ANTICOAGULATION IN EXTREMES OF BODY WEIGHT

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OVERVIEW

- LMWH and DOACs
- Treatment and prophylaxis
- Dosing
- Monitoring

What is not covered?

- Extended discussion of anticoagulation indications
- Discussion regarding dose reduction with other indications (renal/hepatic function)
- Dosing of LMWH in pregnancy
- Unfractionated heparin

BBC NEWS

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BRIEFING PAPER

Number 3336, 20 March 2018

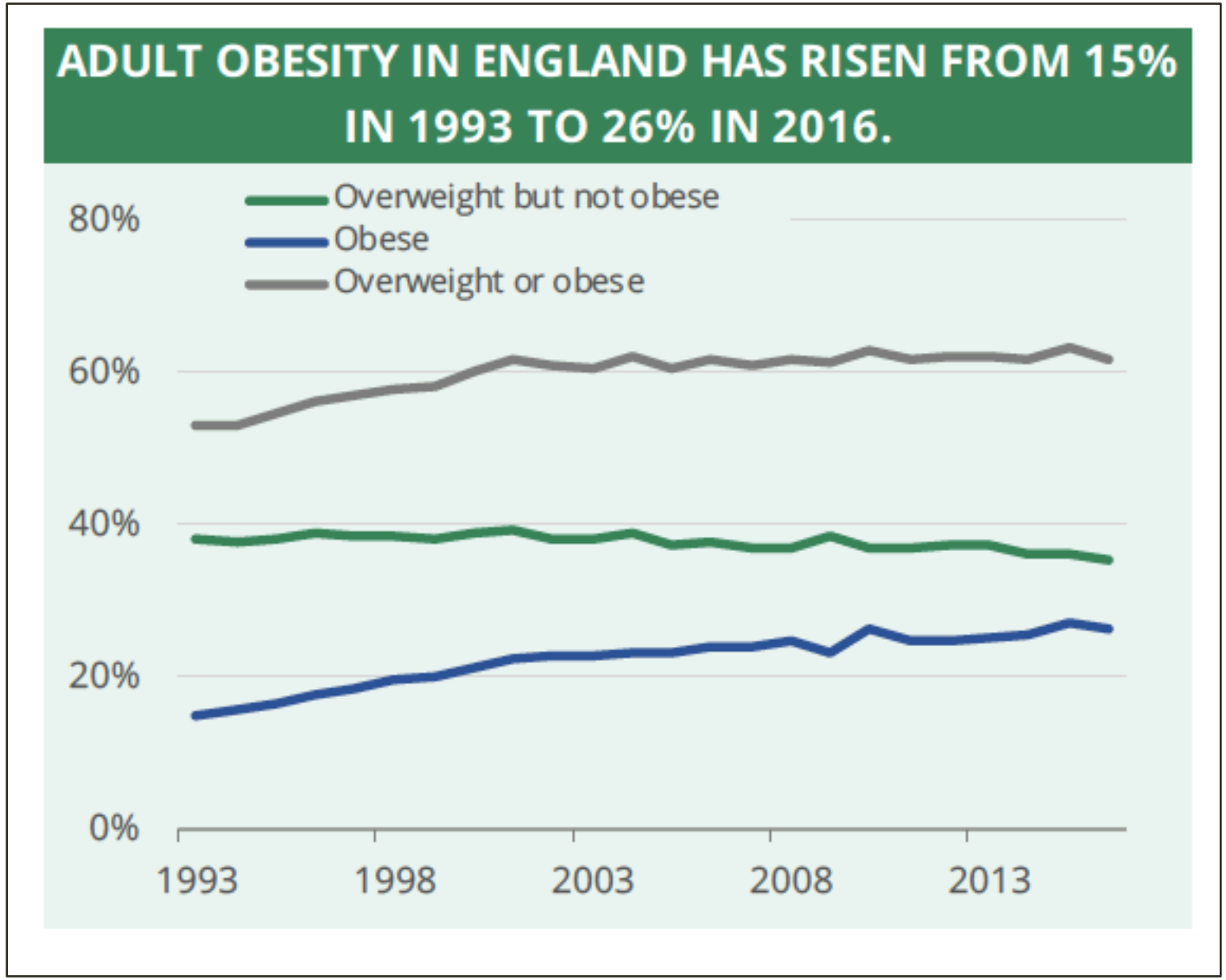
Obesity Statistics

By Carl Baker

DEFINING OBESITY

$$\text{BMI (Metric)} = \frac{\text{Weight (kg)}}{\text{Height x Height (m)}}$$

Classification	BMI
Underweight	< 18.5
Normal weight	18.5 - 24.9
Overweight	25.0 - 29.9
Obese: Class I	30.0 - 34.9
Obese: Class II	35.0 - 39.9
Obese: Class III	40.0+


