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REVIEW

Update on antithrombotic therapy and body mass: a clinical consensus statement of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and the European Society of Cardiology Working Group on Thrombosis

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Obesity and underweight are a growing health problem worldwide and a challenge for clinicians concerning antithrombotic therapy, due to the associated risks of thrombosis and/or bleeding. This clinical consensus statement updates a previous one published in 2018, by reviewing the most recent evidence on antithrombotic drugs based on body size categories according to the World Health Organization classification. The document focuses mostly on individuals at the extremes of body weight, i.e. underweight and moderate-to-morbid obesity, who require antithrombotic drugs, according to current guidelines, for the treatment or prevention of cardiovascular diseases or venous thromboembolism. Managing antithrombotic therapy or thromboprophylaxis in these individuals is challenging, due to profound changes

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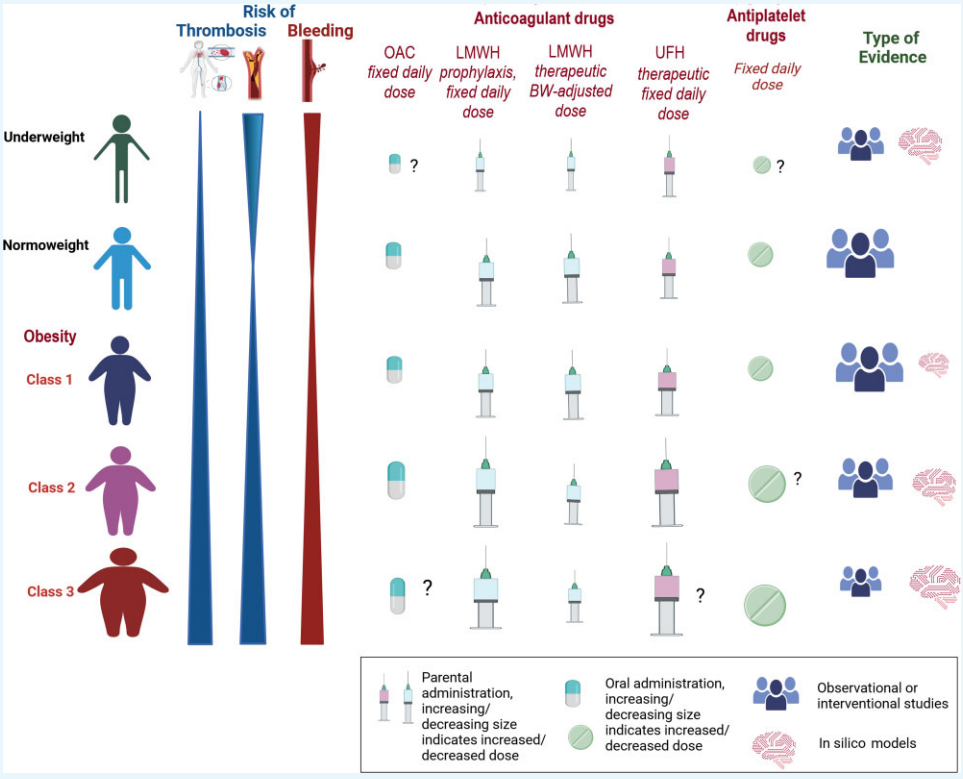
in body composition, metabolism and organ function, and altered drug pharmacokinetics and pharmacodynamics, as well as weak or no evidence from clinical trials. The document also includes artificial intelligence simulations derived from *in silico* pharmacokinetic/pharmacodynamic models, which can mimic the pharmacokinetic changes and help identify optimal regimens of antithrombotic drugs for severely underweight or severely obese individuals. Further, bariatric surgery in morbidly obese subjects is frequently performed worldwide. Bariatric surgery causes specific and additional changes in metabolism and gastrointestinal anatomy, depending on the type of the procedure, which can also impact the pharmacokinetics of antithrombotic drugs and their management. Based on existing literature, the document provides consensus statements on optimizing antithrombotic drug management for underweight and all classes of obese patients, while highlighting the current gaps in knowledge in these complex clinical settings, which require personalized medicine and precision pharmacology.

Graphical Abstract



Risks of thrombosis and bleeding, antithrombotic drug management, and supporting type of evidence across body size categories. From left to right: a causal relationship between obesity and deep vein thrombosis (DVT) risk has been suggested by Mendelian randomization studies. Generally, DVT risk linearly increases from underweight to the highest body mass index classes. Despite the low risk of underweight individuals, underweight seems to have a worse prognosis once venous thrombosis has occurred. The risk of arterial thrombosis increases from normoweight to severe obesity, while the risk associated with being underweight remains less clear, possibly mimicking a U-shaped relationship. A U-shaped relationship seems to describe the risk of major bleeding associated with body size. However, the anatomical site and type of bleeding, underlying risk factors, and prognosis differ at the two extremes. Optimizing the dosing of antithrombotic drugs both in underweight and class ≥2 obese individuals is supported by pharmacokinetic/pharmacodynamic (PK/PD) studies and data from post hoc analyses of randomized studies, observational, and registry data as well as by artificial intelligence simulations of *in silico* PK/PD models generated by population and randomized clinical trial experimental measurements. In underweight individuals, most evidence indicates better safety of reducing the daily doses of standard, fixed-dose antithrombotic drugs, while increasing the fixed dose is suggested for those in class ≥2 obesity. For body weight-adjusted antithrombotic drugs, individuals with higher classes of obesity may be overdosed due to a major imbalance between lean and fat mass that has a major impact on drug PK and bioavailability. On the other hand, if capping is us-//-ed, this may result in underdosing at the upper extreme of body size. Further details are reported in the *Central Tables 1* and *2*. LMWH, low-molecular-weight heparin; OAC, oral anticoagulation; UFH, unfractionated heparin.

Keywords Obesity • Obesity classes • Underweight • BMI • Antithrombotic drugs • Antiplatelet drugs • Cardiovascular diseases • Cardiovascular diseases • Drug variability • Artificial intelligence drug modelling

Abbreviations

ABCD-GENE	Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping
ACS	acute coronary syndrome
ACT	activated clotting time
ADAPTABLE	Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness
AF	atrial fibrillation
AI	artificial intelligence
AM	active metabolite
aPTT	activated partial thromboplastin time
ASCEND	A Study of Cardiovascular Events in Diabetes
AUC	area under the curve
BARC	Bleeding Academy Research Consortium
b.i.d.	bis in die (twice daily)
BMI	body mass index
BS	bariatric surgery
BW	body weight
CAD	coronary artery disease
CCS	chronic coronary syndrome
CHANCE	Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events
CPB	cardiopulmonary bypass
CYP	cytochrome P-450
CVD	cardiovascular diseases
DAP	dual antithrombotic therapy
DAPT	dual antiplatelet therapy
DDI	drug–drug interaction
DOAC	direct oral anticoagulants
DPI	dual pathway inhibition
DVT	deep vein thrombosis
ELDERLY-ACS	Early Aggressive Versus Initially Conservative Therapy in Elderly Patients With Non-ST-Elevation Acute Coronary Syndrome
ENGAGE-AF TIMI48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction
ERAS	enhanced recovery after surgery
GLP-1RA	glucagon-like peptide-1 receptor agonist
GPI	glycoprotein IIb/IIIa inhibitor
HOST-EXAM	Harmonizing Optimal Strategy for Treatment of Coronary Artery Disease EXtended Antiplatelet Monotherapy
HR	hazard ratio
IBW	ideal body weight
ICH	intracerebral haemorrhage
INR	international normalized ratio
ISAR-REACT	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
IV	intravenous
LBW	lean body weight
LMWH	low-molecular-weight heparin
MU	marginal ulceration
NSTEMI	non-ST-elevation myocardial infarction
OAC	oral anticoagulants
od	once daily
OR	odds ratio
PAD	peripheral artery disease
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PD	pharmacodynamic
PE	pulmonary embolism
PK	pharmacokinetic
PPI	proton pump inhibitors
PRU	platelet reactivity unit
RAM	risk assessment model
RCT	randomized clinical trial
RECOVERY	Randomized Evaluation of COVID-19 Therapy
RYGB	Roux-en-Y gastric bypass
SAPT	single antiplatelet therapy
SG	sleeve gastrectomy
STEMI	ST-elevation myocardial infarction
TAT	triple antithrombotic therapy
TAVI	transcatheter aortic valve implantation
TICO	Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome
TROPICAL-ACS	Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes
TTR	time in therapeutic range
UFH	unfractionated heparin
Vd	volume of distribution
VKA	vitamin K antagonist
VTE	venous thromboembolism
WHO	World Health Organization

Introduction

The obesity epidemics continue to rise worldwide (globesity),[1,2] favoured by 'obesogenic' environments. In 2019, the prevalence of obesity in Europe ranged between 11% (Italy) and 26% (Ireland) for women, and between 11% (Romania) and 30% (Malta) for men,[3] with high obesity-related health care costs and loss in productivity (~€70 billion in 2016).[4] The COVID-19 pandemic has emphasized the globesity burden,[5] while fighting obesity might increase the prevalence of underweight children and adolescents, the so-called 'dual burden household'.[6] Particularly, severe obesity (*Table 1*) is rising in Europe and North America.[7,8] Notably, severely obese individuals aged 50–75 years have an ~30% reduction of life in good health and half the years without chronic disease compared with non-obese individuals.[9] Conversely, the prevalence of underweight adult men and women has decreased, reaching <2% in the USA.[10] In Asia, the double burden of under- and overweight is shifting toward obesity.[11]

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

Despite the health burden and costs, the extremes of body size remain under-represented or excluded from cardiovascular randomized clinical trials (RCTs)[18] and drug development processes.[19] As both obesity and underweight differently affect the risk of thrombosis, bleeding, and antithrombotic drug pharmacology,[20–22] the European Society of Cardiology (ESC) Working Groups on Cardiovascular Pharmacotherapy and on Thrombosis assembled a task force to update the 2018 scientific document on antithrombotic drugs at the extremes of body mass.[23] As in the previous document, we focus on patients with a clear indication for antithrombotic treatment or prophylaxis, especially with severe obesity and underweight, because of their complexity and limited evidence. We also update the pharmacology

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

Classification	Body mass index (kg/m^2)[a]	Body weight (kg) or ideal body weight[b]
Underweight	<18.5 Subcategories: Mild thinness 17–18.49 Moderate thinness: 16–16.99 Severe thinness: <16	<60 kg or ≤56.2 kg[c]
Normal weight	18.5–24.99 Asian population[d] 18.5–22.9	≥60 up to 70 kg[e] or >56.3 up to 76.6 kg[c]
Overweight (pre-obesity)	25–29.99 Asian population >23 to 24.99	>70 up to 100 kg[e] or 76.7 up to 92.0 kg[c]
Obesity (overall)	≥30 Asian population >25 to 27.5	>100[e] or ≥92.1 kg[c] or >20% than the ideal body weight[b]
Class 1	30–34.99 Asian population >27.5 to 32.5	
Class 2 (moderate obesity)	35–39.99 Asian population >32.5 to 37.5	>100% than the ideal body weight[b]
Class 3 (severe or morbid obesity)	≥40 to 49.99 Asian population >37.5[f]	≥150[e] or ≥122.9 kg[c]
Class 4[d] (superobesity)	≥50 to 59.99	>225% than the ideal body weight
Class 5[g] (super-super or extreme obesity)	≥60	

