ESC European Society of Cardiology

European Heart Journal (2018) **39**, 1672–1691
doi:10.1093/eurheartj/ehy066

Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis

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Received 24 August 2017; revised 8 November 2017; editorial decision 25 January 2018; accepted 8 February 2018; online publish-ahead-of-print 2 March 2018

Introduction

The success of trials that have shown net clinical benefits of antithrombotic drugs as well as the increasing prevalence of cardiovascular diseases in an ageing population have led to more widespread use of antiplatelet and anticoagulant drugs. At the same time, extremely low and high body weight (BW) are becoming more common due to a higher prevalence of frailty, associated with greater life expectancy, and the global epidemic of obesity, 'globesity', respectively.[1–3] These extreme BWs may affect cardiovascular risk as well as the pharmacokinetics of antithrombotic drugs, some of which have relatively narrow therapeutic windows.

The ESC Working Group on Thrombosis consequently assembled a task group to examine the key issues related to this topic and to address the question of whether modified antithrombotic management strategies are required for patients at the extremes of BW. Greater focus is given to obesity due to its higher prevalence among patients with cardiovascular disease and the associated complexities in terms of pharmacology and pathophysiology.

Definitions

The simplest and most universal definition of underweight, overweight, and obesity relies on body mass index [BMI; BW (kg) divided by the square of the height (metres) (kg/m^2)][1] (*Table 1*). Obesity is also defined as BW >20% above ideal BW (IBW),[4] and 'morbid' obesity as >100% above IBW. However, the exact definition of obesity, reflecting excess body fat, remains problematic. In addition to defining obesity, BMI shows a U-shaped correlation with mortality and

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Table 1 Classifications of different body mass categories

Classification	Body mass index (kg/m^2)[a]	Total body weight (kg)
Underweight	<18.5	<60 kg[b] or ≤ 56.2 kg[c]
	Sub-categories:	
	Mild thinness 17–18.49	
	Moderate thinness: 16–16.99	
	Severe thinness: <16	
Normal weight	18.5–24.99	≥60 up to 70 kg[b] or > 56.3 up to 76.6 kg[c]
Overweight (pre-obesity)	25–29.99	>70 up to 100 kg[b] or 76.7 up to 92.0 kg[c]
Obesity	≥30	>100 kg[b] or ≥ 92.1 kg[c]; or > 20% greater than the ideal body weight[d]
Class 1	30–34.99	
Class 2 (moderate obesity)	35–39.99	>100% greater than the ideal body weight[d]
Class 3 (severe or morbid obesity)	≥40	≥150 kg[b] or ≥ 122.9 kg[c]
Class 4 (super-obesity)[227]	≥50	>225% greater than the ideal body weight
Class 5 (super-super or extreme obesity)[228]	≥60	—

[a]According to the WHO classification for adults [≥20 years, female, and male subjects; http://www.who.int/topics/obesity/en/ (January 2018)] unless otherwise indicated.
[b]Thresholds often used to define underweight in RCT or clinical studies for both female and male subjects.
[c]According to the Centers for Disease Control and Prevention for adults (both male and female subjects) with height of 5 feet 9 inch [https://www.cdc.gov/obesity/adult/defining.html (January 2018)].
[d]Ideal body weight according to modified Devine's formula: men: 51.65 kg + 1.85 kg/inch of height greater than 5 feet; Women: 48.67 kg + 1.65 kg/inch of height greater than 5 feet.[226]

displays a complex relationship with cardiovascular diseases (*Take home figure*).[5,6] Using the BMI classification, obesity affects 33.9% of USA adults[1] and between 10% (Italy) and 23% (UK) of European adults,[1] with a steadily increasing prevalence worldwide.[1] Premature deaths are increased up to five-fold in morbidly-obese subjects.[5] The annual cost of treating obesity complications is estimated at ≈$51.6 billion in the USA[4] and ≈€81 billion in Europe,[7] corresponding to ≈2–8% of the total national healthcare expenditure in the European countries.

There are numerous drawbacks when using BMI to classify obesity and as a cardiovascular risk marker. First, fat mass, a contributor to cardiovascular risk, shows limited correlation with BMI, particularly in the older population.[8] Recent evidence suggests that BMI is a stronger predictor of mortality than adiposity,[9] probably because higher non-fat mass also increases vascular risk. This makes BMI a good marker of cardiovascular risk if not necessarily the best measure of adiposity.[10,11] Second, ethnic differences and the gradual global increase in BMI values cast doubts over the 'normal range' definition.[3,12] Third, BMI does not differentiate between metabolically-healthy and metabolically-unhealthy obesity, the latter characterised by increased visceral fat and insulin resistance, which are seen frequently in the metabolic syndrome.[13] Earlier studies suggested that metabolically-healthy obesity is associated with low cardiovascular risk, but recent work indicates increased vascular events in this population compared with lean individuals, albeit at a lower rate than metabolically-abnormal obesity.[14,15] To further complicate matters, studies suggest that overweight and class 1 obese individuals (*Table 1*) with established vascular disease have a better prognosis than their lean counterparts, commonly referred to as the 'obesity paradox'.[16,17] However, lower BW may be an indicator of ill health due to co-morbidities, potentially explaining the unfavourable outcome in the low BW group. Alternative clinic-based methods to diagnose obesity include BW, waist circumference (WC) and waist-to-hip ratio (WHR) (see Supplementary material online, *Table S1*). Although BW *per se* is an inaccurate obesity measure,[18] it remains clinically relevant because it is used to calculate drug doses. In contrast, WC is a good measure of abdominal and/or intra-abdominal fat, whereas WHR additionally reflects body composition in the gluteofemoral area. Waist circumference and WHR have shown associations with cardiac mortality,[19,20] and may better reflect obesity than BMI, particularly in older individuals and in 'sarcopenic obesity' (increased fat with reduced lean mass).[8] Whilst WC and WHR certainly have value in assessing obesity, these measurements can be cumbersome in daily practice and susceptible to errors compared with BMI.

Consensus statement

Although abdominal obesity may more accurately reflect cardiovascular risk, it is not systematically reported in trials and registries, and the focus of this review is on extremes of BW. Despite various flaws, BMI is the most frequently reported measure of obesity and a reasonable marker of cardiovascular risk. Therefore, this document will focus on BMI as an indicator of obesity, but will also refer to other measures, as appropriate, with a shift to BW when addressing drug doses. Given the U-shaped association between BMI and mortality, this document will also examine response to antithrombotic therapy and clinical outcome in individuals with abnormally-low BMI.

Increased or decreased body mass: thrombotic and bleeding risks

Thrombotic risk

In obesity, adipose tissue consists of adipocytes and different cell types in the vascular stroma,[21–24] releasing inflammatory and pro-coagulant mediators (*Figure 1*).[25–30] Moreover, obesity increases lipid

