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(Article begins on next page)

1 **Update on Antithrombotic therapy and body mass. A Clinical Consensus Statement of the**
2 **ESC Working Group on Cardiovascular Pharmacotherapy and the ESC Working Group**
3 **on Thrombosis**

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7 **DOI**

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ORIGINAL UNEDITED MANUSCRIPT

1 **Abbreviations**

- 2 ABCD-GENE: Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and
3 Genotyping
4 ACS: Acute Coronary Syndrome
5 ACT: Activated Clotting Time
6 ADAPTABLE: Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term
7 Effectiveness
8 AI: artificial intelligence
9 AM: Active Metabolite
10 AF: Atrial Fibrillation
11 aPTT: activated Partial Thromboplastin Time
12 ASCEND: A Study of Cardiovascular Events in Diabetes
13 AUC: Area Under the Curve
14 BARC: Bleeding Academy Research Consortium
15 bid: Bis In Die (twice daily)
16 BMI: Body Mass Index
17 BS: Bariatric Surgery
18 BW: body weight
19 CAD: Coronary Artery Disease
20 CCS: Chronic Coronary Syndrome
21 CHANCE: Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events
22 CPB: Cardiopulmonary bypass
23 CYP: Cytochrome P-450
24 CVD: Cardiovascular diseases
25 DAPT: Dual Antiplatelet Therapy
26 DDI: Drug-Drug Interaction
27 DOAC: Direct oral anticoagulants
28 DPI: Dual pathway Inhibition
29 DVT: Deep Vein Thrombosis
30 ELDERLY-ACS: Early Aggressive Versus Initially Conservative Therapy in Elderly Patients
31 With Non-ST-Elevation Acute Coronary Syndrome
32 ERAS: Enhanced Recovery After Surgery
33 ENGAGE-AF TIMI48: Effective Anticoagulation with Factor Xa Next Generation in Atrial
34 Fibrillation–Thrombolysis in Myocardial Infarction
35 GPI: Glycoprotein IIb/IIIa inhibitor
36 HOST-EXAM: Harmonizing Optimal Strategy for Treatment of Coronary Artery Disease
37 EXtended Antiplatelet Monotherapy
38 HR: hazard ratio
39 IBW: Ideal Body Weight
40 ICH: Intra Cerebral Hemorrhage
41 INR: International Normalized Ratio
42 ISAR-REACT: Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for
43 Coronary Treatment
44 i.v.: Intravenous
45 LBW: lean body weight
46 LMWH: Low Molecular Weight Heparin
47 MU: Marginal ulceration
48 NSTEMI: non-ST elevation MI
49 OAC; Oral Anticoagulants
50 od: Once Daily

- 1 OR: Odds Ratio
- 2 PAD: Peripheral Artery Disease
- 3 PCC: Prothrombin Complex Concentrate
- 4 PCI: Percutaneous coronary intervention
- 5 PD: Pharmacodynamic
- 6 PK: Pharmacokinetic
- 7 PE: Pulmonary Embolism
- 8 PPI: Proton Pump Inhibitors
- 9 PRU: Platelet Reactivity Unit
- 10 RAM: Risk Assessment Model
- 11 RCT: Randomized clinical trial
- 12 RECOVERY: Randomized Evaluation of Covid-19 Therapy
- 13 RYGB: Roux-en-Y gastric bypass
- 14 SAPT: Single Antiplatelet Therapy
- 15 SG: Sleeve Gastrectomy
- 16 STEMI: ST-elevation myocardial infarction
- 17 TAT: Triple Antithrombotic Therapy
- 18 TAVI: Transcatheter Aortic Valve Implantation.
- 19 TICO: Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation
- 20 Sirolimus-Eluting Stent for Acute Coronary Syndrome
- 21 TROPICAL ACS: Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet
- 22 Treatment For Acute Coronary Syndromes
- 23 TTR: Time In Therapeutic Range
- 24 UFH: Unfractionated Heparin
- 25 Vd: Volume of Distribution
- 26 VKA: Vitamin-K Antagonist
- 27 VTE: Venous Thromboembolism
- 28 WHO: World Health Organization

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1 Abstract

2 Obesity and underweight are a growing health problem worldwide and a challenge for
3 clinicians concerning antithrombotic therapy, due to the associated risks of thrombosis and/or
4 bleeding.

5 This clinical consensus statement updates a previous one published in 2018, by reviewing the
6 most recent evidence on antithrombotic drugs based on body size categories according to the
7 World Health Organization classification. The document focuses mostly on individuals at the
8 extremes of body weight, i.e. underweight and moderate-to-morbid obesity who require
9 antithrombotic drugs, according to current guidelines, for the treatment or prevention of
10 cardiovascular diseases or venous thromboembolism.

11 Managing antithrombotic therapy or thromboprophylaxis in these individuals is challenging,
12 due to profound changes in body composition, metabolism and organ function, altered drug
13 pharmacokinetics and pharmacodynamics, as well as weak or no evidence from clinical trials.
14 The document also includes artificial intelligence simulations derived from *in silico*
15 pharmacokinetic/pharmacodynamic models, which can mimic the pharmacokinetic changes
16 and help identify optimal regimens of antithrombotic drugs for severely underweight or
17 severely obese individuals.

18 Further, bariatric surgery in morbidly obese subjects is increasingly frequently performed
19 worldwide. Bariatric surgery causes specific and additional changes in metabolism and
20 gastrointestinal anatomy, depending on the type of the procedure, which can also impact the
21 pharmacokinetics of antithrombotic drugs and their management.

22 Based on existing literature, the document provides consensus statements on optimising
23 antithrombotic drug management for underweight and all classes of obese patients, while

- 1 highlighting the current gaps in knowledge in these complex clinical settings, which require
- 2 personalized medicine and precision pharmacology.

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1 1.0 Introduction

2 The obesity epidemics continue to rise worldwide (globesity),^{1,2} favored by ‘obesogenic’
3 environments. In 2019, the prevalence of obesity in Europe ranged between 11% (Italy) and
4 26% (Ireland) for women, and between 11% (Romania) and 30% (Malta) for men,³ with high
5 obesity-related health care costs and loss in productivity (~70 billion euro in 2016).⁴ The
6 COVID-19 pandemic has emphasized the globesity burden,⁵ while fighting obesity might
7 increase the prevalence of underweight children and adolescents, the so-called “dual burden
8 household”.⁶ ~~is producing the so-called “dual burden household”, whereby calorie restriction in~~
9 ~~adults is increasing the prevalence of underweight children and adolescents, except in Western~~
10 ~~Europe.~~ Particularly, severe obesity (**Table 1**) is rising in Europe and North America.^{7,8}
11 Notably, severely obese individuals aged 50-75 years have ~30% reduction of life in good
12 health and half the years without chronic disease compared to non-obese individuals.⁹
13 Conversely, the prevalence of underweight adult men and women has decreased, reaching <2%
14 in the US.¹⁰ In Asia, the double burden of under- and overweight is shifting toward obesity.¹¹

15 The term "obesity paradox" was created to imply that obesity, despite being a major
16 cardiovascular risk factor, may confer a survival benefit in acute cardiovascular
17 decompensation (myocardial infarction-MI, heart failure-HF).¹² However, major
18 methodological limitations sustain this concept: retrospective studies with intrinsic biases, no
19 prospective studies with the ‘obesity paradox’ as a primary goal, few studies on weight change,
20 and possible dependence on age.¹³ Moreover, severe obesity was uncommon when this concept
21 was developed.¹⁴

22 Despite the health burden and costs, the extremes of body size remain under-represented or
23 excluded from cardiovascular randomized clinical trials (RCT)¹⁵ and drug development
24 processes.¹⁶ As both obesity and underweight differently affect the risk of thrombosis, bleeding
25 and antithrombotic drug pharmacology,¹⁷⁻¹⁹ the European Society of Cardiology (ESC)

1 Working Groups on Cardiovascular Pharmacotherapy and on Thrombosis assembled a task
2 force to update the 2018 scientific document on antithrombotic drugs at the extremes of body
3 mass.²⁰ As in the previous document, we focus on patients with a clear indication for
4 antithrombotic treatment or prophylaxis, especially with severe obesity and underweight,
5 because of their complexity and limited evidence. We also update the pharmacology of
6 antithrombotic drugs following bariatric surgery (BS),²¹ and include data from artificial
7 intelligence (AI) *in silico* models and simulations of antithrombotic drug regimens at the
8 extremes of body size.²²

9

10 **2.0 Methodology and definitions**

11 The authors, selected on their complementary expertise (**Supplementary material**), performed
12 a systematic review of the literature (**Supplementary Table S1**), evaluated evidence according
13 to the current ESC Scientific Document policy (**Figure 1**)²³ and reached consensus through
14 Delphi methodology on three rounds.²⁴

15 Body size classes are defined according to the World Health Organization (WHO) based on
16 BMI, expressed as kg/m^2 , and/or total body weight (BW) expressed in kg (**Table 1**).²⁵ While
17 we acknowledge the limitations of BMI metrics versus adipose tissue imaging, waist-hip ratio
18 or waist circumference (WC), nevertheless, most of the evidence on antithrombotic drugs refers
19 to BMI. We will address underweight but not frailty which is addressed in another ESC
20 scientific document.²⁶

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2 **3.0 Changes in drug disposition**

3 Obesity, especially class ≥ 2 , can modify drug pharmacokinetics (PK), resulting in inadequate
4 drug dosing for both fixed-dose and BW-adjusted medications (**Figure 2**). Since
5 gastrointestinal transit is accelerated and gastric emptying shortened, the absorption and
6 bioavailability of some oral drugs can be reduced.^{27,28} The drug's volume of distribution (Vd)
7 can be affected by the reduced lean-to-fat ratio, thereby increasing for lipophilic drugs
8 (**Graphical Abstract**). For hydrophilic drugs, like low molecular weight heparin (LMWH), Vd
9 nonlinearly increases with BW. Thus BW-adjusted dosing may result in over-dosing in
10 severely obese individuals (**Figure 2**). In obese subjects drug's lipophilic characteristics further
11 impact PK, and liver biotransformation, through some cytochrome P450 enzymes, can be
12 reduced (**Figure 2**).²⁹

13 Bariatric surgery (BS) for long-term correction of morbid obesity, is increasing again after
14 COVID.³⁰ BS comprises restrictive (e.g. sleeve gastrectomy-SG, adjustable gastric banding-
15 AGB) and malabsorptive (e.g. Roux-en-Y gastric bypass-RYGB, duodenal switch)
16 interventions that trigger nutritional deficiencies, modify drug absorption, gastrointestinal
17 blood flow, pH and transit time (**Figure 2 and 3**).^{31,32} Since absorption of most antithrombotic
18 drugs occurs in the proximal small intestine and, to a lesser extent, in the distal part of the
19 stomach, the type of BS can significantly affect antithrombotic drug's PK.³²

20 ***Consensus statement***

21 Extremes of BWs or BMIs as well as bariatric surgery can variably affect the
22 pharmacokinetics of lipophilic and hydrophilic drugs.



24

1 4.0 Arterial and venous thrombosis

2 Obesity is a risk factor for atherothrombosis^{33,34} and venous thromboembolism (VTE)^{35,36}
3 **(Graphical Abstract)**. A Swedish population-based study of men born between 1945 and
4 1961, followed for 40 years, showed that for each standard deviation (SD) increase in BMI
5 during childhood and puberty, there was a linear increase in VTE³⁵ and arterial thrombosis³⁴ in
6 adulthood. A fourfold increase in coronary heart disease (CHD) for each 5 kg/m² BMI increase
7 above 25 has been reported.¹⁸ In a population study, BW at 20 years and midlife was directly
8 associated with weight gain through life and subclinical coronary atherosclerosis.³⁴

9 The impact of BMI on peripheral arterial disease (PAD) is less clear. Obese patients with PAD
10 show accelerated functional decline, while weight loss improves walking distance.³³ In
11 contrast, patients with low BMI and PAD show an increased risk of cardiovascular and all-
12 cause mortality, limb ischemia and major cardiovascular events.³³

13 Increasing BMI is associated with an increased risk of cardioembolic and non-cardioembolic
14 stroke,³⁷ likely secondary to the unhealthy metabolic status of severely-obese patients.^{38,39}
15 Class 3 obesity is particularly associated with ischemic stroke³⁸ compared to lower obesity
16 classes or normal BMI, while in-hospital post-stroke mortality was lower in class 1-2 obese
17 patients.⁴⁰ Notably, in the Swedish twin registry, an obesogenic environment increased
18 cardiovascular risk, especially in individuals without obesity-predisposing genetic variants.⁴¹

19 Limited data suggests that underweight (BMI<18) individuals have increased
20 atherothrombosis¹⁹ and a 2.3-fold increased risk of cardiovascular disease (CVD) as compared
21 to normal weight, age-matched subjects.¹⁷

22 Mendelian randomisation studies ~~show suggest~~ causality of ~~a causal link between~~ obesity and
23 on VTE:^{42,43} for each SD increase in genetically-predicted BMI, the odds ratio (OR) of VTE
24 was 1.59 (95% confidence interval-CI: 1.20-1.93).⁴² In the UK Biobank, each kg/m² BMI

1 increase was associated with a 10% increase in VTE,⁴³ and a BMI>40 was associated with a 3-
 2 fold increase in VTE (hazard ratio [HR] 3.4, 2.87-4.03) compared to normal weight.⁴⁴ A recent
 3 case-control study shows that individuals with obesity classes ≥ 2 , aged >50 years, have a 6.2-
 4 fold increased risk of VTE compared to class 1 obesity or normal BW.⁴⁵ In a registry of
 5 children born between 1930 and 1989,⁴⁶ a BMI >90th percentile at 7 and 13 years was
 6 associated with a ~1.5 fold increase in future VTE compared to lower BMIs.⁴⁶ In over two
 7 million women, pre-menopausal, class 3 obese women showed the highest VTE incidence
 8 versus normal BMI, both antepartum (OR 2.9, 2.2-3.8) and postpartum (OR 3.6, 2.9-4.6), while
 9 underweight showed an opposite trend.⁴⁷