[a] According to the WHO classification for adults (≥20 years, female and male subjects; http://www.who.int/topics/obesity/en/) unless otherwise indicated.
[b] Ideal body weight according to modified Devine's formula: men: *51.65 kg + 1.85 kg/inch of height* > 5 feet; women: *48.67 kg + 1.65 kg/inch of height* > 5 feet.[12]
[c] Centers for Disease Control and Prevention for adults (both male and female subjects) with a height of 5 feet 9 inches (https://www.cdc.gov/nchs/fastats/body-measurements.htm).
[d] Mason *et al.*[13]
[e] Thresholds often used to define underweight in RCT or clinical studies for both female and male subjects.
[f] In Asian populations, additional cut-off points have been added to reflect the risk of cardiometabolic disease associated with overweight/obesity in this population.
[g] Nguyen *et al.*[14]

of antithrombotic drugs following bariatric surgery (BS),[24] and include data from artificial intelligence (AI) *in silico* models and simulations of antithrombotic drug regimens at the extremes of body size.[25]

Methodology and definitions

The authors, selected on their complementary expertise (Supplementary material), performed a systematic review of the literature (Supplementary material online, *Table S1*), evaluated evidence according to the current ESC scientific document policy (*Figure 1*),[26] and reached consensus through Delphi methodology on three rounds.[27]

Body size classes are defined according to the World Health Organization (WHO) based on body mass index (BMI), expressed as kilograms per square metre (kg/m^2), and/or total body weight (BW) expressed in kilograms (*Table 1*).[28] While we acknowledge the limitations of BMI metrics vs. adipose tissue imaging, waist–hip ratio or waist circumference, nevertheless, most of the evidence on antithrombotic drugs refers to BMI. We will address underweight but not frailty, which is addressed in another ESC scientific document.[29]

Changes in drug disposition

Obesity, especially class ≥2, can modify drug pharmacokinetics (PK), resulting in inadequate drug dosing for both fixed-dose and BW-adjusted medications (*Figure 2*). Since gastrointestinal transit is accelerated and gastric emptying shortened, the absorption and bioavailability of some oral drugs can be reduced.[30,31] The drug's volume of distribution (Vd) can be affected by the reduced lean-to-fat ratio, thereby increasing for lipophilic drugs (Graphical Abstract). For hydrophilic drugs, like low-molecular-weight heparin (LMWH), Vd nonlinearly increases with BW. Thus, BW-adjusted dosing may result in overdosing in severely obese individuals (*Figure 2*). In obese subjects, drug's lipophilic characteristics further impact PK, and liver biotransformation, through some cytochrome P450 enzymes, can be reduced (*Figure 2*).[32]

Bariatric surgery for long-term correction of morbid obesity is increasing again after COVID.[38] BS comprises restrictive [e.g. sleeve gastrectomy (SG) and adjustable gastric banding] and malabsorptive (e.g. Roux-en-Y gastric bypass-RYGB and duodenal switch) interventions that trigger nutritional deficiencies and modify drug absorption, gastrointestinal blood flow, pH, and transit time (*Figures 2* and *3*).[33,39] Since absorption of most antithrombotic drugs occurs in the proximal

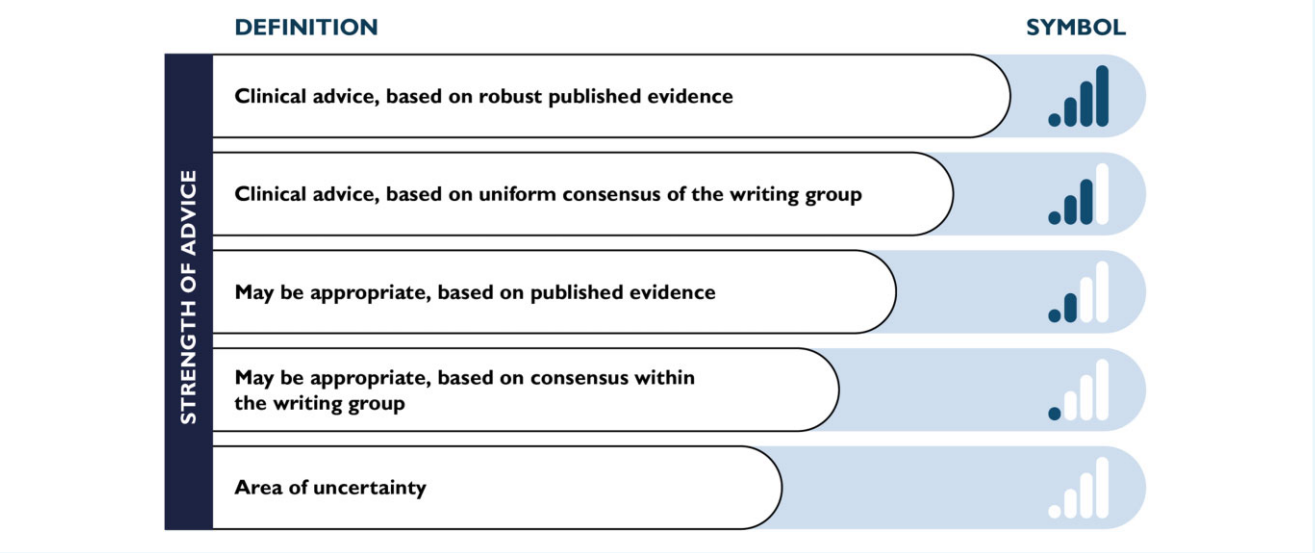


Figure 1 Scale and symbols representing the strength of advice statements, based on evidence and consensus of the writing group, as recommended for the European Society of Cardiology scientific documents.

small intestine and, to a lesser extent, in the distal part of the stomach, the type of BS can significantly affect antithrombotic drug PK.[33]

Consensus statement

Extremes of BWs or BMIs as well as BS can variably affect the PK of lipophilic and hydrophilic drugs.

Arterial and venous thrombosis

Obesity is a risk factor for atherothrombosis[40,41] and venous thromboembolism (VTE)[42,43] (Graphical Abstract). A Swedish population-based study of men born between 1945 and 1961, followed for 40 years, showed that for each standard deviation (SD) increase in BMI during childhood and puberty, there was a linear increase in VTE[42] and arterial thrombosis[41] in adulthood. A four-fold increase in coronary heart disease for each 5 kg/m^2 BMI increase above 25 has been reported.[21] In a population study, BW at 20 years and midlife was directly associated with weight gain through life and subclinical coronary atherosclerosis.[41]

The impact of BMI on peripheral arterial disease (PAD) is less clear. Obese patients with PAD show accelerated functional decline, while weight loss improves walking distance.[40] In contrast, patients with low BMI and PAD show an increased risk of cardiovascular and all-cause mortality, limb ischaemia, and major cardiovascular events.[40]

Increasing BMI is associated with an increased risk of cardioembolic and non-cardioembolic stroke,[44] likely secondary to the unhealthy metabolic status of severely obese patients.[45,46] Class 3 obesity is particularly associated with ischaemic stroke[45] compared with lower obesity classes or normal BMI, while in-hospital post-stroke mortality was lower in class 1–2 obese patients.[47] Notably, in the Swedish twin registry, an obesogenic environment increased cardiovascular risk, especially in individuals without obesity-predisposing genetic variants.[48]

Limited data suggest that underweight (BMI <18) individuals have increased atherothrombosis[22] and a 2.3-fold increased risk of cardiovascular disease (CVD) as compared with normal-weight, age-matched subjects.[20]

Mendelian randomization studies suggest causality of obesity on VTE[49,50]: for each SD increase in genetically predicted BMI, the odds ratio (OR) of VTE was 1.59 [95% confidence interval (CI): 1.20–1.93].[49] In the UK Biobank, each kg/m^2 BMI increase was associated with a 10% increase in VTE,[50] and a BMI >40 was associated with a three-fold increase in VTE [hazard ratio (HR) 3.4, 2.87–4.03] compared with normal weight.[51] A recent case–control study shows that individuals with obesity classes ≥2, aged >50 years, have a 6.2-fold increased risk of VTE compared with class 1 obesity or normal BW.[52] In a registry of children born between 1930 and 1989,[53] a BMI >90th percentile at 7 and 13 years was associated with a ∼1.5-fold increase in future VTE compared with lower BMIs.[53] In over 2 million women, pre-menopausal, class 3 obese women showed the highest VTE incidence vs. normal BMI, both antepartum (OR 2.9, 2.2–3.8) and postpartum (OR 3.6, 2.9–4.6), while underweight showed an opposite trend.[54]

Underweight individuals show a low risk of VTE[55] (Graphical Abstract), but higher all-cause mortality and bleeding post-VTE as compared with normal-weight subjects.[56] Medically ill, severely underweight patients (BMI 15) have a three-fold increase in VTE during 77-day follow-up vs. reference BMI (28), unlike class 1 to 3 obese subjects.[57]

Consensus statements

Obesity increases the risk of atherothrombosis.[41–43,48,53]

Mendelian randomization studies suggest causality of obesity on VTE.[49,50]

Higher obesity classes show the greatest VTE risk.[54,55]

Underweight is associated with a lower risk of VTE,[54,55] but with a higher rate of post-VTE complications, including mortality.[56,57]

Whether underweight increases the risk of atherothrombosis is uncertain.[22]

Thrombosis after surgery

A BMI <18 or >50 showed the highest VTE incidence after general surgery, with a U-shaped curve.[58,59] After orthopaedic surgery, patients with class ≥2 obesity showed a two-fold increase in pulmonary embolism (PE) vs. normoweight individuals.[60] In >5 million individuals undergoing major surgery, patients of all obesity classes had a higher risk of VTE, but not of bleeding, compared with normal weight.[61]

During 30 days post-BS in 600 000 morbidly obese subjects (~20% BMI >50), VTE occurred in 0.3% of patients after SG and 0.4% after RYGB.[62] In ~20 000 post-BS patients, VTE doubled in individuals with a pre-surgery BMI >50 compared with a BMI 35–50, regardless of age.[63] In >350 000 patients from a US registry, VTE was higher in individuals with a BMI >60 undergoing laparoscopic RYGB or SG (ORs 1.85, 1.40–2.44, and 1.62, 1.32–1.99, respectively) vs. a BMI of 35–50.[64] VTE increased after laparoscopic RYGB, but not SG, in patients with a BMI between 50 and 59 compared with a BMI between 35 and 49.9.[64] Moreover, BS lowers long-term thrombotic risk. In 566 individuals with an average BMI of 40 and previous MI undergoing BS (RYGB or SG), major adverse cardiovascular events (MACEs) were reduced by 56% during 8-year follow-up vs. controls.[65] Similarly, in a recent meta-analysis, long-term CVDs were reduced after all types of BS vs. non-BS-treated obese individuals.[66]

Consensus statements

Obesity classes ≥2 are associated with the highest risk of VTE following major general as well as bariatric surgeries.[63,64]

BS appears to lower long-term cardiovascular complications.[65,66]

