Update on antithrombotic therapy and body mass. A Clinical consensus Statement of the ESC Working Group on Cardiovascular

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

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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
AI: artificial intelligence
AM: Active Metabolite
AF: Atrial Fibrillation
aPTT: activated Partial Thromboplastin Time
ASCEND: A Study of Cardiovascular Events in Diabetes
AUC: Area Under the Curve
BARC: Bleeding Academy Research Consortium
bid: 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
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
ERAS: Enhanced Recovery After Surgery
ENGAGE-AF TIMI48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction
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: Intra Cerebral Hemorrhage
INR: International Normalized Ratio
ISAR-REACT: Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
i.v.: Intravenous
LBW: lean body weight
LMWH: Low Molecular Weight Heparin
MU: Marginal ulceration
NSTEMI: non-ST elevation MI
OAC; Oral Anticoagulants
od: Once Daily

OR: Odds Ratio
PAD: Peripheral Artery Disease
PCC: Prothrombin Complex Concentrate
PCI: Percutaneous coronary intervention
PD: Pharmacodynamic
PK: Pharmacokinetic
PE: Pulmonary Embolism
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

Abstract

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 in body composition, metabolism and organ function, 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 ~~increasingly~~ 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 optimising 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.

1.0 Introduction

The obesity epidemics continue to rise worldwide (globesity),[1,2] favored 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 euro 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] ~~is producing the so-called "dual burden household", whereby calorie restriction in adults is increasing the prevalence of underweight children and adolescents, except in Western Europe.~~ Particularly, severe obesity (**Table 1**) is rising in Europe and North America.[7,8] Notably, severely obese individuals aged 50-75 years have ~30% reduction of life in good health and half the years without chronic disease compared to non-obese individuals.[9] Conversely, the prevalence of underweight adult men and women has decreased, reaching <2% in the US.[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, heart failure-HF).[12] 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.[13] Moreover, severe obesity was uncommon when this concept was developed.[14]

Despite the health burden and costs, the extremes of body size remain under-represented or excluded from cardiovascular randomized clinical trials (RCT)[15] and drug development processes.[16] As both obesity and underweight differently affect the risk of thrombosis, bleeding and antithrombotic drug pharmacology,[17-19] 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.[20] 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 of antithrombotic drugs following bariatric surgery (BS),[21] and include data from artificial intelligence (AI) *in silico* models and simulations of antithrombotic drug regimens at the extremes of body size.[22]

2.0 Methodology and definitions

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

Body size classes are defined according to the World Health Organization (WHO) based on BMI, expressed as kg/m^2, and/or total body weight (BW) expressed in kg (**Table 1**).[25] While we acknowledge the limitations of BMI metrics versus adipose tissue imaging, waist-hip ratio or waist circumference (WC), 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.[26]

3.0 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.[27,28] 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 over-dosing 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**).[29]

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

Consensus statement

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

4.0 Arterial and venous thrombosis

Obesity is a risk factor for atherothrombosis[33,34] and venous thromboembolism (VTE)[35,36] (**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[35] and arterial thrombosis[34] in adulthood. A fourfold increase in coronary heart disease (CHD) for each 5 kg/m^2 BMI increase above 25 has been reported.[18] In a population study, BW at 20 years and midlife was directly associated with weight gain through life and subclinical coronary atherosclerosis.[34]

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.[33] In contrast, patients with low BMI and PAD show an increased risk of cardiovascular and all-cause mortality, limb ischemia and major cardiovascular events.[33]

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

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

Mendelian randomisation studies ~~show~~ suggest causality of ~~a causal link between~~ obesity ~~and~~ on VTE:[42,43] 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).[42] In the UK Biobank, each kg/m^2 BMI

increase was associated with a 10% increase in VTE,[43] and a BMI>40 was associated with a 3-fold increase in VTE (hazard ratio [HR] 3.4, 2.87-4.03) compared to normal weight.[44] 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 to class 1 obesity or normal BW.[45] In a registry of children born between 1930 and 1989,[46] a BMI >90th percentile at 7 and 13 years was associated with a ~1.5 fold increase in future VTE compared to lower BMIs.[46] In over two million women, pre-menopausal, class 3 obese women showed the highest VTE incidence versus 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.[47]

Underweight individuals show a low risk of VTE[48] (**Graphical Abstract**), but higher all-cause mortality and bleeding post-VTE as compared to normal-weight subjects.[49] Medically-ill, severely underweight patients (BMI 15) have a 3-fold increase in VTE during 77-day follow-up versus reference BMI (28), unlike class 1 to 3 obese subjects.[50]

Consensus statements

Obesity increases the risk of atherothrombosis.[34-36,41,46]

Mendelian randomization studies suggest causality of obesity on VTE ~~Obesity seems to be is causally related to VTE~~.[42,43]

Higher obesity classes show the greatest VTE risk.[47,48]

Underweight is associated with a lower risk of VTE,[47,48] but with a higher rate of post-VTE complications, including mortality.[49,50]

Whether underweight increases the risk of atherothrombosis is uncertain.[19]