ADULT OBESITY IN ENGLAND HAS RISEN FROM 15% IN 1993 TO 26% IN 2016.
Overweight but not obese
Obese
Overweight or obese
80%
60%
40%
20%
0%
1993
1998
2003
2008
2013

PROBLEMS

Obesity = BMI ≥ 30

BMI ≥ 30 ≠ obesity

Weight ≥ 100kg ≠ obesity

- Lack of information/weight
- Lack of evidence
- No universally agreed strategy
- Should we cap?
- Under-dosing just as dangerous as overdosing
- Be ‘pragmatic’

FACTORS INFLUENCING DRUG CONCENTRATION

Absorption/route

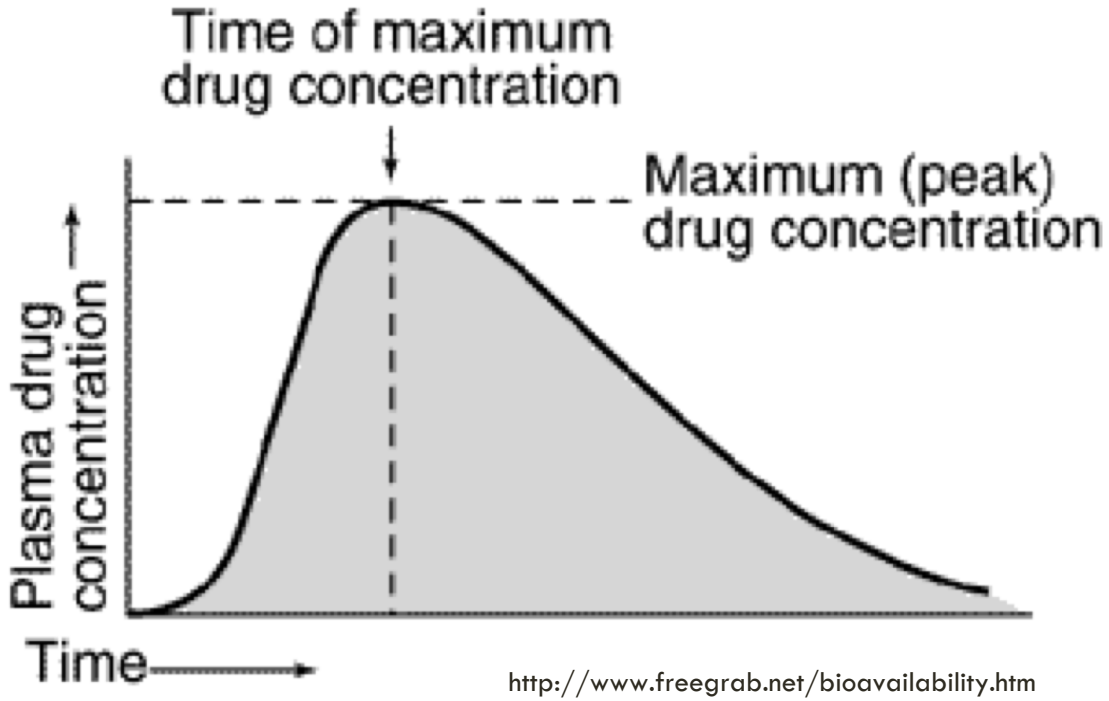
Volume of distribution

- Size of molecule
- Ionization
- Lipid solubility
- Ability to cross membranes

Drug clearance

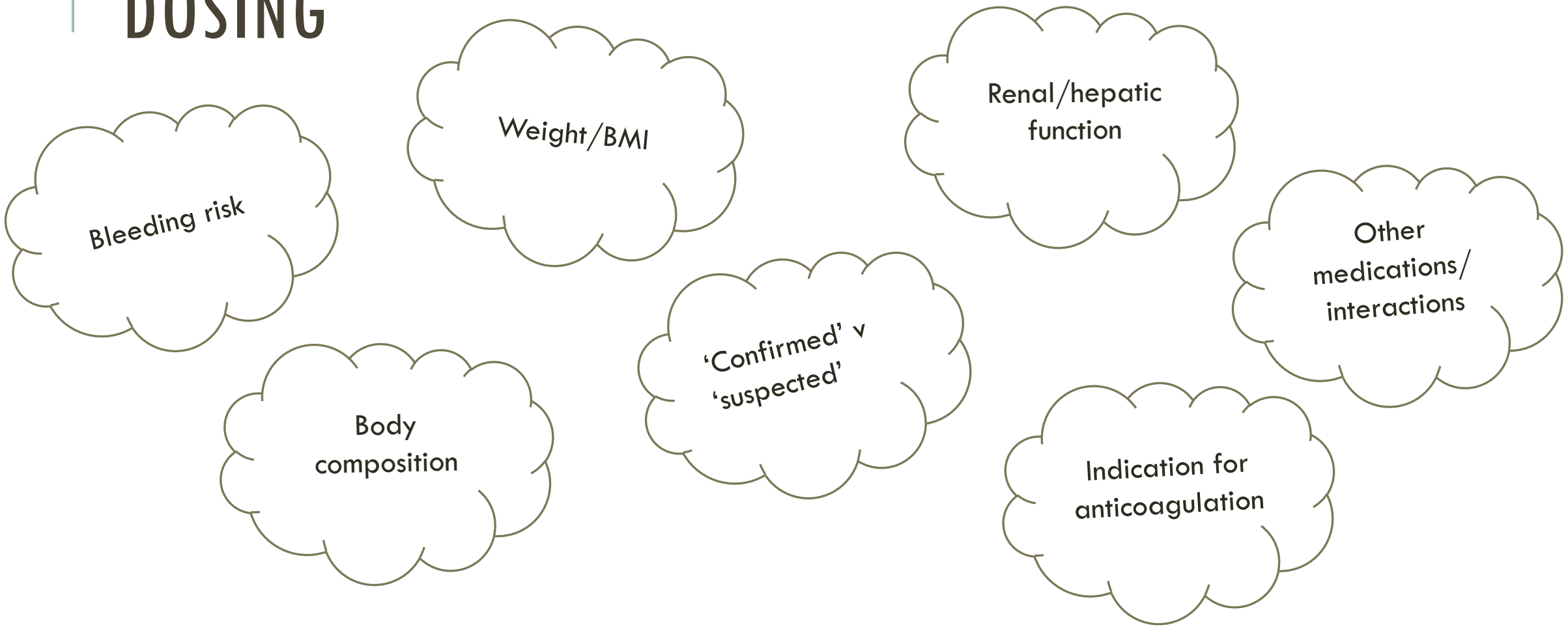
- Renal function
- Hepatic metabolism/P450 pathway

Area under the curve (AUC)



http://www.freegrab.net/bioavailability.htm

FACTORS INFLUENCING ANTICOAGULATION DOSING



WHEN SHOULD WE MEASURE DEGREE OF ANTICOAGULATION?

Kitchen S, Gray E, Mackie I, Baglin T, Makris M; BCSH committee. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014 Sep;166(6):830-41. doi: 10.1111/bjh.12975.

Table II. Circumstances when measurement of anticoagulant concentration may be useful.

- In the presence of spontaneous or traumatic haemorrhage
- Following suspected overdose
- When patients are taking another interacting drug
- To monitor efficacy in patients presenting with new thrombosis whilst on the anticoagulant
- When emergency surgery is required
- In patients due to have neuraxial anesthesia for elective or emergency procedures or surgery
- In patients requiring elective surgery and in whom the drug may still be present
