Antithrombotic therapy at extremes of body weight:

an expert position paper of the ESC Working Group on Thrombosis

Supplementary material

1. Methodology and how we reached a consensus

Members of the writing group were chosen based on their area of expertise, considering the plan of the document. They prepared their contribution in pairs, consistently within their area of expertise. They also drafted each consensus statement at the end of their section. The entire document was then assembled by the two Chairs, circulated to all the writing group Members, who discussed and proposed changes (when applicable) for the entire document, including the consensus statements. The extent of disagreement before full consensus was reached was expressed on average by 10% (or less) of the Authors who made proposals of changes for the consensus statements. In the final submitted version, all the consensus statements were read and approved by each member of the writing group.

2. Changes in organ function and bariatric surgery

The volume of distribution (Vd) generally increases with body mass index (BMI) and total body weight (BW) seems a suitable size descriptor for Vd.[1] In the absence of kidney and liver dysfunction, clearance can also increase and lean BW (LBW) seems a suitable indicator for predicting clearance changes.[1] Drug properties, co-morbidities and degree of obesity further widen variability in drug response. Due to several, sometimes opposing and time-dependent obesity-associated changes, the overall effect of moderate and severe (class ≥2) obesity on drug pharmacokinetics is poorly predictable,[2] and critical for drugs with a narrow therapeutic index. Approximately 15% of drugs targeting '*blood formation, coagulation and thrombosis*' and 10% of cardiovascular drugs are BW-adjusted, while 30% and 50% of them have kidney function-adjusted dosing, respectively.[3] Indirect body size descriptors (BMI, BW, LBW, ideal BW) have limitations in defining drug dosage because they rely on the assumption that body composition is similar in obese and non-obese subjects. Thus, the optimal descriptor to inform therapeutic strategies in obese patients remains undefined.[1, 4] The pharmacokinetic effects of obesity on other cardiovascular drugs are summarized in **Table S3**. Importantly, cardiovascular drugs have limited pre-marketing evidence for moderate-to-severe obesity and underweight (BMI >35 and <17kg/m^2, respectively), and these patients are underrepresented in randomized trials.

Bariatric interventions include restrictive (sleeve gastrectomy, adjustable gastric banding) and/or malabsorptive (Roux-en-Y gastric bypass, duodenal switch) procedures[5]

that, along with their impact on BW loss, variably affect gastrointestinal anatomy, motility and function, and cause nutritional deficiencies.[6, 7] Data on the long-term effects of different bariatric procedures on the pharmacokinetics of orally-administered, fixed-dose drugs are limited and heterogeneous.[7, 8] Roux-en-Y gastric bypass, by increasing gastric pH and accelerating stomach emptying, can affect gastric-pH-dependent oral drug absorption.[8, 9] The residual length of small bowel and/or colon can affect absorption and biotransformation (**Table S2**).[8, 10] These effects appear drug- and procedure-dependent.[11]

3. Oral and parenteral antiplatelet drugs

3.1 Dipyridamole

Dipyridamole is a pyrimidi-pyridimine compound that inhibits platelet phosphodiesterase thereby preventing the degradation of cyclic AMP (c-AMP) to AMP, which reduces platelet reactivity. Dipyridamole at high doses may prevent platelet adhesion to exposed vascular sub-endothelial tissue. The real benefit in the setting of cardiovascular diseases was never demonstrated beyond particular evidence in the secondary prevention of stroke. A network meta-analysis[12] showed the benefit of a combination of aspirin 50mg plus dipyridamole 400mg against placebo [OR 0.69 (CI 95% 0.56, 0.89)] at the cost of a clear increase in the risk of any bleeding [OR 1.95 (CI 95% 1.43, 2.78)]. In the PROFESS study, obesity (BMI ≥30 kg/m2) did not influence the incidence of the primary outcome in the aspirin plus dipyridamole arm.[13]

Consensus statement: There is no evidence to support modification of dipyridamole dose according to BW or BMI.