4.1. Thrombosis after surgery

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

During 30 days post-BS in 600,000 morbidly-obese subjects (~20% BMI>50), VTE occurred in 0.3% of patients after SG and in 0.4% after RYGB.[55] In ~20,000 post-BS patients, VTE doubled in individuals with pre-surgery BMI>50 compared to BMI 35-50, regardless of age.[56] In >350,000 patients from a US registry, VTE was higher in individuals with BMI >60 undergoing laparoscopic RYGB or SG (ORs 1.85, 1.40–2.44 and 1.62, 1.32–1.99, respectively) versus BMI of 35-50.[57] VTE increased after laparoscopic RYGB, but not SG, in patients with a BMI between 50-59 compared to BMIs between 35-49.9.[57] Moreover, BS lowers long-term thrombotic risk. In 566 individuals with an average BMI of 40 and previous MI undergoing BS (RYGB or SG), MACE were reduced by 56% during 8-year follow-up versus controls.[58] Similarly, in a recent meta-analysis, long-term CVDs were reduced after all types of BS versus non-BS-treated obese individuals.[59]

Consensus statements

Obesity classes ≥2 are associated with the highest risk of VTE following major general as well as bariatric surgeries.[56, 57]

BS appears to lower long-term cardiovascular complications.[58,59]

5.0 Bleeding

Intracerebral haemorrhage (ICH) seems to differ at BMI extremes. Deep ICH/microbleeds seem linked with obesity, partly for associated hypertension, and with underweight[60,61] 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.[61]

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

5.1 Bleeding after invasive procedures

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

Trans-radial 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).[67] In transcatheter aortic valve implantation (TAVI), there is an L-shaped relation with BMI, and overweight-class 1 patients show the lowest mortality and complications rates,[68] with no additional protective effects for higher obesity classes.[69] However, in observational studies and TAVI registries, severe obesity is ~15%, thus under-represented.[70,71] Whether trans-carotid is

safer than trans-femoral access across all obesity classes is unknown.[72,73] A recent registry suggests lower 5-year mortality of surgical versus TAVI aortic valve replacement in class 1-2 obese subjects.[74] However, this was not confirmed in RCTs including only obesity class 1.[75]

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

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

Consensus statements

Most evidence indicates a U-shaped relationship between the extremes of BMI and unprovoked bleeding.[60,61]

Obesity may be associated with reduced non-access site bleeding after TAVI [69,77,78,82]

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.[72,73,83]

6. Oral anticoagulants (OAC)

6.1 Vitamin-K antagonist (VKA)

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.[84] In 10,167 post-VTE patients, BMI and time in therapeutic range (TTR) were linearly correlated, with the lowest TTR in patients with BMI<25 or BW<60 and the highest TTR in class 2-3 obesity[85] (**Graphical Abstract** and **Central Table 1**), which can also partly explain the 'obesity paradox' of better outcomes in VKA-treated obese patients, although more VKA-specific pathways can be involved.[86]

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

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 one year, but remains lower than pre-BS.[89] The fast reduction in warfarin dose post-BS can depend on anatomical upper GI, metabolic and nutritional changes.[27,28] 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**).[81]

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 4-factor PCC capping,[90] 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.[91]

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.[84,85,87,88,92]

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

Following BS, switching from parenteral to oral anticoagulation (VKA or 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 4 factor-PCC at BW-adjusted over fixed dosing, with prompt and frequent INR monitoring.[93,94]

6.2 Direct oral anticoagulants (DOAC)

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

~~analyses,~~ thus the number of those patients and events in each trial were small.[88,95] A recent meta-analysis of the 4 major RCTs totaling 89,494 patients with AF ~~and class 3 obesity~~, reported that a combined endpoint of stroke, systemic embolism, death and bleeding, i.e. the net clinical outcome, was lower with DOAC versus warfarin (HR 0.91, 95% CI, 0.87–0.95) in the whole obese (BMI ≥30) subgroup.[95] However, this composite benefit was attenuated at the highest BMIs (eg 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 to VKA.[95] ~~(OR 0.71, 0.62–0.81)~~. Another recent meta-analysis on 18 studies (16 observational), totaling 287,125 AF patients, showed a more favourable benefit and risk profiles of DOAC versus 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.[96] 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 warfarin.[97]A retrospective cohort of 5,183 patients with AF grouped for 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.[98] 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 BMI <18.5 and obesity class 3.[99] 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 ~~including~~ class 3 obesity was <5% of the trial population with 5 thrombotic events ~~with a non-significant 30% relative reduction in the area under the curve (AUC) for apixaban~~.[100] A recent meta-analysis including 13 studies of patients with VTE and BMI ≥40 or BW ≥120 showed a lower risk of both recurrent VTE and major bleeding associated with anti-Xa DOACs versus VKA (OR 0.72,