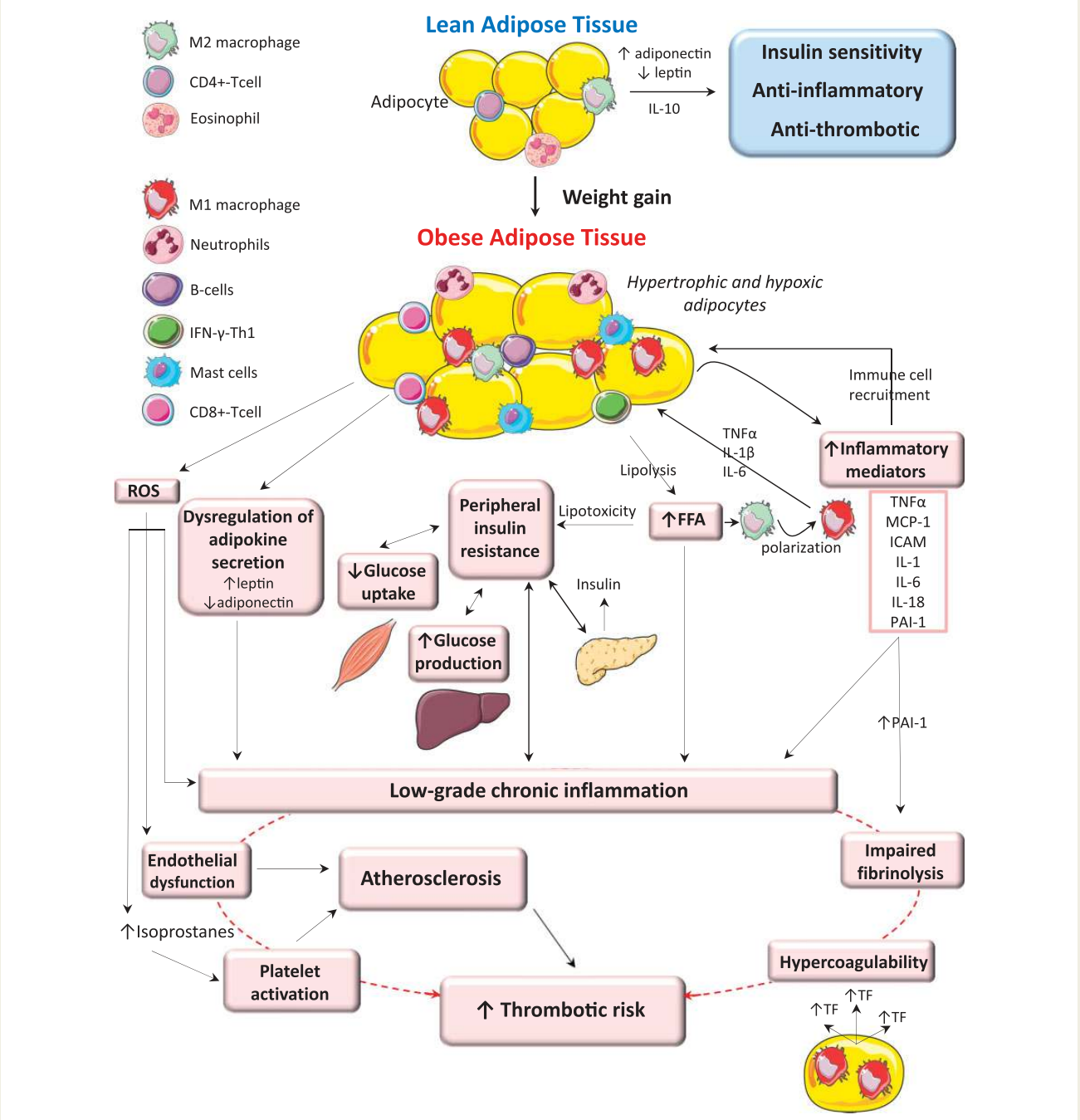


Figure 1 Pathophysiological consequences of obesity. Normal adipose tissue is composed of adipocytes and immune cells with anti-inflammatory potential (M2-macrophages, CD4 T cells, and eosinophils), contributing to interleukin-10 release, which, combined with secretion of adiponectin, exerts insulin-sensitizing, anti-inflammatory, and antithrombotic effects. During weight gain, adipocytes become hypertrophic, hypoxic and dysfunctional, releasing pro-inflammatory molecules that attract pro-inflammatory cells (neutrophils, CD8 T cells, B cells, mast cells, and interferon-γ-Th1). These cells amplify secretion of pro-inflammatory cytokines and chemokines into the bloodstream, promoting chronic low-grade inflammation. In addition, macrophages, polarized towards a pro-inflammatory M1 phenotype, remove the dead adipocytes and release tissue factor, which is the factor VII/factor VIIa receptor and physiologically triggers coagulation. Tissue factor/factor VIIa complex initiates pro-inflammatory and pro-angiogenic responses. Tissue factor/factor VIIa-proteinase-activated receptor-2 signalling promotes macrophage-mediated inflammation. Adipocytes and stromal cells express plasminogen activator inhibitor-1, especially in visceral adipose tissue, leading to increased circulating plasminogen activator inhibitor-1, which inhibits the urokinase- and tissue-type plasminogen activators and exerts anti-fibrinolytic and pro-thrombotic activities. Obesity also induces release of free fatty acids, which contribute to macrophage polarization and induce lipotoxicity, insulin resistance, isoprostane generation through reactive oxygen species and platelet activation. FFA, free fatty acids; ICAM, intercellular adhesion molecule; MCP-1, monocyte chemoattractant protein-1; TAFI, thrombin activatable fibrinolysis inhibitor; TNFα, tumour necrosis factor alpha.

peroxidation and isoprostane formation,[31] which can activate platelets.[32] Markers of platelet activation increase in obese subjects, including CD40L, P-selectin, microparticles, and urinary thromboxane metabolites.[33]

Poor vascular supply of expanding obese tissue can induce hypoxia and adipocyte cell death.[34,35] Cytokines from obese adipose tissue induce a low-grade systemic inflammation that promotes atherosclerosis, endothelial dysfunction, and a prothrombotic status (*Figure 1*).[30] Chronic low-grade inflammation, TF-dependent signalling, and free fatty acids release induce peripheral insulin resistance and exhaust insulin secretion, increasing the risk of type 2 diabetes.[23,36–38]

Epidemiological data demonstrating a relationship between increasing BW and thrombotic risk have been recorded since the mid-20th century.[39] However, a key issue is whether this association is causal. Even if causal, it is uncertain whether there is a direct impact of high BW on thrombotic risk or an indirect effect mediated by the higher prevalence of diabetes, hypertension, vascular disease, and immobility. Substantial BW loss, such as following bariatric surgery, has been shown to improve cardiovascular risk profile, at least in part due to decreased prevalence of co-morbidities such as diabetes, hypertension, and immobility.[40]

Venous thromboembolism

Studies of the incidence and prevalence of venous thromboembolism (VTE) have focused on hospitalized patients and identified risk factors including trauma, surgery, malignancy, heart failure, age and immobility.[39] Among patients with ultrasound-confirmed deep vein thrombosis (DVT), the most frequent risk factors are hypertension (50%), recent surgery (38%), immobility (34%), cancer (32%), and obesity (27%).[41] The risk of DVT is increased 2.5-fold in obese vs. non-obese subjects and, in 112 822 nurses, obesity (BMI ≥ 30 kg/m^2) independently increased the risk of pulmonary embolism (PE) 2.9-fold.[42] Factors contributing to post-operative VTE in obese patients include impaired fibrinolytic activity, the release of tissue thromboplastin and venous stasis during prolonged immobility.[43]

Arterial disease

In studies of coronary plaque morphology and cardiovascular deaths in women, elevated BMI, age, diabetes, and hyperlipidaemia were all associated with a higher frequency of plaque rupture.[44] Body mass index ≥30 kg/m^2 is associated with a higher cardiovascular mortality, when compared with other BMI categories (18.5–22.4; 22.5–24.9; 25–29.9 kg/m^2)[45] both in men and women, as shown by a prospective study of >100 000 subjects from the Nurses' Health Study and Health Professionals Follow-up Study, over 32 years of follow-up.[46] The same increase in cardiovascular events and mortality in obese subjects is true for Asian populations, especially for BMI ≥32.5 kg/m^2.[47] Elevated fibrinogen appears to be an independent risk factor for cardiovascular disease, with evidence suggesting a causal role in thrombosis and potentially a mechanism through which key risk factors, including obesity, may exert their pro-thrombotic effects.[48,49]

Significant weight loss following bariatric surgery in morbidly-obese subjects is associated with reductions in thrombin generation, cholesterol, triglycerides, and haemoglobin A1$_c$.[40,50] Experimental studies in obesity have also shown a receptor-dependent effect of leptin[51] on platelet function, suggesting the potential for non-surgical mechanisms to modify the excess thrombotic risks observed in morbid obesity.

Consensus statement

Amongst other adverse effects on cardiovascular risk, obesity is associated with a pro-thrombotic state and increases the risk of atherothrombotic events, VTE and cardiovascular mortality (*Take home figure*).

Bleeding risk

Spontaneous bleeding

Prospective studies of subjects with no previous vascular disease show a positive association between incident intracerebral haemorrhage (ICH) and BMI ≥30 kg/m^2, attenuated after adjustment for hypertension.[52–56] Specifically, among 900 000 adults followed on average for 13 years, the hazard ratio (HR) was 1.53 [95% confidence interval (CI) 1.32–1.78] per 5 kg/m^2 increase.[56] Extreme BMIs and location of ICH also appear relevant, as case–control multivariate-analysis studies have reported significant associations between lobar as well as deep ICH and BMI <18.5 kg/m^2[57,58] and, conversely, between deep ICH/microbleeds and obese BMIs,[59,60] the latter partly mediated by hypertension.[60] Thus, a U-shaped correlation may exist for deep, but not lobar, ICH across the BMI spectrum.[58] In 93 918 low-risk individuals enrolled in six aspirin primary prevention trials, the rate of major extracranial bleeding, but not of haemorrhagic stroke, increased significantly with increasing BMI (rate ratio = 1.24, 95% CI 1.13–1.35, per 5-kg/m^2 increase), independently of aspirin allocation.[61]

In adjusted analyses, examples of the so-called 'obesity paradox' among patients either diagnosed with or at high risk of vascular disease[17] include: (i) more incident ICH among low BMI (<24 kg/m^2)[58,62]; (ii) less haemorrhagic transformation after ischaemic stroke among patients with BMI above vs. below 25 kg/m^2;[63] (iii) BMI independently associated with better long-term survival post-ICH (hazard ratio = 0.91 per 1-kg/m^2 increase; 95% CI 0.87–0.95).[64]

