Antithrombotic therapy and body mass:

an expert position paper of the ESC Working Group on Thrombosis

Bianca Rocca[1], Keith A.A. Fox[2], Ramzi A. Ajjan[3], Felicita Andreotti[4], Colin Baigent[5], Jean-Philippe Collet[6], Erik L. Grove[7], Sigrun Halvorsen[8], Kurt Huber[9], João Morais[10], Carlo Patrono[1], Andrea Rubboli[11], Ingebjorg Seljeflot[12], Dirk Sibbing[13], Agneta Siegbahn[14], Jurrien Ten Berg[15], Gemma Vilahur[16], Freek W.A. Verheugt[17], Lars Wallentin[18], Thomas W. Weiss[9], Johann Wojta[19] and Robert F. Storey[20]

[1]Institute of Pharmacology, Catholic University School of Medicine, Rome, Italy;
[2]Centre for Cardiovascular Science, University and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom;
[3]Leeds Institute for Cardiovascular and Metabolic Medicine, the LIGHT Laboratories, University of Leeds, Leeds, LS2 9JT, United Kingdom;
[4]Cardiovascular Department, Catholic University Hospital, Rome, Italy;
[5] MRC Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, United Kingdom ;
[6] Sorbonne Université Paris 06 (UPMC), ACTION Study Group , INSERM UMR_S 1166, Institut de Cardiologie, Pitié-Salpêtrière Hospital (AP-HP), Paris, France;
[7]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark & Faculty of Health, Department of Clinical Medicine, Aarhus University, Aarhus Denmark;
[8]Department of Cardiology, Oslo University Hospital Ulleval and University of Oslo, Oslo, Norway;
[9]3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital, and Sigmund Freud University, Medical School, Vienna, Austria;
[10] Division of Cardiology, Leiria Hospital Center, Leiria, Portugal
[11]Division of Cardiology, Laboratory of Interventional Cardiology, Ospedale Maggiore, Bologna, Italy;
[12]Center for Clinical Heart Research, Department of Cardiology, Oslo University Hospital Ullevål and University of Oslo, Norway;
[13]Department of Cardiology, Munich University Clinic, Ludwig-Maximilians-Universität, Munich, Germany and DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany;
[14]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden;
[15]Department of Cardiology, St Antonius hospital, Nieuwegein the Netherlands;
[16]Cardiovascular Science Institute-ICCC, IIB-Sant Pau, CiberCV, Hospital de Sant Pau, Barcelona, Spain;
[17]Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, Netherlands;
[18]Department of Medical Sciences, Cardiology, Uppsala University & Uppsala Clinical Research Center, Uppsala, Sweden;

[19]Department of Internal Medicine II, Medical University Vienna; Core Facilities, Medical University Vienna; Luwdwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria;
[20]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom.

Corresponding Author:

Bianca Rocca, MD, PhD
Department of Pharmacology
Catholic University School of Medicine
Rome, Italy
Email: bianca.rocca@unicatt.it; b.rocca@tiscali.it
Phone: +39 06 30154253
Fax: +39 06 3050159

Acknowledgements: This paper is dedicated to the memory of the late Professor Steen Husted.

Word count total: 6200 (without references)

Abstract

Increasing prevalence of cardiovascular disease and new evidence on the effects of antithrombotic therapies have expanded the use of antiplatelet and anticoagulant drugs. In addition, extremely low and high body weights have become more common due to frailty associated with ageing and to the global epidemic of obesity, 'globesity', respectively. These extreme body weights affect cardiovascular risk, including mortality, as well as the pharmacokinetics and safety profiles of antithrombotic drugs, some of which have a relatively narrow therapeutic window.

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

Further research is warranted to optimize antithrombotic therapy in underweight as well as in different classes of obese patients, to guide dosing, dose-adjustment and/or reference intervals, and to establish whether the balance of benefits and risks of antithrombotic drugs can be improved.

Key words: obesity; underweight; body mass index; antiplatelet agents; anticoagulants.

1. Introduction

The success of trials that have shown net clinical benefits of antithrombotic drugs as well as the increasing prevalence of cardiovascular diseases in an ageing population have led to more widespread use of antiplatelet and anticoagulant drugs. At the same time, extremely low and high body weight (BW) are becoming more common due to a higher prevalence of frailty, associated with greater life expectancy, and the global epidemic of obesity, 'globesity', respectively.[1, 2,3] These extreme BWs may affect cardiovascular risk as well as the pharmacokinetics of antithrombotic drugs, some of which have relatively narrow therapeutic windows.

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

2. Definitions

The simplest and most universal definition of underweight, overweight and obesity relies on body mass index [BMI; BW (kg) divided by the square of the height (metres) (kg/m^2)][1] (**Table 1**). Obesity is also defined as BW >20% above ideal BW (IBW),[4] and "morbid" obesity as >100% above IBW. However, the exact definition of obesity, reflecting excess body fat, remains problematic. In addition to defining obesity, BMI shows a U-shaped correlation with mortality and displays a complex relationship with cardiovascular diseases (**Figure 1**).[5, 6] Using the BMI classification, obesity affects 33.9% of US adults[1] and between 10% (Italy) and 23% (UK) of European adults,[1] with a steadily increasing prevalence worldwide.[1] Premature deaths are increased up to 5-fold in morbidly-obese

subjects.[5] The annual cost of treating obesity complications is estimated at ≈$51.6 billion in the US[4] and ≈€81 billion in Europe,[7] corresponding to ≈2%–8% of the total national healthcare expenditure in the European countries.

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

may better reflect obesity than BMI, particularly in older individuals and in “sarcopenic obesity” (increased fat with reduced lean mass).[8] Whilst WC and WHR certainly have value in assessing obesity, these measurements can be cumbersome in daily practice and susceptible to errors compared with BMI.

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

3. Increased Body Mass: thrombotic and bleeding risks

3.1 Thrombotic risk

In obesity, adipose tissue consists of adipocytes and different cell types in the vascular stroma**,**[21-24] releasing inflammatory and pro-coagulant mediators (**Figure 2**).[25, 26,27, 28 29, 30] Moreover, obesity increases lipid peroxidation and isoprostane formation,[31] which can activate platelets.[32] Markers of platelet activation increase in obese subjects, including CD40L, P-selectin, microparticles and urinary thromboxane metabolites.[33]

Poor vascular supply of expanding obese tissue can induce hypoxia and adipocyte cell death.[34,35] Cytokines from obese adipose tissue induce a low-grade systemic inflammation that promotes atherosclerosis, endothelial dysfunction and a prothrombotic status (**Figure 2**).[30] Chronic low-grade inflammation, TF-dependent signaling, and free

fatty acids release induce peripheral insulin resistance and exhaust insulin secretion, increasing the risk of type 2 diabetes.[23, 36-38]

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

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

Arterial disease*.* In studies of coronary plaque morphology and cardiovascular deaths in women, elevated BMI, age, diabetes, and hyperlipidaemia were all associated with a higher frequency of plaque rupture.[44] BMI ≥30kg/m^2 is associated with a higher cardiovascular mortality in men and women, as compared to other BW categories (18.5-22.4; 22.5-24.9; 25-29.9 kg/m^2) in a prospective study of >100,000 subjects from the Nurses' Health Study and Health Professionals Follow-up Study, over 32 years of follow-

up.[45] The same increase in cardiovascular events and mortality in obese subjects is true for Asian populations, especially for BMI ≥32.5kg/m^2.[46] Elevated fibrinogen appears to be an independent risk factor for cardiovascular disease, with evidence suggesting a causal role in thrombosis and potentially a mechanism through which key risk factors, including obesity, may exert their pro-thrombotic effects.[47, 48]

Significant weight loss following bariatric surgery in morbidly-obese subjects is associated with reductions in thrombin generation, cholesterol, triglycerides and haemoglobin A1$_c$.[40, 49] Experimental studies in obesity have also shown a receptor-dependent effect of leptin[50] on platelet function, suggesting the potential for non-surgical mechanisms to modify the excess thrombotic risks observed in morbid obesity.

Consensus statement. Amongst other adverse effects on cardiovascular risk, obesity is associated with a pro-thrombotic state and increases the risk of atherothrombotic events, VTE and cardiovascular mortality (Figure 1).

3.2 Bleeding risk

Spontaneous bleeding. Prospective studies of subjects with no previous vascular disease show a positive association between incident intracerebral haemorrhage (ICH) and BMI ≥30kg/m^2, attenuated after adjustment for hypertension.[51-55] Specifically, among 900,000 adults followed on average for 13 years, the hazard ratio (HR) was 1.53 (95%CI: 1.32-1.78) per 5kg/m^2 increase.[55] Extreme BMIs and location of ICH also appear relevant, as case-control multivariate-analysis studies have reported significant associations between lobar as well as deep ICH and BMI <18.5kg/m^2 [56, 57] and, conversely, between deep ICH/microbleeds and obese BMIs,[58, 59] the latter partly mediated by hypertension.[59] Thus, a U-shaped correlation may exist for deep, but not lobar, ICH across the BMI spectrum.[57] In 93,918 low-risk individuals enrolled in six aspirin primary prevention trials, the rate of major extracranial bleeding, but not of haemorrhagic stroke, increased

significantly with increasing BMI (rate ratio=1.24, 95%CI:1.13-1.35, per 5-kg/m^2 increase), independently of aspirin allocation.[60]

In adjusted analyses, examples of the so-called 'obesity paradox' among patients either diagnosed with or at high risk of vascular disease[17] include: i) more incident ICH among low BMI (<24kg/m^2)[57, 61]; ii) less haemorrhagic transformation after ischaemic stroke among patients with BMI above vs. below 25kg/m^2;[62] iii) BMI independently associated with better long-term survival post-ICH (HR=0.91 per 1-kg/m^2 increase; 95%CI:0.87-0.95).[63]

Peri-procedural bleeding. In patients undergoing percutaneous coronary intervention (PCI), underweight BMI <18.5kg/m^2 has an increased risk of bleeding, and class 1-2 obesity a reduced risk.[64-66] Among 16,783 patients undergoing PCI at a single centre,[67] the incidence of transfusion across BMI followed a U-shaped pattern, with similar transfusion rate in class ≥3 obese and underweight patients, while class 1 obese patients had the lowest risk of major bleeding (odds ratio [OR]=0.68, 95% confidence interval [CI]:0.48-0.97). This association persisted after adjustment for confounders. The better outcome for bleeding in the middle of the BMI spectrum, from 25 to 34.9kg/m^2, suggested the existence of a U-shaped "bleeding obesity paradox" where severe obesity (≥40kg/m^2) confers no apparent protection from bleeding[65, 67] or premature death.[68] A recent US registry of 96,381 patients undergoing PCI confirmed this trend,[66] and a Japanese study also showed the highest bleeding risk in the lowest BMI group.[69] Radial approach to PCI is particularly safer than the transfemoral approach for patients with BMI <25 or >40kg/m^2.[66]

Overweight and class 1 obesity (from 25 to 35 kg/m2) do not seem to increase the risk of bleeding associated with transcutaneous aortic valve replacement compared to normal BW, whereas sarcopenia is associated with increased mortality and data are few or lacking for class 2 and 3 obesity, respectively.[70-74] Thus overweight and class 1 obesity seem protective for short and long-term mortality,[75] with a J-shaped trend whereby highest

degrees of obesity (class 2+) seem associated with increasing mortality vs. class 1/overweight categories.[76, 77] Obesity does not appear to increase the risk of bleeding associated with cardiac surgery although class ≥2 obesity, but not lesser degrees of obesity, as well as small body size are associated with generally worse outcomes, including mortality compared to normal or overweight BW and body size;[78-81] in addition, any degree of obesity may increase the risk of sternal wound infection. [82, 83]

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

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

4. Body mass-related and bariatric surgery-related changes in organ function relevant for drug's PK

Obesity modifies body composition, including plasma proteins, kidney, liver and heart function (**Table 2**),[84-86] thus affecting absorption, volume of distribution (Vd), metabolism and/or elimination of several drugs. Bariatric interventions include restrictive and/or malabsorptive procedures[87] that, along with their impact on BW loss, variably affect gastrointestinal anatomy, motility and function, and may cause nutritional deficiencies (**Web Addenda Table S2**).[88-91] Moderate and severe underweight (**Table 1**) are often associated with kidney dysfunction,[92] cancer, frailty, ageing, critical illness and unhealthy

life-style, which can variably affect some pharmacokinetic processes (**Table 2**). Additional details are in the *online material*.