95% CI 0.57-0.91 and 0.74, 95%CI 0.58-0.95, respectively),[101] 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).[102] ~~A non-significant trend towards a similar efficacy and safety of anti-Xa DOACs and VKA has been reported in class ≥2 obese patients with VTE.~~ A meta-analyses of 5 observational studies in >6,000 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.[103] ~~for DOAC versus VKA report ~40% lower major bleeding~~. ~~However, in another retrospective cohort of class 3 obese patients, DOAC and warfarin showed similar efficacy and safety.~~ ~~One observational study~~ Some data suggested higher gastrointestinal bleeding risk associated with dabigatran compared to other DOACs.[104] ~~A retrospective study of AF patients on DOACs showed more major bleeding in severe obesity versus normal weight.~~ A systematic review of patients with an indication for OAC, concluded that rivaroxaban, apixaban, or dabigatran may be used at standard doses in all patients with BMI < 40, whereas rivaroxaban and apixaban have more data in those with BMI > 40.[105] 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 ~~from RCTs and observational studies (median BW>120, 84% BMI≥40)~~, with many patients with drug concentrations outside the intervals measured in the main phase 3 RCTs (**Tables 2 and 3**).[100,104,106,107] 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 ischemic stroke and major bleeding with DOAC versus VKA.[108] However, in a mixed-ethnicity AF cohort including 28.9% underweight patients, DOAC and VKA showed similar efficacy and safety,[109] while other studies reported a higher safety of DOACs in underweight individuals as compared to VKA.[110-112] 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.[95] Major bleeding probability was similar in DOAC-treated patients across all BMIs (from underweight to severe obesity), while for VKA was maximal at lower BMIs.[95] The probability of ICH was high in underweight individuals, independently of the OAC agent.[95] In the Swedish registry of 26,047 AF, DOAC-treated patients major bleeding and mortality were higher in underweight patients versus normal weight.[99]

Simulations based on population PK models, mostly derived from RCT available measurements for the anti-Xa DOACs,[113-115] did not show any major impact of extreme BWs as covariates significantly affecting PK/PD, while low-BW (<60) was often associated with reduced kidney function and affected mostly by dabigatran, as it is almost exclusively renally-excreted[115] (**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.[21,116] Apixaban and edoxaban are mainly absorbed in the small intestine, rivaroxaban in the stomach, dabigatran between the lower stomach and the duodenum.[31] Measuring drug levels may be useful in patients (re)starting DOACs post-BS after re-feeding, also considering their high BMIs and substantial post-BS malabsorption (**Figures 2 and 3**).[117]

Idarucizumab is a humanised monoclonal antibody fragment[118] 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 phase 3 RCT,[119] 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 class 1 and 2, DOACs show a benefit-risk profile similar to that of normal-weight individuals.[85,95-97,101]

Based on limited data, the anti-Xa DOACs appear effective ~~and safe~~ in patients with AF and/or VTE and obesity class ≥3.[96,120,121]

In underweight patients, anti-Xa DOACs appear safer than VKA.[95,110,111]

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*.[100,95,108,107,109]

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.[117,120]

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

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

6.3 Parenteral anticoagulants

6.3.1 Unfractionated heparin (UFH)

The highly-variable anticoagulant response to IV 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 STEMI, and in 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 60-80s.[122] Timely anticoagulation during IV UFH, facilitated by dosing nomograms, is associated with reduced complications in acute VTE,[123] but nomograms were developed with poor representation of obese patients. For patients with class ≥2 obesity (or BW>160), conventional nomograms tend to generate "overdosing" compared to normal or class 1 obese patients, as reflected by aPTT or anti-Xa measurements.[20] Overdosing of UFH may increase bleeding and require high doses of protamine for reversal in cardiac surgery, which may then increase bleeding and transfusions.[124]

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.[125] 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.[126] 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[127] compared protamine standard dosing versus 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,[127] although this study included patients ≤120 kg, with no data for morbid obesity.

Consensus statements

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

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

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

6.3.2 Low molecular weight heparin (LMWH)

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

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

heparins (UFH, enoxaparin, bemiparin or nadroparin) provided similar VTE protection and bleeding risk as standard, fixed-dose therapy (**Table 4**).[132] 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**).[133]

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.[134] In a systematic review, BW-based LMWH dosing suggested in post-surgical or medical patients with obesity was: enoxaparin 0.5 mg/kg od or bid, tinzaparin 75 IU/kg od,[105] and higher prophylactic LMWH dose has also been suggested by others (3,000-4,000 anti-Xa IU bid for class 3 obesity in VTE prophylaxis).[135]

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

A Cochrane review and a meta-analysis on thromboprophylaxis post-BS, concluded that higher-dose heparins (UFH, parnaparin, nadroparin, enoxaparin) provided little or no additive benefit compared to standard-dose prophylaxis.[21] 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.[138,139] A recent meta-analysis comparing augmented versus 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).[140] 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 RYGS (BMI 49.4±4.4), 4-week

treatment with 5,700 IU nadroparin, 1/3 had peak anti-Xa activity below target range, and the anti-Xa activity was significantly and inversely correlated with BW (TBW (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 bid, dalteparin 5,000 IU bid, or tinzaparin 75 IU/kg od).[105] Aside from dosing, the optimal duration of thromboprophylaxis remains unclear. Although the VTE risk following BS is low-moderate, it is high as compared to non-obese post-surgery patients and still the main cause of mortality.[141,142] The majority of VTE occur after discharge, ~70% within the first month.[141] Risk assessment models (RAM), like the Caprini score[143] or the BariClot tool developed for BS[144] 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.[136,137]

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.[105,132,133,135]

The use of BW-based or 'higher than usual' fixed doses of LMWH are advised in obesity grade ≥2 or BW >120 following BS.[105]

Extended VTE prophylaxis post-BS may be appropriate in patients at high thromboembolic risk.[143,144]

In non-bariatric surgery or medical in-patients, whether a higher-than-standard dose of LMHW 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.[21,140]