Periprocedural bleeding

In patients undergoing percutaneous coronary intervention (PCI), underweight BMI <18.5 kg/m^2 has an increased risk of bleeding, and class 1–2 obesity a reduced risk.[65–67] Among 16 783 patients undergoing PCI at a single centre,[68] the incidence of transfusion across BMI followed a U-shaped pattern, with similar transfusion rate in class ≥3 obese and underweight patients, while class 1 obese patients had the lowest risk of major bleeding [odds ratio (OR)=0.68, 95% CI 0.48–0.97]. This association persisted after adjustment for confounders. The better outcome for bleeding in the middle of the BMI spectrum, from 25 to 34.9 kg/m^2, suggested the existence of a U-shaped 'bleeding obesity paradox' whereas severe obesity (≥40 kg/m^2) confers no apparent protection from bleeding[66,68] or premature death.[69] A recent USA registry of 96 381 patients undergoing PCI confirmed this trend,[67] and a Japanese study also showed the highest bleeding risk in the lowest BMI group.[70] Radial approach to PCI is particularly safer than the trans-femoral approach for patients with BMI <25 or >40 kg/m^2.[67]

Overweight and class 1 obesity (from 25 to 35 kg/m^2) do not seem to increase the risk of bleeding associated with transcatheter aortic valve implantation (TAVI) compared with normal BW, whereas data are too limited for class 2 and 3 obesity to draw definite

conclusions.[71–75] In contrast, patients with sarcopenia, evident in up to three-quarters of patients with BMI <25 kg/m^2 undergoing TAVI, had 55% increase in mortality.[73] Thus overweight and class 1 obesity seem protective for short and long-term mortality,[76] with a J-shaped trend whereby highest degrees of obesity (class ≥2) show association with increasing mortality vs. class 1/overweight categories.[77,78] Obesity does not appear to increase the risk of bleeding associated with cardiac surgery, although class ≥2 obesity, but not lesser degrees of obesity, as well as small body size are generally associated with adverse clinical outcome, including increased mortality;[79–82] in addition, any degree of obesity may increase the risk of sternal wound infection.[83,84]

Consensus statement

The available evidence suggests a U-shaped relation between BMI and spontaneous bleeding, with an enhanced risk of lobar and deep ICH, among underweight individuals, and a greater risk of deep ICH and extracranial bleeding among obese individuals, the latter partly explained by hypertension. Blood pressure should be carefully controlled in individuals receiving antithrombotic therapy, particularly those with obesity.

Compared with individuals with normal BMI, periprocedural bleeding may be increased in underweight (BMI < 18.5 kg/m^2) and class 3+ obese (≥40 kg/m^2) patients but not in patients with lower degrees of obesity. Radial, rather than femoral, access for PCI is particularly advisable for these patients, whenever feasible.

Underweight patients undergoing TAVR and cardiac surgery have a higher risk of mortality, and class ≥2 obese patients have also an increased risk of complications, including mortality, thus extreme BW categories need special surgical and post-surgery care.

Body mass-related and bariatric surgery-related changes in organ function relevant for drugs' PK

Obesity modifies body composition, including plasma proteins, kidney, liver and heart function (*Table 2*),[85–87] thus affecting absorption, volume of distribution (Vd), metabolism and/or elimination of several drugs. Bariatric interventions include restrictive and/or malabsorptive procedures[88] that, along with their impact on BW loss, variably affect gastrointestinal (GI) anatomy, motility and function, and may cause nutritional deficiencies (see Supplementary material online, *Table S2*).[89–92] Moderate and severe underweight (*Table 1*) are often associated with kidney dysfunction,[93] cancer, frailty, ageing, critical illness, and unhealthy life-style, which can variably affect some pharmacokinetic processes (*Table 2*). Additional details are in the Supplementary material online.

Consensus statement

Obesity, underweight and bariatric surgery generate major metabolic and organ changes that variably affect the pharmacology of several drugs. Pharmacokinetic data and *in silico* models are needed during drug development, especially for moderate-to-severe obesity (BMI ≥ 35 kg/m^2)[94,95] or underweight (<17 kg/m^2) and following bariatric procedures given the GI anatomical changes and major BW loss,[92,94] to predict the optimal regimen for BW-adjusted and fixed-dose drugs.

Oral and parenteral antiplatelet drugs

Aspirin

A study involving 100 aspirin-treated subjects with type-2 diabetes and 75 high-risk non-diabetic patients showed that increased BW independently predicted incomplete inactivation of platelet cyclooxygenase-1 by low-dose (100 mg daily), enteric-coated aspirin in both groups.[96] Higher values of BW or BMI have been consistently associated with lower aspirin responsiveness, as assessed by high residual serum thromboxane B_2, platelet function or urinary thromboxane metabolites in both healthy subjects and high-risk patients.[97–100] The organ and metabolic changes produced by obesity can markedly affect the distribution, binding and elimination of lipophilic aspirin.[101] Thus, a faster inactivation of aspirin may occur in the gut, plasma and/or liver through increased deacetylation by esterases and phase II conjugation enzymes, whose activity can be induced by obesity.[101] Lower bioavailability of some enteric-coated preparations of low-dose aspirin and poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition, particularly in heavier subjects.[99,100] Higher BW was associated with faster recovery of platelet cyclooxygenase-1 activity during the 24-h dosing interval, normalized by a twice-daily low-dose aspirin regimen.[96] A small study showed that also doubling the daily dose could restore a nearly-complete platelet thromboxane inhibition.[100] However, outcome studies are lacking.

In contrast to pharmacodynamic studies, a meta-analysis of six primary prevention trials of aspirin vs. control involving >95 000 asymptomatic subjects at low-to-average risk, showed that the proportional reduction in serious vascular events did not differ significantly (P for trend = 0.08) between BMI <25, 25–29.9, or ≥30 kg/m^2.[61] However, it should be emphasized that <20% of all serious vascular events occurred in subjects with BMI ≥30 kg/m^2,[61] thereby limiting the statistical power to reliably assess the efficacy of aspirin in this Subgroup. Two small studies on morbidly-obese patients (BMI ≥40 kg/m^2) suggest improved pharmacodynamics and pharmacokinetics of low-dose aspirin after bariatric surgery.[102,103] Obesity is associated with increased risk of colorectal cancer in the Lynch syndrome but this risk is abrogated by aspirin (600 mg daily).[104] Such patients may benefit from obesity prevention and/or regular aspirin. Importantly, a recent nationwide study of 601 527 users of low-dose aspirin showed an ≈30% relative risk increase of adverse ischaemic events soon after a non-clinically driven (i.e. absence of major surgery or bleeding) discontinuation of aspirin.[105] Adherence to aspirin may be particularly critical in the obese population, given their increased cardiovascular risk.

Consensus statement

In the absence of convincing evidence for superior GI safety of enteric-coated vs. plain aspirin, plain rather than enteric-coated aspirin formulation should be preferred when used as monotherapy in patients with BMI ≥35 kg/m^2 or BW >120 kg. Limited data are available on aspirin dosing for BMI ≥40 kg/m^2 and after bariatric surgery. It is reasonable to double the daily dose or shorten the dosing interval (twice-daily) for BMI ≥40 kg/m^2. Long-term adherence to low-dose aspirin treatment must be an important treatment goal, especially in the obese population.

Table 2 Organ changes according to BW changes and their effect on pharmacokinetics

Organ/apparatus	Obese vs. non-obese	Underweight vs. normal weight
Lean mass	↑ Decreased Vd for hydrophilic compounds	Normal or ↓ depending on the presence of malnourishment secondary to chronic diseases, smoking, disability, frailty, age, unhealthy lifestyle Increased Vd for hydrophilic compounds
Fat mass	↑ Increased or normal Vd for lipophilic compounds	↓ Decreased or normal Vd for lipophilic compounds
Lean and fat mass ratio	↓ Variable PK effects	Normal or ↑, depending on the causes of underweight Variable PK effects
Tissue perfusion	↓	Normal or ↓, depending on the causes of underweight
Blood volume	Increased	Normal or ↓, depending on the causes of underweight
Body water	↓ Lower concentration of drugs in low-perfused tissues	Normal or ↓, depending on the causes of underweight Variable PK effects
Acute phase proteins, free fatty acids, α1 acid glycoprotein	↑ Increased or normal protein-drug binding and reduced free plasma concentration	Normal or ↑, depending on the causes of underweight Variable PK effects
Heart	'Obesity cardiomyopathy', excess of epicardial fat, left ventricular hypertrophy, and dysfunction, left atrial enlargement. Mostly reversible with weight loss or bariatric surgery Variable tissue blood supply	Normal or ↓ function depending on co-morbidities Normal or reduced tissue blood supply
Liver	*Early stages:* Increase in hepatic blood flow; hepatic clearance normal or increased; normal or increased biotransformation *Later stages:* Non-alcoholic fatty liver or cirrhosis may develop	Normal or ↓ function depending on co-morbidities
Phase I enzymes (CYP450)	Reduced 3A4, Increased 1A2, 2E1, 2C9, reduced 2J2 expression or activities Variable CYP450-dependent biotransformation	Normal
Phase II enzymes	Increased glucuronidation and sulfation; increased biotransformation	Normal
Kidney	*Early stages:* Increase in kidney weight, GFR, blood flow. increased renal clearance *Later stages:* Chronic kidney disease may develop Drugs should be adjusted based on the measured rather than calculated CrCl on Cockcroft-Gault equation with actual BW which over-estimates CrCl in obese and morbidly-obese adults CrCl can be calculated on IBW, LBW or actual $BW_{0.4}$, however the reference equation remains undefined in obese (all classes) subjects	Normal or ↓ function depending on co-morbidities Cockcroft-Gault equation seems applicable to underweight adults

BW, body weight; CrCl, creatinine clearance; CYP450, cytochrome P-450; GFR, glomerular filtration rate; IBW, ideal body weight; LBW, lean body weight; Vd, volume of distribution.