Consensus statement: Obesity, underweight and bariatric surgery generate major metabolic and organ changes that variably affect the pharmacology of several drugs. Pharmacokinetic data and *in silico* models are needed during drug development, especially for moderate-to-severe obesity (BMI≥35kg/m^2)[93, 94] or underweight (<17kg/m^2) and following bariatric procedures given the GI anatomical changes and major BW loss,[91, 93] to predict the optimal regimen for BW-adjusted and fixed-dose drugs.

5. Oral and parenteral antiplatelet drugs

5.1 Aspirin

A study involving 100 aspirin-treated subjects with type-2 diabetes and 75 high-risk non-diabetic patients showed that increased BW independently predicted incomplete inactivation of platelet cyclooxygenase-1 by low-dose (100 mg daily), enteric-coated aspirin in both groups.[95] Higher values of BW or BMI have been consistently associated with lower aspirin responsiveness, as assessed by high residual serum thromboxane B_2, platelet function or urinary thromboxane metabolites in both healthy subjects and high-risk patients.[96-99] The organ and metabolic changes produced by obesity can markedly affect the distribution, binding and elimination of lipophilic aspirin.[100] Thus, a faster inactivation of aspirin may occur in the gut, plasma and/or liver through increased deacetylation by esterases and phase II conjugation enzymes, whose activity can be induced by obesity.[100] Lower bioavailability of some enteric-coated preparations of low-dose aspirin and poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition, particularly in heavier subjects.[98, 99] Higher BW was associated with faster recovery of platelet cyclooxygenase-1 activity during the 24-hour dosing interval, normalized by a twice-daily low-dose aspirin regimen.[78] A small study showed that also

doubling the daily dose could restore a nearly-complete platelet thromboxane inhibition.[99] However, outcome studies are lacking.

In contrast to pharmacodynamic studies, a meta-analysis of six primary prevention trials of aspirin versus control involving >95,000 asymptomatic subjects at low-to-average risk, showed that the proportional reduction in serious vascular events did not differ significantly (p for trend=0.08) between BMI <25, 25-29.9, or ≥30 kg/m^2.[60] However, it should be emphasized that <20% of all serious vascular events occurred in subjects with BMI ≥30 kg/m^2,[60] thereby limiting the statistical power to reliably assess the efficacy of aspirin in this sub-group. Two small studies on morbidly-obese patients (BMI ≥40kg/m^2) suggest improved pharmacodynamics and pharmacokinetics of low-dose aspirin after bariatric surgery.[101, 102] Obesity is associated with increased risk of colorectal cancer in the Lynch syndrome but this risk is abrogated by aspirin (600mg daily).[103] Such patients may benefit from obesity prevention and/or regular aspirin. Importantly, a recent nationwide study of 601,527 users of low-dose aspirin showed an ≈ 30% relative risk increase of adverse ischemic events soon after a non-clinically driven (i.e. absence of major surgery or bleeding) discontinuation of aspirin.[104] Adherence to aspirin may be particularly critical in the obese population, given their increased arterial risk.

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

5.2 $P2Y_{12}$ inhibitors

Thienopyridines: clopidogrel. Several studies have reported poor responsiveness to clopidogrel, expressed as reduced platelet inhibition and/or active metabolite concentration, associated with a high BMI or BW,[105-111] independently of type of body size descriptor.[111] BMI, age and lipid profile account for ≈25% of the variability in clopidogrel responsiveness.[109] An integrated pharmacokinetic modelling based on the Pharmacogenomics of AntiPlatelet Intervention study[109, 112] showed that obesity class ≥2, associated with a poor- or intermediate-metabolizer genotype (homozygous or heterozygous for loss-of-function alleles in CYP2C19, respectively), would require ≥300mg/day clopidogrel maintenance dose.[113] In the LEADERS trial, BMI independently predicted major adverse cardiac events at 1-year in patients on clopidogrel 75mg daily.[114] Patients deemed low-responders had a significantly higher BMI (30 [15-66] vs 29 [12-69]kg/m^2), and high-dose clopidogrel (600mg loading dose followed by 150mg/day) was insufficient to overcome the poor response. However, BMI *per se* was not independently associated with clinical outcome in this study.[115] Conversely, BMI had no impact on clinical outcome in studies comparing a strategy of platelet function monitoring and dose-adjustment of antiplatelet therapy to a more conventional approach without monitoring/dose adjustment. This was unrelated to the patients´ risk profile.[116, 117]

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

Thienopyridines: prasugrel. Studies on stable coronary artery disease (CAD)[111] and myocardial infarction (MI)[118] showed lower platelet inhibition and active metabolite

concentration in prasugrel-treated patients with higher BMI and/or BW. However, this effect was not confirmed or was only modest in other studies,[119-121] including the pharmacokinetic analysis of the TRITON-TIMI 38 trial.[122] An observational study of obese CAD patients without (n=114) and with (n=222) the metabolic syndrome suggested that the reduced antiplatelet effect of prasugrel might be associated with the metabolic syndrome rather than obesity itself, although numbers of obese patients were too few to exclude an effect of obesity *per se*.[123] Prasugrel achieved greater platelet inhibition than clopidogrel after a loading dose in obese patients without diabetes but this difference was no longer significant after 1 week due to increase in platelet inhibition with clopidogrel maintenance therapy.[124] Prasugrel 5mg in patients weighing <60kg is associated with an exposure to the active metabolite similar to 10mg in non-underweight patients.[125] In the TRITON-TIMI 38 trial, bleeding was largely confined to patients with lower BW and a high exposure to prasugrel active metabolite.[126, 127]

***Consensus statement**:* ESC guidelines recommend prasugrel in preference to clopidogrel regardless of BW or BMI in ACS.[128] The impact of high BW seems less relevant for prasugrel compared with clopidogrel. Halved prasugrel maintenance dose (5mg/day) is recommended in patients weighing <60kg.

Ticagrelor. The pharmacodynamics of ticagrelor depends on its plasma levels and, to a lesser extent, its active metabolite AR-C124910XX.[129, 130] Moreover, ticagrelor has an effect on cellular adenosine uptake of uncertain clinical significance, possibly linked to adverse effects such as dyspnoea.[131] Both ticagrelor and AR-C124910XX levels are independently influenced by BW; in patients with prior MI, ticagrelor clearance was 6% higher and 11% lower, whereas AR-C124910XX clearance was 26% higher and 34% lower for those weighing 110 and 50kg, respectively, compared with an 83kg patient.[132] However, there is no evidence that BW has a relevant influence on either the efficacy or safety of ticagrelor. In the PLATO study, there were >5,000 obese patients (28% of the trial

population) and there was no significant interaction for the efficacy and safety endpoints with ticagrelor 90mg twice-daily compared to clopidogrel in obese (BMI≥30kg/m^2) versus non-obese patients, nor in those above versus below 60kg.[133] Similarly, in the PEGASUS-TIMI 54 study, there was no significant interaction for efficacy or safety with ticagrelor 90mg or 60mg twice-daily compared to placebo for those above or below 81kg.[134] However, patients with diabetes mellitus appeared to have greater absolute risk reduction in ischaemic events, including CAD-related death, with ticagrelor.[135] Further modelling, using pharmacokinetic data, indicate a wide therapeutic window for ticagrelor, with variations in plasma levels having little impact on efficacy and safety.[136] There appears to be a modest relationship between ticagrelor plasma levels and dyspnea, minor bleeding and ventricular pauses,[137-139] which is not so strong as to lead to a significant influence of BW on ticagrelor's safety and tolerability.[136, 140] Paradoxically, in the PLATO study, patients with ticagrelor-related dyspnoea tended to have higher BW.[137] Doses as low as 60 mg twice-daily seem to provide a consistently high level of platelet $P2Y_{12}$ inhibition.[129]

Consensus statement: ticagrelor is recommended in preference to clopidogrel in ACS patients without dose adjustment according to BW.[128] Limited data are currently available for morbidly-obese patients. Future research should establish whether ticagrelor 60 mg twice-daily should be considered as an alternative to 90 mg twice-daily in ACS patients weighing <60kg.

5.3 Body mass and DAPT duration. see Web Addenda.

5.4 Glycoprotein IIb-IIIa inhibitors (GPIs)

Given their narrow therapeutic window, all available GPIs (abciximab, eptifibatide and tirofiban) must be carefully BW-adjusted. There are sparse data on the impact of BW on the safety or efficacy of GPIs. In the prospective, randomized TARGET trial, abciximab was compared with tirofiban in 4,809 patients undergoing PCI with bare-metal stent implantation,[141] and 36% of the patients had BMI >30 kg/m^2. With respect to

thromboembolic events at 30 days (death, non-fatal MI and urgent target vessel reintervention), there was no difference between obese and non-obese patients, while TIMI major bleeding was lower in the patients with higher BMI (0.4% vs. 1.1%, P=0.01).[141] Six-month death and MI rates were similar in obese and non-obese patients.

Inaccurate weight-adjusted dosing of tirofiban and abciximab may be common and addressing this may reduce associated bleeding risk.[142] BW-adjusted dosing charts are often included in the insert package of some GPIs. The safety of GPIs on top of the increasingly used ticagrelor or prasugrel has never been studied.

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

5.5 Cilostazol, Dipyridamole, Vorapaxar, Cangrelor: see Web Addenda

6. Oral and parenteral anticoagulants

6.1 Vitamin-K antagonist (VKA)

Limited data are available on the impact of BW and/or BMI on the pharmacokinetics and dosing of VKA at treatment initiation and during maintenance.[143-148] A significantly longer time to achieve a therapeutic International Normalized Ratio (INR) and higher dose requirement of VKAs have been reported for the initiation phase in obese, especially morbidly-obese, versus non-obese subjects.[143, 144] A positive correlation between BMI and warfarin maintenance dose has been consistently reported.[145-147] In one retrospective study of 831 patients, weekly maintenance dose increased by 0.69mg per 1kg/m^2 BMI increase.[147] Obesity has been independently associated with improved anticoagulation control in warfarin-treated elderly patients (≥75 years),[149] but whether this applies to younger patients remains unproven. BMI >30kg/m^2 independently predicted anticoagulation reversal failure using weight-based prothrombin complex concentrates.[150]

While studies in underweight patients are lacking, data including wide BMI ranges (from 13.4kg/m^2)[145-147] suggest a shorter time to achieve the therapeutic INR at initiation, and lower warfarin dose at initiation and maintenance in underweight vs. normal individuals. Therefore, in obese and underweight patients, the efficacy and safety profile might be different.[125-127] Moreover, whether the therapeutic INR range should be similar in underweight, normal-weight and severely-obese patients is unknown.