Therapeutic dosing. A meta-analysis[133] included studies of patients with obesity on heparin for VTE, AF or CAD and compared BW-based standard (1 mg/kg) versus reduced (<1 mg/kg, average 0.8 mg/kg) dosing. 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) versus 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.[105] A recent registry of VTE treatment showed fewer complications with reduced, BW-based dose LMWH.[145]

For tinzaparin the treatment dose in patients with BW >120 has not been determined[146] and for dalteparin dose capping is indicated by the FDA at BW <56 and >99[147] based on studies in cancer patients (**Central Table 1**). However, some guidelines suggest using BW-adjusted dosing and avoiding capping.[131,148]

In ACS ESC Guidelines, where acute invasive angiography is not anticipated, enoxaparin at a standard BW-based dose (1 mg/kg bid) without capping has a class 2 recommendation.[122] However, based on previous studies,[20] bleeding increases in patients weighing >150 kg receiving 1 mg/kg twice-daily enoxaparin versus 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 to 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.[149]

Consensus statements

Current LMWH therapeutic regimens for VTE[105] and ACS[122] are BW-adjusted, with dose-capping at the highest BWs. However, there is insufficient evidence that dose capping improves safety or efficacy as compared to a BW-based regimen with no capping in obesity class ≥2.

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

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

6.3.3 Fondaparinux

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

Consensus statements

In VTE prophylaxis, fixed-dose fondaparinux is not advised if BW <50 kg.[150,151]

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

7. Antiplatelet drugs

7.1 Acetylsalicylic acid (ASA)

An individual patient data, post-hoc meta-analysis of ten, placebo-controlled RCTs suggested a lower antithrombotic efficacy of 75-100 mg once-daily ASA in participants weighing ≥70 compared to <70 kg, while ASA doses ≥325mg had the opposite interaction (**Table 5**).[153] 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 BMI <25 or >30 and/or BW <70 or ≥70 were consistent with the main trial's populations (**Table 5**).[154-157] In the ASCEND placebo-controlled RCT involving diabetic patients in primary prevention,[158] ASA 100mg od was significantly more effective than placebo in individuals with BMI >30 or BW >70 versus lower values (**Table 5**). In the ADAPTABLE secondary prevention, RCT, ASA 325mg was not superior to 81mg in reducing MACE in the overall population and in pre-specified BW subgroups below and above 70kg[155] (**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,[159] a large study compared standard 81mg (n=1,097) versus weight-adjusted dosing (n=1,187), 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 to 81 mg with no differences in safety.[160]

Consistently with RCT data, ASA PD is similar in class 1 obese vs. non-obese subjects,[161] while class ≥2 obese subjects on 100 mg ASA od (mean BW 111±21 and BMI 39.4±5.1)[162] 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 BW >110 or BMI >35.[162] Consistently, patients on secondary prevention with 100mg daily ASA and average BW >102 or >BMI 38[163] or in the highest BMI or BW quartiles,[164,165] showed lower peripheral platelet inhibition ~~response~~ versus non-obese individuals, ~~while they adequately responded to an~~ and a degree of inhibition similar to non-obese subjects was obtained by doubling the od dose.[163,165] Notably, doubling the low-dose aspirin dose does not inhibit cyclooxygenase 2 *in vivo*.[166,167] Among 1,002 pregnant women on

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

In silico PK/PD model and simulations of ASA predicted a reduced platelet inhibition in moderate-to-severe obesity, which was reproduced by ~~halving~~ reducing the systemic bioavailability from 50% (as in normal subjects) down to 25%.[169,170] According to the model, either doubling low-dose od (eg 200 mg) or a twice-daily low-dose restored the PD response.[169] Whether an optimal PD translates into an improved clinical benefit-risk profile remains to be established. Consistently, in the RECOVERY trial[171] that randomized hospitalized COVID-19 patients to 150 mg ASA od versus 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.[20] Data are summarized in the **Central Table 2**.

Consistent with reduced response and drug bioavailability in morbid obesity, ASA PD improved after BS,[172] with increased AUC and Cmax[28] few months post-RYGB or SG, likely reflecting higher absorption and drug ~~exposure~~ bioavailability following BS and weight loss.[173]

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

Consensus statements

No change in low-dose ASA dosing is advised for obesity class 1.[155,158,163]

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

Post-BS, continuing low-dose ASA, when indicated, is advised together with a PPI for gastroprotection.[172,178]

7.2 $P2Y_{12}$ inhibitors

7.2.1 Clopidogrel

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

PK/PD *in silico* model for clopidogrel confirmed BW as significantly and inversely affecting AM formation, AUC and platelet inhibition,[180] especially for class≥2 obese individuals.[181] Model simulations predicted the need for higher loading and maintenance doses in severely-obese versus over- and normal-weight subjects to reach similar platelet inhibition.[180] For BMIs >35 and intermediate- or poor-metabolizer status based on *CYP2C19* alleles, the model predicts that clopidogrel maintenance dose should be increased to 300 and 450mg, respectively.[180] 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.[182]