$P2Y_{12}$ inhibitors

Thienopyridines: clopidogrel

Several studies have reported poor responsiveness to clopidogrel, expressed as reduced platelet inhibition and/or active metabolite concentration, associated with a high BMI or BW,[106–112] independently of type of body size descriptor.[112] BMI, age and lipid profile account for ≈25% of the variability in clopidogrel responsiveness.[110] An integrated pharmacokinetic modelling based on the Pharmacogenomics of AntiPlatelet Intervention study[110,113] showed that obesity class ≥2, associated with a poor- or intermediate-metabolizer genotype (homozygous or heterozygous for loss-of-function alleles in CYP2C19, respectively), would require ≥300 mg/day clopidogrel maintenance dose.[114] In the LEADERS trial, BMI independently predicted major adverse cardiac events at 1-year in patients on clopidogrel 75 mg daily.[115] Patients deemed low-responders had a significantly higher BMI [30 (15–66) vs. 29 (12-69) kg/m^2], and high-dose

clopidogrel (600 mg loading dose followed by 150 mg/day) was insufficient to overcome the poor response. However, BMI *per se* was not independently associated with clinical outcome in this study.[116] Conversely, BMI had no impact on clinical outcome in studies comparing a strategy of platelet function monitoring and dose-adjustment of antiplatelet therapy to a more conventional approach without monitoring/dose adjustment. This was unrelated to the patients' risk profile.[117,118]

Consensus statement

There is insufficient evidence to support modification of clopidogrel dosing or switch to more potent $P2Y_{12}$ inhibitor according to BMI or BW. However, significantly less clopidogrel active metabolite and lower degree of platelet inhibition are associated with class ≥2 obesity, especially in those with a poor or intermediate metabolizer genotype. ESC guidelines recommend a more potent $P2Y_{12}$ inhibitor in ACS patients without contraindication or requirement for oral anticoagulant therapy.

Thienopyridines: prasugrel

Studies on stable coronary artery disease (CAD)[112] and myocardial infarction (MI)[119] showed lower platelet inhibition and active metabolite concentration in prasugrel-treated patients with higher BMI and/or BW. However, this effect was not confirmed or was only modest in other studies,[120–122] including the pharmacokinetic analysis of the TRITON-TIMI 38 trial.[123] An observational study of obese CAD patients without ($n = 114$) and with ($n = 222$) the metabolic syndrome suggested that the reduced antiplatelet effect of prasugrel might be associated with the metabolic syndrome rather than obesity itself, although numbers of obese patients were too few to exclude an effect of obesity *per se*.[124] Prasugrel achieved greater platelet inhibition than clopidogrel after a loading dose in obese patients without diabetes but this difference was no longer significant after 1 week due to increase in platelet inhibition with clopidogrel maintenance therapy.[125] Prasugrel 5 mg in patients weighing <60 kg is associated with an exposure to the active metabolite similar to 10 mg in non-underweight patients.[126] In the TRITON-TIMI 38 trial, bleeding was largely confined to patients with lower BW and a high exposure to prasugrel active metabolite.[127,128]

Consensus statement

ESC guidelines recommend prasugrel in preference to clopidogrel regardless of BW or BMI in ACS.[129] The impact of high BW seems less relevant for prasugrel compared with clopidogrel. Halved prasugrel maintenance dose (5 mg/day) is recommended in patients weighing <60 kg.

Ticagrelor

The pharmacodynamics of ticagrelor depends on its plasma levels and, to a lesser extent, its active metabolite AR-C124910XX.[130,131] Moreover, ticagrelor has an effect on cellular adenosine uptake of uncertain clinical significance, possibly linked to adverse effects such as dyspnoea.[132] Both ticagrelor and AR-C124910XX levels are independently influenced by BW; in patients with prior MI, ticagrelor clearance was 6% higher and 11% lower, whereas AR-C124910XX clearance was 26% higher and 34% lower for those weighing 110 and 50 kg, respectively, compared with an 83 kg patient.[133] However, there is no evidence that BW has a relevant influence on either the efficacy or safety of ticagrelor. In the PLATO study, there were >5000 obese patients (28% of the trial population) and there was no significant interaction for the efficacy and safety endpoints with ticagrelor 90 mg twice-daily compared with clopidogrel in obese (BMI ≥ 30 kg/m^2) vs. non-obese patients, nor in those above vs. below 60 kg.[134] Similarly, in the PEGASUS-TIMI 54 study, there was no significant interaction for efficacy or safety with ticagrelor 90 mg or 60 mg twice-daily compared with placebo for those above or below 81 kg.[135] However, patients with diabetes mellitus appeared to have greater absolute risk reduction in ischaemic events, including CAD-related death, with ticagrelor.[136] Further modelling, using pharmacokinetic data, indicate a wide therapeutic window for ticagrelor, with variations in plasma levels having little impact on efficacy and safety.[137] There appears to be a modest relationship between ticagrelor plasma levels and dyspnoea, minor bleeding and ventricular pauses,[138–140] which is not so strong as to lead to a significant influence of BW on ticagrelor's safety and tolerability.[137,141] Paradoxically, in the PLATO study, patients with ticagrelor-related dyspnoea tended to have higher BW.[138] Doses as low as 60 mg twice-daily seem to provide a consistently high level of platelet $P2Y_{12}$ inhibition.[130]

Consensus statement

Ticagrelor is recommended in preference to clopidogrel in ACS patients without dose adjustment according to BW.[129] Limited data are currently available for morbidly-obese patients. Future research should establish whether ticagrelor 60 mg twice-daily should be considered as an alternative to 90 mg twice-daily in ACS patients weighing <60 kg.

Body mass and dual antiplatelet therapy duration

see Supplementary material online.

Glycoprotein IIb-IIIa inhibitors

Given their narrow therapeutic window, all available glycoprotein IIb-IIIa inhibitors (GPIs) (abciximab, eptifibatide, and tirofiban) must be carefully BW-adjusted. There are sparse data on the impact of BW on the safety or efficacy of GPIs. In the prospective, randomized TARGET trial, abciximab was compared with tirofiban in 4809 patients undergoing PCI with bare-metal stent implantation,[142] and 36% of the patients had BMI > 30 kg/m^2. With respect to thromboembolic events at 30 days (death, non-fatal MI, and urgent target vessel reintervention), there was no difference between obese and non-obese patients, while TIMI major bleeding was lower in the patients with higher BMI (0.4% vs. 1.1%, $P = 0.01$).[142] Six-month death and MI rates were similar in obese and non-obese patients.

Inaccurate weight-adjusted dosing of tirofiban and abciximab may be common and addressing this may reduce associated bleeding risk.[143] BW-adjusted dosing charts are often included in the insert package of some GPIs. The safety of GPIs on top of the increasingly used ticagrelor or prasugrel has never been studied.

Consensus statement

Care should be taken to avoid over- or under-dosing of GPIs by accurate determination of BW and reference to approved dosing tables, in order to administer the correct dose and reduce bleeding complications.

Cilostazol, Dipyridamole, Vorapaxar, and Cangrelor

see Supplementary material online.

Oral and parenteral anticoagulants

Vitamin-K antagonist

Limited data are available on the impact of BW and/or BMI on the pharmacokinetics and dosing of vitamin-K antagonist (VKA) at treatment initiation and during maintenance.[144–149] A significantly longer time to achieve a therapeutic International Normalized Ratio (INR) and higher dose requirement of VKAs have been reported for the initiation phase in obese, especially morbidly-obese, vs. non-obese subjects.[144,145] A positive correlation between BMI and warfarin maintenance dose has been consistently reported.[146–148] In one retrospective study of 831 patients, weekly maintenance dose increased by 0.69 mg per 1 kg/m^2 BMI increase.[148] Obesity has been independently associated with improved anticoagulation control in warfarin-treated elderly patients (≥75 years),[150] but whether this applies to younger patients remains unproven. Body mass index >30 kg/m^2 independently predicted anticoagulation reversal failure using weight-based prothrombin complex concentrates.[151]

While studies in underweight patients are lacking, data including wide BMI ranges (from 13.4 kg/m^2)[146–148] suggest a shorter time to achieve the therapeutic INR at initiation, and lower warfarin dose at initiation and maintenance in underweight vs. normal individuals. Therefore, in obese and underweight patients, the efficacy and safety profile might be different.[125–127] Moreover, whether the therapeutic INR range should be similar in underweight, normal-weight and severely-obese patients is unknown.