	Underweight	Obesity (class ≥2)	Post-bariatric surgery
Absorption	↓ **gastrointestinal absorption** depending on the underlying causes/disorder (e.g. malabsorption, refeeding syndrome, mpaired gut wall function) **Variable s.c. or transdermal absorption**: prefer alternative routes	↑gastric emptying time, gastric pH, intestinal motility, gut wall permeability thus ↓ **time to C_{max}** Oral bioavailability may ↑ when BMI >40 mg/m^2 ↑s.c. adipose tissue but ↓ local blood flow, thus **slow transdermal, s.c. or i.m.** (too short needles) **absorption**	↑gastric pH and gastric emptying time, slower small intestinal transit: ↓ **time to C_{max}**, ↑T_{max} ↓ upper small intestine tract **Use of oral solutions** or opened capsules may be appropriate**
Distribution	**Body water: normal or ↓**, based on causes of underweight ↓ **adipose tissue and LBW** **Normal or ↑ lean/fat body mass ratio** depending on causes of underweight ↓ cardiac output ↓ **drug protein binding** (hypoalbuminemia) ↓ **Vd of lipophilic drugs, ↑ Cmax** **Normal or ↑ Vd of hydrophilic drugs** ↓ **albumin: ↑ free fraction** of acidic drugs (i.e. warfarin) ↑ α1 acid glycoprotein	↓**lean/fat body mass ratio** ↑ blood volume, cardiac output and organ (splanchnic, hepatic, renal) blood flow ↓ **blood flow in fat tissue, becoming a slowly-emptying store for lipophilic drugs** ↑ Vd in LBT, ↓ C_{max} for hydrophilic drugs, no change in half-life (dose based on LBW) ↑↑ Vd into fat tissue and half-life (dose based on TBW) for lipophilic drugs: ↓ C_{max} Changes in Vd cannot be predicted only on lipophilicity ↑ **acute phase proteins, α1 acid glycoprotein, FFA, plasma lipids** ↓ **free fraction of drugs (i.e. warfarin)**	↓ cardiac output (20%) ↓ **Vd of lipophilic drugs as compared to pre-surgery, due to the decrease in fat mass** ↓ **half-life of drugs that accumulate in the adipose tissue, as compared to pre-BS** Not described
Metabolism	Liver function variable depending on the underlying causes of underweight	↑**liver size, hepatic blood flow and first-pass effect of drugs** with high and moderate hepatic extraction **If NAFLD/NASH:** ↓ hepatic blood flow, metabolizing enzymes and transporters ↓ biliary clearance (bile stasis or duct disease)	↓ liver size (20%) Possible ↓ first-pass metabolism RYGB: delayed inlet of bile and pancreatic secretions; **possible ↓ absorption of lipophilic, low soluble drugs**
Excretion	↓ metabolic rate: ↑ **parent compound levels, but ↓ active metabolites** ↑ **CYP2E1, CYP3A4, UGT and SULT activities** No changes in 1A2 and 2C9, 2C19, P-gp	↓**CYP3A4, 2C19, 2B6 and UGT (phase II) activities** No change: CYP1 A2, 2C9, 2D6 and 2E1 activities normal or ↑ P-gp **Differences reported for hepatic vs. intestinal CYP450s** ↓ **Biotransformation reduced if NAFLD**	**Restoration of CYP3A4, 2C19, 2E1, and UDPGT activities versus pre-surgery** **2C9 activity**, No change in P-gp
	↓ **or normal GFR** based on causes of underweight Serum creatinine overestimates kidney function	↑ kidney size and renal blood flow, ↑**GFR at initial phases** ↓ **GFR (high intra-glomerular pressure and comorbidities) later.** Uncertain impact on renal drug clearance	Limited fluid intake after BS can impair renal function and ↓ drug excretion Normalization of GFR at 1 year

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 comorbidities, reduced renal function, and changes in plasma proteins. Severe obesity is associated with relevant changes in the gastrointestinal tract, body size composition (fat vs. lean mass ratio and plasma proteins), kidney, and liver functions, including the activity of the cytochrome P450 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 pharmacokinetics. Data post-bariatric surgery refer mainly to Roux-en-Y gastric bypass surgery. **Oral liquid formulations should not contain non-absorbable sugars due to dumping syndrome risk; open capsules if allowed according to the summary of product characteristics. Based on Angeles *et al.*,[33] Krogstad *et al.*,[34] Kvitne *et al.*,[35,36] and Sandvik *et al.*[37] BMI, body mass index; Cmax, peak plasma concentrations; CYP, cytochrome P450; FFA, free fatty acids; GFR, glomerular filtration rate; LBT, lean body tissue; LBW, lean body weight; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; P-gp, P-glycoprotein; s.c., subcutaneous; t1/2, elimination half-life; TBW, total body weight; Tmax, time to reach Cmax; UDPGT, uridine diphosphate glycosyltransferase enzymes; Vd, volume of distribution.

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**

Figure 3 Relevant steps in managing morbidly obese individuals who have one or more ongoing indication(s) for antithrombotic drugs and undergo bariatric surgery and some relevant points to be checked and considered before and immediately after bariatric surgery and at long-term afterwards, providing that the indication for one or more antithrombotic drug (both for treatment and prophylaxis) persists. BMI, body mass index; BW, body weight; (D)OAC, (direct) oral anticoagulant; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonists.

Bleeding

Intracerebral haemorrhage (ICH) seems to differ at BMI extremes. Deep ICH/microbleeds seem linked with obesity, partly for associated hypertension, and with underweight[67,68] with a U-shaped relationship (Graphical Abstract). Lobar ICH is associated with low BW, while a BMI ≥25 was reported to protect against haemorrhagic transformation of ischaemic stroke and was associated with better outcomes in Asians.[68]

A BMI >30 was associated with a worse course after non-variceal upper gastrointestinal bleeding, a significant increase in endoscopic interventions and resource utilization compared with non-obese subjects, but mortality was similar.[69]

Bleeding after invasive procedures

After coronary artery bypass graft surgery (CABG), bleeding is inversely associated with BMI from underweight to a BMI >40.[70] Consistently, severe obesity (BMI ≥40) was associated with reduced post-operative bleeding in 12 330 post-CABG patients,[70] while lower BMIs required more blood and cryoprecipitate transfusions.[71] In >95 000 post-CABG patients, bleeding significantly contributed to peri-operative mortality and early post-operative morbidity only in the low-weight group.[72] Despite a reduction in bleeding at higher BMIs, higher long-term mortality was associated with both underweight and severe obesity post-percutaneous coronary intervention (post-PCI).[73]

Transradial access for coronary angiography and PCI is associated with fewer bleeding and access site complications, including in those with extreme BMIs (i.e. <18.5 and ≥40).[74] In transcatheter aortic valve implantation (TAVI), there is an L-shaped relation with BMI, and overweight class 1 patients show the lowest mortality and complication rates,[75] with no additional protective effects for higher obesity classes.[76] However, in observational studies and TAVI registries, severe obesity is ~15%, thus under-represented.[77,78] Whether transcarotid is safer than transfemoral access across all obesity classes is unknown.[79,80] A recent registry suggests lower 5-year mortality of surgical vs. TAVI aortic valve replacement in class 1–2 obese subjects.[81] However, this was not confirmed in RCTs including only obesity class 1.[82]

In predominantly elderly, TAVI patients, being underweight seems also a frailty discriminator, partly explaining worse outcomes and safety.[83,84] In 42 000 US patients, a BMI <19 showed a higher relative risk (RR) of 1.57 (1.27–1.95) of in-hospital blood transfusion post-TAVI, vs. normoweight.[85] Recent analyses suggest higher complications for a BMI <20,[86] while mortality appears comparable to other BMI classes.[75]

After BS, bleeding occurs in 0.8–5.8% of patients depending on the approach (endoscopic and open), type of BS, and follow-up duration. Early post-operative bleeding usually associates with staple-line leakage,[87] while later bleeding (>6 weeks post-BS) relates to marginal ulceration (MU) at the gastrojejunal anastomosis,[87] reported in 0.6–16% of patients post-RYGB, which worsens outcomes.[88] Proton pump inhibitors (PPIs) can prevent MU bleeding.[88]

Consensus statements

Most evidence indicates a U-shaped relationship between the extremes of BMI and unprovoked bleeding.[67,68]

Obesity may be associated with reduced nonaccess site bleeding after TAVI.[76,84,85,89]

A tight control of risk factors, e.g. blood pressure to prevent ICH, post-operative care, gastroprotection, and choice of access site (radial for PCI) are advised to reduce bleeding risk at the extremes of body size.[79,80,90]

Oral anticoagulants

Vitamin K antagonist

Obesity can affect the PK of warfarin, phenprocoumon and acenocoumarol (*Figure 2*). Retrospective studies showed that class 3 obese patients require a longer time to achieve therapeutic international normalized ratio (INR), and ∼20% higher weekly maintenance doses than normal-weight individuals.[91] In 10 167 post-VTE patients, BMI and time in therapeutic range (TTR) were linearly correlated, with the lowest TTR in patients with a BMI <25 or a BW <60 and the highest TTR in class 2–3 obesity[92] (Graphical Abstract and *Central Table 1*), which can also partly explain the 'obesity paradox' of better outcomes in vitamin K antagonist (VKA)-treated obese patients, although more VKA-specific pathways can be involved.[93]

Small studies on VKA-treated underweight patients indicate a shorter interval to therapeutic INR, a lower weekly maintenance dose,[94] and a poor TTR (mainly supratherapeutic INR).[92,95] Warfarin-treated, atrial fibrillation (AF) underweight patients had twice the risk of thrombotic, but not bleeding, outcomes.[92,95]

A meta-analysis including 160 morbidly obese patients on warfarin for VTE, prosthetic mechanical valve, or AF, who underwent BS, showed that weekly warfarin dose consistently drops in the first 3 months post-BS, then slowly increases and stabilizes within 1 year, but remains lower than pre-BS.[96] The fast reduction in the warfarin dose post-BS can depend on anatomical upper gastrointestinal, metabolic, and nutritional changes.[30,31] Following BS, gastrointestinal bleeding was reported in 17 out of 160 patients on warfarin, with no thrombotic events, emphasizing the risk of upper gastrointestinal bleeding and MU post-BS, exacerbated by warfarin, and the importance of gastroprotection (*Figure 3*).[88]

Prothrombin complex concentrate (PCC) dosing to reverse INR and VKA in case of major bleeding is usually BW-adjusted and capped at a fixed dose for BW ≥100 kg. Recent studies have questioned the efficacy of four-factor PCC capping,[97] but more studies are needed to assess safety and efficacy of the uncapped, BW-based dosing across the entire BW spectrum. Limited data suggest that the timing for VKA reversal (INR <2) with vitamin K is similar between normal BW and all obesity classes.[98]

Consensus statements

Underweight and obesity class ≥2 affect loading and maintenance doses for all VKAs. More frequent INR monitoring and dose adjustment are advised, during the starting and maintenance periods.[91,92,94,95,99]

Following BS, it is advised to resume VKA with a reduction in the weekly dose by ∼30% as compared with pre-surgery, to monitor INR frequently in the 12 months post-surgery and to use gastroprotection, preferably with a PPI.[30,31,88,96]

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

In class 1–2 obese individuals with major bleeding while on VKA, it is advised to administer four-factor PCC at BW-adjusted over fixed dosing, with prompt and frequent INR monitoring.[100,101]