3.2 Cilostazol

Cilostazol is a phosphodiesterase III inhibitor with multiple pharmacological effects that include vasodilation, inhibition of platelet activation and aggregation. Cilostazol is approved in some countries to manage peripheral artery disease (PAD), but the benefit in cardiac disease is limited to reduction in the rates of in-stent restenosis without any significant benefit for MACE.[14].

Consensus statement: There is no evidence to support modification of cilostazol dose according to BW or BMI.

3.3 Vorapaxar

Vorapaxar is a selective antagonist of the protease-activated receptor-1 (PAR-1), on human platelets, approved in post-MI patients without a previous history of stroke or TIA and in patients with PAD, on the basis of the TRA 2P-TIMI trial.[15] Vorapaxar achieves a high level of PAR-1 inhibition following a loading dose or after more than 2 weeks of 2.5mg daily maintenance dose without current evidence of safety concerns related to plasma level.[16] As compared to subjects in the normal-to-overweight range (60-100 kg), subjects weighing <60 kg show a higher exposure to vorapaxar, as reflected by a 35% and 33% increases in Cmax and area under the curve (AUC) respectively.[17] Obese subjects (defined as BW >100 kg) show a ≈20% less exposure, according to the same parameters.[17]

Consensus statement: Based on pharmacological and clinical trial data, caution is recommended in administering vorapaxar to patients with BW <60kg,[17] also considering the increased bleeding risk associated with this category of patients, while there is no evidence to modify dosing in heavier (>100 kg) patients.

3.4 Cangrelor

Cangrelor is an intravenous, reversible platelet $P2Y_{12}$ inhibitor, achieving high level of receptor inhibition at the therapeutic dose. Currently, there is no evidence to suggest that any action other than standard, careful BW-adjusted dosing is required. Patients weighing <60 kg were ≈5% of the CHAMPION PHOENIX trial, which randomized 11,145 patients to BW-based cangrelor or fixed-dose clopidogrel (300 or 600 mg). The primary outcome (death, MI, revascularization and stent thrombosis at 48 hrs) was unaffected by low BW (OR 0.75 95%CI: 0.39-1.45; and 0.79, 95%CI 0.66-0.94, below and above 60 kg, respectively, p=0.35).[18] The moderate/severe GUSTO bleeding rates in the cangrelor arm were 0.5% and 2.2% in patients above or below 60 kg, respectively, but the absolute numbers were too small to allow any statistically-meaningful analysis.[18] Higher drug clearance has been reported in heavier patients,[19] however the impact of BW on drug exposure is addressed by the BW-based dosing. Moreover, care is required if transitioning from cangrelor to either clopidogrel or prasugrel since it blocks the binding of clopidogrel and prasugrel active metabolites to the $P2Y_{12}$ receptor and this negative interaction might be exacerbated by relative underdosing of clopidogrel or prasugrel in class ≥2 obese patients.

Consensus statement: current evidence does not support modifying BW-based drug dosing of cangrelor in under- or over-weight patients. Transition from cangrelor to either clopidogrel or prasugrel should be performed with care. An accurate measure of BW is needed, especially at extremes of BW in order to avoid under- or overdosing.

5. DAPT duration and Body Mass.

There is no available sub-analysis for any BW range (high and/or low) in the majority of the trials exploring different DAPT duration, and namely the DES-LATE, EXCELLENT, ITALIC, OPTIMIZE, PRODIGY, RESET, SECURITY, IVUS-XLP, ISAR-SAFE, and OPTIDUAL trials, and also a recent meta-analysis of DAPT duration trials did not include BW data.[20]

The PEGASUS-TIMI 54 trial included clinical outcomes according to BW using groups above and below the median BW of trial participants of 81kg, showing no significant interaction between these BW categories in clinical outcomes. The DAPT trial included a pre-specified above and below BMI 30 kg/m2 that showed safety and efficacy outcomes consistent with the overall trial population in obese patients. The I_LOVE_IT trial, comparing 6 vs. 12 months DAPT with biodegradable polymer sirolimus-eluting stents, included a sub-analysis below and ≥30 kg/m^2 BMI, which showed a trend in favour of a 12-month DAPT in obese subjects, although the total number of events in the obese patients was very low (4 in the 6-months and 1 in the 12-months DAPT groups).