Consensus statement: While BW and/or BMI can affect warfarin dose requirement, their impact on clinical practice appears limited, given routine INR monitoring and consequent dose adjustments for maintenance of the therapeutic range. Closer surveillance may be needed in underweight and obese patients. The relationship between therapeutic INR range and BMI categories remains unexplored. In obese individuals with major bleeding on VKA, prothrombin concentrates should be used at appropriate doses (35-50 mg/kg)[151] and INR promptly and frequently monitored given the likelihood of reversal failure.

6.2 Direct FXa and FIIa inhibitors

In healthy subjects, apixaban maximal plasma concentration (Cmax) and the area-under-the-curve (AUC) inversely correlate with BW (38-175kg) and BMI (17-54kg/m^2),[128] showing a ≈25-30% increase below 50kg and ≈25-30% decrease above 120kg vs. normal weight (65-85kg). Phase III trial data of orthopaedic surgery prophylaxis showed a higher safety of enoxaparin vs. apixaban in underweight patients.[129] In the ARISTOTLE trial, safety and efficacy of apixaban vs. warfarin were similar in patients with non-valvular atrial fibrillation (AF) above and below 60kg.[130, 131] However, a proportion of underweight patients with age ≥80 years and/or creatinine ≥1.5mg/dL already received a reduced dose (2.5 mg twice-daily). Among 17,913 not-underweight patients, 40% had BMI ≥30 kg/m^2 and only ≈5% a BMI ≥40kg/m^2.[152] As compared to normal BMI, obesity was associated

with lower mortality (OR=0.63, 95%CI: 0.54-0.74), but there were no differences in rates of stroke/systemic embolism (OR=0.79,95%CI:0.61-1.02) and major bleeding (OR=0.91,95%CI:0.74-1.1). However, in class ≥3 obese patients, 8 and 11 primary events occurred in the apixaban and warfarin arms, respectively, hampering any reliable conclusion.

Edoxaban Cmax is ≈40% increased in patients weighing <60kg,[153] leading to 50% dose reduction in the HOKUSAI-VTE[133] and ENGAGE AF-TIMI 48[134] trials for this category. In HOKUSAI-VTE, 12% of the patients were underweight and the primary outcome was comparable to the non-underweight population.[133] Half dose in the ENGAGE-AF trial resulted in ≈30% lower exposure to edoxaban,[135] which may explain the significant reduction of major bleeding vs. full dose edoxaban-treated patients, but differences in efficacy were not observed.[134] No data are available on edoxaban across different degrees of obesity.

The pharmacokinetics of rivaroxaban have been reported in patients weighing <50kg (BMI 19.3±1.1kg/m^2) or >120kg (43.5±4.2kg/m^2), showing no clinically-relevant changes in AUC and Cmax.[154] Pharmacokinetic models based on DVT[155] and ACS patients[156] showed minimal influence of BW on Cmax. Consistently, obesity (i.e. BMI≥30 kg/m^2) did not affect the safety/efficacy profile of rivaroxaban in the EINSTEIN-DVT and –PE,[157] EINSTEIN-CHOICE,[157] ROCKET-AF[158] (subgroups with BMI≤25, 26-35, >35kg/m^2) trials. However, the proportion of patients with class ≥2 obesity was ≈13% of the entire population and data should be interpreted with caution. A recent small phase I study on 10mg single-dose rivaroxaban suggests no effect of bariatric surgery on the AUC in morbidly-obese patients.[159] In the COMPASS study, a pre-specified subgroup analysis showed no significant interaction between weight below and above 60kg, and the primary safety and efficacy endpoint with rivaroxaban 2.5 mg twice-daily plus aspirin compared to

aspirin alone. Patients <60kg were 9.5% of the entire population and there was no pre-specified analysis for obese patients.[160]

The pharmacokinetic analysis of the RE-LY trial in AF patients showed that BW independently affected dabigatran concentration with ≈21% increase or reduction of dose-normalized plasma concentrations for BW <50 or >100kg, respectively, vs. 50-100kg.[161] BW significantly influences the apparent Vd of dabigatran (0.77% increase per 1-kg increase above 80 kg).[161] In RE-LY, patients weighing <50kg and >100kg were 2% and 16% of the total population (n=18,113), without major effects on efficacy or safety across subgroups.[162] In the RE-COVER trial in VTE prevention, patients with BMI >35kg/m^2 were 12% of the total population, with very few events.[148] Thus, information on dabigatran in different degrees of obesity is limited. For patients weighing <50kg without renal impairment, a 'close clinical surveillance' is indicated without dose-reduction.[163]

Consensus statements: in underweight (≤60kg) patients, edoxaban dose should be halved and apixaban dose should be halved if underweight is associated with renal impairment (creatinine >133µmol/L) or age >80 years. Dabigatran data are limited <50kg, high drug concentrations are reached and 'close clinical surveillance' is recommended. Rivaroxaban dosing does not require reduction. The bleeding risk of underweight patients should always be carefully evaluated. In obese patients, especially with BMI ≥40kg/m^2, data are extremely limited or absent, thus questioning the use of direct anticoagulants in this category, in preference to VKA.[164, 165] Peak and trough anti-Xa activity (FXa inhibitors), ecarin clotting time (ECT) or diluted thrombin time (dTT) (dabigatran) should be checked in severe obesity, switching to VKA if results are different-than expected.[164]

Evidence on direct oral inhibitors for DVT prophylaxis post-bariatric surgery is also limited.[143, 144,159] Thus, low-molecular-weight heparins (LMWHs) might be preferred given a longer experience. Repeated measurements of anti-Xa activity or ECT should be

considered for FXa and thrombin inhibitors, respectively, at short- and mid-term after bariatric procedures.

6.3 Unfractionated heparin (UFH)

Because the anticoagulant response to UFH is highly variable among acute patients,[166] BW-based UFH therapy is routinely monitored and adjusted using the activated partial thromboplastin time (aPTT) in most clinical conditions, and the activated clotting time (ACT) during PCI or cardiopulmonary bypass surgery.[166] However, BW-based UFH dosing nomograms were developed with poor representation of obese patients, especially class ≥2.[167] Several subsequent studies showed that, for class ≥2 obesity (or BW >160kg), the conventional nomogram tends to generate overdosing, with higher aPTT and/or shorter time to reach therapeutic aPTT as compared to normal, overweight or class 1 obese patients.[168-171] This finding seems dependent on a progressive reduction in the Vd of UFH with increasing BMI, with a proportional loss of the direct linear relationship between BW and dosing (as reflected by aPTTs). Consistently, in different clinical settings (VTE, ACS, critical illness, AF), patients with class ≥3 obesity or BW >165kg require ≈15-20% less BW-based UFH.[168, 170, 171] Some studies used adjusted BW rather than total BW to calculate UFH dosing in obesity.[170] However, the best body indicator for dosing UFH in obese patients as alternative to BW remains undefined. Moreover, an inaccurate BW estimate can affect a relevant fraction of acute patients and clinical outcomes.[142]

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

6.4 Low-molecular-weight heparins

Prophylactic regimens. Fixed-dose enoxaparin shows an inverse linear correlation between the AUC or anti-Xa activity and BW between 50 and 150kg,[172] with the lowest levels in moderately-to-severely obese patients.[173, 174] Similar data are reported for

dalteparin.[175] Thus, underweight or high degrees of obesity may achieve inappropriate anti-Xa levels. Consistently, some studies showed reduced efficacy of standard fixed LMWH dosing in class ≥3 obese patients, who also have a high associated VTE risk.[174-176] Thus, enoxaparin 40 mg twice- rather than once-daily or dalteparin 7,500 rather than 5,000IU have been advocated for BMI ≥40kg/m^2.[174, 177, 178] For BMI >50kg/m^2 and normal creatinine clearance, up to 60mg enoxaparin twice-daily has proven effective.[179, 180] The ACCP guidelines recommend LMWH doses '*higher than usual for non-obese patients*' in obese subjects undergoing bariatric surgery.[181] A pragmatic ≈30% increase of prophylactic fixed LMWH doses has been proposed in morbid obesity.[174] Moreover, BW-based prophylaxis has been tested in class ≥2 obesity, showing a superior anti-Xa target activity vs. fixed dosing.[175, 182-185] BW-based prophylaxis seems superior to fixed dosing also in women with BMI ≥40kg/m^2 undergoing caesarean sections.[186] However, whether better anti-FXa target levels correspond to a higher efficacy and whether increasing fixed dose is superior to BW-based dosing for class ≥2 obesity remain unknown.[54, 175, 187] Measuring anti-FXa activity can be useful in obesity class ≥3 or BW >190kg, especially in high VTE risk patients,[175] but it is not routinely recommended.[54, 173, 174] Consistently, the product characteristics acknowledge lack of consensus for adjustment of prophylactic enoxaparin doses for BMI >30kg/m^2 or BW >120kg.[188] Also, dalteparin and tinzaparin have not been formally tested for BW >90 and >105kg, respectively.[175] Conversely, an increased drug exposure with fixed prophylactic enoxaparin dose has been observed in low-BW women (<45kg) and men (<57kg), and in critically-ill patients with BMI ≤18.5kg/m^2.[189, 190] Considering that standard fixed-dose LMWH regimens might overdose underweight patients, small, preliminary, non-randomized studies investigated reduced-dose enoxaparin (<40mg daily),[189, 191] showing appropriate anticoagulation levels.