10 Underweight individuals show a low risk of VTE⁴⁸ (**Graphical Abstract**), but higher all-cause
 11 mortality and bleeding post-VTE as compared to normal-weight subjects.⁴⁹ Medically-ill,
 12 severely underweight patients (BMI 15) have a 3-fold increase in VTE during 77-day follow-up
 13 versus reference BMI (28), unlike class 1 to 3 obese subjects.⁵⁰

14 **Consensus statements**

15 Obesity increases the risk of atherothrombosis.^{34-36,41,46}

16 Mendelian randomization studies suggest causality of obesity on VTE. Obesity
 17 seems to be is causally related to VTE.^{42,43}

18 Higher obesity classes show the greatest VTE risk.^{47,48}

19 Underweight is associated with a lower risk of VTE,^{47,48} but with a higher rate of
 20 post-VTE complications, including mortality.^{49,50}

21 Whether underweight increases the risk of atherothrombosis is uncertain.¹⁹



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1 4.1. Thrombosis after surgery

2 BMI<18 or >50 showed the highest VTE incidence after general surgery, with a U-
3 shaped curve.^{51, 52} After orthopaedic surgery, patients with class ≥ 2 obesity showed a 2-fold
4 increase in PE versus normoweight individuals.⁵³ In >5 million individuals undergoing major
5 surgery, patients of all obesity classes had a higher risk of VTE, but not of bleeding, compared
6 to normal weight.⁵⁴

7 During 30 days post-BS in 600,000 morbidly-obese subjects (~20% BMI>50), VTE occurred
8 in 0.3% of patients after SG and in 0.4% after RYGB.⁵⁵ In ~20,000 post-BS patients, VTE
9 doubled in individuals with pre-surgery BMI>50 compared to BMI 35-50, regardless of age.⁵⁶
10 In >350,000 patients from a US registry, VTE was higher in individuals with BMI >60
11 undergoing laparoscopic RYGB or SG (ORs 1.85, 1.40–2.44 and 1.62, 1.32–1.99, respectively)
12 versus BMI of 35-50.⁵⁷ VTE increased after laparoscopic RYGB, but not SG, in patients with a
13 BMI between 50-59 compared to BMIs between 35-49.9.⁵⁷ Moreover, BS lowers long-term
14 thrombotic risk. In 566 individuals with an average BMI of 40 and previous MI undergoing BS
15 (RYGB or SG), MACE were reduced by 56% during 8-year follow-up versus controls.⁵⁸
16 Similarly, in a recent meta-analysis, long-term CVDs were reduced after all types of BS versus
17 non-BS-treated obese individuals.⁵⁹

18 *Consensus statements*

19 Obesity classes ≥ 2 are associated with the highest risk of VTE following major
20 general as well as bariatric surgeries.^{56, 57}

21 BS appears to lower long-term cardiovascular complications.^{58,59}



23 5.0 Bleeding

1 Intracerebral haemorrhage (ICH) seems to differ at BMI extremes. Deep ICH/microbleeds
2 seem linked with obesity, partly for associated hypertension, and with underweight^{60,61} with a
3 U-shaped relationship (**Graphical Abstract**). Lobar ICH is associated with low BW, while a
4 BMI ≥ 25 was reported to protect against haemorrhagic transformation of ischaemic stroke and
5 was associated with better outcomes in Asians.⁶¹

6 BMI > 30 was associated with a worse course after non-variceal upper gastrointestinal bleeding,
7 a significant increase in endoscopic interventions and resource utilization compared to non-
8 obese subjects, but mortality was similar.⁶²

9 **5.1 Bleeding after invasive procedures**

10 After coronary artery bypass graft surgery (CABG), bleeding is inversely associated with BMI
11 from underweight to BMI > 40 .⁶³ ~~Despite a reduction in bleeding at higher BMI, increased long-~~
12 ~~term mortality was associated with both underweight and severe obesity.~~ Consistently, severe
13 obesity (BMI ≥ 40) was associated with reduced postoperative bleeding in 12,330 post-CABG
14 patients,⁶³ while lower BMIs required more blood and cryoprecipitate transfusions.⁶⁴ In
15 $> 95,000$ post-CABG patients, bleeding significantly contributed to perioperative mortality and
16 early post-operative morbidity only in the low-weight group.⁶⁵ Despite a reduction in bleeding
17 at higher BMIs, higher long-term mortality was associated with both underweight and severe
18 obesity post-PCI.⁶⁶

19 Trans-radial access for coronary angiography and PCI is associated with fewer bleeding and
20 access site complications, including in those with extreme BMIs (i.e. < 18.5 and ≥ 40).⁶⁷ In
21 transcatheter aortic valve implantation (TAVI), there is an L-shaped relation with BMI, and
22 overweight-class 1 patients show the lowest mortality and complications rates,⁶⁸ with no
23 additional protective effects for higher obesity classes.⁶⁹ However, in observational studies and
24 TAVI registries, severe obesity is $\sim 15\%$, thus under-represented.^{70,71} Whether trans-carotid is

1 safer than trans-femoral access across all obesity classes is unknown.^{72,73} A recent registry
2 suggests lower 5-year mortality of surgical versus TAVI aortic valve replacement in class 1-2
3 obese subjects.⁷⁴ However, this was not confirmed in RCTs including only obesity class 1.⁷⁵

4 In predominantly elderly, TAVI patients, being underweight seems also a frailty discriminator,
5 partly explaining worse outcomes and safety.^{76,77} In 42,000 US patients, BMI<19 showed a
6 higher relative risk (RR) of 1.57 (1.27-1.95) of in-hospital blood transfusion post-TAVI, versus
7 normoweight.⁷⁸ Recent analyses suggest higher complications for BMI<20,⁷⁹ while mortality
8 appears comparable to other BMI classes.⁶⁸

9 After BS, bleeding occurs in 0.8-5.8% of patients depending on the approach (endoscopic,
10 open), type of BS and follow-up duration. Early post-operative bleeding usually associates with
11 staple line leakage,⁸⁰ while later bleeding (>6 weeks post-BS) relates to marginal ulceration
12 (MU) at the gastro-jejunal anastomosis,⁸⁰ reported in 0.6-16% of patients post-RYGB, which
13 worsens outcomes.⁸¹ Proton pump inhibitors (PPI) can prevent MU bleeding.⁸¹

14 **Consensus statements**

15 Most evidence indicates a U-shaped relationship between the extremes of BMI and
16 unprovoked bleeding.^{60,61}

17 Obesity may be associated with reduced non-access site bleeding after TAVI ^{69,77,78,82}

18 A tight control of risk factors, e.g. blood pressure to prevent ICH, post-operative
19 care, gastroprotection and choice of access site (radial for PCI) are advised to reduce
20 bleeding risk at the extremes of body size.^{72,73,83}



22

1 **6. Oral anticoagulants (OAC)**

2 **6.1 Vitamin-K antagonist (VKA)**

3 Obesity can affect the PK of warfarin, phenprocoumon and acenocoumarol (**Figure 2**).
4 Retrospective studies showed that class 3 obese patients require a longer time to achieve
5 therapeutic international normalized ratio (INR), and ~20% higher weekly maintenance doses
6 than normal-weight individuals.⁸⁴ In 10,167 post-VTE patients, BMI and time in therapeutic
7 range (TTR) were linearly correlated, with the lowest TTR in patients with BMI<25 or BW<60
8 and the highest TTR in class 2-3 obesity⁸⁵ (**Graphical Abstract** and **Central Table 1**), which
9 can also partly explain the ‘obesity paradox’ of better outcomes in VKA-treated obese patients,
10 although more VKA-specific pathways can be involved.⁸⁶

11 Small studies on VKA-treated underweight patients indicate a shorter interval to therapeutic
12 INR, a lower weekly maintenance dose,⁸⁷ and a poor TTR (mainly supra-therapeutic INR).^{85,88}
13 Warfarin-treated, AF underweight patients had twice the risk of thrombotic, but not bleeding,
14 outcomes.^{85,88}

15 A meta-analysis including 160 morbidly-obese patients on warfarin for VTE, prosthetic
16 mechanical valve, or AF, who underwent BS, showed that weekly warfarin dose consistently
17 drops in the first 3 months post-BS, then slowly increases and stabilizes within one year, but
18 remains lower than pre-BS.⁸⁹ The fast reduction in warfarin dose post-BS can depend on
19 anatomical upper GI, metabolic and nutritional changes.^{27,28} Following BS, gastrointestinal
20 bleeding was reported in 17 out of 160 patients on warfarin, with no thrombotic events,
21 emphasizing the risk of upper gastrointestinal bleeding and MU post-BS, exacerbated by
22 warfarin, and the importance of gastroprotection (**Figure 3**).⁸¹

23 Prothrombin complex concentrate (PCC) dosing to reverse INR and VKA in case of major
24 bleeding is usually BW-adjusted and capped at a fixed dose for BW \geq 100 kg. Recent studies

1 have questioned the efficacy of 4-factor PCC capping,⁹⁰ but more studies are needed to assess
2 safety and efficacy of the uncapped, BW-based dosing across the entire BW spectrum. Limited
3 data suggest that the timing for VKA reversal (INR<2) with vitamin K is similar between
4 normal BW and all obesity classes.⁹¹

5 ***Consensus statements***

6 Underweight and obesity class ≥ 2 affect loading and maintenance doses for all VKAs.

7 More frequent INR monitoring and dose adjustment are advised, during the starting and
8 maintenance periods.^{84,85,87,88,92}

9 Following BS, it is advised to resume VKA with a reduction in the weekly dose by
10 ~30% as compared to pre-surgery, to monitor INR frequently in the 12 months post-
11 surgery and to use gastroprotection, preferably with a PPI.^{27,28,81,89}

12 Following BS, switching from parenteral to oral anticoagulation (VKA or DOAC) is
13 advised when patients are post-surgically and nutritionally stabilized.

14 In class 1-2 obese individuals with major bleeding while on VKA, it is advised to
15 administer 4 factor-PCC at BW-adjusted over fixed dosing, with prompt and
16 frequent INR monitoring.^{93,94}

17 18 **6.2 Direct oral anticoagulants (DOAC)**

19 In patients with AF, efficacy and effectiveness of DOACs appear comparable to VKA
20 at the extremes of BMI. In ~~>58,000~~ AF patients participating in the major RCTs of DOACs
21 versus VKA and the median BMI was 28.3 (25.2-32.2) ~~with no data available in morbid~~
22 ~~obesity. A retrospective study including 2,699 patients with class ≥ 3 BMI >40 obese subjects~~
23 ~~on OAC for VTE or AF, showed comparable efficacy and safety of anti Xa DOACs versus~~
24 ~~VKA. However in phase 3 RCTs of anti Xa DOACs in patients with AF and class 3 obesity~~
25 ~~ranged between 4.3-5.5% even if their efficacy and safety appeared similar to VKA in post hoc~~

1 analyses, thus the number of those patients and events in each trial were small.^{88,95} A recent
2 meta-analysis of the 4 major RCTs totaling 89,494 patients with AF and class 3 obesity,
3 reported that a combined endpoint of stroke, systemic embolism, death and bleeding, i.e. the
4 net clinical outcome, was lower with DOAC versus warfarin (HR 0.91, 95% CI, 0.87–0.95) in
5 the whole obese (BMI ≥ 30) subgroup.⁹⁵ However, this composite benefit was attenuated at the
6 highest BMIs (eg class ≥ 3 , P_{trend} 0.001) largely driven by a slight increase in major bleeding,
7 thus safety was weakened for AF, class 3 obese individuals on DOACs as compared to VKA.⁹⁵
8 (~~OR 0.71, 0.62–0.81~~). Another recent meta-analysis on 18 studies (16 observational), totaling
9 287,125 AF patients, showed a more favourable benefit and risk profiles of DOAC versus VKA
10 in obese subjects, overall and across the three obesity classes, except for systemic
11 thromboembolism which was similar between the two treatments in class 3 obesity.⁹⁶ A
12 previous meta-analysis of 89,494 patients with AF and class 3 obesity only, reported that both
13 stroke/systemic embolism (OR 0.71, 0.62–0.81), and major bleeding (0.60; 95% CI: 0.46–0.78),
14 were lower with DOAC than warfarin.⁹⁷ A retrospective cohort of 5,183 patients with AF
15 grouped for BMI < 30 , 30–40 (n=2137), and > 40 (n=358), showed similar efficacy and safety of
16 DOACs across the categories, although class 3 patients were few.⁹⁸ A Swedish nationwide
17 study on 26,047 patients with AF all on DOACs, showed a U-shaped relationship between BMI
18 and major bleeding, with an increased risk at both BMI < 18.5 and obesity class 3.⁹⁹ Additional
19 studies are reported in **Table 2**.

20 For VTE, a post-hoc analysis of a phase 3 RCT showed similar efficacy and safety between
21 apixaban and enoxaparin/VKA across all BMI categories, although including class 3 obesity
22 was $< 5\%$ of the trial population with 5 thrombotic events with a non-significant 30% relative
23 reduction in the area under the curve (AUC) for apixaban.¹⁰⁰ A recent meta-analysis including
24 13 studies of patients with VTE and BMI ≥ 40 or BW ≥ 120 showed a lower risk of both
25 recurrent VTE and major bleeding associated with anti-Xa DOACs versus VKA (OR 0.72,

1 95% CI 0.57-0.91 and 0.74, 95%CI 0.58-0.95, respectively),¹⁰¹ while in another cohort of
2 51,871 patients with VTE, DOAC or VKA had similar effectiveness and safety across all BW
3 classes, including severe obesity (BW >140, n=2167).¹⁰² ~~A non-significant trend towards a~~
4 ~~similar efficacy and safety of anti Xa DOACs and VKA has been reported in class ≥ 2 obese~~
5 ~~patients with VTE.~~ A meta-analysis of 5 observational studies in >6,000 patients with VTE and
6 morbid obesity showed a similar incidence between DOACs and VTE of recurrent VTE or
7 major bleeding over 12 months after the event.¹⁰³ ~~for DOAC versus VKA report ~40% lower~~
8 ~~major bleeding.~~ However, in another retrospective cohort of class 3 obese patients, DOAC and
9 warfarin showed similar efficacy and safety. One observational study Some data suggested
10 higher gastrointestinal bleeding risk associated with dabigatran compared to other DOACs.¹⁰⁴
11 ~~A retrospective study of AF patients on DOACs showed more major bleeding in severe obesity~~
12 ~~versus normal weight.~~ A systematic review of patients with an indication for OAC, concluded
13 that rivaroxaban, apixaban, or dabigatran may be used at standard doses in all patients with
14 BMI <40, whereas rivaroxaban and apixaban have more data in those with BMI >40.¹⁰⁵
15 Additional studies are reported in **Table 2**.