- In patients with renal impairment
- When bridging from one anticoagulant to another
- To assess compliance
- At the extremes of body weight
- In subjects with prior intestinal surgery where it is unclear if absorption will be affected
- Trough levels may be useful to assess potential accumulation in very elderly patients

LMWH: DOSING AND MONITORING

LMWH – PROPHYLACTIC DOSING

NHS

Medicines Q&As

UKCPA | HAT
HAEMOSTASIS, ANTICOAGULATION AND THROMBOSIS

Q&A 326.2

What doses of thromboprophylaxis are appropriate for adult patients at extremes of body weight?

Prepared by the HAT Committee of the UK Clinical Pharmacy Association for NHS healthcare professionals
Before using this Q&A, read the disclaimer at www.ukmi.nhs.uk/activities/medicinesQAs/default.asp
Date Prepared: June 2015

LMWH – PROPHYLACTIC DOSING

	<50kg	50-100kg	100-150kg	>150kg
Enoxaparin	20mg daily*	40mg daily	40mg twice daily*	**60mg twice daily***
Dalteparin	2500 units daily*	5000 units daily	5000 units twice daily*	**7500 units twice daily***
Tinzaparin	**3500 units daily***	**4500 units daily**	**4500 units twice daily***	**6750 units twice daily***

Table 1: Suggested doses of LMWH for thromboprophylaxis in adult patients
* 'off-licence' dose

'Some UK centres (e.g. King's College Hospital, London), use once daily dosing of enoxaparin in obese patients, particularly for ease of use if extended prophylaxis is prescribed, e.g. for patients weighing 100 to 150kg: 80mg once daily, and for patients weighing more than 150kg: 120mg once daily. These doses are 'off-licence'.'