Consensus statement: obese patients are likely underdosed with standard fixed once-daily LMWH regimens. Higher fixed daily or BW-adjusted dosing regimens have

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

Therapeutic regimens. LMWHs in VTE and ACS are BW-adjusted, often with a dose-capping at the highest BW. In the SYNERGY trial, 4,916 ACS patients were treated with enoxaparin 1mg/kg SC every 12 hours, without capping, with no significant differences in death, MI and major bleeding in relation to BMI. However, only ≈3% were morbidly-obese and only 23 patients in the entire study weighed >150kg. Among enoxaparin-treated patients with BMI ≥35 kg/m^2, ≈13% received a lower than recommended dose.[192] The CRUSADE registry included >10,000 enoxaparin-treated ACS patients and showed that patients receiving lower-than-recommended dose were more likely obese (average BMI 30.3kg/m^2, BW 89kg), with median initial doses of 0.65 versus the recommended 1mg/kg SC every 12 hours in patients weighing >150kg ($p<0.001$).[193] Furthermore, patients weighing >150kg and receiving 1mg/kg SC every 12 hours had higher bleeding versus those receiving a lower dose (adjusted OR=2.42, 95%CI:0.7-8.37). Based on the potential over-dosing for BW-based therapeutic LMWH regimens in obese patients, a dose capping is often applied in clinical practice. However, pooled analysis of the ESSENCE and TIMI 11b trials, which randomized uncapped enoxaparin (1 mg/kg) vs. UFH, including 1,774 obese and 4,979 non-obese ACS patients, showed similar safety and efficacy profile of each treatment independently of BMI.[194] The SYNERGY trial also used uncapped enoxaparin dosing, without evidence of increased bleeding. Anti-Xa

monitoring can be considered in patients with BMI ≥40kg/m^2 or >150kg, but it is currently not routinely recommended.[173, 174] A nomogram has been proposed for therapeutic dose adjustment based on anti-Xa monitoring in severe obesity.[43]

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

6.5 Fondaparinux

The elimination of fondaparinux increases with BW (9% increase per 10kg).[195] For DVT or PE treatment, the daily dose is BW-adjusted (5, 7.5 and 10 mg for <50, 50-100 and >100kg, respectively), provided renal function is normal.[195] The MATISSE trial showed the effectiveness of this BW-adjusted regimen.[196] However, the number of patients with vascular events and BMI >35kg/m^2 was too limited to draw any definitive conclusion.[196]

Fondaparinux dosing in ACS and VTE prophylaxis is fixed (2.5mg/die). The anti-Xa activity of 2.5mg inversely correlates with BW between 40 and 100kg.[197] In patients with VTE weighing <50kg, the 2.5mg fixed dose should be used cautiously[195] and is contraindicated by the FDA.[198] On the other hand, a small study on morbidly-obese patients showed an anti-Xa activity below target in ≈50% of patients.[199] The EFFORT trial compared higher prophylactic doses of fondaparinux (5mg/die) and enoxaparin (40mg twice-daily) in morbidly-obese patients undergoing bariatric surgery, showing an adequate anti-Xa activity in 74% and 32% of the patients, respectively.[200] The clinical readout of the anti-Xa levels is unknown.

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

6.6 Bivalirudin. See Web Addenda.

7. Fibrinolytic drugs

Streptokinase and the fibrin-specific plasminogen activators (alteplase, tenecteplase) are used in acute ST-segment elevation MI (STEMI), acute ischaemic stroke, PE, or mechanical heart valve thrombosis.[201-205] Among 444 STEMI patients receiving streptokinase or alteplase, 150 with ICH and 294 matched controls, BW <70kg independently predicted ICH.[206] Importantly, in normal-to-obese patients neither streptokinase nor alteplase are BW-adjusted for STEMI. Alteplase is BW-adjusted only in patients <65kg, while tenecteplase is administered by categories of BW with a capping >90kg[207] (**Table 4**).The probability of artery patency after streptokinase seems inversely related to BW between 62 and 102kg.[208] In acute ischaemic stroke, low BW does not appear to predict bleeding in alteplase-treated patients.[209] Deviations of ≥10% from the recommended dose, occurring in ≈20% of strokes[210, 211] due to inaccurate estimates of BW, are potentially dangerous.[210] Conflicting data relate high BW to ICH risk: in a Swedish registry of 30,000 stroke patients receiving alteplase, BW ≥95kg was an independent predictor of ICH.[212] However, in a US registry of alteplase-treated stroke patients, 5,174 patients with BW >100kg, compared to 76,405 lighter counterparts, showed better survival, fewer ICH, but more moderate-severe disability at discharge.[213] Thus, it is unclear whether BW affects ICH and mortality risks in ischaemic stroke patients treated with BW-adjusted thrombolysis, especially class ≥2 obesity.[214]

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

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

Race and gender may interact with body mass for some antithrombotic drugs. Overall, most of these interactions appear minor and without clinical relevance. Of note, dose-normalized dabigatran concentrations in women were ≈30% higher than in men, independently of BW and age, thus special caution should be exerted in underweight women on dabigatran[161] Further aspects of these interactions and gaps in evidence are discussed in the Web Addenda.

9. Summary, Proposals and Future Work

Complex relationships exist between body mass indicators, metabolic function and cardiovascular risk (**Figure 1**). Furthermore, extremes of body mass impact on most antithrombotic drugs and must be carefully considered in the context of antithrombotic therapy (**Tables 3 and 4**). There is an urgent need for new data on heparin regimens (both LMWH and UFH) for prophylaxis and treatment of extremely obese patients, given also their high underlying VTE risk.[215] In view of the limited published data for many antithrombotic agents in relation to extremes of BW, the following are the specific proposals of this Working Group:

1. Further research is warranted to establish whether the balance of benefits and risks of oral fixed-dose antiplatelet and anticoagulant drugs can be improved through adjustment of their doses according to BW and/or BMI.

2. Future trials of antithrombotic agents should report their efficacy and safety data, as a subsidiary analysis, according to major classifications of BW (e.g. underweight, normal weight, classes of obesity).

3. An independent data depository should be established, with data submitted by the lead investigators of the major published antithrombotic trials, of the efficacy and safety data according to major classifications of BW (e.g. underweight, classes of obesity).

4. The CV risk associated with obesity in the absence of diabetes and its implications for antithrombotic regimens require further study, including the impact on recommended duration, selection of antithrombotic agent, dosing regimens or reference intervals of antithrombotic therapy.

Figure legends

Figure 1. Impact of BMI on clinical events. Extremes of body mass index (BMI) (underweight and higher classes of obesity) are characterized by U-shaped trends for extracranial and deep intracranial bleeding and cardiovascular (CV) mortality and a continuous increase in the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE). Data are from references [45, 46, 190, 216, 217]

Figure 2: Pathophysiological consequences of obesity. Normal adipose tissue is composed of adipocytes and immune cells with anti-inflammatory potential (M2-macrophages, CD4 T cells, and eosinophils), contributing to interleukin- (IL-)10 release, which, combined with secretion of adiponectin, exerts insulin-sensitizing, anti-inflammatory and anti-thrombotic effects. During weight gain, adipocytes become hypertrophic, hypoxic and dysfunctional, releasing pro-inflammatory molecules that attract pro-inflammatory cells (neutrophils, CD8 T cells, B cells, mast cells and interferon-(IFN-)γ-Th1). These cells amplify secretion of pro-inflammatory cytokines and chemokines into the bloodstream, promoting chronic low-grade inflammation. In addition, macrophages, polarized towards a pro-inflammatory M1 phenotype, remove the dead adipocytes and release tissue factor (TF), which is the factor VII (FVII)/FVIIa receptor and physiologically triggers coagulation. TF/FVIIa complex initiates pro-inflammatory and pro-angiogenic responses. TF/FVIIa-PAR-2 signaling promotes macrophage-mediated inflammation. Adipocytes and stromal cells express plasminogen activator inhibitor-1 (PAI-1), especially in visceral adipose tissue, leading to increased circulating PAI-1, which inhibits the urokinase- and tissue-type plasminogen activators (PA) and exerts anti-fibrinolytic and pro-thrombotic activities. Obesity also induces release of free fatty acids (FFA), which contribute to macrophage polarization and induce lipotoxocity, insulin resistance, isoprostane generation through

reactive oxygen species (ROS) and platelet activation. Abbreviations: FFA: free fatty acids; MCP-1: monocyte chemoattractant protein-1; TNFα: tumor necrosis factor alpha; ICAM: intercellular adhesion molecule; TAFI: Thrombin activatable fibrinolysis inhibitor.

10. References

1. http://apps.who.int/bmi/index.jsp.
2. Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KA, Halvorsen S, Huber K, Hylek EM, Lip GY, Montalescot G, Morais J, Patrono C, Verheugt FW, Wallentin L, Weiss TW, Storey RF, Group ESCTW. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J 2015;**36**(46):3238-49.
3. Rao G, Powell-Wiley TM, Ancheta I, Hairston K, Kirley K, Lear SA, North KE, Palaniappan L, Rosal MC, American Heart Association Obesity Committee of the Council on L, Cardiometabolic H. Identification of Obesity and Cardiovascular Risk in Ethnically and Racially Diverse Populations: A Scientific Statement From the American Heart Association. Circulation 2015;**132**(5):457-72.
4. Brolin RE. Bariatric surgery and long-term control of morbid obesity. JAMA 2002;**288**(22):2793-6.
5. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ 2016;**353**:i2156.
6. Hansel B, Roussel R, Diguet V, Deplaude A, Chapman MJ, Bruckert E. Relationships between consumption of alcoholic beverages and healthy foods: the French supermarket cohort of 196,000 subjects. Eur J Prev Cardiol 2015;**22**(2):215-22.
7. Cuschieri S, Mamo J. Getting to grips with the obesity epidemic in Europe. SAGE Open Med 2016;**4**:2050312116670406.
8. Correa MM, Thume E, De Oliveira ER, Tomasi E. Performance of the waist-to-height ratio in identifying obesity and predicting non-communicable diseases in the elderly population: A systematic literature review. Arch Gerontol Geriatr 2016;**65**:174-82.
9. Ortega FB, Sui X, Lavie CJ, Blair SN. Body Mass Index, the Most Widely Used But Also Widely Criticized Index: Would a Criterion Standard Measure of Total Body Fat Be a Better Predictor of Cardiovascular Disease Mortality? Mayo Clin Proc 2016;**91**(4):443-55.
10. Gracia-Marco L, Moreno LA, Ruiz JR, Ortega FB, de Moraes AC, Gottrand F, Roccaldo R, Marcos A, Gomez-Martinez S, Dallongeville J, Kafatos A, Molnar D, Bueno G, de Henauw S, Widhalm K, Wells JC. Body Composition Indices and Single and Clustered Cardiovascular Disease Risk Factors in Adolescents: Providing Clinical-Based Cut-Points. Prog Cardiovasc Dis 2016;**58**(5):555-64.
11. Lawlor DA, Benfield L, Logue J, Tilling K, Howe LD, Fraser A, Cherry L, Watt P, Ness AR, Davey Smith G, Sattar N. Association between general and central adiposity in childhood, and change in these, with cardiovascular risk factors in adolescence: prospective cohort study. BMJ 2010;**341**:c6224.
12. Heymsfield SB, Peterson CM, Thomas DM, Heo M, Schuna JM, Jr. Why are there race/ethnic differences in adult body mass index-adiposity relationships? A quantitative critical review. Obes Rev 2016;**17**(3):262-75.
13. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr., International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S, International Association for the Study of O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;**120**(16):1640-5.
14. Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care 2013;**36**(8):2294-300.
15. Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, Rampal S, Zhao D, Jung HS, Choi Y, Ahn J, Lima JA, Shin H, Guallar E, Ryu S. Metabolically-healthy obesity and coronary artery calcification. J Am Coll Cardiol 2014;**63**(24):2679-86.
16. Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. Circ Res 2016;**118**(11):1752-70.
17. Andreotti F, Rio T, Lavorgna A. Body fat and cardiovascular risk: understanding the obesity paradox. Eur Heart J 2009;**30**(7):752-4.