Consensus statement

While BW and/or BMI can affect warfarin dose requirement, their impact on clinical practice appears limited, given routine INR monitoring and consequent dose adjustments for maintenance of the therapeutic range. Closer surveillance may be needed in underweight and obese patients. The relationship between therapeutic INR range and BMI categories remains unexplored. In obese individuals with major bleeding on VKA, prothrombin concentrates should be used at appropriate doses (35–50 mg/kg)[152] and INR promptly and frequently monitored given the likelihood of reversal failure.

Direct FXa and FIIa inhibitors

In healthy subjects, apixaban maximal plasma concentration (Cmax) and the area under the curve (AUC) inversely correlate with BW (38–175 kg) and BMI (17–54 kg/m^2),[153] showing a ≈25–30% increase below 50 kg and ≈25–30% decrease above 120 kg vs. normal weight (65–85 kg). Phase III trial data of orthopaedic surgery prophylaxis showed a higher safety of enoxaparin vs. apixaban in underweight patients.[154] In the ARISTOTLE trial, safety and efficacy of apixaban vs. warfarin were similar in patients with non-valvular atrial fibrillation (AF) above and below 60 kg.[155,156] However, a proportion of underweight patients with age ≥80 years and/or creatinine ≥1.5 mg/dL already received a reduced dose (2.5 mg twice-daily). Among 17 913 not-underweight patients, 40% had BMI ≥ 30 kg/m^2 and only ≈5% a BMI ≥ 40 kg/m^2.[157] When compared with normal BMI, obesity was associated with lower mortality (OR = 0.63, 95% CI 0.54–0.74), but there were no differences in rates of stroke/systemic embolism (OR = 0.79, 95% CI 0.61–1.02), and major bleeding (OR = 0.91, 95% CI 0.74–1.1). However, in class ≥3 obese patients, 8 and 11 primary events occurred in the apixaban and warfarin arms, respectively, hampering any reliable conclusion.

Edoxaban Cmax is ≈40% increased in patients weighing <60 kg,[158] leading to 50% dose reduction in the HOKUSAI-VTE,[159] and ENGAGE AF-TIMI 48[160] trials for this category. In HOKUSAI-VTE, 12% of the patients were underweight and the primary outcome was comparable to the non-underweight population.[159] Half dose in the ENGAGE-AF trial resulted in ≈30% lower exposure to edoxaban,[161] which may explain the significant reduction of major bleeding vs. full dose edoxaban-treated patients, but differences in efficacy were not observed.[160] No data are available on edoxaban across different degrees of obesity.

The pharmacokinetics of rivaroxaban have been reported in patients weighing <50 kg (BMI 19.3 ± 1.1 kg/m^2) or >120 kg (43.5 ± 4.2 kg/m^2), showing no clinically-relevant changes in AUC and Cmax.[162] Pharmacokinetic models based on DVT[163] and ACS patients[164] have shown minimal influence of BW on Cmax. Consistently, obesity (i.e. BMI ≥ 30 kg/m^2) did not affect the safety/efficacy profile of rivaroxaban in the EINSTEIN-DVT and -PE,[165] EINSTEIN-CHOICE,[165] ROCKET-AF[166] (subgroups with BMI ≤ 25, 26–35, >35 kg/m^2) trials. However, the proportion of patients with class ≥2 obesity was ≈13% of the entire population and data should be interpreted with caution. A recent small phase I study on 10 mg single-dose rivaroxaban suggests no effect of bariatric surgery on the AUC in morbidly-obese patients.[167] In the COMPASS study, a pre-specified subgroup analysis showed no significant interaction between weight below and above 60 kg, and the primary safety and efficacy endpoint with rivaroxaban 2.5 mg twice-daily plus aspirin compared with aspirin alone. Patients <60 kg were 9.5% of the entire population and there was no pre-specified analysis for obese patients.[168]

The pharmacokinetic analysis of the RE-LY trial in AF patients showed that BW independently affected dabigatran concentration with ≈21% increase or reduction of dose-normalized plasma concentrations for BW <50 or >100 kg, respectively, vs. 50–100 kg.[169] BW significantly influences the apparent Vd of dabigatran (0.77% increase per 1-kg increase above 80 kg).[169] In RE-LY, patients weighing <50 kg and >100 kg were 2% and 16% of the total population (n = 18 113), without major effects on efficacy or safety across subgroups.[170] In the RE-COVER trial in VTE prevention, patients with BMI >35 kg/m^2 were 12% of the total population, with very few events.[149] Thus, information on dabigatran in different degrees of obesity is limited. For patients weighing <50 kg without renal impairment, a 'close clinical surveillance' is indicated without dose-reduction.[171]

Consensus statement

In underweight (≤60 kg) patients, edoxaban dose should be halved and apixaban dose should be halved if underweight is associated with renal impairment (creatinine > 133 µmol/L) or age >80 years. Dabigatran data below 50 kg are limited, high drug concentrations are reached and 'close clinical surveillance' is recommended. Rivaroxaban dosing does not require reduction. The bleeding risk of underweight patients should always be carefully evaluated. In obese patients, especially with BMI ≥40 kg/m^2, data are extremely limited or absent, thus questioning the use of direct anticoagulants in this category, in preference to VKA.[172,173] Peak and trough anti-Xa activity (FXa inhibitors), ecarin clotting time (ECT) or diluted thrombin time (dTT) (dabigatran) should be checked in severe obesity, switching to VKA if results are different-than expected.[172]

Evidence on direct oral inhibitors for DVT prophylaxis post-bariatric surgery is also limited.[143,144,167] Thus, low-molecular-weight heparins (LMWHs) might be preferred given a longer experience. Repeated measurements of anti-Xa activity or ECT should be considered for FXa and thrombin inhibitors, respectively, at short- and mid-term after bariatric procedures.

Unfractionated heparin

Because the anticoagulant response to unfractionated heparin (UFH) is highly variable among acute patients,[174] BW-based UFH therapy is routinely monitored and adjusted using the activated partial thromboplastin time (aPTT) in most clinical conditions, and the activated clotting time (ACT) during PCI or cardiopulmonary bypass surgery.[174] However, BW-based UFH dosing nomograms were developed with poor representation of obese patients, especially class ≥2.[175] Several subsequent studies showed that, for class ≥2 obesity (or BW >160 kg), the conventional nomogram tends to generate overdosing, with higher aPTT and/or shorter time to reach therapeutic aPTT when compared with normal, overweight, or class 1 obese patients.[176–179] This finding seems dependent on a progressive reduction in the Vd of UFH with increasing BMI, with a proportional loss of the direct linear relationship between BW and dosing (as reflected by aPTTs). Consistently, in different clinical settings (VTE, ACS, critical illness, AF), patients with class ≥3 obesity or BW >165 kg require ≈15–20% less BW-based UFH.[176,178,179] Some studies used adjusted BW rather than total BW to calculate UFH dosing in obesity.[178] However, the best body indicator for dosing UFH in obese patients as alternative to BW remains undefined. Moreover, an inaccurate BW estimate can affect a relevant fraction of acute patients and clinical outcomes.[143]

Consensus statement

BW-based UFH dosing seems to overdose patients with class ≥3 obesity. Due to the lack of validated algorithms in these patients, careful BW estimation and frequent ACT or aPTT monitoring is required.