16 A wide variability in the peak and trough concentrations of full-dose apixaban and rivaroxaban
17 has been consistently reported in class 3 obese patients ~~from RCTs and observational studies~~
18 ~~(median BW>120, 84% BMI \geq 40),~~ with many patients with drug concentrations outside the
19 intervals measured in the main phase 3 RCTs (**Tables 2 and 3**).^{100,104,106,107} Measuring DOAC
20 levels with specific assays can be appropriate in extremely obese and underweight classes
21 (**Central Table 1**).

22 Underweight Asian patients with AF showed lower ischemic stroke and major bleeding with
23 DOAC versus VKA.¹⁰⁸ However, in a mixed-ethnicity AF cohort including 28.9% underweight
24 patients, DOAC and VKA showed similar efficacy and safety,¹⁰⁹ while other studies reported a
25 higher safety of DOACs in underweight individuals as compared to VKA.¹¹⁰⁻¹¹² In the meta-

1 analysis of RCTs in AF, the probability of major thrombotic events was higher in the lowest
2 BMI range, independently of the type of OAC.⁹⁵ Major bleeding probability was similar in
3 DOAC-treated patients across all BMIs (from underweight to severe obesity), while for VKA
4 was maximal at lower BMIs.⁹⁵ The probability of ICH was high in underweight individuals,
5 independently of the OAC agent.⁹⁵ In the Swedish registry of 26,047 AF, DOAC-treated
6 patients major bleeding and mortality were higher in underweight patients versus normal
7 weight.⁹⁹

8 Simulations based on population PK models, mostly derived from RCT available
9 measurements for the anti-Xa DOACs,¹¹³⁻¹¹⁵ did not show any major impact of extreme BWs as
10 covariates significantly affecting PK/PD, while low-BW (<60) was often associated with
11 reduced kidney function and affected mostly by dabigatran, as it is almost exclusively renally-
12 excreted¹¹⁵ (**Graphical Abstract** and **Central Table 1**).

13 Few data suggest that soon after BS, DOAC concentrations may be affected by malabsorption
14 and reduced oral feeding, thus the optimal timing for restarting DOACs post-BS is
15 unknown.^{21,116} Apixaban and edoxaban are mainly absorbed in the small intestine, rivaroxaban
16 in the stomach, dabigatran between the lower stomach and the duodenum.³¹ Measuring drug
17 levels may be useful in patients (re)starting DOACs post-BS after re-feeding, also considering
18 their high BMIs and substantial post-BS malabsorption (**Figures 2 and 3**).¹¹⁷

19 Idarucizumab is a humanised monoclonal antibody fragment¹¹⁸ reversing dabigatran, with a
20 small extravascular distribution, administered at a fixed dose. In its small phase 3 RCT, the
21 median BW was 75 with no data on BMI classes. Andexanet-alfa is a non-active, FXa decoy
22 protein binding oral and parenteral anti-Xa drugs, with a Vd approximately equivalent to blood
23 volume, therefore minimal distribution into adipose tissue is expected. Andexanet-alfa is
24 administered with a fixed-dose bolus followed by an infusion rate based on the anti-Xa type,

1 time from the last drug intake and dose. In phase 3 RCT,¹¹⁹ BMI averaged 27±6, thus extreme
2 BMIs were under-represented, and without available PK studies at extreme BMIs.

3 **Consensus statements**

4 In patients with AF and/or VTE and obesity class 1 and 2, DOACs show a benefit-risk
5 profile similar to that of normal-weight individuals.^{85,95-97,101}

6 Based on limited data, the anti-Xa DOACs appear effective and safe in patients with AF
7 and/or VTE and obesity class ≥ 3 .^{96,120,121}

8 In underweight patients, anti-Xa DOACs appear safer than VKA.^{95,110,111}

9 Due to possible high PK/PD variability, measuring DOAC concentrations at trough
10 and/or peak is advised during maintenance, in class ≥ 3 obese and severely underweight
11 patients, especially if renal function is reduced*.^{100,95,108,107,109}

12 Despite the lack of data, if a DOAC is used post-BS, measuring plasma levels at peak
13 and/or trough may be appropriate, especially in the first 3 months post-BS.^{117,120}

14 After BS, in patients on single or combined antithrombotic therapy, at prophylactic or
15 therapeutic doses, gastroprotection is advised, preferably with PPIs.⁸¹

16 Data in patients with underweight and obesity class ≥ 3 on DOACs are limited and
17 remain an area of uncertainty, especially in AF.

18 * <45 ml/min/1.73 m²

19 **6.3 Parenteral anticoagulants**

20 **6.3.1 Unfractionated heparin (UFH)**

21 The highly-variable anticoagulant response to IV UFH requires monitoring and dose
22 adjustment based on the activated partial thromboplastin time (aPTT), activated clotting time
23 (ACT) or anti-Xa assay. The 2023 ESC guidelines provide a class I recommendation for UFH
24

1 in STEMI, and in NSTEMI-ACS if early angiography/PCI is anticipated, with a weight-adjusted
2 bolus without capping (70-100 IU/kg) and, for prolonged therapy, titration to target aPTT to
3 60-80s.¹²² Timely anticoagulation during IV UFH, facilitated by dosing nomograms, is
4 associated with reduced complications in acute VTE,¹²³ but nomograms were developed with
5 poor representation of obese patients. For patients with class ≥ 2 obesity (or BW>160),
6 conventional nomograms tend to generate “overdosing” compared to normal or class 1 obese
7 patients, as reflected by aPTT or anti-Xa measurements.²⁰ Overdosing of UFH may increase
8 bleeding and require high doses of protamine for reversal in cardiac surgery, which may then
9 increase bleeding and transfusions.¹²⁴

10 Body metrics other than BW to adjust dosing may be valuable. In an RCT recruiting obese
11 patients undergoing cardiopulmonary bypass, UFH dosing was based on ideal body weight
12 (IBW) or BW. IBW-adjusted dosing resulted in $\approx 15\%$ lower UFH dose and plasma
13 concentrations were better within the target range.¹²⁵ In patients undergoing catheter ablation of
14 AF, including class 2 obese patients, a comprehensive UFH dosing protocol considering IBW
15 and BW, showed that IBW more rapidly achieved and maintained effective ACT levels,
16 irrespective of BMI.¹²⁶ These findings suggest that body size metrics other than BW may
17 improve UFH dosing nomograms and avoid overdosing (**Graphical Abstract and Central**
18 **Table 1**).

19 Protamine reverses UFH with 1:1 posology (1 mg every 100 IU of the initial dose needed for
20 anticoagulation), which does not directly account for UFH clearance and may lead to excessive
21 protamine dosage. A recent RCT¹²⁷ compared protamine standard dosing versus dosing
22 predicted by a mathematical model based on heparin clearance and IBW. A better re-
23 coagulation profile and lower protamine administration was achieved by the IBW-based
24 model,¹²⁷ although this study included patients ≤ 120 kg, with no data for morbid obesity.

Consensus statements

BW-based UFH dosing appears to overdose patients with obesity class ≥ 2 . Due to the lack of validated algorithms in these patients, appropriate estimates of BW and frequent laboratory monitoring are advised.^{122,125,126}

Nomograms adjusted for other dosing scalars, like IBW, may be appropriate to improve dosing and reduce UFH overdosing and the risk of bleeding at both extremes of body size.^{125,126}

Protamine administration nomograms in obesity class ≥ 2 remain an area of uncertainty.

6.3.2 Low molecular weight heparin (LMWH)

Dosing LMWH in patients with extreme BWs is challenging, as anticoagulation can fall outside the target range when a “normal weight” dosing is used.^{128,129} Anti-Xa activity in plasma is the most common biomarker surrogate for clinical outcome of LMWH, used in several studies in obesity, while only few studies are sufficiently powered for clinical outcomes even in the normal BW range¹²⁸⁻¹³⁰ (**Supplementary material, Tables S2 and S3**). Thus, the quality of evidence supporting anti-Xa testing to guide treatment and predict bleeding or thrombotic complications is low. Therapeutic intervals in obesity class ≥ 2 are not established or validated.¹³¹ Instead, anti-Xa assay can be used in selected cases to assess if levels are within the expected target range developed for normal-weight individuals.

Prophylaxis. Under-dosing is possible using standard LMWH dose in obesity class ≥ 2 , and higher fixed-dose or BW-adjusted LMWH prophylaxis may be needed to attain sufficient anticoagulation.²⁰ In a recent meta-analysis, including 11 studies (four RCTs) of class >2 (mean BMI 38-61) obese patients hospitalized for medical or surgical conditions, BW-adjusted

1 heparins (UFH, enoxaparin, bemiparin or nadroparin) provided similar VTE protection and
2 bleeding risk as standard, fixed-dose therapy (**Table 4**).¹³² However, another meta-analysis also
3 including a mixed population (medical, orthopaedic and post-BS patients) revealed that
4 prophylaxis, largely with enoxaparin, at higher-than-standard dosing significantly decreased
5 VTE (OR 0.47, 0.27-0.82) without increasing bleeding (**Table 4**).¹³³

6 A population PK model predicted optimal anti-Xa levels for nadroparin in the prophylaxis of
7 morbid obesity when administered on BW- rather than fixed-dosing.¹³⁴ In a systematic review,
8 BW-based LMWH dosing suggested in post-surgical or medical patients with obesity was:
9 enoxaparin 0.5 mg/kg od or bid, tinzaparin 75 IU/kg od,¹⁰⁵ and higher prophylactic LMWH
10 dose has also been suggested by others (3,000-4,000 anti-Xa IU bid for class 3 obesity in VTE
11 prophylaxis).¹³⁵

12 A recent retrospective study in underweight patients (<55 kg) found that reduced fixed-dose
13 enoxaparin (30 mg od) could achieve anti-Xa levels in range in 75% of patients.¹³⁶ In a study of
14 medical in-patients with BW <45, prophylaxis with reduced, fixed-dosed enoxaparin (<40 mg
15 od) or UFH (<15,000 IU daily) was associated with fewer bleeding versus standard doses.¹³⁷

16 A Cochrane review and a meta-analysis on thromboprophylaxis post-BS, concluded that
17 higher-dose heparins (UFH, parnaparin, nadroparin, enoxaparin) provided little or no additive
18 benefit compared to standard-dose prophylaxis.²¹ Two meta-analyses found no support for BW-
19 adjusted or higher-dose heparin (UFH or LMWH) to prevent VTE, but a trend towards
20 increased risk of bleeding.^{138,139} A recent meta-analysis comparing augmented versus standard
21 LMWH dosing on VTE prophylaxis post-BS, showed uncertain benefit of augmented dosing
22 on VTE protection (OR 0.57, 0.07-4.39), extended duration (10-28 days, OR 0.54, 0.15-1.90)
23 and increased bleeding (OR 3.03, 95% CI 0.38-23.96).¹⁴⁰ Importantly, meta-analyses mainly
24 included cohort studies and few RCTs, thus outcome estimates, as reflected by wide CIs, are
25 uncertain with high risk of bias. Among 50 patients undergoing RYGS (BMI 49.4±4.4), 4-week

1 treatment with 5,700 IU nadroparin, 1/3 had peak anti-Xa activity below target range, and the
 2 anti-Xa activity was significantly and inversely correlated with BW (TBW (r values: -0.410 and
 3 -0.472, for TBW and LBW, respectively). A systematic review suggested higher, fixed LMWH
 4 doses in class 3 obesity (enoxaparin 40 mg bid, dalteparin 5,000 IU bid, or tinzaparin 75 IU/kg
 5 od).¹⁰⁵ Aside from dosing, the optimal duration of thromboprophylaxis remains unclear.
 6 Although the VTE risk following BS is low-moderate, it is high as compared to non-obese
 7 post-surgery patients and still the main cause of mortality.^{141,142} The majority of VTE occur
 8 after discharge, ~70% within the first month.¹⁴¹ Risk assessment models (RAM), like the
 9 Caprini score¹⁴³ or the BariClot tool developed for BS¹⁴⁴ have been used in cohort or registry
 10 studies.

11 ***Consensus statements***

12 It is advised to administer LMWH prophylaxis in underweight patients with caution
 13 and at reduced fixed dosing in patients with severe underweight.^{136,137}

14 BW-based or “higher than usual” fixed doses of LMWH may be appropriate for
 15 surgical and medical prophylaxis in obesity class ≥ 2 or if BW > 120.^{105,132,133,135}

16 The use of BW-based or ‘higher than usual’ fixed doses of LMWH are advised in
 17 obesity grade ≥ 2 or BW > 120 following BS.¹⁰⁵

18 Extended VTE prophylaxis post-BS may be appropriate in patients at high
 19 thromboembolic risk.^{143,144}

20 In non-bariatric surgery or medical in-patients, whether a higher-than-standard dose
 21 of LMWH for prophylaxis provides better efficacy/safety remains unproven.