The 2016 ACC/AHA Guidelines directly indicate that low-body weight (<60 kg) 'may favour shorter duration DAPT' based on the increased bleeding risk associated with this condition, while there is no mention of obesity. The 2017 ESC guidelines on DAPT duration take into consideration the available risk scores for bleeding, which do not include BW as a factor and do not make any direct recommendation on duration concerning BW. However, patients with diabetes mellitus appeared to have a greater absolute benefit from prolonged DAPT in PEGASUS-TIMI 54, including reduction in CAD-related death. Type 2 diabetes mellitus is often associated with obesity as well.

Consensus statement: For low BW, carefully consider the degree of underweight and associated co-morbidities when deciding DAPT duration. For high BW, data on BMI >35 kg/m^2 are missing but the presence of diabetes mellitus associated with obesity may favour prolonged DAPT following MI.

4. Parenteral anticoagulants

4.1 Bivalirudin

Bivalirudin has BW-adjusted dosing for use in PCI (**Table 4**) as well as other rare indications (heparin-induced thrombocytopenia, medical management of non-ST-elevation ACS)[21] and optimal dosing can be controlled by ACT. BW-based dosing of bivalirudin is the

most accurate predictor of achieving target aPTT in obese patients with heparin-induced thrombocytopenia and it was suggested that different dosing strategies are not warranted between obese and non-obese patients.[22] A large retrospective registry showed that bivalirudin decreased bleeding and transfusions as compared to UFH in different obesity classes (from 1 to ≥3); however, the in-hospital mortality was similar for the two drugs in morbidly-obese patients.[23] Still, this non-randomized, retrospective comparison cannot clarify the safety of bivalirudin over UFH throughout the entire BMI spectrum. The ACUITY[24] (bivalirudin vs. UFH or enoxaparin with or without GPIs in ACS) and HORIZONS-AMI[17] (bivalirudin vs. GPI plus UFH in MI) trials did not include pre-specified analyses according to BW or BMI.

The MATRIX trial comparing bivalirudin vs. UFH in ACS patients undergoing PCI included a subanalysis for BMI below and ≥ 25kg/m^2, showing a net clinical benefit in favour of bivalirudin vs. UFH in patients in the overweight range ((≥ 25kg/m^2) as compared to the non-overweight counterpart (p=0.019 for interaction).[19]

The recent VALIDATE-SWEDEHEART trial has recently compared BW-adjusted standard regimens of bivalirudin vs. UFH in MI patients undergoing PCI with the radial-artery access and without planned GPI use at 180 days.[25] The rate of the primary composite endpoint (death, MI, major bleeding) was similar in the two treatment arms, and the pre-specified underweight group (<60 kg, ≈5% of the total population) showed no preferential benefit of UFH vs. bivalirudin as well. A pre-specified analysis for obesity was not reported.

Consensus statement. Bivalirudin is given as a BW-adjusted dosing. Few data are available on efficacy and safety in morbidly-obese or underweight patients.

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

Gender has been repeatedly shown to impact on the prescription of both antiplatelet and anticoagulant drugs[26, 27] with women frequently being undertreated.

Genetic differences seen between different races may have pharmacokinetic implications for some antithrombotics. Here we discuss these issues for individual agents.

5.1 Antiplatelets

Aspirin. The largest meta-analysis of the primary and secondary prevention trials, found no evidence to support a gender-based difference.[28] There are no clinical data on the effects of race on aspirin, because trials generally enrol too few minority groups to allow subgroup analyses to be conducted reliably.

Clopidogrel. A collaborative meta-analysis of four, placebo-controlled trials showed no statistically significant differences of clopidogrel efficacy and safety in men vs. women.[29] Asiatic patients have higher frequency of 2C19 loss-of-function alleles vs. Hispanics and Caucasians[30, 31] and, within the carrier group, Asian patients undergoing PCI seem to have worse outcome as compared to Caucasians.[32] Thus, obese Asian patients might be particularly exposed to clopidogrel poor responsiveness. However, given also the evidence of an overall increased bleeding risk in Asians vs. Caucasians (the 'East Asian paradox'),[33] further data on clinical outcome in the obese populations are needed.