Low-molecular-weight heparins

Prophylactic regimens

Fixed-dose enoxaparin shows an inverse linear correlation between the AUC or anti-Xa activity and BW between 50 and 150 kg,[180] with the lowest levels in moderately-to-severely obese patients.[181,182] Similar data are reported for dalteparin.[183] Thus, underweight or high degrees of obesity may achieve inappropriate anti-Xa levels. Consistently, some studies showed reduced efficacy of standard fixed LMWH dosing in class ≥3 obese patients, who also have a high associated VTE risk.[182–184] Thus, enoxaparin 40 mg twice- rather than once-daily or dalteparin 7500 rather than 5000 IU have been advocated for BMI ≥40 kg/m^2.[182,185,186] For BMI >50 kg/m^2 and normal creatinine clearance, up to 60 mg enoxaparin twice-daily has proven effective.[187,188] The ACCP guidelines recommend LMWH doses '*higher than usual for non-obese patients*' in obese subjects undergoing bariatric surgery (Grade 2C).[189] A pragmatic ≈30% increase of prophylactic fixed LMWH doses has been proposed in morbid obesity.[182] Moreover, BW-based prophylaxis has been tested in class ≥2 obesity, showing a superior anti-Xa target activity vs. fixed dosing.[183,190–193] BW-based prophylaxis seems superior to fixed dosing also in women with BMI ≥40 kg/m^2 undergoing caesarean sections.[194] However, whether better anti-FXa target levels correspond to a higher efficacy and whether increasing fixed dose is superior to BW-based dosing for class ≥2 obesity remain unknown.[55,183,195] Measuring anti-FXa activity can be useful in obesity class ≥3 or BW >190 kg, especially in high VTE risk patients, [183] but it is not routinely recommended.[55,181,182] Consistently, the product characteristics acknowledge lack of consensus for adjustment of prophylactic enoxaparin doses for BMI >30 kg/m^2 or BW >120 kg.[196] Also, dalteparin and tinzaparin have not been formally tested for BW >90 and >105 kg, respectively.[183] Conversely, an increased drug exposure with fixed prophylactic enoxaparin dose has been observed in low-BW women (<45 kg) and men (<57 kg), and in critically-ill patients with BMI ≤18.5 kg/m^2.[197,198] Considering that standard fixed-dose LMWH regimens might overdose underweight patients, small, preliminary, non-randomized studies investigated reduced-dose enoxaparin (<40 mg daily),[197,199] showing appropriate anticoagulation levels.

Consensus statement

Obese patients are likely underdosed with standard fixed once-daily LMWH regimens. Higher fixed daily or BW-adjusted dosing regimens have proven to be efficacious in high-risk, moderate- and morbidly-obese patients. BW-based prophylaxis may also benefit women with BMI ≥40 kg/m^2 undergoing Caesarean sections. Low-molecular-weight heparin at fixed dose should be carefully administered to underweight patients, although specific guidance for dose reduction remains undefined. For class ≥3 obese patients, especially at high thrombotic risk, or severely underweight patients at high bleeding risk, anti-Xa measurement can provide therapeutic guidance. However, the therapeutic anti-Xa range and sample timing in severely obese or underweight patients remain unknown.

Therapeutic regimens

Low-molecular-weight heparins in VTE and ACS are BW-adjusted, often with a dose-capping at the highest BW. In the SYNERGY trial, 4916 ACS patients were treated with enoxaparin 1 mg/kg SC every 12 h, without capping, with no significant differences in death, MI and major bleeding in relation to BMI. However, only ≈3% were morbidly-obese and only 23 patients in the entire study weighed >150 kg. Among enoxaparin-treated patients with BMI ≥35 kg/m^2, ≈13% received a lower than recommended dose.[200] The CRUSADE registry included >10 000 enoxaparin-treated ACS patients and

showed that patients receiving lower-than-recommended dose were more likely obese (average BMI 30.3 kg/m^2, BW 89 kg), with median initial doses of 0.65 vs. the recommended 1 mg/kg SC every 12 h in patients weighing >150 kg ($P < 0.001$).[201] Furthermore, patients weighing >150 kg and receiving 1 mg/kg SC every 12 h had higher bleeding vs. those receiving a lower dose (adjusted OR = 2.42, 95% CI 0.7–8.37). Based on the potential over-dosing for BW-based therapeutic LMWH regimens in obese patients, a dose capping is often applied in clinical practice. However, pooled analysis of the ESSENCE and TIMI 11b trials, which randomized uncapped enoxaparin (1 mg/kg) vs. UFH, including 1774 obese and 4979 non-obese ACS patients, showed similar safety and efficacy profile of each treatment independently of BMI.[202] The SYNERGY trial also used uncapped enoxaparin dosing, without evidence of increased bleeding. Anti-Xa monitoring can be considered in patients with BMI ≥40 kg/m^2 or >150 kg, but it is currently not routinely recommended.[181,182] A nomogram has been proposed for therapeutic dose adjustment based on anti-Xa monitoring in severe obesity.[43]

Consensus statement

There is insufficient evidence that dose capping results in improved safety or efficacy compared with a BW-based regimen without capping in class ≥2 obesity. Anti-Xa monitoring may be useful in class ≥3 obesity.

Fondaparinux

The elimination of fondaparinux increases with BW (9% increase per 10 kg).[203] For DVT or PE treatment, the daily dose is BW-adjusted (5, 7.5, and 10 mg for <50, 50–100, and >100 kg, respectively), provided renal function is normal.[203] The MATISSE trial showed the effectiveness of this BW-adjusted regimen.[204] However, the number of patients with vascular events and BMI >35 kg/m^2 was too limited to draw any definitive conclusion.[204]

Fondaparinux dosing in ACS and VTE prophylaxis is fixed (2.5 mg/die). The anti-Xa activity of 2.5 mg inversely correlates with BW between 40 and 100 kg.[205] In patients with VTE weighing <50 kg, the 2.5 mg fixed dose should be used cautiously[203] and is contraindicated by the FDA.[206] On the other hand, a small study on morbidly-obese patients showed an anti-Xa activity below target in ≈50% of patients.[207] The EFFORT trial compared higher prophylactic doses of fondaparinux (5 mg/die) and enoxaparin (40 mg twice-daily) in morbidly-obese patients undergoing bariatric surgery, showing an adequate anti-Xa activity in 74% and 32% of the patients, respectively.[208] The clinical readout of the anti-Xa levels is unknown.

Consensus statement

For therapeutic DVT and PE, fondaparinux is BW-adjusted. For fixed-dosing use in ACS and VTE prophylaxis, the data suggest a reduced anti-Xa activity for the 2.5 mg daily dose in morbidly-obese patients, but clinical data supporting any dose change are lacking. In VTE prophylaxis, fixed-dose fondaparinux should be avoided or used cautiously if BW <50 kg.

Bivalirudin

See Supplementary material online.

Fibrinolytic drugs

Streptokinase and the fibrin-specific plasminogen activators (alteplase, tenecteplase) are used in acute ST-segment elevation MI (STEMI), acute ischaemic stroke, PE, or mechanical heart valve thrombosis.[209–213] Among 444 STEMI patients receiving streptokinase or alteplase, 150 with ICH and 294 matched controls, BW <70 kg independently predicted ICH.[214] Importantly, in normal-to-obese patients neither streptokinase nor alteplase are BW-adjusted for STEMI. Alteplase is BW-adjusted only in patients <65 kg, while tenecteplase is administered by categories of BW with a capping >90 kg[215] (*Table 4*). The probability of artery patency after streptokinase seems inversely related to BW between 62 and 102 kg.[216] In acute ischaemic stroke, low BW does not appear to predict bleeding in alteplase-treated patients.[217] Deviations of ≥10% from the recommended dose, occurring in ≈20% of strokes[218,219] due to inaccurate estimates of BW, are potentially dangerous.[218] Conflicting data relate high BW to ICH risk: in a Swedish registry of 30 000 stroke patients receiving alteplase, BW ≥95 kg was an independent predictor of ICH.[220] However, in a USA registry of alteplase-treated stroke patients, 5174 patients with BW >100 kg, compared with 76 405 lighter counterparts, showed better survival, fewer ICH, but more moderate-severe disability at discharge.[221] Thus, it is unclear whether BW affects ICH and mortality risks in ischaemic stroke patients treated with BW-adjusted thrombolysis, especially class ≥2 obesity.[222]

Consensus statement

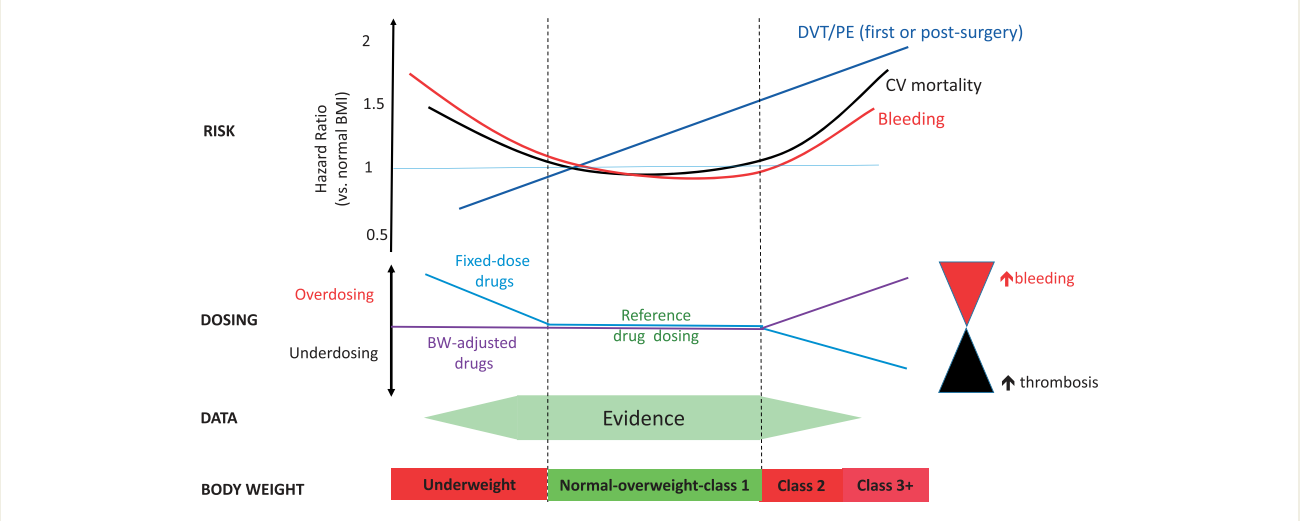
BW should be accurately assessed in patients treated with BW-adjusted regimens of fibrinolytic drugs.