BMI was linearly correlated with high residual $P2Y_{12}$-dependent platelet aggregation in patients on dual antiplatelet therapy (DAPT) with clopidogrel,[183] and a similar phenotype was reported for TAVI patients.[184] In a study using the ABCD-GENE score which includes BMI >30[185] as a factor reducing clopidogrel response, obese patients had the highest residual ADP-

dependent platelet aggregation.[186] 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.[187] However, none of the above studies included severe obesity. A sub-study of the HOST-EXAM RCT analyzed the 2-year adverse outcome in patients on ASA 100 mg or clopidogrel 75mg.[188] Patients with BMI <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 BARC type ≥3 bleeding.[188] The clinical significance of post-hoc analyses of a small non-inferiority trial combining safety and efficacy primary endpoints remains unclear. In the CHANCE RCT on east-Asian patients with minor stroke or TIA, BMI<25 and normal glycated hemoglobin or absence of *CYP2C19* loss-of-function alleles were associated with higher benefit with DAPT-clopidogrel than with ASA monotherapy,[189] while DAPT-clopidogrel was not superior to ASA monotherapy in patients with BMI >25 and no loss-of-function *CYP2C19* alleles.[189] However, these data are limited to a specific ethnicity and are a post-hoc analysis.

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

7.2.2 Prasugrel

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

secondary prevention of cardioembolic stroke in elderly or underweight (<50 kg) patients.[192] In Japan the 3.75 mg formulation has been approved to improve safety and reduce bleeding.[192] In the 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 versus DAPT- low-dose (5 mg) prasugrel.[193] In a subgroup analysis of the ISAAR-REACT-5 RCT, low-dose prasugrel had comparable efficacy but reduced by 30% BARC3-5 bleeding as compared to ticagrelor (90 mg twice-daily) in elderly (>75 years) or with low BW (<60 kg) post-ACS patients[194] 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.[195]

7.2.3 Ticagrelor

Class 1 obesity does not appear to affect ticagrelor PD, while data in class ≥2 obesity are limited.[196] 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.[197] A PK model developed from Asian population's data, showed that low BW, advanced age (inversely) and hypertension predicted bleeding on ticagrelor.[198]

Plasma concentration of ticagrelor, its AM and platelet function at peak and trough in 221 patients on DAPT (ASA plus ticagrelor 90 or 60 mg BID) 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, >30 or BW <85 or >85) was directly correlated with BW and BMI.[199] A post-hoc analysis of the TWILIGHT RCT showed comparable efficacy and safety (BARC 2-5 bleeding) between SAPT-ticagrelor and DAPT (with ASA), in high-risk post-ACS patients, whether normal or obese.[200] 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 TICO trial, BW ≤65 kg, haemoglobin ≤12g/dL, and GFR <60 mL/min/1.73m^2 predicted bleeding in ticagrelor-treated patients.[201]

In a post-hoc analysis of the CHANCE-2 RCT, patients with minor ischaemic stroke or TIA, *CYP2C19* loss-of-function alleles and BMI>28 had a reduced risk of recurrent ischaemic stroke at 90 days when receiving DAPT-ticagrelor versus DAPT-clopidogrel as compared to BMI<28.[202] 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.[191]

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.[180,181,184]

CYP2C19 polymorphisms may particularly affect clopidogrel PD at loading and maintenance dose in underweight or class 2-3 obese individuals, although the clinical impact is unknown.[186,187,189]

No significant difference in efficacy and PK of ticagrelor between normal and obesity class 1 has been reported.[196,197]

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.[189,194,195]

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

Ticagrelor or prasugrel are advised over clopidogrel in class≥2 obese patients,

especially when loss-of-function allele(s) are documented.[180,181]

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

8. Triple antithrombotic therapy (TAT)

See Supplemental material and **Table S5.**

Consensus statements

In class >=3 obese patients undergoing PCI, a longer duration of initial TAT as well as individualization of the doses and/or intervals of administration of antithrombotic drugs, both in TAT and DAT may be appropriate.[203-206]

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

A strict implementation of bleeding prevention and gastroprotection are advised in underweight patients on TAT, owing to the increased bleeding risk, regardless of the type of OAC.[206,207]

9. Dual pathway inhibition

See Supplemental material

Consensus statements

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

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

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

See Supplementary material and **Central Table 2**

Consensus statements

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

The efficacy and safety profile of GPIs in underweight (<18.5kg/m^2) and class ≥3 obese individuals is uncertain.[210]

11. Fibrinolytic drugs

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

Consensus statement

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

12. Interactions between antithrombotic and BW-reducing drugs

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

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

administered. Tirzepatide, a combined GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, by delaying gastric emptying may affect the bioavailability of concomitant oral drugs.[218] By in-vitro-in-vivo modelling, slow gastric emptying does not influence rivaroxaban bioavailability[219] Delayed gastric emptying has variable effects on the absorption of ticagrelor based on studies in patients treated with opioids,[220,221] but no information is available for BW reducing drugs.

Orlistat is an inhibitor of the intestinal CES-1 and -2[222] 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.[223] Reduced CES-2 activity lowers ASA hydrolysis.[223,224] Orlistat has been reported to enhance VKA effects, thus closer INR monitoring INR might be necessary.[225]

Consensus statement

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

13. Antithrombotic drugs under development

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

14. 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 versus 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 sulphate 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 versus DAT
- The DDIs of novel GLP-1RA with oral antithrombotic drugs require caution and further investigation.
- How BS and new anti-obesity 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 RCT 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.

15. 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, 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 personalised medicine, AI and precision clinical pharmacology (**Graphical Abstract**).