18. Komaroff M. For Researchers on Obesity: Historical Review of Extra Body Weight Definitions. J Obes 2016;**2016**:2460285.
19. Bigaard J, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. Obes Res 2003;**11**(7):895-903.
20. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. Am J Clin Nutr 2006;**84**(2):449-60.
21. Fuster JJ, Ouchi N, Gokce N, Walsh K. Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease. Circ Res 2016;**118**(11):1786-807.
22. Apostolopoulos V, de Courten MP, Stojanovska L, Blatch GL, Tangalakis K, de Courten B. The complex immunological and inflammatory network of adipose tissue in obesity. Mol Nutr Food Res 2016;**60**(1):43-57.
23. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;**2014**:943162.
24. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010;**72**:219-46.
25. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;**117**(1):175-84.
26. Amano SU, Cohen JL, Vangala P, Tencerova M, Nicoloro SM, Yawe JC, Shen Y, Czech MP, Aouadi M. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. Cell Metab 2014;**19**(1):162-71.
27. Ruf W, Disse J, Carneiro-Lobo TC, Yokota N, Schaffner F. Tissue factor and cell signalling in cancer progression and thrombosis. J Thromb Haemost 2011;**9 Suppl 1**:306-15.
28. Eden D, Siegbahn A, Mokhtari D. Tissue factor/factor VIIa signalling promotes cytokine-induced beta cell death and impairs glucose-stimulated insulin secretion from human pancreatic islets. Diabetologia 2015;**58**(11):2563-72.
29. Takahashi N, Yoshizaki T, Hiranaka N, Kumano O, Suzuki T, Akanuma M, Yui T, Kanazawa K, Yoshida M, Naito S, Fujiya M, Kohgo Y, Ieko M. The production of coagulation factor VII by adipocytes is enhanced by tumor necrosis factor-alpha or isoproterenol. Int J Obes (Lond) 2015;**39**(5):747-54.
30. Vilahur G, Ben-Aicha S, Badimon L. New insights into the role of adipose tissue in thrombosis. Cardiovasc Res 2017;**113**(9):1046-1054.
31. Davi G, Guagnano MT, Ciabattoni G, Basili S, Falco A, Marinopiccoli M, Nutini M, Sensi S, Patrono C. Platelet activation in obese women: role of inflammation and oxidant stress. JAMA 2002;**288**(16):2008-14.
32. Audoly LP, Rocca B, Fabre JE, Koller BH, Thomas D, Loeb AL, Coffman TM, FitzGerald GA. Cardiovascular responses to the isoprostanes iPF(2alpha)-III and iPE(2)-III are mediated via the thromboxane A(2) receptor in vivo. Circulation 2000;**101**(24):2833-40.
33. Samad F, Ruf W. Inflammation, obesity, and thrombosis. Blood 2013;**122**(20):3415-22.
34. Grant RW, Dixit VD. Adipose tissue as an immunological organ. Obesity (Silver Spring) 2015;**23**(3):512-8.
35. Suga H, Araki J, Aoi N, Kato H, Higashino T, Yoshimura K. Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. J Cutan Pathol 2009;**36**(12):1293-8.
36. Tchkonia T, Thomou T, Zhu Y, Karagiannides I, Pothoulakis C, Jensen MD, Kirkland JL. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metab 2013;**17**(5):644-56.
37. Gomez-Hernandez A, Beneit N, Diaz-Castroverde S, Escribano O. Differential Role of Adipose Tissues in Obesity and Related Metabolic and Vascular Complications. Int J Endocrinol 2016;**2016**:1216783.
38. Molica F, Morel S, Kwak BR, Rohner-Jeanrenaud F, Steffens S. Adipokines at the crossroad between obesity and cardiovascular disease. Thromb Haemost 2015;**113**(3):553-66.
39. Nicolaides A, Irving D, Pretzell M, Dupont P, Lewis J, Desai S, Douglas JN, Kakkar VV, Field ES. The risk of deep-vein thrombosis in surgical patients. Br J Surg 1973;**60**(4):312.
40. Wolfe BM, Kvach E, Eckel RH. Treatment of Obesity: Weight Loss and Bariatric Surgery. Circ Res 2016;**118**(11):1844-55.
41. Goldhaber SZ, Tapson VF, Committee DFS. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. Am J Cardiol 2004;**93**(2):259-62.

42. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Willett WC, Hennekens CH. A prospective study of risk factors for pulmonary embolism in women. JAMA 1997;**277**(8):642-5.
43. Hirsh J, Hull RD, Raskob GE. Epidemiology and pathogenesis of venous thrombosis. J Am Coll Cardiol 1986;**8**(6 Suppl B):104B-113B.
44. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;**97**(21):2110-6.
45. Veronese N, Li Y, Manson JE, Willett WC, Fontana L, Hu FB. Combined associations of body weight and lifestyle factors with all cause and cause specific mortality in men and women: prospective cohort study. BMJ 2016;**355**:i5855.
46. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, Gupta PC, Ramadas K, Inoue M, Tsugane S, Tamakoshi A, Gao YT, Yuan JM, Shu XO, Ozasa K, Tsuji I, Kakizaki M, Tanaka H, Nishino Y, Chen CJ, Wang R, Yoo KY, Ahn YO, Ahsan H, Pan WH, Chen CS, Pednekar MS, Sauvaget C, Sasazuki S, Yang G, Koh WP, Xiang YB, Ohishi W, Watanabe T, Sugawara Y, Matsuo K, You SL, Park SK, Kim DH, Parvez F, Chuang SY, Ge W, Rolland B, McLerran D, Sinha R, Thornquist M, Kang D, Feng Z, Boffetta P, Zheng W, He J, Potter JD. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. BMJ 2013;**347**:f5446.
47. Stec JJ, Silbershatz H, Tofler GH, Matheney TH, Sutherland P, Lipinska I, Massaro JM, Wilson PF, Muller JE, D'Agostino RB, Sr. Association of fibrinogen with cardiovascular risk factors and cardiovascular disease in the Framingham Offspring Population. Circulation 2000;**102**(14):1634-8.
48. Meade TW, Mellows S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, Haines AP, Stirling Y, Imeson JD, Thompson SG. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986;**2**(8506):533-7.
49. Ay L, Kopp HP, Brix JM, Ay C, Quehenberger P, Schernthaner GH, Pabinger I, Schernthaner G. Thrombin generation in morbid obesity: significant reduction after weight loss. J Thromb Haemost 2010;**8**(4):759-65.
50. Unek IT, Bayraktar F, Solmaz D, Ellidokuz H, Sisman AR, Yuksel F, Yesil S. The levels of soluble CD40 ligand and C-reactive protein in normal weight, overweight and obese people. Clin Med Res 2010;**8**(2):89-95.
51. Hogstrom G, Nordstrom A, Eriksson M, Nordstrom P. Risk factors assessed in adolescence and the later risk of stroke in men: a 33-year follow-up study. Cerebrovasc Dis 2015;**39**(1):63-71.
52. Song YM, Sung J, Smith GD, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke - A prospective study in Korean men. Stroke 2004;**35**(4):831-836.
53. Yatsuya H, Toyoshima H, Yamagishi K, Tamakoshi K, Taguri M, Harada A, Ohashi Y, Kita Y, Naito Y, Yamada M, Tanabe N, Iso H, Ueshima H, Japan Arteriosclerosis Longitudinal Study g. Body mass index and risk of stroke and myocardial infarction in a relatively lean population: meta-analysis of 16 Japanese cohorts using individual data. Circ Cardiovasc Qual Outcomes 2010;**3**(5):498-505.
54. Bazzano LA, Gu D, Whelton MR, Wu X, Chen CS, Duan X, Chen J, Chen JC, He J. Body mass index and risk of stroke among Chinese men and women. Ann Neurol 2010;**67**(1):11-20.
55. Prospective Studies C, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;**373**(9669):1083-96.
56. Matsukawa H, Shinoda M, Fujii M, Takahashi O, Yamamoto D, Murakata A, Ishikawa R. Factors associated with lobar vs. non-lobar intracerebral hemorrhage. Acta Neurol Scand 2012;**126**(2):116-21.
57. Biffi A, Cortellini L, Nearnberg CM, Ayres AM, Schwab K, Gilson AJ, Rost NS, Goldstein JN, Viswanathan A, Greenberg SM, Rosand J. Body mass index and etiology of intracerebral hemorrhage. Stroke 2011;**42**(9):2526-30.
58. Kim CK, Kwon HM, Lee SH, Kim BJ, Ryu WS, Kwon HT, Yoon BW. Association of obesity with cerebral microbleeds in neurologically asymptomatic elderly subjects. J Neurol 2012;**259**(12):2599-604.
59. Pezzini A, Grassi M, Paciaroni M, Zini A, Silvestrelli G, Iacoviello L, Di Castelnuovo A, Del Zotto E, Caso V, Nichelli PF, Giossi A, Volonghi I, Simone AM, Lanari A, Costa P, Poli L, Pentore R, Falzone F, Gamba M, Morotti A, Ciccone A, Ritelli M, Guido D, Colombi M, De Gaetano G, Agnelli G, Padovani A, Multicentre

Study on Cerebral Hemorrhage in Italy I. Obesity and the risk of intracerebral hemorrhage: the multicenter study on cerebral hemorrhage in Italy. Stroke 2013;**44**(6):1584-9.
60. Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;**373**(9678):1849-60.
61. Braekkan SK, van der Graaf Y, Visseren FL, Algra A. Obesity and risk of bleeding: the SMART study. J Thromb Haemost 2016;**14**(1):65-72.
62. Kim CK, Ryu WS, Kim BJ, Lee SH. Paradoxical effect of obesity on hemorrhagic transformation after acute ischemic stroke. BMC Neurol 2013;**13**:123.
63. Kim BJ, Lee SH, Ryu WS, Kim CK, Lee J, Yoon BW. Paradoxical longevity in obese patients with intracerebral hemorrhage. Neurology 2011;**76**(6):567-73.
64. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff AM, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). Am J Cardiol 2002;**90**(1):42-5.
65. Powell BD, Lennon RJ, Lerman A, Bell MR, Berger PB, Higano ST, Holmes DR, Jr., Rihal CS. Association of body mass index with outcome after percutaneous coronary intervention. Am J Cardiol 2003;**91**(4):472-6.
66. McDonagh JR, Seth M, LaLonde TA, Khandewal AK, Wohns DH, Dixon SR, Gurm HS. Radial PCI and the obesity paradox: Insights from Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). Catheter Cardiovasc Interv 2016;**87**(2):211-9.
67. Delhaye C, Wakabayashi K, Maluenda G, Belle L, Ben-Dor I, Gonzalez MA, Gaglia MA, Jr., Torguson R, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Body mass index and bleeding complications after percutaneous coronary intervention: does bivalirudin make a difference? Am Heart J 2010;**159**(6):1139-46.
68. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;**368**(9536):666-78.
69. Numasawa Y, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, Nakagawa S, Momiyama Y, Naito K, Fukuda K. Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention in a Japanese real-world multicenter registry. PLoS One 2015;**10**(4):e0124399.
70. Abawi M, Rozemeijer R, Agostoni P, van Jaarsveld RC, van Dongen CS, Voskuil M, Kraaijeveld AO, Doevendans P, Stella PR. Effect of body mass index on clinical outcome and all-cause mortality in patients undergoing transcatheter aortic valve implantation. Neth Heart J 2017.
71. Kische S, D'Ancona G, Agma HU, El-Achkar G, Dissmann M, Ortak J, Oner A, Ketterer U, Barisch A, Levenson B, Ince H. Transcatheter aortic valve implantation in obese patients: Overcoming technical challenges and maintaining adequate hemodynamic performance using new generation prostheses. Int J Cardiol 2016;**220**:909-13.
72. Mok M, Allende R, Leipsic J, Altisent OA, Del Trigo M, Campelo-Parada F, DeLarochelliere R, Dumont E, Doyle D, Cote M, Freeman M, Webb J, Rodes-Cabau J. Prognostic Value of Fat Mass and Skeletal Muscle Mass Determined by Computed Tomography in Patients Who Underwent Transcatheter Aortic Valve Implantation. Am J Cardiol 2016;**117**(5):828-33.
73. Garg L, Agrawal S, Pew T, Hanzel GS, Abbas AE, Gallagher MJ, Shannon FL, Hanson ID. Psoas Muscle Area as a Predictor of Outcomes in Transcatheter Aortic Valve Implantation. Am J Cardiol 2017;**119**(3):457-460.
74. Yamamoto M, Mouillet G, Oguri A, Gilard M, Laskar M, Eltchaninoff H, Fajadet J, Iung B, Donzeau-Gouge P, Leprince P, Leuguerrier A, Prat A, Lievre M, Chevreul K, Dubois-Rande JL, Teiger E, Investigators FR. Effect of body mass index on 30- and 365-day complication and survival rates of transcatheter aortic valve implantation (from the FRench Aortic National CoreValve and Edwards 2 [FRANCE 2] registry). Am J Cardiol 2013;**112**(12):1932-7.