Influence of race and gender on antithrombotics in addition to body mass

Race and gender may interact with body mass for some antithrombotic drugs. Overall, most of these interactions appear minor and without clinical relevance. Of note, dose-normalized dabigatran concentrations in women were ≈30% higher than in men, independently of BW and age, thus special caution should be exerted in underweight women on dabigatran.[169] Further aspects of these interactions and gaps in evidence are discussed in the Supplementary material online.

Key messages and gaps in evidence

- Complex relationships exist between body mass indicators, metabolic function and cardiovascular risk (*Take home figure*).
- Extremes of body mass have an impact on most antithrombotic drugs in terms of dosing, safety and efficacy (*Take home figure*) and must be carefully considered in the context of antithrombotic therapy (*Tables 3* and *4*).
- There is an urgent need for new data on heparin regimens (both LMWH and UFH) for prophylaxis and treatment of extremely obese patients.[225]



Take home figure Impact of body mass index on clinical events and antithrombotic regimens. Upper part: extremes of body mass index (underweight and higher classes of obesity) are characterized by U-shaped trends for extracranial and deep intracranial bleeding and cardiovascular mortality and a continuous increase in the risk of deep vein thrombosis and pulmonary embolism. Data are from references.[45–47,198,223,224] Mid part: reference therapeutic regimens and dosing of antithrombotic drugs are largely based on normal-overweight or class 1 obesity. Thus, fixed-dose drugs might be then over- or under-dosed in severely underweight or severely obese (class 2+) patients, and body weight-adjusted regimens can be over-dosed in severe obesity; this has the potential of impacting on the bleeding and thrombosis balance of each drug regimen, considering also the body weight-associated thrombotic and bleeding risk, independently of antithrombotic drug use. Lower part: high quality evidence on regimens and/or reference intervals have been developed on the normal to low-degree obese patients, while, below and above these categories, the quality of the evidence is progressively and exponentially poorer. In the bottom part of the figure 'Class' indicates classes of obesity as indicated in *Table 1*.

The present Working Group has selected specific pending issues that need to be addressed:

(1) Determining whether the benefit: risk ratio of oral fixed-dose antiplatelet and anticoagulant drugs can be improved using a BW and/or BMI dose adjustment.
(2) Reporting efficacy and safety data of antithrombotic trials according to BW/BMI as a subsidiary or pre-specified analysis, using established classifications of BW (e.g. underweight, normal weight, and classes of obesity), ideally via an independent data depository.
(3) Establishing the associated cardiovascular risk of obesity with or without diabetes and its implications for antithrombotic regimens, including the treatment selection, dosing, duration, and/or reference intervals.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

This article is dedicated to the memory of the late Professor Steen Husted.

Conflict of interest: B.R. reports institutional research grants, research grants from the Italian Medicines Agency (AIFA); consultancy fee from Bayer AG, speaker fees from Amgen, Celgene, Daiichi Sankyo Italia, Novartis Farma, Sanofi; K.A.A.F. reports institutional research grants and lecture fees from AstraZeneca, consultancy and lecture fees from Bayer/Janssen, Sanofi/Regeneron, and consultancy fees from Verseon; R.A.A. reports institutional research grants, consultancy fees, lecture fees and/or educational support from AstraZeneca, Abbott, Avacta, Bayer, Boehringer Ingelheim/Eli Lilly, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Merck Sharp & Dohme; F.A. reports consultancy fees from Actelion, Amgen, Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer, lecture fees from Bayer, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo and Menarini International Foundation; C.B. reports grants from Merck, Bayer, Novartis, and Pfizer that are governed by University of Oxford contracts that protect his scientific independence, and the Clinical Trial Service Unit & Epidemiological Studies Unit has a staff policy of not taking personal payments from industry (with reimbursement sought only for the costs of travel and accommodation to attend scientific meetings); J.P.C. reports research grants from Bristol-Myers Squibb and Medtronic, consulting fees from Bristol-Myers Squibb, and lecture fees from Bristol-Myers Squibb, Roche Diagnostics, Bayer and Servier; E.L.G reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, and Pfizer, advisory board participation for AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb; S.H reports speaker fees from Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Merck, Sanofi; consultancy fees from Bristol-Myers Squibb/Pfizer; K.H. reports lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer. Unrestricted scientific grant from AstraZeneca; J.M. reports consulting and lecture fees from Astra Zeneca, Bayer Healthcare, Boehringer Ingelheim, Merck Sharp and Dhome, Daiichi Sankyo; C.P. reports consulting and lecture fees from Amgen, AstraZeneca, and Bayer AG and an institutional grant from Bayer AG for investigator-initiated research; A.R.

Table 3 Antithrombotic, fixed-dose drugs in underweight and obesity

Drug (clinical use)	Underweight <18.5 kg/m^2	Normal weight (reference)	Obesity		
			Class 1 (30–34.9 kg/m^2)	Class 2 (35–39.9 kg/m^2)	Class ≥3 (≥40 kg/m^2)
Antiplatelet agents (clinical use)					
Aspirin (ACS, CAD, PAD, stroke, alone or in combination)	No change LoE 5[a]	75–100 mg o.d.	No change LoE 1[a]	Insufficient data Enteric coated aspirin should be preferred if possible LoE 3[a]	Small studies suggest to increase the dose, likely doubling the low o.d. dose or increase dosing frequency bid LoE 3[a]
Clopidogrel (ACS, CAD, PAD, stroke, alone or in combination)	No change LoE 5[a]	75 mg o.d.	No change	Reduced active metabolite generation especially in poor metabolizers LoE 3[a]	Reduced active metabolite generation. Pharmacokinetic models would predict increasing daily dose LoE 3[a]
Prasugrel (ACS in combination)	Reduce dose (5 mg) LoE 1[a]	10 mg o.d.	No change LoE 1[a]	No change LoE 2[a]	Inconsistent reports of reduced active metabolite of unknown clinical significance
Ticagrelor (ACS, prior MI, in combination)	No changes; further work needed on dose reduction from 90 to 60 mg bid (ACS) LoE 2[a]	90 mg bid for ACS (12 months); 60 mg bid for MI ≥ 1 year prior	No change LoE 2[a]	No change LoE 2[a]	Insufficient data
Vorapaxar (PAD, post-MI)	Limited data, caution in patients <60 kg LoE 1[a]	2 mg o.d.	No change LoE 2[a]	No change LoE 2[a]	Insufficient data
Anticoagulant agents (clinical use)					
VKA (VTE, AFib, mechanical valve replacement)	Close INR monitoring, consider the underlying bleeding risk LoE 5[a]	INR-adjusted regimen	No change LoE 2[a]	Close INR monitoring LoE 2[a]	Close INR monitoring also during reversal. LoE 2[a] Preferred oral anticoagulant strategy, also after bariatric surgery LoE 5[a]
Apixaban (AFib and VTE)	2.5 mg bid in patients <60 kg and: ≥80 years or serum creatinine ≥1.5 mg/dl LoE 1[a]	AFib: 5 mg bid; VTE: 10 mg bid 7 days and then 5 mg bid	No change LoE 1[a]	Insufficient data	Insufficient data, prefer VKA; monitor peak and through anti-Xa activity if used LoE 5[a]