22 In BS, there is no high-quality evidence supporting higher-than-standard fixed-dose
 23 prophylaxis with LMWH or UFH to provide superior efficacy/safety.^{21,140}

24



1 Therapeutic dosing. A meta-analysis¹³³ included studies of patients with obesity on heparin for
2 VTE, AF or CAD and compared BW-based standard (1 mg/kg) versus reduced (<1 mg/kg,
3 average 0.8 mg/kg) dosing. Reduced dose showed similar efficacy (VTE recurrence), although
4 with wide CIs (OR 0.86, 0.11-6.84), and higher safety (major bleeding OR 0.30; 0.10-0.89)
5 versus conventional dose. A comprehensive review supports reduced BW-based enoxaparin
6 dosing (~0.8 rather than 1/mg/kg) in morbid obesity, although data are based on anti-Xa
7 levels.¹⁰⁵ A recent registry of VTE treatment showed fewer complications with reduced, BW-
8 based dose LMWH.¹⁴⁵

9 For tinzaparin the treatment dose in patients with BW >120 has not been determined¹⁴⁶ and for
10 dalteparin dose capping is indicated by the FDA at BW <56 and >99¹⁴⁷ based on studies in
11 cancer patients (**Central Table 1**). However, some guidelines suggest using BW-adjusted
12 dosing and avoiding capping.^{131,148}

13 In ACS ESC Guidelines, where acute invasive angiography is not anticipated, enoxaparin at a
14 standard BW-based dose (1 mg/kg bid) without capping has a class 2 recommendation.¹²²
15 However, based on previous studies,²⁰ bleeding increases in patients weighing >150 kg
16 receiving 1 mg/kg twice-daily enoxaparin versus a reduced median dose of 0.65 mg/kg twice-
17 daily. Consistently, an *in silico* PK/PD model developed in adults and expanded to children,
18 predicted with a small error, that obese children have ~20% higher peak anti-Xa concentrations
19 under standard BW-based dosing compared to non-obese children, due to reduced weight-
20 normalized clearance. Moreover, enoxaparin was better matched across age and obesity classes
21 using fat-free BW-based dosing.¹⁴⁹

22

ORIGINAL UNEDITED MANUSCRIPT

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Consensus statements

Current LMWH therapeutic regimens for VTE¹⁰⁵ and ACS¹²² are BW-adjusted, with dose-capping at the highest BWs. However, there is insufficient evidence that dose capping improves safety or efficacy as compared to a BW-based regimen with no capping in obesity class ≥ 2 .

For obesity class ≥ 2 , it is advised to reduce by 20%/kg in relative terms therapeutic, BW(per kg)-adjusted dose.^{133 105,149}

Measuring anti-Xa activity at peak and trough may be appropriate to manage LMWH dosing in obesity class ≥ 3 .

6.3.3 Fondaparinux

See Supplementary Material and **Central Table 1**.

Consensus statements

In VTE prophylaxis, fixed-dose fondaparinux is not advised if BW <50 kg.^{150,151}

Based on available evidence, using enoxaparin rather than fondaparinux is advised in class ≥ 2 obese subjects.¹⁵²

7. Antiplatelet drugs

7.1 Acetylsalicylic acid (ASA)

An individual patient data, post-hoc meta-analysis of ten, placebo-controlled RCTs suggested a lower antithrombotic efficacy of 75-100 mg once-daily ASA in participants weighing ≥ 70 compared to <70 kg, while ASA doses ≥ 325 mg had the opposite interaction (**Table 5**).¹⁵³

Subsequent RCTs and meta-analyses on ASA monotherapy with pre-specified BMI- or BW-



1 related subgroups, could not confirm the 70 kg threshold, since efficacy and safety in
2 subgroups with BMI <25 or >30 and/or BW <70 or \geq 70 were consistent with the main trial's
3 populations (**Table 5**).¹⁵⁴⁻¹⁵⁷ In the ASCEND placebo-controlled RCT involving diabetic
4 patients in primary prevention,¹⁵⁸ ASA 100mg od was significantly more effective than placebo
5 in individuals with BMI >30 or BW >70 versus lower values (**Table 5**). In the ADAPTABLE
6 secondary prevention, RCT, ASA 325mg was not superior to 81mg in reducing MACE in the
7 overall population and in pre-specified BW subgroups below and above 70kg¹⁵⁵ (**Table 5**).
8 However, in those RCTs, obese patients were largely class 1, thus no outcome data are
9 available on class \geq 2 obesity. Since low-dose ASA is used to prevent thrombosis after
10 arthroplasty,¹⁵⁹ a large study compared standard 81mg (n=1,097) versus weight-adjusted dosing
11 (n=1,187), whereby patients \geq 120 kg received 325 mg ASA. In the weight-adjusted cohort,
12 thrombosis was reduced by ~60% at 1 and 6 months post-surgery compared to 81 mg with no
13 differences in safety.¹⁶⁰

14 Consistently with RCT data, ASA PD is similar in class 1 obese vs. non-obese subjects,¹⁶¹
15 while class \geq 2 obese subjects on 100 mg ASA od (mean BW 111 \pm 21 and BMI 39.4 \pm 5.1)¹⁶²
16 show significantly lower inhibition of cyclooxygenase activity from peripheral platelets than
17 non-obese individuals and thus a reduced response. Residual, un-inhibited *ex vivo*
18 cyclooxygenase activity in peripheral platelets appears log-linearly associated with BMI, with a
19 hindered PD at BW >110 or BMI >35.¹⁶² Consistently, patients on secondary prevention with
20 100mg daily ASA and average BW >102 or >BMI 38¹⁶³ or in the highest BMI or BW
21 quartiles,^{164,165} showed lower peripheral platelet inhibition ~~response~~ versus non-obese
22 individuals, while they adequately responded to an and a degree of inhibition similar to non-
23 obese subjects was obtained by doubling the od dose.^{163,165} Notably, doubling the low-dose
24 aspirin dose does not inhibit cyclooxygenase 2 *in vivo*.^{166,167} Among 1,002 pregnant women on

1 low-dose ASA for eclampsia, class 3 obesity was associated with significantly-reduced
2 response versus lower BMIs.¹⁶⁸

3 *In silico* PK/PD model and simulations of ASA predicted a reduced platelet inhibition in
4 moderate-to-severe obesity, which was reproduced by ~~halving~~ reducing the systemic
5 bioavailability from 50% (as in normal subjects) down to 25%.^{169,170} According to the model,
6 either doubling low-dose od (eg 200 mg) or a twice-daily low-dose restored the PD response.¹⁶⁹
7 Whether an optimal PD translates into an improved clinical benefit-risk profile remains to be
8 established. Consistently, in the RECOVERY trial¹⁷¹ that randomized hospitalized COVID-19
9 patients to 150 mg ASA od versus placebo, the ASA dose was selected 'to ensure sufficient
10 inhibition of platelet cyclooxygenase-1 activity in all participants, including those who were
11 overweight,' based on our previous document.²⁰ Data are summarized in the **Central Table 2**.

12 Consistent with reduced response and drug bioavailability in morbid obesity, ASA PD
13 improved after BS,¹⁷² with increased AUC and C_{max}²⁸ few months post-RYGB or SG, likely
14 reflecting higher absorption and drug ~~exposure~~ bioavailability following BS and weight loss.¹⁷³

15 Multiple studies reported that nonsteroidal anti-inflammatory drugs (NSAIDs) and ASA only at
16 high doses increase the risk of MU.^{148,174-177} A large meta-analysis (~25,000 patients) showed
17 that low-dose ASA did not increase MU (HR 0.56, 0.37-0.86) versus non-ASA treated
18 individuals, while high-dose did (HR 1.90, 1.41-2.58).¹⁷⁴ Pre- and post-operative PPIs can
19 prevent MU,¹⁴⁸ and PPIs ensure safe gastroprotection when low-dose ASA is following
20 RYGB.¹⁷⁸

21 ***Consensus statements***

22 No change in low-dose ASA dosing is advised for obesity class 1.^{155,158,163}



1 For low-dose ASA, either doubling the once-daily low-dose of ASA or
2 shortening the dosing interval (bid) of ASA in patients with obesity class ≥ 2 is
3 advised to improve the PD response.^{162,170,171}



4 Post-BS, continuing low-dose ASA, when indicated, is advised together with a
5 PPI for gastroprotection.^{172,178}



7 7.2 P2Y₁₂ inhibitors

8 7.2.1 Clopidogrel

9 Pre-clinical models show reduced clopidogrel biotransformation into active metabolite (AM),
10 higher carboxylesterase-1 (CES) clearance and reduced platelet inhibition in obese mice,¹⁷⁹
11 explaining data of low AM formation in obese subjects.²⁰

12 PK/PD *in silico* model for clopidogrel confirmed BW as significantly and inversely affecting
13 AM formation, AUC and platelet inhibition,¹⁸⁰ especially for class ≥ 2 obese individuals.¹⁸¹

14 Model simulations predicted the need for higher loading and maintenance doses in severely-
15 obese versus over- and normal-weight subjects to reach similar platelet inhibition.¹⁸⁰ For BMIs
16 >35 and intermediate- or poor-metabolizer status based on *CYP2C19* alleles, the model predicts
17 that clopidogrel maintenance dose should be increased to 300 and 450mg, respectively.¹⁸⁰

18 Moreover, class 3 obesity is associated with reduced *CYP2C19* activity (**Figure 2**)
19 independently of its alleles, which returns to almost-normal values after weight loss with diet or
20 BS.¹⁸²

21 BMI was linearly correlated with high residual P2Y₁₂-dependent platelet aggregation in
22 patients on dual antiplatelet therapy (DAPT) with clopidogrel,¹⁸³ and a similar phenotype was
23 reported for TAVI patients.¹⁸⁴ In a study using the ABCD-GENE score which includes BMI

24 >30 ¹⁸⁵ as a factor reducing clopidogrel response, obese patients had the highest residual ADP-

1 dependent platelet aggregation.¹⁸⁶ In 181 east-Asian patients on DAPT containing clopidogrel
2 or prasugrel, no differences were observed in the higher BMI classes (25-29, ≥ 30) for both
3 treatments.¹⁸⁷ However, none of the above studies included severe obesity. A sub-study of the
4 HOST-EXAM RCT analyzed the 2-year adverse outcome in patients on ASA 100 mg or
5 clopidogrel 75mg.¹⁸⁸ Patients with BMI < 18.5 had higher bleeding (HR 4.14, 1.70–10.05) than
6 patients with BMIs 18.5–22.9, regardless of the antiplatelet agent, while higher BMI classes did
7 not show increased bleeding risk. However, both extremely low and > 30 BMIs were associated
8 with higher all-cause death, non-fatal MI, stroke, readmission due to ACS and BARC type ≥ 3
9 bleeding.¹⁸⁸ The clinical significance of post-hoc analyses of a small non-inferiority trial
10 combining safety and efficacy primary endpoints remains unclear. In the CHANCE RCT on
11 east-Asian patients with minor stroke or TIA, BMI < 25 and normal glycated hemoglobin or
12 absence of *CYP2C19* loss-of-function alleles were associated with higher benefit with DAPT-
13 clopidogrel than with ASA monotherapy,¹⁸⁹ while DAPT-clopidogrel was not superior to ASA
14 monotherapy in patients with BMI > 25 and no loss-of-function *CYP2C19* alleles.¹⁸⁹ However,
15 these data are limited to a specific ethnicity and are a post-hoc analysis.

16 For underweight, a sub-study of the TROPICAL-ACS RCT showed that guided de-escalation
17 from DAPT-prasugrel to DAPT-clopidogrel was associated with better efficacy and safety in
18 patients with BMI < 25 compared to normal and overweight subgroups.¹⁹⁰ However, platelet
19 aggregation should be interpreted with caution because its translation in clinical efficacy and
20 safety remains unproven.¹²² No data on clopidogrel post-BS were found. Data are summarized
21 in **Central Table 2**.

22 7.2.2 Prasugrel

23 An *in silico* PK/PD model recently developed for prasugrel,¹⁹¹ confirmed that only low BW is a
24 relevant covariate for prasugrel response. In the PRASTO-II RCT, low-dose clopidogrel (50
25 mg od) showed comparable efficacy and safety to very-low dose prasugrel (3.75 mg od) in

1 secondary prevention of cardioembolic stroke in elderly or underweight (<50 kg) patients.¹⁹² In
2 Japan the 3.75 mg formulation has been approved to improve safety and reduce bleeding.¹⁹² In
3 the ELDERLY-ACS RCT, cardiovascular mortality and adverse events, including BARC 2-3
4 bleeding, were similar in elderly (>75 years) patients with low BMI (<25) on DAPT-
5 clopidogrel versus DAPT- low-dose (5 mg) prasugrel.¹⁹³ In a subgroup analysis of the ISAAR-
6 REACT-5 RCT, low-dose prasugrel had comparable efficacy but reduced by 30% BARC3-5
7 bleeding as compared to ticagrelor (90 mg twice-daily) in elderly (>75 years) or with low BW
8 (<60 kg) post-ACS patients¹⁹⁴ In a post-hoc analysis of this RCT, DAPT-ticagrelor or -
9 prasugrel had efficacy and safety across the spectrum of BMIs consistent with the overall trial
10 population.¹⁹⁵

11 **7.2.3 Ticagrelor**

12 Class 1 obesity does not appear to affect ticagrelor PD, while data in class ≥ 2 obesity are
13 limited.¹⁹⁶ A PK/PD model developed in healthy [BMI of 22.7 (19.1-27.8)] or post-ACS [BMI
14 23.5 (18.3-33.1)] Chinese individuals indicated BW, diet and sex were the major covariates.¹⁹⁷
15 A PK model developed from Asian population's data, showed that low BW, advanced age
16 (inversely) and hypertension predicted bleeding on ticagrelor.¹⁹⁸

17 Plasma concentration of ticagrelor, its AM and platelet function at peak and trough in 221
18 patients on DAPT (ASA plus ticagrelor 90 or 60 mg BID) from two RCTs showed that BMI
19 inversely correlated with 90 mg ticagrelor and AM plasma concentration at peak and trough.
20 Residual platelet function at trough in different classes of BMIs (<25, 25-29, >30 or BW <85 or
21 >85) was directly correlated with BW and BMI.¹⁹⁹ A post-hoc analysis of the TWILIGHT RCT
22 showed comparable efficacy and safety (BARC 2-5 bleeding) between SAPT-ticagrelor and
23 DAPT (with ASA), in high-risk post-ACS patients, whether normal or obese.²⁰⁰ However, in
24 this analysis patients with class ≥ 2 obesity or underweight were under-represented since

1 average BMI was ~28.5. In a post-hoc analysis of the TICO trial, BW \leq 65 kg, haemoglobin
2 \leq 12g/dL, and GFR $<$ 60 mL/min/1.73m² predicted bleeding in ticagrelor-treated patients.²⁰¹