Direct oral anticoagulants

In patients with AF, efficacy and effectiveness of DOACs appear comparable to VKA at the extremes of BMI. In AF patients participating in the major RCTs of DOACs vs. VKA, the median BMI was 28.3 (25.2–32.2) and class 3 obesity ranged between 4.3% to 5.5%; thus, the number of those patients and events in each trial was small.[95,102] A recent meta-analysis of the four major RCTs, totalling 89 494 patients with AF, reported that a combined endpoint of stroke, systemic embolism, death, and bleeding, i.e. the net clinical outcome, was lower with DOAC vs. warfarin (HR 0.91, 95% CI, 0.87–0.95) in the whole obese (BMI ≥30) subgroup.[102] However, this composite benefit was attenuated at the highest BMIs (e.g. class ≥3, P_{trend} 0.001) largely driven by a slight increase in major bleeding; thus, safety was weakened for AF, class 3 obese individuals on DOACs as compared with VKA.[102] Another recent meta-analysis on 18 studies (16 observational), totalling 287 125 AF patients, showed a more favourable benefit and risk profile of DOAC vs. VKA in obese subjects, overall and across the three obesity classes, except for systemic thromboembolism, which was similar between the two treatments in class 3 obesity.[103] A previous meta-analysis of 89 494 patients with AF and class 3 obesity only reported that both stroke/systemic embolism (OR 0.71, 0.62–0.81) and major bleeding (0.60; 95% CI: 0.46–0.78) were lower with DOAC than with warfarin.[104] A retrospective cohort of 5183 patients with AF, grouped for a BMI <30, 30–40 ($n = 2137$), and >40 ($n = 358$), showed similar efficacy and safety of DOACs across the categories, although class 3 patients were few.[105] A Swedish nationwide study on 26 047 patients with AF, all on DOACs, showed a U-shaped relationship between BMI and major bleeding, with an increased risk at both a BMI <18.5 and obesity class 3.[106] Additional studies are reported in *Table 2*.

For VTE, a post hoc analysis of a phase 3 RCT showed similar efficacy and safety between apixaban and enoxaparin/VKA across all BMI categories, although class 3 obesity was <5% of the trial population with five thrombotic events.[111] A recent meta-analysis including 13 studies of patients with VTE and a BMI ≥40 or a BW ≥120 showed a lower risk of both recurrent VTE and major bleeding associated with anti-Xa DOACs vs. VKA (OR 0.72, 95% CI 0.57–0.91, and 0.74, 95% CI 0.58–0.95, respectively),[114] while in another cohort of 51 871 patients with VTE, DOAC, or VKA had similar effectiveness and safety across all BW classes, including severe obesity (BW >140, $n = 2167$).[110] A meta-analyses of five observational studies in >6000 patients with VTE and morbid obesity showed a similar incidence between DOACs and VTE of recurrent VTE or major bleeding over 12 months after the event.[112] Some data suggested higher gastrointestinal bleeding risk associated with dabigatran compared with other DOACs.[116] A systematic review of patients with an indication for oral anticoagulants (OACs) concluded that rivaroxaban, apixaban, or dabigatran may be used at standard doses in all patients with a BMI <40, whereas rivaroxaban and apixaban have more data in those with a BMI >40.[117] Additional studies are reported in *Table 2*.

A wide variability in the peak and trough concentrations of full-dose apixaban and rivaroxaban has been consistently reported in class 3 obese patients, with many patients with drug concentrations outside the intervals measured in the main phase 3 RCTs (*Tables 2* and *3*).[111,116,118,119] Measuring DOAC levels with specific assays can be appropriate in extremely obese and underweight classes (*Central Table 1*).

Underweight Asian patients with AF showed lower ischaemic stroke and major bleeding with DOAC vs. VKA.[108] However, in a mixed-ethnicity AF cohort including 28.9% underweight patients, DOAC and VKA showed similar efficacy and safety,[113] while other studies reported a higher safety of DOACs in underweight individuals as compared with VKA.[130–132] In the meta-analysis of RCTs in AF, the probability of major thrombotic events was higher in the lowest BMI range, independently of the type of OAC.[102] Major bleeding

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

	Underweight	Normal weight (reference)	Obesity Class 1	Obesity Class 2	Obesity 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 b.i.d. 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 b.i.d. (acute VTE) 5 mg b.i.d. (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[a] Consider monitoring peak and/or trough for severe underweight Unknown efficacy and safety. Caution due to high bleeding risk	20 mg o.d. (Afib and VTE >21 days) 15 mg b.i.d. (acute VTE) 10 mg o.d. (>6 months post-VTE) 2.5 mg b.i.d. (stable CAD/PAD; post-ACS)	No change No change	No change No change	Suggest monitoring peak and/or through anti-Xa activity if used, and if concentrations are too low, switch to VKA Unknown efficacy and safety
Edoxaban	30 mg o.d. if BW ≤60 kg Caution for bleeding risk of underweight Consider monitoring peak and/or trough for severe underweight	60 or 30 mg o.d. (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 b.i.d. (AFib and VTE) 110 mg b.i.d. (AFib and VTE if ≥80 years or eGFR <50 mL/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
LMWH fixed dosing (thromboprophylaxis)	Limited data Risk of overdosing, consider measure anti-Xa activity	Enoxaparin 40 mg o.d. Dalteparin 5000 IU o.d. Tinzaparin 4500 IU o.d.	No change	Increase daily dose or frequency (b.i.d.) in patients at high risk[b]: Enoxaparin: 40 mg b.i.d. Dalteparin: 7500 o.d. Consider measuring anti-Xa activity	Increase dose Enoxaparin: 40–60 mg b.i.d. Dalteparin: 5000 U b.i.d. Consider measuring anti-Xa activity Tinzaparin: BW-adjusted dose of 50–75 IU/kg may be considered

Central Table 1 Continued

	Underweight	Normal weight (reference)	Obesity Class 1	Obesity Class 2	Obesity Class ≥3
LMWH (ACS and VTE treatment)	No change but limited data Consider measuring anti-Xa activity	VTE treatment: Enoxaparin: 1 mg/kg b.i.d. Dalteparin 200 IU/kg o.d. or divided in b.i.d. Tinzaparin 175 IU/kg o.d. or divided in b.i.d. ACS: Enoxaparin 1 mg/kg b.i.d. Dalteparin 120 IU/kg b.i.d. (dose capping at 10 000 IU b.i.d.)	VTE treatment: no change (for dalteparin limited data, consider dose capping at 20 000 IU)	VTE treatment (b.i.d. dosing) Enoxaparin: reduce dose by ~20% (most data in BMI >40) Consider measuring anti-Xa activity Tinzaparin: limited data at BW >140 kg Consider measuring anti-Xa activity Dalteparin: limited data, consider dose capping and measuring anti-Xa activity, consider using another LMWH ACS: unknown if reduced dose/dose capping, consider measuring 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 i.v. bolus (max 5000 IU) and 12–15 IU/kg/h infusion (max 1000 IU/h) monitoring aPTT During PCI: 70–100 IU/kg i.v. in patients not anticoagulated, 50–70 IU/kg if concomitant GPI, monitor ACT	No change and careful aPTT monitoring for possible under- and overdosing		
Fondaparinux	Contraindicated or generally avoided	Thromboprophylaxis: 2.5 mg o.d. VTE: 7.5 mg o.d. ACS 2.5 mg o.d.	No change or for VTE 10 mg o.d.[c] if BW >100 kg	VTE: 10 mg o.d.[c] ACS: 2.5 mg o.d. Prophylaxis: 2.5 mg o.d. (limited data)	Limited data for all indications, use LMWH
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	1.5×10^6 IU i.v. 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 >120 kg

Central Table 1 Continued

	Underweight	Normal weight (reference)	Class 1	Obesity Class 2	Class ≥3
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 to 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 of 100 mg Stroke: ceiling dose of 90 mg (stroke)	No data
Tenecteplase	STEMI: <60 kg: 30 mg and consider associated bleeding risk	STEMI: 60 to <70 kg: 35 mg; 70 to <80 kg: 40 mg Stroke: 0.25 mg/kg Half dosing in patients older than 75 years	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.
AFib, atrial fibrillation; AI, artificial Intelligence; ACS, acute coronary syndromes; b.i.d., bis in die; CAD, coronary artery diseases; IU, international units; LMWH, low-molecular-weight heparin; o.d., once daily; PAD, peripheral artery disease; PD, pharmacodynamics; PK, pharmacokinetics; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Caution for bleeding risk of underweight: 15 mg o.d. possibly considered >21 days post-VTE days, until extended treatment.
[b]For example, in bariatric surgery, previous VTE, strong family history of VTE, and thrombophilia.
[c]Should not be used if moderately (eGFR <60 mL/min/1.73 m^2), severely (eGFR <30 mL/min/1.73 m^2) reduced renal function.

probability was similar in DOAC-treated patients across all BMIs (from underweight to severe obesity), while for VKA was maximal at lower BMIs.[102] The probability of ICH was high in underweight individuals, independently of the OAC agent.[102] In the Swedish registry of 26 047 AF, DOAC-treated patients, major bleeding and mortality were higher in underweight patients vs. normal weight.[106]

Simulations based on population PK models, mostly derived from RCT available measurements for the anti-Xa DOACs,[133–135] did not show any major impact of extreme BWs as covariates significantly affecting PK/pharmacodynamic (PD), while low BW (<60) was often associated with reduced kidney function and affected mostly by dabigatran, as it is almost exclusively renally excreted[135] (Graphical Abstract and *Central Table 1*).

Few data suggest that soon after BS, DOAC concentrations may be affected by malabsorption and reduced oral feeding; thus, the optimal timing for restarting DOACs post-BS is unknown.[24,136] Apixaban and edoxaban are mainly absorbed in the small intestine, rivaroxaban in the stomach, and dabigatran between the lower stomach and the duodenum.[39] Measuring drug levels may be useful in patients (re)starting DOACs post-BS after refeeding, also considering their high BMIs and substantial post-BS malabsorption (*Figures 2* and *3*).[137]

Idarucizumab is a humanized monoclonal antibody fragment[138] reversing dabigatran, with a small extravascular distribution, administered at a fixed dose. In its small phase 3 RCT, the median BW was 75 with no data on BMI classes. Andexanet-alfa is a non-active, FXa decoy protein binding oral and parenteral anti-Xa drugs, with a Vd approximately equivalent to blood volume; therefore, minimal distribution into adipose tissue is expected. Andexanet-alfa is administered with a fixed-dose bolus followed by an infusion rate based on the anti-Xa type, time from the last drug intake and dose. In a phase 3 RCT,[139] BMI averaged 27 ± 6; thus, extreme BMIs were under-represented, and without available PK studies at extreme BMIs.