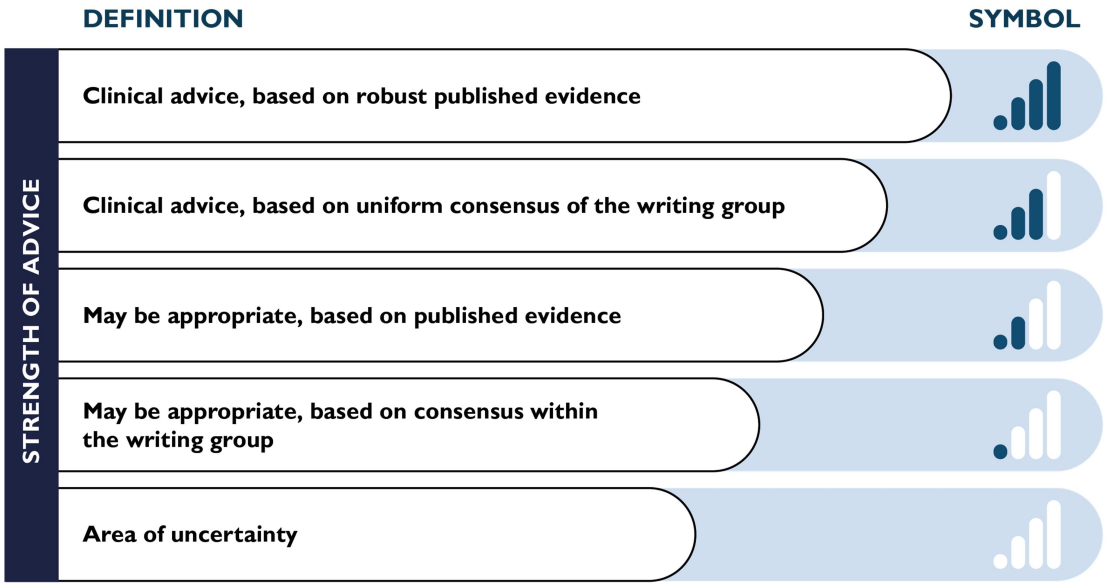


Figure 1. Scale and symbols representing the strength of advice statements, based on evidence and consensus of the writing group, as recommended for the ESC scientific documents.

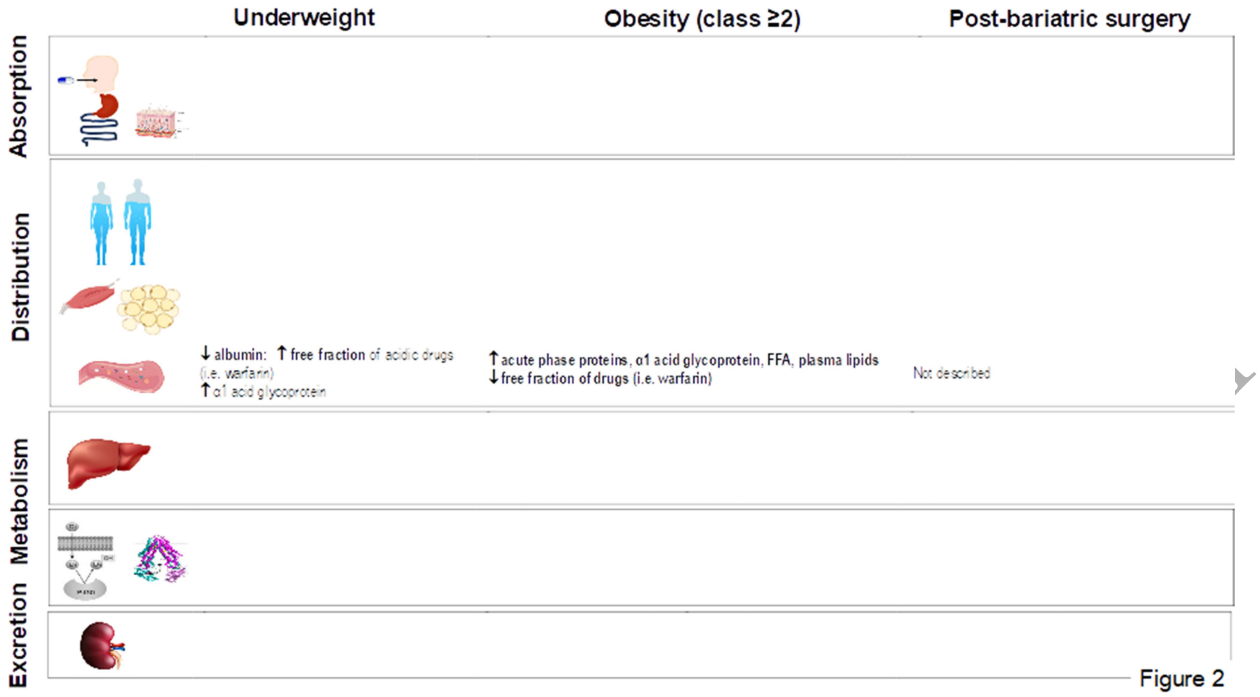


Figure 2. Antithrombotic drugs can be affected by marked changes in body size in each step of their pharmacokinetics, i.e. absorption, distribution, metabolism and excretion. Underweight is commonly associated with co-morbidities, reduced renal function, and changes in plasma proteins. Severe obesity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