3 In a post-hoc analysis of the CHANCE-2 RCT, patients with minor ischaemic stroke or TIA,
4 *CYP2C19* loss-of-function alleles and BMI $>$ 28 had a reduced risk of recurrent ischaemic stroke
5 at 90 days when receiving DAPT-ticagrelor versus DAPT-clopidogrel as compared to
6 BMI $<$ 28.²⁰² A recent systematic review on population PK/PD models identified low BW, Asian
7 ethnicity and old age as significant covariates for predicting bleeding on ticagrelor 90 mg,
8 suggesting that 60 mg may provide a “safer” drug concentration in these populations.¹⁹¹

9 ***Consensus statements***

10 In patients with obesity class \geq 2 and in need of clopidogrel treatment, a higher
11 maintenance dose of clopidogrel, likely doubled, may be appropriate to achieve an
12 adequate PD response.^{180,181,184}

13 *CYP2C19* polymorphisms may particularly affect clopidogrel PD at loading and
14 maintenance dose in underweight or class 2-3 obese individuals, although the clinical
15 impact is unknown.^{186,187,189}

16 No significant difference in efficacy and PK of ticagrelor between normal and
17 obesity class 1 has been reported.^{196,197}

18 Clinical and PD data for 90 mg ticagrelor in class \geq 2 obese and underweight patients
19 are very limited.

20 Reduced dose prasugrel (5 mg or 3.75 mg in Japan) or standard dose clopidogrel
21 may be appropriate, rather than 90 mg ticagrelor, in underweight patients.^{189,194,195}

22 In patients with severe underweight, a lower dose (60mg) ticagrelor may be
23 appropriate, which seems safer, although the evidence is limited.¹⁹¹

24 Ticagrelor or prasugrel are advised over clopidogrel in class \geq 2 obese patients,



1 especially when loss-of-function allele(s) are documented.^{180,181}

2 It is not advised to test platelet aggregation for adjusting antiplatelet therapy (either
3 single or dual) after-BS.²⁸

4

5 **8. Triple antithrombotic therapy (TAT)**

6 See Supplemental material and **Table S5**.

7 ***Consensus statements***

8 In class ≥ 3 obese patients undergoing PCI, a longer duration of initial TAT as well as
9 individualization of the doses and/or intervals of administration of antithrombotic
10 drugs, both in TAT and DAT may be appropriate.²⁰³⁻²⁰⁶

11 Underweight is associated with high bleeding during TAT, regardless of the type of
12 OAC.²⁰⁷

13 A strict implementation of bleeding prevention and gastroprotection are advised in
14 underweight patients on TAT, owing to the increased bleeding risk, regardless of the
15 type of OAC.^{206,207}

16

17 **9. Dual pathway inhibition**

18 See Supplemental material

19 ***Consensus statements***

20 The benefit-risk profile of DPI in patients with chronic atherothrombotic diseases
21 seems preserved up to obesity class 2, while it is unknown for obesity class ≥ 3 .²⁰⁸

22 The risk of bleeding and the atherothrombotic risk reduction in underweight
23 patients are not known

24

10. IV antiplatelet drugs: cangrelor and glycoprotein IIb/IIIa inhibitors (GPI)

See Supplementary material and **Central Table 2**

Consensus statements

The efficacy and safety profile of cangrelor seem not affected by obesity classes 1 to 3, while bleeding may be increased by cangrelor in underweight patients.²⁰⁹

The efficacy and safety profile of GPIs in underweight (<18.5kg/m²) and class ≥ 3 obese individuals is uncertain.²¹⁰

11. Fibrinolytic drugs

See **Supplementary Material** and **Central Table 1**

Consensus statement

Dosing regimens for most fibrinolytics are BW-adjusted and careful adherence to approved labels and nomograms is advised.²¹¹⁻²¹⁵

12. Interactions between antithrombotic and BW-reducing drugs

Incretin mimetic agents have been recently approved as anti-obesity drugs, thus data on drug-drug interactions (DDI) are limited (**Table S6**).

GLP-1 receptor agonists, by hindering gastric emptying and motility, may affect absorption or gut metabolism of antithrombotic agents. No interactions were found between semaglutide, at steady state, and warfarin, digoxin, metformin, or lisinopril.²¹⁶ Similarly, no interactions were detected between parenteral dulaglutide and warfarin.²¹⁷ However, semaglutide delays gastric emptying and therefore can create interactions if drugs, including VKA, are concomitantly

1 administered. Tirzepatide, a combined GLP-1 and glucose-dependent insulinotropic
2 polypeptide receptor agonist, by delaying gastric emptying may affect the bioavailability of
3 concomitant oral drugs.²¹⁸ By in-vitro-in-vivo modelling, slow gastric emptying does not
4 influence rivaroxaban bioavailability²¹⁹ Delayed gastric emptying has variable effects on the
5 absorption of ticagrelor based on studies in patients treated with opioids,^{220,221} but no
6 information is available for BW reducing drugs.

7 Orlistat is an inhibitor of the intestinal CES-1 and -2²²² that metabolize several drugs, including
8 clopidogrel, ASA and prasugrel. CES-1 variants account for the reduced formation of
9 clopidogrel AM and for decreased dabigatran plasma concentrations.²²³ Reduced CES-2
10 activity lowers ASA hydrolysis.^{223,224} Orlistat has been reported to enhance VKA effects, thus
11 closer INR monitoring INR might be necessary.²²⁵

12 **Consensus statement**

13 More frequent INR monitoring is advised for patients on VKA when starting or
14 modifying GLP1-RAs, and to avoid simultaneous oral administration.²¹⁸



16 **13. Antithrombotic drugs under development**

17 In the past five years, novel antithrombotic agents with old or new targets are under clinical
18 development,²²⁶⁻²²⁹ and reported in **Supplemental Material**, with scant data on BMI or BW
19 extremes.

21 **14. Gaps in knowledge**

- 22 • Whether gender may affect safety and efficacy of antithrombotic drugs in morbid
23 obesity and underweight patients needs more studies.

- 1 • Whether reference intervals of VKA and heparins should be similar for all body sizes
2 remains unexplored.
- 3 • More data on DOACs vs. VKA are needed for class ≥ 2 obesity and underweight
4 individuals.
- 5 • More studies should investigate DOACs and their DDIs in the context of obesity, its
6 comorbidities and frequently used co-medications.
- 7 • Whether LMWH prophylaxis at BW-adjusted or higher fixed-dose is more effective and
8 equally safe versus standard fixed dosing in class ≥ 2 obesity remains undetermined
- 9 • RCTs on LMWH dosing strategies for VTE treatment in class ≥ 2 obesity are needed.
- 10 • Studies are needed on protamine sulphate dosing for UFH reversal and on PCC dosing
11 for OAC reversal in class ≥ 2 obese patients.
- 12 • Randomized PD and/or clinical-outcome studies in class ≥ 2 obese individuals
13 comparing higher or more-frequent vs. standard ASA regimens are needed in patients
14 with CVD, undergoing BS and in obese pregnant women requiring ASA.
- 15 • Clopidogrel in low BW and morbid obesity has not been adequately studied in RCTs.
- 16 • Whether the efficacy and safety of fibrinolysis, are affected by BW extremes in STEMI,
17 PE and ischaemic stroke is unknown.
- 18 • Severe obesity remains largely under-represented in RCTs comparing TAT versus DAT
- 19 • The DDIs of novel GLP-1RA with oral antithrombotic drugs require caution and further
20 investigation.
- 21 • How BS and new anti-obesity drugs can influence the PK/PD of some antithrombotic
22 agents needs further data.
- 23 • There is a clinical need to improve risk stratification and to extend thromboprophylaxis
24 after BS in high-risk patients, but there are no RCT of RAM to aid decisions.
25 Cardiovascular RAM post-BS has not been sufficiently developed and validated.

- 1 • There is lack of data on the early and long-term antithrombotic prophylaxis post-BS and
2 on how and when to resume the antithrombotic treatment after surgery.

3

4 **15. Conclusions**

5 Managing patients with an indication for antithrombotic treatment(s) (therapeutic or
6 prophylactic) at the extremes of body size represents a therapeutic challenge (**Graphical**
7 **Abstract and Central Tables 1 and 2**). Most of the evidence relies on subgroup/post-hoc
8 analyses of RCTs or on studies using biomarkers as endpoints (drug concentrations, INR, other
9 coagulation measurements). Population-based PK/PD studies as well as *in silico* AI models and
10 simulations are shedding light on the complexity of drug's metabolism at the extreme of body
11 mass and may guide and tailor the design of future RCTs. Validated PK/PD modelling and
12 simulations could also help prescribing clinicians. For the time being, severe obesity and severe
13 underweight remain specific domains of personalised medicine, AI and precision clinical
14 pharmacology (**Graphical Abstract**).

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| | DEFINITION | SYMBOL |
|--------------------|--|--------|
| STRENGTH OF ADVICE | Clinical advice, based on robust published evidence | |
| | Clinical advice, based on uniform consensus of the writing group | |
| | May be appropriate, based on published evidence | |
| | May be appropriate, based on consensus within the writing group | |
| | Area of uncertainty | |

2

3 **Figure 1.** Scale and symbols representing the strength of advice statements, based on evidence
 4 and consensus of the writing group, as recommended for the ESC scientific documents.

5

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Figure 2

Figure 2. Antithrombotic drugs can be affected by marked changes in body size in each step of their pharmacokinetics, i.e. absorption, distribution, metabolism and excretion. Underweight is commonly associated with co-morbidities, reduced renal function, and changes in plasma proteins. Severe obesity is associated with relevant changes in the gastrointestinal tract, body size composition (fat versus lean mass ratio, plasma proteins), kidney and liver functions, including the activity of the CYP450 enzymes, which can impact drug absorption, distribution, biotransformation and excretion. Bariatric surgery by inducing anatomical modifications in the gastrointestinal tract and metabolic changes can also influence each step of drug's PK.

Note to the Figure. Data post bariatric surgery refers mainly to Roux-en-Y gastric bypass surgery. ** Oral liquid formulations should not contain nonabsorbable sugars due to dumping syndrome risk; open capsules if allowed according to the summary of product characteristics.

Based on references^{230-232,32,233} **Abbreviations:** BMI: body mass index; C_{max}: peak plasma concentrations; CYP: cytochrome P450; FFA: free fatty acids; GFR: glomerular filtration rate;

1 LBT: lean body tissue; LBW: lean body weight; NAFLD: non-alcoholic fatty liver disease;
2 NASH: non-alcoholic steatohepatitis; P-gp: P-glycoprotein; s.c.: subcutaneous; $t_{1/2}$:
3 elimination half-life; TBW: total body weight; T_{max} : time to reach C_{max} ; UDPGT: uridine
4 diphosphate glycosyltransferase enzymes; V_d : volume of distribution.

5

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Figure 3

2

3 **Figure 3.** The figure depicts relevant steps in managing morbidly obese individuals who have
 4 one or more ongoing indication(s) for antithrombotic drugs and undergo bariatric surgery. The
 5 figure depicts some relevant points to be checked and considered before and immediately after
 6 bariatric surgery and at long-term afterwards, providing that the indication for one or more
 7 antithrombotic drug (both for treatment or prophylaxis) persists.

8 **Abbreviations:** BMI: body mass index; BW: body weight; (D)OAC: (direct) oral
 9 anticoagulant; INR: international normalized ratio; LMWH: low molecular weight heparin;
 10 VKA: vitamin K antagonists

11

BEFORE BARIATRIC INTERVENTIONS

Consider the type and extent of surgery: restrictive or metabolic?
 Re-evaluate the indication for single or combined antithrombotic
 drug(s) in the individual patient



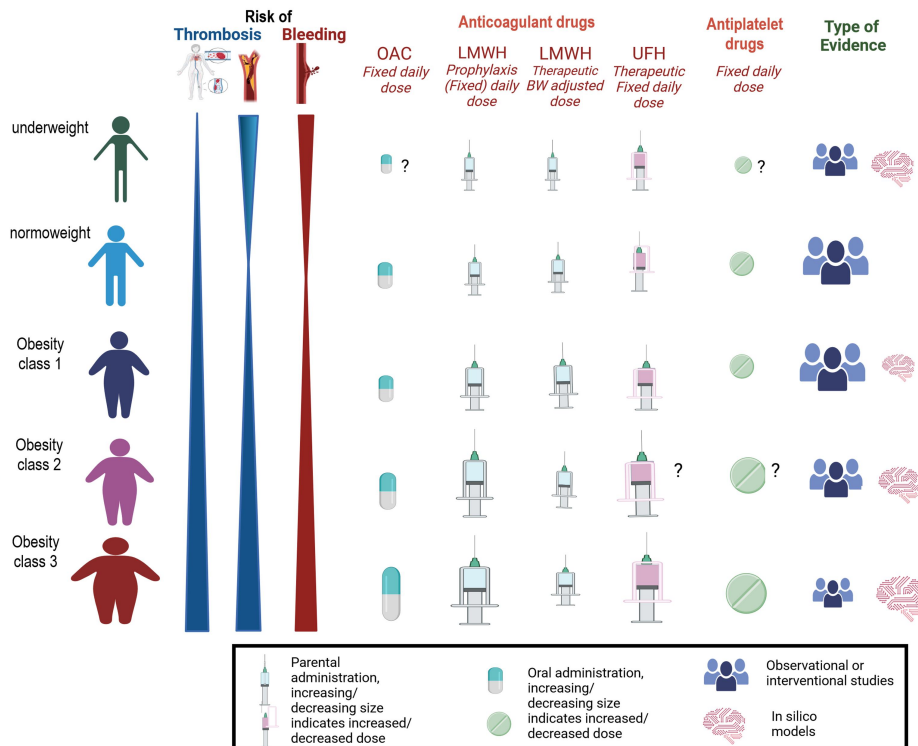
EARLY WEEKS POST-INTERVENTION

(re)-check the indication(s) of ongoing antithrombotic therapy
 Check drug interactions if new drugs (eg antibiotics)
 Check nutrition status
 Enable inter-disciplinary discussion (cardiologist, surgeon, clinical
 pharmacologist, patient)
 Implement gastroprotection
 Prefer LMWH over OAC and individualize fixed- or BW-based
 therapy



MID-LONG TERM POST-INTERVENTION

Consider measuring the plasma concentration for DOAC to fall
 within known intervals at trough and/or peak
 more frequent INR monitoring for VKA



2

3 Graphical Abstract. Risks of thrombosis and bleeding, antithrombotic drug management 4 and supporting type of evidence across body size categories.