Consensus statements

In patients with AF and/or VTE and obesity classes 1 and 2, DOACs show a benefit–risk profile similar to that of normal-weight individuals.[92,102–104,114]

Based on limited data, the anti-Xa DOACs appear effective in patients with AF and/or VTE and obesity class ≥3.[103,140,141]

In underweight patients, anti-Xa DOACs appear safer than VKA.[102,130,131]

Due to possible high PK/PD variability, measuring DOAC concentrations at trough and/or peak is advised during maintenance, in class ≥3 obese and severely underweight patients, especially if renal function is reduced*.[102,111,119–113]

Despite the lack of data, if a DOAC is used post-BS, measuring plasma levels at peak and/or trough may be appropriate, especially in the first 3 months post-BS.[137,140]

After BS, in patients on single or combined antithrombotic therapy, at prophylactic or therapeutic doses, gastroprotection is advised, preferably with PPIs.[88]

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

*<45 mL/min/1.73 m^2

Parenteral anticoagulants

Unfractionated heparin

The highly variable anticoagulant response to intravenous (IV) unfractionated heparin (UFH) requires monitoring and dose adjustment based on the activated partial thromboplastin time (aPTT), activated clotting time (ACT), or anti-Xa assay. The 2023 ESC guidelines provide a class I recommendation for UFH in ST-elevation myocardial infarction (STEMI), and in non-ST-elevation acute coronary syndrome (NSTE-ACS) if early angiography/PCI is anticipated, with a weight-adjusted bolus without capping (70–100 IU/kg) and, for prolonged therapy, titration to target aPTT to 60–80 s.[142] Timely anticoagulation during IV UFH, facilitated by dosing nomograms, is associated with reduced complications in acute VTE,[143] but nomograms were developed with poor representation of obese patients. For patients with class ≥2 obesity (or a BW >160), conventional nomograms tend to generate 'overdosing' compared with normal or class 1 obese patients, as reflected by aPTT or anti-Xa measurements.[23] Overdosing of UFH may increase bleeding and require high doses of protamine for reversal in cardiac surgery, which may then increase bleeding and transfusions.[144]

Body metrics other than BW to adjust dosing may be valuable. In an RCT recruiting obese patients undergoing cardiopulmonary bypass, UFH dosing was based on ideal body weight (IBW) or BW. IBW-adjusted dosing resulted in ≈15% lower UFH dose and plasma concentrations were better within the target range.[145] In patients undergoing catheter ablation of AF, including class 2 obese patients, a comprehensive UFH dosing protocol considering IBW and BW showed that IBW more rapidly achieved and maintained effective ACT levels, irrespective of BMI.[146] These findings suggest that body size metrics other than BW may improve UFH dosing nomograms and avoid overdosing (Graphical Abstract and *Central Table 1*).

Protamine reverses UFH with 1:1 posology (1 mg every 100 IU of the initial dose needed for anticoagulation), which does not directly account for UFH clearance and may lead to excessive protamine dosage. A recent RCT[147] compared protamine standard dosing vs. dosing predicted by a mathematical model based on heparin clearance and IBW. A better re-coagulation profile and lower protamine administration was achieved by the IBW-based model,[147] 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.[142,145,146]

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.[145,146]

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

Low-molecular-weight heparin

Dosing LMWH in patients with extreme BWs is challenging, as anticoagulation can fall outside the target range when a 'normal

Table 2 Studies on efficacy and safety of vitamin K antagonists vs. direct oral anticoagulants in atrial fibrillation and venous thromboembolism 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[107]	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 ($n = 21\,589$)	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[109]	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 severely obese patients with AF No considerations based on obesity classes
Boriani *et al.*, 2020[95]	ENGAGE-AF ($n = 21\,028$) Post hoc analysis	Edoxaban vs. warfarin	AF BMI ≥30 to <35 ($n = 5209$) ≥35 to <40 ($n = 2099$) ≥40 ($n = 1149$)	Comparable efficacy and safety of edoxaban vs. warfarin across class 1–3 obesity in patients with AF
Perino *et al.*, 2021[110]	Retrospective study ($n = 51\,871$)	DOAC vs. warfarin	VTE BW <60 ($n = 1632$) ≥60 to <100 ($n = 30\,645$) ≥100 to <120 ($n = 12\,660$) ≥120 to <140 ($n = 4767$) ≥140 ($n = 2167$)	Comparable efficacy and safety of DOAC vs. warfarin in severely obese patients with VTE
Soyombo *et al.*, 2021[91]	Retrospective study ($n = 433$)	Warfarin	Obesity classes: Normal ($n = 40$) Overweight ($n = 111$) Obesity class 1 ($n = 135$) Obesity class 2 ($n = 45$) Obesity class 3 ($n = 99$)	Increased warfarin doses required with higher obesity classes
Cohen *et al.*, 2021[111]	RCT AMPLYFY ($n = 5384$) Post hoc analysis	Apixaban vs. warfarin	VTE BW ≤ 60 ($n = 476$) >60 to <100 ($n = 3868$) ≥100 to <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[112]	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 severely obese patients with VTE No considerations based on obesity classes
Mhanna *et al.*, 2021[104]	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 severely obese patients with AF No considerations based on obesity classes
Nakao *et al.*, 2022[113]	Retrospective propensity score matching ($n = 29\,135$)	DOAC vs. warfarin	AF BMI <18.5 ($n = 585$) ≥18.5 to <25 ($n = 8427$) ≥25 to <30 ($n = 10\,705$) ≥30 to <35 ($n = 5910$) ≥35 ($n = 3508$)	Comparable efficacy and safety of DOAC vs. warfarin across obesity classes 1–3 in patients with AF

Table 2 Continued

Reference	Study design	Intervention and control	Populations under study	Key findings and source of bias
Zhang *et al.*, 2023[114]	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 severely obese patients with VTE No considerations based on obesity classes
Salah *et al.*, 2023[115]	Meta-analysis of 12 observational studies	DOAC vs. warfarin	AF BMI ≥30/≥40 (n unknown)	Better efficacy of DOAC vs. warfarin in severely obese patients with AF No considerations based on obesity classes
Elad *et al.*, 2023[105]	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[106]	Retrospective study ($n = 26\ 047$)	DOAC	AF BMI groups 18.5 to <25 ($n = 13\ 346$) 25 to <30 ($n = 22\ 269$) 30 to <35 (n =13 909) 35 to <40 ($n = 5440$) ≥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[92]	Retrospective study ($n = 10\ 167$)	Warfarin	VTE BW <60 ($n = 201$) ≥60 to <100 ($n = 5541$) ≥100 to <120 ($n = 2707$) ≥120 to <140 ($n = 1137$) ≥140 ($n = 581$)	Comparable TTR for warfarin across obesity classes in patients with VTE
Patel *et al.*, 2024[102]	Meta-analysis of 4 phase 3 RCTs	DOAC vs. warfarin	AF BMI as a continuous variable as well as grouped in 18.5 to <25 ($n = 9101$) 25 to <30 ($n = 9970$) 30 to <35 ($n = 4280$) 35 to <40 ($n = 1486$) ≥40 ($n = 608$)	Efficacy of DOAC vs. 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

AF, atrial fibrillation; BMI, body mass index (kg/m^2); BW, body weight (kg); DOAC, direct oral anticoagulants; NA, not available; TTR, time in therapeutic range; VTE, venous thromboembolism.

weight' dosing is used.[148,149] 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 range[148–150] (Supplementary material online, *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.[151] Instead, anti-Xa assay can be used in selected cases to assess whether levels are within the expected target range developed for normal-weight individuals.

Prophylaxis

Underdosing is possible using the standard LMWH dose in obesity class ≥2, and higher fixed-dose or BW-adjusted LMWH prophylaxis may be needed to attain sufficient anticoagulation.[23] In a recent meta-analysis, including 11 studies (4 RCTs) of class >2 (mean BMI 38–61) obese patients hospitalized for medical or surgical conditions, BW-adjusted heparins (UFH, enoxaparin, bemiparin, or nadroparin) provided similar VTE protection and bleeding risk as standard, fixed-dose therapy (*Table 4*).[152] However, another meta-analysis also including a mixed population (medical, orthopaedic, and post-BS patients) revealed that prophylaxis, largely with enoxaparin, at higher-than-standard dosing significantly decreased VTE (OR 0.47, 0.27–0.82) without increasing bleeding (*Table 4*).[153]

A population PK model predicted optimal anti-Xa levels for nadroparin in the prophylaxis of morbid obesity when administered on BW rather than fixed dosing.[156] In a systematic review, BW-based LMWH dosing suggested in post-surgical or medical patients with obesity was: enoxaparin 0.5 mg/kg once a day (omni die) (o.d.) or bis in die (twice daily) b.i.d., tinzaparin 75 IU/kg o.d.,[117] and higher prophylactic LMWH dose has also been suggested by others (3000–4000 anti-Xa IU b.i.d. for class 3 obesity in VTE prophylaxis).[157]

A recent retrospective study in underweight patients (<55 kg) found that reduced fixed-dose enoxaparin (30 mg o.d.) could achieve anti-Xa levels in range in 75% of patients.[158] In a study of medical inpatients with a BW <45, prophylaxis with reduced, fixed-dosed enoxaparin (<40 mg o.d.) or UFH (<15 000 IU daily) was associated with fewer bleeding vs. standard doses.[159]

A Cochrane review and a meta-analysis on thromboprophylaxis post-BS concluded that higher-dose heparins (UFH, parnaparin, nadroparin, and enoxaparin) provided little or no additive benefit compared with standard-dose prophylaxis.[24] Two meta-analyses found no support for BW-adjusted or higher-dose heparin (UFH or LMWH) to prevent VTE, but a trend towards increased risk of bleeding.[160,161] A recent meta-analysis comparing augmented vs. standard LMWH dosing on VTE prophylaxis post-BS showed uncertain benefit of augmented dosing on VTE protection (OR 0.57, 0.07–4.39), extended duration (10–28 days, OR 0.54, 0.15–1.90), and increased bleeding (OR 3.03, 95% CI 0.38–23.96).[162] Importantly, meta-analyses mainly included cohort studies and few RCTs; thus, outcome estimates, as reflected by wide CIs, are uncertain with high risk of bias. Among 50 patients undergoing RYGB (BMI 49.4 ± 4.4), 4-week treatment with 5700 IU nadroparin, one-third had peak anti-Xa activity below the target range, and the anti-Xa activity was significantly and inversely correlated with BW (*r* values: −0.410 and −0.472, for TBW and LBW, respectively). A systematic review suggested higher, fixed LMWH doses in class 3 obesity (enoxaparin 40 mg b.i.d., dalteparin 5000 IU b.i.d., or tinzaparin 75 IU/kg o.d.).[117] Aside from dosing, the optimal duration of thromboprophylaxis remains unclear. Although the VTE risk following BS is low-moderate, it is high as compared with non-obese post-surgery patients and still the main cause of mortality.[163,164] The majority of VTE occurs after discharge, ∼70% within the first month.[163] Risk assessment models (RAM), like the Caprini score[165] or the BariClot tool developed for BS,[166] have been used in cohort or registry studies.

Consensus statements

It is advised to administer LMWH prophylaxis in underweight patients with caution and at reduced fixed dosing in patients with severe underweight.[158,159]

BW-based or 'higher than usual' fixed doses of LMWH may be appropriate for surgical and medical prophylaxis in obesity class ≥2 or if BW >120.[117,152,153,157]

The use of BW-based or 'higher than usual' fixed doses of LMWH is advised in obesity grade ≥2 or BW >120 following BS.[117]

Extended VTE prophylaxis post-BS may be appropriate in patients at high thromboembolic risk.[165,166]

In non-BS or medical inpatients, whether a higher-than-standard dose of LMWH for prophylaxis provides better efficacy/safety remains unproven.