Note to the Figure. Data post bariatric surgery refers mainly to Roux-en-Y gastric bypass surgery. ** Oral liquid formulations should not contain nonabsorbable sugars due to dumping syndrome risk; open capsules if allowed according to the summary of product characteristics. Based on references[230-232,32,233] **Abbreviations**: BMI: body mass index; 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

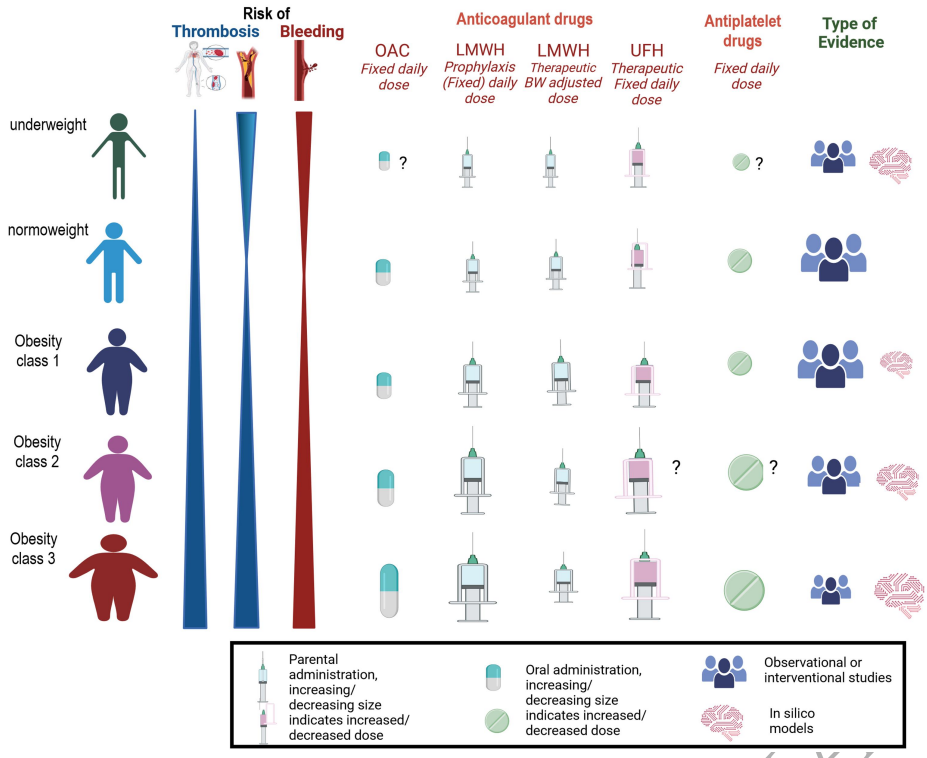
Consider measuring the plasma concentration for DOAC to fall within known intervals at trough and/or peak

more frequent INR monitoring for VKA

Figure 3

Figure 3. The figure depicts relevant steps in managing morbidly obese individuals who have one or more ongoing indication(s) for antithrombotic drugs and undergo bariatric surgery. The figure depicts 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 or prophylaxis) persists.

Abbreviations: 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



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 BMI classes. Despite the low risk of underweight individuals, underweight seem 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 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 RCT 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 BW-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 used, this may result in underdosing at the upper extreme of body size. Further details are reported in the **Central Table 1** and **Central Table 2**. **Abbreviations**: LMHW: low molecular weight heparin, OAC oral anticoagulation. UFH: unfractionated heparin.

Data Availability statement

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

Disclaimer

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

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

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

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

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

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

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

treatment. * e.g in bariatric surgery, previous VTE, strong family history of VTE, thrombophilia; ** should not be used if moderately (eGFR <60 ml/min/1.73 m^2) - severely (eGFR <30 ml/min/1.73 m^2) reduced renal function.

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

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

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

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

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

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

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

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

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

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

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

§§ Ideal Body Weight according to modified Devine's formula: Men*: 51.65 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 [234] ***[235] ^ [236].

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

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

			Overweight (n=111) Obesity class 1 (n=135) Obesity class 2 (n=45) Obesity class 3 (n=99)	
Cohen et al, 2021[100]	RCT AMPLYFY (n=5,384) Post-hoc analysis	Apixaban vs Warfarin	VTE BW ≤60 (n=476) >60-<100 (n=3868) ≥100-<120 (n=750) ≥120 (n=290)	Comparable efficacy and safety of apixaban vs warfarin across body weight subgroups in patients with VTE
Katel, et al 2021[103]	Systemic review and meta-analysis of 5 observational studies	DOAC vs Warfarin	VTE BMI ≥ 40 (n=542) or BW ≥ 120 (n=6100)	Comparable efficacy and safety of DOAC vs warfarin in severe obese patients with VTE No considerations based on obesity classes
Mhanna, et al 2021[97]	Systemic review and meta-analysis of 10 observational studies and 2 RCTs (n=89,494)	DOAC vs Warfarin	AF BMI ≥ 40 (n unknown) or BW ≥ 120 (n unknown)	Better efficacy and safety of DOAC vs warfarin in severe obese patients with AF No considerations based on obesity classes
Nakao, et al 2022[109]	Retrospective Propensity score matching (n=29,135)	DOAC vs Warfarin	AF BMI (kg/m2) <18.5 (n=585) ≥18.5-<25 (n=8427) ≥25-<30 (n=10705) ≥30-<35 (n=5910) ≥35 (n=3508)	Comparable efficacy and safety of DOAC vs warfarin across obesity classes 1-3 in patients with AF
Zhang, et al 2023[101]	Meta-analysis of 11 observational and 2 RCT studies	DOAC vs Warfarin	VTE BMI ≥ 40 (n=6902) Weight ≥ 120 kg (n=7746)	Efficacy and safety of DOAC vs warfarin were improved in severe obese patients with VTE No considerations based on obesity classes
Salah, 2023[239]	Meta-analysis of 12 observational studies	DOAC vs Warfarin	AF BMI ≥30/≥40 (n unknown)	Better efficacy of DOAC vs warfarin in severe obese patients with AF No considerations based on obesity classes