5 From left to right: a causal relationship between obesity and deep vein thrombosis
6 (DVT) risk has been suggested by Mendelian randomization studies. Generally, DVT risk
7 linearly increases from underweight to the highest BMI classes. Despite the low risk of
8 underweight individuals, underweight seem to have a worse prognosis once venous thrombosis
9 has occurred. The risk of arterial thrombosis increases from normoweight to severe obesity,
10 while the risk associated with being underweight remains less clear, possibly mimicking a U-
11 shaped relationship. A U-shaped relationship seems to describe the risk of major bleeding
12 associated with body size. However, the anatomical site and type of bleeding, underlying risk
13 factors and prognosis differ at the two extremes.

1 Optimizing the dosing of antithrombotic drugs both in underweight and class ≥ 2 obese
2 individuals is supported by PK/PD studies and data from post-hoc analyses of randomized
3 studies, observational and registry data as well as by artificial intelligence simulations of *in*
4 *silico* PK/PD models generated by population and RCT experimental measurements. In
5 underweight individuals, most evidence indicates better safety of reducing the daily doses of
6 standard, fixed-dose antithrombotic drugs, while increasing the fixed dose is suggested for
7 those in class ≥ 2 obesity. For BW-adjusted antithrombotic drugs, individuals with higher
8 classes of obesity may be overdosed due to a major imbalance between lean and fat mass that
9 has a major impact on drug PK and bioavailability. On the other hand, if capping is used, this
10 may result in underdosing at the upper extreme of body size. Further details are reported in the
11 **Central Table 1** and **Central Table 2**. **Abbreviations:** LMHW: low molecular weight heparin,
12 OAC oral anticoagulation. UFH: unfractionated heparin.

13

14 **Data Availability statement**

15 No new data were generated or analysed in support of this research.

16

17 **Disclaimer**

18 Since Stefan Agewall, the EIC of the journal, is one of the co-authors of the present document,
19 the paper has been handled independently by another Guest Editor, Prof. Gregory YH Lip

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14

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Central Table 1. Anticoagulant (oral and parenteral) and fibrinolytic drugs in underweight and different classes of obesity, including normal body size as reference.

| | Underweight | Normal weight (reference) | Obesity | | |
|----------------------------|--|--|----------------|--------------------------------------|--|
| | | | Class 1 | Class 2 | Class ≥ 3 |
| Anticoagulant drugs | | | | | |
| VKA | More frequent INR monitoring. Caution for bleeding risk of underweight | INR-adjusted regimen | No change | More frequent INR monitoring | More frequent INR monitoring also during drug reversal |
| Apixaban | 2.5 mg bid if BW < 60 kg and ≥ 80 years or serum creatinine ≥ 133 micromol/L (AFib) Caution for bleeding risk of underweight Consider monitoring peak and/or trough for severe underweight | 10 mg bid (acute VTE); 5 mg bid (AFib and up to 6 months post-VTE); 2.5 mg (> 6 months post-VTE) | No change | Insufficient data to suggest changes | Suggest monitoring peak and/or through anti-Xa activity if used and if concentrations are too low, switch to VKA |
| Rivaroxaban | No change if preserved renal function. # Consider monitoring peak and/or trough for | 20 mg od (Afib, and VTE > 21 days); 15 mg bid (acute VTE); 10 mg od (>6 months | No change | No change | Suggest monitoring peak and/or through anti-Xa activity if used, if concentrations are too low |

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| | | | | | |
|--|---|--|---|--|--|
| | severe underweight Unknown efficacy and safety. Caution due to high bleeding risk | post VTE) 2.5 mg bid (stable CAD/PAD; post-ACS) | No change | No change | switch to VKA Unknown efficacy and safety |
| Edoxaban | 30 mg od if BW ≤60 kg Caution for bleeding risk of underweight Consider monitoring peak and/or trough for severe underweight | 60 mg or 30 mg od (AFib and VTE) | No change | Possibly check peak and/or through anti-Xa activity | Suggest monitoring peak and/or through anti-Xa activity if used and if concentrations are too low switch to VKA |
| Dabigatran | 110 mg if reduced renal function or at high risk of bleeding. Caution for bleeding risk of underweight Consider monitoring peak and/or trough for severe underweight | 150 mg bid (AFib and VTE) 110 mg bid (AFib and VTE if ≥80 years or eGFR<50mL/min) | No change | Possibly check ECT or dTT | Suggest monitoring peak and/or through ecarin clotting time or diluted Thrombin Time if used and if concentrations are too low switch to VKA |
| LMH fixed dosing (thromboprophylaxis) | Limited data Risk of overdosing, consider measure anti-Xa activity | Enoxaparin 40 mg od Dalteparin 5000 IU od, Tinzaparin 4500 IU od | No change | Increase daily dose or frequency (bid) in patients at high risk*: Enoxaparin: 40 mg bid Dalteparin: 7500 od consider measure anti-Xa activity | Increase dose, Enoxaparin: 40-60 mg bid Dalteparin: 5000 U bid consider measure anti-Xa activity Tinzaparin: BW adjusted dose of 50-75 IU/kg may be considered |
| LMWH (ACS and VTE treatment) | No change but limited data, Consider measure anti-Xa activity | VTE treatment: Enoxaparin: 1 mg/kg bid Dalteparin 200 IU/kg od or divided in bid | VTE treatment: No change (for dalteparin limited data, | VTE treatment (bid dosing) Enoxaparin: reduce dose by approx. 20 % (most data in BMI > 40) | |

| | | | | | |
|------------------------------------|--|--|---|--|--|
| | | Tinzaparin 175 IU/kg od or divided in bid ACS: Enoxaparin 1 mg/kg bid Dalteparin 120 IU/kg bid (dose capping at 10,000 IU bid) | consider dose capping at 20000 IU) | Consider measuring anti-Xa activity Tinzaparin: limited data at BW > 140 kg consider measure anti-Xa activity Dalteparin: limited data, consider dose capping and measure anti-Xa activity, consider use another LMWH ACS: unknown if reduce dose / dose capping, consider measure anti-Xa activity | |
| UFH (VTE treatment and ACS) | No change, Careful aPTT or ACT monitoring for possible overdosing | Before coronary angiography: 60–70 IU/kg iv bolus (max 5000 IU) and 12–15 IU/kg/h infusion (max 1000 IU/h) monitoring aPTT; during PCI: 70–100 IU/kg iv in patients not anticoagulated, 50–70 IU/kg if concomitant GPI, monitor ACT | No change and careful aPTT monitoring for possible under- and over-dosing | | |
| Fondaparinux | Contraindicated or generally avoided | Thromboprophylaxis: 2.5 mg od VTE: 7.5 mg od | No change or for VTE 10 mg od** if BW > | VTE: 10 mg od** ACS: 2.5 mg od Prophylaxis: 2.5 mg od | Limited data for all indications, use LMWH |

| | | | | | |
|--|--|---|---|--|--|
| | | ACS 2.5 mg od | 100 kg | (limited data) | |
| Fibrinolytic drugs | | | | | |
| All Fibrinolytic Drugs (Acute MI, PE) | Appropriate measure BW to avoid overdosing | Depends on the agent used | Appropriate measure BW to avoid underdosing | Limited data | |
| Streptokinase | Higher likelihood of achieving artery patency at 62 kg vs. normal BW | 1.5x10 ⁶ IU IV infusion w/out heparins (30-60 min STEMI, 60 min mechanical heart thrombosis; 120 min for PE) | No change | Worse artery patency for BW 100-105 kg vs. 62 kg | No data > 120kg |
| Alteplase | For patients <65 kg in STEMI 15 mg bolus, then 0.75 mg/kg over 30 min (up to 50 mg), then 0.5 mg/kg over 60 min (maximum 35 mg) | Patients >65-67 kg STEMI fixed dosing: 15 mg bolus, 50 mg over 30 min, then 35 mg over 60 min (max 100 mg) Stroke: 0.9 mg/kg; Massive PE: 100 mg. | Fixed regimen as in normal BW for STEMI; Stroke: ceiling dose of 90 mg | STEMI: Ceiling dose: 100 mg Stroke: ceiling dose 90 mg (stroke) | No data |
| Tenecteplase | STEMI: <60 kg: 30 mg and consider associated bleeding risk | STEMI: 60-<70 kg: 35 mg; 70-<80 kg: 40 mg; stroke: 0.25mg/kg Half dosing in patients older than 75 | STEMI: 80-90 kg, 45 mg | STEMI >90 kg: 50 mg | STEMI: no data available Increase of clearance with increasing BW |

Underweight, normoweight and obesity classes as defined in Table 1. 'No change' refers to the same treatment as in normal BMI/BW subjects as reference population; #Caution for bleeding risk of underweight: 15 mg OD possibly considered > 21 days post-VTE days, until extended

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treatment. * e.g in bariatric surgery, previous VTE, strong family history of VTE, thrombophilia; ** should not be used if moderately (eGFR <60 ml/min/1.73 m²) - severely (eGFR <30 ml/min/1.73 m²) reduced renal function.

Abbreviations: AFib: atrial fibrillation; AI: artificial Intelligence; ACS: acute coronary syndromes; bid: bis in die; CAD: coronary artery diseases; LMWH: low molecular weight heparin; IU: international Units; od: once daily; PAD: peripheral artery disease; PD: pharmacodynamics; PK: pharmacokinetics; UFH: Unfractionated heparin; VKA: vitamin K antagonist; VTE: venous thromboembolism

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Central Table 2. Antiplatelets drugs in underweight and across different classes of obesity, including normal body size as reference.

| Drug | Underweight <18.5 kg/m ² | Normal Weight (reference) | Obesity | | |
|--------------------|--|---|--|--|---|
| | | | Class 1 | Class 2 | Class ≥3 |
| <i>ASA</i> | No change | 75-100 mg od | No change | Likely no change | AI and PD studies suggest doubling the low dose once-daily or increase low-dose dosing frequency (bid) |
| <i>Clopidogrel</i> | No change | 75 mg od | No change | Reduced AM formation especially in poor metabolizers. Suggest change drug or doubling the daily dosing | Reduced active metabolite generation. PK models predict need to at least to double daily dose or change to prasugrel or ticagrelor. |
| <i>Prasugrel</i> | 5 mg (or 3.75 in Japan) OD | 10 mg od | No change | Likely no change | Inconsistent reports of reduced AM of unknown clinical significance. Likely no change |
| <i>Ticagrelor</i> | No changes or reduced dose (60 mg bid) based on PD and AI data. Caution for bleeding risk of underweight | 90 mg bid 60 mg bid ≥ 1 year after ACS | No change | Likely no change | PD data suggest reduced drug concentration of unknown clinical significance. Insufficient data |
| <i>Cangrelor</i> | Appropriate measure of BW to avoid overdosing | 30 µg/kg IV Bolus, and 4 µg/kg/min infusion | Appropriate measure of BW to avoid under- or over- | | |

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| | | | dosing |
|-------------|--|--|---|
| GPIs | Appropriate measure of BW to avoid overdosing Eptifibatide: BW-driven dosing chart in the FDA insert package for BW 37-59 kg Tirofiban: BW-driven dosing chart in the insert package for BW 30-62 kg | Abciximab: 0.25 mg/kg IV bolus, 0.125 µg/kg/min (maximum of 10 µg/min) IV infusion. Eptifibatide: 180 µg/kg IV bolus, 2 µg/kg/min IV infusion (if CrCl ≥ 50 mL/min). Tirofiban: 25 µg/kg IV bolus and 0.15 µg/kg/min (if CrCl > 60 mL/min) | Appropriate measure of BW to avoid underdosing Eptifibatide: BW-driven dosing chart in the FDA insert package for BW up to 121 kg Tirofiban: BW-driven dosing chart in the insert package for BW up to 153 kg |

Underweight, normo-weight and obesity classes as defined in Table 1. 'no change' refers to the treatment in normal BMI/BW subjects as reference population.

Abbreviations: AM: active metabolite; ASA: acetylsalicylic acid; bid: bis in die ACS: acute coronary syndromes; ACT: activated clotting time; BW: body weight; aPTT: activated partial thromboplastin time; BW: body weight; CrCl: creatinine clearance; FDA: Food and Drug Administration; GPI: glycoprotein inhibitors; IU: international Units; PCI: percutaneous coronary intervention; STEMI: acute ST-segment elevation myocardial infarction; PE: pulmonary embolism.

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Table 1. Classifications of different body mass categories in men and women according to the World Health Organization (WHO)

| <i>Classification</i> | <i>Body Mass Index (kg/m²)[#]</i> | <i>Body Weight (kg) or Ideal Body Weight^{§§}</i> |
|---|--|---|
| <i>Underweight</i> | < 18.5 Sub-categories: Mild thinness 17-18.49 Moderate thinness: 16-16.99 Severe thinness: <16 | <60 kg or ≤56.2 kg* |
| <i>Normal weight</i> | 18.5-24.99 Asian population*** 18.5-22.9 | ≥60 up to 70 kg [°] or >56.3 up to 76.6 kg* |
| <i>Overweight (pre-obesity)</i> | 25-29.99 Asian population >23-24.99 | >70 up to 100 kg [°] or 76.7 up to 92.0 kg* |
| <i>Obesity (overall)</i> | ≥30 Asian population >25-27.5 | >100 kg [°] or ≥92.1 kg* or >20% greater than the ideal body weight ^{§§} |
| <i>Class 1</i> | 30-34.99 Asian population >27.5-32.5 | |
| <i>Class 2 (moderate obesity)</i> | 35-39.99 Asian population >32.5-37.5 | >100% greater than the ideal body weight ^{§§} |
| <i>Class 3 (severe or morbid obesity)</i> | ≥40-49.99 Asian population >37.5** | ≥150 kg [°] or ≥122.9 kg* |
| <i>Class 4*** (super-obesity)</i> | ≥50-59.99 | >225% greater than the ideal body weight |
| <i>Class 5[^] (super-super or extreme obesity)</i> | ≥60 | |

according to the WHO classification for adults (≥20 years, female and male subjects; <http://www.who.int/topics/obesity/en/>) unless otherwise indicated; ° thresholds often used to define underweight in RCT or clinical studies for both female and male subjects;

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*Centers for Disease Control and Prevention for adults (both male and female subjects) with a height of 5 feet 9 ins (<https://www.cdc.gov/nchs/fastats/body-measurements.htm>).