75. Lv W, Li S, Liao Y, Zhao Z, Che G, Chen M, Feng Y. The 'obesity paradox' does exist in patients undergoing transcatheter aortic valve implantation for aortic stenosis: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2017;**25**(4):633-642.
76. De Palma R, Ivarsson J, Feldt K, Saleh N, Ruck A, Linder R, Settergren M. The obesity paradox: An analysis of pre-procedure weight trajectory on survival outcomes in patients undergoing transcatheter aortic valve implantation. Obes Res Clin Pract 2017.
77. Gonzalez-Ferreiro R, Munoz-Garcia AJ, Lopez-Otero D, Avanzas P, Pascual I, Alonso-Briales JH, Trillo-Nouche R, Pun F, Jimenez-Navarro MF, Hernandez-Garcia JM, Moris C, Gonzalez Juanatey JR. Prognostic value of body mass index in transcatheter aortic valve implantation: A "J"-shaped curve. Int J Cardiol 2017;**232**:342-347.
78. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Effects of obesity and small body size on operative and long-term outcomes of coronary artery bypass surgery: a propensity-matched analysis. Ann Thorac Surg 2005;**79**(6):1976-86.
79. Lindhout AH, Wouters CW, Noyez L. Influence of obesity on in-hospital and early mortality and morbidity after myocardial revascularization. Eur J Cardiothorac Surg 2004;**26**(3):535-41.
80. Nolan HR, Davenport DL, Ramaiah C. BMI Is an Independent Preoperative Predictor of Intraoperative Transfusion and Postoperative Chest-Tube Output. Int J Angiol 2013;**22**(1):31-6.
81. Kuduvalli M, Grayson AD, Oo AY, Fabri BM, Rashid A. The effect of obesity on mid-term survival following coronary artery bypass surgery. Eur J Cardiothorac Surg 2003;**23**(3):368-73.
82. Kim J, Hammar N, Jakobsson K, Luepker RV, McGovern PG, Ivert T. Obesity and the risk of early and late mortality after coronary artery bypass graft surgery. Am Heart J 2003;**146**(3):555-60.
83. Rahmanian PB, Adams DH, Castillo JG, Chikwe J, Bodian CA, Filsoufi F. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. Am J Cardiol 2007;**100**(11):1702-8.
84. Leykin Y, Miotto L, Pellis T. Pharmacokinetic considerations in the obese. Best Pract Res Clin Anaesthesiol 2011;**25**(1):27-36.
85. Jain R, Chung SM, Jain L, Khurana M, Lau SW, Lee JE, Vaidyanathan J, Zadezensky I, Choe S, Sahajwalla CG. Implications of obesity for drug therapy: limitations and challenges. Clin Pharmacol Ther 2011;**90**(1):77-89.
86. Alpert MA, Omran J, Bostick BP. Effects of Obesity on Cardiovascular Hemodynamics, Cardiac Morphology, and Ventricular Function. Curr Obes Rep 2016;**5**(4):424-434.
87. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. Nat Rev Gastroenterol Hepatol 2017;**14**(3):160-169.
88. Stein J, Stier C, Raab H, Weiner R. Review article: The nutritional and pharmacological consequences of obesity surgery. Aliment Pharmacol Ther 2014;**40**(6):582-609.
89. Titus R, Kastenmeier A, Otterson MF. Consequences of gastrointestinal surgery on drug absorption. Nutr Clin Pract 2013;**28**(4):429-36.
90. Gesquiere I, Hens B, Van der Schueren B, Mols R, de Hoon J, Lannoo M, Matthys C, Foulon V, Augustijns P. Drug disposition before and after gastric bypass: fenofibrate and posaconazole. Br J Clin Pharmacol 2016;**82**(5):1325-1332.
91. Azran C, Wolk O, Zur M, Fine-Shamir N, Shaked G, Czeiger D, Sebbag G, Kister O, Langguth P, Dahan A. Oral drug therapy following bariatric surgery: an overview of fundamentals, literature and clinical recommendations. Obes Rev 2016;**17**(11):1050-1066.
92. Sato Y, Fujimoto S, Konta T, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Asahi K, Kurahashi I, Ohashi Y, Watanabe T. U-shaped association between body mass index and proteinuria in a large Japanese general population sample. Clin Exp Nephrol 2014;**18**(1):75-86.
93. Darwich AS, Pade D, Ammori BJ, Jamei M, Ashcroft DM, Rostami-Hodjegan A. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol 2012;**64**(7):1008-24.
94. Giaretta A, Rocca B, Di Camillo B, Maria Toffolo G, Patrono C. In silico modeling of the antiplatelet pharmacodynamics of low-dose aspirin in health and disease. Clin Pharmacol Ther 2017.

95. Rocca B, Santilli F, Pitocco D, Mucci L, Petrucci G, Vitacolonna E, Lattanzio S, Mattoscio D, Zaccardi F, Liani R, Vazzana N, Del Ponte A, Ferrante E, Martini F, Cardillo C, Morosetti R, Mirabella M, Ghirlanda G, Davi G, Patrono C. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. J Thromb Haemost 2012;**10**(7):1220-30.
96. Patrono C, Rocca B. Type 2 Diabetes, Obesity, and Aspirin Responsiveness. J Am Coll Cardiol 2017.
97. Mayer K, Bernlochner I, Braun S, Schulz S, Orban M, Morath T, Cala L, Hoppmann P, Schunkert H, Laugwitz KL, Kastrati A, Sibbing D. Aspirin treatment and outcomes after percutaneous coronary intervention: results of the ISAR-ASPI registry. J Am Coll Cardiol 2014;**64**(9):863-71.
98. Cox D, Maree AO, Dooley M, Conroy R, Byrne MF, Fitzgerald DJ. Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. Stroke 2006;**37**(8):2153-8.
99. Peace A, McCall M, Tedesco T, Kenny D, Conroy RM, Foley D, Cox D. The role of weight and enteric coating on aspirin response in cardiovascular patients. J Thromb Haemost 2010;**8**(10):2323-5.
100. Sankaralingam S, Kim, RB, Padwal, RS. The Impact of Obesity on the Pharmacology of Medications Used for Cardiovascular Risk Factor Control. Canadian Journal of Cardiology 2015;**31**:167-176.
101. Norgard NB, Monte SV, Fernandez SF, Ma Q. Aspirin responsiveness changes in obese patients following bariatric surgery. Cardiovasc Ther 2017.
102. Mitrov-Winkelmolen L, van Buul-Gast MC, Swank DJ, Overdiek HW, van Schaik RH, Touw DJ. The Effect of Roux-en-Y Gastric Bypass Surgery in Morbidly Obese Patients on Pharmacokinetics of (Acetyl)Salicylic Acid and Omeprazole: the ERY-PAO Study. Obes Surg 2016;**26**(9):2051-8.
103. Movahedi M, Bishop DT, Macrae F, Mecklin JP, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML, Dunlop MG, Ho JW, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar RS, Side L, Scott RJ, Thomas HJ, Vasen HF, Burn J, Mathers JC. Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study. J Clin Oncol 2015;**33**(31):3591-7.
104. Sundstrom J, Hedberg J, Thuresson M, Aarskog P, Johannesen KM, Oldgren J. Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events: A Swedish Nationwide, Population-Based Cohort Study. Circulation 2017;**136**(13):1183-1192.
105. Bonello-Palot N, Armero S, Paganelli F, Mancini J, De Labriolle A, Bonello C, Levy N, Maillard L, Barragan P, Dignat-George F, Camoin-Jau L, Bonello L. Relation of body mass index to high on-treatment platelet reactivity and of failed clopidogrel dose adjustment according to platelet reactivity monitoring in patients undergoing percutaneous coronary intervention. Am J Cardiol 2009;**104**(11):1511-5.
106. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. Obesity is associated with poor response to clopidogrel and an increased susceptibility to protease activated receptor-1 mediated platelet activation. Transl Res 2013;**161**(5):421-9.
107. Wagner H, Angiolillo DJ, Ten Berg JM, Bergmeijer TO, Jakubowski JA, Small DS, Moser BA, Zhou C, Brown P, James S, Winters KJ, Erlinge D. Higher body weight patients on clopidogrel maintenance therapy have lower active metabolite concentrations, lower levels of platelet inhibition, and higher rates of poor responders than low body weight patients. J Thromb Thrombolysis 2014;**38**(2):127-36.
108. Nardin M, Verdoia M, Sartori C, Pergolini P, Rolla R, Barbieri L, Schaffer A, Marino P, Bellomo G, Suryapranata H, De Luca G, Novara Atherosclerosis Study G. Body Mass Index and Platelet Reactivity During Dual Antiplatelet Therapy With Clopidogrel or Ticagrelor. J Cardiovasc Pharmacol 2015;**66**(4):364-70.
109. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;**302**(8):849-57.
110. Sibbing D, von Beckerath O, Schomig A, Kastrati A, von Beckerath N. Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. Am J Cardiol 2007;**100**(2):203-5.
111. Jakubowski JA, Angiolillo DJ, Zhou C, Small DS, Moser BA, Ten Berg JM, Brown PB, James S, Winters KJ, Erlinge D. The influence of body size on the pharmacodynamic and pharmacokinetic response to clopidogrel and prasugrel: a retrospective analysis of the FEATHER study. Thromb Res 2014;**134**(3):552-7.