In BS, there is no high-quality evidence supporting higher-than-standard fixed-dose prophylaxis with LMWH or UFH to provide superior efficacy/safety.[24,162]

Therapeutic dosing

A meta-analysis[153] included studies of patients with obesity on heparin for VTE, AF, or coronary artery disease (CAD) and compared BW-based standard (1 mg/kg) vs. reduced (<1 mg/kg, average 0.8 mg/kg) dosing. The reduced dose showed similar efficacy (VTE recurrence), although with wide CIs (OR 0.86, 0.11–6.84), and higher safety (major bleeding OR 0.30, 0.10–0.89) vs. the conventional dose. A comprehensive review supports reduced BW-based enoxaparin dosing (∼0.8 rather than 1/mg/kg) in morbid obesity, although data are based on anti-Xa levels.[117] A recent registry of VTE treatment showed fewer complications with reduced, BW-based-dose LMWH.[167]

For tinzaparin the treatment dose in patients with a BW >120 has not been determined[168] and for the dalteparin dose capping is indicated by the Food and Drug Administration (FDA) at a BW <56 and >99[169] based on studies in cancer patients (*Central Table 1*). However, some guidelines suggest using BW-adjusted dosing and avoiding capping.[151,170]

In ACS ESC Guidelines, where acute invasive angiography is not anticipated, enoxaparin at a standard BW-based dose (1 mg/kg b.i.d.) without capping has a class 2 recommendation.[142] However, based on previous studies,[23] bleeding increases in patients weighing >150 kg receiving 1 mg/kg twice-daily enoxaparin vs. a reduced median dose of 0.65 mg/kg twice-daily. Consistently, an *in silico* PK/PD model, developed in adults and expanded to children, predicted with a small error that obese children have ∼20% higher peak anti-Xa concentrations under standard BW-based dosing compared with non-obese children, due to reduced weight-normalized clearance. Moreover, enoxaparin was better matched across age and obesity classes using fat-free BW-based dosing.[171]

Consensus statements

Current LMWH therapeutic regimens for VTE[117] and ACS[142] are BW-adjusted, with dose capping at the highest BWs. However, there is insufficient evidence that dose capping improves safety or efficacy as compared with 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.[117,153,171]

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

Fondaparinux

See Supplementary material and *Central Table 1*.

Consensus statements

In VTE prophylaxis, fixed-dose fondaparinux is not advised if BW <50 kg.[172,173]

Based on available evidence, using enoxaparin rather than fondaparinux is advised in class ≥2 obese subjects.[174]

Antiplatelet drugs

Acetylsalicylic acid

An individual patient data, post-hoc meta-analysis of 10, placebo-controlled RCTs suggested a lower antithrombotic efficacy of 75–100 mg once-daily acetylsalicylic acid (ASA) in participants weighing ≥70 compared with <70 kg, while ASA doses ≥325 mg had the opposite interaction (*Table 5*).[175] Subsequent RCTs and meta-analyses on ASA monotherapy, with pre-specified BMI- or BW-related subgroups, could not confirm the 70 kg threshold, since efficacy and safety in subgroups with a BMI <25 or >30 and/or a BW <70 or ≥70

Table 3 Intervals of concentration reported in phase 3 trials or summary of product characteristics for different direct oral anticoagulants 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)	Log*P*
Dabigatran–AF					
150 mg b.i.d., 25th to 75th percentiles	61–143[120]; 200 (90th percentile)[120]	117–275[120]	34–35[120]	60–70 (moderate tissue distribution)[122]	5.17
110 mg b.i.d., 10th to 90th percentiles	28–155[121]	52–275[121]			
Dabigatran–VTE					
150 mg b.i.d., 25th to 75th percentiles	39–95[120]; 146 (90th percentile)[120]	117–275[120]			
Apixaban–AF					
5 mg b.i.d., 5th to 95th percentiles	41–230[123]	91–321[123]	87[123]	21[123]	2.22
2.5 mg b.i.d., 5th to 95th percentiles	34–162[123]	69–221[123]			
Apixaban–VTE					
10 mg b.i.d., 5th to 95th percentiles	41–335[123]	111–572[123]			
5 mg b.i.d., 5th to 95th percentiles	22–177[123]	59–302[123]			
2.5 mg b.i.d., 5th to 95th percentiles	11–90[123]	30–153[123]			
Edoxaban–AF					
60 mg o.d., 5th to 95th percentiles	19–62[124](or 16-43)[125]	125–245[126] (or 145–288)[125]	55	107	1.61
30 mg o.d., 25th to 75th percentiles	10–32[124] (or 8-21)[125]	55–120[126] (or 73–146)[125]			
Edoxaban–VTE					
60 mg o.d., 25th to 75th percentiles	10–39[127]	149–317[127]			
30 mg o.d., 25th to 75th percentiles	8–32[127]	99–225[127]			
Rivaroxaban–AF					
20 mg o.d., 5th to 95th percentiles	25–124[128]	206–347[128]	90–95[128]	50[128]	1.74
15 mg o.d., 5th to 95th percentiles	7–127[129]	159–573[129]			
Rivaroxaban–VTE					
20 mg o.d., 5th to 95th percentiles	6–239[128]	22–535[128]			
10 mg o.d., 5th to 95th percentiles	4–51[128]	7–273[128]			
Rivaroxaban–ACS and stable atherosclerotic diseases					
2.5 mg b.i.d., 5th to 95th percentiles	4–18[128]	13–123[128]			

ACS, acute coronary syndromes; AF, atrial fibrillation; VTE, venous thromboembolism; log*P*, coefficient of partition of the drug, i.e. 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.

were consistent with the main trial's populations (*Table 5*).[176–179] In the A Study of Cardiovascular Events in Diabetes (ASCEND) placebo-controlled RCT involving diabetic patients in primary prevention,[180] ASA 100 mg o.d. was significantly more effective than placebo in individuals with a BMI >30 or a BW >70 vs. lower values (*Table 5*). In the Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness (ADAPTABLE) secondary prevention, RCT, ASA 325 mg was not superior to 81 mg in reducing MACE in the overall population and in pre-specified BW subgroups below and above 70 kg[177] (*Table 5*). However, in those RCTs, obese patients were largely class 1; thus, no outcome data are available on class ≥2 obesity. Since low-dose ASA is used to prevent thrombosis after arthroplasty,[181] a large study compared standard 81 mg (n = 1097) vs. weight-adjusted dosing (n = 1187), whereby patients ≥120 kg received 325 mg ASA. In the weight-adjusted cohort, thrombosis was reduced by ∼60% at 1 and 6 months post-surgery compared with 81 mg with no differences in safety.[182]

Consistently with RCT data, ASA PD is similar in class 1 obese vs. non-obese subjects,[187] while class ≥2 obese subjects on 100 mg ASA o.d. (mean BW 111 ± 21 and BMI 39.4 ± 5.1)[183] show significantly lower inhibition of cyclooxygenase activity from peripheral platelets than non-obese individuals and thus a reduced response. Residual, un-inhibited *ex vivo* cyclooxygenase activity in peripheral platelets appears log-linearly associated with BMI, with a hindered PD at a BW >110 or a BMI >35.[183] Consistently, patients on secondary prevention with 100 mg daily ASA and an average BW >102 or a BMI >38,[192] or in the highest BMI or BW quartiles,[185,193] showed lower peripheral platelet inhibition vs. non-obese individuals, and a degree of inhibition similar to non-obese subjects was obtained by doubling the o.d. dose.[192,193] Notably, doubling the low-dose aspirin dose does not inhibit cyclooxygenase 2 *in vivo*.[194,195] Among 1002 pregnant women on low-dose ASA for eclampsia, class 3 obesity was associated with significantly reduced response vs. lower BMIs.[184]

An *in silico* PK/PD model and simulations of ASA predicted a reduced platelet inhibition in moderate-to-severe obesity, which was reproduced by reducing the systemic bioavailability from 50% (as in normal subjects) down to 25%.[196,197] According to the model, either doubling low-dose o.d. (e.g. 200 mg) or a twice-daily low-dose

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[24]	**Bariatric surgery thromboprophylaxis** Higher-dose heparin vs. standard-dose heparin Ebrahimifard 2012[24]: A comparison between two different prophylactic doses of UFH for deep venous thrombosis prevention in laparoscopic bariatric surgery (5000 × 3 IU vs. 5000 × 2 IU) for 15 days (publication not found, only clinical registration—Iranian web site), *n* = 700? (unpublished data) Imberti 2014[24]: Prophylaxis of venous thromboembolism with low-molecular-weight heparin in bariatric surgery: a prospective, randomized pilot study evaluating two doses of parnaparin (BAFLUX Study): parnaparin 4250 vs. 6400/o.d., 7–11 days, *n* = 258 Kalfarentzos 2001[24]: Prophylaxis of venous thromboembolism using two different doses of low-molecular-weight heparin (nadroparin) in bariatric surgery: nadroparin 5700 IU vs. 9500 IU o.d. until discharge, *n* = 60 Steib 2016[24]: Once vs. twice-daily injection of enoxaparin for thromboprophylaxis in bariatric surgery: effects on antifactor Xa activity and procoagulant microparticles: enoxaparin treatment (4000, 6000, or 2 × 4000 IU, respectively, *n* =164) Enoxa vs. fondaparinux Steel 2015[24]: The EFFORT trial, preoperative enoxaparin vs. post-operative fondaparinux for thromboprophylaxis in bariatric surgical patients: 40 mg enoxaparin twice daily or 5 mg fondaparinux sodium once daily. *n* = 198 Starting pre- vs. post-operatively Abdelsalam 2021[24]: enoxaparin 1 mg/kg × 1 (max 120 mg), one group started 12 h pre-operatively, the other post-operatively 15 days, *n* = 100 (duplex) Chemo + mechano vs. mechano alone Ahmad 2021[24]: Combined mechanical and pharmacological prophylaxis vs. mechanical prophylaxis alone. 40 mg × 1 enoxaparin 12 h before then daily for 2 weeks + mechanical, the other group on mechanical prophylaxis, *n* = 150, note—silent DVTS	*Higher-dose heparin* may result in little or no difference in the risk of *VTE* (RR 0.55, 95% CI 0.05–5.99; 4 studies, 597 participants) *major bleeding* (RR 1.19, 95% CI 0.48–2.96; I^2 = 8%; 4 studies, 597 participants; low-certainty) in people undergoing bariatric surgery *Enoxa vs. fonda:* little or no difference in the risk of *VTE* (RR 0.83, 95% CI 0.19–3.61; 1 study, 175 participants) or *DVT* (RR 0.83, 95% CI 0.19–3.61; 1 study, 175 participants) *Heparin started before vs. after* Heparin 12 h before surgery vs. after surgery may result in little or no difference in the risk of VTE (RR 0.11, 95% CI 0.01–2.01; 1 study, 100 participants) or DVT (RR 0.11, 95% CI 0.01–2.01; 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). *Chemical±mechanical prophylaxis vs only mechanical*: Combining may reduce VTE events (RR 0.05, 95% CI 0.00–0.89; NNT = 9; 1 study, 150 participants; low-certainty). Unable to assess the effect of this intervention on major bleeding or mortality (effect not estimable), or on PE or adverse events (not measured) *Conclusion:* The certainty of the evidence is limited by small sample sizes, few or no events, and risk of bias concerns
DOACs vs. 'conventional anticoagulants' long-term treatment (≥3 months) on broad patient population—not only obesity		
Li *et al.*, Cochrane Database of Systematic Reviews 2023[154]	Large-quality RCTs comparing DOACs vs. conventional anticoagulants (VKAs, DTI, anti-Xa DOACs, UFH, LMWHs, and fondaparinux) in the treatment of *PE* (≥3 months)	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
Wang *et al.*, Cochrane Database of Systematic Reviews 2023[155]	Large-quality RCTs comparing DOACs vs. conventional anticoagulants (VKAs, DTI, anti-Xa DOACs, UFH, LMWH, and fondaparinux) in the treatment of *DVT* (≥3 months)	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