**In Asian populations additional cut off points have been added to reflect the risk of cardiometabolic disease associated with overweight/obesity in this population;

§§ Ideal Body Weight according to modified Devine's formula: Men: $51.65 \text{ kg} + 1.85 \text{ kg/inch of height}$ greater than 5 feet; Women: $48.67 \text{ kg} + 1.65 \text{ kg/inch of height}$ greater than 5 feet²³⁴ ***²³⁵ \wedge ²³⁶.

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Table 2. Studies on efficacy and safety of VKA versus DOAC in AF and VTE across the spectrum of body mass

| Reference | Study design | Intervention and control | Populations under study | Key findings and source of bias |
|------------------------------------|--|--------------------------|--|--|
| Kushnir, et al 2019 ²³⁷ | Retrospective Study (n=795) | DOAC vs Warfarin | AF or VTE BMI ≥40 (n=NA) | Comparable efficacy and safety of DOAC vs warfarin in severely obese patients with AF or VTE |
| Lee, et al 2019 ¹⁰⁸ | Propensity score matching (n=21,589) | DOAC vs Warfarin | AF BW ≤60 kg (n=21589) | Better efficacy and safety of DOAC vs warfarin in AF patients with underweight Single ethnicity, translation to other ethnicities not studied |
| Kido, et al 2020 ²³⁸ | Meta-analysis of 1 RCT and 4 observational studies | DOAC vs Warfarin | AF BMI > 40 (n unknown) Or BW>120 (n unknown) | Comparable efficacy but better safety of DOAC vs warfarin in severe obese patients with AF No considerations based on obesity classes |
| Boriani et al. 2020 ⁸⁸ | ENGAGE-AF (n=21,028) Post-hoc analysis | Edoxaban vs Warfarin | AF BMI ≥30-<35 (n=5209) ≥35-<40 (n=2099) ≥40 (n=1149) | Comparable efficacy and safety of edoxaban vs warfarin across classes 1-3 obesity in patients with AF |
| Perino, et al 2021 ¹⁰² | Retrospective Study (n=51,871) | DOAC vs Warfarin | VTE BW <60(n=1632) ≥60-<100 (n=30645) ≥100-<120(n=12660) ≥120-<140 (n=4767) ≥140(n=2167) | Comparable efficacy and safety of DOAC vs warfarin in severely obese patients with VTE |
| Soyombo, et al 2021 ⁸⁴ | Retrospective Study (n=433) | Warfarin | Obesity classes Normal (n=40) | Increased warfarin doses required with higher obesity classes |

| | | | | |
|-------------------------------------|---|-------------------------|--|---|
| | | | Overweight (n=111) Obesity class 1 (n=135) Obesity class 2 (n=45) Obesity class 3 (n=99) | |
| Cohen et al, 2021 ¹⁰⁰ | RCT AMPLYFY (n=5,384) Post-hoc analysis | Apixaban vs Warfarin | VTE BW ≤60 (n=476) >60-<100 (n=3868) ≥100-<120 (n=750) ≥120 (n=290) | Comparable efficacy and safety of apixaban vs warfarin across body weight subgroups in patients with VTE |
| Katel, et al 2021 ¹⁰³ | Systemic review and meta-analysis of 5 observational studies | DOAC vs Warfarin | VTE BMI ≥ 40 (n=542) or BW ≥ 120 (n=6100) | Comparable efficacy and safety of DOAC vs warfarin in severe obese patients with VTE No considerations based on obesity classes |
| Mhanna, et al 2021 ⁹⁷ | Systemic review and meta-analysis of 10 observational studies and 2 RCTs (n=89,494) | DOAC vs Warfarin | AF BMI ≥ 40 (n unknown) or BW ≥ 120 (n unknown) | Better efficacy and safety of DOAC vs warfarin in severe obese patients with AF No considerations based on obesity classes |
| Nakao, et al 2022 ¹⁰⁹ | Retrospective Propensity score matching (n=29,135) | DOAC vs Warfarin | AF BMI (kg/m ²) <18.5 (n=585) ≥18.5-<25 (n=8427) ≥25-<30 (n=10705) ≥30-<35 (n=5910) ≥35 (n=3508) | Comparable efficacy and safety of DOAC vs warfarin across obesity classes 1-3 in patients with AF |
| Zhang, et al 2023 ¹⁰¹ | Meta-analysis of 11 observational and 2 RCT studies | DOAC vs Warfarin | VTE BMI ≥ 40 (n=6902) Weight ≥ 120 kg (n=7746) | Efficacy and safety of DOAC vs warfarin were improved in severe obese patients with VTE No considerations based on obesity classes |
| Salah, 2023 ²³⁹ | Meta-analysis of 12 observational studies | DOAC vs Warfarin | AF BMI ≥30/≥40 (n unknown) | Better efficacy of DOAC vs warfarin in severe obese patients with AF No considerations based on obesity classes |

| | | | | |
|---|--------------------------------------|----------------------|---|---|
| Elad, et al 2023 ⁹⁸ | Retrospective Study (n=5183) | DOAC | AF BMI groups <30 (n=2688) ≥30 to <40 (n=2137) ≥40 (n=358) | Comparable efficacy and safety of DOAC across obesity classes in AF patients |
| Fritz Hansson, et al 2023 ²⁴⁰ | Retrospective study (n=26,047) | DOAC | AF BMI groups 18.5-<25 (n=13,346) 25-<30(n= 22,269) 30-<35(n=13,909) 35-<40(n=5,440) ≥40 (n=2902) | Comparable effect of DOAC vs. VKA on stroke across obesity classes except for class 3. Trend for higher mortality and lower net clinical outcome in DOAC-treated patients in class 3 obesity |
| Din, et al 2023 ⁸⁵ | Retrospective Study (n=10,167) | Warfarin | VTE BW <60(n=201) ≥60-<100(n=5541) ≥100-<120 (n=2707) ≥120-<140 (n=1137) ≥140 (n=581) | Comparable TTR for warfarin across obesity classes in patients with VTE |
| Patel et al, 2024 ⁹⁵ | Meta-analysis of 4 phase 3 RCTs | DOAC vs. warfarin | AF BMI as a continuous variable as well as grouped in 18.5-<25(n=9101) 25-<30(n=9970) 30-<35(n=4280) 35-<40(n=1486) ≥40 (n=608) | Efficacy of DOAC versus warfarin in atrial fibrillation was consistent all BMI and BW categories, whereas safety tended to be reduced at a higher BMI and BW as well as the composite the net clinical outcome combining efficacy and safety endpoints, including death |

Abbreviations. AF: atrial fibrillation; BMI: body mass index (kg/m²); BW: body weight (kg); DOAC: direct oral anticoagulants; VTE: venous thromboembolism; TTR: time in therapeutic range; NA: not available.

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Table 3. Intervals of concentration reported in phase III trials or summary of product characteristics for different DOACs according to approved indications and daily dosing.

| DOAC Indication and dose | Concentration at trough (ng/ml) | Concentration at peak (ng/ml) | Protein binding (%) | Volume of distribution at steady state (L) | LogP |
|--|--|--|----------------------------|--|-------------|
| <i>Dabigatran-AF</i> 150 mg bid, 25th-75th percentile | 61-143 ²⁴¹ , 200 (90 th percentile) ²⁴² | 117 – 275 ^{241,242} | | | 5.17 |
| 110 mg bid, 10th-90th percentile | 28-155 ²⁴³ | 52-275 ²⁴³ | 34-35 ^{241,242} | 60-70 (moderate tissue distribution). ²²⁵ | |
| <i>Dabigatran-VTE</i> 150 mg bid, 25th-75th percentile | 39-95 ^{241,242} , 146 (90 th percentile) ²⁴¹ | 117- 275 ^{241,242} | | | |
| <i>Apixaban-AF</i> 5 mg bid, 5th-95th percentile | 41 – 230 ^{244,245} | 91 – 321 ^{244,245} | | | |
| 2.5 mg bid, 5th-95th percentile | 34-162 ^{244,245} | 69-221 ²⁴⁴ | 87 ^{244,245} | 21 ^{244,245} | 2.22 |
| <i>Apixaban-VTE</i> 10 mg bid, 5-95 percentile | 41-335 ^{244,245} | 111-572 ^{244,245} | | | |
| 5 mg bid, 5th-95th percentile | 22-177 ^{244,245} | 59-302 ^{244,245} | | | |
| 2.5 mg bid, 5th-95th percentile | 11-90 ^{244,245} | 30-153 ^{244,245} | | | |
| <i>Edoxaban-AF</i> 60 mg, od (5-95 percentile) | 19-62 ^{246 246} (or 16-43) ²⁴⁷ | 125- 245 ²⁴⁸ (or 145- 288) ²⁴⁷ | | | 1.61 |
| 30 mg, od (25-75 percentile) | 10-32 ²⁴⁶ (or 8-21) ²⁴⁷ | 55-120 ^{248 248} (or 73- 146) ²⁴⁷ | 55 | 107 | |

| | | | | | |
|--|-------------------------|--------------------------|----------------------|-----------------------|------|
| Edoxaban-VTE | | | | | |
| 60 mg, od (25-75 percentile) | 10-39 ²⁴⁹ | 149-317 ²⁴⁹ | | | |
| 30 mg, od (25-75 percentile) | 8-32 ²⁴⁹ | 99-225 ²⁴⁹ | | | |
| Rivaroxaban-AF | | | | | |
| 20 mg od (5-95 percentile) | 25 – 124 ²⁵⁰ | 206 – 347 ²⁵⁰ | | | |
| 15 mg od (5-95 percentile) | 7-127 ²⁵¹ | 159-573 ²⁵¹ | 90-95 ²⁵⁰ | 50 ^{250 250} | 1.74 |
| Rivaroxaban-VTE | | | | | |
| 20 mg od (5-95 percentile) | 6-239 ²⁵⁰ | 22-535 ²⁵⁰ | | | |
| 10 mg od (5-95 percentile) | 4-51 ²⁵⁰ | 7-273 ²⁵⁰ | | | |
| Rivaroxaban-ACS and stable atherosclerotic diseases | | | | | |
| 2.5 mg bid (5-95 percentile) | 4-18 ²⁵⁰ | 13-123 ²⁵⁰ | | | |

Abbreviations: ACS: acute coronary syndromes; AF: atrial fibrillation; VTE : venous thromboembolism ; LogP : coefficient of partition of the drug, ie the ratio of the concentration of the un-ionized compound at equilibrium between organic and aqueous phases. High lipophilicity ($\log P > 5$) often contributes to high metabolic turnover, low solubility, and poor oral absorption, while low lipophilicity can negatively impact permeability and potency.

Table 4. Summary of the studies on heparins pre- and post-bariatric surgery

| Reference | Studies included | Summary of the results |
|---|--|--|
| Cochrane Database of Systematic Reviews ²¹ | <p>Bariatric surgery Thromboprophylaxis</p> <p>higher-dose heparin versus standard-dose heparin</p> <p><u>Ebrahimifard 2012</u>; A comparison between two different prophylactic doses of UFH for deep venous thrombosis prevention in laparoscopic bariatric surgery (5000 x 3 IU vs 5000 x 2 IU) for 15 days (publication not found, only clin registration – Iranian web site), n=700? (unpublished data)</p> <p><u>Imberti 2014b</u>: Prophylaxis of Venous Thromboembolism with Low Molecular Weight Heparin in Bariatric Surgery: a Prospective, Randomised Pilot Study Evaluating Two Doses of Parnaparin (BAFLUX Study): Parnaparin 4250 vs 6400 / od, 7-11 days n=258</p> <p><u>Kalfarentzos 2001</u>; Prophylaxis of Venous Thromboembolism Using Two Different Doses of Low-Molecular-Weight Heparin (Nadroparin) in Bariatric Surgery: nadroparin 5700 IU vs 9500 IU od until discharge, n=60</p> <p><u>Steib 2016</u>: Once versus twice daily injection of enoxaparin for thromboprophylaxis in bariatric surgery: effects on antifactor Xa activity and procoagulant microparticles: enoxaparin treatment (4000, 6000, or 2 x 4000 IU, respectively, n=164</p> <p>Enoxa vs fondaparinux</p> <p><u>Steel 2015</u>: The EFFORT trial, preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: 40mg enoxaparin twice daily or 5mg fondaparinux sodium once daily. n=198</p> <p>Starting pre vs postop</p> <p><u>Abdelsalam 2021</u>: enoxaparin 1 mg/kg x 1 (max 120 mg), one group started 12 h preop, the other postop. 15 days, n=100 (duplex)</p> | <p><u>Higher-dose heparin</u> may result in little or no difference in the risk of VTE (RR 0.55, 95% CI 0.05 to 5.99; 4 studies, 597 participants) major bleeding (RR 1.19, 95% CI 0.48 to 2.96; I² = 8%; 4 studies, 597 participants; low-certainty) in people undergoing bariatric surgery.</p> <p><u>Enoxa vs fonda</u>: little or no difference in the risk of VTE (RR 0.83, 95% CI 0.19 to 3.61; 1 study, 175 participants) or DVT (RR 0.83, 95% CI 0.19 to 3.61; 1 study, 175 participants).</p> <p><u>Heparin started before vs after</u> Heparin 12 hours before surgery versus after surgery may result in little or no difference in the risk of VTE (RR 0.11, 95% CI 0.01 to 2.01; 1 study, 100 participants) or DVT (RR 0.11, 95% CI 0.01 to 2.01; 1 study, 100 participants). The evidence on major bleeding, all-cause mortality and VTE-related mortality is uncertain (effect not estimable or very low-certainty evidence).</p> <p><u>Chemical+mechanical prophylaxis vs only mechanical</u>: Combining may reduce VTE events (RR 0.05, 95% CI 0.00 to 0.89; NNT = 9; 1 study, 150 participants; low-certainty).</p> |