112. Horenstein RB, Madabushi R, Zineh I, Yerges-Armstrong LM, Peer CJ, Schuck RN, Figg WD, Shuldiner AR, Pacanowski MA. Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers. J Clin Pharmacol 2014;**54**(8):865-73.
113. Samant S, Jiang XL, Peletier LA, Shuldiner AR, Horenstein RB, Lewis JP, Lesko LJ, Schmidt S. Identifying clinically relevant sources of variability: The clopidogrel challenge. Clin Pharmacol Ther 2017;**101**(2):264-273.
114. Sarno G, Garg S, Onuma Y, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, van Geuns RJ, Eerdmans P, Garcia-Garcia HM, van Es GA, Goedhart D, de Vries T, Juni P, Meier B, Windecker S, Serruys P. The impact of body mass index on the one year outcomes of patients treated by percutaneous coronary intervention with Biolimus- and Sirolimus-eluting stents (from the LEADERS Trial). Am J Cardiol 2010;**105**(4):475-9.
115. Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, Tanguay JF, Cannon CP, Topol EJ. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. Circulation 2011;**124**(10):1132-7.
116. Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrie D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monsegu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthelemy O, Beygui F, Silvain J, Vicaut E, Montalescot G, Investigators A. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;**367**(22):2100-9.
117. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrie D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet JL, Lattuca B, Pouillot C, Varenne O, Boueri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem JE, Abtan J, Rousseau H, Collet JP, Vicaut E, Montalescot G, investigators A. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;**388**(10055):2015-2022.
118. Mayer K, Orban M, Bernlochner I, Braun S, Schulz S, Gross L, Hadamitzky M, Schunkert H, Laugwitz KL, Massberg S, Kastrati A, Sibbing D. Predictors of antiplatelet response to prasugrel during maintenance treatment. Platelets 2015;**26**(1):53-8.
119. Olivier CB, Schnabel K, Weber S, Zhou Q, Bode C, Moser M, Diehl P. Platelet reactivity after administration of third generation P2Y12-antagonists does not depend on body weight in contrast to clopidogrel. J Thromb Thrombolysis 2016;**42**(1):84-9.
120. Small DS, Li YG, Ernest CS, 2nd, April JH, Farid NA, Payne CD, Winters KJ, Rohatagi S, Ni L. Integrated analysis of pharmacokinetic data across multiple clinical pharmacology studies of prasugrel, a new thienopyridine antiplatelet agent. J Clin Pharmacol 2011;**51**(3):321-32.
121. Ernest CS, 2nd, Small DS, Rohatagi S, Salazar DE, Wallentin L, Winters KJ, Wrishko RE. Population pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel in aspirin-treated patients with stable coronary artery disease. J Pharmacokinet Pharmacodyn 2008;**35**(6):593-618.
122. Wrishko RE, Ernest CS, 2nd, Small DS, Li YG, Weerakkody GJ, Riesmeyer JR, Macias WL, Rohatagi S, Salazar DE, Antman EM, Wiviott SD, Braunwald E, Ni L. Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. J Clin Pharmacol 2009;**49**(8):984-98.
123. Pankert M, Quilici J, Loundou AD, Verdier V, Lambert M, Deharo P, Bonnet G, Gaborit B, Morange PE, Valero R, Dutour A, Bonnet JL, Alessi MC, Cuisset T. Impact of obesity and the metabolic syndrome on response to clopidogrel or prasugrel and bleeding risk in patients treated after coronary stenting. Am J Cardiol 2014;**113**(1):54-9.
124. Darlington A, Tello-Montoliu A, Rollini F, Ueno M, Ferreiro JL, Patel R, Desai B, Guzman LA, Bass TA, Angiolillo DJ. Pharmacodynamic effects of standard dose prasugrel versus high dose clopidogrel in non-diabetic obese patients with coronary artery disease. Thromb Haemost 2014;**111**(2):258-65.
125. Erlinge D, Ten Berg J, Foley D, Angiolillo DJ, Wagner H, Brown PB, Zhou C, Luo J, Jakubowski JA, Moser B, Small DS, Bergmeijer T, James S, Winters KJ. Reduction in platelet reactivity with prasugrel 5 mg in

low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. J Am Coll Cardiol 2012;**60**(20):2032-40.
126. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, Investigators T-T. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;**357**(20):2001-15.
127. Riesmeyer JS, Salazar DE, Weerakkody GJ, Ni L, Wrishko RE, Ernest CS, 2nd, Luo J, Li YG, Small DS, Rohatagi S, Macias WL. Relationship between exposure to prasugrel active metabolite and clinical outcomes in the TRITON-TIMI 38 substudy. J Clin Pharmacol 2012;**52**(6):789-97.
128. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J, Management of Acute Coronary Syndromes in Patients Presenting without Persistent STSEotESoC. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;**37**(3):267-315.
129. Storey RF, Angiolillo DJ, Bonaca MP, Thomas MR, Judge HM, Rollini F, Franchi F, Ahsan AJ, Bhatt DL, Kuder JF, Steg PG, Cohen M, Muthusamy R, Braunwald E, Sabatine MS. Platelet Inhibition with Ticagrelor 60 mg Compared with 90 mg Twice-daily in the PEGASUS-TIMI 54 study. J Am Coll Cardiol 2016;**67**:1145-54.
130. Storey RF, Angiolillo D, Patil S, Desai B, Ecob R, Husted S, Emanuelsson H, Cannon C, Becker R, Wallentin L. Inhibitory Effects of Ticagrelor Compared to Clopidogrel on Platelet Function in Patients with Acute Coronary Syndromes: the PLATO PLATELET Substudy J Am Coll Cardiol 2010;**56**:1456-62.
131. Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJJ. Characterization of the Adenosine Pharmacology of Ticagrelor Reveals Therapeutically Relevant Inhibition of Equilibrative Nucleoside Transporter 1. Journal of Cardiovascular Pharmacology and Therapeutics 2014;**19**(2):209-219.
132. Roshammar D, Bergstrand M, Andersson T, Storey RF, Hamren B. Population pharmacokinetics of ticagrelor and AR-C124910XX in patients with prior myocardial infarction. Int J Clin Pharmacol Ther 2017;**55**(5):416-424.
133. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, for the PLATO Investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009;**361**(11):1045-1057.
134. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI 54 Steering Committee and Investigators. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. N Engl J Med 2015;**372**:1791-800.
135. Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, Im K, Murphy SA, Held P, Braunwald E, Sabatine MS, Steg PG. Reduction in Ischemic Events With Ticagrelor in Diabetic Patients With Prior Myocardial Infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016;**67**(23):2732-2740.
136. Röshammar D, Nyberg J, Andersson T, Stanski D, Storey RF, Hamrén B. Exposure-Response Analyses Supporting Ticagrelor Dosing Recommendation in Patients With Prior Myocardial Infarction. J Clin Pharmacol 2016;**online**.
137. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, Steg PG, Khurmi NS, Emanuelsson H, Cooper A, Cairns R, Cannon CP, Wallentin L. Characterisation of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. Eur Heart J 2011;**32**:2945-53.
138. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF. Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor

Antagonist, Compared With Clopidogrel, in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome: Primary Results of the DISPERSE-2 Trial. J Am Coll Cardiol 2007;**50**(19):1844-1851.
139. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;**27**:1038-1047.
140. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, French J, Held C, Horrow J, Husted S, Lopez-Sendon J, Lassila R, Mahaffey KW, Storey RF, Harrington RA, Wallentin L. Bleeding complications with the $P2Y_{12}$ receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011;**32**(23):2933-2944.
141. Martin JL, Jia G, Martin SS, Shapiro TA, Herrmann HC, Dibattiste PM, Topol EJ, Moliterno DJ. The relationship of obesity to ischemic outcomes following coronary stent placement in contemporary practice. Catheter Cardiovasc Interv 2006;**67**(4):563-70.
142. de Lorenzo-Pinto A, Bueno H, Cuellar-Basterrechea B, Herranz-Alonso A, Perez-Sanz C, Rodriguez-Gonzalez CG, Iglesias-Peinado I, Fernandez-Aviles F, Sanjurjo-Saez M. Optimisation of antithrombotic therapy in patients with acute coronary syndrome to reduce bleeding episodes. Int J Clin Pract 2016;**70**(2):156-62.
143. Yoo SH, Nah HW, Jo MW, Kang DW, Kim JS, Koh JY, Kwon SU. Age and body weight adjusted warfarin initiation program for ischaemic stroke patients. Eur J Neurol 2009;**16**(10):1100-5.
144. Wallace JL, Reaves AB, Tolley EA, Oliphant CS, Hutchison L, Alabdan NA, Sands CW, Self TH. Comparison of initial warfarin response in obese patients versus non-obese patients. J Thromb Thrombolysis 2013;**36**(1):96-101.
145. Absher RK, Moore ME, Parker MH. Patient-specific factors predictive of warfarin dosage requirements. Ann Pharmacother 2002;**36**(10):1512-7.
146. Routledge PA, Chapman PH, Davies DM, Rawlins MD. Factors affecting warfarin requirements. A prospective population study. Eur J Clin Pharmacol 1979;**15**(5):319-22.
147. Mueller JA, Patel T, Halawa A, Dumitrascu A, Dawson NL. Warfarin dosing and body mass index. Ann Pharmacother 2014;**48**(5):584-8.
148. Patel JP, Roberts LN, Arya R. Anticoagulating obese patients in the modern era. Br J Haematol 2011;**155**(2):137-49.
149. Senoo K, Lip GY. Body Mass Index and Adverse Outcomes in Elderly Patients With Atrial Fibrillation: The AMADEUS Trial. Stroke 2016;**47**(2):523-6.
150. Chu C, Tokumaru S, Izumi K, Nakagawa K. Obesity increases risk of anticoagulation reversal failure with prothrombin complex concentrate in those with intracranial hemorrhage. Int J Neurosci 2016;**126**(1):62-6.
151. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA, Ozier Y, Riddez L, Schultz A, Vincent JL, Spahn DR. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;**20**:100.
152. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, Hanna M, Hijazi Z, Jansky P, Lopes RD, Wallentin L. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Eur Heart J 2016;**37**(38):2869-2878.
153. Yin OQ, Tetsuya K, Miller R. Edoxaban population pharmacokinetics and exposure-response analysis in patients with non-valvular atrial fibrillation. Eur J Clin Pharmacol 2014;**70**(11):1339-51.
154. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 2007;**47**(2):218-26.
155. Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P, Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. Clin Pharmacokinet 2011;**50**(10):675-86.