Prasugrel. PK studies showed that gender influenced active metabolite generation by <8% after adjusting for BW and age,[34] which is a threshold considered not-clinically relevant. The TRITON-TIMI trial showed no differences according to gender[35]. Asians seem to generate 20-30% higher active metabolite after both loading and maintenance dosing of prasugrel,[36] which seems only in part explained by an average lower BW,[37] but its clinical impact, especially in underweight or obese patients, remains unknown. There was no pre-specified analysis based on race on the TRITON-TIMI trial.

Ticagrelor. Neither gender nor race appeared to affect the efficacy or safety of ticagrelor in the PLATO trial.[38-40]

However, regarding race, it should be remarked that post-hoc analyses of race in individual trials that have yielded extreme results should be disregarded, unless replicable, and future pre-specified analyses are required. Overall, evidence on race is scarce and a need exists to include East Asian patients in trials to assess the efficacy and safety of prasugrel and ticagrelor over clopidogrel.[41]

5.2 Oral anticoagulants

Vitamin-K Antagonists (VKA). In an analysis of the AMADEUS trial data, women tended to have lower Time in Therapeutic Range (TTR) compared to men.[42] Ethnicity has also been shown to influence drug prescriptions with black patients having poorer control of the quality of warfarin than white and hispanic[43]. Indeed, besides gender and other variables, race is a predictor of TTR in the SAME-TT2R2 score.[44] Whether again this influence is mediated by differences in body mass cannot be established given the lack of dedicated analyses.

Anti-Xa agents. There is no evidence that gender[45, 46] or race[46-48] have a major clinically-relevant impact on rivaroxaban and apixaban. For edoxaban, female patients show ≈13% lower clearance, which is not clinically relevant.[49] Consistently, in the ENGAGE trial,

pre-specified subgroup analyses did not show any influence of gender and ethnicity,[50, 51] although Asians were only 10% of the total enrolled population.

Dabigatran. Dose-normalized dabigatran concentrations in female subjects were significantly ≈30% higher than in males in the RE-LY trial, independently of other variables.[52] Subgroup analyses for gender in this trial did not show significant effects, but females were under-represented as compared to males.[53] Very large population studies on dabigatran usage showed that female gender was associated with higher bleeding than males as compared to the VKA-treated counterpart,[54] and independently predicted GI bleeding as compared to the dabigatran-treated male conterpart.[55] Therefore, female, underweight patients might be particularly exposed to high dabigatran concentration and bleeding risk, as compared to males. Dabigatran PK and clinical profiles seem unaffected by race.[53, 56, 57] Overall, it should be underlined that Hispanic and Black ethnicities are consistently poorly represented in all phase III trials of direct oral anticoagulations, and the majority of ethnicity-related differences refer to non-Hispanic White vs. Asian races.[58] This is particularly relevant in the context of obesity, because of the sharp increase in class 2+ obesity in non-Hispanic Blacks and Hispanics (https://www.cdc.gov/obesity/data/adult.html; https://stateofobesity.org/disparities/; accessed Oct 2017).

5.3 Parenteral anticoagulants

UFH. There is one report suggesting that Asians might have a slight prolongation (14 sec within the 300-350 sec range) of ACT following the bolus of UFH before PCI as compared to non-Asians. However, the effect seems minor and the clinical significance unknown, particularly since drug dosing is monitored by ACT (or aPTT in case of VTE).

Bivalirudin. Gender and geographical location (EU vs. non-EU) did not affect the efficacy of bivalirudin vs. UFH in the HORIZON-AMI and EUROMAX trials.[59] However, in the recent VALIDATE-SWEDEHEART trial recruiting MI patients undergoing PCI with radial-access and without planned GPIs,[25] there was a trend toward a more favorable outcome associated with bivalirudin vs. heparin in female as compared to male patients (p=0.05 for interaction), with females being 26% of the enrolled population. However, whether the combination gender-BW had different outcomes as compared to the general population is unknown.