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| | <p>Chemo + mechano vs Mechano alone <u>Ahmad 2021</u>: Combined mechanical and pharmacological prophylaxis versus mechanical prophylaxis alone. 40 mg x 1 enoxaparin 12 h before then daily for 2 weeks + mechanical, the other group on mechanical prophylaxis, n=150, Note – silent DVTS</p> | <p>Unable to assess the effect of this intervention on major bleeding or mortality (effect not estimable), or on PE or adverse events (not measured)</p> <p>Conclusion: The certainty of the evidence is limited by small sample sizes, few or no events, and risk of bias concerns.</p> |
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DOACs vs “conventional anticoagulants” long term treatment (≥ 3 months) on broad patient population – not only obesity

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| <p>Li, Cochrane Database of Systematic Reviews 2023²⁵²</p> | <p>Large quality RCTs comparing DOACs vs conventional anticoagulants (VKAs, DTI, Anti-Xa DOACs, UFH, LMWHs and fondaparinux) in the treatment of <u>PE</u> (≥ 3 months)</p> | <p>Probably little or no difference between DOACs and conventional anticoagulation in the prevention of recurrent PE, recurrent VTE, DVT, all-cause mortality, and major bleeding</p> |
| <p>Wang, Cochrane Database of Systematic Reviews 2023²⁵³</p> | <p>Large quality RCTs comparing DOACs vs conventional anticoagulants (VKAs, DTI, anti-Xa DOACs, UFH, LMWH and fondaparinux) in the treatment of <u>DVT</u> (≥ 3 months)</p> | <p>When treating people with a DVT, current evidence shows there is probably a similar effect between DOACs and conventional anticoagulants in the prevention of recurrent VTE, DVT, and death. Direct oral anticoagulants reduced major bleeding compared to conventional anticoagulation</p> |

Abbreviations: ACS: acute coronary syndromes; AFib: atrial fibrillation; CI: confidential interval; DTI: direct thrombin inhibitors; DVT: deep veing thrombosis; IU: international Unit; VTE: venous thromboembolism; DOAC: direct Oral Anticoagulant; NNH: number needed to harm; NNT: number needed to treat; VKA: vitamin K antagonists; PE: pulmonary embolism; RCTs: randomized clinical trials; RR: relative risk; UFH: unfractionated heparin; LMWH: low molecular weight heparin;.

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Table 5 Effect of body size and bariatric surgery on pharmacodynamics and/or clinical outcomes of acetylsalicylic acid

| Reference | Total population and obese individuals | ASA regimen | Primary Endpoints | Results | Limitations |
|--------------------------------------|---|---|---|---|---|
| Rothwell et al., 2018 ¹⁵³ | Meta-analysis of RCTs of ASA in primary and secondary prevention, n=117,279 | Higher doses (300, 325 or ≥500 mg) vs lower doses (75–100 mg) or placebo in primary prevention RCTs | SVE: stroke [ischaemic, intracerebral, or subarachnoid haemorrhage], myocardial infarction, vascular death, other coronary death, and other major ischaemic vascular events, excluding unstable angina and transient ischaemic attack | Low-dose ASA: < 70 kg: HR for SVE 0.75 [0.65–0.85]; ≥70 kg: HR 0.95 [0.86–1.04]; 1.09 [0.93–1.29] Higher doses: 325 mg ASA reduced SVE in participants weighing 70 kg or more (HR 0.83 [95% CI 0.70–0.98], p=0.028) and 500 mg ASA reduced SVE (0.55 [0.28–1.09], p=0.086) and SVE or death (0.52 [0.30–0.89], p=0.017) in 90 kg or more | Post-hoc analyses Some analyses were based on small numbers, and trials were not set up to compare ASA effectiveness for people of different weights |
| ASCEND trial, 2018 ¹⁵⁸ | 15,480 with type 2 diabetes and no known SVE. Median follow-up: 7.4 years | ASA 100 mg/day, or placebo. ASA mean BMI 30.8±6.2 Placebo mean BMI 30.6±6.3 Pre-specified analyses for BMI < 25; 25–30; >30 and BW below or above | SVE: MI, stroke or TIA, or vascular death, excluding any confirmed intracranial hemorrhage Safety: major bleeding defined as BARC2-5 type | SVE: placebo 9.6% (n=743) ASA: 8.5% (n=658), HR: 0.88 (95% CI, 0.79–0.97) P=0.01 BMI subgroups: < 25, HR 1.02 (0.81–1.28) 25–30 HR 0.97 (0.83–1.13) >30 HR 0.76 (0.66–0.88) P=0.01 BW subgroups < 70: 1.17 (0.90–1.52) ≥ 70 0.83 (0.75–0.92) p=0.02 | ASA significantly reduced SVE in primary prevention, with a benefit higher than the bleeding risk (NNT/NNH 0.81). Trend toward a superior benefit in obese class 1 patients with no increase in major bleeding, with a NNT of 35 and a NNT/NNH ratio of 0.4. |

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| | | 70 kg | | <p>BARC 2,3 and 5 bleeding Control: 3.2% (n=245) ASA: 4.1% (n=314) RR 1.29; 95% CI, 1.09-1.52; P= 0.003 No heterogeneity across BMI or BW categories for major bleeding</p> | |
| Petrucci et al., 2019 ¹⁶² | Proof of concept, intervention study including 16 healthy and morbid obese (mean BMI 39.2±5.1 kg/m ²) subjects | ASA 100-mg od for 3-4 weeks | <p>Assess whether/how BW and BMI affect the PD of ASA, as assessed by serum thromboxane B₂ measurements.</p> <p>In silico model and simulations for ASA dosing in class ≥2 obese individuals</p> | ASA PD assessed according to serum thromboxane B ₂ measured 24 hours after the last ASA intake (trough level) | <p>Class ≥2 obesity associated with reduced ASA PD and platelet inhibition. Once daily low-dose ASA was insufficient to adequately inhibit platelet activation at BMI >35 and BW >120 kg. Log relationship between BW or BMI were Log correlated with a poor ASA PD.</p> <p>The <i>in-silico</i> model predicted that for class ≥2 obesity a dose of 200 mg od or 100 mg bid would be needed for re-establishing an adequate response</p> |
| Finneran et al., 2019 ¹⁶⁸ | 1002 pregnant women with pre-eclampsia | Double-blind, randomized, placebo-controlled trial comparison of 60 mg ASA od versus placebo | PD assessed by maternal serum TXB ₂ levels at 3 time points: randomization (13-26 weeks' gestation), second trimester (at least 2 weeks after | Among stratified BMI low-dose ASA groups, women with class 3 obesity had the lowest odds of undetectable TXB ₂ levels in the second trimester (adjusted odds ratio [aOR], 0.33; 95% confidence interval | The 60 mg dosing is rarely used as compared to other regimens in the low-dose range (75, 81,100 mg). High-risk morbid obese women receiving low-dose ASA for the prevention of |

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| | | | randomization and 24-28 weeks' gestation), and third trimester (34-38 weeks' gestation | [CI], 0.15-0.72) and third trimester (aOR, 0.30; 95% CI, 0.11-0.78) as well as at both time points (aOR, 0.09; 95% CI, 0.02-0.41) | preeclampsia may need higher ASA dosing or frequency. |
| Furtado et al., 2019 ¹⁶⁴ | 438 patients on DAPT due to ACS | DAPT including standard low-dose ASA once-daily, Mean BW 75.6 ± 15.8 kg, mean BMI 27.3 ± 4.9 kg/m ² | Assessment of serum TXB2 and platelet function testing across different quartiles of BW and BMI | The highest body size quartile (either BMI or BW) associated with impaired PD. | The highest quartile included all obesity classes, thus no data are available in this study in each obesity class |
| Woods et al., 2020 ²⁵⁴ | Post-hoc analysis of the ASPREE trial including 19,114, low-risk, healthy elderly subjects in primary prevention Elderly participants weighing <70 kg (n=6,428) and ≥70 kg (N=10,749) FU: 4.7 years | Randomization: ASA 100 mg/day enteric-coated or placebo Follow-up 4.7 years Mean BMI in the whole trial population 28.1 ± 4.8. | Primary endpoint: disability-free survival MACE: non-prespecified, secondary endpoints, defined as coronary heart disease fatalities, other coronary, rapid cardiac, sudden cardiac but excluding cardiac failure deaths, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke Whether body size (BMI < 25 or BW < 70kg) modulated the efficacy of ASA vs. placebo. 12,633/19,114 individuals ≥ 70 kg | Analyses by sub-groups based on body size metrics were consistent with the overall trial | The effect of low-dose ASA on CVD events was not contingent on BW or other measures of body size in the older participants in ASPREE. The risk of major bleeding with ASA was not attenuated in heavier individuals. Limitations: MACE were not a primary endpoint, Class ≥2 subjects were likely not or minimally represented; non pre-specified, post-hoc analysis |

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|-----------------------------------|---|--|---|--|--|
| Lee et al., 2021 ¹⁶¹ | 316 patients on dual antiplatelet therapy following angioplasty and stenting. | Patients with class 1 obesity and CAD | Thromboxane generation and platelet reactivity to arachidonic acid | The results of all tests did not differ significantly between patients without and with a body weight ≥ 70 kg | The study suggests no changes in ASA PD in class 1 obesity |
| Halbur et al., 2021 | 2403 patients who underwent total hip or knee arthroplasty at one institution, on for VTE prophylaxis with low-dose ASA | Retrospective observational study. In the BW-based cohort, patients weighing ≥ 120 kg received 325mg ASA bid, those < 120 kg received 81 mg bid for 4 weeks. Control cohort (n=1156): patients received 81 mg ASA bid irrespective of BW. | VTE and gastrointestinal bleeding events were identified through chart review at 42 days and 6 months postoperatively. Gastrointestinal bleeding at the same timepoints | The BW-based cohort had a significantly lesser incidence of VTE at 42 days (P = .03, relative risk [RR] 0.31, 95% CI 0.12-0.82) and 6 months (P = .03, RR 0.38, 95%CI 0.18-0.80). No difference in gastrointestinal bleeding between the cohorts at 42 days (P = .69) or 6 months (P = .92). | Non randomized design. Suggestion of need to factor patient BW when determining postoperative VTE prophylaxis with low-dose ASA. |
| Hasan et al., 2021 ²⁵⁵ | Observational study 420 who underwent elective knee replacement, 277 obese (BMI ≥ 30 kg/m ²) | ASA 75 mg daily (increased to 150 mg daily) vs apixaban 2.5 mg bid | Incidence of postoperative VTE, leaking wounds during the hospital stay, and 30-day any readmission | ASA was as effective as apixaban in preventing VTE and readmission, independently of body size | Observational study. |
| Jones et al., | 15,076 patients with established | Randomized comparison 81 | Primary effectiveness outcome: composite of | No difference of efficacy among the two regimens (HR | Class ≥ 2 obesity under-represented (75 th percentile |

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| 2021 ¹⁵⁵ | CVD and indication for secondary prevention with ASA | mg or 325 mg of ASA per day. Median BW 90 kg | death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke, assessed in a time-to-event analysis. Primary safety outcome was hospitalization for major bleeding. | 1.02; 95% confidence interval [CI], 0.91-1.14); no difference in safety (HR 1.18; 95% CI, 0.79 to 1.77). Subgroup analysis according to BW threshold of 70 kg did not show any heterogeneity of results. | of BW was 103 kg) The subgroup analysis according to BW of 70 kg was not pre-specified |
| Tang et al., 2021 ²⁵⁶ | Retrospective review of 1,578 knee or hip arthroplasties including different BMI categories: normal (n=335), overweight (n=511), class 1 (n=408), class 2 (n=232), class 3 (n=92) | Efficacy and safety of ASA 81 or 325 mg/day prescribed is safe and effective in obese versus normal-weight patients undergoing arthroplasty | Primary endpoint: 90-day postoperative VTE Other endpoints: bleeding, wound complications, deep infections, and mortality | No difference in the incidence of VTE and other complications across different BMI categories | Observational study, ASA doses non-randomly assigned. |
| Puccini et al., 2023 ¹⁸³ | Cross-sectional study Patients with chronic CAD and a normal BMI (BMI 18.5–25 kg/m ² , n=23) or obese (BMI ≥ 25 kg/m ² , n=41) | ASA 100 mg/day and clopidogrel 75 mg/day. | Evaluate the platelet reactivity in overweight and obese patients and chronic CAD treated with dual antiplatelet therapy | Assessed by impedance aggregometry in patients with CCS receiving DAPT (ASA plus clopidogrel). | Very small observational study. The clinical significance of platelet aggregation is currently unknown. |
| Portela et al., | 24,770 patients post RYGB, 1911 | Meta-analysis of observational | Incidence of marginal ulceration post RYGB | Patients on low-dose ASA did not have an increased risk | Low-dose ASA can be safely resumed post BS. |

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| 2023 ²⁵⁷ | with ASA use and 22,859 without. | and RCT studies to assess the risk of post-surgery margin ulcer associated with ASA use | BS | of marginal ulcer (HR 0.56, .37-.86), while those on high dose did (HR 1.90, 1.41-2.58) |
|---------------------|----------------------------------|---|----|---|

Abbreviations: AA: arachidonic acid; ASA: acetylsalicylic acid; ADP: adenosine diphosphate. BMI: body mass index. BS: bariatric surgery; BW: body weight (kg); CAD: coronary artery disease; CCS: chronic coronary syndromes; CV cardiovascular. CVD: cardiovascular disease. DAPT: dual antiplatelet therapy; EC: enteric-coated. FU: follow-up. MACE: Major adverse CV events. HR: hazard ratio; MI: myocardial infarction. PD: pharmacodynamics; PK: pharmacokinetics; RCTs: randomized clinical trials. RYGB: Roux-en-Y gastric bypass surgery; RR: relative risk; sTXB₂: serum thromboxane B₂; SVE: serious vascular events; VTE: Venous thromboembolism; ASCEND: A Study of Cardiovascular Events in Diabetes. ASPREE: Aspirin in Reducing Events in the Elderly

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