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ENOXAPARIN – TREATMENT DOSING (VTE)

	Standard dosing	Notes
Enoxaparin Clexane	1.5mg/kg OD (150 IU/kg) 1.0mg/kg BD (100 IU/kg)	'After repeated SC 150 IU/kg (1.5 mg/kg) once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while maximum plasma anti-Xa activity level is not increased. **Bazinet et al (2005)** – no dose adjustments required Bazinet, A., Almanric, K., Brunet, C., Turcotte, I., Martineau, J., Caron, S., Blais, N. & Lalonde, L. (2005) Dosage of enoxaparin among obese and renal impairment patients. Thrombosis Research, 116, 41–50. **Green and Duffull (2003)** – '1mg/kg every 8 hours based on LBW' Green, B. & Duffull, S.B. (2003) Developing a dosing strategy for enoxaparin in obese patients. British Journal of Clinical Pharmacology, 56, 96–103.
https://www.medicines.org.uk/emc/product/1695/smpc		

DALTEPARIN – TREATMENT DOSE (VTE)

	Standard dosing	**Notes**
Dalteparin Fragmin	200 IU/kg OD	'*Singl*e daily doses' 100mg/kg BD dosing
https://www.medicines.org.uk/emc/product/4245/smpc		

DALTEPARIN – TREATMENT DOSE (VTE)

	Standard dosing	Notes
Dalteparin Fragmin	200 IU/kg OD	'*Single* daily doses' 100mg/kg BD dosing
https://www.medicines.org.uk/emc/product/4245/smpc		

Weight (kg)	Dose
< 46	7,500 IU
46-56	10,000 IU
57-68	12,500 IU
69-82	15,000 IU
83 and over	18,000 IU

Abbreviations: IU = International Unit

The single daily dose should not exceed 18,000 IU.

DALTEPARIN – TREATMENT DOSE (VTE)

	Notes
Dalteparin Fragmin	'In cancer patients with body weight < 40kg at time of venous thromboembolic event, Fragmin should not be used for extended treatment of symptomatic VTE and prevention of its recurrences due to lack of data' **Yee and Duffull (2000)** – Base dose on total or adjusted body weight, not LBW Yee, J.Y.V. & Duffull, S.B. (2000) The effect of body weight on dalteparin pharmacokinetics. European Journal of Clinical Pharmacology, 56, 293–297. **Wilson et al (2001)** – No capping Wilson, S.J.-A., Wilbur, K., Burton, E. & Anderson, D.R. (2001) Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low molecular weight heparin for the treatment of venous thromboembolism. Haemostasis, 31, 42–48. **Al-Yaseen et al (2005)** – No capping Al-Yaseen, E., Wells, P.S., Anderson, J., Martin, J. & Kovacs, M.J. (2005) The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. Journal of Thrombosis and Haemostasis, 3, 100–102. Conclude cap at 18,000IU unjustified
https://www.medicines.org.uk/emc/product/4245/smpc	

TINZAPARIN – TREATMENT DOSE (VTE)

	Standard dosing	Notes
Tinzaparin Innohep	175 IU/kg OD	**Hainer et al (2002)** – no capping required Hainer, J.W., Barrett, J.S., Assaid, C.A., Fossler, M.J., Cox, D.S., Leathers, T. & Leese, P.T. (2002) Dosing in heavy-weight / obese patients with the LMWH, Tinzaparin: a pharmacodynamic study. Thrombosis Haemostasis, 87, 817–823. **Barrett et al (2001)** – no capping required Barrett, J.S., Gibiansky, E., Hull, R.D., Plane`s, A., Pentikis, H., Hainer, J.W., Hua, T.A. & Gastonguay, M. (2001) Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. International Journal of Clinical Pharmacology and Therapeutics, 39, 431–446. **Diepstraten et al (2009)** – Advise to cap in morbid obesity with an upper limit of 28 000 IU/day for 160kg person used Diepstraten, J., van Kralingen, S., Snijder, R.J., Hackeng, C.M., Ramshorst, B.V. & Knibbe, C.A.J. (2009) Treatment of pulmonrary embolism in an extremley obese patient – case report. Obesity Surgery, 19, 1186–1189.
https://www.medicines.org.uk/emc/product/3632/smpc		