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

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

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

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

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

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

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

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

	Chemo + mechano vs Mechano alone Ahmad 2021: Combined mechanical and pharmacological prophylaxis versus mechanical prophylaxis alone. 40 mg x 1 enoxaparin 12 h before then daily for 2 weeks + mechanical, the other group on mechanical prophylaxis, n=150, Note – silent DVTS	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, Cochrane Database of Systematic Reviews 2023[252]	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, Cochrane Database of Systematic Reviews 2023[253]	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

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

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

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

		70 kg		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	
Petrucci et al., 2019[162]	Proof of concept, intervention study including 16 healthy and morbid obese (mean BMI 39.2± 5.1 kg/m^2) subjects	ASA 100-mg od for 3-4 weeks	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 hours 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 relationship 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 od or 100 mg bid would be needed for re-establishing an adequate response
Finneran et al., 2019[168]	1002 pregnant women with pre-eclampsia	Double-blind, randomized, placebo-controlled trial comparison of 60 mg ASA od versus placebo	PD assessed by maternal serum TXB_2 levels at 3 time points: randomization (13-26 weeks' gestation), second trimester (at least 2 weeks after	Among stratified BMI low-dose ASA groups, women with class 3 obesity had the lowest odds of undetectable TXB_2 levels in the second trimester (adjusted odds ratio [aOR], 0.33; 95% confidence interval	The 60 mg dosing is rarely used as compared to other regimens in the low-dose range (75, 81,100 mg). High-risk morbid obese women receiving low-dose ASA for the prevention of

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

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

2021[155]	CVD and indication for secondary prevention with ASA	mg or 325 mg of ASA per day. Median BW 90 kg	death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke, assessed in a time-to-event analysis. Primary safety outcome was hospitalization for major bleeding.	1.02; 95% confidence interval [CI], 0.91-1.14); no difference in safety (HR 1.18; 95% CI, 0.79 to 1.77). Subgroup analysis according to BW threshold of 70 kg did not show any heterogeneity of results.	of BW was 103 kg) The subgroup analysis according to BW of 70 kg was not pre-specified
Tang et al., 2021[256]	Retrospective review of 1,578 knee or hip arthroplasties including different BMI categories: normal (n=335), overweight (n=511), class 1 (n=408), class 2 (n=232), class 3 (n=92)	Efficacy and safety of ASA 81 or 325 mg/day prescribed is safe and effective in obese versus normal-weight patients undergoing arthroplasty	Primary endpoint: 90-day postoperative VTE Other endpoints: bleeding, wound complications, deep infections, and mortality	No difference in the incidence of VTE and other complications across different BMI categories	Observational study, ASA doses non-randomly assigned.
Puccini et al., 2023[183]	Cross-sectional study Patients with chronic CAD and a normal BMI (BMI 18.5–25 kg/m2, n=23) or obese (BMI ≥ 25 kg/m2, n=41)	ASA 100 mg/day and clopidogrel 75 mg/day.	Evaluate the platelet reactivity in overweight and obese patients and chronic CAD treated with dual antiplatelet therapy	Assessed by impedance aggregometry in patients with CCS receiving DAPT (ASA plus clopidogrel).	Very small observational study. The clinical significance of platelet aggregation is currently unknown.
Portela et al.,	24,770 patients post RYGB, 1911	Meta-analysis of observational	Incidence of marginal ulceration post RYGB	Patients on low-dose ASA did not have an increased risk	Low-dose ASA can be safely resumed post BS.

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

Abbreviations: AA: arachidonic acid; ASA: acetylsalicylic acid; ADP: adenosine diphosphate. BMI: body mass index. BS: bariatric surgery; BW: body weight (kg); CAD: coronary artery disease; CCS: chronic coronary syndromes; CV cardiovascular. CVD: cardiovascular disease. DAPT: dual antiplatelet therapy; EC: enteric-coated. FU: follow-up. MACE: Major adverse CV events. HR: hazard ratio; MI: myocardial infarction. PD: pharmacodynamics; PK: pharmacokinetics; RCTs: randomized clinical trials. RYGB: Roux-en-Y gastric bypass surgery; RR: relative risk; $sTXB_2$: serum thromboxane B_2; SVE: serious vascular events; VTE: Venous thromboembolism; ASCEND: A Study of Cardiovascular Events in Diabetes. ASPREE: Aspirin in Reducing Events in the Elderly