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

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[175]	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 [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	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[180]	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, and >30 and BW below or above 70 kg	SVE: MI, stroke or TIA, or vascular death, excluding any confirmed intracranial haemorrhage Safety: major bleeding defined as BARC 2–5 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), $P = 0.02$ 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	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 an NNT of 35 and an NNT/NNH ratio of 0.4
Petrucci *et al.*, 2019[183]	Proof of concept, intervention study including 16 healthy and morbid obese (mean BMI 39.2 ± 5.1 kg/m^2) subjects	ASA 100 mg o.d. for 3–4 weeks	Assess whether/how BW and BMI affect the PD of ASA, as assessed by serum thromboxane B_2 measurements *In silico* model and simulations for ASA dosing in class ≥2 obese individuals	ASA PD assessed according to serum thromboxane B_2 measured 24 h after the last ASA intake (trough level)	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 relationships between BW or BMI were log correlated with a poor ASA PD The *in silico* model predicted that for class ≥2 obesity a dose of 200 mg o.d. or 100 mg b.i.d. would be needed for re-establishing an adequate response

Table 5 Continued

Reference	Total population and obese individuals	ASA regimen	Primary endpoints	Results	Limitations
Finneran *et al.*, 2019[184]	1002 pregnant women with pre- eclampsia	Double-blind, randomized, placebo-controlled trial comparison of 60 mg ASA o.d. vs. 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 randomization and 24–28 weeks' gestation), and third trimester (34–38 weeks' gestation	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 (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)	The 60 mg dosing is rarely used as compared with other regimens in the low-dose range (75, 81, and 100 mg) High-risk morbidly obese women receiving low-dose ASA for the prevention of pre-eclampsia may need higher ASA dosing or frequency
Furtado *et al.*, 2019[185]	438 patients on DAPT due to ACS	DAPT including standard low-dose ASA once-daily, mean BW 75.6 $\pm$15.8 kg, mean BMI 27.3 $\pm$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[186]	Post hoc analysis of the ASPREE trial including 19 114, low-risk, healthy elderly subjects in primary prevention Elderly participants weighing <70 kg (n = 6428) and ≥70 kg (n = 10 749) Follow-up 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 $\pm$ 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 ischaemic stroke Whether body size (BMI <25 or BW <70 kg) modulated the efficacy of ASA vs. placebo 12 633/19 114 individuals ≥70 kg	Analyses by subgroups 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: MACEs were not a primary endpoint, Class ≥2 subjects were likely not or minimally represented; non-pre-specified, post hoc analysis
Lee *et al.*, 2021[187]	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

Table 5 Continued

Reference	Total population and obese individuals	ASA regimen	Primary endpoints	Results	Limitations
Halbur *et al*., 2021[182]	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 325 mg ASA b.i.d., those <120 kg received 81 mg b.i.d. for 4 weeks. Control cohort ($n = 1156$): patients received 81 mg ASA b.i.d. irrespective of BW.	VTE and gastrointestinal bleeding events were identified through chart review at 42 days and 6 months post-operatively Gastrointestinal bleeding at the same timepoints	The BW-based cohort had a significantly lesser incidence of VTE at 42 days [$P = 0.03$, relative risk (RR) 0.31, 95% CI 0.12–0.82] and 6 months ($P = 0.03$, RR 0.38, 95% CI 0.18–0.80) No difference in gastrointestinal bleeding between the cohorts at 42 days ($P = 0.69$) or 6 months ($P = 0.92$)	Non-randomized design Suggestion of need to factor patient BW when determining post-operative VTE prophylaxis with low-dose ASA
Hasan *et al*., 2021[188]	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 b.i.d.	Incidence of post-operative 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*., 2021[177]	15 076 patients with established CVD and indication for secondary prevention with ASA	Randomized comparison 81 mg or 325 mg of ASA per day. Median BW 90 kg	Primary effectiveness outcome: composite of 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	No difference of efficacy among the two regimens [HR 1.02; 95% confidence interval (CI), 0.91–1.14]; no difference in safety (HR 1.18; 95% CI, 0.79–1.77). Subgroup analysis according to BW threshold of 70 kg did not show any heterogeneity of results	Class ≥2 obesity under-represented (75th percentile of BW was 103 kg) The subgroup analysis according to BW of 70 kg was not pre-specified
Tang *et al*., 2021[189]	Retrospective review of 1578 knee or hip arthroplasties including different BMI categories: normal ($n = 335$), overweight ($n = 511$), class 1 ($n = 408$), class 2 ($n = 232$), and class 3 ($n = 92$)	Efficacy and safety of ASA 81 or 325 mg/day prescribed is safe and effective in obese vs. normal-weight patients undergoing arthroplasty	Primary endpoint: 90-day post-operative 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

Table 5 Continued

Reference	Total population and obese individuals	ASA regimen	Primary endpoints	Results	Limitations
Puccini *et al.*, 2023[190]	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.*, 2023[191]	24 770 patients post-RYGB, 1911 with ASA use and 22 859 without	Meta-analysis of observational and RCT studies to assess the risk of post-surgery margin ulcer associated with ASA use	Incidence of marginal ulceration post-RYGB BS	Patients on low-dose ASA did not have an increased risk of marginal ulcer (HR 0.56, 0.37–0.86), while those on high dose did (HR 1.90, 1.41–2.58)	Low-dose ASA can be safely resumed post-BS

AA, arachidonic acid; ADP, adenosine diphosphate; ASA, acetylsalicylic acid; ASCEND, A Study of Cardiovascular Events in Diabetes; ASPREE, Aspirin in Reducing Events in the Elderly; 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; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; PD, pharmacodynamics; PK, pharmacokinetics; RCTs, randomized clinical trials; RR, relative risk; RYGB, Roux-en-Y gastric bypass surgery; $sTXB_2$, serum thromboxane B_2; SVE, serious vascular events; VTE, venous thromboembolism.

restored the PD response.[196] Whether an optimal PD translates into an improved clinical benefit–risk profile remains to be established. Consistently, in the RECOVERY trial[198] that randomized hospitalized COVID-19 patients to 150 mg ASA o.d. vs. placebo, the ASA dose was selected 'to ensure sufficient inhibition of platelet cyclooxygenase-1 activity in all participants, including those who were overweight', based on our previous document.[23] Data are summarized in *Central Table 2*.

Consistent with reduced response and drug bioavailability in morbid obesity, ASA PD improved after BS,[199] with increased area under the curve (AUC) and Cmax[31] few months post-RYGB or SG, likely reflecting higher absorption and drug bioavailability following BS and weight loss.[200]

Multiple studies reported that non-steroidal anti-inflammatory drugs and ASA only at high doses increase the risk of MU.[170,191–203] A large meta-analysis (~25 000 patients) showed that low-dose ASA did not increase MU (HR 0.56, 0.37–0.86) vs. non-ASA-treated individuals, while high-dose did (HR 1.90, 1.41–2.58).[191] Pre- and post-operative PPIs can prevent MU,[170] and PPIs ensure safe gastroprotection when low-dose ASA is following RYGB.[204]

Consensus statements

No change in low-dose ASA dosing is advised for obesity class 1.[177,180,192]

For low-dose ASA, either doubling the once-daily dose or shortening the dosing interval (b.i.d.) in patients with obesity class ≥2 is advised to improve the PD response.[183,197,198]

Post-BS, continuing low-dose ASA, when indicated, is advised together with a PPI for gastroprotection.[199,204]

$P2Y_{12}$ inhibitors

Clopidogrel

Pre-clinical models show reduced clopidogrel biotransformation into active metabolite (AM), higher carboxylesterase-1 (CES) clearance, and reduced platelet inhibition in obese mice,[205] explaining data of low AM formation in obese subjects.[23]

An *in silico* PK/PD model for clopidogrel confirmed BW as significantly and inversely affecting AM formation, AUC, and platelet inhibition,[206] especially for class ≥2 obese individuals.[207] Model simulations predicted the need for higher loading and maintenance doses in severely obese vs. over- and normal-weight subjects to reach similar platelet inhibition.[206] For BMIs >35 and intermediate- or poor-metabolizer status based on *CYP2C19* alleles, the model predicts that the clopidogrel maintenance dose should be increased to 300 and 450 mg, respectively.[206] Moreover, class 3 obesity is associated with reduced CYP2C19 activity (*Figure 2*) independently of its alleles, which returns to almost normal values after weight loss with diet or BS.[208]

BMI was linearly correlated with high residual $P2Y_{12}$-dependent platelet aggregation in patients on dual antiplatelet therapy (DAPT) with clopidogrel,[190] and a similar phenotype was reported for TAVI patients.[209] In a study using the Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping (ABCD-GENE) score, which includes a BMI >30[210] as a factor reducing clopidogrel response, obese patients had the highest residual adenosine diphosphate (ADP)-dependent platelet aggregation.[211] In 181 East Asian patients on DAPT containing clopidogrel or prasugrel, no differences were observed in the higher BMI classes (25–29, ≥30) for both treatments.[212] However, none of the above studies included severe obesity. A substudy of the Harmonizing Optimal Strategy for Treatment of Coronary Artery Disease EXtended Antiplatelet Monotherapy (HOST-EXAM) RCT analysed the 2-year adverse outcome in patients on ASA 100 mg or clopidogrel 75 mg.[213] Patients with BMIs <18.5 had higher bleeding (HR 4.14, 1.70–10.05) than patients with BMIs 18.5–22.9, regardless of the antiplatelet agent, while higher BMI classes did not show increased bleeding risk. However, both extremely low and >30 BMIs were associated with higher all-cause death, non-fatal MI, stroke, readmission due to ACS, and Bleeding Academy Research Consortium (BARC) type ≥3 bleeding.[213] The clinical significance of post hoc analyses of a small non-inferiority trial combining safety and efficacy primary endpoints remains unclear. In the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) RCT on East Asian patients with minor stroke or TIA, a BMI <25 and normal glycated haemoglobin or absence of *CYP2C19* loss-of-function alleles were associated with higher benefit with DAPT–clopidogrel than with ASA monotherapy,[214] while DAPT–clopidogrel was not superior to ASA monotherapy in patients with a BMI >25 and no loss-of-function *CYP2C19* alleles.[214] However, these data are limited to a specific ethnicity and are a post hoc analysis.

For underweight, a substudy of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) RCT showed that guided de-escalation from DAPT–prasugrel to DAPT–clopidogrel was associated with better efficacy and safety in patients with a BMI <25 compared with normal and overweight subgroups.[215] However, platelet aggregation should be interpreted with caution because its translation in clinical efficacy and safety remains unproven.[142] No data on clopidogrel post-BS were found. Data are summarized in *Central Table 2*.