156. Xu XS, Moore K, Burton P, Stuyckens K, Mueck W, Rossenu S, Plotnikov A, Gibson M, Vermeulen A. Population pharmacokinetics and pharmacodynamics of rivaroxaban in patients with acute coronary syndromes. Br J Clin Pharmacol 2012;**74**(1):86-97.
157. Di Nisio M, Vedovati MC, Riera-Mestre A, Prins MH, Mueller K, Cohen AT, Wells PS, Beyer-Westendorf J, Prandoni P, Bounameaux H, Kubitza D, Schneider J, Pisters R, Fedacko J, Fontes-Carvalho R, Lensing AW. Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. Thromb Haemost 2016;**116**(4):739-46.
158. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;**365**(10):883-91.
159. Kroll D, Stirnimann G, Vogt A, Lai DLL, Borbely YM, Altmeier J, Schadelin S, Candinas D, Alberio L, Nett PC. Pharmacokinetics and pharmacodynamics of single doses of rivaroxaban in obese patients prior to and after bariatric surgery. Br J Clin Pharmacol 2017;**83**(7):1466-1475.
160. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S, Investigators C. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;**377**(14):1319-1330.
161. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L, Investigators R-L. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;**63**(4):321-8.
162. Liesenfeld KH, Lehr T, Dansirikul C, Reilly PA, Connolly SJ, Ezekowitz MD, Yusuf S, Wallentin L, Haertter S, Staab A. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemost 2011;**9**(11):2168-75.
163. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf.
164. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;**14**(6):1308-13.
165. Czuprynska J, Patel JP, Arya R. Current challenges and future prospects in oral anticoagulant therapy. Br J Haematol 2017.
166. Garcia DA, Baglin TP, Weitz JI, Samama MM, American College of Chest P. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;**141**(2 Suppl):e24S-43S.
167. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med 1993;**119**(9):874-81.
168. Riney JN, Hollands JM, Smith JR, Deal EN. Identifying optimal initial infusion rates for unfractionated heparin in morbidly obese patients. Ann Pharmacother 2010;**44**(7-8):1141-51.
169. Barletta JF, DeYoung JL, McAllen K, Baker R, Pendleton K. Limitations of a standardized weight-based nomogram for heparin dosing in patients with morbid obesity. Surg Obes Relat Dis 2008;**4**(6):748-53.
170. Fan J, John B, Tesdal E. Evaluation of heparin dosing based on adjusted body weight in obese patients. Am J Health Syst Pharm 2016;**73**(19):1512-22.
171. Hohner EM, Kruer RM, Gilmore VT, Streiff M, Gibbs H. Unfractionated heparin dosing for therapeutic anticoagulation in critically ill obese adults. J Crit Care 2015;**30**(2):395-9.
172. Frederiksen SG, Hedenbro JL, Norgren L. Enoxaparin effect depends on body-weight and current doses may be inadequate in obese patients. Br J Surg 2003;**90**(5):547-8.

173. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI, American College of Chest P. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;**133**(6 Suppl):141S-159S.
174. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009;**43**(6):1064-83.
175. Egan G, Ensom MH. Measuring anti-factor xa activity to monitor low-molecular-weight heparin in obesity: a critical review. Can J Hosp Pharm 2015;**68**(1):33-47.
176. Kucher N, Leizorovicz A, Vaitkus PT, Cohen AT, Turpie AG, Olsson CG, Goldhaber SZ. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;**165**(3):341-5.
177. Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. J Thromb Thrombolysis 2016;**41**(3):475-81.
178. Simoneau MD, Vachon A, Picard F. Effect of prophylactic dalteparin on anti-factor Xa levels in morbidly obese patients after bariatric surgery. Obes Surg 2010;**20**(4):487-91.
179. Borkgren-Okonek MJ, Hart RW, Pantano JE, Rantis PC, Jr., Guske PJ, Kane JM, Jr., Gordon N, Sambol NC. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis 2008;**4**(5):625-31.
180. Simone EP, Madan AK, Tichansky DS, Kuhl DA, Lee MD. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. Surg Endosc 2008;**22**(11):2392-5.
181. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW, American College of Chest P. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;**133**(6 Suppl):381S-453S.
182. Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol 2012;**87**(7):740-3.
183. Rondina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res 2010;**125**(3):220-3.
184. Ludwig KP, Simons HJ, Mone M, Barton RG, Kimball EJ. Implementation of an enoxaparin protocol for venous thromboembolism prophylaxis in obese surgical intensive care unit patients. Ann Pharmacother 2011;**45**(11):1356-62.
185. Miranda S, Le Cam-Duchez V, Benichou J, Donnadieu N, Barbay V, Le Besnerais M, Delmas FX, Cuvelier A, Levesque H, Benhamou Y, Armengol G. Adjusted value of thromboprophylaxis in hospitalized obese patients: A comparative study of two regimens of enoxaparin: The ITOHENOX study. Thromb Res 2017;**155**:1-5.
186. Overcash RT, Somers AT, LaCoursiere DY. Enoxaparin dosing after cesarean delivery in morbidly obese women. Obstet Gynecol 2015;**125**(6):1371-6.
187. Ikesaka R, Delluc A, Le Gal G, Carrier M. Efficacy and safety of weight-adjusted heparin prophylaxis for the prevention of acute venous thromboembolism among obese patients undergoing bariatric surgery: a systematic review and meta-analysis. Thromb Res 2014;**133**(4):682-7.
188. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Lovenox_30/WC500218186.pdf.
189. Carter C, Bushwitz J, Gowan M, Pope H, Human T, Gibson G, Owen E, Hampton N, Whitman C. Clinical Experience With Pharmacological Venous Thromboembolism Prophylaxis in the Underweight and Critically Ill. Ann Pharmacother 2016;**50**(10):832-9.
190. Barba R, Marco J, Martin-Alvarez H, Rondon P, Fernandez-Capitan C, Garcia-Bragado F, Monreal M, investigators R. The influence of extreme body weight on clinical outcome of patients with venous thromboembolism: findings from a prospective registry (RIETE). J Thromb Haemost 2005;**3**(5):856-62.
191. Betthauser K, Pope H, Gowan M, Human T. Practice Patterns of Venous Thromboembolism Prophylaxis in Underweight, Critically Ill Patients with Neurologic Injury. Neurocrit Care 2017.

192. Mahaffey KW, Tonev ST, Spinler SA, Levine GN, Gallo R, Ducas J, Goodman SG, Antman EM, Becker RC, Langer A, White HD, Aylward PE, Col JJ, Ferguson JJ, Califf RM, Investigators ST. Obesity in patients with non-ST-segment elevation acute coronary syndromes: results from the SYNERGY trial. Int J Cardiol 2010;**139**(2):123-33.
193. Spinler SA, Ou FS, Roe MT, Gibler WB, Ohman EM, Pollack CV, Alexander KP, Peterson ED. Weight-based dosing of enoxaparin in obese patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE initiative. Pharmacotherapy 2009;**29**(6):631-8.
194. Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM, Essence, Investigators TB. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 2003;**146**(1):33-41.
195. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000403/WC500027746.pdf.
196. Davidson BL, Buller HR, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob GE, Segers AE, Lensing AW, Matisse I. Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Matisse trials. J Thromb Haemost 2007;**5**(6):1191-4.
197. Yuri M, Tabe Y, Tsuchiya K, Sadatsuki R, Aoki J, Horii T, Iba T, Ohsaka A. Evaluation of Factor Xa-Specific Chromogenic Substrate Assays and the Determination of Pharmacokinetics of Fondaparinux. Clin Appl Thromb Hemost 2016;**22**(5):453-8.
198. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf.
199. Martinez L, Burnett A, Borrego M, Streeter JC, Townsend K, Garcia D. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. Am J Health Syst Pharm 2011;**68**(18):1716-22.
200. Steele KE, Canner J, Prokopowicz G, Verde F, Beselman A, Wyse R, Chen J, Streiff M, Magnuson T, Lidor A, Schweitzer M. The EFFORT trial: Preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: a randomized double-blind pilot trial. Surg Obes Relat Dis 2015;**11**(3):672-83.
201. Task Force on the management of STseamiotESoC, Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;**33**(20):2569-619.
202. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Guidelines ESCCfP, Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;**42**(4):S1-44.
203. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarria VV, Demchuk AM, Bath PM, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Roffe C, Pandian J, Billot L, Woodward M, Li Q, Wang X, Wang J, Chalmers J, Investigators E, Coordinators. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. N Engl J Med 2016;**374**(24):2313-23.
204. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M, Task Force for the D, Management of Acute Pulmonary Embolism of the European Society of C. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;**35**(43):3033-69, 3069a-3069k.

205. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;**141**(2 Suppl):e576S-e600S.
206. Simoons ML, de Jaegere P, van Domburg R, Boersma E, Maggioni AP, Franzosi MG, Knatterud G, Leimberger JD, Califf R, Schroder R, Knatterud G, Braunwald E. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. Lancet 1993;**342**(8886-8887):1523-8.
207. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000306/WC500026892.pdf.
208. Lundergan CF, Reiner JS, McCarthy WF, Coyne KS, Califf RM, Ross AM. Clinical predictors of early infarct-related artery patency following thrombolytic therapy: importance of body weight, smoking history, infarct-related artery and choice of thrombolytic regimen: the GUSTO-I experience. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. J Am Coll Cardiol 1998;**32**(3):641-7.
209. Gensicke H, Wicht A, Bill O, Zini A, Costa P, Kagi G, Stark R, Seiffge DJ, Traenka C, Peters N, Bonati LH, Giovannini G, De Marchis GM, Poli L, Polymeris A, Vanacker P, Sarikaya H, Lyrer PA, Pezzini A, Vandelli L, Michel P, Engelter ST, Thrombolysis in Stroke Patients c. Impact of body mass index on outcome in stroke patients treated with intravenous thrombolysis. Eur J Neurol 2016;**23**(12):1705-1712.
210. Garcia-Pastor A, Diaz-Otero F, Funes-Molina C, Benito-Conde B, Grandes-Velasco S, Sobrino-Garcia P, Vazquez-Alen P, Fernandez-Bullido Y, Villanueva-Osorio JA, Gil-Nunez A. Tissue plasminogen activator for acute ischemic stroke: calculation of dose based on estimated patient weight can increase the risk of cerebral bleeding. J Thromb Thrombolysis 2015;**40**(3):347-52.
211. Barrow T, Khan MS, Halse O, Bentley P, Sharma P. Estimating Weight of Patients With Acute Stroke When Dosing for Thrombolysis. Stroke 2016;**47**(1):228-31.
212. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, Wahlgren N, Ahmed N, Investigators S. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke 2012;**43**(6):1524-31.
213. Hassan AE, Chaudhry SA, Jani V, Grigoryan M, Khan AA, Adil MM, Qureshi AI. Is there a decreased risk of intracerebral hemorrhage and mortality in obese patients treated with intravenous thrombolysis in acute ischemic stroke? J Stroke Cerebrovasc Dis 2013;**22**(4):545-9.
214. Branscheidt M, Schneider J, Michel P, Eskioglou E, Kaegi G, Stark R, Fischer U, Jung S, Arnold M, Wertli M, Held U, Wegener S, Luft A, Sarikaya H. No Impact of Body Mass Index on Outcome in Stroke Patients Treated with IV Thrombolysis BMI and IV Thrombolysis Outcome. PLoS One 2016;**11**(10):e0164413.
215. Moulin PA, Dutour A, Ancel P, Morange PE, Bege T, Ziegler O, Berdah S, Frere C, Gaborit B. Perioperative thromboprophylaxis in severely obese patients undergoing bariatric surgery: insights from a French national survey. Surg Obes Relat Dis 2017;**13**(2):320-326.
216. Yang G, De Staercke C, Hooper WC. The effects of obesity on venous thromboembolism: A review. Open J Prev Med 2012;**2**(4):499-509.
217. Delluc A, Mottier D, Le Gal G, Oger E, Lacut K. Underweight is associated with a reduced risk of venous thromboembolism. Results from the EDITH case-control study. J Thromb Haemost 2009;**7**(4):728-9.