Pharmacokinetics of rivaroxaban do not change significantly according to extreme BMI

- Obesity (i.e. BMI ≥30 kg/m^2) did not affect the safety/efficacy profile of the EINSTEIN-DVT and –PE, EINSTEIN-CHOICE, and ROCKET-AF (subgroups with BMI ≤25, 26-35, >35kg/m^2) trials (class ≥2 obesity was ≈13% of the entire population).

Consensus statements: rivaroxaban dose does not need reduction in underweight.

Clin Pharmacokinet 2011;**50**(10):675-86
Br J Clin Pharmacol 2012;**74**(1):86-97

DABIGATRAN

- BW affects dabigatran concentration with parallel ≈21% increase and reduction of dose-normalized plasma concentrations <50 and >100Kg, respectively, vs. 50-100kg.[137]
- BW significantly influences Vd of dabigatran (0.77% increase per 1-kg increase, >80 kg).[137]
- In RE-LY, patients <50 kg and >100kg were 2% and 16% of the total population (n=18,113), without major effects on efficacy and safety across subgroups.[138]
- In the RE-COVER trial, patients with BMI >35kg/m^2 were 12% of the total population, with very few events.[127] Thus, information on dabigatran in different degrees of obesity is limited.

→ *Consensus statements*: For patients weighing <50kg without renal impairment, a 'close clinical surveillance' is indicated without dose-reduction. In underweight (≤60 kg) patients, dabigatran dose should be reduced in association with reduced renal function (creatinine <133 µmol)

J Am Coll Cardiol 2014;**63**(4):321-8.
J Thromb Haemost 2011;**9**(11):2168-75

OAT in underweight and obesity

Drug	Underweight <18.5 kg/m²	Normal Weight (reference)	Obesity		
			Class 1 30-34.9 kg/m²	Class 2 35-39.9 kg/m²	Class ≥3 ≥40 kg/m²
VKA	Close INR monitoring	INR-adjusted regimen	**No change**	**Close INR monitoring**	**Close INR monitoring during reversal. Preferred OAC**
Apixaban (AFib & VTE)	2.5 mg bid if <60kg and ≥80yrs or creat ≥1.5 mg/dl	AFib: 5 mg bid; VTE: 10 mg bid 7 days and then 5 mg bid	No change	Insufficient data	Insufficient data, prefer VKA; check peak &through anti-Xa activity if used
Rivaroxaban (AFib, VTE, post-ACS)	No change. ACS caution with DAPT if BW<60 kg	AFib: 20 mg od VTE: 10 mg od ACS: 2.5 mg bid	No change	No change	
Edoxaban (AFib & VTE)	30 mg for BW≤60 kg	60 mg od	No change	No data. Check peak & through anti-Xa activity.	
Dabigatran (AFib & VTE)	Close surveillance in patients <50 kg	AFib: 150 mg bid VTE: 220 mg od	No change	Insufficient data. Check ECT or dTT	No data. Prefer VKA. Check peak & through ECT or dTT.

Conclusions

- Evaluate the bleeding risk of underweight patients
- Data are limited in obese patients with **BMI ≥40kg/m^2→CAUTION**
- Peak and trough anti-Xa activity (FXa inhibitors), ecarin clotting time (ECT) or diluted thrombin time (dTT) (dabigatran) should be checked → **switch to VKA if results are different than expected.**
- Evidence on direct inhibitors for **DVT prophylaxis post-bariatric** surgery is extremely limited → prefer LMWH. Repeated monitoring of anti-Xa activity or ECT at short- and mid-term.

J Thromb Haemost 2016;**14**(6):1308-13
Br J Clin Pharmacol 2017;**83**(7):1466-1475.

Antithrombotic therapy and body mass:

an expert position paper of the ESC Working Group on Thrombosis

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