Continued

Table 3 *Continued*

Drug (clinical use)	Underweight <18.5 kg/m^2	Normal weight (reference)	Obesity		
			Class 1 (30–34.9 kg/m^2)	Class 2 (35–39.9 kg/m^2)	Class ≥3 (≥40 kg/m^2)
Rivaroxaban (AFib, VTE; post-ACS)	No change for AFib and VTE. LoE 1[a]	AFib: 20 mg o.d.	No change LoE 1[a]	No change LoE 1[a]	Insufficient data, prefer VKA; check peak and through anti-Xa activity if used LoE 5[a]
		VTE prophylaxis: 10 mg o.d.			
	ACS (2.5 mg bid): caution if co-administered with clopidogrel and aspirin for BW < 60 kg LoE 5[a]	ACS: 2.5 mg bid			
	No change for AFib and VTE.				
Edoxaban (AFib and VTE)	30 mg for BW ≤ 60 kg LoE 1[a]	60 mg o.d.	No change LoE 2[a]	No data. Check peak and through anti-Xa activity if used LoE 5[a]	
Dabigatran (AFib, VTE)	Very limited data. Patients <50 kg have higher plasma levels and close surveillance is needed, especially if women LoE 2[a]	AFib: 150 mg bid	No change LoE 2[a]	Insufficient data. Check ECT or dTT if used. LoE 5[a]	No data, prefer VKA; check peak and through ECT or dTT if used. LoE 5[a]
		VTE prophylaxis: 220 mg o.d.			
LMWH-fixed dosing (VTE prophylaxis)	Risk of overdosing, Limited evidence with <40 mg o.d. enoxaparin in underweight patients LoE 2[a]	Depending on the type of LMWH. Enoxaparin 40 mg o.d.	No change LoE 2[a]	Increase dose/frequency in patients at high VTE risk or undergoing bariatric surgery (e.g. enoxaparin 40 mg bid) LoE 2[a]	Increase dose (≈30%) (e.g. enoxaparin 60 mg bid, dalteparin 7500 U) LoE 2[a]
		Dalteparin 5000 IU o.d.			Consider anti-FXa activity measuring LoE 3[a]
Fondaparinux-fixed dosing (VTE, ACS)	Contraindicated or reduced dose (5 mg o.d.) if BW < 50kg LoE 1[a]	VTE: 7.5 mg o.d.	No change (up to 100 kg) LoE 1[a]	VTE: 10 mg o.d. in subjects >100 kg	Limited data for VTE and ACS
		ACS: 2.5 mg o.d.		ACS: 2.5 mg o.d. LoE 1[a]	

ACS, acute coronary syndromes; Afib, atrial fibrillation; BW, body weight; bid, twice daily (bis in die); dTT, dilute thrombin time; ECT, ecarin clottin time; INR, international normalized ratio; LMWH, low molecular weight heparin; VKA, vitamin K antagonists; VTE, venous thromboembolism; Xa, activated Factor X.
[a]LoE: level of evidence according to the Oxford Center for Evidence Based Medicine [http://www.cebm.net/index.aspx? o=5653 (January 2018)]. For full prescribing details in VTE and dose adjustments according to clinical characteristics as well as dose regimens for VTE prophylaxis, see also the relevant Summary of Product Characteristics.

report consulting, lecture fees and institutional grants from Astra Zeneca, Bayer, Boehringer Ingelheim, BMS Pfizer and Daiichi-Sankyo; D.S. reports consulting and lecture fees from Eli Lilly, MSD, Pfizer, Daiichi Sankyo, Bayer Vital, Astra Zeneca and Roche Diagnostics, and research grants from Roche Diagnostics and Daiichi Sankyo; A.S. reports institutional research grants from Bristol-Myers Squibb/Pfizer, AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim; J.t.B. reports Advisory, consulting and speakers fees from AstraZeneca, Eli

Table 4 BW-adjusted antithrombotic drug regimens in underweight and obesity

Drug	Underweight <18.5 kg/m^2	Normal weight (reference)	Obesity		
			Class 1 (30–34.9 kg/m^2)	Class 2 (35–39.9 kg/m^2)	Class ≥3 (≥40 kg/m^2)
Antiplatelet agents (clinical use)					
Cangrelor (PCI)	Careful measure of BW to avoid overdosing LoE 5[a]	30 μg/kg IV Bolus, and 4 μg/kg/min infusion	Careful measure of BW to avoid underdosing LoE 5[a]		
GPIs (PCI)	Careful measure of BW to avoid overdosing Eptifibatide: BW-driven dosing chart in the FDA insert package for BW 37–59 kg Tirofiban: BW-driven dosing chart in the insert package for BW 30–62 kg	Abciximab: 0.25 mg/kg IV bolus, 0.125 μg/kg/min (maximum of 10 μg/min) IV infusion Eptifibatide: 180 μg/kg IV bolus, 2 μg/kg/min IV infusion (if CrCl ≥50 mL/min) Tirofiban: 25 μg/kg IV bolus and 0.15 μg/kg/min (if CrCl >60 mL/min)	Careful measure of BW to avoid underdosing LoE 2[a] 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		
Anticoagulant agents (clinical use)					
LMWH (ACS and VTE treatment)	No change LoE 2[a]	Enoxaparin: 1 or 1.5 mg/kg every 12 h Dalteparin 200 IU/kg	No change or dose capping for dalteparin (18 000 IU/d)	Unknown whether dose should be capped, anti-Xa measuring can be useful LoE 5[a]	
UFH (VTE treatment and ACS)	No change Careful aPTT or ACT monitoring for possible overdosing LoE 5[a]	Before coronary angiography: 60–70 IU/kg iv bolus (max 5000 IU) and 12–15 IU/kg/h infusion (max 1000 IU/h) monitoring aPTT; during PCI: 70–100 IU/kg iv in patients not anticoagulated, 50–70 IU/kg if concomitant GPI, monitor ACT	No change and careful aPTT monitoring for possible under- and over-dosing LoE 3[a]		
Bivalirudin (PCI for ACS)	No change BW-based dosing table in the insert package from 43 to 62 kg	0.75 mg/kg IV bolus and 1.75 mg/kg/h	No change BW-based dosing table in the insert package up to 152 kg	No change BW-based dosing table in the insert package up to 152 kg	No data >152 kg
Fibrinolytic agents (clinical use)					
All fibrinolytics (acute MI, PE)	Carefully check BW to avoid overdosing	Depends on the agent used	Careful measure of BW to avoid underdosing LoE 5[a]		Limited data
Streptokinase	Higher likelihood of achieving artery patency at 62kg vs. normal BW	1.5 × 10^6 IU IV infusion w/out heparins (30–60 min STEMI, 60min mechanical heart thrombosis; 120 min for PE)	No change	Worse artery patency for BW 100–105 kg vs. 62 kg	No data > 120kg
Alteplase	For patients <65 kg in STEMI 15 mg bolus, then 0.75 mg/kg over 30 min (up to 50 mg), then 0.5 mg/kg over 60 min (maximum 35 mg)	Patients >65–67 kg STEMI fixed dosing: 15 mg bolus, 50 mg over 30 min, then 35 mg over 60 min (max 100 mg) Stroke: 0.9 mg/kg Massive PE: 100 mg	Fixed regimen as in normal BW for STEMI Stroke: ceiling dose of 90 mg	STEMI: Ceiling dose: 100 mg Stroke: ceiling dose 90 mg (stroke)	No data

Continued

Table 4 *Continued*

Drug	Underweight <18.5 kg/m^2	Normal weight (reference)	Obesity		
			Class 1 (30–34.9 kg/m^2)	Class 2 (35–39.9 kg/m^2)	Class ≥3 (≥40 kg/m^2)
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: 0.25mg/kg Half dosing in patients older than 75	STEMI: 80–90 kg, 45 mg	STEMI >90 kg: 50 mg	STEMI: No data available Increase of clearance with increasing BW LoE 3[a]

ACS, acute coronary syndromes; ACT, activated clotting time; aPTT, activated partial thromboplastin time; BW, body weight; CrCl, creatinine clearance; FDA, Food and Drug Administration; GPI, glycoprotein inhibitors; IU, international Units; PCI, percutaneous coronary intervention; STEMI, acute ST-segment elevation myocardial infarction; PE, pulmonary embolism.
[a]LoE: level of evidence according to the Oxford Centre for Evidence Based Medicine [http://www.cebm.net/index.aspx? o=5653 (January 2018)].

Lilly, Daiichi Sankyo, the Medicines Company, Accumetrics, Boehringer-Ingelheim, BMS, Pfizer, Bayer, and research grants: from ZonMw, AstraZeneca; L.W. reports institutional research grants, consultancy fees, lecture fees, and travel support from Bristol-Myers Squibb/Pfizer, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, institutional research grants from Merck & Co., Roche Diagnostics, consultancy fees from Abbott. Holds two patents licensed to Roche Diagnostics; G.V. reports governmental research grants and lecture fees from Astra Zeneca; F.W.V. reports institutional grants from Bayer Healthcare, and consulting and speaker fees from Bayer Healthcare, Daiichi-Sankyo, BMS/Pfizer, Boehringer-Ingelheim, and AstraZeneca; T.W. reports institutional research grants, consultancy fees, lecture fees, or travel support from Astra Zeneca, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Medtronic, Menarini, Novartis, Sanofi Aventis, Sanova, Servier, Vifor: R.F.S. reports institutional research grants, consultancy fees and lecture fees from AstraZeneca, institutional research grants and consultancy fees from PlaqueTec, consultancy fees from Actelion, Avacta, Bayer, Bristol Myers Squibb/Pfizer, Novartis, The Medicines Company, ThermoFisher Scientific. All other authors declared no conflict of interest.

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