Prasugrel

An *in silico* PK/PD model recently developed for prasugrel[216] confirmed that only low BW is a relevant covariate for prasugrel response. In the PRASTO-II RCT, low-dose clopidogrel (50 mg o.d.) showed comparable efficacy and safety to very low-dose prasugrel (3.75 mg o.d.) in secondary prevention of cardioembolic stroke in elderly or underweight (<50 kg) patients.[217] In Japan, the 3.75 mg formulation has been approved to improve safety and reduce bleeding.[217] In the Early Aggressive Versus Initially Conservative Therapy in Elderly Patients With Non-ST-Elevation Acute Coronary Syndrome (ELDERLY-ACS) RCT, cardiovascular mortality and adverse events, including BARC 2–3 bleeding, were similar in elderly (>75 years) patients with low BMI (<25) on DAPT–clopidogrel vs. DAPT–low-dose (5 mg) prasugrel.[218] In a subgroup analysis of the ISAAR-REACT-5 RCT, low-dose prasugrel had comparable efficacy but reduced by 30% BARC 3–5 bleeding as compared with ticagrelor (90 mg twice-daily) in elderly (>75 years) or with low-BW (<60 kg) post-ACS patients.[219] In a post hoc analysis of this RCT, DAPT–ticagrelor or –prasugrel had efficacy and safety across the spectrum of BMIs consistent with the overall trial population.[220]

Ticagrelor

Class 1 obesity does not appear to affect ticagrelor PD, while data in class ≥2 obesity are limited.[221] A PK/PD model developed in healthy [BMI of 22.7 (19.1–27.8)] or post-ACS [BMI 23.5 (18.3–33.1)] Chinese individuals indicated BW, diet, and sex were the major covariates.[222] A PK model developed from Asian population data showed that low BW, advanced age (inversely), and hypertension predicted bleeding on ticagrelor.[223]

Plasma concentration of ticagrelor, its AM, and platelet function at peak and trough in 221 patients on DAPT (ASA plus ticagrelor 90

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

Drug	Underweight <18.5 kg/m^2	Normal weight (reference)	Obesity		
			Class 1	Class 2	Class ≥3
ASA	No change	75–100 mg o.d.	No change	Likely no change	AI and PD studies suggest doubling the low-dose once-daily or increase low-dose dosing frequency (b.i.d.)
Clopidogrel	No change	75 mg o.d.	No change	Reduced AM formation especially in poor metabolizers. Suggest changing 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
Prasugrel	5 mg (or 3.75 in Japan) o.d.	10 mg o.d.	No change	Likely no change	Inconsistent reports of reduced AM of unknown clinical significance Likely no change
Ticagrelor	No changes or reduced dose (60 mg b.i.d.) based on PD and AI data Caution for bleeding risk of underweight	90 mg b.i.d. 60 mg b.i.d. ≥1 year after ACS	No change	Likely no change	PD data suggest reduced drug concentration of unknown clinical significance Insufficient data
Cangrelor	Appropriate measure of BW to avoid overdosing	30 μg/kg i.v. bolus, and 4 μg/kg/min infusion	Appropriate measure of BW to avoid under- or over 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 i.v. bolus, 0.125 μg/kg/min (maximum of 10 μg/min) i.v. infusion Eptifibatide: 180 μg/kg i.v. bolus, 2 μg/kg/min i.v. infusion (if CrCl ≥50 mL/min) Tirofiban: 25 μg/kg i.v. 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, normoweight, and obesity classes as defined in *Table 1*. 'No change' refers to the treatment in normal BMI/BW subjects as reference population.
ACS, acute coronary syndromes; ACT, activated clotting time; AM, active metabolite; aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; b.i.d., bis in die; BW, body weight; BW, body weight; CrCl, creatinine clearance; FDA, Food and Drug Administration; GPI, glycoprotein inhibitors; IU, international units; PCI, percutaneous coronary intervention; PE, pulmonary embolism; STEMI, ST-segment elevation myocardial infarction.

or 60 mg b.i.d.) from two RCTs showed that BMI inversely correlated with 90 mg ticagrelor and AM plasma concentration at peak and trough. Residual platelet function at trough in different classes of BMIs (<25, 25–29, and >30 or BW <85 or >85) was directly correlated with BW and BMI.[224] A post hoc analysis of the TWILIGHT RCT showed comparable efficacy and safety (BARC 2–5 bleeding) between single antiplatelet therapy–ticagrelor and DAPT (with ASA), in high-risk post-ACS patients, whether normal or obese.[225] However, in this analysis patients with class ≥2 obesity or underweight were under-represented since average BMI was ∼28.5. In a post hoc analysis of the Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome (TICO) trial, BW ≤65 kg, haemoglobin ≤12 g/dL, and glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 predicted bleeding in ticagrelor-treated patients.[226]

In a post hoc analysis of the CHANCE-2 RCT, patients with minor ischaemic stroke or TIA, *CYP2C19* loss-of-function alleles and a BMI >28 had a reduced risk of recurrent ischaemic stroke at 90 days when receiving DAPT–ticagrelor vs. DAPT–clopidogrel as compared with a BMI <28.[227] A recent systematic review on population PK/PD models identified low BW, Asian ethnicity, and old age as significant covariates for predicting bleeding on ticagrelor 90 mg, suggesting that 60 mg may provide a 'safer' drug concentration in these populations.[216]

Consensus statements

In patients with obesity class ≥2 and in need of clopidogrel treatment, a higher maintenance dose of clopidogrel, likely doubled, may be appropriate to achieve an adequate PD response.[206,207,209]

CYP2C19 polymorphisms may particularly affect clopidogrel PD at the loading and maintenance dose in underweight or class 2–3 obese individuals, although the clinical impact is unknown.[211,212,214]

No significant difference in efficacy and PK of ticagrelor between normal and obesity class 1 has been reported.[221,222]

Clinical and PD data for 90 mg ticagrelor in class ≥2 obese and underweight patients are very limited.

Reduced-dose prasugrel (5 mg or 3.75 mg in Japan) or standard-dose clopidogrel may be appropriate, rather than 90 mg ticagrelor, in underweight patients.[214,219,220]

In patients with severe underweight, a lower dose (60 mg) ticagrelor may be appropriate, which seems safer, although the evidence is limited.[216]

Ticagrelor or prasugrel is advised over clopidogrel in class ≥2 obese patients, especially when loss-of-function allele(s) are documented.[206,207]

It is not advised to test platelet aggregation for adjusting antiplatelet therapy (either single or dual) post-BS.[31]

Triple antithrombotic therapy

See Supplemental material and Supplementary material online, *Table S5*.

Consensus statements

In class ≥3 obese patients undergoing PCI, a longer duration of initial triple antithrombotic therapy (TAT) as well as individualization of the doses and/or intervals of administration of antithrombotic drugs, both in TAT and dual antithrombotic (DAT), may be appropriate.[228–231]

Underweight is associated with high bleeding during TAT, regardless of the type of OAC.[232]

A strict implementation of bleeding prevention and gastroprotection is advised in underweight patients on TAT, owing to the increased bleeding risk, regardless of the type of OAC.[231,232]

Dual pathway inhibition

See Supplemental material.

Consensus statements

The benefit–risk profile of dual pathway inhibition (DPI) in patients with chronic atherothrombotic diseases seems preserved up to obesity class 2, while it is unknown for obesity class ≥3.[233]

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

IV antiplatelet drugs: cangrelor and glycoprotein IIb/IIIa inhibitors

See Supplementary material and *Central Table 2*.

Consensus statements

The efficacy and safety profile of cangrelor seems not affected by obesity classes 1 to 3, while bleeding may be increased by cangrelor in underweight patients.[234]

The efficacy and safety profile of glycoprotein inhibitors (GPIs) in underweight (<18.5 kg/m^2) and class ≥3 obese individuals is uncertain.[235]

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.[236–240]

Interactions between antithrombotic and BW-reducing drugs

Incretin mimetic agents have been recently approved as antiobesity drugs; thus, data on drug–drug interactions (DDI) are limited (Supplementary material online, *Table S6*).

Glucagon-like peptide-1 receptor agonists (GLP-1RA), 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.[241] Similarly, no interactions were detected between parenteral dulaglutide and warfarin.[242] However, semaglutide delays gastric emptying and therefore can create interactions if drugs, including VKA, are concomitantly administered. Tirzepatide, a combined GLP-1RA and glucose-dependent insulinotropic polypeptide receptor agonist, by delaying gastric emptying may affect the bioavailability of concomitant oral drugs.[243] By *in vitro–in vivo* modelling, slow gastric emptying does not influence rivaroxaban bioavailability.[244] Delayed gastric emptying has variable effects on the absorption of ticagrelor based on studies in patients treated with opioids,[245,246] but no information is available for BW-reducing drugs.

Orlistat is an inhibitor of the intestinal CES-1 and -2[247] that metabolize several drugs, including clopidogrel, ASA, and prasugrel. CES-1 variants account for the reduced formation of clopidogrel AM and for decreased dabigatran plasma concentrations.[248] Reduced CES-2 activity lowers ASA hydrolysis.[248,249] Orlistat has been reported to enhance VKA effects; thus, closer INR monitoring INR might be necessary.[122]

Consensus statement

More frequent INR monitoring is advised for patients on VKA when starting or modifying GLP1-RAs, and to avoid simultaneous oral administration.[243]

Antithrombotic drugs under development

In the past 5 years, novel antithrombotic agents with old or new targets are under clinical development,[250–253] and reported in Supplemental material, with scant data on BMI or BW extremes.

Gaps in knowledge

- Whether gender may affect safety and efficacy of antithrombotic drugs in morbid obesity and underweight patients needs more studies.
- Whether reference intervals of VKA and heparins should be similar for all body sizes remains unexplored.
- More data on DOACs vs. VKA are needed for class ≥2 obesity and underweight individuals.
- More studies should investigate DOACs and their DDIs in the context of obesity, its comorbidities, and frequently used co-medications.
- Whether LMWH prophylaxis at BW-adjusted or higher fixed-dose is more effective and equally safe vs. standard fixed dosing in class ≥2 obesity remains undetermined.
- RCTs on LMWH dosing strategies for VTE treatment in class ≥2 obesity are needed.
- Studies are needed on protamine sulfate dosing for UFH reversal and on PCC dosing for OAC reversal in class ≥2 obese patients.
- Randomized PD and/or clinical outcome studies in class ≥2 obese individuals comparing higher or more-frequent vs. standard ASA regimens are needed in patients with CVD, undergoing BS and in obese pregnant women requiring ASA.
- Clopidogrel in low BW and morbid obesity has not been adequately studied in RCTs.
- Whether the efficacy and safety of fibrinolysis are affected by BW extremes in STEMI, PE, and ischaemic stroke is unknown.
- Severe obesity remains largely under-represented in RCTs comparing TAT vs. DAT.
- The DDIs of novel GLP-1RA with oral antithrombotic drugs require caution and further investigation.
- How BS and new antiobesity drugs can influence the PK/PD of some antithrombotic agents needs further data.
- There is a clinical need to improve risk stratification and to extend thromboprophylaxis after BS in high-risk patients, but there are no RCTs of RAM to aid decisions. Cardiovascular RAM post-BS has not been sufficiently developed and validated.
- There is lack of data on the early and long-term antithrombotic prophylaxis post-BS and on how and when to resume the antithrombotic treatment after surgery.

Conclusions

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

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

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

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