Fondaparinux. Male gender and decreasing BW were independent predictors of major bleeding in a meta-analysis of VTE prevention trials,[60] while there were no gender-related difference in the pooled analysis of OASIS-5 and -6 trials.[61]

Table S1. Contribution of waist circumference to type 2 diabetes (T2DM), hypertension and cardiovascular disease (CVD)

Classification	***Waist circumference and risk for T2DM, Hypertension and CVD#***	
	Men ≤102 cm ***Women ≤88 cm***	***Men ≥ 102 cm*** ***Women ≥ 88 cm***
Underweight	--	--
Normal weight	--	--
Overweight (pre-obesity)	Increased	High
Obese	High	Very high
Class 1	High	Very high
Class 2 (moderate obesity)	Very High	Very High
Class 3 *(severe or morbid obesity)*	Extremely High	Extremely High
Class 4 *(super-obesity)*	Extremely High	Extremely High
Class 5 *(super-super or extreme obesity)*	Extremely High	Extremely High

https://www.diabetes.ca/diabetes-and-you/healthy-living-resources/weight-management/waist-circumference;

***** //www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm

Table S2. Metabolic effects of bariatric procedures vs. pre-surgery.

Procedure	*Drug*	*Effect*
Roux-en-Y gastric bypass [8, 9, 62-64]	Metoprolol (some BCS class I)*	Unaffected
	Fenofibrate, propanolol and lipophilic, neutral compound of BCS class 2 obesity*[10]	Unaffected
	Posaconazole, omeprazole and lipophilic, weak bases of BCS class 2 obesity[10]	Increased gastric pH and reduced solubility and exposure by 30-50% (AUC and Cmax)
	Morphine	3-fold increased absorption and exposure (Cmax and AUC)
	Atorvastatin	Highly variable reports.
	Digoxin	Total exposure not affected vs. controls
	Warfarin	Fat malabsorption and vitamin K deficiency, less predictable INR response. More frequent INR monitoring.
	Oral Furosemide	Faster absorption but no AUC or Cmax differences vs. controls
	Metoprolol, nifedipine, isosorbide. Extended-release formulations	Likely reduced absorption of drugs absorbed in the colon, including extended-release formulations of any drug.
Any bariatric surgery associated with extended resection of small bowel[9]	Digoxin	Bioavailability of digoxin directly dependent on the length of remaining jejunum. More frequent monitoring may be needed.
Extended colonic resection[8, 9]	Hydrochlorothiazide	Reduced AUC (halved) vs. controls
Jejunoileal bypass[8, 9, 63]	Atorvastatin	Increased AUC vs. pre-surgery (approx. 2 folds)
	Hydrochlorothiazide	Reduced AUC (halved) vs. controls
Biliopancreatic diversion with duodenal switch[9, 63]	Atorvastatin	Increased AUC vs. pre-surgery
Any bariatric surgery[65]	CYP3A4 metabolism (midazolam as probe drug)	Increased activity vs. pre-surgery

Abbreviations: AUC: Area Under the Curve; INR: international normalised ratio; BCS: Biopharmaceutical Classification System; Cmax maximal plasma concentration; RYGB: Roux-en-Y gastric bypass. *BCS class I: high solubility and high permeability drugs, class II: poor solubility and high permeability drugs.

Table S3. Pharmacokinetic or pharmacodynamic changes on obese vs. non-obese subjects for cardiovascular drugs other than antithrombotics

Drug class or agent	*PK*	*Clinical readouts*
Beta blockers-lipophilic agents[3] (propranolol, metoprolol, nebivolol)	Increased Vd Clearance unchanged/decreased (propranolol) Clearance increased (metorpolol, nebivolol)	Calculate loading doses using LBW to account for higher lean tissue. Titration by monitoring heart rate and blood pressure
Beta blockers-hydrophilic agents[3] (atenolol, sotalol)	Clearance and Vd unchanged, metabolism dependent on liver function	Titration by monitoring heart rate and blood pressure
Verapamil	Increased Vd Prolonged elimination	Calculate loading dose on TBW and maintenance dose on IBW
Atorvastatin	Not affected	--
Digoxin	Decreased Vd	TDM more often

Abbreviations: Vd: volume of distribution, LBW: lean body weight; IBW: ideal body weight; TDM: therapeutic drug monitoring.

6. References

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