DOACS: DOSING AND MONITORING

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Dabigatran Pradaxa	• No dose adjustment is necessary • close clinical surveillance is recommended in patients with a body weight < 50 kg • Weight <50kg 'minor' risk for elevation of plasma dabigatran levels
https://www.medicines.org.uk/emc/product/4703/smpc	

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Rivaroxaban Xarelto	• No dose adjustment • Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary
https://www.medicines.org.uk/emc/product/6402/smpc	

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Apixaban Eliquis	• VTEt - No dose adjustment required • NVAF - No dose adjustment required, unless criteria for dose reduction are met • Low body weight (< 60 kg) may increase haemorrhagic risk • Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30% lower exposure and body weight < 50 kg was associated with approximately 30% higher exposure
https://www.medicines.org.uk/emc/product/2878/smpc	

DOSING OF DOACS IN EXTREMES OF WEIGHT

	Low body weight recommendations (as per SPC)
Edoxaban Lixiana	• For patients with body weight ≤ 60 kg, the recommended dose is 30 mg Lixiana once daily • In Phase 3 clinical studies (both NVAF and VTE indications) patients with body weight ≤ 60 kg had a 50% edoxaban dose reduction and had similar efficacy and less bleeding when compared to warfarin
https://www.medicines.org.uk/emc/product/6906/smpc	

USE OF THE DIRECT ORAL ANTICOAGULANTS IN OBESE PATIENTS: GUIDANCE FROM THE SSC OF THE ISTH

J THROMB HAEMOST. 2016 JUNE ; 14(6): 1308–1313. DOI:10.1111/JTH.13323

Guidance statements

We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m^2 and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF.

We suggest that DOACs should not be used in patients with a BMI of > 40 kg m^2 or a weight of > 120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about underdosing in the population at the extreme of weight.

If DOACs are used in a patient with a BMI of > 40 kg m^2 or a weight of > 120 kg, we suggest checking a drug-specific peak and trough level (anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs). If the level falls within the expected range, continuation of the DOAC seems reasonable. However, if the drug-specific level is found to be below the expected range (Table S1) [17,24,26–29], we suggest changing to a VKA rather than adjusting the dose of the DOAC.

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MEASURING DOAC LEVELS

1. When to take DOAC level? 2-3 hours after dose
2. Which bottle to take sample in?
3. Inform laboratory if urgent
4. How to interpret results?

INTERPRETATION OF DOAC ASSAYS

Table III. Expected plasma concentrations of Oral Direct Inhibitors.

Drug	Dose	Peak levels mean and range	Trough levels mean and range	References
Apixaban	2·5 mg bd	0·062 mg/l (CV 37%)	0·021 mg/l (CV 17%)	Frost *et al* (2013)
Apixaban	5 mg bd	0·128 mg/l (CV 10%)	0·050 mg/l (CV 20%)	Frost *et al* (2013)
Dabigatran	150 mg bd	0·184 mg/l (95% CI 0·064–0·443)	0·090 mg/l (0·031–0·225)	Van Ryn *et al* (2010)
Rivaroxaban	10 mg od	0·125 mg/l (0·091–0·195)	0·009 mg/l (0·001–0·038)	Mueck *et al* (2008)
Rivaroxaban	20 mg od	0·223 mg/l (0·16–0·36)	0·022 mg/l (0·004–0·096)	Mueck *et al* (2008)

CV, coefficient of variation; 95% CI, 95% confidence interval.

Kitchen S, Gray E, Mackie I, Baglin T, Makris M; BCSH committee. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014 Sep;166(6):830-41. doi: 10.1111/bjh.12975.

MEASURING ANTI-XA LEVELS

1. When to take anti-Xa level?
   - Pre and 4 hours post (Trust – 2 hours)
   - After third dose
2. Which bottle to take sample in?
3. Inform laboratory if urgent
4. How to interpret results?
   - 'Pre' (trough) once daily dosing <0.2 IU/ml
   - 'Prophylaxis' 0.2 – 0.4 IU/ml
   - 'Post' (peak) 0.5-1.0 IU/ml

CONCLUSION

- No universally agreed dosing strategy
- Follow Trust guidance and discuss cases
- Should we be adopting a Trust wide weight adjusted prophylaxis protocol?
- Pragmatic dosing of treatment dose LMWH in obesity with monitoring
- DOAC monitoring in extremes of weight (discussion with haemostasis team regarding target levels)

THANK YOU FOR LISTENING

ANY QUESTIONS?